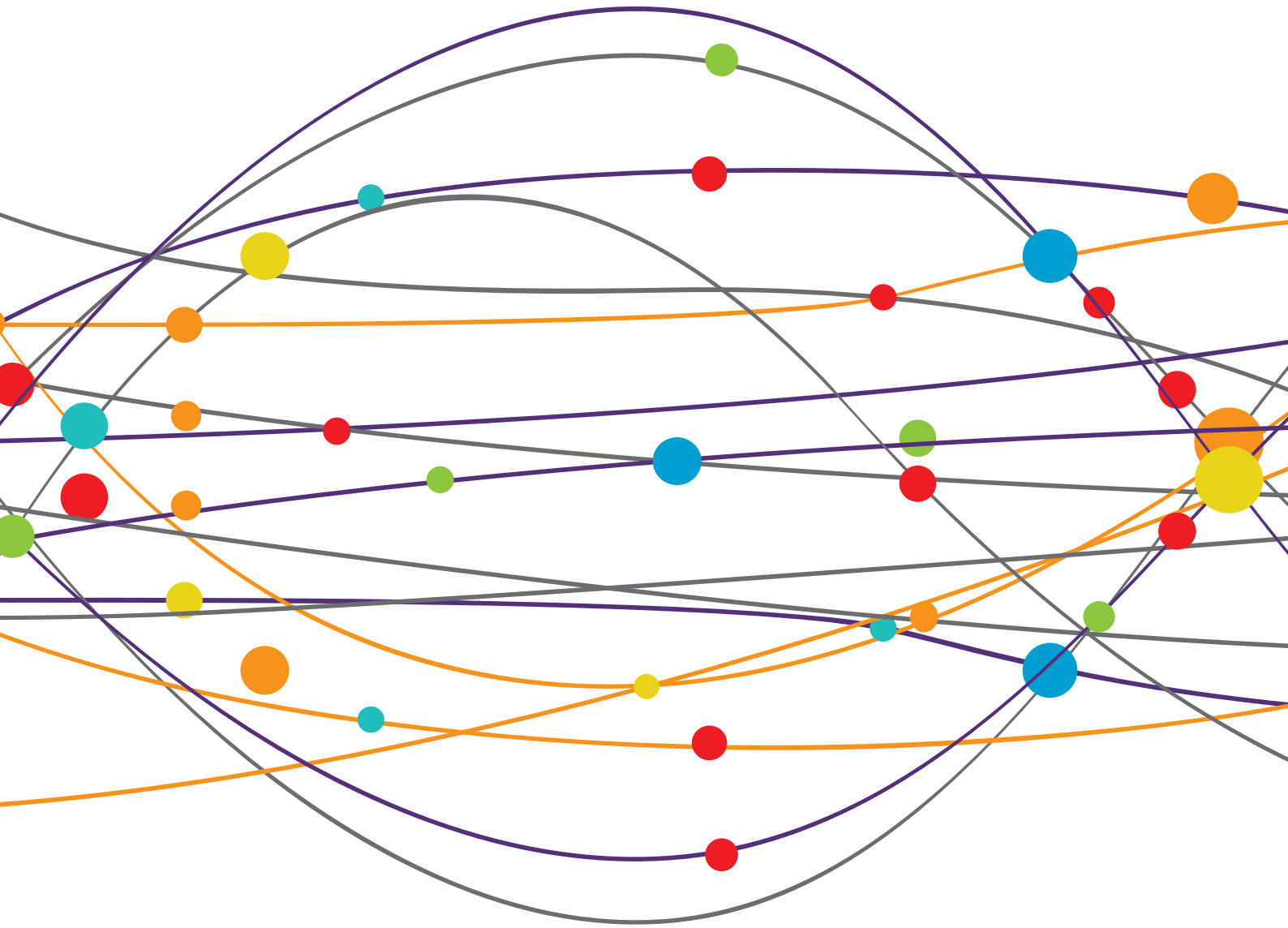
NEUROREHABILITATION EDITOR'S PICK 2021

EDITED BY: Giorgio Sandrini, Thomas Platz and Ross D. Zafonte
PUBLISHED IN: Frontiers in Neurology



frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88971-205-2
DOI 10.3389/978-2-88971-205-2

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

NEUROREHABILITATION EDITOR'S PICK 2021

Topic Editors:
Giorgio Sandrini, Fondazione Cirna Onlus, Italy
Thomas Platz, University of Greifswald, Germany
Ross D. Zafonte, Harvard Medical School, United States

Citation: Sandrini, G., Platz, T., Zafonte, R. D., eds. (2021). Neurorehabilitation Editor's Pick 2021. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88971-205-2

Table of Contents

frontiers in Neurology

CLINICAL TRIAL
published: 19 February 2019
doi: 10.3389/fneur.2019.00115

Short-Term Effects of Focal Muscle Vibration on Motor Recovery After Acute Stroke: A Pilot Randomized Sham-Controlled Study

Massimiliano Toscano [1,2], Claudia Celletti [3], Alessandro Viganò [1,4], Alberto Altarocca [3], Giada Giuliani [1], Tommaso B. Jannini [1], Giulio Mastria [1], Marco Ruggiero [1], Ilaria Maestrini [1], Edoardo Vicenzini [1], Marta Altieri [1], Filippo Camerota [3] and Vittorio Di Piero [1]*

[1] Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy, [2] Department of Neurology, Fatebenefratelli Hospital, Rome, Italy, [3] Physical Medicine and Rehabilitation Division, Umberto I University Hospital, Rome, Italy, [4] Department of Anatomy, Histology, Forensic Medicine and Orthopaedics, Sapienza University of Rome, Rome, Italy

OPEN ACCESS

Edited by:
Ina M. Tarkka, University of Jyväskylä, Finland

Reviewed by:
Marianna Capecci, Polytechnical University of Marche, Italy
Cristiano De Marchis, Università degli Studi Roma Tre, Italy
Józef Alfons Opara, Jerzy Kukuczka Academy of Physical Education in Katowice, Poland

***Correspondence:**
Massimiliano Toscano
massimiliano.toscano@uniroma1.it

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *10 September 2018*
Accepted: *29 January 2019*
Published: *19 February 2019*

Citation:
Toscano M, Celletti C, Viganò A, Altarocca A, Giuliani G, Jannini TB, Mastria G, Ruggiero M, Maestrini I, Vicenzini E, Altieri M, Camerota F and Di Piero V (2019) Short-Term Effects of Focal Muscle Vibration on Motor Recovery After Acute Stroke: A Pilot Randomized Sham-Controlled Study. Front. Neurol. 10:115. doi: 10.3389/fneur.2019.00115

Repetitive focal muscle vibration (rMV) is known to promote neural plasticity and long-lasting motor recovery in chronic stroke patients. Those structural and functional changes within the motor network underlying motor recovery occur in the very first hours after stroke. Nonetheless, to our knowledge, no rMV-based studies have been carried out in acute stroke patients so far, and the clinical benefit of rMV in this phase of stroke is yet to be determined. The aim of this randomized double-blind sham-controlled study is to investigate the short-term effect of rMV on motor recovery in acute stroke patients. Out of 22 acute stroke patients, 10 were treated with the rMV (vibration group–VG), while 12 underwent the sham treatment (control group–CG). Both treatments were carried out for 3 consecutive days, starting within 72 h of stroke onset; each daily session consisted of three 10-min treatments (for each treated limb), interspersed with a 1-min interval. rMV was delivered using a specific device (Cro®System, NEMOCO srl, Italy). The transducer was applied perpendicular to the target muscle's belly, near its distal tendon insertion, generating a 0.2–0.5 mm peak-to-peak sinusoidal displacement at a frequency of 100 Hz. All participants also underwent a daily standard rehabilitation program. The study protocol underwent local ethics committee approval (ClinicalTrial.gov NCT03697525) and written informed consent was obtained from all of the participants. With regard to the different pre-treatment clinical statuses, VG patients showed significant clinical improvement with respect to CG-treated patients among the NIHSS ($p < 0.001$), Fugl-Meyer ($p = 0.001$), and Motricity Index ($p < 0.001$) scores. In addition, when the upper and lower limb scales scores were compared between the two groups, VG patients were found to have a better clinical improvement at all the clinical end points. This study provides the first evidence that rMV is able to improve the motor outcome in a cohort of acute stroke patients, regardless of the pretreatment clinical status. Being a safe and well-tolerated intervention, which is easy to perform at the bedside, rMV may represent a valid complementary non-pharmacological therapy to promote motor recovery in acute stroke patients.

Keywords: stroke, acute stroke, focal muscle vibration, motor recovery, stroke rehabilitation, neural plasticity

INTRODUCTION

Stroke is the leading cause of long-term disability (1), mostly because of incomplete functional recovery post-stroke with more than half of stroke survivors aged 65 and over exhibiting reduced mobility (2).

Furthermore, it remains unclear which is the most effective training protocol for rehabilitation of a paretic limb, as do the factors underlying recovery of motor function. A growing body of evidence from neuroimaging (3) and neurophysiological studies (4) indicate that a focal brain lesion resulting from stroke may trigger structural and functional changes in perilesional and remote brain regions. In fact, a stroke lesion can directly damage the motor pathways as well as alter the balance of excitatory and inhibitory influences within the motor network, both in the affected and unaffected hemisphere. Therefore, a modulation of this network, by acting on brain plasticity and network relearning, may be crucial for the recovery of motor function after stroke.

From this point of view, one of the most effective modulators of cortical motor and somatosensory structures is repeated sensory input (5). Muscle vibration is a strong proprioceptive stimulus, which, at low amplitudes, preferentially produces Ia fiber afferent input and reaches both the SI and M1 directly. The specific pattern of direct connections linking SI and M1 cortices may provide the anatomical substrate for the role muscle vibration plays in reorganizing the motor and somatosensory cortices (6–9).

In particular, a repetitive focal muscle vibration (rMV) at a fixed low frequency of 100 Hz rMV, applied during a voluntary contraction, may induce both prolonged changes in the excitatory/inhibitory state of the primary motor cortex in healthy subjects (10), and long-term changes of motor performance in patients as well (11).

A recent study using transcranial magnetic stimulation showed that rMV therapy, combined with physiotherapy, helped to reduce abnormalities of both the corticospinal excitability and the intracortical inhibitory systems in the damaged hemisphere of chronic stroke patients (12). Interestingly, the clinical and neurophysiological changes lasted for at least 2 weeks after the end of rMV treatment and were related to a decrease in spasticity and increase in motor function. In chronic stroke patients, two different studies demonstrated that rMV treatment may improve the functional ability of the upper (13) and lower limb (14).

The structural and functional changes within the motor network that underlie motor recovery occur in the immediate few hours after stroke; thus, it seems to be crucial to understand if it is possible to act on them during the acute phase of stroke, in order to improve stroke rehabilitation. Very few studies have been carried out on acute stroke patients so far, and none of those used rMV in the acute stage of stroke.

The aim of the present randomized double-blind sham-controlled study is to investigate the effects of rMV on motor recovery in acute stroke patients.

MATERIALS AND METHODS

Subjects

We prospectively examined consecutive patients admitted to our Stroke Unit for ischemic or hemorrhagic stroke within 72 h from symptom onset. Inclusion criteria were: age>18, first ever stroke detected by Magnetic Resonance Imaging (MRI) or Computer Tomography (CT) scan, motor deficit of the upper and/or lower limb; ability to perform at least a minimal isometric voluntary contraction of the affected limb. We excluded patients with TIA, or rapidly improving stroke, cerebral venous thrombosis or presenting with aphasia, neglect, or apraxia. Those patients who were on drugs active at the central nervous system level at the time of the recruitment have been excluded as well.

The study protocol underwent local ethics committee approval ("Policlinico Umberto I of Rome" Ethics committee); the clinical trial was registered in the ClinicalTrial.gov database (NCT03697525). Written informed consent was obtained from all of the participants. The study was conducted in conformity with the ethical standard, according to the Declaration of Helsinki.

Experimental Design

This is a prospective randomized double-blind sham-controlled study. After enrollment (T-0), patients were randomly placed into the vibration group (VG) or the control group (CG), by using a computer-generated randomization list. VG patients received rMV treatment while those of CG received the sham one. Both treatments were carried out during the 1st, 2nd, and 3rd day after enrollment. Physio kinesitherapy (PT) was carried out in all patients every day, starting soon after T-0 clinical evaluation. Patients were re-evaluated after 4 ± 1 days (T-1), at the end of treatment (see **Figure 1** for the study flow chart).

Clinical Evaluation

Upon admission, all participants' demographic details and medical history were recorded. All patients underwent a clinical examination, performed at all time-points by an experienced investigator, blinded to the group assignment and different from the recruiting one. Clinical evaluation consisted of stroke severity evaluation, by means of NIH Stroke Scale (15); motor and functional limbs abilities were evaluated by using both the Fugl-Meyer scale (16–18), and the Motricity Index (19); spasticity was assessed with Ashworth scale, modified by Bohannon and Smith (20).

Physiotherapy (PT)

All participants underwent a 1-h daily rehabilitation session (for each treated limb), which included passive/active movements, mobilization, and proprioceptive neuromuscular facilitation of the affected limb.

Before treatment, the physical therapist was instructed about duration, frequency, and content of therapy in order to ensure uniformity in treatment procedures and blinded to patients' treatment allocation.

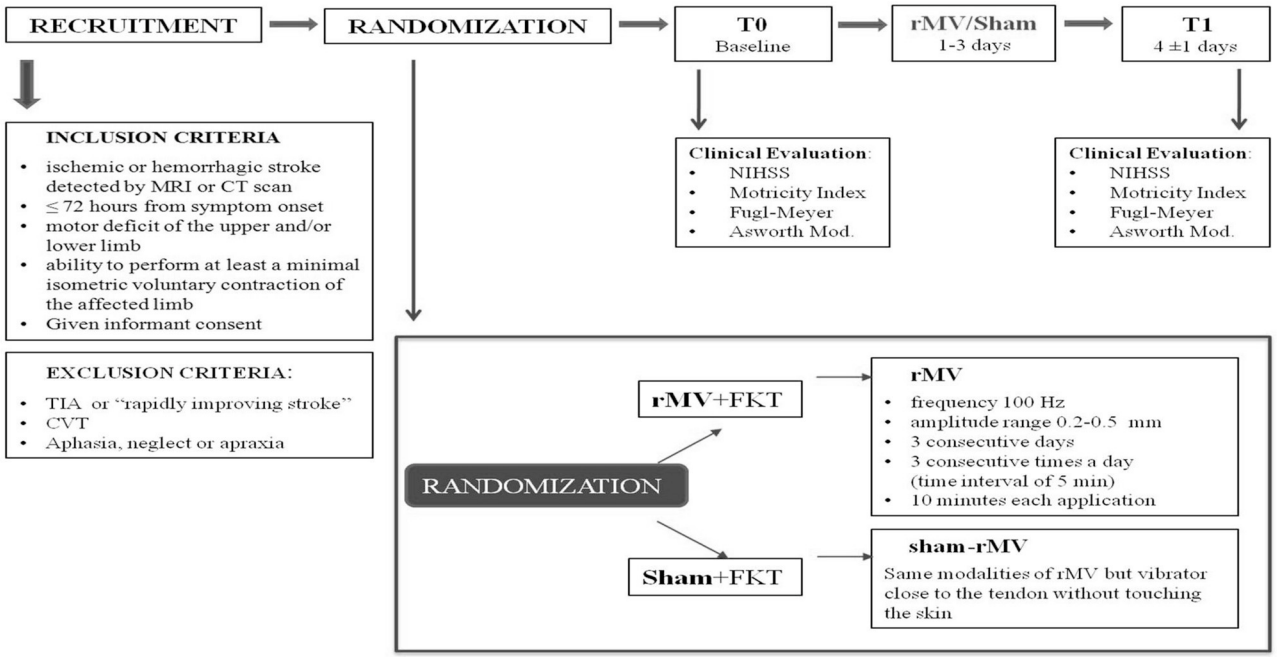


FIGURE 1 | Study flow chart.

Repetitive Focal Muscle Vibration (rMV)

rMV was delivered using a specific device that consisted of an electromechanical transducer, a mechanical support, and an electronic control device (Cro®System, NEMOCO srl, Italy). A mechanical arm permitted the transducer to be placed on the treatment site and to deliver the vibration at bedside, with patients placed supine; the support was rigidly anchored to the floor to guarantee good mechanical contact with tissue.

The transducer was applied perpendicular to the target muscle's belly (flexor carpi radialis and the biceps brachii for the upper limb, and/or over the rectus femoris for the lower limb treatment), near its distal tendon insertion. It generated a sinusoidal displacement of 0.2–0.5 mm (peak to peak); this parameter were used since small vibration amplitudes are effective for stimulating Ia afferents and for avoiding tonic vibration reflex as well (21, 22). Considering that Ia afferents can fire synchronously with vibration frequencies up to 80–120 Hz (23, 24), vibration characteristics were set to 100 Hz.

The rMV treatment was delivered for 3 consecutive days by two trained physiatrists; each daily session consisted of three 10-min vibration treatment (for each treated limb), separated with a 1-min interval. Otherwise, sham rMV was carried by positioning the vibrator close to the tendon but without touching the skin. In this condition, patients were only subject to the faint buzzing sound of the vibrator (13). In those patients who had a motor deficit of both the upper and the lower limb, the interventions (i.e., rMV and sham) were applied separately and in succession (1-min interval) to both limbs.

To increase response to vibration, during both the treatments (i.e., rMV and sham), patients were required to make a mild voluntary contraction (22, 25) of the treated muscle. On the other hand, during the intervals, patients were asked to relax the muscle.

Statistical Analysis

We assessed the normality of the distributions with the Shapiro-Wilk Normality Test. According to the result of normality analysis, Student's *T*-test for paired samples or Wilcoxon test for paired samples were used to analyze clinical and neuroradiological difference between the two groups (i.e., VG e CG).

To investigate differences over time (from T-0 to T-1) between the two groups concerning clinical end-points (i.e. NIHSS, Fugl-Meyer, Motricity Index, and Ashworth scales score), we adopted two different analyses: the analysis of variance (ANOVA) allowed to compare the two groups in terms of clinical improvement expressed as difference between T-1 and T-0 scales score (ΔT-1-T-0). Moreover, by means of the analysis of variance for repeated measures (ANOVA-RM) with Tukey *post-hoc* analysis, we also analyzed clinical improvement expressed as over time repeated measures.

The *P*-value level of significance throughout the statistical analysis was set at 0.05, considering Bonferroni correction. Statistical analysis was conducted with the SPSS software package for Windows, release 22.0.

RESULTS

We recruited 22 patients (14 males, mean age 67 ± 13 years) in the acute phase of stroke (mean time from stroke: 43.9 ± 18.9 h).

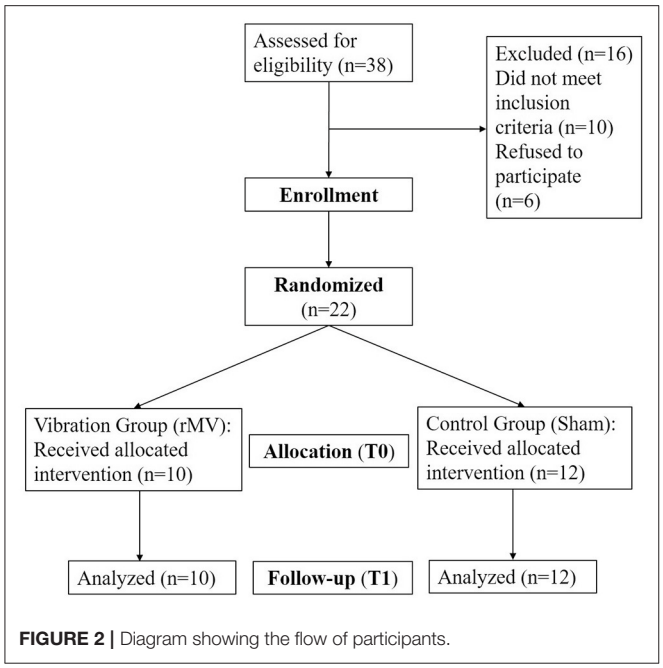


FIGURE 2 | Diagram showing the flow of participants.

All patients were right-handed. None of them were treated with mechanical thrombectomy nor received any thrombolytic treatment. Twelve patients were treated with antiplatelet agents. None of the patients had sensory deficit as assessed by the NIHSS.

After the randomization, 10 patients were treated with the rMV (VG), while 12 underwent the sham treatment (CG) (see **Figure 2** for the diagram showing the flow of participants). None of the treated patients complained side effects during (e.g., pain) or after the vibration treatment.

Two patients (1 VG, 1 CG) were treated only on the upper limb, 4 patients (2 VG, 2 CG) only on the lower one, and the remaining 16 patients (6 VG, 8 CG) on both the limbs.

Differences between VG and CG in term of demographic data, stroke characteristics and clinical features are shown in **Table 1**.

The two groups of stroke patients did not differ for age ($p = 0.39$), sex ($p = 0.16$), stroke type ($p = 0.39$), lesion side ($p = 0.23$), stroke localization ($p = 0.23$), and for the presence of major cerebrovascular risk factors. Univariate analysis did neither show any difference between the two groups regarding both the stroke severity upon admission, (NIHSS score–VG: 12.4 ± 4.09; CG: 10±3.22; $p = 0.13$), and the mean time between rMV treatment and stroke (VG: 45 ± 20.4 h; CG 43±18.4 h; $p = 0.8$).

Analysis of variance (ANOVA) showing difference between T-1 and T-0 scores (ΔT1-T0) for each clinical variable (i.e., NIHSS, Fugl-Meyer, Motricity Index e Ashworth Modified) is reported in **Figure 3**. Patients treated with rMV (VG) had a significant clinical improvement with respect to those treated with a sham-rMV among the NIHSS ($p < 0.001$), Fugl-Meyer ($p = 0.001$), and Motricity Index ($p < 0.001$) scores.

Only five patients (3 VG, 2 CG) had post-stroke spasticity, with a maximum modified Ashworth scale (MAS) score of 1 (i.e., very slight increase in the muscle tone); no difference in the MAS score were found between groups ($p = 0.668$).

TABLE 1 | Univariate Analysis: significant demographic data, medical history, clinical and neuro-anatomical characteristics according to the type of treatment.

		rMV *N* = 10 *n*(%)	SHAM *N* = 12 *n*(%)	*p*-value
Age	(Mean ± *SD*)	64.70 ± 17.24	69.50 ± 7.3	0.39
Sex	Male	8 (80)	6 (50)	0.16
	Female	2 (20)	6 (50)	
Time from stroke	(Hours)	45 ± 20.4	43 ± 18.4	0.81
Stroke Type	Ischemic	4 (40)	8 (66.7)	0.39
	Hemorrhagic	4 (40)	2 (16.7)	
	Both	2 (20)	2 (16.7)	
Stroke	Cortical	3 (30)	4 (33.3)	0.80
Localization	Subcortical	4 (40)	4 (33.3)	
	Brainstem	1 (10)	0	
	Cortico-subcortical	2 (20)	4 (33.3)	
Stroke Side	Right	6 (60)	4 (33.3)	0.23
	Left	4 (40)	8 (66.7)	
	Bilateral	0	0	
CAD (Coronary Artery disease)		7 (70)	10 (83.3)	0.13
Smoke		2 (20)	6 (50)	0.16
Hypertension		8 (80)	8 (66.7)	0.51
Diabetes		2 (20)	4 (33.3)	0.51
Hypercholesterolemia		4 (40)	6 (50)	0.66
Atrial Fibrillation		2 (20)	0	0.11
Previous	No	8 (80)	8 (66.7)	0.89
Stroke	Ischemic	1 (10)	4 (33.3)	
	Hemorrhagic	1 (10)	0	
Cardiac Failure		1 (10)	0	0.28
NIHSS (T0)	(Mean ± *SD*)	12.4 ± 4.09	10 ± 3.22	0.13

By comparing the Fugl-Meyer and Motricity Index scales scores separately for the upper and the lower limb, VG patients were found to have a better clinical improvement at all the clinical end points (Arm: Fugl-Meyer $p < 0.001$, Motricity Index $p < 0.001$; Leg: Fugl-Meyer $p = 0.013$, Motricity Index $p < 0.001$) (**Figure 4**).

Analysis of variance for repeated measures (ANOVA-RM) with Tukey *post-hoc* analysis, allowed us to analyze the clinical improvement expressed as over time repeated measures for each clinical end-point (**Figures 5**, **6**). VG patients showed a better clinical improvement with respect to CG patients in terms of stroke severity assessed by NIHSS ($p < 0.001$), and of Fugl-Meyer ($p = 0.001$) and Motricity Index scale score ($p < 0.001$). The better motor outcome of the rMV-treated patients was confirmed for the upper and the lower limb, separately (Arm: Fugl-Meyer $p = 0.005$, Motricity Index $p = 0.003$; Leg: Fugl-Meyer $p < 0.001$, Motricity Index $p < 0.001$).

Tukey *post-hoc* analysis showed that ANOVA-RM significance was only due to rMV patients clinical improvement from T-0 to T-1 (rMV T-0-T-1: NIHSS $p < 0.001$; Fugl-Meyer tot $p < 0.001$; Fugl-Meyer Arm $p < 0.001$; Fugl-Meyer Leg $p < 0,001$; Motricity

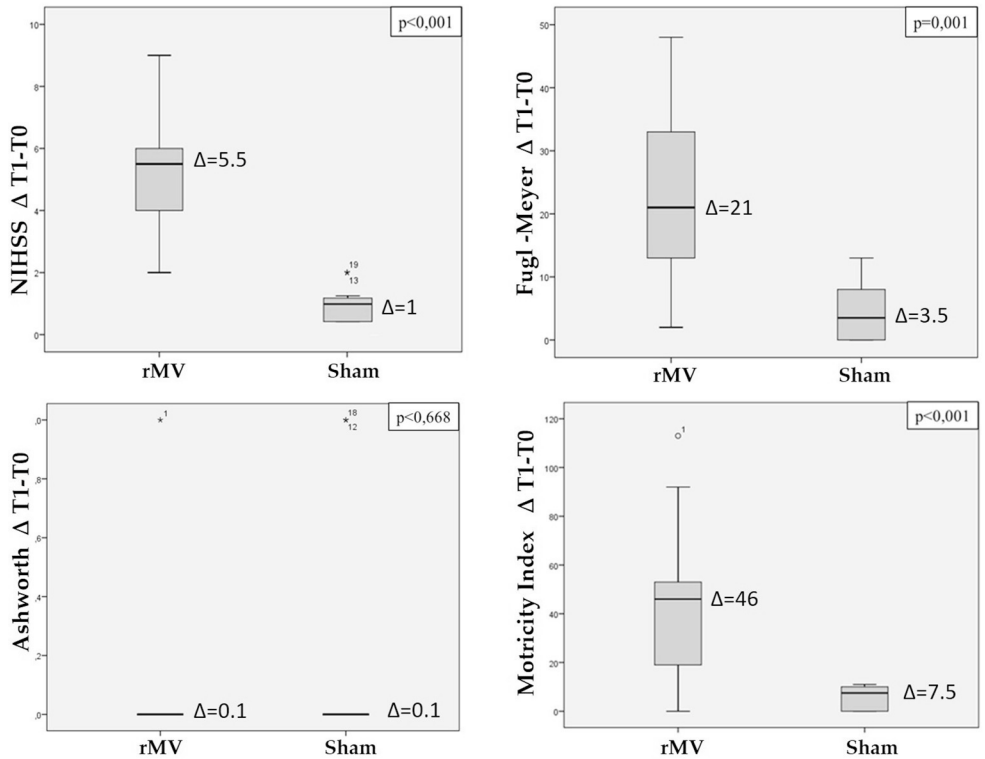


FIGURE 3 | Box plot with Interquartile Range (IQR) distribution of the difference between T1 and T0 scales values (NIHSS, total Fugl-Meyer, total Motricity Index, Ashworth modified) in patients treated with rMV and in those treated with sham-rMV. ANOVA's *p*-value for comparison of the variable between the two groups is reported on the top of each the figure.

Index tot $p < 0.001$; Motricity Index Arm $p < 0.001$; Motricity Index Leg $p < 0.001$), but the Fugl-Meyer Arm (sham-rMV T0-T1: Fugl-Meyer Arm $p = 0.02$). In fact, this analysis did not show any difference between groups regarding the pre-treatment clinical status (NIHSS: $p = 0.36$; Fugl-Meyer Tot: $p = 0.09$; Fugl-Meyer Arm: $p = 0.08$; Fugl-Meyer Leg: $p = 0.99$; Motricity Index Tot: $p = 0.18$; Motricity Index Arm: $p = 0.21$; Motricity Index Leg: $p = 0.62$).

DISCUSSION

Focal repetitive muscle vibration (rMV) is a safe and well-tolerated intervention which is easy to perform at the bedside, and promotes neural plasticity and long-lasting motor recovery in chronic stroke patients (12).

Although much evidence exists of the efficacy of focal muscle vibration in the chronic phase, the clinical benefit in the very acute phase of stroke is yet to be determined. From a clinical point of view, the reason why this issue is crucial, is that those structural and functional changes within the motor network that underlie the motor recovery after stroke occur in the very first hours after stroke. To our knowledge, no studies have been carried out to investigate the effect of rMV on motor recovery in the acute phase of stroke so far.

Our data show that the rMV intervention can consistently improve motor outcome in a cohort of acute stroke patients. In fact, patients with stroke treated with rMV (VG) had a significant clinical improvement compared to those treated with a sham-rMV as shown by improved NIHSS ($p < 0.001$), Fugl-Meyer ($p = 0.001$), and Motricity Index ($p < 0.001$) scores, regardless the different baseline clinical status, or the different stroke characteristics (stroke type, side or localization of stroke lesion and so on).

The neural substrates underlying motor recovery in the acute phase of stroke are still a matter of debate. Despite the role of the hyperactivation of several cortical areas in both the affected and in the unaffected hemisphere being still unclear, ipsilesional M1 is widely thought to represent the most effective target for rehabilitation therapy (26, 27). This has become a milestone since pioneering studies described how the integrity and or over-activation of the lesioned hemisphere's motor cortex (ipsilesional M1) related to better post-stroke motor recovery (28–30).

Thus, in our opinion, the primary mechanism by which rMV may improve motor recovery after acute stroke is through a direct action on the ipsilesional motor cortex. In detail, the repeated muscle vibration produces a repeated sensory input that reaches M1 directly, via Ia fiber afferent input (6–9), thereby leading to an improvement of functional ability of the affected limb by means of an intrinsic plasticity-related mechanism (11, 13).

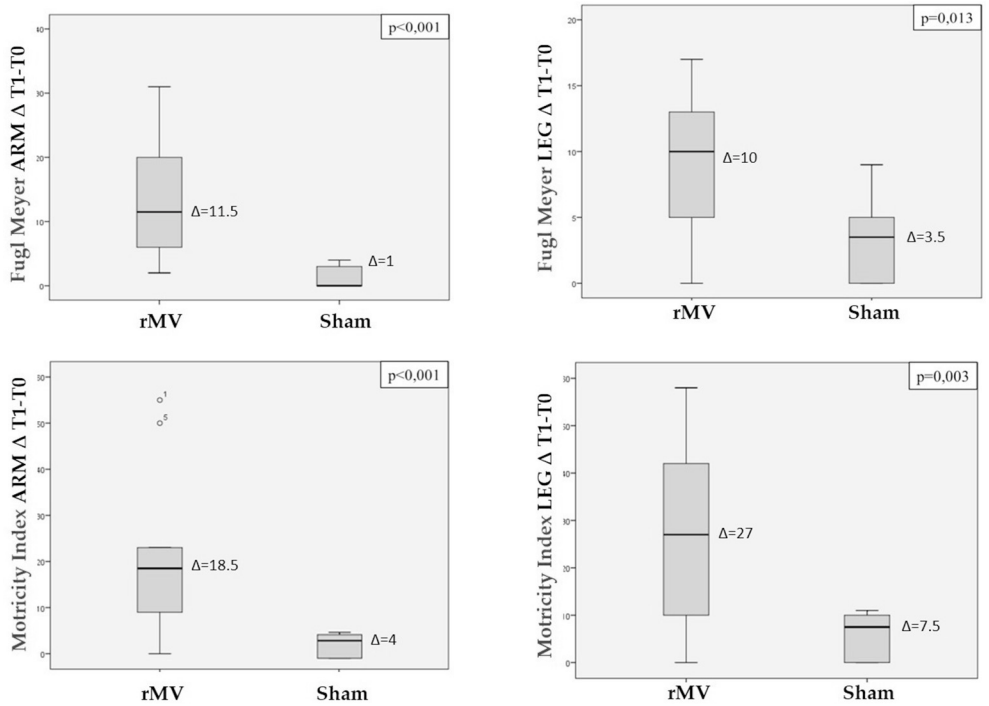


FIGURE 4 | Box plot with Interquartile Range (IQR) distribution of the difference between T1 and T0 scales values (Fugl-Meyer arm, Fugl-Meyer leg, Motricity Index arm and Motricity Index leg) in patients treated with rMV and in those treated with sham-rMV. ANOVA's *p*-value for comparison of the variable between the two groups is reported on the top of each the figure.

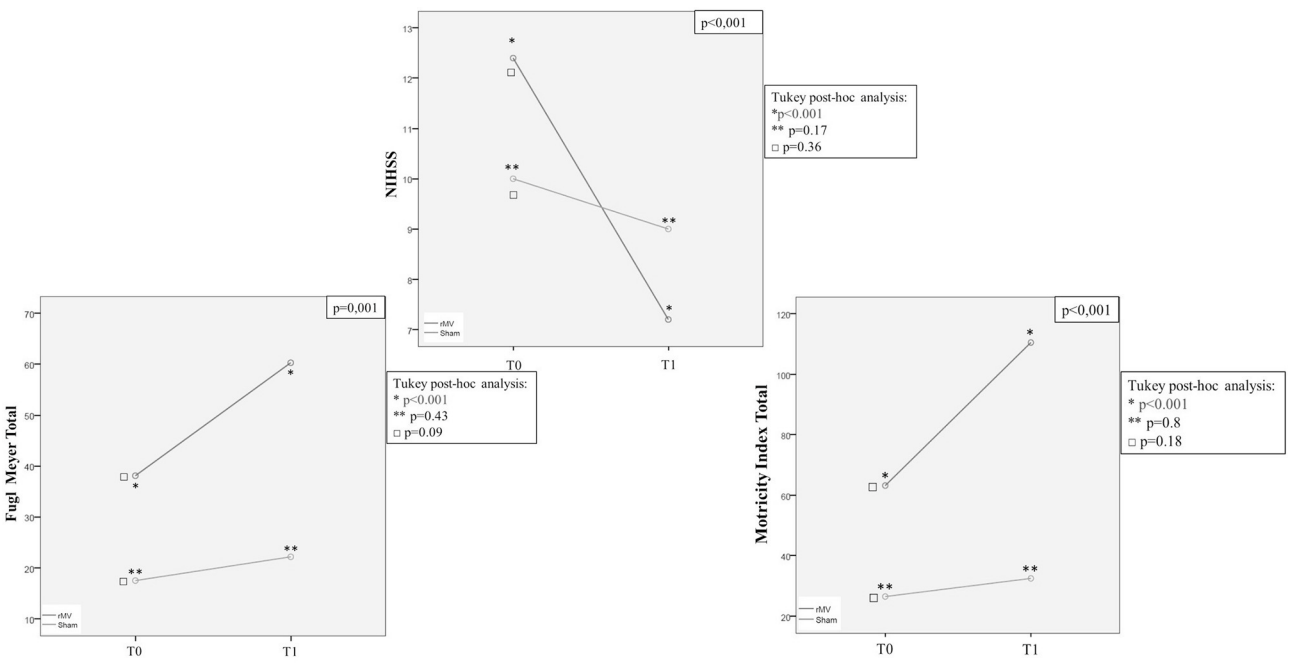


FIGURE 5 | ANOVA for Repeated Measures (ANOVA-RM) with Tukey *post-hoc* analysis: T0 and T1 mean values (NIHSS, total Fugl-Meyer, total Motricity Index, Ashworth modified) in patients treated with rMV (blue line) and in those treated with sham-rMV (green line).

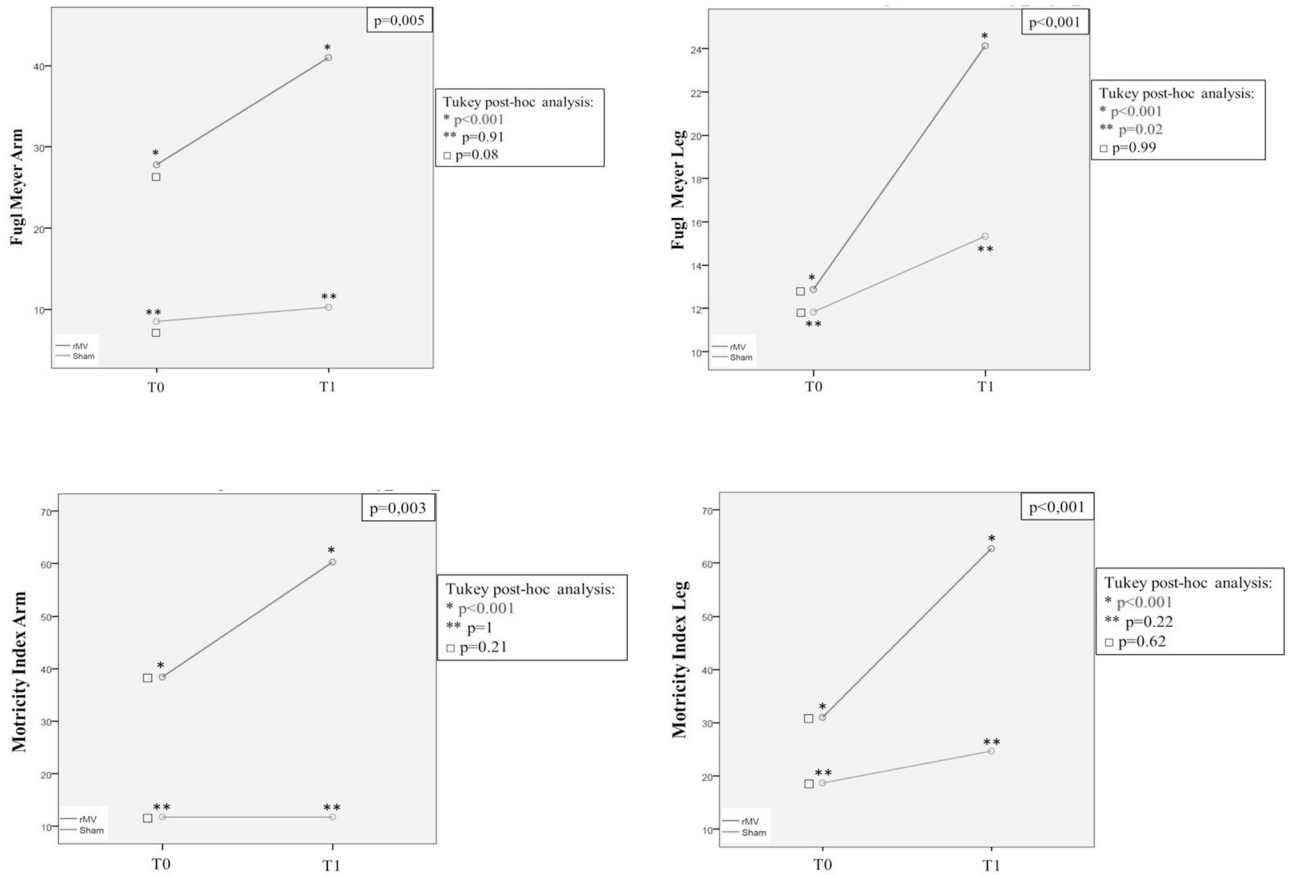


FIGURE 6 | ANOVA for Repeated Measures (ANOVA-RM) with Tukey *post-hoc* analysis: T0 and T1 mean values (Fugl-Meyer arm, Fugl-Meyer leg, Motricity Index arm and Motricity Index leg) in patients treated with rMV (blue line) and in those treated with sham-rMV (green line).

An additional mechanism that may be involved in the rMV-induced motor recovery in acute stroke, probably concurrent with the direct action on ipsilesional M1, entails the changes in perilesional brain regions triggered by the focal brain lesion and their connections to the spinal cord motor neurons.

The recruitment of secondary brain structures, due to the capability to establish and consolidate new neural networks in response to a change in the environment (i.e., neuroanatomical plasticity), has been described in the acute phase, especially in those patients with greater motor impairment. This compensative recruitment (i.e., increased activity) is not "maladaptive" because the effects of TMS disruption have demonstrated that their activity is functionally significant (31); nevertheless, it leads to an incomplete recovery (32). The main reason is that the projections from ipsilateral non-primary motor areas to spinal cord motor neurons are less numerous and less efficient at exciting spinal cord motor neurons than those from M1 (30, 33, 34).

Considering that the focal muscle vibration represents a strong proprioceptive stimulus which is able to produce substantial neurophysiological changes also at a peripheral level, it is probably also able to induce synaptic plasticity at the Ia-motoneuron synapse level, thereby increasing the effectiveness of these cortical-spinal connections. In light of this, it is intriguing that a recent study reported that rMV was able to induce long-term depression-like plasticity in specific spinal cord circuits, depending on the muscle vibrated (22).

Thus, our hypothesis is that rMV could drive motor recovery by also acting on spinal cord plasticity, namely by making the projections from secondary motor areas to spinal motor neurons more active and efficient. This mechanism could be of particular relevance in patients with higher motor impairment. Moreover, considering that the secondary motor areas (e.g., PMd) have prominent bilateral connections to the spinal cord (32), one might speculate that this mechanism is able also to act on interhemispheric imbalance involving hyperexcitability of the contralesional hemisphere, whose modulation may have a pivotal, although still unclear, role in motor recovery after stroke (27, 33).

Finally, a possible role of rMV in reducing spasticity when applied to the spastic muscles of hemiplegic limbs in post-stroke patients as also been suggested (13, 35, 36). Among the

whole population of recruited patients, we found a mild increase in muscle tone in 5 patients, with no difference between the two groups in Ashworth modified score changes. A possible explanation of this datum is that we evaluated stroke patients in the very acute phase of stroke, whereas spasticity usually develops after several weeks after stroke. Moreover, the very slight increase (with a maximum MAS score of 1) probably did not allow finding a statistical difference between groups. Anyway, there are evidences of spasticity development in the early time course of stroke (37). It would be therefore intriguing to perform a follow-up study to investigate whether this datum is merely due to the timing of spasticity assessment, or if we somehow were able to prevent the spasticity by stimulating the proprioceptive system since the very acute phase (38).

A limitation of the study is that, due to the peculiar emergency setting of the acute Stroke Unit, patients were asked to perform a mild voluntary contraction without measurement of the performed contraction with visual EMG feedback. Moreover, due to the relatively low number of patients, we were not able to perform a multivariate analysis to avoid all stroke-related clinical bias. That notwithstanding, to have further evidences of the role of an intrinsic mechanism more than one linked to patients' clinical characteristic (as already demonstrated in the chronic phase), we evaluated motor outcome by separately analyzing the ΔT1-T0 Fugl-Meyer and Motricity Index scales scores of the upper limb and those of the lower limb. Also, in this, case SG patients were found to have a better clinical improvement at all the clinical end-points (Arm: Fugl-Meyer $p < 0{,}001$, Motricity Index $p < 0.001$; Leg: Fugl-Meyer $p = 0.013$, Motricity Index $p < 0.001$).

With the same goal in mind, we also analyzed clinical improvement expressed as over-time repeated measures by means of the analysis of variance for repeated measures (ANOVARM) with Tukey *post-hoc* analysis. We found that, for all the clinical end-points analyzed except Fugl-Meyer Arm, the significance of patients' clinical improvement from T0 to T1 was exclusively due to rMV treatment (rMV T0-T1: NIHSS $p < 0.001$; Fugl-Meyer Tot $p < 0.001$; Fugl-Meyer Arm $p < 0.001$; Fugl-Meyer Leg $p < 0.001$; Motricity Index Tot $p < 0.001$; Motricity Index Arm $p < 0.001$; Motricity Index Leg $p < 0.001$); this is important because a minimal improvement is somehow expected because of the PT treatment and because of the stroke natural clinical history as well. Moreover, also when expressed as over-time repeated measures, VG better clinical outcome was independent from the different initial clinical status; interestingly, rMV-related recovery was even more consistent in patients with a more severe stroke in terms of NIHSS, which supports the hypothesis of a plasticity-based intrinsic mechanism being responsible for the better motor recovery of stroke patients treated with rMV in the acute phase of stroke.

However, addressing the plasticity-based mechanisms underlying the rMV-induced motor recovery after stroke does however, go beyond the main clinical purpose of our study. Thus, further RCTs are needed to draw conclusions on this specific issue.

Regarding the main outcome of our study, our data provides the first evidence that the rMV intervention can improve motor outcome in a cohort of stroke patients regardless the different baseline clinical status, or the different stroke characteristics.

CONCLUSIONS

This study provided the first evidence that repetitive focal muscle vibration (rMV), when combined with physiotherapy, is able to improve motor outcome in a cohort of stroke patients, even when performed in the very acute phase of stroke. As a safe and well-tolerated intervention, which is easy to perform at bedside, rMV may represent a valid complementary non-pharmacological therapy to promote motor recovery in acute stroke patients.

AUTHOR CONTRIBUTIONS

MT: study design, manuscript preparation, data collection, statistical analysis, blinding overview; CC: rMV execution, manuscript preparation; AV: clinical evaluation, manuscript preparation; AA: clinical scales' implementation and review; GG and TJ: recruitment, demographic details, and medical history record; GM and MR: literature review, ethics committee; IM: literature review, manuscript review; EV and MA: data interpretation, manuscript review; FC: rMV execution, manuscript review, physio kinesitherapy overview; VDP: data interpretation, manuscript review, coordination between specialists.

ACKNOWLEDGMENTS

We would like to thank Mr. Daniel L. Holder for his precious support and advice.

REFERENCES

1. Stroke-Unit-Trialists'-Collaboration. Organized inpatient (stroke unit) care for stroke. functional recovery after stroke is usually incomplete and often associated with persistent involvement of upper limbs. *Cochrane Database Syst Rev.* (2000) 2:CD000197.
2. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol.* (2009) 8:741–54. doi: 10.1016/S1474-4422(09)70150-4
3. Grefkes C, Fink GR. Reorganization of cerebral networks after stroke: new insights from neuroimaging with connectivity approaches. *Brain* (2011) 134:1264–76. doi: 10.1093/brain/awr033
4. Talelli P, Greenwood RJ, Rothwell JC. Arm function after stroke: neurophysiological correlates and recovery mechanisms assessed by transcranial magnetic stimulation. *Clin Neurophysiol.* (2006) 117:1641–59. doi: 10.1016/j.clinph.2006.01.016

5. Ward NS, Cohen LG. Mechanisms underlying recovery of motor function after stroke. *Arch Neurol.* (2004) 61:1844–8. doi: 10.1001/archneur.61.12.1844
6. Heath CJ, Hore J, Phillips CG. Inputs from low threshold muscle and cutaneous afferents of hand and forearm to areas 3a and 3b of baboon's cerebral cortex. *J Physiol.* (1976) 257:199–227. doi: 10.1113/jphysiol.1976.sp011364
7. Jones EG, Porter R. What is area 3a? *Brain Res.* (1980) 203:1–43.
8. Ghosh S, Brinkman C, Porter R. A quantitative study of the distribution of neurons projecting to the precentral motor cortex in the monkey (M. *fascicularis). J Comp Neurol.* (1987) 259:424–44. doi: 10.1002/cne.902590309
9. Huerta MF, Pons TP. Primary motor cortex receives input from area 3a in macaques. *Brain Res.* (1990) 537:367–71. doi: 10.1016/0006-8993(90)90388-R
10. Marconi B, Filippi GM, Koch G, Pecchioli C, Salerno S, Don R, et al. Long-term effects on motor cortical excitability induced by repeated muscle vibration during contraction in healthy subjects. *J Neurol Sci.* (2008) 275:51–9. doi: 10.1016/j.jns.2008.07.025
11. Brunetti O, Filippi GM, Lorenzini M, Liti A, Panichi R, Roscini M, et al. Improvement of posture stability by vibratory stimulation following anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc.* (2006) 14:1180–7. doi: 10.1007/s00167-006-0101-2
12. Marconi B, Filippi GM, Koch G, Giacobbe V, Pecchioli C, Versace V, et al. Long-term effects on cortical excitability and motor recovery induced by repeated muscle vibration in chronic stroke patients. *Neurorehabil Neural Repair.* (2011) 25:48–60. doi: 10.1177/1545968310376757
13. Caliandro P, Celletti C, Padua L, Minciotti I, Russo G, Granata G, et al. Focal muscle vibration in the treatment of upper limb spasticity: a pilot randomized controlled trial in patients with chronic stroke. *Arch Phys Med Rehabil.* (2012) 93:1656–61. doi: 10.1016/j.apmr.2012.04.002
14. Paoloni M, Mangone M, Scettri P, Procaccianti R, Cometa A, Santilli V. segmental muscle vibration improves walking in chronic stroke patients with foot drop: a randomized controlled trial. *Neurorehabil Neural Repair* (2010) 24:254–62. doi: 10.1177/1545968309349940
15. Brott T, Adams HPJ, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurement of acute cerebral infarction: a clinical examination scale. *Stroke* (1989) 20:864–70. doi: 10.1161/01.STR.20.7.864
16. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient, I: a method for evaluation of physical performance. *Scand J Rehabil Med.* (1975) 7:13–31.
17. Sanford J, Moreland J, Swanson LR, Stratford PW, Gowland C. Reliability of the fugl-meyer assessment for testing motor performance in patients following stroke. *Phys Ther.* (1993) 73:447–54. doi: 10.1093/ptj/73.7.447
18. Rödén-Jüllig A, Britton M, Gustafsson C, Fugl-Meyer A. Validation of four scales for the acute stage of stroke. *J Intern Med.* (1994) 236:125–36. doi: 10.1111/j.1365-2796.1994.tb01274.x
19. Demeurisse G, Demol O, Robaye E. Motor evaluation in vascular hemiplegia. *Eur Neurol.* (1980) 19:382–9. doi: 10.1159/000115178
20. Bohannon RW, Smith MB. Interrater reliability of a modified ashworth scale of muscle spasticity. *Phys Ther.* (1987) 67:206–7. doi: 10.1093/ptj/67.2.206
21. Fallon JB, Macefield VG. Vibration sensitivity of human muscle spindles and golgi. *Muscle Nerve* (2007) 36:21–9. doi: 10.1002/mus.20796
22. Rocchi L, Suppa A, Leodori G, Celletti C, Camerota F, Rothwell J, et al. Plasticity induced in the human spinal cord by focal muscle vibration. *Front Neurol.* (2018) 2:935. doi: 10.3389/fneur.2018.00935
23. Roll JP, Vedel JP. Kinaesthetic role of muscle afferents in man, studied by tendon vibration and microneurography. *Exp Brain Res.* (1982) 47:177–90. doi: 10.1007/BF00239377
24. Souron R, Farabet A, Féasson L, Belli A, Millet GY, Lapole T. Eight weeks of local vibration training increases dorsiflexor muscle cortical voluntary activation. *J Appl Physiol.* 122:2017. doi: 10.1152/japplphysiol.00793.2016
25. Fattorini L, Ferraresi A, Rodio A, Azzena GB, Filippi GM. Motor performance changes induced by muscle vibration. *Eur J Appl Physiol.* (2006) 98:79–87. doi: 10.1007/s00421-006-0250-5
26. Buetefisch CM. Role of the contralesional hemisphere in post-stroke recovery of upper extremity motor function. *Front Neurol.* (2015) 6:214. doi: 10.3389/fneur.2015.00214
27. Dodd KC, Nair VA, Prabhakaran V. Role of the contralesional vs. ipsilesional hemisphere in stroke recovery. *Front Hum Neurosci.* (2017) 11:469. doi: 10.3389/fnhum.2017.00469
28. Di Piero V, Chollet FM, MacCarthy P, Lenzi GL, Frackowiak RS. Motor recovery after acute ischaemic stroke: a metabolic study. *J Neurol Neurosurg Psychiatry* (1992) 55:990–6. doi: 10.1136/jnnp.55.11.990
29. Carr LJ, Harrison LM, Evans AL, Stephens JA. Patterns of central motor reorganization in hemiplegic cerebral palsy. *Brain* (1993) 116:1223–47. doi: 10.1093/brain/116.5.1223
30. Fridman EA, Hanakawa T, Chung M, Hummel F, Leiguarda RC, Cohen LG. Reorganization of the human ipsilesional premotor cortex after stroke. *Brain* (2004) 127:747–58. doi: 10.1093/brain/awh082
31. Turton A, Wroe S, Trepte N, Fraser C, Lemon RN. Contralateral and ipsilateral EMG responses to transcranial magnetic stimulation during recovery of arm and hand function after stroke. *Electroencephalogr Clin Neurophysiol.* (1996) 101:316–28. doi: 10.1016/0924-980X(96)95560-5
32. Johansen-Berg H, Rushworth MF, Bogdanovic MD, Kischka U, Wimalaratna S, Matthews PM. The role of ipsilateral premotor cortex in hand movement after stroke. *Proc Natl Acad Sci USA.* (2002) 99:14518–23. doi: 10.1073/pnas.222536799
33. Ward NS. Plasticity and the functional reorganization of the human brain. *Int J Psychophysiol.* (2005) 58:158–61. doi: 10.1016/j.ijpsycho.2005.02.009
34. Ward NS, Frackowiak RS. The functional anatomy of cerebral reorganisation after focal brain injury. *J Physiol Paris.* (2006) 99:425–36. doi: 10.1016/j.jphysparis.2006.03.002
35. Noma T, Matsumoto S, Etoh S, Shimodozono M, Kawahira K. Anti-spastic effects of the direct application of vibratory stimuli to the spastic muscles of hemiplegic limbs in post-stroke patients. *Brain Inj.* (2009) 23:623–31. doi: 10.1080/02699050902997896
36. Noma T, Matsumoto S, Shimodozono M, Etoh S, Kawahira K. Anti-spastic effects of the direct application of vibratory stimuli to the spastic muscles of hemiplegic limbs in post-stroke patients: a proof-of-principle study. *J Rehabil Med.* (2012) 44:325–30. doi: 10.2340/16501977-0946
37. Wissel J, Manack A, Brainin M. Toward an epidemiology of poststroke spasticity. *Neurology* (2013) 80(3 Suppl. 2):S13–9. doi: 10.1212/WNL.0b013e3182762448
38. Guang H, Ji L, Shi Y. Focal vibration stretches muscle fibers by producing muscle waves. *IEEE Trans Neural Syst Rehabil Eng.* (2018) 26:839–46. doi: 10.1109/TNSRE.2018.2816953

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CLINICAL TRIAL
published: 19 February 2019
doi: 10.3389/fneur.2019.00113

High Intensity Physical Rehabilitation Later Than 24 h Post Stroke Is Beneficial in Patients: A Pilot Randomized Controlled Trial (RCT) Study in Mild to Moderate Ischemic Stroke

Yanna Tong [1,2], Zhe Cheng [1,2], Gary B. Rajah [1,3], Honglian Duan [1,2], Lipeng Cai [1,2], Nan Zhang [1,2], Huishan Du [1,2], Xiaokun Geng [1,2,3] and Yuchuan Ding [1,3]**

[1] China-America Institute of Neuroscience, Beijing Luhe Hospital, Affiliated to Capital Medical University, Beijing, China, [2] Department of Neurology, Beijing Luhe Hospital, Affiliated to Capital Medical University, Beijing, China, [3] Department of Neurosurgery, Wayne State University School of Medicine, Detroit, MI, United States

OPEN ACCESS

Edited by:
Nicola Smania,
University of Verona, Italy

Reviewed by:
Alessandro Picelli,
University of Verona, Italy
Paolo Tonin,
Sant'Anna Institute, Italy

***Correspondence:**
Yuchuan Ding
yding@med.wayne.edu
Xiaokun Geng
xgeng@med.wayne.edu

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 29 November 2018
Accepted: 28 January 2019
Published: 19 February 2019

Citation:
Tong Y, Cheng Z, Rajah GB, Duan H, Cai L, Zhang N, Du H, Geng X and Ding Y (2019) High Intensity Physical Rehabilitation Later Than 24 h Post Stroke Is Beneficial in Patients: A Pilot Randomized Controlled Trial (RCT) Study in Mild to Moderate Ischemic Stroke. Front. Neurol. 10:113. doi: 10.3389/fneur.2019.00113

Objective: Very early mobilization was thought to contribute to beneficial outcomes in stroke-unit care, but the optimal intervention strategy including initiation time and intensity of mobilization are unclear. In this study, we sought to confirm the rehabilitative effects of different initiation times (24 vs. 48 h) with different mobilization intensities (routine or intensive) in ischemic stroke patients within three groups.

Materials and Methods: We conducted a randomized and controlled trial with a blinded follow-up assessment. Patients with ischemic stroke, first or recurrent, admitted to stroke unit within 24 h after stroke onset were recruited. Eligible subjects were randomly assigned (1:1:1) to 3 groups: Early Routine Mobilization in which patients received <1.5 h/d out-of-bed mobilization within 24–48 h after stroke onset, Early Intensive Mobilization in which patients initiated ≥3 h/d mobilization at 24–48 h after the stroke onset, and Very Early Intensive Mobilization in which patients received≥3 h/d mobilization within 24 h. The modified Rankin Scale score of 0–2 was used as the primary favorable outcome.

Results: We analyzed 248 of the 300 patients (80 in Early Routine Mobilization, 82 in Very Early Intensive Mobilization and 86 in Early Intensive Mobilization), with 52 dropping out (20 in Early Routine Mobilization, 18 in Very Early Intensive Mobilization and 14 in Early Intensive Mobilization). Among the three groups, the Early Intensive Mobilization group had the most favorable outcomes at 3-month follow-up, followed by patients in the Early Routine Mobilization group. Patients in Very Early Intensive Mobilization received the least odds of favorable outcomes. At 3 month follow up, 53.5%, ($n = 46$) of patients with Early Intensive Mobilization showed a favorable outcome (modified Rankin Scale 0–2) ($p = 0.041$) as compared to 37.8% ($n = 31$) of patients in the Very Early Intensive Mobilization.

Conclusions: Post-stroke rehabilitation with high intensity physical exercise at 48 h may be beneficial. Very Early Intensive Mobilization did not lead to a favorable outcome at 3 months.

Clinical Trial Registration: www.chictr.org.cn, identifier ChiCTR-ICR-15005992.

Keywords: acute care, ischemic stroke, early mobilization, intensity, rehabilitation

INTRODUCTION

Ischemic stroke leads to profound neurological deficits and lasting physical disability (1–4). The use of exercise-mediated adaptations to attenuate physical disability after stroke is an emerging arena in neurotherapeutics (2, 5, 6). However, fundamental questions regarding initiation time, intensity, and type of exercise, as well as other factors that affect rehabilitation remain unclear (7–9). While current guidelines recommend starting out-of-bed activity "early" during the acute phase of care, such guidelines do not specify how or if early exercise optimizes outcomes (10, 11). Many published studies have shown inconsistent results regarding the efficacy and safety of very early mobilization (VEM) after acute stroke. In a series of studies on A Very Early Rehabilitation Trail (AVERT), the authors did not recommend a certain initiation time for rehabilitation, while the study demonstrated an unfavorable outcome may be caused by a mobilization within 24 h after onset of stroke (12–15). A multicenter SEVEL (Early Sitting in Ischemic Stroke Patients) trial also did not find a significant functional improvement while initiating an early sitting protocol within 24 h after stroke onset. However, similar studies of VEM in India (16) and Japan (17), provided preliminary evidence that very early mobilization within 24 h of stroke onset was feasible, safe and cost effective The recent Cochrane systematic review of very early initiation of rehabilitation (VEI) (18) also concluded that the efficacy of VEI remains to be established. The optimal time for commencing mobilization in stroke patients remains unknown although the majority of studies address VEM. Furthermore, few studies have focused on the intensity of mobilization. The latest guidelines for management of acute ischemic stroke (10) from the American Stroke Association indicate that high-dose mobilization within 24 h of stroke onset should not be performed because it can reduce the odds of a favorable outcome at 3 months. The optimal dose of mobilization remains unknown. We surmise that an optimal rehabilitation strategy should be based on a proper combination of timing and intensity. It is highly important to understand how to rapidly and safely administer exercise after stroke. Therefore, the primary aim of our randomized controlled trial was to compare 24 h, the very early initiation time, to the 48 h, early initiation time of therapy with respect to patient outcomes. We also sought to characterize different intensities of mobilization and their relationship to functional outcomes. We sought to determine the effect of two major factors; timing and intensity, on rehabilitative outcome. Our clinical hypothesis was that intensive, early, but not too early out-of-bed activity would improve functional outcomes at 3 months. The primary outcome was to be assessed at 3 months using mRS scores.

MATERIALS AND METHODS

Study Design and Setting

This is a single center randomized controlled trial. The study was conducted at the Stroke Unit of the Department of Neurology, Beijing Luhe Hospital, Capital Medical University, from January 1, 2015 to December 31, 2017. The institutional ethics committees approved the study. The trial was registered in the Chinese Clinical Trial Registry (ChiCTR-ICR-15005992).

Participants

During the recruitment period, the principal investigator screened all patients admitted to stroke unit according to the following criteria.

Inclusion criteria: Patients aged 18–80 years, with a confirmed first or recurrent ischemic stroke admitted to our stroke unit within 24 h of onset, without disturbance of consciousness (score <2 for the first item of the NIHSS) and being able to react to verbal commands, were included in the study. Treatment with recombinant tissue plasminogen activator (rtPA) was allowed. Informed consent was obtained from each patient or his/her guardian before randomization.

Exclusion criteria included: (1) Premorbid disability (mRS>2); (2) Diagnosed transient ischemic attack (TIA); (3) Early acute deterioration, direct admission to the intensive care unit; (4) Any other serious medical illness or unstable coronary condition; (5) Systolic blood pressure lower than 110 mmHg or higher than 220 mmHg, oxygen saturation lower than 92% with oxygen supplementation, resting heart rate of <40 beats per min or more than 110 beats per min, temperature <38.5°C; (6) Treatment with thrombectomy; (7) Enrollment in another intervention trial.

The baseline characteristics of the subjects were collected at the beginning, including age, sex, stroke side, severity, and risk factors (hypertension, diabetes mellitus, ischemic heart disease, hypercholesterolemia, smoking, atrial fibrillation, previous stroke, or transient ischemic attack). Premorbid disability, admission Rankin score, rtPA treatment, daily training time and time to first mobilization after symptom onset were recorded. Physiological parameters such as temperature, heart rate, blood pressure, and saturation were also recorded twice a day as routine procedure. Neurological impairment was assessed by the 11-item National Institutes of Health Stroke Scale (NIHSS) version with a total score of 42 points (19) on admission and at discharge. The severity of the stroke was classified as mild (NIHSS score < 8), moderate (NIHSS score 8–16) or severe (NIHSS score>16) (20).

Intervention

All patients satisfying the inclusion criteria and giving consent were randomly assigned (1:1:1) to three groups by a computer generated randomization procedure using opaque envelopes: Early Routine Mobilization Group (ERM, early but not intensive), Early Intensive Mobilization (EIM) and Very Early Intensive Mobilization (VEIM). All participants received usual standard medical care (such as anti-platelet, anti-coagulation, anti-lipidemic, anti-hypertension or anti-inflammatory injury treatment) according to their conditions.

(1) ERM Protocol- besides standard medical care, patients in this group started <1.5 h/d (lower dose) of out-of-bed mobilization within 24–48 h after stroke onset.
(2) EIM Protocol- besides standard medical care, patients in EIM started the ≥3 h/d out-of-bed mobilization within 24–48 h after stroke onset.
(3) VEIM Protocol- besides standard medical care, patients in VEIM started the ≥3 h/d of out-of-bed mobilization within 24 h of stroke onset.

Out-of-bed mobilization included sitting, standing, and walking which were performed with or without assistance as described by the "A Very Early Rehabilitation Trial" (AVERT) Protocol (14). No special equipment was used, and mobilization included the use of standing bed and wheelchair, when necessary. All mobilization protocols were adjusted to the patients' tolerance, needs and abilities and were delivered by professional therapists or nurses. The frequency, dose, and content of mobilization varied according to physical ability and were recorded in detail by therapists or nurses. Dose monitoring was done by a specially assigned staff to ensure good compliance for this study. Physicians were asked to evaluate patients with deteriorating conditions during the exercise and to postpone mobilization when necessary. Mobilization continued for 10–14 days including the weekend.

Outcome Assessment

The primary outcome was measured with the modified Rankin Scale (mRS) and defined as favorable mRS of 0–2 (no or minimum disability) at 3 months after stroke, while a poor outcome was defined as scores of 3–6 (moderate or severe disability, or death). Assessments during hospitalization were performed in person, or via telephone by a trained assessor at the follow-up period.

Statistical Analysis

Sample size was estimated from our preliminary experimental results in which stroke patients were divided to two groups: very early mobilization group (within 24 h of stroke onset) and early mobilization group (24–48 h of stroke onset). Our preliminary experimental planning revealed a difference of 20% in the prevalence of patients showing a Rankin score [0–2] at 3 month after stroke onset: 35% in the very early mobilization group vs. 55% in the early mobilization group. Calculation was performed based on a type I error risk of 5% and a power of 80%, in a two-sided approach. A total of 94 patients per group was calculated as necessary to show a difference of 20% in the prevalence of patients showing a favorable outcome (Rankin score 0–2) at 3 month after stroke onset. Final planning saw the sample size adjusted to a total of 100 patients per group.

Data of all patients who completed the protocols and follow-up were analyzed and we used a Per-protocol (PP) analysis. Statistical analysis was performed using the Statistical Package for Social Science (SPSS), version 19.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered significant. Descriptive statistics were used to analyze all demographic and clinical characteristics. Continuous data was presented as mean (standard deviation) and categorical data was presented as a number and percentage. Continuous variables consistent with the normal distribution were compared by the independent samples *t*-test or analysis of variance (ANOVA), otherwise by rank sum test. Categorical variables were compared using chi-square testing.

RESULTS

From January 1, 2015 to December 31, 2017, 300 patients were assigned randomly (1:1:1) to three groups. 248 (82.7%) patients finished the training and follow-up assessment, 80 in ERM, 82 in VEIM and 86 in EIM groups, while 52 patients (20 in ERM, 18 in VEIM and 14 in EIM) dropped out for various reasons (**Figure 1**). Baseline characteristics including age, gender, risk factors and pre-morbid disability were similar among study groups (**Table 1**). The stroke severity at admission was evaluated with the NIHSS. There was no significant difference in the three groups (**Table 1**). Most of the patients had a first time ischemic stroke (85.0% in ERM, 79.3% in VEIM, 82.6% in EIM) and all the enrolled patients had mild or moderate strokes with NIHSS scores <8, or between 8 and 16. Patients with NIHSS scores more than 16 were either unconscious or unable to tolerate the rehabilitation procedures. The median daily training time of patients in VEIM (184.6 min) and EIM (184.1 min) were significantly ($p < 0.001$) longer than that of patients in ERM (53.4 min), while time to first mobilization after the symptom onset was significantly ($p < 0.001$) shorter in VEIM (16.8 h) than in ERM (41.0 h) and EIM (38.0 h) (**Table 2**).

We used mRS 0–2 (minimum or no disability) for the primary favorable outcome. Although we did not see significant differences among the three groups in 3-month follow-up, the percentage of primary favorable outcomes was highest in EIM and lowest in VEIM (**Figure 2** and **Table 3**). Furthermore, 53.5% of patients in EIM group had favorable outcomes (mRS 0–2) at 3 months, in contrast to 37.8% of the patients in VEIM, this difference was statistically significant (**Table 3**). In addition, more patients in EIM (53.5%) showed a favorable outcome as compared to ERM (45%), even though the difference did not reach a significant level. Taken together, EIM appeared to be the most beneficial rehabilitation program with statistically better results at 3 months, followed by ERM, while the VEIM group had the lowest positive outcomes at 3 months. mRS shift data again revealed positive functional shifts in mRS for the EIM group (**Figure 2**).

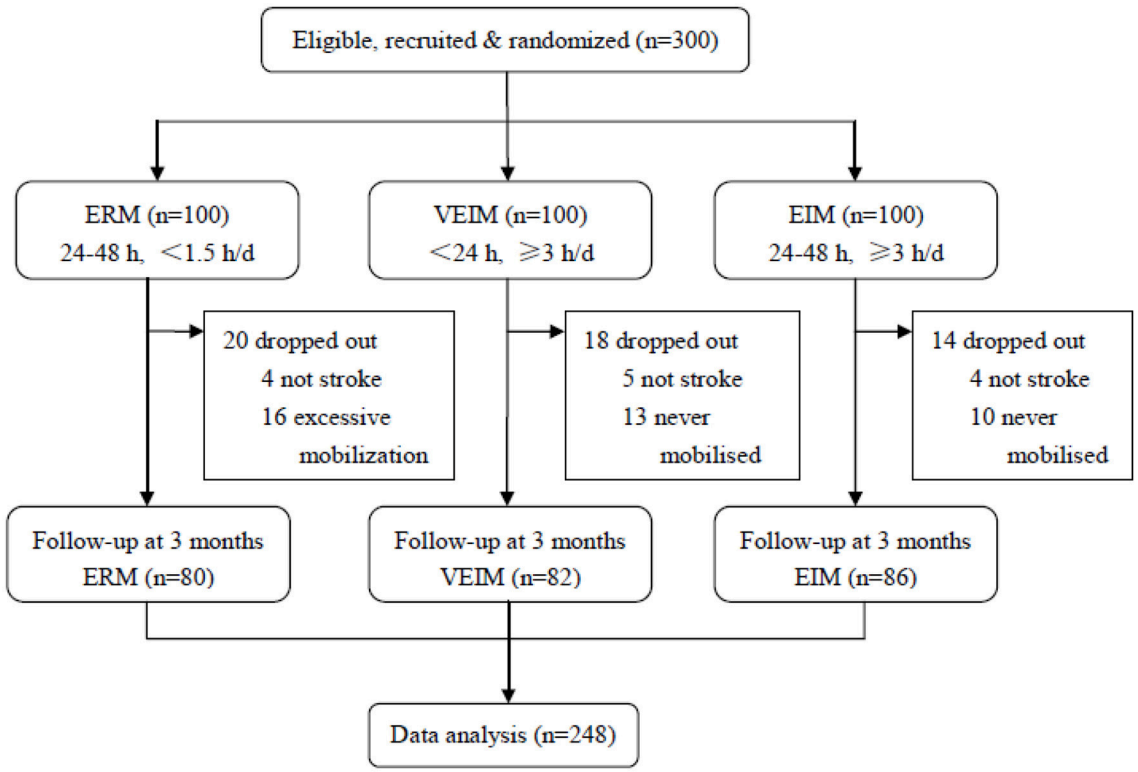


FIGURE 1 | Trial profile. ERM, Early Routine Mobilization; VEIM, Very Early Intensive Mobilization; EIM, Early Intensive Mobilization. Three hundred patients were assigned randomly (1:1:1) to three groups. Two hundred and forty-eight (82.7%) patients finished the training and follow-up assessment, 80 in ERM, 82 in VEIM and 86 in EIM groups, while 52 patients (20 in ERM, 18 in VEIM, and 14 in EIM) dropped out for various reasons. In total, 80 in ERM, 86 patients in EIM and 82 patients in VEIM finished the training and the follow-up, and were thus analyzed.

DISCUSSION

In the present study, we identified that more patients with utilization of the early (24–48 h) intensive mobilization (EIM) program received a favorable functional outcome, as compared to early (24–48 h) but not intensive (routine) mobilization (ERM), although the difference was not statistically significant. We then confirmed that EIM was better able to improve functional outcomes than VEIM at 3 months. In contrast to EIM, VEIM showed a poorer outcome overall at 3 months. A higher intensity but not too early mobilization appeared most beneficial in our study for rehabilitation after acute stroke.

As compared to AVERT (12–15), the pioneering studies in the realm of very early mobilization, the present study shared several similarities, although our study was a single center study and had a relatively small sample size. Our study was randomized and controlled, and the study duration was up to 14 days. We used same definition of "very early mobilization" for out-of-bed interventions commenced within 24 h after stroke, the same interventions for out-of-bed mobilization, and the same outcome measure (mRS scores). Very comparable results were observed in the higher dose (≥3 h/d out-of-bed mobilization), very early mobilization protocol (initiating within 24 h post stroke) in both studies. This mobilization protocol was associated with a reduction in the odds of a favorable outcome at 3-months follow-up, despite the 2011 AVERT follow-up suggesting VEIM may fast track ambulation recovery (21). It was not until the final 2015 AVERT results published in Lancet did the VEIM group results change suggesting worse outcomes at 3 months for this group (15). Thus, the question of the therapeutic efficacy of VEIM was left unsettled. Our results seem to confirm this therapy is not useful.

Importantly, as compared to AVERT, the present study was unique as follows: (1) we directly compared very early (within 24 h) and early (24–48 h) mobilization with the same intensive mobilization (≥3 h/d); (2) we directly compared routine (<1.5 h/d) and intensive (≥3 h/d) mobilization with same early initiation (24–48 h). In addition, the protocol of intensity in our trial was described in more details. In AVERT, the concept of intensity mobilization in intervention group (VEM) was blurred as it was just double the control group dose, without a specific amount of daily training time duration. A retrospective cohort study (22) consisting of 360 patients demonstrated that subjects who received >3.0 h of therapy daily made significantly more functional gains than those receiving <3.0 h daily. Therefore, we used this duration for intensive mobilization and 1.5 h per day for routine mobilization.

TABLE 1 | Baseline characteristics of the patients.

	VEIM ($n = 82$)	EIM ($n = 86$)	ERM ($n = 80$)	*P*
Age (years)	60.2 ± 10.5 (32–80)	60.9 ± 10.7 (30–80)	62.1 ± 10.3 (39–80)	0.491
<65	52 (63.4%)	54 (62.8%)	49 (61.3%)	0.958
65–80	30 (36.6%)	32 (37.2%)	31 (38.7%)	–
Sex (male)	67 (81.7%)	66 (76.7%)	57 (71.3%)	0.290
RISK FACTORS				
Hypertension	54 (65.8%)	68 (79.1%)	54 (67.5%)	0.120
Diabetes mellitus	22 (26.8%)	32 (37.2%)	32 (40.0%)	0.176
Ischemic heart disease	9 (11.0%)	13 (15.1%)	12 (15.0%)	0.679
Atrial fibrillation	5 (6.1%)	5 (5.8%)	10 (12.5%)	0.208
Hypercholesterolemia	62 (75.6%)	61 (71.9%)	49 (61.3%)	0.130
Smoking	34 (41.4%)	32 (37.2%)	27 (33.8%)	0.597
Previous stroke or TIA	17 (20.7%)	15 (17.4%)	12 (15.0%)	0.631
Pre-morbid disability				0.447
mRS 0	79 (96.3%)	82 (95.3%)	79 (98.8%)	
mRS 1	3 (3.7%)	4 (4.7%)	1 (1.2%)	
mRS 2	0	0	0	
ADMISSION RANKIN SCORE				
mRS 0	0	0	0	
mRS 1	12 (14.6%)	14 (16.3%)	16 (20.0%)	
mRS 2	17 (20.7%)	25 (29.1%)	16 (20.0%)	
mRS 3	21 (25.6%)	19 (22.1%)	20 (25.0%)	
mRS 4	28 (34.1%)	27 (31.4%)	26 (32.5%)	
mRS 5	4 (4.9%)	1 (1.2%)	2 (2.5%)	
mRS 6	0	0	0	
Rankin score [0–2]	29 (35.3%)	39 (45.4%)	32 (40.0%)	
STROKE SEVERITY				
NIHSS score	5.9 (1–16)	5.8 (1–16)	6.0 (1–16)	0.752
Mild(1–7)	58 (70.7%)	63 (73.2%)	50 (62.5%)	0.298
Moderate(8–16)	24 (29.3%)	23 (26.8%)	30 (37.5%)	
Severe(>16)	0	0		
rtPA treatment (yes)	21 (25.6%)	15 (17.4%)	20 (25%)	0.368

TABLE 2 | Initiating time and intensity of mobilization.

	VEIM ($n = 82$)	EIM ($n = 86$)	ERM ($n = 80$)
Daily training time per person (min)	184.6 (180–220)	184.1 (180–220)	53.4 (30–90)
Time to first mobilization (h)	16.8 ± 5.2 (5–23)	38.0 ± 6.4 (25–47)	41.0 ± 4.4 (29–48)

AVERT found the higher dose, very early mobilization protocol was associated with a reduction in the odds of a favorable outcome (modified Rankin Scale [mRS] 0–2) at 3 months (15). One notable limitation of this trial is that most patients (roughly 60%) in usual care group started out-of-bed therapy within 24 h of stroke onset, rather than more than 24 h as it was designed (15). As a result, the difference between the intervention and control groups regarding initiation time for mobilization, though statistically significant, was small—mean 18.5 vs. 22.4 h. However, the difference in intensity between the two groups was significant, with the intervention group spending

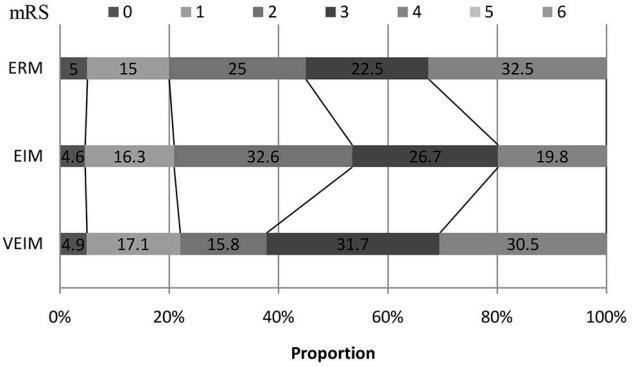


FIGURE 2 | mRS shift: the percentage of patients achieving each mRS score at 3 months. ERM, Early Routine Mobilization; VEIM, Very Early Intensive Mobilization; EIM, Early Intensive Mobilization; mRS, modified Rankin Scale.

TABLE 3 | Outcome at three months.

	VEIM ($n = 82$)	EIM ($n = 86$)	ERM ($n = 80$)	*p*
Favorable outcome (mRS 0–2)	31 (37.8%)	46 (53.5%)	36 (45%)	0.041 (VEIM vs. EIM) 0.353 (VEIM vs. ERM) 0.274 (EIM vs. ERM)
mRS Category 0	4 (4.9%)	4 (4.6%)	4 (5%)	
1	14 (17.1%)	14 (16.3%)	12 (15%)	
2	13 (15.8%)	28 (32.6%)	20 (25%)	
3	26 (31.7%)	23 (26.7%)	18 (22.5%)	
4	25 (30.5%)	17 (19.8%)	26 (32.5%)	
5	0	0	0	
6	0	0	0	

almost three times longer out of bed than controls (201.5 vs. 70 min). Given this, the difference in intensity probably played a greater role on outcomes than the difference in initiation time in AVERT. Our study sought to rectify this conundrum and determined the factor of initiation time with the same intensity and the factor of intensity with the same initiation time on outcome at 3 months after stroke. With significantly different initiation times between the two groups (EIM 38.0 h vs. VEIM 16.8 h) and almost the same intensity (EIM 184.1 min vs. VEIM 184.6 min), we found patients in EIM had significantly greater odds of favorable outcomes than patients in VEIM. Obviously, the difference in initiation time played a unique role in the outcomes of our study.

In order to better understand whether very early rehabilitation is beneficial or harmful, it is important to assess physiologic and animal studies. Given the labile blood pressure in the peri stroke period (23), very early mobilization could reduce cerebral blood flow and harm the ischemic penumbra (24). This maybe related to head position and redistribution of blood to other organs, especially standing musculature. Furthermore, the poor outcome caused by very early and intensive mobilization may be related to a disturbed auto regulatory regional cerebral

blood flow (rCBF). Under physiologic conditions, the cerebral auto-regulation mechanisms keep the cerebral blood flow (CBF) relatively stable. During acute stroke, the cerebral auto-regulation mechanisms are impaired and any fluctuation in blood pressure can affect the CBF directly (25). Moreover, recent research indicates that moderate exercise is associated with an increase in cerebral blood flow (CBF). Increases in exercise intensity up to 60% of maximal oxygen uptake elevated CBF (26–28). If more than that level, CBF was decreased despite the increased cerebral metabolic demand during early and intensive exercise in VEIM, possibly acting as an independent harmful influence on cerebral function (27, 28). Krakauer and colleagues (29) considered that too early mobilization of the affected limbs after brain injury may hamper brain plasticity as it may weaken GABA-mediated tonic inhibition. Reducing GABA-mediated inhibition in the first few days after stroke onset may enlarge the infarct size (29).

Several animal experiments support the notion that very early rehabilitation is not beneficial (30–32). Exercise training in rats beginning at 24 h post-stroke was associated with enlargement of ischemic lesions compared with animals who began training at 7 days (30). Shen et al. (31) found that hyperglycolysis and activation of nicotinamide adenine dinucleotide phosphate oxidase (NOX) was associated with an elevation in apoptotic cell death. This was increased in rats after very early exercise (6 h-24 h), but not after late exercise (3 days). Li et al. (32) found that inflammatory cytokines were increased at 6 h but not at 24 h or 3 days with exercise in rats, and apoptotic cell death was enhanced by very early exercise in association with increased expression of pro-apoptotic proteins. Although correlative age data between rats and humans may be imperfect, a study has suggested that 24 h for an adult rat corresponds to 30 days for an adult human (33). It raises possibility that a 24 h exercise implementation in rats would simulate human conditions at a latter time point in rehabilitation. Furthermore not all rat studies have shown exercise therapy at 24 h to be harmful, Zhang et al. (34) reported smaller tissue infarct sizes and improved outcomes.

In the present study, the patients recruited were not representative of the whole stroke population since patients with severe aphasia, disturbance of consciousness or thrombectomy were excluded.. As our study was conducted at one center, we did not recruit enough patients (100 in the 3 groups) to fulfill our initial Power Assessment. However, the relatively small sample size and single-center nature of the study have nevertheless suggested a meaningful conclusion that high intensity physical rehabilitation later than 24 h post stroke is beneficial in patients. The beneficial effects of early but not too early with intensive mobilization protocol warrant a future randomized and controlled multicenter trial study with a larger sample size. We also confirmed the previous findings of the AVERT study that VEIM therapy should not be used outside of a randomized trial.

AUTHOR CONTRIBUTIONS

YT, GR, LC, and NZ performed the study, analyzed data, and prepared the manuscript. YD, HoD, XG, and GR designed the study and revised the manuscript. YT, ZC, and HuD evaluated the subjects.

ACKNOWLEDGMENTS

The work was supported in part by Beijing Municipal Science Technology Commission (Z151100003915134), the National Natural Science Foundation of China (81501141), Science and Technology Project of Beijing Municipal Education Commission (KM201610025028), the Beijing NOVA program (xx2016061), and Science and Technology Plan of Beijing Tongzhou District (KJ2017CX043).

REFERENCES

1. Li M, Xu G, Xie J, Chen C. A review: motor rehabilitation after stroke with control based on human intent. *Proc Inst Mech Eng H* (2018) 232:344–60. doi: 10.1177/0954411918755828
2. Ivey FM, Hafer-Macko CE, Macko RF. Exercise rehabilitation after stroke. *NeuroRx* (2006) 3:439. doi: 10.1016/j.nurx.2006.07.011
3. Li WA, Geng X, Ding Y. Stroke is a global epidemic: new developments in clinical and translational cerebrovascular diseases research. *Neurol Res.* (2017) 39:475. doi: 10.1080/01616412.2017.1330307
4. Hafeez A, Liu L, Ding Y. Ongoing progress and new developments in the clinical approach to stroke and cerebrovascular disease: new paradigms: a novel outlook into stroke. *Neurol Res.* (2016) 38:477. doi: 10.1080/01616412.2016.1192264
5. Forrester LW, Wheaton LA, Luft AR. Exercise-mediated locomotor recovery and lower-limb neuroplasticity after stroke. *J Rehabil Res Dev*. (2008) 45:205. doi: 10.1682/JRRD.2007.02.0034
6. Nie J, Yang X. Modulation of synaptic plasticity by exercise training as a basis for ischemic stroke rehabilitation. *Cell Mol Neurobiol.* (2017) 37:5. doi: 10.1007/s10571-016-0348-1
7. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, et al. Correction to: guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* (2017) 48:e369. doi: 10.1161/STR.0000000000000098
8. Bernhardt J, Godecke E, Johnson L, Langhorne P. Early rehabilitation after stroke. *Curr Opin Neurol.* (2017) 30:48. doi: 10.1097/WCO.0000000000000404
9. Reuter B, Gumbinger C, Sauer T, Wietholter H, Bruder I, Diehm C, et al. Access, timing and frequency of very early stroke rehabilitation - insights from the Baden-Wuerttemberg stroke registry. *BMC Neurol.* (2016) 16:222. doi: 10.1186/s12883-016-0744-7
10. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* (2018) 49:e46–110. doi: 10.1161/STR.0000000000000158
11. Gittler M, Davis AM. Guidelines for adult stroke rehabilitation and recovery. *JAMA* (2018) 319:820. doi: 10.1001/jama.2017.22036
12. Langhorne P, Wu O, Rodgers H, Ashburn A, Bernhardt J. A very early rehabilitation trial after stroke (AVERT): a phase III, multicentre, randomised controlled trial. *Health Technol Assess.* (2017) 21:1–120. doi: 10.3310/hta21540
13. Bernhardt J, Dewey H, Thrift A, Collier J, Donnan G. A very early rehabilitation trial for stroke (AVERT): phase II safety and feasibility. *Stroke* (2008) 39:390–6. doi: 10.1161/STROKEAHA.107.492363

14. Bernhardt J, Dewey H, Collier J, Thrift A, Lindley R, Moodie M, et al. A Very Early Rehabilitation Trial (AVERT). *Int J Stroke* (2006) 1:169. doi: 10.1111/j.1747-4949.2006.00044.x
15. AVERT Trial Collaboration group. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet* (2015) 386:46–55. doi: 10.1016/S0140-6736(15)60690-0
16. Chippala P, Sharma R. Effect of very early mobilisation on functional status in patients with acute stroke: a single-blind, randomized controlled trail. *Clin Rehabil*. (2016) 30:669–75. doi: 10.1177/0269215515596054
17. Matsui H, Hashimoto H, Horiguchi H, Yasunaga H, Matsuda S. An exploration of the association between very early rehabilitation and outcome for the patients with acute ischaemic stroke in Japan: a nationwide retrospective cohort survey. *BMC Health Serv Res*. (2010) 10:213. doi: 10.1186/1472-6963-10-213
18. Bernhardt J, Thuy MN, Collier JM, Legg LA. Very early versus delayed mobilisation after stroke. *Cochrane Database Syst Rev*. (2009) 21:CD006187. doi: 10.1002/14651858.CD006187.pub2
19. Kasner SE. Clinical interpretation and use of stroke scales. *Lancet Neurol*. (2006) 5:603–12. doi: 10.1016/S1474-4422(06)70495-1
20. Briggs DE, Felberg RA, Malkoff MD, Bratina P, Grotta JC. Should mild or moderate stroke patients be admitted to an intensive care unit? *Stroke* (2001) 32:871–6. doi: 10.1161/01.STR.32.4.871
21. Cumming TB, Thrift AG, Collier JM, Churilov L, Dewey HM, Donnan GA, et al. Very early mobilization after stroke fast-tracks return to walking: further results from the phase II AVERT randomized controlled trial. *Stroke* (2011) 42:153–8. doi: 10.1161/STROKEAHA.110.594598
22. Wang H, Camicia M, Terdiman J, Mannava MK, Sidney S, Sandel ME. Daily treatment time and functional gains of stroke patients during inpatient rehabilitation. *PM R*. (2013) 5:122–8. doi: 10.1016/j.pmrj.2012.08.013
23. Saver JL. Blood pressure management in early ischemic stroke. *JAMA* (2014) 311:469–70. doi: 10.1001/jama.2013.282544
24. Olavarria VV, Arima H, Anderson CS, Brunser AM, Munoz-Venturelli P, Heritier S, et al. Head position and cerebral blood flow velocity in acute ischemic stroke: a systematic review and meta-analysis. *Cerebrovasc Dis*. (2014) 37:401–8. doi: 10.1159/000362533
25. Dawson SL, Panerai RB, Potter JF. Serial changes in static and dynamic cerebral autoregulation after acute ischaemic stroke. *Cerebrovasc Dis*. (2003) 16:69–75. doi: 10.1159/000070118
26. Kinni H, Guo M, Ding JY, Konakondla S, Dornbos D III, Tran R, et al. Cerebral metabolism after forced or voluntary physical exercise. *Brain Res*. (2011) 1388:48–55. doi: 10.1016/j.brainres.2011.02.076
27. Secher NH, Seifert T, Van Lieshout JJ. Cerebral blood flow and metabolism during exercise: implications for fatigue. *J Appl Physiol.* (1985) 104:306–14. doi: 10.1152/japplphysiol.00853.2007
28. Ogoh S, Ainslie PN. Cerebral blood flow during exercise: mechanisms of regulation. *J Appl Physiol.* (1985) 107:1370–80. doi: 10.1152/japplphysiol.00573.2009
29. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: what can be learned from animal models? *Neurorehabil Neural Repair*. (2012) 26:923–31. doi: 10.1177/1545968312440745
30. Risedal A, Zeng J, Johansson BB. Early training may exacerbate brain damage after focal brain ischemia in the rat. *J Cereb Blood Flow Metab.* (1999) 19:997–1003. doi: 10.1097/00004647-199909000-00007
31. Shen J, Huber M, Zhao EY, Peng C, Li F, Li X, et al. Early rehabilitation aggravates brain damage after stroke via enhanced activation of nicotinamide adenine dinucleotide phosphate oxidase (NOX). *Brain Res*. (2016) 1648 (Pt. A):266–76. doi: 10.1016/j.brainres.2016.08.001
32. Li F, Shi W, Zhao EY, Geng X, Li X, Peng C, et al. Enhanced apoptosis from early physical exercise rehabilitation following ischemic stroke. *J Neurosci Res*. (2017) 95:1017–24. doi: 10.1002/jnr.23890
33. Andreollo NA, Santos EF, Araujo MR, Lopes LR. Rat's age versus human's age: what is the relationship? *Arq Bras Cir Dig.* (2012) 25:49–51. doi: 10.1590/S0102-67202012000100011
34. Zhang P, Yu H, Zhou N, Zhang J, Wu Y, Zhang Y, et al. Early exercise improves cerebral blood flow through increased angiogenesis in experimental stroke rat model. *J Neuroeng Rehabil.* (2013) 10:43. doi: 10.1186/1743-0003-10-43

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 07 May 2019
doi: 10.3389/fneur.2019.00465

Spasticity Assessment Based on the Maximum Isometrics Voluntary Contraction of Upper Limb Muscles in Post-stroke Hemiplegia

Hui Wang[1,2†], *Pingao Huang*[1,2†], *Xiangxin Li*[1], *Oluwarotimi Williams Samuel*[1], *Yun Xiang*[1,3] *and Guanglin Li*[1*]

[1] CAS Key Laboratory of Human-Machine Intelligence-Synergy Systems, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China, [2] Shenzhen College of Advanced Technology, University of Chinese Academy of Sciences, Shenzhen, China, [3] The Rehabilitation Department, Shenzhen Sixth People's Hospital (Nanshan hospital), Shenzhen, China

OPEN ACCESS

Edited by:
Sheng Li,
University of Texas Health Science Center at Houston, United States

Reviewed by:
Zafer Keser,
University of Texas Health Science Center at Houston, United States
Manuel F. Mas,
University of Puerto Rico, Puerto Rico

***Correspondence:**
Guanglin Li
gl.li@siat.ac.cn

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 06 March 2019
Accepted: 17 April 2019
Published: 07 May 2019

Citation:
Wang H, Huang P, Li X, Samuel OW, Xiang Y and Li G (2019) Spasticity Assessment Based on the Maximum Isometrics Voluntary Contraction of Upper Limb Muscles in Post-stroke Hemiplegia. Front. Neurol. 10:465. doi: 10.3389/fneur.2019.00465

Background: The assessment of muscle properties is an essential prerequisite in the treatment of post-stroke patients with limb spasticity. Most existing spasticity assessment approaches do not consider the muscle activation with voluntary contraction. Including voluntary movements of spastic muscles may provide a new way for the reliable assessment of muscle spasticity.

Objective: In this study, we investigated the effectiveness and reliability of maximum isometrics voluntary contraction (MIVC) based method for spasticity assessment in post-stroke hemiplegia.

Methods: Fourteen post-stroke hemiplegic patients with arm spasticity were asked to perform two tasks: MIVC and passive isokinetic movements. Three biomechanical signals, torque, position, and time, were recorded from the impaired and non-impaired arms of the patients. Three features, peak torque, keep time of the peak torque, and rise time, were computed from the recorded MIVC signals and used to evaluate the muscle voluntary activation characteristics, respectively. For passive movements, two features, the maximum resistance torque and muscle stiffness, were also obtained to characterize the properties of spastic stretch reflexes. Subsequently, the effectiveness and reliability of the MIVC-based spasticity assessment method were evaluated with spearman correlation analysis and intra class correlation coefficients (ICCs) metrics.

Results: The results indicated that the keep time of peak torque and rise time in the impaired arm were higher in comparison to those in the contralateral arm, whereas the peak torque in the impaired side was significantly lower than their contralateral arm. Our results also showed a significant positive correlation ($r = 0.503$, $p = 0.047$) between the keep time (t_k) and the passive resistant torque. Furthermore, a significantly positive correlation was observed between the keep time (tk) and the muscle stiffness ($r = 0.653$, $p = 0.011$). Meanwhile, the ICCs for intra-time measurements of MIVC ranged between 0.815 and 0.988 with one outlier.

Conclusion: The findings from this study suggested that the proposed MIVC-based approach would be promising for the reliable and accurate assessment of spasticity in post-stroke patients.

Keywords: spasticity assessment, post-stroke, maximum isometrics voluntary, voluntary activation, reliability

INTRODUCTION

Spasticity, commonly defined as motor disorder, can be characterized by velocity-dependent increase in muscle tone with exaggerated tendon jerks that will affect the muscle voluntary activation (1). It has been reported in previous studies that about 40% of post-stroke survivors suffer from spasticity (2, 3), leading to a huge burden on a large number of patients and challenges to the care givers (4, 5). To treat patients with spasticity, a number of different approaches such as local botulinum toxin injection, physical and occupational therapies, electrical neuro stimulation, and surgical interventions, have been commonly used in clinic (2, 6, 7). While the clinical practices have showed that these approaches are effective for spasticity treatments, their clinical efficacy would be further improved if the spasticity assessments are more reliable and accurate. Currently, the commonly used spasticity treatments are the clinical scale methods such as Ashworth Scale and Modified Ashworth Scale (MAS) which could provide some useful information on whether spasticity exists or not and what the severity of spasticity are with several levels (such as 0–4) (8, 9). The most widely applied MAS method is relatively easy to implement, but its assessment outcomes could be only used for passive movements' assessment (10, 11) and greatly depend on the physicians' experience (12, 13). With these issues, the MAS method has been questioned by several researchers over time (13, 14) These discrete level assessment methods could roughly group spasticity, however, they could not provide sufficiently reliable or accurate information for assessing spasticity that would be necessary for guiding spasticity treatments (15, 16).

With the limitations of the clinical scale methods, some methods based on the analysis of features associated with neurophysiologic/biomechanical measurements have been proposed in previous studies for accurately evaluating the spasticity in patients (17–22). It should be noted that most of the previous neurophysiologic/biomechanical spasticity assessment methods will be greatly affected by individual differences among patients and partial side effect (23, 24). In order to overcome these limitations, a number of quantitative methods have been developed for spasticity assessment in patients (25). For examples, the H-reflex, H/M ratios, and dynamic electromyogram (EMG) response to mechanical stimuli based approaches, have been proposed and investigated for spasticity assessment in patients (17, 26). Although these neurophysiological based methods appear to be promising, they are still limited by several factors including inadequate electrode placement, electrode-skin resistance, and physiological status of the muscles amongst others (23). In addition, these neurophysiology-based methods usually lack a direct correlation between the neurophysiological assessment outcome and the clinical scale outcome, which makes the clinicians be difficult to assess the spasticity status of patients (27). Further, biomechanical methods driven by the initiation of different kinds of muscular movements including isokinetic, isometric, isotonic have equally been used for assessment of muscle characteristics especially via rehabilitation training (28). And the maximum isometrics voluntary contraction (MIVC) used in assessing the characteristics of voluntary muscle activation is considered as a useful approach for quantifying the neuromuscular properties of the spastic muscles (29). Although isokinetic test method is considered as a standard approach for assessing the stretch reflex with respect to spasticity only in the context of passive movement, it cannot discriminate between neural component and muscle component (21). Additionally, it is unknown whether the MIVC method could offer a useful measure for assessing the neuromuscular properties of spastic muscles.

Currently, the peak resistive torque and stiffness that are calculated with isokinetic dynamometry are considered as the "gold standard" for the evaluation of spasticity (16) and even the most existing spasticity assessment approaches are based on the evaluation of the neurophysiologic/biomechanical response to stretch reflexes (30). However, the muscle activation characteristics with voluntary contraction are completely neglected in these methods (31). It is unknown whether the voluntary movements of spastic muscles are useful in the reliable assessment of muscle spasticity. After all, the evaluation of the muscles response to voluntary movements (voluntary muscle activation) have rarely been considered to date, and the relationship between the spastic muscle tone and muscle voluntary activation remains unclear (31, 32). In addition, it is also unclear what the relationship between the spastic muscle tone and muscle voluntary activation are.

In this study, a new spasticity assessment method based on MIVC was proposed and its performance in evaluating the spasticity status in post-stroke hemiplegia with an upper limb spasticity was investigated. Current method was compared with the conventional passive stretch method as well as the MAS method. In addition, three biomechanical features (peak reflex torque, keep time of the peak torque, and rise time of the peak torque) derived from MIVC were proposed to quantitatively assess upper limb spasticity. Additionally, further investigations were conducted to evaluate the changes in the voluntary muscle activation properties between the impaired and non-impaired arms, using correlation between the features from current method and conventional passive stretch reflex approach in chronic stroke survivors with spasticity. Criterion validity was examined as convergent construct validity (using the Spearman's correlation coefficient) and concurrent validity (using analysis

TABLE 1 | Summarized demographic information of all the subjects according to MAS ($N = 14$)*.

MAS scores	No. subjects	Impaired side	Age(years)
1	5	4R/1L	49.6 ± 9.7
1+	5	2R/2L	45.3 ± 3.1
2	4	3R/2L	45.5 ± 4.9

*Age was shown in Mean ± SD, and the MAS as range, impaired side (Right or Left) and gender (Male or Female) as distribution.

of variance) (11). The reliability of the MIVC measurements was further evaluated using repeated measurements intra class correlation coefficients (ICCs).

MATERIALS AND METHODS

Participant Information

In this study, we enrolled a total of 14 chronic post-stroke hemiplegia (11 males and 3 females) with different degrees of elbow flexor spasticity (MAS = 1, 1+, 2), age of 47.36 ± 6.54 years, and an average post-stroke time of 6.18 ± 2.47 months. All the participants were observed to be in their post stroke recovery stages (Time since stroke is more than 1 month), and their summarized demographic information was listed in **Table 1**. The inclusion criteria for subjects were (1) hemiplegia secondary to a single ischemic or hemorrhage stroke; (2) at least 1 months post-stroke; (3) elbow flexor spasticity of the impaired side <3 (rated by MAS); (4) being able to understand and follow instructions related to the experiment; and (5) being able to give written informed consent. The exclusion criteria were (1) a history of multiple strokes or bilateral involvement; (2) presence of muscle contraction that would limit full elbow range of movement on the impaired side; (3) existence of function failure in important organs such as heart, lung, liver, and kidney. The experiment was approved by the human research ethics committee of the Shenzhen Nanshan hospital and all the subjects gave written informed consent prior to their participation in the study. In addition, all the experiments were performed in accordance with the relevant guidelines and regulations.

Experiment Procedure

A commercial motor function rehabilitation system HUMAC NORM (Computer Sports Medicine Inc. CSMI, USA) was used to record biomechanical signals (speed, torque, and position) in the study. The body weight and other necessary features of each subject were also regularly recorded before the experiments. During an experiment, each subject lay comfortably on an examination bed, and the MIVC signals associated with the impaired and non-impaired arms were recorded by HUMAC NORM device, as shown in **Figure 1**. Each subject was asked to hold the handle of HUMAC NORM device with a normal force and to perform the maximum isometric voluntary contraction at an elbow joint angle of about zero degree for three sessions. When one session was finished, their arms of a subject were relaxed for a rest at least 15 s before doing next session. In order to minimize the effect of muscle fatigue on the spasticity assessment, the MIVC signal recordings from the third MIVC trial was excluded. Subsequently, the range of the elbow joint angle was tested in a rest session after their arms have been passively stretched to avoid muscle fatigue. Then, they further performed three passive isokinetic contractions using their impaired limb with at least 20 s rest session in between. And three constant passive stretch speeds of elbow flexors, 60°/s, 40°/s, and 20°/s, were considered in the study. For each stretch speed, the participants repeated three trials of passive isokinetic contraction. The onset elbow angle was about zero degree and the end position was the approximate maximum elbow movement angle.

Neuromechanical Parameters (T_p, T_k, T_r)

The elbow torque acquired with the HUMAC NORM device from the MIVC task was filtered by a 3rd order Butterworth low pass filter with a cutoff frequency of 1 Hz. The peak torque (T_p) was defined as the maximum torque of an isometric maximum voluntary contraction of the elbow flexors. T_p represents the muscle strength of the participants and the keep time (T_k) was defined as the duration for which the muscle strength was maintained (above 80%*maximum torque), and T_k equally indicates the muscle endurance (25). The rise time (T_r) is defined as 0.1* maximum torque to 0.8* maximum torque for a given trial, where $T_r$indicate muscle power (**Figure 2**). The peak torque was normalized by individual body weight to reduce the subject individual differences among patients (26).

The muscle stiffness characteristic was determined by fitting a slope to the stress–stretch data by means of linear regression between the points of 0.25*maximum stress and 0.75*maximum stress for a given trial (**Figure 3**).This portion of the typically sigmoidal response was well-described by the linear regression, as verified in the results section (27).

Statistics

The signal processing task was performed with MATLAB R2015b (Math Works) programming tool and all statistical analyses were carried out with SPSS (version 17.0) software. Meanwhile, the paired sample T-test was applied to examine if there was a significant difference between impaired side and non-impaired side. Criterion validity was investigated as convergent construct validity (using Spearman's correlation Coefficient) and concurrent validity (using analysis of variance and Tukey's *post-hoc* test). Correlations between the proposed features of MIVC (T_p, T_k, T_r), MAS and biomechanical measures (peak reflex torque and reflex stiffness) were analyzed using Spearman's coefficient. Statistical significance level was set at $p\text{-}value < 0.05$ and false discovery rate (FDR) analyses were provided with FDR correction (p-value was convert to q-value, and $q = p^*n/rank$, in the equation n denotes the comparison time and rank denotes the order of p-value from small to big). The reliability of MIVC measurements was evaluated using repeated measurements ICCs with 95% confidence intervals (CIs). The ICC was calculated using a two-way mixed-effect model with an agreement coefficient. ICC values would vary from 0 to 1.

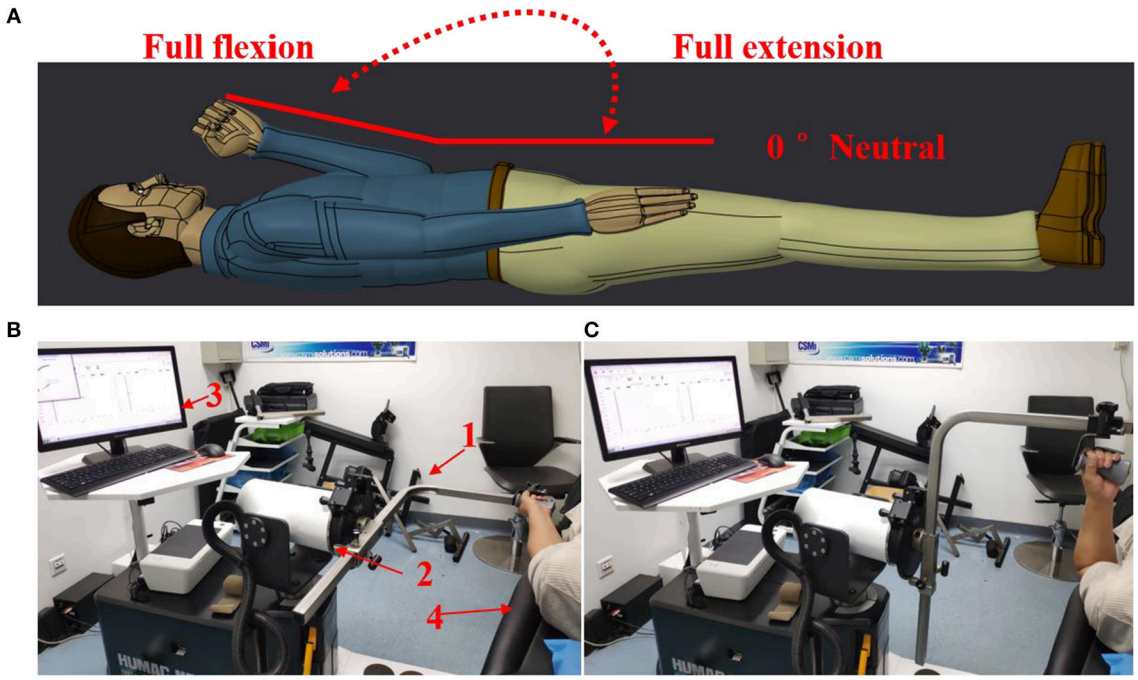


FIGURE 1 | Experimental setting. **(A)** The definition for the range of movement with elbow joint. **(B)** Maximum isometric voluntary contraction at an elbow joint angle of about zero degree Test for both arms and HUMAC NORM device introduction, 1: elbow/shoulder handle, 2: dynamometer, 3: computer display and control platform, 4: examination bed; **(C)** Elbow passive isokinetic contractions test for impaired limb.

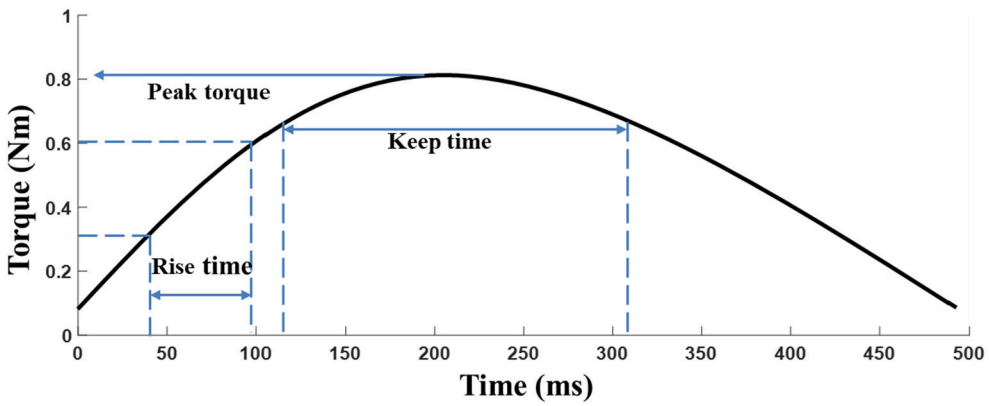


FIGURE 2 | Description of the neuromechanical parameters for the MIVC.

RESULTS

For each subject, the properties of maximum isometric voluntary contraction from the impaired and non-impaired sides were analyzed, and the MIVC Features (T_p, T_k, T_r) were compared between the impaired and non-impaired sides. Then the effect of the velocity on the passive stretch associated with the respective muscles was investigated. Further, the relationship that exists between the proposed features of MIVC, MAS, and biomechanical measures was examined using correlation and linear regression analysis techniques. Finally, the reliability of the MIVC measurements was assessed with ICCs and Bland-Altman plot.

The Properties of MIVC on the Impaired and Non-impaired Sides

As shown in **Figure 4**, the MIVC features (peak torque, keep time, rise time) were significantly different between the impaired and non-impaired arms for each subject. Generally speaking, for all the subjects, the mean of the peak torque T_p on their impaired side was less than that on their non-impaired side. For 11 of 14

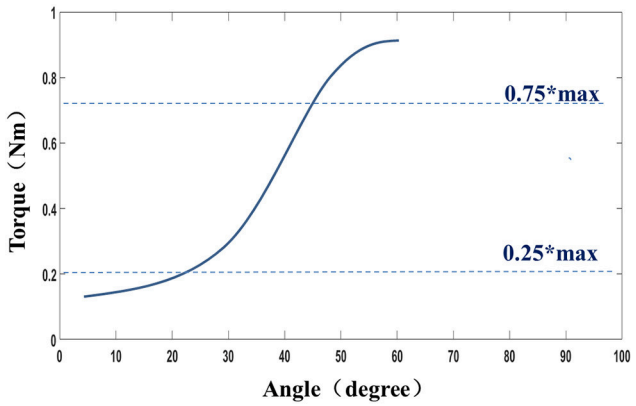


FIGURE 3 | Definition of the stiffness.

subjects, the keep time of peak torque T_k on their impaired side was lower in comparison to that on their non-impaired side. And for 12 of 14 subjects, compared to their non-impaired side, the rise times of peak torque T_r were greater on their impaired side.

Our statistical analysis results show that the difference between the impaired and non-impaired side (**Table 2**) with respect to the three MIVC features was significant. During the maximum isometric voluntary contraction, the mean of the peak torque T_p on the impaired side (0.147 ± 0.086 Nm) was less than that on the non-impaired side (0.465 ± 0.202 Nm) ($p < 0.001$, $q < 0.001$). Meanwhile, the mean of the keep time of peak torque T_k was lower on the impaired side (0.147 ± 0.086 s) than on the non-impaired side (0.465 ± 0.202 s) ($p = 0.037$, $q = 0.037$). Furthermore, the mean of the rise time of peak torque T_r was greater on the impaired side (0.147 ± 0.086 s) than on the non-impaired side (0.465 ± 0.202 s) ($p = 0.029$, $q = 0.044$). The p-values were converted to q value with FDR correction, and the significant test results remained the same.

Analysis Based on Velocity-Dependent Responses of Passive Stretch

In general, there was no obvious change in velocity-dependent mechanical response of passive stretch with peak torque. In fact, the results obtained from a repeated one-way ANOVA analysis did not reflect a meaningful effect of stretch velocity for peak torque response [$F_{3,4} = 0.89$, $p = 0.42$] (**Figure 5A**). It was observed that the response at higher velocities showed greater individual variation as indicated by the SEM bars. The slight differences in passive resistive torque between the three stretch velocities indicated that the stretch reflex of the muscle may be induced by the all the three stretch velocities. And the elbow angular velocity threshold for inducing stretch reflex response was lower than 20°/s. Additionally, it can be observed from **Figure 5A** that the velocity-dependent mechanical response in passive stretch increases correspondingly with the stiffness. And the outcome of one-way repeated ANOVA indicated that there was a significant effect in stretch velocity for stiffness response. **Figure 5B** shows the direct relationship between the stiffness in elbow flexors and the velocity. Similarly, there was a significant effect of stretch velocity [$F_{3,4} = 14.7$, $p < 0.001$]. The response at higher velocities represented greater individual variation as shown by the SEM bars.

Correlation Between MIVC-Features and Biomechanical Assessments

The correlation coefficients between the MIVC-features and stretch measurements were computed and presented in **Table 3**. It can be seen from **Table 3** that there was a strong positive relationship between the peak resistant torque from the passive stretch test at 60°/s and the T_k from the MIVC ($r = 0.503$, $p = 0.047$). In addition, a strong positive relationship between the muscle stiffness from the passive stretch velocity at 60°/s and the T_k from the MIVC ($r = 0.653$, $p = 0.011$) was also obtained as shown in **Figure 6**. No other association between the MIVC features and passive stretch measurements was observed. It should be noted that no significant correlation between MIVC indexes and the MAS was observed while only the correlation between the T_p and the MAS was approximate significant ($r = -0.503$, $p = 0.061$). Further, evaluation of the associations between the MAS scores and the passive stretch measurements did not confirm any correlations results obtained via Spearman coefficients (P).

Reliability of MIVC Measurements With Intra Class Correlation Coefficient

Generally, our experimental results showed that the reliability of the MIVC measures was very fine. The ICC results were presented in **Table 4**. It can be seen from **Table 4** that the ICC values ranged between 0.653 and 0.990, and the Peak torque of the MIVC showed the best reliability with a coefficient of 0.99 (excellent reliability) for the non-impaired limb, and 0.96 for the impaired limb. The keep time of the MIVC also showed great reliability characteristics with a coefficient of 0.82 for the impaired limb and 0.98 for the non-impaired limb. The rise time of the MIVC showed the worst reliability with a coefficient of 0.65 for the non-impaired arm.

We went further and visualized bias systematically using Bland-Altman graph. In this regard, the Bland-Altman plots indicated that there was no bias for the repeated two measurements (**Figure 7**). Meanwhile, the data points were distributed equally above and below the zero lines, which indicated no bias. For T_k, T_r from the impaired side, only one points was out of the boundary lines (−1.96*SD, 1.96*SD). For T_p, T_r from the non-impaired side, only one points was out of the boundary lines. These results suggested the reproducibility of the MIVC features.

DISCUSSION

Effective spasticity management usually results to restoration of biomechanics, improvement of motor control, strengthening of weak muscles, and improvement of muscle endurance. Recent evidences suggest that voluntary activation change of the spastic muscle may contribute more to disability than abnormal stretch reflex in post-stroke patient (33). However,

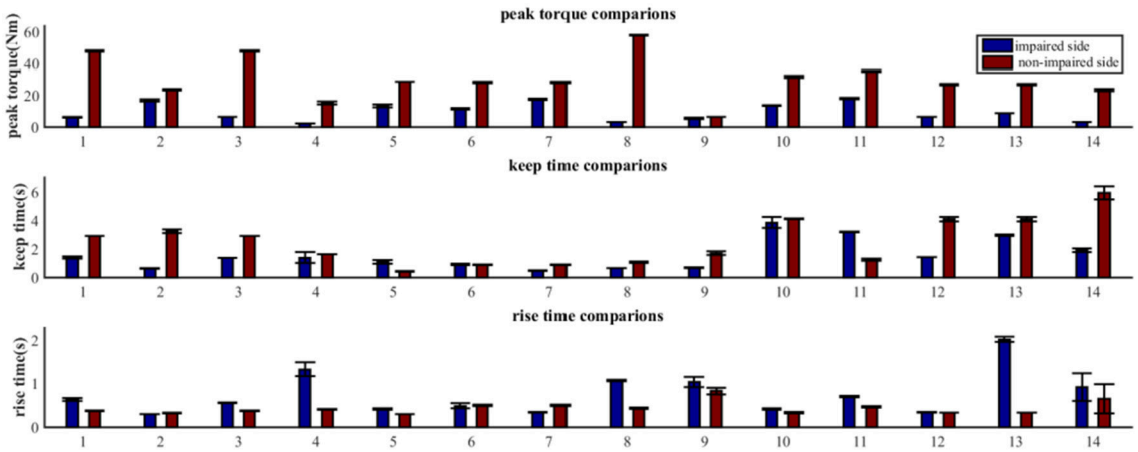


FIGURE 4 | Comparative analysis of MIVC features between the impaired and non-impaired arms across all the 14 recruited subjects (Mean ± SEM).

TABLE 2 | Comparison of MIVC features between impaired side and non-impaired side.

Features	Impaired side (Mean ± SEM)	Non-impaired (Mean ± SEM)	Impaired-Non-impaired (*P*-value)	FDR corrected (*q*-value)
T_p	9.614 ± 1.492	30.660 ± 3.566	<0.001	<0.001
T_k	1.586 ± 0.281	2.524 ± 0.438	0.037	0.037
T_r	0.757 ± 0.129	0.441 ± 0.039	0.029	0.044

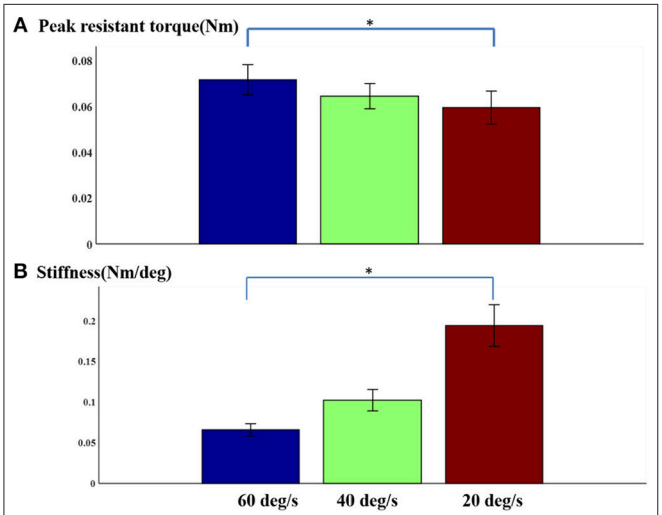


FIGURE 5 | (A) Normalized peak torque and **(B)** stiffness at three speeds Mean ± SEM, * represents statistical significance).

only a fraction of the existing related works have focused on muscle voluntary activation with maximum voluntary contraction, thus a study on the relationship between muscle tone and voluntary activation is desirable. To the best of our knowledge, this study might be the first study to systematically investigate and assess spasticity with MIVC features. Our experimental results indicated that the proposed MIVC features would correlate with muscle tone, which were important indicators for spasticity rehabilitation. And the MIVC features were reliable in terms of providing consistent test results. In addition, the relationship between the MIVC and passive stretch movement as well as the MIVC feature differences between the impaired and non-impaired arms were investigated in the study. We found that the biomechanical tests results provided experimental evidence that T_k could be effectively used to assess post-stroke spasticity.

Relationship Between Passive Stretch Mechanical Features and MAS

A relatively weak relationship was observed between the passive torque, muscle stiffness, and the MAS. This observation is in line with those reported in a number of previous studies (14, 34, 35), which indicates that the MAS based methods might be not a very suitable means for reliably assessing spasticity in patients. A velocity dependent increase in passive resistant torque was equally observed with a peak resistant torque that kept increasing especially at higher passive velocity. For instance, the peak resistant torque from high velocity of 40°/s and 60°/s were found to be larger than the peak resistant torque from low velocity of 20°/s and 40°/s, correspondingly. Interestingly, other previous investigators have reported a progressive increase in biceps brachii resistive torque at stretch velocities >40°/s in normal subjects and patients with spinal cord injury which corroborates the findings from the current study (34). It should be noted that the stretch reflex-mediated response and non-reflex response were not distinguished. Meanwhile, the muscle stiffness increased linearly in response to increasing passive velocity, whereas velocity dependent response was observed. The stiffness strongly correlates with passive resistant at the three levels of passive stretch velocity. These results were also consistent with those reported in some previous studies (36, 37).

TABLE 3 | Spearman correlation analysis among MIVC features, stretch reflex features, and MAS (Correlation coefficient and *P*-value).

Variables	MAS	tp_60	sti_60	tp_40	sti_40	tp_20	sti_20
T_p	−0.503 (0.067)	0.209 (0.474)	0.270 (0.350)	0.257 (0.375)	0.165 0.573)	0.257 (0.375)	0.196 0.503)
T_k	0.084 (0.776)	0.503* (0.047)	0.653* (0.011)	0.424 (0.131)	−0.147 (0.615)	0.516 (0.059)	0.196 (0.503)
T_r	0.000 (1)	−0.152 (0.604)	0.037 (0.899)	−0.148 (0.615)	−0.099 (0.736)	−0.183 (0.532)	0.258 (0.374)

**tp_60, tp_40, and tp_20 individually represent the peak torque from passive stretch of three velocity 60°/s, 40°/s, 20°/s. sti_60,sti_40 and sti_20 are similar.*

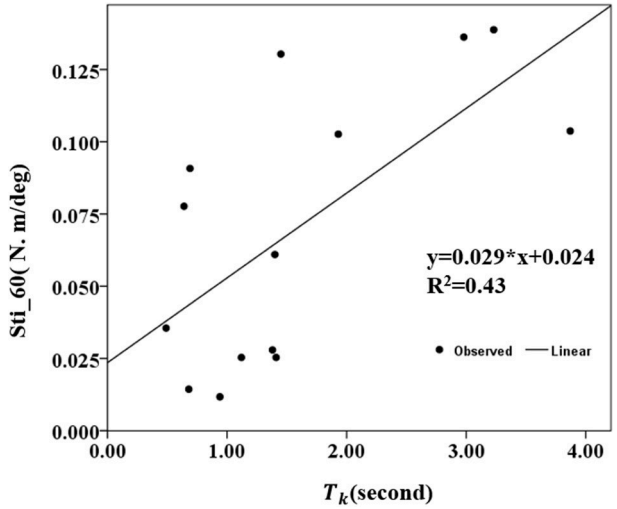


FIGURE 6 | Conelation between the stiffness of 60°/s and the keep time *(T_k)* of the MIVC with linear regression analysis.

TABLE 4 | The repeated measurements intra class correlation coefficients (ICCs) with 95% confidence intervals (CIs) of the MIVC features.

Feature*	First measurement (mean ± SEM)	Second measurement (mean ± SEM)	ICC (95% CI)
a_T_p	9.202 ± 1.438	8.471 ± 1.321	0.962 (0.881–0.988)
h_T_p	30.443 ± 3.578	28.709 ± 3.632	0.988 (0.988–0.999)
a_T_k	1.652 ± 0.30	1.575 ± 0.263	0.815 (0.425–0.941)
h_T_k	2.271 ± 0.373	2.171 ± 0.344	0.975 (0.922–0.992)
a_T_r	0.885 ± 0.175	0.639 ± 0.125	0.893 (0.666–0.966)
h_T_r	0.440 ± 0.039	0.394 ± 0.014	0.653 (−0.081 to 0.889)

**a_Tp indicates the peak torque from the impaired side, h_Tp indicates the peak torque from the non-impaired side, others are similar.*

Correlation Between the MIVC Features and Passive Stretch Measurement

Investigations on the correlation between MIVC and passive stretch revealed a fairly strong relationship between the passive torque, stiffness, and the T_k, indicating that the proposed method is clinically relevant. The weak relationship that was observed between the passive torque, stiffness, and T_p, T_r shows that there is a low association between the measured passive stretch and the muscle strength in the spastic arm. In other words, T_p and T_r may be not suitable for muscle spasticity assessment. At 20°/s, the Peak torque would be low and insensitive to reflex–mediated response, thus accounting for the reflex response and non-reflex response. Hence, this would be a reasonable explanation for the significant correlation observed between MIVC features and passive stretch response at 60°/s, and insignificant correlation between the MIVC features and passive stretch response at 20°/s.

Voluntary Muscle Activation Between the Impaired Side and Non-impaired Side

With the investigation of the characteristics of the muscles on the impaired arm and that of the contralateral side based on extracted MIVC features (T_p, T_k, T_r), it was interesting in that there was a significant difference between the muscle activation patterns/properties of both arms. In fact, the Peak torque value associated with the impaired arm was found to be significantly smaller compared to that of the non-impaired side (26). Meanwhile, the Keep time was also observed to be significantly smaller on the impaired side than non-impaired side. Additionally, the Rise time was significantly higher on the impaired side than the non-impaired side which is consistent with the results reported in some previous studies (33, 38). In other words, the above discussed results indicated that the muscle strength of the impaired side and the endurance of the impaired side were both reduced.

Reliability of MIVC Measurements

By examining the reliability of the MIVC features with repeated measurements for spasticity assessment, we found that the relatively high reliability could be achieved with an interclass correlation coefficient of 0.653–0.988. Also, the reliability analysis based on the Bland-Altman plots indicated that the MIVC method is reliable. Although the results were limited to the elbow flexor muscle group, we believe them to be positive enough to use MIVC characters for grading spasticity. If patients are tested with a greater latency between measurements, ratings of spasticity might differ more than in this study. Such differences, however, might be a manifestation of variations in muscle spasticity.

LIMITATIONS

Despite the good performances of the MIVC based features for spasticity assessment, the proposed MIVC method also has some limitations. Firstly, it should be noted that certain post-stroke patients especially those in the soft palsy phase could hardly perform MIVC with their impaired arm because their muscle force would be usually too low to perform any active

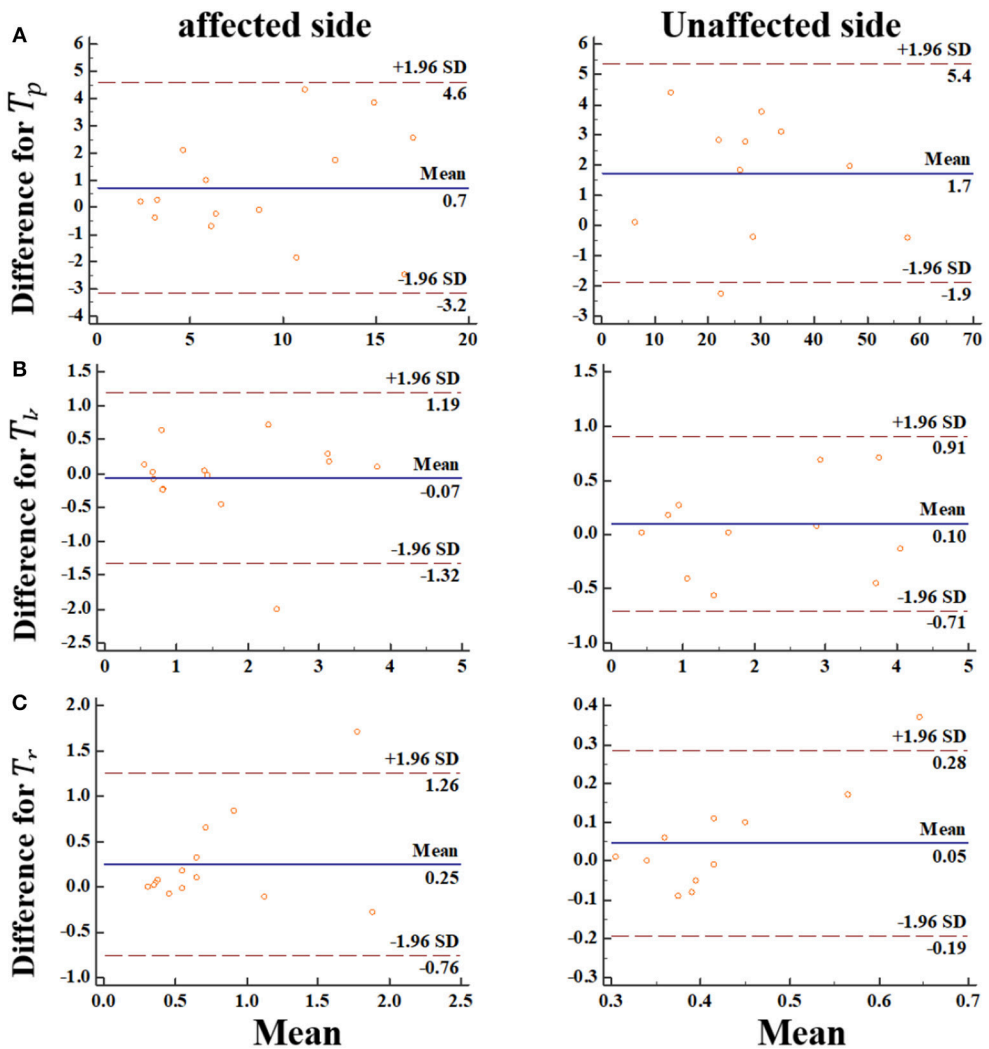


FIGURE 7 | The Bland-Altman plot for the MIVC features, longitudinal axes indicates the mean of two measurements, transverse axes indicates the difference of the two measurements.**(A)** Peak torque T_P; **(B)** Keep time T_k; **(C)** rise time T_r.

movement (38). In this regard, the currently investigated MIVC features may not provide optimal results when used to assess the spasticity status of their impaired arm. Secondly, most hospitals often are equipped with dynamometer, but the technical support that is needed to record the time-torque response for MIVC and analyze the data, may be unavailable. Thirdly, as lack of sufficient clinical data and control study, it would be hard to propose the diagnostic criteria for spasticity assessment with MIVC.

CONCLUSION

This study provides some experimental evidence that the muscle voluntary activation characterized by Keep time of the Peak torque from the MIVC correlates with severity of spasticity in chronic stroke survivors. The performance of the proposed MIVC method for spasticity assessment was extensively investigated with results revealing its reliability and accuracy based on dataset from14 post-stroke survivors. The findings of this study could provide potential insight on the development of smart intelligent devices that would facilitate efficient spasticity assessment in stroke survivors, which is necessary for active rehabilitation.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the supplementary files.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the human research ethics committee

of the Shenzhen Nanshan hospital with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the human research ethics committee of the Shenzhen Nanshan hospital.

AUTHOR CONTRIBUTIONS

HW analyzed the data and drafted the manuscript. HW, PH, and YX acquired the data. PH, GL, XL, and OS discussed the idea and experiments of this study and the revised the manuscript.

FUNDING

This research was partly supported by National Natural Science Foundation of China Grants (#61603375, #U1613207, and #U1613222) and the Shenzhen Science and Technology Plan Project (JCYJ20160331185848286).

ACKNOWLEDGMENTS

The authors would like to thank all the patients who participated in this study. We thank the clinical and administrative staffs at the Shenzhen Nanshan Hospital for facilitating this research.

REFERENCES

1. Lance JW. Spasticity: disordered motor control. In: Feldman RG, Young RR, Koella WP, editors. *Spasticity: Disordered Motor Control*. Chicago, IL: Year Book Medical Publishers (1980). p 485–94.
2. Francisco GE, McGuire JR. Poststroke spasticity management. *Stroke.* (2012) 43:3132−6. doi: 10.1161/STROKEAHA.111.639831
3. Huang FC, Patton JL. Movement distributions of stroke survivors exhibit distinct patterns that evolve with training. *J Neuroeng Rehabil.* (2016) 13:23. doi; 10.1186/s12984-016-0132-y
4. Walker MF, Fisher RJ, Korner-Bitensky N, McCluskey A, Carey LM. From what we know to what we do: translating stroke rehabilitation research into practice. *Int J Stroke.* (2013) 8:11–7. doi: 10.1111/j.1747-4949.2012.00974.x
5. Wang H, Wang L, Xiang Y, Zhao N, Li X, Chen S, et al. Assessment of elbow spasticity with surface electromyography and mechanomyography based on support vector machine. In: *International Conference of the IEEE Engineering in Medicine & Biology Society*. Seogwipo (2017) 3860 p.
6. Barnes M, Bhakta B, Moore P, Richardson D, Salisbury C, Thornton H, et al. *The Management of Adults With Spasticity Using Botulinum Toxin: A Guide to Clinical Practice. Radius Healthcare Surrey*. Surrey (2001).
7. Logan LR. Rehabilitation techniques to maximize spasticity management. *Top Stroke Rehabil.* (2011) 18:203–11. doi: 10.1310/tsr1803-203
8. Ashworth B. Preliminary trial of carisoprodol in multiple sclerosis. *Practitioner.* (1964) 192:540–2.
9. Bohannon RW, Smith MB. Interrater reliability of a Modified Ashworth Scale of muscle spasticity. *Phys Ther.* (1987) 67: 206–7.
10. Charalambous CP. Interrater reliability of a modified Ashworth scale of muscle spasticity. In *Classic Papers in Orthopaedics*. Berlin: Springer (2014). p. 415–7.
11. Pandyan AD, Price CI, Barnes MP, Johnson GR. A biomechanical investigation into the validity of the modified Ashworth Scale as a measure of elbow spasticity. *Clin Rehabil.* (2003) 17:290–3. doi: 10.1191/0269215503cr610oa
12. Bar-On L, Aertbelien E, Wambacq H, Severijns D, Lambrecht K, Dan B, et al. A clinical measurement to quantify spasticity in children with cerebral palsy by integration of multidimensional signals. *Gait Posture.* (2013) 38:141–7. doi: 10.1016/j.gaitpost.2012.11.003
13. Fleuren JFM, Voerman GE, Errenwolters CV, Snoek GJ, Rietman JS, Hermens HJ, et al. Stop using the Ashworth Scale for the assessment of spasticity. *J Neurol Neurosurg Psychiatry.* (2009) 81:46–52. doi: 10.1136/jnnp.2009.177071
14. Blackburna M, Vlieta PV, Moorea P, Mockettb S. Reliability of the modified ashworth scale in the assessment of lower limb spasticity in stroke patients. *Physiotherapy.* (1999) 85:371–1.
15. Aloraini SM, Gäverth J, Yeung E, MacKay-Lyons M. Assessment of spasticity after stroke using clinical measures: a systematic review. *Disability Rehabil.* (2015) 37:2313–23. doi: 10.3109/09638288.2015.1014933
16. Boudarham J, Roche N, Teixeira M, Hameau S, Robertson J, Bensmail D, et al. Relationship between neuromuscular fatigue and spasticity in chronic stroke patients: a pilot study. *J Electromyogr Kinesiol.* (2014) 24:292–9. doi: 10.1016/j.jelekin.2013.11.006
17. Kai S, Nakabayashi K. Evoked EMG makes measurement of muscle tone possible by analysis of the H/M ratio. In *Electrodiagnosis in New Frontiers of Clinical Research*. London: InTech (2013).
18. Li L, Shin H, Li X, Li S, Zhou P. Localized electrical impedance myography of the biceps brachii muscle during different levels of isometric contraction and fatigue. *Sensors (Basel).* (2016) 16:581. doi: 10.3390/s16040581
19. Lindberg PG, Gaverth J, Islam M, Fagergren A, Borg J, Forssberg H. Validation of a new biomechanical model to measure muscle tone in spastic muscles. *Neurorehabil Neural Repair.* (2011) 25:617–25. doi: 10.1177/1545968311403494
20. McPherson JG, Stienen AH, Drogos JM, Dewald JP. Modification of spastic stretch reflexes at the elbow by flexion synergy expression in individuals with chronic hemiparetic stroke. *Arch Phys Med Rehabil.* (2018) 99:491–500. doi: 10.1016/j.apmr.2017.06.019
21. Sin M, Kim W-S, Cho K, Cho S, Paik N-J. Improving the test-retest and inter-rater reliability for stretch reflex measurements using an isokinetic device in stroke patients with mild to moderate elbow spasticity. *J Electromyogr Kinesiol.* (2018) 39:120–7. doi: 10.1016/j.jelekin.2018.01.012
22. Szczerbik E, Kalinowska M, Graff K, Olczak-kowalczyk D. Dabrowska-Gontarczyk A, Jelonek E, et al. Use of instrumented spasticity tests in clinical applications. Preliminary results. *Biomed Hum Kinet.* (2015) 7:23–8. doi: 10.1515/bhk-2015-0004
23. Wang L, Guo X, Peng F, Wei Y, Samuel OW, Huang P, et al. A new EMG-based index towards the assessment of elbow spasticity for post-stroke patients. In: *International Conference of the IEEE Engineering in Medicine & Biology Society*. Seogwipo (2017) 3640 p.
24. Wang L, Guo X, Samuel OW, Huang P, Wang H, Li G. Normalization factor for the assessment of elbow spasticity with passive stretch measurement: maximum torque VS. body weight. *Conf Proc IEEE Eng Med Biol Soc.* (2018) 2018:388–91. doi: 10.1109/EMBC.2018.8512435
25. Krueger E, Scheeren EM, Nogueira-Neto GN, Button VL, Nohama P. A new approach to assess the spasticity in hamstrings muscles using mechanomyography antagonist muscular group. *Conf Proc IEEE Eng Med Biol Soc.* (2012) 2012:2060–3. doi: 10.1109/EMBC.2012.6346364
26. Li S, Liu J, Bhadane M, Zhou P, Rymer WZ. Activation deficit correlates with weakness in chronic stroke: Evidence from evoked and voluntary EMG recordings. *Clin Neurophysiol.* (2014) 125:2413–7. doi: 10.1016/j.clinph.2014.03.019
27. Sorinola IO, White CM, Rushton DN, Newham DJ. Electromyographic response to manual passive stretch of the hemiplegic wrist: accuracy, reliability, and correlation with clinical spasticity assessment and function. *Neurorehabil Neural Repair.* (2009) 23:287–94. doi: 10.1177/1545968308321778
28. Morris SL, Williams G. A historical review of the evolution of the Tardieu Scale. *Brain Injury.* (2018) 32:665–9. doi: 10.1080/02699052.2018.1432890
29. Prasartwuth O, Taylor JL, Gandevia SC. Maximal force, voluntary activation and muscle soreness after eccentric damage to human elbow

flexor muscles. *J Physiol.* (2005) 567:337–48. doi: 10.1113/jphysiol.2005.087767
30. Biering-Sorensen F, Nielsen JB, Klinge K. Spasticity-assessment: a review. *Spinal Cord.* (2006) 44:708–22. doi: 10.1038/sj.sc.3101928
31. Cadigan EWJ, Collins BW, Philpott DTG, Kippenhuck G, Brenton M, Button DC. Maximal voluntary activation of the elbow flexors is under predicted by transcranial magnetic stimulation compared to motor point stimulation prior to and following muscle fatigue. *Front Physiol.* (2017) 8:707. doi: 10.3389/fphys.2017.00707
32. Eken MM, Dallmeijer AJ, Doorenbosch CA, Dekkers H, Becher JG, Houdijk H. Assessment of muscle endurance of the knee extensor muscles in adolescents with spastic cerebral palsy using a submaximal repetitions-to-fatigue protocol. *Arch Phys Med Rehabil.* (2014) 95:1888–94. doi: 10.1016/j.apmr.2014.05.010
33. Brændvik SM, Elvrum AK, Vereijken B, Roeleveld K. Involuntary and voluntary muscle activation in children with unilateral cerebral palsy – Relationship to upper limb activity. *Eur J Paediatr Neurol.* (2013) 17:274–9. doi: 10.1016/j.ejpn.2012.11.002
34. Lee HM, Huang YZ, Chen JJ, Hwang IS. Quantitative analysis of the velocity related pathophysiology of spasticity and rigidity in the elbow flexors. *J Neurol Neurosurg Psychiatry.* (2002) 72:621–9. doi: 10.1136/jnnp.72.5.621
35. Schmit BD, Dhaher Y, Dewald JPA, Rymer WZ. Reflex torque response to movement of the spastic elbow: theoretical analyses and implications for quantification of spasticity. *Ann Biomed Eng.* (1999) 27:815–29.
36. Bizzini M, Mannion AF. Reliability of a new, hand-held device for assessing skeletal muscle stiffness. *Clin Biomech.* (2003) 18:459–61. doi: 10.1016/S0268-0033(03)00042-1
37. Orand A, Miyasaka H, Takeda K, Tanino G, Chihara T, Beppu H, et al. Reliability of stiffness measurement device during passive isokinetic spastic wrist movements of healthy subjects and hemiplegics. *Biocybernet Biomed Eng.* (2017) 37:114–23. doi: 10.1016/j.bbe.2016.09.001
38. Li S, Bhadane M, Gao F, Zhou P. The reticulospinal pathway does not increase its contribution to the strength of contralesional muscles in stroke survivors as compared to ipsilesional side or healthy controls. *Front Neurol.* (2017) 8:627. doi: 10.3389/fneur.2017.00627

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 25 June 2019
doi: 10.3389/fneur.2019.00567

A Systematic Review of International Clinical Guidelines for Rehabilitation of People With Neurological Conditions: What Recommendations Are Made for Upper Limb Assessment?

Jane Burridge[1], Margit Alt Murphy[2], Jaap Buurke[3,4], Peter Feys[5], Thierry Keller[6], Verena Klamroth-Marganska[7], Ilse Lamers[5], Lauren McNicholas[1], Gerdienke Prange[3,8], Ina Tarkka[9], Annick Timmermans[5] and Ann-Marie Hughes[1]*

[1] Faculty of Environmental and Life Sciences, University of Southampton, Southampton, United Kingdom, [2] Institute of Neuroscience and Physiology, Rehabilitation Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [3] Roessingh Research and Development, Enschede, Netherlands, [4] Faculty of Electrical Engineering, Mathematics and Computer Science, University of Twente, Enschede, Netherlands, [5] REVAL Rehabilitation Research Center, Faculty of Rehabilitation Sciences, Hasselt University, Hasselt, Belgium, [6] Tecnalia Research & Innovation, San Sebastian, Spain, [7] Zurich University of Applied Science (ZHAW), Winterthur, Switzerland, [8] Faculty of Engineering Technology, University of Twente, Enschede, Netherlands, [9] Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

OPEN ACCESS

Edited by:
Mariano Serrao, Sapienza University of Rome, Italy

Reviewed by:
Giovanni Morone, Fondazione Santa Lucia (IRCCS), Italy
Marianna Capecci, Marche Polytechnic University, Italy

***Correspondence:**
Jane Burridge
Jhb1@soton.ac.uk

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *08 January 2019*
Accepted: *13 May 2019*
Published: *25 June 2019*

Citation:
Burridge J, Alt Murphy M, Buurke J, Feys P, Keller T, Klamroth-Marganska V, Lamers I, McNicholas L, Prange G, Tarkka I, Timmermans A and Hughes A-M (2019) A Systematic Review of International Clinical Guidelines for Rehabilitation of People With Neurological Conditions: What Recommendations Are Made for Upper Limb Assessment? Front. Neurol. 10:567. doi: 10.3389/fneur.2019.00567

Background: Upper limb impairment is a common problem for people with neurological disabilities, affecting activity, performance, quality of life, and independence. Accurate, timely assessments are required for effective rehabilitation, and development of novel interventions. International consensus on upper limb assessment is needed to make research findings more meaningful, provide a benchmark for quality in clinical practice, more cost-effective neurorehabilitation and improved outcomes for neurological patients undergoing rehabilitation.

Aim: To conduct a systematic review, as part of the output of a European COST Action, to identify what recommendations are made for upper limb assessment.

Methods: We systematically reviewed published guidance on measures and protocols for assessment of upper limb function in neurological rehabilitation via electronic databases from January 2007–December 2017. Additional records were then identified through other sources. Records were selected for inclusion based on scanning of titles, abstracts and full text by two authors working independently, and a third author if there was disagreement. Records were included if they referred to "rehabilitation" and "assessment" or "measurement". Reasons for exclusion were documented.

Results: From the initial 552 records identified (after duplicates were removed), 34 satisfied our criteria for inclusion, and only six recommended specific outcome measures and /or protocols. Records were divided into National Guidelines and other practice guidelines published in peer reviewed Journals. There was agreement that assessment is critical, should be conducted early and at regular intervals and that there is a need for

standardized measures. Assessments should be conducted by a healthcare professional trained in using the measure and should encompass body function and structure, activity and participation.

Conclusions: We present a comprehensive, critical, and original summary of current recommendations. Defining a core set of measures and agreed protocols requires international consensus between experts representing the diverse and multi-disciplinary field of neurorehabilitation including clinical researchers and practitioners, rehabilitation technology researchers, and commercial developers. Current lack of guidance may hold-back progress in understanding function and recovery. Together with a Delphi consensus study and an overview of systematic reviews of outcome measures it will contribute to the development of international guidelines for upper limb assessment in neurological conditions.

Keywords: practice guidelines, neurological conditions, upper limb, outcome and process assessment, systematic review, guidelines, impairment, activity

INTRODUCTION

Worldwide prevalence of stroke in 2010 was 33 million, with 16.9 million people having a first stroke, of which 795,000 were American and 1.1 million European (1). It has been estimated that approximately one third of people fail to regain upper limb capacity, despite receiving therapy (2). This has important implications for both individuals and the wider society as reduced upper limb function is associated with dependence and poor quality of life for both patients and carers (3–5) and impacts on national economies (6).

While stroke has the highest prevalence, other neurological conditions such as Multiple Sclerosis (MS), Spinal Cord Injury (SCI), and Traumatic Brian Injury, have a significant incidence and there are often similarities in presentation, and treatment and therefore assessment. The worldwide incidence of SCI is 40–80 cases per million population and the estimated European mean annual rate of MS incidence is 4.3 cases per 100,000 (7). Recently, Kister et al. (8) reported that 60% of people with MS have impaired hand function. The impact of upper limb dysfunction on ADL is higher than in stroke, as both sides are often affected (9). Although dysfunction after SCI depends on level of injury, upper limb function is consistently cited as a health priority. The incidence rate of TBI in Europe is about 235 per 100,000 population (10). Outcome data among European countries are very heterogeneous. From the US however, it is known that about 1.1% of the population suffer a TBI resulting in long term disability (11).

Rationale

Providing evidence-based and cost-effective upper limb rehabilitation is a priority for patients and healthcare services and is increasingly important because of the growth in new technology-based interventions designed to augment conventional occupational therapy and physical therapy. Outcome data are key to delivering best practice and identifying which interventions are effective. To design trials that will deliver unequivocal results, so that useful, and only useful interventions can be translated into clinical practice and delivered optimally, we need to understand the complexity and interaction between patient and intervention. To do that requires a large amount of comparable data—i.e., data generated from an agreed small set of valid outcome measures (OM) using agreed protocols. By standardizing OM and protocols, aggregated data can be mined to generate a better understanding of what interventions are effective, at what dose, when, with whom and in what setting they should be used. This will enable clinicians to make better informed decisions and thus improve patient outcomes. Agreed, widely used, valid and practical OMs and assessment protocols are important in research into and treatment of all neurological conditions, but may be particularly important in conditions where incidence is lower and therefore data sets smaller.

Guidelines on best practice aim to improve treatment standards, including rehabilitation, and directing future research. And, as we argue above, OMs are key to achieving that goal. It would seem reasonable therefore that clinical guidelines would be a source of guidance on selection of OMs and protocols for their use. In this study, we have therefore systematically reviewed recent and current guidelines on stroke, MS, SCI, and TBI. We have excluded all other neurological disabilities such as Parkinson's Disease and cerebellar ataxia as the assessment protocols and tools for these conditions are very different. We have extracted recommendations on assessment in terms of outcome measures (OM), frequency of assessment and who should conduct assessments, when and with what purpose.

Objectives

This study is one of three components in the development of European Guidelines on assessment of the upper limb in neurological conditions. Two studies have already been published: A Delphi study which reported the views of experts (12) and an overview of systematic reviews of OMs (13). The project was driven by a realization that progress in upper limb neurological rehabilitation research and consequently improvement in quality of care was hampered by the absence

of consensus on OMs and protocols for assessment. To conduct effective metanalysis requires multiple clinical studies to use the same measures using comparable protocols, and for the same OMs to be used in clinical practice. Practice guidelines are an obvious source of information on useful measures and protocols for assessment. The objective of this study was therefore to explore published and web-based guidance and to extract and synthesize recommendations on assessment measures and protocols for assessment of upper limb function for people with neurological conditions.

Research Question

Our research question was: What recommendations are made by international clinical guidelines for the assessment of the upper limb in neurological conditions?

METHODS

Study Design and Search Strategy

Published studies were identified through Pubmed and Evidence Search databases (MEDLINE in Ovid, Embase, CINAHL, AMED, Web of Science, PEDro and Google Scholar) for the period from January 2007 to December 2017. The search strategy comprised the following medical subject heading (MeSH) terms: *stroke, multiple sclerosis, spinal cord injuries* and *neurological rehabilitation* with filters for *guidelines, recommendations, practice guidelines* and *consensus development conference.* The search was as follows *(((((“Stroke”[Mesh]) OR “Multiple Sclerosis”[Mesh]) OR “Spinal Cord Injuries”[Mesh]) OR “Traumatic Brain Injury”[Mesh]) OR “Neurological Rehabilitation”[Mesh])) AND (((Practice Guideline[pt] OR Recommendation OR Guideline[pt] OR Consensus Development Conference[pt])) AND (“2007/01/01”[PDat]: “2017/12/31”[PDat])).* Using the search engine Google, applying the terms “[nation],” guideline, “stroke,” members of the COST action searched for their National Stroke Guidelines in their respective languages: UK, Netherlands, Italy, Spain, Germany, Switzerland, Sweden and Estonia. Using the same terms, we also searched, in English for any other National Guidelines from any country for stroke, SCI, MS, TBI or Neurological Conditions. Additional records were also identified through other sources, especially references from the retrieved records.

Systematic Review Protocol and Data Extraction

Two review authors (JB and AH) independently screened references for relevance based on their abstract, and methodological quality, where there were any disagreements the wider group were consulted. Records were only included in the review if they referred to upper limb “assessment” or “measurement” and “physical rehabilitation” of “neurological disorders” and were either a “National Guideline” or either “practice guideline” or “recommendations” published in a peer-reviewed Journal. Additional studies were identified from references within the records and, where they satisfied these criteria were included in the review. Although our interest was primarily in upper limb assessment, the guideline literature usually encompassed the broad topic of assessment, i.e., both upper and lower limb, activities of daily living and impact on quality of life. Such articles were screened, but only included for further review when guidelines on upper limb assessment were included. We did not use a standard tool to assess quality. Records that satisfied the criteria for inclusion were then categorized by two independent authors (AH and JB) into: National guideline; other practice guidelines or recommendations published in peer-reviewed journals or web-based resources and then by condition into: stroke; multiple sclerosis (MS); Spinal cord injury (SCI), traumatic brain injury (TBI) or “other neurological conditions.” Each record was then reviewed (LM, JB and AH). Data were then extracted from each record and tabulated.

Data Analysis

Based on the review a classification structure (see below) was designed to reflect the relevant areas in which recommendations were made.

Classification structure:

1. Why assessment is important
2. When during the rehabilitation should assessment be conducted
3. Clinical Utility—who should conduct the assessment
4. Single vs. multiple OMs within the ICF Framework
5. Assessment of body function and structures (impairment) and activity
6. Assessment of Activities of Daily Living (ADL) and participation
7. Psychometric properties and appropriateness of OMs
8. Self-Efficacy and goal orientated measures—assessment integrated into therapy.

RESULTS

The records retrieved for the review and the results of the selection process are shown in the flow diagram (**Figure 1**).

Study Selection Characteristics

Our primary aim was to review and synthesize recommendations for the selection and use of upper limb OMs (both conventional and technology-based) in neurorehabilitation. Our search identified no records that focussed exclusively on the UL and the majority made only brief reference to either assessment or measurement tools (14–18). Where reference was made to measurement there was explicit consensus that measures should follow the World Health Organization (WHO) International Classification of Function (ICF) framework (19, 20).

Synthesized Findings

Of the 34 publications included in the review only six (two National Guidelines)

recommended specific measures of body function and structures, activity and participation (14, 15, 17, 18, 21, 22). Seven recommended global scales but gave no specific measures for the upper limb (23–28). Most National Guidelines focussed on

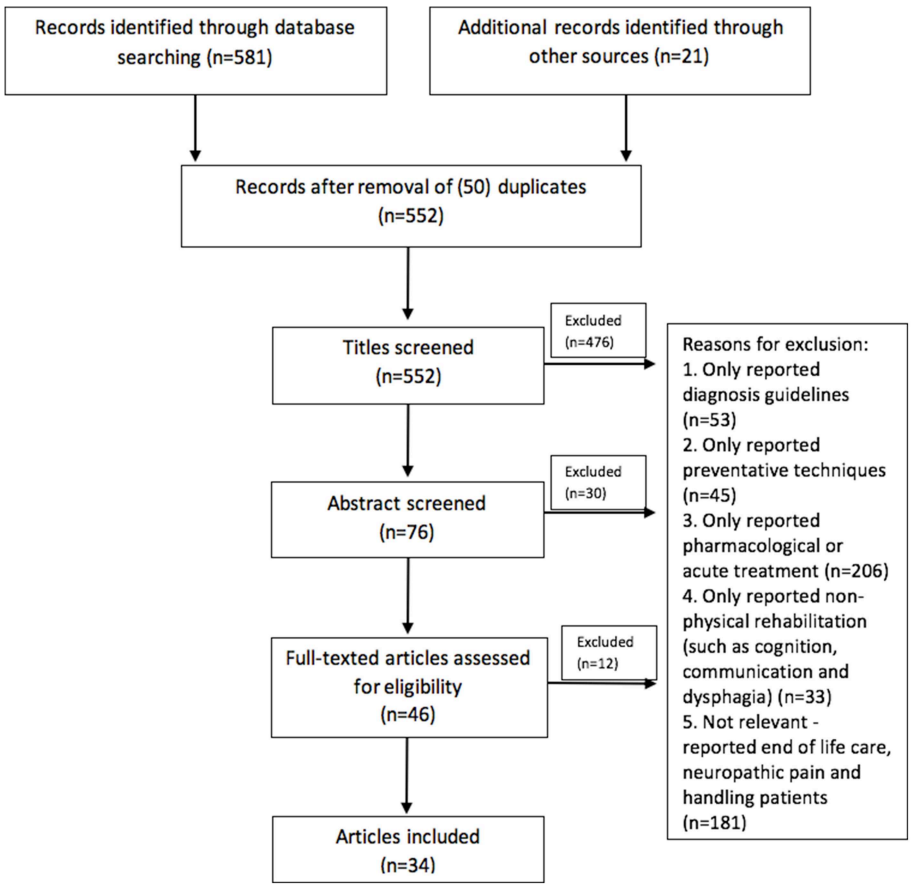


FIGURE 1 | Flow diagram of the studies retrieved for the review.

service delivery. Some acknowledged that standardized OMs are required for effective neurorehabilitation, without reference to specific tools or how they should be chosen. The need for OMs that encompass all domains of the ICF was agreed.

Nine publications referred to the importance of global or upper limb assessments being conducted by appropriately trained or qualified healthcare professionals (HCP) (22, 29–36). Protocols for and timing of assessment was only included in four records (17, 21, 22, 37). In total, reviews identified 47 different global and upper limb specific OMs, but only one referred to effectiveness, validity or reliability of the recommended measures (17).

Fourteen National Guidelines were included in the review (**Table 1**) from the following countries: The Netherlands, Sweden, UK (4), Scotland (2), Estonia, South Africa, Singapore, Australia, New Zealand and the USA. National guidelines were condition specific: 11 stroke, 1 brain injury, 1 SCI and 1 MS. National Guidelines provided the most comprehensive and broad recommendations. All National stroke guidelines except the South African (33) and Swedish (55) make some reference to assessment, but in almost all cases it was brief, non-specific and not related either to rehabilitation or the UL. There were two exceptions to this.

The Dutch National guideline (17), provided very comprehensive recommendations on the diagnostic process and included recommendations for specific tools, within each ICF domain, that should be used for diagnosis—to allow informed clinical decision-making; to predict recovery and to assess progress. Recommendations are summarized as follows: Any patient with a stroke should be systematically assessed in terms of body functions, activities, and participation prior to the start of the physical therapy process, preferably using reliable, valid, and responsive measurement instruments. These measurements should be administered at predefined moments during the physical therapy process, in order to objectively monitor the patient's clinical course. Basic upper limb measurement should include: muscle strength, dexterity and ADL. Tools were selected by the guideline development team on the basis of their reliability, responsiveness, predictive and construct validity, and finally their practical feasibility. They make recommendation for future practice: *"many publications fail to report follow-up data, and if they do, the timing of follow-up assessments varies widely. This means that the long-term added value of nearly all interventions is unknown."* It is suggested that *"frequent and systematic assessment of functional changes over time (monitoring)"* is an important factor contributing to higher

TABLE 1 | Summary of the National Guideline records included in the review.

Record	Year	Summary of recommendations	Recommended measures
Australian Stroke Foundation (38). (Stroke)	2017	Use of valid measures; assessment made by trained clinicians. No reference to physical assessment of the upper limb	None
Winsteinet al. (14) (Stroke)	2016	Recommends a single assessment used throughout the course of stroke recovery	Computerized questionnaire: *"Activity Measure for Post-Acute Care"*; dynamometer (grip strength) (39); electro-goniometer (range of motion) (40) and Frey filaments (tactile sensory deficits) (41). Fugl-Meyer (42) and Box and Block Test (43)
Royal College of Physicians (16) (Stroke)	2016	Use of the WHO ICF and instruments appropriate to the intervention. Clinicians should be trained in the use of measurement scales; set agreed goals (including patient and carers)	None
Veerbeek et al. Dutch Guidelines (17) (Stroke)	2014	Measures that are valid, reliable, responsive and feasible within each ICF domain. Use for diagnosis, clinical decision-making, to predict recovery, and assess progress. Measure at predefined times to monitor recovery e.g., within one week of admission and discharge (or when transferring care) end of the 1st week, 3rd and 6th month post-stroke. Consider measures before each multidisciplinary meeting.	Motricity Index (44); Fugl-Meyer (FMA UE) (42) Frenchay Arm Test [FAT]) (45), Action Research Arm Test (ARAT) (46) and Nine Hole Peg Test (NHPT) (43). MAS (47); Nottingham Extended ADL (48); Global measures: SSQoL (49); Barthel Index (50), NIHSS (51)
NICE, Multiple Sclerosis (32). (MS)	2014	No reference to upper limb problems. Assessment should be conducted by a "healthcare professional with appropriate expertise in rehabilitation and MS".	None
SIGN. Guideline 130 Brain injury rehabilitation in adults (26) (TBI)	2013	Brief reference to assessment and OM: "A range of tools can assist in the assessment and setting of goals"; no specific recommendations on measures or timing.	COPM (52), FIM/FAM (53), Barthel Index (50).
NICE. Stroke rehabilitation in adults - NICE guideline (28) (Stroke)	2013	Screen for impairment, activity limitations, participation restrictions, and environmental factors to direct treatment on admission and on transfer from hospital to community. Standardized valid and reliable screening instruments should be used by HCPs who have appropriate skills and training. Wrist and hand splints should be assessed and fitted by trained HCPs. In research, the primary outcome measure should be improvement in function, with secondary outcomes assessing impairment, function, and quality of life.	NIHSS (51); Barthel Index (50)
NSCISB. The National Spinal Cord Injury Strategy Board (54). (SCI)	2012	Only reference to rehabilitation is passive movement to maintain joint range with no reference to assessment.	None
Bryer et al. The South African guideline (33) (Stroke)	2011	Early assessment and planning of discharge and comprehensive assessment of medical problems, impairments and disabilities by specialist staff is needed.	None
Swedish National Board of_Health and Welfare. Quality and efficiency of stroke care in Sweden (55). (Stroke)	2011	No recommendations for OM.	None recommended
Venketasubramanian et al. Singapore Clinical Practice Guidelines Workgroup on Stroke (56) (Stroke)	2011	Recommends multi-disciplinary medical assessment in acute stroke or transient ischemic attack (TIA). No reference to UE assessment	None
Guideline 118. SIGN. Management of patients with stroke (57). (Stroke)	2011	Assessment of patient's needs to set goals and re-assess progress against goals. No reference to UE assessment	None
Estonian clinical guidelines for stroke rehabilitation (27) (Stroke)	2011	Use of valid and standardized measures including assessment of sensorimotor function, cognition, speech, and ADL in predefined time points.	NIHSS (51), FIM (53), Barthel Index (50), Modified Ashworth Scale (58); Berg Balance Test (59)
New Zealand Clinical guidelines for Stroke Management (60). (Stroke)	2010	Reference to assessment in acute care and of those who want to return to work.	None

quality of care. They recommend considering measures before each multidisciplinary meeting.

The US National Guideline (14) also makes comprehensive recommendations on assessment for best clinical practice. It acknowledges the need for a single assessment used throughout the course of stroke recovery, referring to measures of body function/structure and citing the upper limb motor section of the Fugl-Meyer scale or the Box and Block Test for measuring arm motor deficits. The Australian Guideline (38), focuses on interventions, but recommends assessment using valid measures, although without reference to physical assessment of the upper limb. The New Zealand (60) guideline makes recommendations on all aspects of stroke management and prevention based on level of evidence, expert opinion and clinical experience, however, the only reference to assessment is in relation to acute care and of people who want to return to work.

Six UK Guidelines (of which two were Scottish) were found: three for Stroke (16, 28, 61), one for SCI (54), one for brain injury (62), and one for MS (32). The Royal College of Physicians (RCP) stroke Guideline is a comprehensive guideline for best clinical practice. The RCP Guideline considered the general principles of measurement in stroke rehabilitation, for example the importance of measuring function and understanding which domain of the WHO ICF framework an instrument is measuring. It states that instruments should be appropriate to the intervention in question and clinicians should be trained in the use of measurement scales to ensure consistent use within the team. The National Institute of Clinical Excellence (NICE) recommendations (28) guidelines were mainly concerned with the organization of health and social care and specifically the delivery of best practice. Specific recommendations were: screening on admission and on transfer from hospital to community using the WHO ICF to provide information on functional abilities; use of standardized screening instruments; treatment and assessment should be provided by HCPs who have appropriate skills and training and patients should be assessed and fitted for wrist and hand splints by trained HCPs. The third UK guideline on MS makes no reference to upper limb problems, however does specify that assessments should be conducted by a "healthcare professional with appropriate expertise in rehabilitation and MS." The fourth UK Guideline, on SCI (63) also makes no reference to upper limb assessment, focusing only on medical assessment except for brief reference to the need for a musculoskeletal assessment including spasticity, joint range of movement, and pain. Neither the Singapore (56) nor the Swedish (55) Guidelines make recommendations on assessment. The Singapore Guidelines [1](56) state the importance of assessment in acute stroke, giving recommendations, but make no reference to assessment in rehabilitation. Although not an official National publication, we have included the Canadian Web-based Stroke Rehabilitation Evidence-Based Review SREBR guidelines[1] which provide comprehensive recommendations on assessment and present level of evidence for a wide range of clinical scales. The SREBR consolidates the best available scientific evidence for the effectiveness of stroke rehabilitation and is an excellent resource. The review is constantly updated and includes a substantial section on OMs. The SREBR used the ICF Framework and in addition to the usual measures of reliability and validity, also considered appropriateness and responsiveness (floor and ceiling effects), precision, interpretability, acceptability, feasibility, and the thoroughness of testing. The scope is very wide, including tests for cognition, depression etc. It does not address upper limb assessments *per se*, but includes a number of UL focussed impairment and activity measures, which are scored in each category.

Nineteen other articles were included in the review (**Table 2**). Peer review articles were generally less comprehensive than the National Guidelines and often focused on a specific area of neurological rehabilitation, for example Occupational Therapy or tele-rehabilitation. They were however more focused on upper limb OMs and some gave recommendations for specific measures.

In total, 51 outcome measures were recommended, of which 39 addressed stroke (76%), 5 TBI (10%), 3 SCI (6%), 1 MS (2%). Four outcome measures (8%) were recommended without specifying which pathology it should be used for. Regarding stroke guidelines, the most frequently recommended OMs were NIHSS (5), FIM (4), Barthel Index (3), and FMA (3). For the other pathologies, recommended OMs were scattered across different OMs.

We have synthesized recommendations made by the National Guidelines and published articles under the following headings: Why, when and by whom assessments should be conducted and what should be measured.

Why Assessment Is Important

"Not Everything That Counts Can Be Counted" (81) but without valid, reliable and sensitive measures that are meaningful to patients, clinicians and researchers our field cannot advance. We will not know what works, when or with whom. Neurological rehabilitation is complex in terms of both patients and intervention (26, 57) There are few interventions or conditions for which there is a single measure as there is for example in testing a new drug for hypertension. Winstein (14) acknowledges the challenge faced in assessing services, patient outcomes and effectiveness of neurological rehabilitation stating that: *"the array of rehabilitation services delivered to stroke patients in the United States is broad and highly heterogeneous, varying in the type of care settings used; in the duration, intensity, and type of interventions delivered."* and that this *"brings with it challenges in terms of determining the quality of care delivered by the system"* and *"in terms of assessment of which research findings…are applicable to the system."* Alexander (78) identified the need for agreed measures in their multi-disciplinary study of current and evolving tools for evaluating people with spinal cord Injury (SCI), reporting that none of the findings of major clinical trials of new interventions had translated into standard care and argued that to achieve translation, "*agreed, appropriate and valid primary end points and intervention protocols are needed."*

[1](http://www.ebrsr.com/)

TABLE 2 | Summary of the peer reviewed and practice guideline records included in the review.

Record	Year	Summary of recommendations	Recommended measures
Wechesler et al. (23) (Stroke)	2017	Improve quality monitoring and outcomes and consider sharing patient data. NIHSS score done remotely during transit to hospital (64)	NIHSS score (51)
Intitut National d'excellence en sante et en sociaux—(TBI)	2017	Guidance on global assessment and rehabilitation interventions including motor control. No specific reference to, or recommendation for UE assessment	None
ATAXIA UK. *Ataxia UK* (24) (Non-specific pathology)	2016	No reference to UE specifically. Measure patient engagement and satisfaction with the performance of an activity,	Assessment of Motor and Process Skills (AMPS) (65), Goal Attainment Scale (GAS) (66), Canadian Occupational Performance Measure (COPM) (52), self-efficacy tools and quality of life measures.
Wolf et al. (67) (Stroke)	2015	No recommendations for assessment	None
Hebert et al. Canadian stroke best practice recommendations (37) (Stroke)	2015	Assessment within 48 h including: function, safety, physical readiness, and ability to learn and participate in rehabilitation. No specific reference to UE	None
Majersik et al. (25) (Stroke)	2015	Studies exploring genetic factors should also measure stroke outcomes. Medical and global outcomes, impairment and activity early post stroke, at 3 months and ideally at 6 and 12-months' post stroke. Document access to and amount of therapy	No specific upper limb measures. NIHSS (51), GAS (66), FIM (53)
Haselkorn (68) (Stroke)	2015	No specific recommendations	None
College of Occupational Therapists and Association Of Chartered Physiotherapists in Neurology. (15). (Splinting. Non-specific pathology)	2015	Use valid and reliable measures across the ICF framework. Global measures are unlikely to be sensitive to changes, but should be included; choice and timing of OM is important. Recommendations for future research include use, choice and timing of OM	Arm activity measure (69) Visual analog scale (70); ARAT (46)
Potter et al. (71). (MS)	2014	Important to consider measures that can be used in different settings (hospital vs. home) to track patients over a long period	No specific recommendations
Billinger et al. (72). (Stroke)	2014	No specific OM for UL	None
Finlay and Evans (metastatic spinal cord compression). (21) (SCI)	2014	Pain, motor and sensory dysfunction assessment should be carried out within 24–48 h of admission and prior to discharge. Pain should be re-assessed at least daily. Only when the MSCC is deemed stable or more active rehab is permitted can the full assessment be completed. A wide range of measures can be obtained through: http://www.rehabmeasures.org/default.aspx	Light touch sensation; Sharp/blunt or pin prick sensation; Joint proprioception; Muscle power (myotome chart and Oxford classification); Muscle tone: flaccidity or spasticity (MAS) (58); Joint ROM (active/passive) and muscle length; Personal activities of Daily Living (PADL): Activities of Daily Living (ADL):
Ontaneda et al. (MS) (73). (MS)	2012	A universally accepted measurement instrument that is precise, reliable, easy to administer, captures key neurological domains affected by MS, is sensitive at all levels of disability and accurately reflects neurological and neuropsychological disability is still lacking. Agreeing on single clinical measure that is useful at all stages of the disease is challenging	Multiple Sclerosis Functional Composite (MSFC) approach. Recommends the development of a database focused on MSFC and follow-up projects aimed at developing patient-reported outcomes, imaging markers, and biological markers of the MS disease process.
Canadian EBRSR (http://www.ebrsr.com/) (18) (Stroke)	2012	Use of the ICF Framework; reference to reliability, validity, appropriateness and responsiveness (floor and ceiling effects), precision, interpretability, acceptability, feasibility. Does not address UE assessments per se, but includes a number of UE focussed impairment and activity measures, which are scored in each category. Provides information for selection of most appropriate measure.	Impairment: FMA (69), and MAS (47, 74) Activity: ARAT (46), B&B (43), Chedoke-McMaster (75), FIM (53), 9HPT (43, 76), WMFT (77) Participation: COPM (52)
Miller et al. (34). (Stroke)	2010	Hypertonicity should be assessed, but no recommended tools. The MAS has poor validity and inter-rater reliability. Other measures have not been shown to be feasible clinically. Acknowledges importance of trained assessors. Recommends ADL Assessment post-discharge from rehabilitation	15 Upper Limb Motor assessments are listed as 'commonly used'

(Continued)

TABLE 2 | Continued

Record	Year	Summary of recommendations	Recommended measures
		Tools should be agreed by the MDT and be valid and reliable. No reference to UE	
Hachinski et al. (35). (Stroke)	2010	Calls for consensus on, then implementation of, standardized clinical and surrogate assessments. No reference to UL Tools for measuring the biology of stroke recovery are needed to inform optimal timing, intensity, duration, and content of therapy. The best standardized measures of behavior and outcomes after stroke need to be defined and used in clinical practice. Standardized rater training needs to be developed. Surrogate markers of treatment effect could also be used as predictive tools for outcome and thus be of value for entry criteria in clinical trials or in evaluating treatment outcomes and guide clinical decision-making. No specific reference to UL assessment.	None
VA/DOD The Management of Stroke Rehabilitation (22) (Stroke)	2010	NIHSS performed by trained, certified assessors within the first 24 h, and consider re-assessing prior to discharge from acute care. Motor function assessed at impairment and activity levels using assessments with established psychometric properties. A standardized assessment tool should be used to assess ADL/IADL A MDT assessment should be undertaken to establish the patient's rehabilitation needs and goals.	Functional Independence Measure (FIM) (53). NIHSS (51) Motor function: muscle strength for all muscle groups, active and passive range of motion, muscle tone, ability to isolate the movements of one joint from another, gross and fine motor co-ordination. The daily use of the paretic extremity should be assessed using a self-report measure (e.g., the Motor Activity Log) (47) and accelerometery.
Alexander et al. (78) (SCI):	2009	Evaluation of UE impairment is important, but generic tests of hand function are ill-suited for use with persons with SCI, with the exception of the Grasp and Release test - developed to assess the effect of a neuroprosthesis.	Grasp and release test (79)
Gall et al. (63) (SCI).	2008	No reference to upper limb assessment, except for brief general mention of spasticity, joint range of movement, and pain assessment	None
Steeves et al. (80). (SCI)	2007	Recommends assessment of UE function, including sensation in clinical trials and acknowledges lack of agreement and absence of SCI specific tests for SCI and lack of sensitivity in current measures. Discusses a range of tools without giving specific recommendations	Accurate sensitive and functional measures
Bayley et al., ABIKUS (36) (TBI).	2007	Recommendations based on a systematic review. Recommends assessment of spasticity and motor function by trained professionals	None

When During the Rehabilitation Period Should Assessments be Conducted?

Nine publications (seven stroke) referred to timing of assessments in relation to rehabilitation recommending soon after admission and on transfer of care. Beyond that there was wide variation, particularly in frequency of assessments. The Dutch Guidelines recommended that patients were assessed within 1 week of admission and discharge (or when transferring treatment to another colleague) and at the end of the 1st week, 3rd and 6th month post-stroke. They also recommended considering measures before each multidisciplinary meeting. The NZ guidelines stated that patients should be assessed when treatment choices were being made, as assessments were fundamental to measuring deficits, planning goals, and planning management. It recommended that all assessments occurred as soon as possible after admission (aiming for within the first 2 days) with the stroke team working together so as not to overburden the patient by duplicating questions.

The COT and ACPIN Report (82) was concerned with splinting and suggested that specified outcomes should be recorded at baseline and at defined intervals, but they did not suggest what these should be (25). Winstein (14), recommends that *"all patients should undergo a formal assessment of their rehabilitation needs before discharge"* and Finlay (21) recommend that physiotherapy assessments be carried out within 24–48 h of admission and that the assessment should include pre-admission mobility and motor

dysfunction. The Canadian best practice guidelines state initial screening and assessment should be conducted within 48 h by rehabilitation professionals.

There were only two publications which referenced timing of assessment in MS and SCI, The American Physical Therapy Association Neurology Section task force recommended using OM to track MS patient status over a long-term period or as patients transition across settings (71). The Guidelines and Audit Implementation Network (GAIN) recommends PT and OT therapy assessments (pain, motor and sensory dysfunction) for SCI should be carried out within 24–48 h of admission and prior to discharge.

Clinical Utility—Who Should Conduct the Assessment

A strong consensus was found in favor of assessments being conducted by appropriately trained HCPs. Patients with difficulties in performance of daily activities should be assessed by a clinician trained in the use of whichever scales are chosen to ensure consistency of their use within the team and an understanding of their purposes and limitations (60). This view is supported by (34) recommending that clinicians obtain not only training to establish administration and scoring consistency, but also, routine retraining to ensure they maintain this consistency (71). They highlight the fact that although OMs have benefits in physical therapist practice multiple barriers interfere with their use, most notably, a limited understanding of how to select and apply the best OM.

Single vs. Multiple and Specific OMs, Within the ICF Framework

No records recommended a single OM with the exception of Winstein (14) who suggested the use of a computerized questionnaire called the *"Activity Measure for Post-Acute Care"* as an outcome measure for all stroke patients to "*track stroke rehabilitation outcome."* Billinger (72) suggested that accelerometery was likely to be used as an OM for future clinical trials as it measured changes in free-living physical activity and compliance with exercise programmes.

There was consensus between the Dutch, UK, and US guidelines that patients should be assessed in each domain of the ICF framework, but conflict between using a single measure to enable progress to be monitored throughout recovery and multiple measures to allow for changes in setting, goals and ability levels. The US guidelines recommend multiple OMs whereas the most recent stroke guidelines from the UK National Institute for Health and Care Excellence (NICE) (28) recommend primary and secondary OMs, with the primary assessing function and secondary including measures of impairment, activity limitation and quality of life. The Scottish Intercollegiate Guidelines Network (26) recommended using a range of assessment tools to assist goal-setting. Multiple OMs were often recommended (14, 15, 17, 21, 71) arguing, for example, that it would be challenging to select only 1 or 2 OMs for use with all people with Motor Neurone Disease (MD) and Multiple Sclerosis (MS) (83, 84) due to variation in disability levels and treatment in a variety of settings. Ontaneda (73) concurred, recommending different OMs for people at different stages of MS and the RCOT (85) agreed with (71) that a *"one size fits all"* intervention with a single outcome measure was of limited, if any, value. The SIGN TBI guideline (26) stated that because rehabilitation interventions usually target multiple or complex outcomes, and because individual goals vary, a single measure may be impossible or inappropriate.

Assessment of Body Function and Structures (Impairment)

The US Guidelines were skeptical about the use of measures in the body structure and function (impairment) domain of the ICF framework, considering that the psychometric properties of tools had not been established. They referred specifically to measures of spasticity/hypertonicity citing the equivocal evidence for validity and inter-rater reliability for the Modified Ashworth Scale. The VA/DOD Guidelines (22) however, made very strong and clear recommendations for measuring motor function both at the impairment (ability to move in a coordinated manner in designated patterns) and at the activity level (performance in real life or simulated real life tasks) using assessments with established psychometric properties.

In terms of measuring spasticity, Miller et al. (34) acknowledged the problem of validity and interrater reliability of the most commonly used Modified Ashworth Scale, but that other spasticity measures reported in the literature have problems with respect to clinical feasibility and the range of joints that could be assessed. Alexander (78) was one of the few to discuss the use of electrophysiological measurements such as Electromyography (EMG), Motor Evoked Potentials (MEPs) and Somatosensory Evoked Potentials (SEPs) to assess spinal conductivity and spasticity in SCI. Hachinski (35) was one of the few records to refer to the need for assessments to measure the mechanisms of recovery. It reported the consensus of a "Synergium," commissioned to finding new ways of accelerating progress in reducing the risks, effects, and consequences of stroke.

Assessment of Activities of Daily Living (ADL) and Participation

While upper limb function has a significant impact on ADL, QoL and participation, it is beyond the scope of this review to consider in detail the recommendations for OMs in these categories, especially as they do not specifically assess the upper limb. The Dutch guidelines, however, proposed a range of measures to assess factors that may impact on recovery of UL function and therefore ability to participate in everyday life (17).

Psychometric Properties and Appropriateness of OMs

The Australian Guidelines recommended that Clinicians use tools that meet the needs of the patient and are valid and reliable in the stroke population. The NZ guidelines added that while, because of the enormous variety of assessment tools and measures, they did not make specific recommendations, it was important to choose a specific tool based on the validity

(in a stroke population), reliability, and availability. Miller (34) recommended standardized, valid and reliable test procedures to document the severity of upper and lower limb impairment and to document the levels of assistance needed for mobility. Alexander (78) emphasized the importance of using measures that were valid, reliable and sensitive in the SCI population and concluded that further work was needed on existing measures to identify the most appropriate tools for specific targets. Finlay (21) directed the reader to The Rehabilitation Measures Databases[2] both of which provide information on a wide range of useful assessments and OMs. These are excellent repositories of measures, providing information on conditions where they might be used, availability, time taken to complete the tests, training required to conduct them and links to references, some of which include data on psychometric properties. They do not, however, make recommendations *per se*.

Self-Efficacy and Goal Orientated Measures—Assessment Integrated Into Therapy

The RCP (16) recommended that people with stroke should be helped to identify goals with specific, time-bound and measurable outcomes, but does not recommend specific measurement tools to assess whether goals have been achieved. There is a clear distinction between measuring what a person "can do" and what they "do do." Many of the standardized, recommended and commonly used measures of impairment and activity do not address the latter, whereas Patient Reported Outcome Measures (PROMs) and measures of self-efficacy, focus on what the patient actually does (or reports doing) in their day-to-day life. In relation to this, Ataxia UK (24), stated that OMs should focus on engagement and satisfaction because a tool that measures impairment does not always demonstrate effectiveness. The Management of Stroke Rehabilitation Report (22) recommended both a self-report measure (e.g., the Motor Activity Log) and an objective measure (e.g., accelerometry) to assess daily use of the affected upper limb and also as a motivational or self-management tool for participants taking part in clinical trials (72). Despite these recommendations, the review of OMs used in (neurorehabilitation) limb splinting evaluation studies, conducted by the Royal College of Occupational Therapy (RCOT) and Association of Physiotherapists in Neurology (ACPIN), found that patient satisfaction was the least common OM used (82).

Risk of Bias

Data sources were predominantly English language, which may have biased the main findings. However, in mitigation, as authors, who were members of the COST Action, covered several languages we were able to search for (and include) National Stroke Guidelines in a range of languages. Differences in health care systems worldwide may also have been a source of bias reflected in the recommendations made in the primary publications.

[2]http://www.rehabmeasures.org/default.aspx and http://www.neuropt.org/professional-resources/neurology-section-outcome-measures-recommendations

Finally, the quality of identified guidelines was not evaluated with a standard tool such as AGREE II (Appraisal of Guidelines for REsearch and Evaluation). AGREE generates summary scores, in which all items and domains have equal weight. This tool is useful in judging the quality of the Guidelines and was used in Jolliffe et al.'s recent systematic review of Clinical Guidelines for Stroke and other Acquired Brain Injuries (86). However, their aim was to identify high quality guidelines, whereas ours was more specific; to "identify what recommendations are made for upper limb assessment." Instead we therefore used descriptive analysis to identify evidence-based consensus on upper limb assessment across multiple pathologies to generate an in-depth knowledge of the quality and content of each guideline.

DISCUSSION

Summary of Main Findings

Our review of National Guidelines and published articles on recommendations for OMs in UL rehabilitation following Stroke, MS, SCI, and other neurological conditions has identified some areas in which there is a clear consensus. For example, that assessment is important in neurological rehabilitation, should encompass all domains of ICF Framework and that, with one exception, multiple OMs should be used. Where recommendations included protocols for use of OMs, there was no disagreement to the following: they should be applied by HCPs who are trained to use them and at regular intervals during the rehabilitation pathway. Although intervals vary, global measures are recommended within 24 h of admission and UL specific measures within 1 week. All published articles and Guidelines recommend early assessment and assessment prior to discharge, while many recommend far more frequent assessments. The importance of linking assessment to goal-setting (24, 57, 61), the use of measures to encourage and motivate patients (24) as well as the importance of patient reported outcome measures (PROMS) (22) was evident. These recommendations reflected recognition of the importance of self-efficacy and independence and PROMS to assess what a patient actually does rather than can do is important. What we found lacking was recommendation to use specific outcome measures for which validity and reliability have been demonstrated. There was also lack of consensus on which measures should be used; although there was more agreement about global measures of participation and ADL than UL specific measures of impairment and activity limitation. The FIM for example is recommended in six reviews.

There was very little agreement across the Guidelines about what outcome measures should be used, even within pathologies and the categories of the ICF (**Table 3**). Even regarding the condition for which the majority of OM recommendations were made (76%), stroke, guidelines fail to agree on a specific set of OMs to be used. The most frequently recommended OMs in stroke guidelines were three global stroke OMs (NIHSS, FIM, Barthel Index) and only 1 specific upper limb OM (FMA). Two of those regarded OMs on Activity level (global), NIHSS, and FIM, between which no consensus was apparent either.

TABLE 3 | Frequency with which different outcome measures were recommended in total and for each pathology included in the review.

Domain	Outcome measures	Total number of records/References	Number of records per pathology				
			Stroke	MS	SCI	TBI	Other
Impairment	Fugl-Mayer Assessment (FMA)	3 (14, 17, 18)	3	0	0	0	0
	Modified Ashworth Scale (MAS)	2 (17, 21)	1	0	1	0	0
	Muscle power (Myotome chart and Oxford grading)	1 (21)	0	0	1	0	0
	Passive Range of motion	2 (21, 22)	1	0	1	0	0
	Electro-goniometer (range of motion)	1 (14)	1	0	0	0	0
	Grip strength (e.g. Jamar dynamometer)	1 (14)	1	0	0	0	0
	Co-ordination and selective muscle activity	1 (22)	1	0	0	0	0
	Grasp and release test	1 (78)	0	0	1	0	0
	Box and Block test (BBT)	1 (14)	1	0	0	0	0
	Nine-hole-peg-test (9HPT)	2 (17, 18)	2	0	0	0	0
	Motricity Index (MI)	1 (17)	1	0	0	0	0
Impairment (Sensation and Pain)	Visual Analog Scale (VAS)	1 (15)	1	0	0	0	0
	Light touch	1 (21)	0	0	1	0	0
	von-Frey filaments	1 (14)	1	0	0	0	0
	Proprioception	1 (21)	0	0	1	0	0
Activity (UL)	Wolf Motor Function Test (WMFT)	1 (18)	1	0	0	0	0
	Assessment of Motor Processes and Skills (AMPS)	1 (24)	0	0	0	0	1
	Arm Activity Measure	1 (15)	0	0	0	0	1
	Action Research Arm Test (ARAT)	3 (15, 17, 18)	2	0	0	0	1
	Chedoke McMaster	1 (18)	1	0	0	0	0
	Computerized questionnaire	1 (14)	1	0	0	0	0
	Frenchay Arm test (FAT)	1 (17)	1	0	0	0	0
Activity (Global)	National Institute of Health Stroke Scale (NIHSS)	5 (17, 22, 25, 27, 28)	5	0	0	0	0
	Canadian Occupational Performance Measure (COPM)	1 (62)	1	0	0	1	0
	Goal Attainment Scale (GAS)	2 (24, 25)	1	0	0	0	1
	Functional Independence Measure (FIM)	5 (18, 22, 25–27)	4	0	0	1	0
	Multiple Sclerosis Functional Composite (MSFC)	1 (73)	0	1	0	0	0
	Motor Activity Log (MAL)	1 (22)	1	0	0	0	0
	Berg Balance Scale (BBS)	1 (27)	1	0	0	0	0
Participation and QoL	Barthel Index (BI)	4 (17, 26–28)	3	0	0	1	0
	Personal Activities of Daily Living (PADL)	1 (21)	0	0	0	1	0
	Nottingham Extended ADL	1 (17)	1	0	0	0	0
	Stroke Specific Quality of Life Scale (SSQoL)	1 (17)	1	0	0	0	0
	Total = 52		39	1	3	5	4

Without an internationally agreed core set of outcome measures that satisfy the requirements identified in this review, progress in neurorehabilitation will remain hampered and data will be wasted. From the research perspective, it is well-known that clinical trials of conventional and novel interventions are expensive, often return equivocal results and frequently fail to recruit adequate samples of patients. An important way that we can advance the field of neurorehabilitation, gain a better understanding of the recovery processes and disease progression and understand what works, with whom, when and in what dose is through meta-analysis of multiple trials, audits and longitudinal studies. Meta-analysis can only be done effectively if common outcome measures have been applied. Lack of meta-analyses impacts not only research into effectiveness of existing and novel therapies but also in delivering best practice.

National strategies and frameworks continue to emphasize the need for informed decision making in healthcare that are

research led and evidence-based, yet the UK, Australian and US National Clinical Guidelines for Stroke indicate that there is limited research to assess efficacy of rehabilitation technologies, either individually or in combination (14, 16, 31).

Limitations

This systematic review has explored "National Guidelines," or "practice guidelines," and "recommendations" published in peer-reviewed journals, focusing on assessment of the UL. We did not generate quantitative data, conduct a statistical analysis or use a standardized tool to assess the quality of the publications (see section on risk Bias above). We included all guidelines that satisfied our criteria and have not provided critical analysis of the quality of each publication.

CONCLUSION

Clinical practice guidelines provide very little specific guidance on assessment of the UL, even within ICF domains and/or pathology-specific recommendations. Agreement on a core set of OMs is not achieved by systematic reviews of guidelines such as this, predominantly due to a lack of explicit OM recommendations in most of the identified guides. Nevertheless, our extensive and rigorous review has provided a comprehensive summary of current recommendations, and therefore arguably current use of OMs. Defining a core set of measures and agreed protocols requires international consensus between experts representing the diverse and multi-disciplinary field of neurorehabilitation. The group should include representation from research and clinical practitioners as well as rehabilitation technology researchers and commercial developers, so that recommendations are made cognoscente of the future potential for technology in assessment and neurorehabilitation. If such a consensus was achieved, a standardized approach to assessment would make research findings more meaningful and provide a benchmark for quality in clinical practice and potentially improved standards and more cost-effective neurorehabilitation. Our review has identified agreement that assessment is critical and should encompass body function and structure, activity and participation and that there is a need for standardized measures.

AUTHOR CONTRIBUTIONS

JanB led the project and was the main author of the manuscript. All authors contributed to conception, protocol, and design of study and to acquisition of data. Critical revision of the report for important intellectual content. JanB and AH conducted the initial literature search and LM conducted an updated search. JanB, AH, and LM screened records with input from all other authors where needed.

FUNDING

This work was supported by the European Cooperation in Science and Technology (COST) TD 1006.

ACKNOWLEDGMENTS

This review formed part of the COST Action TD 1006 A European Network on Robotics for Neurorehabilitation. It was an interdisciplinary EU-funded research network concentrating on the coordination of European research in the area of rehabilitation robotics.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation.* (2016) 133:e38–360. doi: 10.1161/CIR.0000000000000350
2. Houwink A, Nijland RH, Geurts AC, Kwakkel G. Functional recovery of the paretic upper limb after stroke: who regains hand capacity? *Arch Phys Med Rehabil.* (2013) 94:839–44. doi: 10.1016/j.apmr.2012.11.031
3. Mayo NE, Wood-Dauphinee S, Côté R, Durcan L, Carlton J. Activity, participation, and quality of life 6 months poststroke. *Arch Phys Med Rehabil.* (2002) 83:1035–42. doi: 10.1053/apmr.2002.33984
4. Morris JH, van Wijck F, Joice S, Donaghy M. Predicting health related quality of life 6 months after stroke: the role of anxiety and upper limb dysfunction. *Disabil Rehabil.* (2013) 35:291–9. doi: 10.3109/09638288.2012.691942
5. Sprigg N, Selby J, Fox L, Berge E, Whynes D, Bath PM, et al. Very low quality of life after acute stroke: data from the Efficacy of Nitric Oxide in Stroke trial. *Stroke.* (2013) 44:3458–62. doi: 10.1161/STROKEAHA.113.002201
6. Nichols M, Townsend N, Luengo-Fernandex P, Leal J, Gray A, Scarborough P, et al. European Cardiovascular Disease Statistics 2012. In: EUROPEAN HEART Network ESOC and Antipolis S, editors. *European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis*. Brussels (2012).
7. Pugliatti M, Rosati G, Carton H, Riise T, Drulovic J, Vécsei L, et al. The epidemiology of multiple sclerosis in Europe. *Eur J Neurol.* (2006) 13:700–22. doi: 10.1111/j.1468-1331.2006.01342.x
8. Kister I, Bacon TE, Chamot E, Salter AR, Cutter GR, Kalina JT, et al. Natural history of multiple sclerosis symptoms. *Int J MS Care.* (2013) 15:146–56. doi: 10.7224/1537-2073.2012-053
9. Bertoni R, Lamers I, Chen CC, Feys P, Cattaneo D. Unilateral and bilateral upper limb dysfunction at body functions, activity and participation levels in people with multiple sclerosis. *Mult Scler J.* (2015) 21:1566–74. doi: 10.1177/1352458514567553
10. Tagliaferri F, Compagnone C, Korsic M, Servadei F, Kraus, JJAN. A systematic review of brain injury epidemiology in Europe. *Acta Neurochir.* (2006) 148:255–68. doi: 10.1007/s00701-005-0651-y
11. Zaloshnja E, Miller T, Langlois JA, Selassie AW. Prevalence of long-term disability from traumatic brain injury in the civilian population of the United States, (2005). *J Head Trauma Rehabil.* (2008) 23:394–400. doi: 10.1097/01.HTR.0000341435.52004.ac
12. Hughes A-M, Bouças SB, Burridge JH, Alt Murphy M, Buurke J, Feys P, et al. Evaluation of upper extremity neurorehabilitation using technology: a European Delphi consensus study within the EU COST Action Network on Robotics for Neurorehabilitation. *J Neuroeng Rehabil.* (2016) 13:86. doi: 10.1186/s12984-016-0192-z
13. Alt Murphy M, Resteghini C, Feys P, Lamers I. An overview of systematic reviews on upper extremity outcome measures after stroke. *BMC Neurol.* (2015) 15:29. doi: 10.1186/s12883-015-0292-6
14. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, et al. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke.* (2016) 47:e98–169. doi: 10.1161/STR.0000000000000098

15. RCOT. *Splinting for the Prevention and Correction of Contractures in Adults With Neurological Dysfunction: Practice Guideline for Occupational Therapists and Physiotherapists*. Royal College of Occupational Therapists (RCOT) (2015).
16. Royal College of Physicians. *National Clinical Guideline for Stroke*. 5th ed. Royal College of Physicians (RCP) (2016).
17. Veerbeek JM, van Wegen EEH, van Peppen RPS, Hendriks HJM, Rietberg MB, van der Wees, J, et al. *KNGF Clinical Practice Guideline for Physical Therapy in Patients With Stroke*. Royal Dutch Society for Physical Therapy (2014).
18. Teasell R, Cotoi A, Chow J, Wiener J, Iliescu A, Hussein N, et al. *Evidence-Based Review of Stroke Rehabilitation.* (2016). Available online at: http://www.ebrsr.com (accessed May 20, 2019).
19. World Health Organisation. *International Classification of Functioning, Disability and Health (ICF).* (2001). Available online at: http://www.who.int/classifications/icf/en/ (accessed March 23, 2013).
20. World Health Organisation. *How to Use the ICF: A Practical Manual for Using the International Classification of Functioning, Disability and Health (ICF).* Exposure draft for comment (2013).
21. Finlay P and Evans N. *Guidelines for the Rehabilitation of Patients With Metastatic Spinal Cord Compression (MSCC)*. Assessment and care provision by occupational therapists and physiotherapists in the acute sector. Guidelines and Audit Implementation Network (GAIN) (2014).
22. VA/DOD. Management of Stroke Rehabilitation Working Group. Clinical practice guideline for the management of stroke rehabilitation. *J Rehabil Res Dev.* (2010) 47:1–43.
23. Wechsler LR, Demaerschalk BM, Schwamm LH, Adeoye OM, Audebert HJ, Fanale CV, et al. Telemedicine quality and outcomes in stroke: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2017) 48:e3–25. doi: 10.1161/STR.0000000000000114
24. Bates C, Baxter P, Bonney H, Bremner F, Bunn L, Carrillo Perez-Tome M, et al. *Management of the Ataxias: Towards Best Clinical Practice*. University of Plymouth PEARL (2016). Available online at: https://pearl.plymouth.ac.uk. Faculty of Health and Human Sciences School of Health Professions 2016-07-31 Management of the ataxias towards best clinical practice Bates; http://hdl.handle.net/10026.1/10486.
25. Majersik JJ, Cole JW, Golledge J, Rost NS, Chan YF, Gurol ME, et al. Recommendations from the international stroke genetics consortium, part 1: standardized phenotypic data collection. *Stroke.* (2015) 46:279–84. doi: 10.1161/STROKEAHA.114.006839
26. SIGN. *Guideline 130 Brain Injury Rehabilitation in Adults - Full Guideline* (2013).
27. Pürg K, Lukmann A, Tammik T. *Insuldi Taastusravi Eesti Ravijuhend*. Eesti Taastusraviarstide Selts (2011).
28. NICE. *Stroke Rehabilitation in Adults - NICE Guideline* (2013).
29. NICE, NIFHACCE. *Stroke Rehabilitation in Adults.* (2013). Available online at: https://www.nice.org.uk/guidance/cg162
30. RCP. *National Clinical Guideline for Stroke*. 5th ed. Royal College of Physicians (RCP) (2016).
31. Stroke Foundation. *National Clinical Guidelines for Stroke Management* (2017).
32. NICE. *Multiple Sclerosis in Adults: Management* (2014).
33. Bryer A, Connor MD, Haug P, Cheyip B, Staub H, Tipping B, et al. The South African guideline for the management of ischemic stroke and transient ischemic attack: recommendations for a resource-constrained health care setting. *Int J Stroke.* (2011) 6:349–54. doi: 10.1111/j.1747-4949.2011.00629.x
34. Miller EL, Murray L, Richards L, Zorowitz RD, Bakas T, Clark P, et al. Comprehensive overview of nursing and interdisciplinary rehabilitation care of the stroke patient: a scientific statement from the American Heart Association. *Stroke.* (2010) 41:2402–48. doi: 10.1161/STR.0b013e3181e7512b
35. Hachinski V, Donnan GA, Gorelick PB, Hacke W, Cramer SC, Kaste M, et al. Stroke: working toward a prioritized world agenda. *Int J Stroke.* (2010) 5:238–56. doi: 10.1111/j.1747-4949.2010.00442.x
36. Bayley M, Teasell R, Marshall S, Cullen N, Colantonio A, Kua A. *ABIKUS Evidence Based Recommendations for Rehabilitation of Moderate to Severe Acquired Brain Injury*. Toronto, ON: Ontario Neurotrauma Foundation (2007).
37. Hebert D, Lindsay MP, Mcintyre A, Kirton A, Rumney PG, Bagg S, et al. Canadian stroke best practice recommendations: stroke rehabilitation practice guidelines, update 2015. *Int J Stroke.* (2016) 11:459–84. doi: 10.1177/1747493016643553
38. Boddice G, Brauer S, Gustafsson L, Kenardy J, Hoffmann T. *Clinical Guidelines for Stroke Management 2010* (2010).
39. Bohannon RW, Peolsson A, Massy-Westropp N, Desrosiers, J, Bear-Lehman JJP. Reference values for adult grip strength measured with a Jamar dynamometer: a descriptive meta-analysis. *Physiotherapy*. (2006) 92:11–5. doi: 10.1016/j.physio.2005.05.003
40. Shiratsu, A, andCoury, H. J. C. B. (2003). Reliability and accuracy of different sensors of a flexible *electrogoniometer*. 18:682–684. doi: 10.1016/S0268-0033(03)00110-4
41. Fruhstorfer H, Gross W, Selbmann O. von Frey hairs: new materials for a new design. *Eur J Pain.* (2001) 5:341–342. doi: 10.1053/eujp.2001.0250
42. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The poststroke hemiplegic patient: a method for evaluation of physical performance. *Scand J Rehabil Med.* (1975) 7:13–31.
43. Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the Box and Block test of manual dexterity. *Am J Occup Ther*. (1985) 39:386–91. doi: 10.5014/ajot.39.6.386
44. Demeurisse G, Demol O, Robaye E. Motor evaluation in vascular hemiplegia. Eur *Neurol*. (1980) 19:382–9. doi: 10.1159/000115178
45. Heller A, Wade DT, Wood VA, Sunderland A, Hewer RL, Ward E. Arm function after stroke: measurement and recovery over the first three months. *J Neurol Neurosurg Psychiatry.* (1987) 50:714–719. doi: 10.1136/jnnp.50.6.714
46. Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. *Int J Rehabil Res.* (1981) 4:483–92. doi: 10.1097/00004356-198112000-00001
47. Carr JH, Shepherd RB, Nordholm L, Lynne D. Investigation of a new motor assessment scale for stroke patients. *Phys Ther*. (1985) 65:175–80. doi: 10.1093/ptj/65.2.175
48. Nouri F, Lincoln N. An extended activities of daily living scale for stroke patients. *Clin Rehabil.* (1987) 1:301–5. doi: 10.1177/026921558700100409
49. Williams LS, Weinberger M, Harris LE, Clark DO, Biller J. Development of a stroke-specific quality of life scale. *Stroke.* (1999) 30:1362–9. doi: 10.1161/01.STR.30.7.1362
50. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index: a simple index of independence useful in scoring improvement in the rehabilitation of the chronically ill (1965). doi: 10.1037/t02366-000
51. Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke.*(1989) 20:864–70. doi: 10.1161/01.STR.20.7.864
52. Law M, Baptiste S, Mccoll M, Opzoomer A, Polatajko, H, Pollock, N. The Canadian occupational performance measure: an outcome measure for occupational therapy. *Can J Occup Ther*. (1990) 57:82–7. doi: 10.1177/000841749005700207
53. Keith R, Granger CV, Hamilton BB, Sherwin FS. The functional independence measure: a new tool for rehabilitation. *Adv Clin Rehabil.* (1987) 2:6–18.
54. NSCISB. *The Initial Management of Adults With Spinal Cord Injuries*. The National Spinal Cord Injury Strategy Board (2012).
55. Swedish_National_Board_of_Health_and_Welfare. *Quality and Efficiency of Stroke Care in Sweden* (2011).
56. Venketasubramanian N, Pwee KH, Chen CP. Singapore ministry of health clinical practice guidelines on stroke and transient ischemic attacks. *Int J Stroke.* (2011) 6:251–8. doi: 10.1111/j.1747-4949.2011.00602.x
57. SIGN. *Guideline 118: Management of Patients With Stroke: Rehabilitation, Prevention and Management of Complications, and Discharge Planning - Quick Reference Guide*. Scottish Intercollegiate Guidelines Network – SIGN (2011).
58. Pandyan AD, Johnson GR, Price CI, Curless R, Barnes, MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clin Rehabil.* (1999) 13:373–83. doi: 10.1191/026921599677595404
59. Berg K, Wood-Dauphine S, Williams, J, Gayton D. Measuring balance in the elderly: preliminary development of an instrument. *Physiother Can.* (1989) 41:304–11. doi: 10.3138/ptc.41.6.304
60. NZ. *New Zealand Clinical guidelines for Stroke Management*. Wellington (2010).

61. SIGN. *Guideline 108: Management of Patients With Stroke or TIA: Assessment, Investigation, Immediate Management and Secondary Prevention - Full Guideline* (2017).
62. SIGN. *Guideline 130 Brain Injury Rehabilitation in Adults*. National Clinical Guideline (2013).
63. Gall, A Turner-Stokes L. *Chronic Spinal Cord Injury: Management of Patients in Acute Hospital Settings*. Royal College of Physicians (2008). doi: 10.7861/clinmedicine.8-1-70
64. Schwamm LH, Audebert HJ, Amarenco P, Chumbler NR, Frankel MR, George MG, et al. Recommendations for the implementation of telemedicine within stroke systems of care. *Stroke.* (2009) 40:2635–60. doi: 10.1161/STROKEAHA.109.192361
65. Park S, Fisher AG, Velozo CA. Using the assessment of motor and process skills to compare occupational performance between clinic and home settings. *Am J Occup Ther.* (1994) 48:697–709. doi: 10.5014/ajot.48.8.697
66. Kiresuk TJ Sherman RE. Goal attainment scaling: a general method for evaluating comprehensive community mental health programs. *Community Ment Health J.* (1968) 4:443–53. doi: 10.1007/BF01530764
67. Wolf TJ, Chuh A, Floyd T, Mcinnis, K, Williams E. Effectiveness of occupation-based interventions to improve areas of occupation and social participation after stroke: An evidence-based review. *Am J Occup Ther.* (2015) 69:6901180060p1–11. doi: 10.5014/ajot.2015.012195
68. Haselkorn JK, Hughes C, Rae-Grant A, Henson LJ, Bever CT, LO AC, et al. Summary of comprehensive systematic review: rehabilitation in multiple sclerosis Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology.* (2015) 85:1896–903. doi: 10.1212/WNL.0000000000002146
69. Ashford S, Turner-Stokes L, Siegert R, Slade M. Initial psychometric evaluation of the Arm Activity Measure (ArmA): a measure of activity in the hemiparetic arm. *Clin Rehabil.* (2013) 27:728–40. doi: 10.1177/0269215512474942
70. Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. *Ann Rheum Dis.* (1978) 37:378–81. doi: 10.1136/ard.37.4.378
71. Potter K, Cohen ET, Allen DD, Bennett SE, Brandfass KG, Widener GL, et al. Outcome measures for individuals with multiple sclerosis: recommendations from the American Physical Therapy Association Neurology Section task force. *Phys Ther.* (2014) 94:593–608. doi: 10.2522/ptj.20130149
72. Billinger SA, Arena R, Bernhardt J, Eng JJ, Franklin BA, Johnson CM, et al. Physical activity and exercise recommendations for stroke survivors. *Stroke.* (2014) 45:2532–53. doi: 10.1161/STR.0000000000000022
73. Ontaneda D, Larocca N, Coetzee T, Rudick R. Revisiting the multiple sclerosis functional composite: proceedings from the National Multiple Sclerosis Society (NMSS) Task Force on Clinical Disability Measures. *Mult Scler.* (2012) 18:1074–80. doi: 10.1177/1352458512451512
74. Carr J, Shepherd R. *A Motor Relearning Program for Stroke.* Oxford, Butterworth-Heinemann (1987).
75. Gowland C, Stratford P, Ward M, Moreland J, Torresin W, van Hullenaar S, et al. Measuring physical impairment and disability with the Chedoke-McMaster Stroke Assessment. *Stroke.* (1993) 24:58–63. doi: 10.1161/01.STR.24.1.58
76. Mathiowetz V, Weber K, Kashman N, Vollard G. Adult norms for the Nine-Hole Peg Test of finger dexterity. *Occup Ther J Res.* (1985) 5:24–38. doi: 10.1177/153944928500500102
77. Wolf SL, Catline PA, Ellis M, Archer AL, Morgan B, Piacentino A. Assessing Wolf Motor Function Test as outcome measure for research in patients after stroke. *Stroke.* (2001) 32:1635–9. doi: 10.1161/01.STR.32.7.1635
78. Alexander MS, Anderson K, Biering-Sorensen F, BLIGHT AR, Brannon R, Bryce T, et al. Outcome measures in spinal cord injury: recent assessments and recommendations for future directions. *Spinal Cord.* (2009) 47:582–91. doi: 10.1038/sc.2009.18
79. Mulcahey M, Hutchinson D, Kozin S. (Assessment of upper limb in tetraplegia: considerations in evaluation and outcomes research. *J Rehabil Res Dev.* 2007) 44:91. doi: 10.1682/JRRD.2005.10.0167
80. Steeves J, Lammertse D, Curt A, Fawcett J, Tuszynski M, Ditunno J, et al. Guidelines for the conduct of clinical trials for spinal cord injury (SCI) as developed by the ICCP panel: clinical trial outcome measures. *Spinal Cord.* (2007) 45:206–21. doi: 10.1038/sj.sc.3102008
81. EINSTEIN. Available online at: https://quoteinvestigator.com/2010/05/26/everything-counts-einstein/ (accessed May 20, 2019).
82. College of Occupational Therapists AND Association of Chartered Physiotherapists in Neurology C. *Splinting for the Prevention and Correction of Contractures in Adults With Neurological Dysfunction: Practice Guideline for Occupational Therapists and Physiotherapists*. Royal College of Occupational Therapists (2015).
83. Lamers I, Kelchtermans S, Baert I, Feys P. Upper limb assessment in multiple sclerosis: a systematic review of outcome measures and their psychometric properties. *Arch Phys Med Rehabil.* (2014) 95:1184–200. doi: 10.1016/j.apmr.2014.02.023
84. Lamers I, Feys P. Assessing upper limb function in multiple sclerosis. *Mult Scler J.* (2014) 20:775–84. doi: 10.1177/1352458514525677
85. Royal College of Occupational Therapists R. *Occupational Therapy for People With Parkinson's: Best Practice Guidelines*. Royal College of Occupational Therapists (2010).
86. Jolliffe L, Lannin NA, Cadilhac DA, Hoffmann T. Systematic review of clinical practice guidelines to identify recommendations for rehabilitation after stroke and other acquired brain injuries. *BMJ Open.* (2018) 8:e018791. doi: 10.1136/bmjopen-2017-018791

Conflict of Interest Statement: TK was employed by Fundation Tecnalia Research and Innovation.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 15 November 2019
doi: 10.3389/fneur.2019.01187

Aerobic Training and Mobilization Early Post-stroke: Cautions and Considerations

Susan Marzolini[1,2,3]*, *Andrew D. Robertson*[4,5], *Paul Oh*[1,2,3], *Jack M. Goodman*[1,2], *Dale Corbett*[3,6], *Xiaowei Du*[1,7] and *Bradley J. MacIntosh*[3,8]

[1] KITE, Toronto Rehab-University Health Network, Toronto, ON, Canada, [2] Department of Exercise Sciences, Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, ON, Canada, [3] Canadian Partnership for Stroke Recovery, Toronto, ON, Canada, [4] Schlegel-University of Waterloo Research Institute for Aging, University of Waterloo, Waterloo, ON, Canada, [5] Department of Kinesiology, University of Waterloo, Waterloo, ON, Canada, [6] Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, ON, Canada, [7] School of Kinesiology and Health Studies, Queen's University, Kingston, ON, Canada, [8] Sunnybrook Health Sciences Center, Toronto, ON, Canada

Knowledge gaps exist in how we implement aerobic exercise programs during the early phases post-stroke. Therefore, the objective of this review was to provide evidence-based guidelines for pre-participation screening, mobilization, and aerobic exercise training in the hyper-acute and acute phases post-stroke. In reviewing the literature to determine safe timelines of when to initiate exercise and mobilization we considered the following factors: arterial blood pressure dysregulation, cardiac complications, blood-brain barrier disruption, hemorrhagic stroke transformation, and ischemic penumbra viability. These stroke-related impairments could intensify with inappropriate mobilization/aerobic exercise, hence we deemed the integrity of cerebral autoregulation to be an essential physiological consideration to protect the brain when progressing exercise intensity. Pre-participation screening criteria are proposed and countermeasures to protect the brain from potentially adverse circulatory effects before, during, and following mobilization/exercise sessions are introduced. For example, prolonged periods of standing and static postures before and after mobilization/aerobic exercise may elicit blood pooling and/or trigger coagulation cascades and/or cerebral hypoperfusion. Countermeasures such as avoiding prolonged standing or incorporating periodic lower limb movement to activate the venous muscle pump could counteract blood pooling after an exercise session, minimize activation of the coagulation cascade, and mitigate potential cerebral hypoperfusion. We discuss patient safety in light of the complex nature of stroke presentations (i.e., type, severity, and etiology), medical history, comorbidities such as diabetes, cardiac manifestations, medications, and complications such as anemia and dehydration. The guidelines are easily incorporated into the care model, are low-risk, and use minimal resources. These and other strategies represent opportunities for improving the safety of the activity regimen offered to those in the early phases post-stroke. The timeline for initiating and progressing exercise/mobilization parameters are contingent on recovery stages both

OPEN ACCESS

Edited by:
Alessandro Picelli,
University of Verona, Italy

Reviewed by:
Massimo Venturelli,
University of Verona, Italy
Niamh C. Kennedy,
Ulster University, United Kingdom

***Correspondence:**
Susan Marzolini
susan.marzolini@uhn.ca

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *11 August 2019*
Accepted: *25 October 2019*
Published: *15 November 2019*

Citation:
Marzolini S, Robertson AD, Oh P, Goodman JM, Corbett D, Du X and MacIntosh BJ (2019) Aerobic Training and Mobilization Early Post-stroke: Cautions and Considerations. Front. Neurol. 10:1187. doi: 10.3389/fneur.2019.01187

from neurobiological and cardiovascular perspectives, which to this point have not been specifically considered in practice. This review includes tailored exercise and mobilization prescription strategies and precautions that are not resource intensive and prioritize safety in stroke recovery.

Keywords: exercise, rehabilitation, mobilization, stroke, recovery

INTRODUCTION

Approximately 13.7 million strokes occur worldwide every year–almost 38,000 per day (1). About one third of strokes are fatal, and another third leave survivors with permanent disability. Animal studies show favorable effects of early aerobic exercise interventions, which take advantage of the optimal time window for neural repair (2). However, little is known about the efficacy and safety of mobilization and aerobic exercise for augmenting or prolonging neural repair in the hyper-acute (0–24 h) and acute phases (1–7 days) post-stroke in humans [see **Table 1** for definitions of phases post-stroke (3)]. While initiating exercise earlier in recovery may be beneficial, there is little evidence to justify the safety of early interventions with respect to neurobiological changes that could impact stroke volume, cell death, inflammation, or oxidative stress. Indeed, considerable preclinical evidence indicates it is not safe in the hyper-acute phase (4–7). Yet in clinical practice, patients are being mobilized within 12 h of admission, and aerobic training is being prescribed during in-patient rehabilitation (8–13) despite there being no guidelines for the safe prescription of intensity, duration, progression, and modality parameters during this time period (14).

Mobilization

Most contemporary stroke care guidelines and position papers advocate against "high-dose" or "intensive" out-of-bed activities within 24 h of stroke onset (15–19). The A Very Early Rehabilitation Trial (AVERT) played a key role as the results demonstrate a neutral or potentially negative effect of mobilization initiated within the first 24 h (20). Unfortunately, specific recommendations over and above the timing of the intervention are not provided in any set of guidelines. United Kingdom (UK) guidelines advise that mobilization within 24 h of onset should only be for patients who require little to no assistance (17). The guidelines further suggest that those with difficulty moving early after stroke, but who are medically stable, should be offered frequent, short daily mobilizations (sitting out of bed, standing, or walking), typically beginning between 24 and 48 h of stroke onset. Canadian guidelines advocate that frequent, out-of-bed activity within 24 h of stroke onset is not recommended, but that mobilization may be reasonable for some patients (18). Similarly, the National Institute for Health and Care Excellence guidelines recommend that, based in part on the committee's clinical experience, people who do not need help to sit out of bed, stand or walk, should be mobilized (sit, stand, or walk) in the first 24 h after symptom onset as the clinical condition permits, otherwise citing evidence suggesting that initiating high-intensity mobilization should not be offered in this time frame (21). Neither the UK nor Canadian guidelines defines what constitutes "high-dose," "intensive," or "frequent" mobilization. In addition, details on pre-participation health screening, contraindications to mobilization, and safe progression are minimal or absent. These recommendations have not considered the temporal biological changes occurring in the brain during recovery or how types of mobilization such as sitting, standing, and walking can affect these processes.

TABLE 1 | Timeframes for phase of stroke.

Phase of stroke	Elapsed time from stroke onset	
Hyper-acute	0–24 h	Early Phases of Stroke
Acute	1–7 days	
Early subacute	7 days−3 months	
Late subacute	3–6 months	
Chronic	>6 months	

Time frames have been adapted from Bernhardt et al. (3).

Aerobic Exercise

Best practice guidelines are less clear in terms of aerobic exercise training. They indicate that given the potential benefits of aerobic exercise, little justification exists for not incorporating aerobic exercise into the care of the majority of cases once the individual is medically stable (22). They do acknowledge, however, a dearth of evidence regarding safety and effects of aerobic exercise prescribed in the acute phase post-stroke. As with mobilization, pre-participation screening criteria, cautions, considerations, and recommendations for intensity or other parameters of the exercise program in the hyper-acute and acute phases post-stroke represent gaps in knowledge.

Herein, we review the literature to advance consideration on the appropriate timing for the initiation of mobilization and aerobic exercise. We conduct a focused examination of the literature to determine the rate of recovery of arterial blood pressure (BP) dysregulation, cardiac complications, blood-brain barrier disruption, hemorrhagic stroke transformation, and ischemic penumbra viability. We contrast this to an estimate of when cerebral autoregulation (CA) is sufficiently restored so as to protect the brain from these possible disruptions that could be intensified with mobilization and aerobic exercise. We review the outcomes and methodology of studies that address the effects of mobilization and aerobic exercise in the hyper-acute and acute stages of stroke that help to inform a safety and efficacy framework. We also discuss countermeasures to protect

the brain from exposure to potentially adverse circulatory effects before, during, and following exercise/mobilization sessions. Because neurobiological and cardiovascular recovery continues beyond the acute phase in some cases, our safety related recommendations may extend to the early subacute phase of recovery (7 days to 3 months).

PERIPHERAL AND CEREBRAL CIRCULATORY CONSIDERATIONS FOR EXERCISE AND MOBILIZATION

Peripheral and cerebral circulatory changes that occur from the hyper-acute to early subacute phase post-stroke can leave the brain vulnerable to possible adverse effects of mobilization and physical activity-induced perturbations. Mobilization and aerobic exercise, depending on the intensity and type, result in rising noradrenaline and adrenaline plasma concentrations that increase systemic BP (23–25) that can be passed onto the vulnerable cerebral circulation. Within this context, awareness of the post-stroke status of CA, the blood brain barrier (BBB), and resting systemic BP regulation is critical. Hemorrhagic stroke warrants additional considerations, such as stroke progression and hematoma expansion following an intracerebral hemorrhage (ICH) and delayed ischemia and vasospasm following a subarachnoid hemorrhage (SAH). Insight into the progression and severity of these impairments can guide the timing of initiation, the intensity of activity, the level of implementation of the suggested strategies, and when the strategies can be gradually reduced or phased out.

Cerebral Autoregulation Impairment Following Stroke

The importance of CA in the early phases post-stroke is evident from studies on final infarct size and neurological outcome (26–28). The classic view of CA is a static paradigm which describes the regulation of stable cerebral blood flow (CBF) over a wide range of perfusion pressures (∼50–150 mmHg), although the nature of the CBF "plateau" and limits of BP within which CBF is regulated has recently come under scrutiny (29). In contrast, dynamic CA characterizes the cerebrovascular response to dynamic changes in blood pressure (30). Compelling evidence shows that CA can be impaired in the early phases following ischemic, intracerebral, and subarachnoid hemorrhagic strokes, and that restoration of normal CA function take up to 3 months post-stroke (26, 31–40). This implies that in the early phases post-stroke the brain may not be fully protected from fluctuations in BP that occur with mobilization or aerobic exercise. Poor CA appears to be associated with damage to the neurovascular unit and consequently threatens survival of neurons and glial cells (41, 42). While this sequelae is largely untested in humans, it is prudent to consider the clinical implications.

Ischemic Stroke and Cerebral Autoregulation

Knowledge of the temporal profile of CA recovery would help in estimating when the brain is adequately protected from BP fluctuations associated with mobilization or exercise. Collectively, studies (described in detail in the **Supplementary Materials**) suggest impaired CA at baseline with worsening in the first 1–2 weeks and recovery by ∼3 months post-ischemic stroke (see **Figure 1**). However, a limitation of the reviewed studies is the lack of measurements conducted between 1 and 3 months and thus recovery may occur earlier.

Association between cerebral autoregulation impairment and clinical outcomes

CA impairment contributes to poorer outcomes following ischemic stroke, including higher all-cause mortality and larger infarct size (26, 43). In a pooled analysis of two data sets (n = 45 ischemic stroke patients), impairment in CA around day 6 post-stroke was associated with poorer 4-month clinical outcome measured by the modified Rankin Scale (mRS) (27). In a separate study (n = 46), impaired CA very early (<6 h) post-stroke was associated with hemorrhagic transformation and cerebral edema at 24 h (28). Moreover, Castro et al. demonstrated that poorer efficacy of dynamic CA within 6 h of ischemic stroke resulted in larger infarct volumes at 24 h and poorer neurologic outcomes at 3 months measured by mRS (n = 30) (26). In fact, the odds of living independently (mRS 0–2) at 3 months were 14-fold higher when CA had recovered at 6 h post-stroke. This study was especially important as it suggests that impaired CA is not just a reflection of the severity of the stroke at baseline, but predicts adverse outcome independent of baseline National Institutes of Health Stroke Scale (NIHSS) score and age (26, 44).

Impaired cerebral autoregulation, hypotensive episodes, and the ischemic penumbra

The brain has less protection against acute episodes of hypotension than hypertension following stroke (type not specified) and brain injury (45–48). These findings are provocative and intriguing; they challenge a conventional safety concern of the hypertensive response when it comes to monitoring BP as a clinical indicator for safe exercise and mobilization. Preventing hypotensive episodes may be a greater safety concern than previously thought. Hypotension can occur after prolonged inactive standing and upon cessation of an exercise session (i.e., post-exercise hypotension). It is sensible to assume that the combination of reduced BP and poor CA can potentially foster hypoperfusion. The fate of the ischemic penumbral tissue surrounding the stroke core is one aspect of acute stroke management where low BP is a well-established hazard and for which transient hypotensive episodes could play a role. Whether the penumbral tissue succumbs to the necrotic core will depend on cerebral perfusion pressure and collateral supply (49). This potentially salvageable ischemic penumbra exists for at least 24 h post-stroke and can persist for days [for review (50–53)]. Compromised cells may recover if conditions are ideal, however hypotension, stress, and other challenges could cause their demise. While the effects of repeated hypotensive episodes related to activity (e.g., posture change, prolonged standing, post-dynamic exercise) have not been examined post-stroke, strategies to mitigate their occurrence should be considered. Precautionary guidelines are provided in **Tables 4–6**.

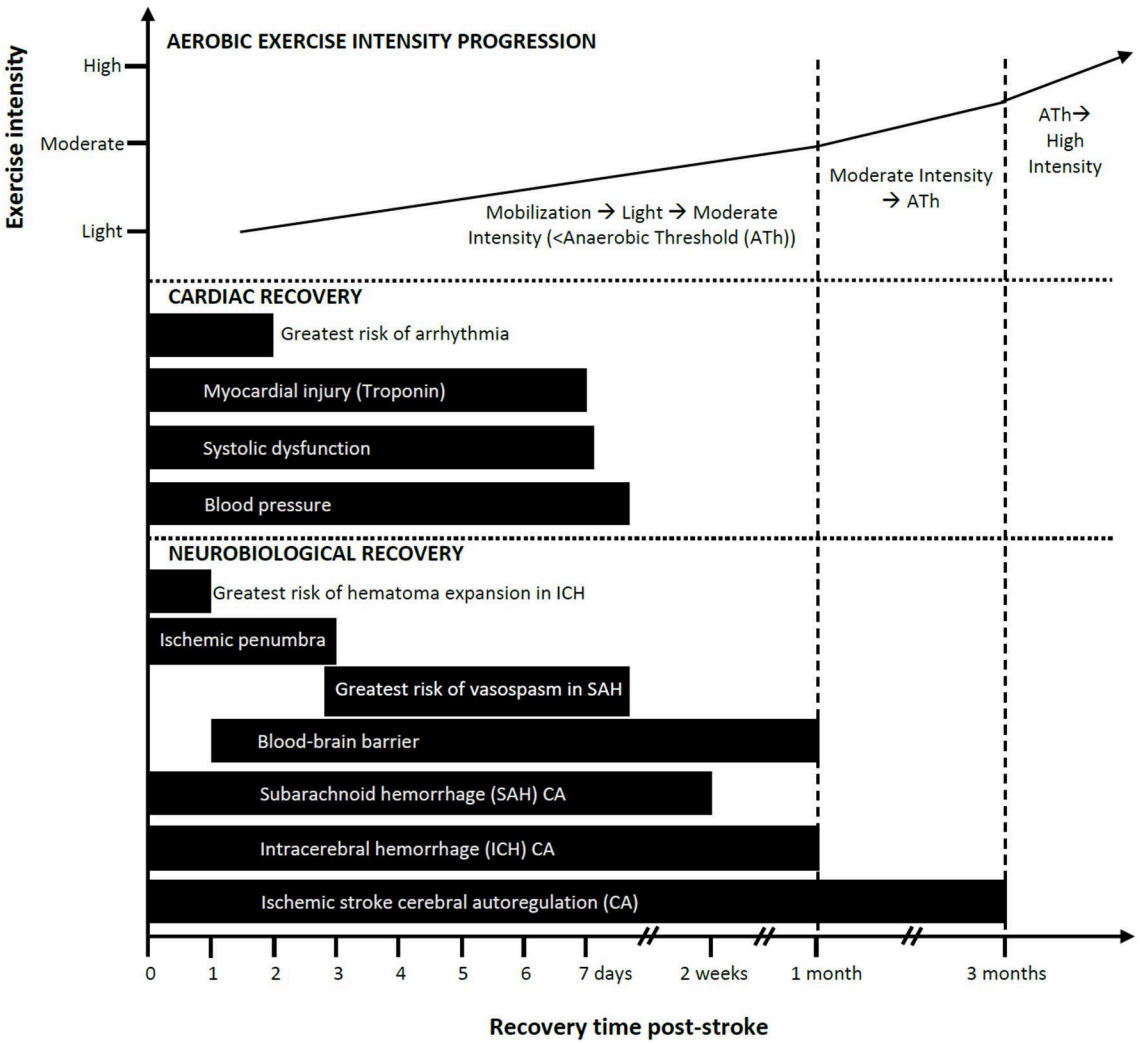


FIGURE 1 | Progression of mobilization and aerobic exercise intensity in relation to estimated neurobiological and cardiac recovery post-stroke: a conceptual model. Aerobic exercise can ideally increase in intensity as a function of elapsed time post-stroke and should be guided based on cardiopulmonary fitness measures such as the anaerobic threshold (Ath). Safe and recommended periods to introduce exercise/mobilization post-stroke are shown here as varying by cardiac and neurobiological recoveries. Impaired cerebral autoregulation after ischemic stroke is listed here as the longest time to recovery. Recovery is based on available evidence.

Intracerebral Hemorrhage and Cerebral Autoregulation

While fewer studies have assessed CA following ICH compared to ischemic stroke, the evidence suggests there is little to no CA impairment at baseline, worsening from days 3–12, and recovery by ∼1 month post-ICH (see **Figure 1**; described in detail in the **Supplementary Materials**). A limitation is that there is a dearth of measurements conducted between days 12 and 30 thus recovery could occur earlier than 1 month.

Impaired cerebral autoregulation, association with clinical outcomes, and recovery time

While ICH is not associated with a penumbra at risk for further infarction (as in ischemic stroke) (69), hematoma expansion can occur in the first 24 h (as observed in 39 of 103 patients) (70) and may be exacerbated by less intense BP management (i.e., allowing higher BP) (71). This is likely mediated by lack of cerebral protection that under normal circumstances is offered by CA. Indeed, poorer CA is documented at 3–5 days post-ICH, and is associated with poor clinical status, ventricular hemorrhage, lower cerebral perfusion pressure, and worse functional recovery at 90 days ($n = 26$) (72). In a larger study ($n = 43$), impaired CA at days 4–6 was a predictor of poorer mRS at 90 days. This association was independent of the hematoma location, ICH volume, BP, neurological status (NIHSS), age, and sex (31). Given the adverse effects of higher systemic BP on hemorrhage expansion early post-ICH when CA is impaired, elevations in BP during mobilization and/or exercise could further exacerbate hematoma expansion.

Subarachnoid Hemorrhagic Stroke and Cerebral Autoregulation

The exact time course of CA recovery following SAH is not known. The available evidence (described in detail in the **Supplementary Materials**) suggests a recovery profile that features impairment through days 1–4 that gradually deteriorates, in some cases, before recovering by days 10–14 post-stroke (see **Figure 1**).

Association between impaired cerebral autoregulation and delayed ischemia and vasospasm

Otite et al. reported that of 68 patients with SAH, 62% developed angiographic vasospasm, and 19% had delayed cerebral ischemia on days 2–4 post-hospital admission (33). CA was impaired in those who developed vasospasm and delayed ischemia compared to those who did not, and was highly predictive of these adverse conditions. Indeed, consistent evidence indicates that dynamic CA is impaired post-SAH (38–40, 73–75), which is thought to play a role in delayed cerebral ischemia (76) and infarction after SAH (77–79). Loss of cerebral protection is clinically significant as vasospasm is a leading cause of morbidity and mortality after SAH and ischemia may occur when autoregulation does not compensate. Therefore, mobilization or exercise prescriptions that result in BP fluctuations should be considered carefully during days ∼3–7 after aneurysmal SAH when there is elevated risk for delayed ischemia and vasospasm (33, 80, 81) and BP countermeasure strategies should be employed.

Blood-Brain Barrier Disruption

The BBB protects neural tissue and the microenvironment by regulating the movement of molecules between blood and brain (82). BBB disruption allows proteins, cells, and large molecules to move from the lumen space into the brain parenchyma. The infiltration and accumulation of peripheral immune cells, pro-inflammatory cytokines, and an excess of water and other potentially toxic elements into the brain leads to progression of injury, cerebral edema, and increases the risk of hemorrhage following stroke (especially following tissue plasminogen activator (tPA) or delayed tPA treatment) (83, 84).

There appears to be two phases of BBB disruption after ischemic stroke (85, 86). As early as 2 h after ischemia in primates (87), and as early as 6 h in humans (88), the BBB has increased permeability. Early reperfusion can reverse BBB changes, but if reperfusion occurs later it may exacerbate endothelial injury. The second phase of BBB injury occurs within 24–72 h post-stroke and can result in greater tissue damage in humans (86). Low level BBB dysfunction has been detected up to 1 month following ischemic stroke (spontaneous reperfusion) in humans (89). BBB dysfunction is more likely to remain elevated in people with larger infarcts in the subacute phase (86). Animal studies also indicate that BBB function can take up to 3–4 weeks to recover post-ischemia with peak dysfunction at around 7 days (90–92) (see **Figure 1**).

Intensive exercise is documented to transiently induce hyperperfusion and cerebral edema, subsequent to mechanical disruption of the BBB in healthy and obese individuals (93–95). Although these physiological effects are temporary and not known to induce structural brain damage, possible adverse effects of higher intensity exercise may be of concern for up to ∼1 month post-stroke in some patients. This is in part owing to BBB dysfunction and loss of its structural integrity occurring in people following ischemic and hemorrhagic stroke leaving the brain more vulnerable to damage (83, 86, 96).

While the effects of exercise on BBB function have not been measured in people following stroke, it is likely that CA dysfunction does not adequately counter the elevation in systemic BP during higher intensity exercise (95), thereby increasing the risk of cerebral hyperperfusion injury and BBB disruption (93). Consider also that superimposed on impaired CA and BBB dysfunction is elevated resting BP that occurs in up to 84% of stroke patients mostly in the acute phase post-stroke (97–100). This further challenges CA and BBB function to maintain homeostasis. Although there is a decrease in BP during the first 10 days following stroke, it remains elevated in about a third of cases (97–101). Thus, mobilization and aerobic exercise in the presence of elevated resting BP, impaired CA, and BBB disruption may theoretically interfere with the supply-demand relationship of cerebral oxygen delivery and ultimately contribute to deleterious hemodynamic effects.

Hydration status and environmental temperature are other factors that may exacerbate BBB dysfunction during exercise. Although there is some conflicting evidence (102), endurance exercise in a warm environment may lead to increased BBB permeability in healthy individuals (103, 104) and is likely related to dehydration and/or brain temperature. Heightened temperature in the first few days of stroke, due to mild fever or exercise, has the potential to exacerbate cell death which is still evolving at this time, contributing to poorer functional outcomes (105, 106). Thus, appropriate precautions should be practiced by ensuring the patient is hydrated before initiating activity and avoiding activity in a warm environment or during fever.

BBB disruption is generally considered detrimental post-stroke; however, in some cases increased permeability may be beneficial. For example, infiltrating macrophages post-ICH stroke may be involved in hematoma resolution (96) and certain types of leukocytes could be protective in ischemic stroke (107, 108). In addition, indirect evidence in obese and healthy populations suggests that exercise-induced BBB leakage detected may lead to acutely elevated levels of neurotrophic factors in the blood such as brain derived neurotrophic factor (BDNF) (94, 109) that would support neuronal survival and growth. However, the evidence of increased peripheral BDNF levels concomitant with evidence of BBB leakage in these exercise studies may be largely related to increased production through muscle action and restricted cerebral uptake, suggesting little to no benefit. Further studies are required to disentangle these effects.

Effect of Age, Diabetes, and Hypertension on Blood-Brain Barrier Recovery and Cerebral Autoregulation

There is a rationale for delaying moderate to higher intensity exercise in the elderly, as well as those with persistent hypertension and/or diabetes/hyperglycemia (See **Table 2** Guideline 1, **Figure 1**, and **Supplementary Materials**). CA impairment may be more problematic among stroke patients

with comorbid diabetes, as suggested from observations of impaired CA in type II diabetes studies (116, 117) and higher mortality rates in those with hyperglycemia at the time of stroke (118). In addition, the time course of recovery of BBB function can be affected by age, hypertension and/or diabetes/hyperglycemia and should be considered when screening patients for initiating mobilization and aerobic exercise (119).

Blood Pressure

Elevated resting BP is common during acute stroke, thus should be a central consideration of exercise prescription. Current guidelines state aerobic exercise is not recommended post-stroke if the person has resting systolic (SBP) and diastolic BP (DBP) $>$ 200 mmHg and $>$110 mmHg, respectively (22). These upper limits may be appropriate for people in the late subacute phase of stroke, but are less established in the early phases post-stroke given impaired CA and the effect on BBB integrity. A further activity-related elevation in BP from a resting SBP of 200 mmHg, is indeed a challenge to CA. Moreover, it may be prudent to establish a lower BP threshold, below which is a risk of hypoperfusion episodes. Until such data are available, we suggest a more conservative approach than is currently practiced. Even with more contemporary guidelines advocating for more tightly managed BP early in ischemic and ICH stroke (15, 120), it continues to be important to determine these thresholds for safe exercise. The Scandinavian Candesartan Acute Stroke Trial highlights the challenge of controlling BP. Ischemic or hemorrhagic stroke patients (n=293) with a resting SBP of at least 140 mmHg were randomized to receive either candesartan or a placebo. BP at 7 days post-stroke was similar between the treatment and placebo group, with pressure in both groups remaining elevated (147/82 mmHg (SD 23/14) in the candesartan group and 152/84 mmHg (SD 22/14) in the placebo group) (101). Other studies report a mean decrease in BP during the first 10 days following stroke, but BP tends to remain elevated in one third of cases (97–100).

Hyper-acute and acute phases post-stroke are often characterized by BP instability. Within 24 h after stroke, SBP can decrease by 28 $\pm$ 11% either spontaneously or with medication (121). Increased systolic and/or diastolic ambulatory BP variability within 7 days of ischemic stroke has been associated with increased risk of recurrent stroke and composite cardiovascular endpoints, and poorer functional outcomes within 12 months of the stroke (122–124). Therefore, along with upper and lower BP boundaries, a maximal rate of change over 24 h, or a limit of BP variability (systolic and diastolic) that indicates stability, should be an additional screening criteria to ensure safe early exercise post-stroke (see **Table 2** Guideline 1).

Monitoring BP in Advance of Aerobic Exercise and Mobilization: Screening Recommendations

While there is little evidence to support a specific BP threshold, there is a precedent for pre-activity BP screening criteria. A recent study in 708 post-ischemic stroke patients demonstrated increased odds of cognitive impairment at 3 months for patients in the lowest and highest systolic BP (SBP) quintiles within 7 days of stroke (Q1, 102–127 mmHg and Q5, 171–215 mmHg), relative to the middle quintile (Q3, 143–158 mmHg) after adjustment (55). Similarly, better outcomes were observed for patients in the middle quintile of diastolic BP (DBP) (Q3, 93–102 mmHg). This association continued for up to 6 months post-stroke. From a cardiac risk standpoint, baseline SBP $<$ 110 mmHg predisposes people post-stroke to sudden cardiac adverse events (110). Further, lower early BP (DBP $<$ 70, SBP $<$ 155 mmHg) is a predictor of death within 90 days of acute ischemic stroke compared to those in the ranges of DBP 70–105 mmHg and SBP 155–220 mmHg (43) (see **Table 2** Guideline 1).

CARDIAC CONSIDERATIONS FOR EXERCISE AND MOBILIZATION (SEE TABLE 3 GUIDELINE 2)

Cardiovascular complications are a major cause of morbidity and mortality following stroke, and thus can affect the timing and intensity of the exercise prescription, as well as provide screening criteria particularly in the hyper-acute and acute phases post-stroke. Knowledge of the prevalence, time since first

TABLE 2 | Guideline 1.0: Pre-participation screening criteria based on peripheral and cerebral circulatory considerations.

This section provides blood pressure guidelines prior to early aerobic exercise (specifically hyper-acute and acute). A list of safe indications to consider are provided here:

- Consider either very light activity (following precautions in guidelines 3.0–6.0) or delaying aerobic exercise if resting systolic blood pressure is $<$120 mmHg, or higher than 170 mmHg.
- Consider either very light activity (following precautions in guidelines 3.0–6.0) or delaying aerobic exercise if resting diastolic blood pressure is $<$80 mmHg, or higher than 105 mmHg.
- A series of 4–10 resting blood pressures performed over the course of 1–3 days should be stable. The day to day variation in SBP should be $<$30%.
- Patients that are elderly, have diabetes/hyperglycemia, and/or persistent hypertension should be considered higher risk stroke subgroups thus it is advisable to delay moderate to higher intensity exercise post-stroke (see **Figure 1**).
- Consider delaying higher intensity exercise for people with blood glucose level of $\geq$160 mg/dL ($\geq$9 mmol/L) measured within the first 48 h of stroke.
- There should be no evidence of dehydration prior to initiating activity. Warm environmental temperatures should be avoided and replacement of fluids recommended.
- Caution is warranted for those patients with the following conditions: anemia, early neurological deterioration, chest infection, and pulmonary emboli (110–115).

Patients should be screened on a case-by-case basis.

presentation, and other cardiac medical history information can guide the practitioner.

Cardiac Complications and Morbidity and Mortality

Cardiac-related complications are the second leading cause of mortality within the first month after the stroke event (125, 126). Among 444 patients with first cerebral infarct, 17% died within the first month of the stroke (50% of deaths were due to the cerebral infarct, 12% due to cardiovascular events, and 38% for other reasons) (125). Of 980 patients with first ischemic stroke enrolled in the Northern Manhattan Study, 5% died in the first month post-stroke; the major cause of death at 55% were neurological causes, while 19% were cardiac (126). Prosser et al. revealed a more specific temporal profile of early cardiac morbidity and mortality (110). Of 846 patients followed during the first 3 months after acute ischemic stroke, the proportion of deaths due to neurological and cardiac causes were 43.9% ($n = 79$) and 19.4% ($n = 35$), respectively. Most of the neurologic deaths occurred in the first 2 weeks post-stroke, while cardiac deaths were highest in the second week. Furthermore, 19% ($n = 161$) of all patients experienced at least one serious cardiac adverse event within 3 months of the stroke that peaked in frequency between day 2 and 3 post-stroke. Cardiac complications included non-fatal arrhythmias, acute myocardial infarction, pulmonary edema/moderate-severe cardiac failure, and cardiac death.

The Brain-Heart Connection

The high rate of cardiac manifestations following acute stroke highlights the brain-heart connection. Cardiac conditions that occur following stroke may be unrelated complications of stroke, or directly related to the underlying cause of the stroke such as atrial fibrillation in the case of cardioembolic stroke. Compelling evidence shows that brain damage is a causative factor in some cardiac conditions. The mechanistic basis underlying stroke-induced myocardial damage is complex and multi-factorial, potentially involving activation of the hypothalamic-pituitary-adrenal axis, dysregulation of the autonomic system, inflammation, gut microbiome dysbiosis, immune activation, and dysregulation of the autonomic nervous system and catecholamine "surge" (127). Catecholamine surge is associated with cardiac damage, myocardial stunning, an influx of inflammatory cells in the heart, and increased release of intracellular calcium ions and myocyte dysfunction (128–131). This is hypothesized to lead to ECG and structural cardiac changes even when there is no underlying heart disease. While, some of these stroke-induced changes can be mild or transient, some can be severe or potentially fatal.

Effects of Stroke on the Heart

Effects of a stroke on the heart can include reduced ejection fraction, regional wall motion abnormalities, ECG changes, and arrhythmias (e.g., ventricular and supraventricular tachyarrhythmias, ST segment change, QT prolongation, tall and inverted *T* waves, and prominent *U* waves) and cardiac damage which can lead to chronic heart failure, as well as neurogenic stress-induced cardiomyopathy (most commonly transient left ventricular (LV) apical ballooning). Exercise therapists should have an understanding of the brain-heart interaction as there is a potential for exercise to interfere with recovery of cardiac function when introduced in the hyper-acute to acute phases post-stroke. Conversely, when cardiac function is compromised, early exercise may interfere with recovery of the brain. Specifically, the cardiac manifestations of stroke that reduce cardiac output that occur mostly in the hyper-acute and acute post-stroke phases can affect CBF when CA may be impaired. As demonstrated in a pre-clinical study of induced unilateral stroke, CBF becomes dependent on cardiac output in the absence of intact CA (132). Therefore, when autoregulatory control in the ischemic brain region is impaired early post-stroke, CBF is in part dependent on cardiac output in both positive and negative directions. This reliance on cardiac output has also been demonstrated in people with valvular disease where cardiac output is attenuated during exercise (133).

The clinical impact of cardiac output on the stroke brain is not well-established; compensatory responses to maintain cerebral oxygen metabolism, and the perfusion thresholds may be variable between human and animals (134). However, several studies have demonstrated that CBF is reduced in people with lower cardiac ejection fraction after stroke and in those with heart failure (135–137). One study showed that a change in posture from supine to upright resulted in a greater reduction in CBF-velocity in people with heart failure compared to an age- and sex-matched control group (138). Therefore, some of the cardiac manifestations following stroke can affect cardiac output and threaten perfusion to ischemic brain tissue (139). Initiating exercise in the presence of impaired CA superimposed on these cardiac abnormalities might compromise brain health. We suggest that people with systolic cardiac dysfunction (ventricular wall motion abnormalities and reduced ejection fraction), arrhythmias that compromise cardiac output, and elevated cardiac enzymes indicating cardiac damage maintain light activity/aerobic exercise until CA recovery and the cardiac complication is resolved and stable (see **Table 3** Guideline 2.0 and **Figure 1**) (the rate of cardiac recovery is described in detail in the **Supplementary Materials**). While most studies report declines in cardiac contractile (systolic) performance, impaired diastolic dysfunction may also accompany declines in systolic function, particularly in patients diagnosed with neurogenic stress cardiomyopathy, which includes clinical symptoms of reduced LV ejection fraction, ventricular wall motion abnormalities, and elevated cardiac-specific serum enzymes (127).

Systolic Dysfunction and Poor Outcomes

Studies in consecutive hospital admissions for ischemic stroke demonstrated that between 13 and 29% of people had reduced LV systolic dysfunction (i.e., ejection fraction of <50%) (140–142). In SAH, depressed LV function and cardiac regional wall motion abnormalities are reported in 13–25% of cases. Although these complications are usually reversible, they are associated with high mortality, delayed cerebral ischemia, and poor functional outcomes (139, 143–148). A recent study examined SAH patients within 24 h of admission and found

focal and global cerebral perfusion were significantly lower in 35 people with cardiac dysfunction (myocardial wall motion abnormality and/or positive cardiac troponin level) compared to 37 people without cardiac dysfunction (139). The authors point out that it is unknown if the link between cardiac dysfunction and cerebral perfusion is causal or if it is due to external causes that influence both cardiac function and cerebral perfusion such as a catecholamine surge. However, a recent preclinical study in focal cerebral ischemia demonstrated that increased sympathetic activity is a driver of the development of chronic systolic dysfunction (149).

Another link between systolic dysfunction and poor outcomes is the presence of low SBP at baseline in the acute phase. Prosser et al. have demonstrated that a baseline SBP of <110 mmHg predisposes people post-stroke to sudden cardiac adverse events (110). Stead et al. have reported that lower early BP (DBP < 70 or SBP < 155 mmHg) is a predictor of death within 90 days of acute ischemic stroke compared to those considered normotensive (DBP 70–105 and SBP 155–220 mmHg) (43). It has been suggested that the relationship between lower BP early after stroke and mortality is in part explained by the association with early cardiac adverse events reflecting LV dysfunction (110). Nevertheless, the prevalence of systolic dysfunction, the association with poor outcome, and the effect on cerebral perfusion suggests that avoiding moderate to high intensity aerobic exercise until recovery is recommended.

Time of onset and recovery of systolic dysfunction

LV dysfunction can develop after 1–4 days and can persist for more than 8 days post-stroke (described in detail in **Supplementary Materials**, **Figure 1**) (143, 150). Routine echocardiography is not typically recommended for the early management of acute stroke (15, 120, 151), except among patients with suspected embolic stroke despite normal neurovascular imaging (151). Cardiac-specific troponin and ECG are routine, however, and can provide insight on echocardiogram abnormalities (152–155).

Cardiac Arrhythmias

Cardiac arrhythmias are frequent in acute stroke and associated with higher morbidity and mortality (156). Up to 90% of patients will have ECG changes within the first 24 h of ischemic stroke and 22% are reported to have a cardiac arrhythmia; this is a common cause of death after acute ischemic stroke (157, 158). ECG abnormalities are more frequent in patients with SAH ranging from a prevalence of 27–100% with ∼37.5% experiencing cardiac arrhythmias (144, 145, 157). Arrhythmias can be related to underlying cardiac disease, the stroke event itself, or simply coincidental. Cardiac arrhythmias are not only potentially life threatening (156), but like systolic cardiac dysfunction may compromise cardiac output and thus also have the potential to affect CBF. For example, atrial fibrillation can reduce cardiac output by as much as 17% in the non-stroke population (159, 160), limiting LV filling ("atrial kick"), and by extension, cerebral perfusion during exercise (161, 162). Ventricular arrhythmias, such as frequent premature beats, interpolated premature beats, bigeminy, and trigeminy can cause variable effects on hemodynamics including reduced ejection fraction and stroke volume (163) in people with no known history of stroke. The effect of the above arrhythmias on reduced CBF early post-stroke when CA is impaired has not been reported but is likely to be intensified.

Recovery and correlates of arrhythmias

The risk of clinically significant cardiac arrhythmias is highest in the first 24–48 h following stroke (see **Figure 1** and **Supplementary Materials**) (164, 165).

Patients at higher risk of a clinically relevant arrhythmia following stroke are those who are older, those with more severe neurological deficits (NIHSS), and those with a greater lesion size (164, 165). Insular cortex ischemic strokes are associated with ventricular tachycardia/fibrillation, heart blocks, bradycardia, supraventricular tachycardia, and atrial flutter/fibrillation (156). Patients who fit this profile may benefit from more intensive cardiac monitoring strategies, such as ECG monitoring during the first exercise session or undergoing a pre-participation exercise stress test with ECG monitoring.

Myocardial Injury and Stress

Injury to the myocardium can occur in the acute stage of ischemic, SAH, and ICH in the absence of any cardiac cause. Cardiac lesions may not always be indicative of perfusion abnormalities (166) or affect cardiac output, but they have been characterized as subendocardial microinfarcts with possible damage to both myocytes and nerve terminals (129, 167). Van der Bilt et al. examined myocardium in 25 patients who died of SAH and 18 controls (131). Results revealed a significantly higher influx of inflammatory cells in the myocardium of SAH patients, indicative of myocarditis, relative to controls. Thrombi in intramyocardial arteries were found in 22 SAH patients and 1 control. Myocytolysis was detected in six SAH patients but not in controls.

Cardiac damage can also be detected by elevated serum cardiac troponin levels; a biochemical marker emanating from damaged sarcomeres. Assessment of troponin levels (subunits I and T) provides a high tissue specificity and clinical sensitivity for detecting myocardial necrosis (168). Elevated troponin levels have been detected in up to 21% of ischemic, 18% of ICH, and 52% of SAH strokes in people hospitalized with and without known cardiac disease (152, 155, 169–171). It is thought that elevated troponin levels may be due in part to a catecholamine-related contraction band necrosis (stunned myocardium) rather than underlying CAD (153, 172).

Elevated troponin is independently associated with higher in-hospital mortality, increased risk of delayed cerebral ischemia, and poor outcome across all stroke types (152, 169, 170, 173). In SAH, troponin level is positively correlated with stroke severity, arrhythmias, and regional wall motion abnormalities (153, 174, 175). Elevated troponin in people following ischemic stroke is also correlated with wall motion abnormalities (154). Specifically, of 137 consecutive hospital admissions for ischemic stroke, 17.5% ($n = 24$) had elevated troponin and 67% ($n = 16$ of 24) of those with elevated troponin had a new wall motion abnormality on echocardiogram. Wrigley et al. reported

TABLE 3 | Guideline 2.0: Cardiac screening criteria.

The goal following stroke is to initiate an exercise program as soon as the patient is clinically stable. Exercise should be prescribed with caution when initiated within 2 weeks post-stroke given that almost 2 out of every 10 patients experience an early serious cardiac adverse event. Adverse event occurrence peaks between day 2 and 3 post-stroke, with deaths from neurological and cardiac issues peaking during the second week.

A patient is considered safe to initiate exercise if they satisfy the following criteria:

- No symptoms of coronary artery disease such as chest pain or shortness of breath in the past 24 h.
- No changes or normalization of the ECG in the past 12 h.
- No current significant ECG abnormalities such as frequent ventricular premature beats (≥3 in 10), or QT prolongation.
- No new signs of uncompensated heart failure in the previous 7 days.
- Troponin levels are normal within 3 days of stroke, or are normal 3–7 days following detection of elevated troponin levels.
- In patients with atrial fibrillation, systolic dysfunction, or other issues that reduce cardiac output, light intensity exercise should be maintained until these issues have resolved or until expected recovery of CA. Precautions for avoiding hypotensive episodes (orthostatic hypotension, prolonged standing, and post-exercise hypotension), should be followed during very early and early mobilization (see guidelines 3–5).

Cardiac-specific troponin measures and ECG monitoring are standard of care post-stroke at most institutions. Thus, the results should be reviewed prior to initiating exercise/mobilization following SAH, ischemic, and ICH stroke types especially in the hyper-acute and acute phases. ECG monitoring of people with insular strokes may be prudent. Delaying exercise in patients with elevated troponin with no evidence of CAD is recommended given the micro damage and associated ECG abnormalities and wall motion abnormalities.

that, among >1,500 patients with acute ischemic stroke, 21% had elevated levels of troponin and 10% had echocardiogram findings of interest; most being reduced ejection fraction and wall motion abnormalities (155). Moreover, high troponin levels were independently associated with echocardiogram abnormalities. Most, but not all people post-stroke with elevated troponin will have concomitant ECG changes suggestive of myocardial ischemia (152, 153). Therefore, although echocardiogram results may not be available to detect cardiac manifestations post-stroke, both cardiac-specific troponin and ECG are recommended in acute stroke (15, 120).

Correlates of risk of myocardial injury

Cerebral infarctions involving specific brain regions including the insular cortex and right inferior parietal lobule have been associated with elevated troponin levels indicative of myocardial damage (176). Specifically, in patients with right middle cerebral artery infarction, damage to the insular cortex was involved in 88% of patients with elevated cardiac troponin and 33% of patients without elevated troponin levels in the weeks after ischemic stroke (176). Indeed, insular cortex and parietal lobe infarctions have been associated with adverse cardiac outcomes and cardiac dysfunction in human and animal model studies (177–179). In addition, cardiac troponin levels have been reported to be higher in patients with more severe strokes compared to those with less severe strokes (NIHSS) (180, 181) and positively associated with the stroke lesion volume (182).

Time of onset and recovery of myocardial injury

Kolin and Norris report that focal myocardial damage required at least 6 h to develop after onset of the acute neurological event and was not observed after the second week (183). Serial measures of troponin I in SAH reveal that troponin levels peaked between day 1–3 post-stroke and subsequently declined over 7 days (147, 153, 184, 185) (see **Figure 1** and **Supplemental Materials** for more details). While the effects of exercise on the myocardium in the early stage of stroke in people with elevated troponin levels is not known, it may be prudent to maintain light aerobic activity for at least 7 days and up to 1 month post-stroke (see **Figure 1**) given the demonstrated microscopic damage and associated wall motion abnormalities.

Coronary Artery Disease

Myocardial infarction and cardiac surgery will not be reviewed because exercise guidelines following these events are well-documented (186). It is important, however, to note that coronary artery disease (CAD) can remain undiagnosed due to lack of symptoms and/or unremarkable resting ECG (187, 188).

MOBILIZATION AND AEROBIC EXERCISE IN THE HYPER-ACUTE AND ACUTE PHASES POST-STROKE

Effect of Mobilization in Hyper-Acute to Acute Phases Post-stroke

A meta-analysis of nine randomized controlled studies (2,803 participants) implementing very early mobilization—defined as out of bed activity 24–48 h post-stroke—was published in 2017 (189). The AVERT study was the largest study in the analysis (20). Pooled analyses revealed that when compared to usual care control, early mobilization resulted in similar safety outcomes (e.g., falls with injury, neurological deterioration, death) but was not associated with additional functional improvements or mortality advantage at follow-up, or in reducing pulmonary infection, deep vein thrombosis, urinary tract infection, pulmonary embolism. One study in the meta-analysis, Sundseth et al. (190) randomized stroke patients post-stroke to early mobilization either within 24 h ($n = 27$) or 24–48 h ($n = 29$) after admission. The type and amount of early mobilization activity were not controlled: e.g., each patient was mobilized out of bed "several times per day." The safety-related exclusion criteria included a mRS score ≤ 1 and acute coronary disease. No resting BP criteria or exclusion of people with orthostatic hypotension were reported. Results revealed non-significant trends for poorer outcome (mRS 3–6), higher death rate and dependency, and poorer neurological functioning in the very early mobilization group, although this study may be limited by the sample size.

In a subsequent study, 104 people with severe stroke were randomized to soft physiotherapy (20 min per day) vs. intensive physiotherapy (soft physiotherapy plus 45 min of intensive exercise/day) initiated within the first 72 h after stroke for 2 weeks (10 sessions) (191). Similar to the meta-analysis discussed

above, no between-group differences were reported in mRS score, Functional Independence Measurement, mobility, change in Postural Assessment Scale for Stroke, or quality-of-life measure after 90 days. Unfortunately, no measure of "dose" of activity or pre-participation screening criteria based on resting BP, eye conditions (e.g., retinopathy), orthostatic hypotension, glycemic control, or cardiac abnormalities were reported, despite 70% of participants having a history of hypertension, 19% with diabetes, and 10% with cardiac issues.

The results of the most influential study in the 2017 meta-analysis also demonstrated a neutral and potentially deleterious effect of very early mobilization initiated within the first 24 h of stroke (20). The AVERT trial was a multi-center, single-blind randomized control trial conducted in 56 stroke units, 5 countries, and 2,104 ischemic and ICH stroke patients. The activity intervention was modest and included 10–30 min of active sitting, and/or a minimum of 10 min of standing, and/or walking that continued for 14 days or until discharge. The time to first mobilization for intervention and control was a median [interquartile range (IQR)] of 18.5 h (12.8–22.3) vs. 22.4 h (16.5–29.3), respectively. The median (IQR) time out of bed for intervention and control groups was 31 (16.5–50.5) vs. 10 (0–18) min per day, respectively. Three months post-stroke, a smaller proportion of people in the early mobilization group scored favorably (0–2) on the mRS compared to usual care (46 vs. 50%, respectively; adjusted odds ratio 0.73, 95% CI 0.59–0.90, $p = 0.004$). In particular, patients with severe stroke (NIHSS > 16, $n = 291$) and ICH ($n = 255$) tended to show a less favorable outcomes in the early intervention treatment, with ICH patients possibly more susceptible to death.

To further define a "dose" of out-of-bed activity associated with better outcomes regression models (two for usual care and two for all patients regardless of group assignment) [Table e-1 (192)] controlled for age, stroke severity (NIHSS), and frequency and duration of mobilization (either daily amount or total amount). An earlier start to mobilization and more frequent daily activity was a predictor of improved mRS outcome in all models. The only difference between the analyses was that in the usual care group, while daily amount of activity did not significantly influence outcome, a greater total amount of activity predicted worse outcomes. In both groups, greater daily amount and total amount of activity predicted poorer outcomes. This suggests that when mobilization is started later as suggested in the contemporary guidelines, greater amount of daily activity may not have an influence, but should be undertaken more frequently. The finding that a greater total amount of activity during hospitalization (up to 14 days) had a negative effect was likely influenced in part by longer hospital stay in those with greater medical complications but requires verification. Also, the variability in frequency and daily amount of out of bed activity may be in part driven by patient, family, institutional, health care professional, medical, and other factors. Thus, data from this secondary analysis should be viewed with caution.

As mentioned previously, most of the contemporary stroke care guidelines and position papers published since the release of the AVERT results advocate against "high-dose" or "intensive," out-of-bed activities within 24 h of stroke onset without further specification of dose (15–19). Indeed, the dose of activity in the first 24 h was not reported in the AVERT study and although the median dose was reported as 31 (16.5–50.5) min of out-of-bed activity over ∼14 days, it is likely that the first few mobilization sessions performed would be low intensity activity of shorter duration and then gradually progressed over the ∼14 day intervention. While the AVERT investigators caution against interpretation (192), the results of Classification and Regression Tree (CART) analysis suggest that overall, younger individuals are likely to fair well. Older adults (76–86 years), without mild or severe strokes, have better outcomes with a median dose of ∼2 sessions of 6.5 min of activity per day or, for longer duration of activity, a dose equivalent to at least 1–2 min of out-of-bed activity every hour of the day (i.e., ∼11 sessions) if targeting the median dose. The optimal timing of the initial dose is not clear and it is possible that adverse outcome may be related in part to the type of initial activity prescribed, such as prolonged standing as discussed in section Protecting the Brain During Mobilization.

Safety Screening Criteria for Very Early Mobilization in AVERT

Another consideration for improving outcomes with an early mobilization intervention is related to having appropriate pre-participation screening criteria. The AVERT study excluded participants with a resting SBP of <110 or >220 mmHg. In acute stroke, where CA is disturbed and many have a history of hypertension and risk for orthostatic hypotension, protection would likely be compromised in some patients using this criterion. In addition, pre-participation criteria for a safe lower limit of resting BP should be re-evaluated (see section Peripheral and Cerebral Circulatory Considerations for Exercise and Mobilization Guideline 1.0). Another factor to consider is that almost one-quarter of the patients in the AVERT study had a diagnosis of diabetes and screening criteria for hyperglycemia was not reported. Further, one-quarter of the patients from both groups in the AVERT study had a diagnosis of atrial fibrillation, although it is unclear how many were currently in this rhythm, should have followed Guidelines 3.0–5.0, **Tables 4–6** to avoid cerebral hypoperfusion episodes associated with activity until recovery of CA.

Effects of Aerobic Exercise Within 48 H Post-stroke

To our knowledge there is only one study examining aerobic training within 2 days of stroke onset. Strømmen et al. conducted a single group prospective study in 20 people with mild to no disability (mRS of 0–2) that initiated exercise 41.5 ± 14 h after onset of symptoms (193). The intervention included two sessions of low intensity (50% of predicted heart rate reserve; HRR) treadmill training (body weight support when needed) per day for the first 5 days and two sessions 30 days later (193). Each session was 30 min in duration, with rest breaks (sitting or standing) as needed. Exclusion criteria included

symptoms, infection, unstable cardiac condition, resting SBP above 180 mmHg, and conditions hindering treadmill training. Of the 20 participants, over half developed non-serious adverse events occurring in 14% of all 224 treadmill training sessions. Specifically, eight people developed 19 episodes of dizziness (with two patients ending four sessions pre-maturely due to dizziness), three people developed blisters or superficial wounds, one person had three non-injurious falls getting on or off the treadmill, one patient had five episodes of pain in the lower extremities, and one patient had three episodes of tiredness. Not included in the adverse events, nine patients became exhausted and ended a total of 24 exercise sessions early. No neurological deterioration was detected. Participants attained the target exercise intensity in only 31% of sessions. The difficulties encountered by these minimally disabled patients attempting to reach an exercise intensity slightly above "light" suggests that our recommendation to initiate light intensity exercise in the acute phase of exercise is a more feasible and realistic goal for patients. Counteracting adverse events is discussed in section Protecting the Brain During Mobilization. We await the results of ongoing clinical trials examining early exercise interventions (194).

The preclinical data suggest that very early exercise (i.e., within 6 h) may exacerbate brain injury, while early (i.e., ∼24 h) and relatively late training (i.e., >3 days) may be beneficial. The **Supplemental Materials** provides further description on relevant animal studies but the preclinical field of research is outside the scope of this review.

PROTECTING THE BRAIN DURING MOBILIZATION

Orthostatic Hypotension (See Table 4 Guideline 3)

Orthostatic hypotension (OH) can impact stroke survivors. OH is defined as a sustained reduction in either SBP of at least 20 mmHg or DBP of at least 10 mmHg, within 2–3 min of standing, or after a head-up tilt to at least 60 degrees, preceded by a 10-min period of quiet lying (195). For resting supine SBP of >160 mmHg, the OH threshold for a drop in SBP is increased to 30 mmHg. Symptoms of OH can include dizziness, nausea, dyspnea, diaphoresis, and diplopia that can sometimes lead to vasovagal syncope (196, 197). The pathogenesis of OH helps to elucidate the possible mechanism for adverse long-term outcomes. When assuming an upright posture, blood volume is redistributed below the diaphragm (198). This leads to a decrease in venous return, cardiac output, and arterial BP. In healthy individuals, a compensatory reflex is activated by baroreceptors in the carotid arteries and aorta to restore BP and cardiac output by increasing heart rate, contractility and vascular resistance. In people following stroke and the elderly, however, arterial stiffening likely impairs cardiovagal baroreflex sensitivity (199, 200) and interferes with these countermeasures. CA dysfunction likely intensifies the effect. Moreover, primary baroreflex dysregulation has been identified as a cause of OH (201).

Prevalence and Incidence of Orthostatic Hypotension and Hypotensive Episodes in People Post-stroke

Among 71 stroke adults in in-patient rehabilitation, 52% had OH during a tilt table test measured within 3 days of stroke (61). It is notable that 68% of these cases were asymptomatic, emphasizing the importance of careful BP monitoring during early phase mobilization post-stroke. Further, Carlsson et al. reported that 23% of 226 patients within 4 weeks of mixed diagnosis stroke demonstrated OH, which persisted for up to 1 year (202). In a small study of the early phases post-ischemic stroke ($n = 13$), Treger et al. reported that 40% of individuals exhibited symptomatic OH at 1 week of in-patient rehabilitation (range 15–45 days post-stroke). One month later (45–75 days post-stroke), these patients had the same symptoms, albeit less severe in some cases (203). Panayiotou et al. reported a slightly lower incidence of postural hypotension (19% of 40 people) 1–2 days following acute mild or moderate ischemic stroke. This study reported hypotension after 1 min of standing but pressure had recovered after 5 min in most of the patients (204). This study also provides preliminary evidence that OH prevalence may be related to stroke severity.

Langhorne et al. monitored BP (using either automatic continuous or manual methods) in patients randomized to early mobilization vs. standard care (205). Among 32 patients post-stroke in the first 72 h of admission, there were 28 episodes of DBP dropping below 70 mmHg and 5 episodes where it rose above 120 mmHg, 18 episodes of SBP dropping below 110 mm Hg and 2 where it exceeded 220 mmHg, 7 episodes of bradycardia (heart rate dropping below 50 bpm) and 15 episodes of tachycardia (heart rate exceeding 100 bpm). No differences in the frequency of these events by early mobilization verses usual care were reported; however, an unfavorable neurological impact may be greater in the early mobilization group given BBB and CA dysfunction. Unfortunately, the events that may have precipitated these episodes such as posture change, activity, prolonged standing, post-exercise hypotension were not reported but serve to highlight the frequency of these events that occur at a time when the brain is vulnerable to hypoperfusion and hyperperfusion.

Orthostatic Hypotension and Activation of the Coagulation Cascade

Physical countermeasures and other strategies may mitigate the effects of OH for stroke survivors, but this concept is largely untested. Furthermore, avoiding activity at times when OH is probable may contribute to better long-term outcomes. We discuss some possible mechanisms. First, changes in posture may trigger the coagulation cascade. In an observational study of 178 adults with unexplained syncope (non-stroke), activation of the coagulation cascade occurred after only 3 min of head up tilt at 70 degrees (206, 207). This hypercoagulable state can persist for ∼20 min following a postural change (208). These changes were observed in both individuals with OH as well as those with other syncope etiology. Orthostatic-driven coagulation may in part explain the increased risk of cardiovascular events that are reported in people who experience OH.

Orthostatic Hypotension and Reduced Cerebral Blood Flow Velocity

In addition to the hypercoagulable state, repeated acute hypotensive episodes early-post-stroke may contribute to hypoperfusion. Pooled data from four studies demonstrated a significant decrease in CBF velocity when head position moved from either 0 or 15 degrees to a 30-degree upright head position (209). Patients ($n = 57$) were within 6 days of mostly large vessel ischemic strokes. One study in the review measured the impact of a change in backrest tilt following large ischemic stroke with 7 of 18 participants having had decompressive hemicraniectomy (210). Moving from horizontal to 15 degrees and then to 30 degrees over a two step 10-min period decreased CBF velocity by 25% and also reduced intracranial pressure and cerebral perfusion pressure. BP showed a significant decline from baseline at both 15 and 30 degrees. The decrease in CBF was even larger in the subset of patients with hemicraniectomy. The rate of posture change that would minimize hypoperfusion and the time course for CBF and BP to return to baseline levels after posture change is unknown and therefore an area of future investigation. Such information would help define specific guidelines for protecting individuals from repeated episodes of hypoperfusion and increased fall risk.

The coexistence of diabetes may increase the prevalence of OH in patients with stroke and may intensify the effect on CBF, as the prevalence of OH in the pre-diabetic and diabetic population is ∼18 and 26%, respectively (211). One study documented a reduction in mean CBF velocity of 23% upon active standing from a supine position in people with diabetes and no stroke (116). The prevalence of OH and effect on CBF in people with both diabetes and stroke requires investigation.

Orthostatic Hypotension Is Associated With Cognitive Decline and Poorer Physical Function

Physical and cognitive functions are both relevant in the context of OH. The effect of both hypotensive episodes and aortic stiffness on cerebral function has been measured in cross-sectional and longitudinal studies, but not in people with stroke. These studies demonstrate that there is an association between OH and cognitive decline (60, 212). Indeed, the impact of OH on cognitive decline is significant, with a pooled analysis of data indicating a 21% (95% confidence interval: 9–35%) increased

TABLE 4 | Guideline 3.0: Precautions for avoding orthostatic hypotension.

OH is common post-stroke. There is an opportunity to use this clinical indication to guide exercise and early mobilization. While there is some evidence that repeated episodes of standing may improve orthostatic tolerance over time in some populations (54), until there is further research specific to stroke, precautions to prevent OH should be taken until at least after the expected recovery of CA when the brain is better protected from hypotensive episodes.

In view of the high prevalence of OH in the early phases of stroke that may be asymptomatic and result in reduced CBF, the following precautions and strategies are suggested:

- Factors Predisposing People to OH Requiring Careful Monitoring
  - Patients who experienced any of the following 12 symptoms of orthostatic intolerance pre-stroke (symptoms would present within 3 min of standing and resolve when sitting or lying down): dizziness, lightheadedness, fatigue, blackouts, nausea, instability, ringing in the ears, vertigo, headache, syncope, confusion, and sweating.
  - People with tightly controlled blood pressure (e.g., SBP below 120 mmHg and/or DBP below 80 mmHg in ischemic stroke) (55). Refer to Guideline 1.0 for lower blood pressure limits prior to commencing early mobilization/exercise prescription.
  - People with diabetes, dehydration (blood electrolytes, urea nitrogen, and creatinine), anemia (hemoglobin and hematocrit levels), hemicraniectomy, and intracranial atherosclerotic stenosis.
  - Medications such as beta-adrenergic blockers, renin-angiotensin system antagonists, diuretics, antidepressants, or sedatives, which can cause or aggravate OH (56).
- Avoid exercise after large meals (57).
- In those with signs and/or symptoms of OH, schedule exercise or mobilization for those prescribed beta blockade medication at a time of day when the medication is less effective unless the risk of high blood pressure outweighs risk of hypotensive episode.
- Minimize posture change or institute an incremental change in backrest tilt posture from 30–50 to 70 degrees (>10 min for each increment) concomitant with lower limb movement (active or passive) to activate the muscle pump, when possible (58).
- Timing of Assessment for OH: Measure changes in blood pressure and heart rate and monitor symptoms when moving from supine (10 min supine) to standing (after 1 and 3 min) at the same time of day as the mobilization or exercise session will be performed (59).
- Until further research has been conducted, we suggest the following OH thresholds based on resting blood pressure (systolic/diastolic; SBP/DBP) values:
  - *SBP < 128 and/or DBP < 82: A sustained reduction in either SBP or DBP of at least 15 or 7 mmHg, respectively, after 3 min of standing or after a head-up tilt of at least 60 degrees with or without OH symptoms (60).
  - SBP 128–158 mmHg and/or DBP 82–102 mmHg: A sustained reduction in either SBP or DBP of at least 20 mmHg or 10 mmHg, respectively, after 3 min of standing or after a head-up tilt to at least 60 degrees with or without OH symptoms.
  - SBP > 158 mmHg and/or DBP > 102 mmHg: A sustained reduction in SBP and/or DBP of at least 30 or 10 mmHg, respectively, after 3 min of standing or after a head-up tilt to at least 60 degrees with or without OH symptoms.
- Using an ambulatory blood pressure monitoring device, measure blood pressure for the first 2–3 training/mobilization sessions. Monitor from supine through to 90 min post-exercise. Repeat monitoring when there is a change in exercise modality or change in medication (listed above) in those with suspected OH (i.e., measured or in people with symptoms of orthostatic intolerance listed above).
- Precautions should continue to be practiced throughout care in those with signs and/or symptoms of OH as it is likely to continue into chronic stroke especially in those with coexisting diabetes.

**This conservative recommendation is based on data demonstrating subclinical OH is associated with increased risk of dementia (60), most people post-stroke are asymptomatic during OH (61) and people post-ischemic stroke with SBP ≤ 127 mmHg and/or DBP of ≤82 mmHg are more susceptible to OH (55).*

risk of dementia (60). Of note, subclinical OH (i.e., a fall of ≥15 mmHg in systolic and/or ≥7 mmHg in DBP after 2 min of standing from sitting) with symptoms in the previous week also increased the risk/incidence of cognitive impairment in older hypertensive individuals (60).

Overall, these data indirectly support the notion of careful monitoring and prevention of OH episodes during mobilization for people post-stroke be considered. There are clear research opportunities, including randomized trial design, that build from the limited literature (213). As little as a 15-degree change in head position is shown to decrease CBF significantly in the acute phase post-stroke. Thus, minimal and gradual changes in head and body position preferably with concomitant stepping or lower limb movement to activate the venous muscle pump to counteract pooling of blood (58), should be carried out carefully when preceding initiation of aerobic exercise or mobilization.

Orthostatic Hypotension and Increased Falls Risk

OH is clinically important after stroke because of the increased fall risk. Although the incidence varies among studies, up to 37% of post-stroke inpatients report at least 1 fall (214–216), accounting for up to 40% of all adverse hospital events post-stroke (217). Surprisingly few studies, if any, have prospectively examined the association between falls and OH early post-stroke. This may explain why current risk prediction models have had unacceptable performance in predicting falls post-stroke (218).

Rethinking the Definition of OH for Detecting Clinically Relevant OH Post-stroke

Regarding detection of clinically relevant OH, there is no empirical evidence to support that the established BP decline thresholds defined as OH will provide cerebral protection in early stroke. It is possible that in the presence of impaired CA, a less dramatic fall that does not exceed these thresholds could be of equal clinical importance in both those with and without hypertension. A re-evaluation of this threshold is needed as hypoperfusion during the hyper-acute and acute phases post-stroke may result in a collapse of the blood supply to the vulnerable ischemic penumbra leading to stroke progression. Indeed, the safety related criteria for excluding patients from participating in the AVERT study was if the patients' SBP dropped by more than 30 mmHg when the back of the bed was raised to >70° of hip flexion or during sitting both for normotensive and hypertensive individuals (20). This may have in part explained the less favorable outcomes by 3 months in the early vs. late mobilization cohort, especially in those with more severe stroke (NIHSS > 16, $n = 291$), a cohort that may have greater CA impairment. Future studies should determine the BP reduction threshold that results in significant reductions in CBF velocity in normotensive and hypertensive individuals with and without impaired CA early post-stroke to inform safety related screening criteria. A more conservative guideline for reduction in BP upon standing should be considered when mobilizing and prescribing exercise until further research is conducted in this area.

Prolonged Standing (See Table 5 Guideline 4.0)

Prolonged static standing (i.e., >5 min) is an orthostatic and CA challenge; it is an activity with no dynamic movement and can lead to a reduction in arterial BP and cardiac output. As in OH, prolonged standing can trigger the coagulation cascade, called orthostatic hypercoagulability. For example, when healthy individuals stand stationary for ∼20–30 min, venous pooling of ∼20% of the blood volume occurs in the lower extremities with a subsequent plasma volume loss to surrounding tissue of ∼12% (219, 220). This orthostatic stress and plasma shift of filterable elements and water into the interstitial space is associated with an increased concentration of coagulation factors and other proteins that are larger and non-diffusible in the lower extremity vasculature, subsequently causing hypercoagulability (208, 220, 221).

A recent study measured coagulability in 22 patients within 1 year of mild ischemic stroke (most were prescribed antiplatelet medication) and 22 age-matched healthy controls before and after 5 min of sitting followed by 6 min of quiet prolonged standing (221). The orthostatic challenge resulted in a significant activation of the coagulation system in both groups. However, activation was more easily shifted toward a higher hypercoagulable state in ischemic stroke than in healthy controls. This study demonstrates that a mere 6 min of inactive standing can be problematic post-stroke. A decrease in plasma volume, an increase in plasma protein, and a net higher coagulability has been demonstrated in healthy subjects after 30 min of standing (220). Other types of prolonged inactivity (recumbency and sitting) have also been shown to activate the coagulation cascade (222).

Prolonged standing leads to reduced venous return, cardiac output, and BP. When this is not countered by a baroreflex mediated increase in sympathetic outflow and vagal inhibition, the reduced cardiac output may threaten brain perfusion (223). CBF, in part, depends on cardiac output (139). Heel raises are a simple strategy to counter these effects and activate the skeletal muscle pump. Increasing intravenous pressure facilitates venous return to the heart. Faghri et al. demonstrated that 30 min of stationary standing by 15 able bodied and 14 spinal cord-injured subjects resulted in significant reductions in cardiac output in both groups (224). During 30 min of dynamic standing, however, both groups were able to maintain cardiac output at baseline levels by way of either electrical stimulation (in spinal cord injury) or voluntary activation (in controls) of postural leg muscles (10–15 s of heel raises with 60 s rest repeated for 30 min).

In people with lower extremity hemiparesis, an inability to voluntarily activate the muscle pump optimally may intensify impaired venous return and the subsequent effects. Passive dorsiflexion and ankle rotation can increase mean and peak blood velocities in the common femoral vein in healthy individuals (68). Therefore, an early mobilization strategy for those with significant hemiparesis and/or poor lower extremity motor control is to replace placid standing with side-to-side or forward and backward stepping (support by non-affected upper extremity) that would force at least passive movement of the ankle joint.

Unfortunately, studies examining in-hospital activity tend to cluster as opposed to distinguish between standing, walking,

and upright forms of activity (11, 20). This was the case in the AVERT study; thus, there may be scientific justification to isolate prolonged standing from other forms of mobilization in future trial design (20). Two of the three types of mobilization activities prescribed in the AVERT study were standing (i.e., a minimum of 10 min of standing and/or walking) and sitting. The results from the CART analysis of the AVERT study, indicating a benefit from activity intervals shorter than 6 min, aligns with research presented in this section which shows that the coagulation cascade is triggered after only 6 min of prolonged standing and only 3 min following a change in posture.

Also, shorter exercise protocols may elicit a smaller post-exercise hypotensive response than longer protocols (225, 226). Although the results are mixed, CA has been reported in some studies as being more impaired in those with more severe strokes. This may in part explain why those with more severe stroke had a more favorable outcome with more frequent sessions compared to less daily sessions in the AVERT study. Specifically, CART analysis revealed a more favorable outcome (mRS of 0–2) in patients with more severe stroke (NIHSS of >13.5) who performed a median of >2.75 daily sessions (16.2%) rather than less daily sessions (3.7%), and a more favorable outcome for those in the usual care group than the intervention group, potentially due to the later initiation of mobilization. This more severe cohort might also have greater mobility deficits and be more likely to be prescribed static standing or sitting out-of-bed activities rather than walking. Thus, more frequent instead of longer daily sessions may be of some benefit. Indeed, it is likely that upon first mobilization within the first 24 h, most of the activity in people with more severe motor impairments would be sitting or standing and gradually progressed over the 14 days of the intervention to walking, placing many at risk. Therefore, until further investigation, delaying prolonged static standing, especially in those with severe stroke or instituting countermeasures is recommended until there is some recovery of BBB and CA. Future studies should test these hypotheses and examine the effects of walking, standing, or sitting separately to help determine safe prescription parameters.

PROTECTING THE BRAIN AFTER AND DURING AEROBIC EXERCISE

Post-exercise Hypotension (See Table 6 Guideline 5)

Post-exercise hypotension (PEH) is a reduction in arterial BP below resting levels that lasts minutes to hours following a bout of dynamic exercise, with a nadir typically at ∼10–30 min post-exercise (227–229). During exercise, BP and cardiac output increase; after cessation of exercise, however, the average decline in BP can be ∼8/9 (SBP/DBP) mmHg below baseline in non-stroke populations [reviewed by MacDonald et al. (230)]. The reduction in BP can be large enough to lead to presyncopal signs and symptoms, and possibly syncope (231, 232). The causes of PEH remain unclear but may result from peripheral vasodilation that is not completely offset by a matched increase in cardiac output. Just as with OH and prolonged standing, reduced cardiac output during PEH may threaten perfusion to brain tissue (223) because CBF is dependent on cardiac output (139). Notably, PEH compromises CA function in healthy individuals (67, 93), so it likely has an exaggerated effect on cerebral hemodynamics in people with stroke who may already have compromised CA. Also, while there is considerable heterogeneity in the PEH response, it appears to be greater in magnitude and lasts longer in hypertensive compared to normotensive individuals (227, 232). The average reduction in SBP/DBP is ∼14/9 mmHg in the hypertensive population (230). As hypertension is a common risk factor for stroke and is commonly elevated in the hyper-acute and acute phases post-stroke, an even more pronounced reduction in BP may occur. The prevalence and effects of PEH in people with stroke with or without hypertension, however, is an area that requires further research.

Subjective symptoms of pre-syncope that are associated with PEH are dizziness, nausea, faintness, visual disturbances, hearing disturbances, and fatigue. Previous studies have reported a high prevalence of symptoms similar to these mostly observed in the acute phases post-stroke. In section Mobilization and Aerobic Exercise in the Hyper-Acute and Acute Phases Post-stroke, we reviewed a study that demonstrated that over half of a group of 20 stroke patients undergoing an aerobic treadmill exercise intervention a mean of 42 h post-stroke developed non-serious adverse events, some of which included dizziness and tiredness (193). Further, Langhorne et al. reported that from among 32 patients with and without an early mobilization intervention stroke, there were 28 episodes where DBP dropped below 70 mmHg and 18 episodes where SBP dropped below 110 mmHg within 72 h of stroke onset (205). While the circumstances under which these symptoms and episodes of low BP arose were not reported, it is reasonable to assume that some were related to OH or PEH, particularly given the high prevalence reported in healthy individuals (233).

TABLE 5 | Guideline 4.0: Precautions for preventing adverse effects from prolonged standing.

- Avoid prolonged (> 5 min) stationary standing, especially after prolonged sitting.
  - It is possible that even shorter periods of prolonged stationary standing may be detrimental.
  - In a situation that necessitates prolonged standing, recommendations are to engage the muscle pump by doing ∼10–15 s (4–5 repetitions) of rhythmic heel raises or squats (with support if required) alternating with 60 s rest.
- Early mobilization strategies for those with significant hemiparesis and/or poor lower extremity motor control is to do the following:
  - Replace placid standing with side-to-side or forward and backward stepping (support by non-affected upper extremity) that would force at least passive movement of the ankle joint.
  - Perform passive or active ankle movements on a BOSU ball with affected leg in standing with support by non-affected upper and lower extremity. Activate the non-affected limb by also performing heel raises.

TABLE 6 | Guideline 5.0: Precautions to prevent post-exercise or mobilization hypotension.

Strategies to counteract post-exercise hypotension should be practiced in the early phases post-stroke in the setting of compromised CA. While the lasting effects of post-exercise hypotension (PEH) are not known, these precautions are not likely to significantly alter benefit, be a burden to the patient, or increase risk.
It should be emphasized that people who experience post-exercise symptoms or syncope should be investigated for other serious pathologies including arrhythmias, carotid disease, cerebral vasospasm or other issues.

Pre-exercise precautions

- Avoid exercise in the early morning as CA is more likely to be impaired (62, 63).
- Avoid exercise in the hot and/or humid weather. Exercise performed with additional heat stress may worsen the degree of orthostatic intolerance and extend the deficit in CA even after return to resting body temperature in healthy individuals (64).
- Ensure adequate hydration prior to and during exercise and replace fluids post-exercise (64).
- Avoid a large carbohydrate meal and allow at least 2 h post-meal before initiating exercise to reduce postprandial splanchnic hyperemia and subsequent hypotension.
- When designing an exercise and risk factor modification program, the education component should be delivered prior to exercise, so as to avoid static upright postures (e.g., prolonged sitting) post-exercise.

Exercise precautions

- In at least the acute phase post-stroke, light intensity exercise is recommended while avoiding high intensity exercise owing to increased risk of PEH. This is especially important in those who have experienced symptoms post-exercise and those with resting hypertension or borderline hypertension.
  - Symptoms of PEH can include dizziness, nausea, faintness, visual disturbances, hearing disturbances, and fatigue
- Shorter exercise protocols have been shown to elicit less of a PEH response than longer protocols. Therefore, exercise intervals of 5–10 min each, alternating with active recovery periods should be prescribed. Active recovery includes seated/standing activity that engages the skeletal muscle pump.
- In some cases, support stockings/socks may be of benefit (65, 66).

Post-exercise precautions

- The cool-down period should not be neglected and should be a formal component of the exercise prescription.
  - The cool down period should include ≥5 min of a gradual ramping down to very low intensity activity. A rapid decrease in blood pressure post-exercise results in less effective dynamic CA especially in the first 10 min of recovery post-exercise (67).
  - People with resting hypertension or borderline hypertension should include a 10-min cool down period as PEH is greater in magnitude and can last longer and may be further exacerbated when ambient temperatures and humidity exists.
  - On the stationary cycle, gradually reducing cycling resistance should be the primary way to reduce workload in the cool-down period while maintaining pedaling cadence to allow more frequent muscle pump activity.
- Repeated rhythmic ¼ squats or heel raises should be performed for at least 10 min and up to 30 min following cessation of exercise. This should be sufficient to move blood toward the heart.
  - After cool-down, lower limb movement should be periodically undertaken for at least 10 min following cessation of exercise to engage the mechanical muscle pump and reverse the shift of blood volume as this has been shown to reduce occurrence of PEH in healthy individuals (65).
  - Engage the muscle pump by doing ∼10–15 s (3–4 repetitions) of rhythmic ¼ squats or heel raises (with support if required) alternating with 60 s of rest for at least the first 10 min post-exercise (∼25 in total). These should then be repeated 2 more times (every 10 min for a further 20 min).
  - Strategies for those with severe hemiparesis and/or poor lower extremity motor control is to perform passive lower limb movement (68) or perform side-to-side or forward and backward stepping (support by non-affected upper extremity). Affected-side ankle movements on a BOSU ball or other activities such as seated heel raises can also be performed.

Aerobic Exercise Characteristics and Post-exercise Hypotension

An understanding of the exercise characteristics that may precipitate PEH will help to develop countermeasures for prevention. Exercise engaging a greater volume of muscle mass and longer compared to shorter exercise protocols promotes greater reductions in BP during the recovery period (225, 226). This may be another factor contributing to the pre-specified secondary finding of the AVERT study where better outcomes resulted with a greater frequency of daily mobilization sessions when total time remained constant. Even very low intensity exercise can reduce CBF below resting levels in the post-exercise recovery period. In one study, 11 healthy individuals were assessed using PET oxygen-15-labeled water following 20 min of mostly very low intensity exercise (30% of estimated HRR). Results revealed that regional CBF decreased 8–13% during PEH compared to rest (234).

A series of studies demonstrate that PEH is more pronounced with higher intensity exercise than lower intensity exercise resulting in accelerated development of PEH, greater impairment in post-exercise CA and reductions in CBF velocity (235). Indeed, more intense exercise results in impaired functionality of dynamic CA measured in the post-exercise recovery period in healthy individuals (67, 93, 236). In healthy sedentary individuals, Boeno et al. reported that high intensity interval training resulted in reductions in SBP of 18 mmHg that occurred at the 15th min of recovery while continuous training at 70% of maximal heart rate (matched for volume) resulted in a reduction of 13 mmHg at the 30th min, compared to resting measures (228). Mündel et al. measured post-exercise orthostatic tolerance during an orthostatic challenge (head-up tilt and lower body negative pressure) in eight young healthy volunteers following 1 h of cycling exercise at intensities of 30 and 70% of predicted HRR (229). Following exercise at 70% HRR, the time to presyncope occurred 32% sooner than following exercise at 30% HRR (15.9 vs. 23.6 min, respectively).

Preventing Post-exercise Hypotension and Reduced Cerebral Blood Flow Velocity

Syncope typically occurs when the person is standing motionless for the first 5–10 min post-exercise given the loss of the muscle pump to aid in venous return. Passive recovery by standing or sitting places the vasodilated vessels in the periphery below the

heart level and may exacerbate venous pooling. **Table 6** includes strategies to prevent or mitigate the effects of PEH.

It is important to point out that while we advocate the mitigation of significant PEH in the early phases post-stroke when CA is impaired, its summative effects over time may contribute significantly to the favorable reduction in BP which may be beneficial when CA is functional (late subacute and chronic phases depending on stroke type), thereby providing a potential cardiovascular benefit. Further research is required to confirm this in the stroke population.

Elevation and Rapid Fluctuations in Mean Arterial Pressure Related to Aerobic Exercise (See Table 7 Guideline 6.0)

The American Heart and American Stroke Association guidelines recommend physical activity and exercise across all phases of stroke recovery (237). Our review of animal studies (see **Supplementary Materials**) suggests initiating exercise in the hyper-acute post-stroke phase with caution if at all. There is scant evidence from human studies to oppose this recommendation. The relationship between CBF and exercise-induced changes in cardiac output, BP, metabolism, arterial blood gases, and neurovascular innervation in healthy populations is poorly understood and far less is known about this complex set of associations in the stroke population. Until there is more research to elucidate the response in the early phases post-stroke a cautious approach should be taken. Given that exercise intensity is the most important parameter of the aerobic exercise prescription from a brain safety and overall efficacy point-of-view, the following section will provide temporal guidelines with respect to aerobic exercise intensity based on available evidence. Strategies will be provided to avoid catecholamine surges and excessive elevation and rapid fluctuations in BP within the first 3 months post-stroke until the expected restoration of CA, BBB, and cardiac function. For a summary of exercise prescription guidelines, see **Table 7** Guideline 6 and the **Figure 1**.

Aerobic Exercise Intensity

Well-established evidence demonstrates that greater gains in cardiorespiratory fitness (CRF) are possible with higher intensity exercise in stroke and other populations (238–241). Given that increases in CRF are associated with reductions in cardiovascular event rates (242–245), and in view of the progressive nature of cardiovascular disease (246, 247) efforts to train individuals following stroke to optimal target intensity levels are warranted. Indeed, epidemiological and clinical evidence demonstrates CRF as a stronger predictor of mortality than smoking, hypertension, type II diabetes, and high cholesterol (243, 248–252). In addition to CRF benefit, there is compelling evidence that higher intensity aerobic exercise training in the early subacute to late subacute phases of stroke provides an advantage to mobility (253, 254) and to cognitive function in late subacute and chronic stroke and healthy populations (255–261). However, to our knowledge the acute and chronic effect of aerobic exercise intensity on resting and dynamic middle cerebral artery blood flow velocity has never been measured at any time following the stroke event. Indeed, the benefits observed from aerobic exercise on cognition and mobility has not been replicated in the hyper-acute to acute phases post-stroke. Currently, the American College of Sports Medicine exercise recommendations for people following stroke advocate prescribing moderate intensity cardiovascular exercise at 40–70% of HRR or an RPE of 11–14 ("light" to <"hard") on the 6–20 Borg scale (186). These guidelines do not specify the timing of when to safely initiate or progress patients to higher intensity aerobic exercise.

Higher Intensity Training in the Early Phases Post-stroke

In view of the data presented in section Peripheral and Cerebral Circulatory Considerations for Exercise and Mobilization, exposure to higher intensity exercise (95) within 1 month of stroke may increase the risk of BBB mechanical breakdown and cerebral hyperperfusion injury (**Figure 1**). The risk could be intensified by elevated and dynamically changing resting BP and structural cardiac complications and arrhythmias. The ischemic penumbra is vulnerable during this time period, and there is a risk of stroke progression, hematoma expansion in ICH, and delayed ischemia and vasospasm in SAH. There is also evidence presented earlier that dynamic CA measured during exercise as well as in recovery in people without stroke is further impaired with high intensity exercise when compared to lower intensity exercise (67, 93, 229, 236, 262). Conversely, there may be benefit from chronic adaptations to early aerobic exercise that leads to improved CA or BBB function (263). However, this has not been tested in people in the early phases post-stroke nor is there evidence of an exercise intensity effect on improved neuroprotection.

Is there an exercise intensity threshold that is safe in the early phases post-stroke? Studies in healthy individuals show that during incremental aerobic exercise, CBF gradually increases in parallel with exercise intensity until ∼60–70% of VO_{2max}. Exceeding this intensity typically results in either a plateau or progressive reduction in CBF toward resting values as induced by cerebral vasoconstriction in concert with exercise-induced hyperventilation [reviewed in Smith et al. (264)]. Prescribing exercise at an intensity below the level of expected peak CBF velocity in the early phases post-stroke may be a safe target to prevent hyperperfusion given that impaired CA may not induce cerebral vasoconstriction at the critical intensity for cerebral protection.

The degree to which CBF and cerebral perfusion are affected during exercise is related to the magnitude of hypocapnia induced by hyperventilation and this can occur at a different intensity relative to VO_{2max} for each individual. Olson et al. conducted a study of 14 healthy individuals and reported that the reduction in CBF velocity occurred above the ventilatory anaerobic threshold (ATh) (at the nadir of V_E/VCO_2) (265). In a similar study of 14 healthy individuals, maximal CBF velocity occurred at the exercise intensity just below the ATh (respiratory exchange ratio $\leq$1.0) during graded incremental exercise tests performed to exhaustion (266). Therefore, there may be utility in using the ATh as a metabolically uniform and individualized threshold intensity for determining safe exercise early post-stroke (i.e., an intensity level that occurs prior to achieving peak CBF velocity). Although CBF response to exercise above and below

the ATh under conditions of impaired CA has not been reported, since CBF velocity peaks at the ATh in healthy individuals, it may be prudent to prescribe exercise intensity below the ATh or where a non-linear increase in ventilation occurs. A non-linear increase in ventilation typically occurs at the level of the ATh, owing to excess CO_2 production (267). Therefore, a graded cardiopulmonary exercise test that is terminated after achieving the ATh early post-stroke would help to determine the intensity parameter of the exercise prescription. However, investigation into the safety of such a test is required. Alternatively, another strategy for guiding exercise intensity is to use the Talk Test. The Talk Test can be used as a surrogate of the ATh (268, 269). The premise is that it is difficult to talk when exercising at or above the ATh.

While exercise just below the ATh may be a safe intensity threshold, it may be a challenge for most people to reach and sustain this intensity owing to disability, fatigue, poor balance, and deconditioning (270). In a study described in section Effects of Aerobic Exercise Within 48 h Post-stroke, people were challenged to reach less than moderate intensity effort when treadmill aerobic exercise was initiated 41.5 ± 14 h post-stroke (193). Over half experienced symptoms and half ended exercise sessions because of exhaustion, some of which could be related to central fatigue (271). Participants attained the targeted exercise intensity (50% of predicted HRR) in only 31% of sessions. Yet, only participants with mild to no disability were included in the study and body weight supported exercise was used when needed. This raises the possibility that only patients with less than mild disability would be able to reach intensity levels during walking that would provide a cardiovascular stimulus sufficient to achieve the neurologic benefit observed in animal models. In a recent study, our group revealed that only 28% of 61 people post-stroke with mild to moderate gait deficits were able to reach a walking intensity at or above the ATh when asked to walk at their maximal speed for 6 min (270). These patients were a mean of 13 ± 23 months post-stroke and time elapsed from the stroke did not influence ability to reach the ATh during the walking assessment ($p = 0.5$). Further, 58.3% were able to reach at most, a level that was 10% lower than the ATh and 73.3% at most, a level that was 15% lower than the ATh. Alternative modalities to walking, such as stationary cycling, may be better tolerated allowing higher intensity exercise but as demonstrated in two small randomized control studies may not result in improvements in ambulation (272, 273). Therefore, a training intensity that is likely feasible during a walking prescription and safe from a cerebral and cardiovascular point-of-view in the early-phases post-stroke is to start at light intensity and progress patients to a heart rate that is 10–15% lower than the heart rate that occurred at the ATh on a cardiopulmonary exercise stress test, or talk test; i.e., less than moderate intensity. Gradual intensity progression may also help to reduce risk of musculoskeletal issues owing to altered gait patterns.

Protecting the Brain From Excessive Elevation and Rapid Fluctuations in Mean Arterial Pressure

Beta-adrenergic blocking medication such as Metoprolol (Lopressor) and Atenolol (Tenormin) are prescribed to ∼30–40% of people post-stroke (274). Beta-adrenergic blockade reduces cardiac output and CBF with exercise (162, 275). Therefore, patients who are prescribed a beta-blocker but are not at high risk of OH can be advised to perform aerobic exercise at a time when the medication is at maximum effect (i.e., ∼2–4 h after oral administration depending on dose) as this may provide an extra level of cerebral protection. This would be expressly important for people with elevated resting BP. Another precaution for patients with borderline high resting BP in the early phases post-stroke is to prescribe exercise that engages a small amount of muscle mass (276), as greater muscle mass engagement is associated with a greater pressor response along with higher catecholamine concentrations that produce a higher BP response (277). For example, avoid prescribing exercise on modalities that engage both upper and lower extremities such as the elliptical machine and rowing ergometer (277). Another strategy to mitigate BP during exercise and for added cerebral protection is to avoid exercising in the morning. While not measured in stroke patients specifically, there can be early morning "surges" in BP and heart rate that have been observed in free-living conditions (278). In addition, early morning CA has been shown to be impaired in healthy people (62).

In healthy adults, there is a 5–10 s CA response time to a change in BP (279). Characterizing time delay has not been studied in humans following stroke. However, repeated exposure to rapidly changing blood flow that is not adequately controlled by CA has been associated with damage to the cerebral capillary bed (41). Therefore, precautions include avoiding exercise that results in rapid fluctuations in BP such as high intensity interval training and rowing in the early phases. The BP changes are likely too rapid to be immediately countered by CA which can result in pulsatile blood flow to the brain. Rowing results in both high concentrations of catecholamines likely related to the large muscle mass engaged and rapid fluctuations in cerebral perfusion pressure (277). In a study of 12 rowers, mean cerebral blood velocity increased to a peak of 88 ± 7 cm s^{-1} during the catch phase of the rowing cycle; this was also the phase that elicited the highest mean BP of 125 ± 14 mmHg. Also, avoiding sudden transitions in intensity by instituting a gradual ramping up or down in intensity during the warm up and cool down period to allow CA function time to respond is recommended.

In addition, avoid prescribing exercises that have an isometric component (like rowing) and that risk performing the Valsalva maneuver. There are multiple phases to the Valsalva maneuver, and each phase can have variable effects on cerebral perfusion pressure (280). CA in healthy individuals in some cases responds too slowly to counteract the sudden changes in BP related to the Valsalva maneuver. In the release phase for example, when there is a sudden release of the strain pressure, there is an elevated risk of cerebral hypoperfusion (281, 282). Early effects of stroke may further slow CA response time and have a deleterious effect. While this requires validation in stroke patients, it is recommended to avoid performing the Valsalva maneuver such as might occur in the catch phase of rowing

TABLE 7 | Guideline 6.0: Strategies to minimize catecholamine surge and increases in mean arterial pressure.

Aerobic exercise intensity (see **Figure 1**):

1. Up to 1 month post-stroke: Mobilization and then gradual progression to light and then moderate intensity aerobic activity [∼10–15% below the level of the anaerobic threshold (ATh)]. Increase light intensity total duration first by ∼5–10 min every 1–2 weeks to ≥20 min (non-continuous preferred in 5–10 min intervals) then gradually increase intensity. The aim being to achieve moderate intensity exercise at the end of the 4 week period in higher functioning less medically complex patients.
2. 1–3 months post- stroke: Gradual progression from moderate intensity (∼10–15% below the level of the ATh) to the ATh if appropriate. First increase duration from 20 min to 30–60 min and then increase intensity.
3. More than 3 months post-stroke: Gradual progression to greater than moderate (ATh) to high intensity continuous or interval aerobic training if appropriate (preferably based on results of a graded exercise stress test with ECG monitoring).

Patients should be appropriately screened for participation and exercise strategies for safe prescription implemented. Exercise and mobilization should be prescribed on a case-by-case basis. Allow time for physiological adaptation after progression of an exercise parameter.

- In people with borderline high resting blood pressure in the first month post-stroke, prescribe exercise that engages a small amount of muscle mass.
- In those not at risk of OH and prescribed beta-blocker medication such as Metoprolol (Lopressor) and Atenolol (Tenormin) perform aerobic exercises at a time when the medication is at maximum effect (i.e., ∼2–4 h after oral administration depending on dose).
- Avoid morning exercise in the early post-stroke phase until more research has been conducted in people following stroke.

Strategies to reduce mean arterial pressure fluctuations

- Avoid exercise that results in rapid and large fluctuations in MAP such as rowing and high intensity interval training, until at least 3 months post-stroke.
- Avoid a sudden transition in exercise intensity by including a gradual ramping up or down in intensity during the warm up and cool down period.
- Avoid the Valsalva-like maneuver (breath holding) and avoid exercise with an isometric component (like rowing).

CONCLUSIONS

The timing of initiation and rate of progression of exercise and activity parameters are contingent on recovery of CA, resting BP, BBB function, hemorrhagic stroke parameters, ischemic penumbra, and cardiac-related complications. All physiological systems must be considered, including cardiac recovery that has to this point not been specifically considered. The early phases post-stroke are a dynamic and volatile time and careful application of mobilization and exercise therapy is required. Mobilization strategies need to mitigate the risk associated with orthostatic hypotension and prolonged standing, while exercise prescriptions need to be cognizant of the extent of BP elevation during exercise as well as the potential for post-exercise hypotension immediately thereafter. The strategies, precautions, and considerations, suggested herein, to safely mobilize patients are not resource intensive. Indeed, they are modifications to what is currently being practiced. We have also provided a more carefully considered screening criteria based on the literature.

Future studies may reveal a more complex association between timing of exercise interventions and recovery. Early interventions may prove beneficial to one parameter of stroke recovery such as cognition, but potentially harmful to another parameter. A profile of characteristics, including coexisting conditions such as diabetes, to identify patients that may benefit from a more rapid progression to higher intensity exercise should be undertaken. We have learned considerably from the AVERT study; however, before other studies of this magnitude and design are undertaken, it may be prudent to measure the acute effects of mobilization or aerobic exercise to help determine possible adverse effects. If detected, then strategies to counter the possible adverse effects of different intensities, duration, and modality during the early critical phases of the recovery continuum on CBF, BBB permeability, the ischemic penumbra, hematoma expansion, and other important physiological outcomes should be determined.

Effective use of early exercise and mobilization after stroke is currently limited by lack of data. Attempting to develop individualized approaches to exercise prescription are warranted but this requires a more holistic evaluation of the stroke survivor's overall fitness to exercise. Deeper and more comprehensive assessments will likely shed important new light in this important area of stroke recovery research.

AUTHOR CONTRIBUTIONS

SM drafted the manuscript. AR and BM critically revised and contributed to the conception and design of all parts of the manuscript. All others critically revised and contributed to the conception and/or design of parts of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01187/full#supplementary-material

REFERENCES

1. *Global Stroke Fact Sheet*. World Stroke Organization (2019). Available online at: http://www.world-stroke.org (accessed February 26, 2019).
2. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: what can be learned from animal models? *Neurorehab Neural Repair*. (2012) 26:923–31. doi: 10.1177/1545968312440745
3. Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: the stroke recovery and rehabilitation roundtable taskforce. *Int J Stroke*. (2017) 12:444–50. doi: 10.1177/1747493017711816

4. Li F, Shi W, Zhao EY, Geng X, Li X, Peng C, et al. Enhanced apoptosis from early physical exercise rehabilitation following ischemic stroke. *J Neurosci Res*. (2017) 95:1017–24. doi: 10.1002/jnr.23890
5. Li F, Geng X, Khan H, Pendy JT Jr, Peng C, Li X, et al. Exacerbation of brain injury by post-stroke exercise is contingent upon exercise initiation timing. *Front Cell Neurosci*. (2017) 11:311. doi: 10.3389/fncel.2017.00311
6. Shen J, Huber M, Zhao EY, Peng C, Li F, Li X, et al. Early rehabilitation aggravates brain damage after stroke via enhanced activation of nicotinamide adenine dinucleotide phosphate oxidase (nox). *Brain Res*. (2016) 1648:266–76. doi: 10.1016/j.brainres.2016.08.001
7. Li F, Pendy JT Jr, Ding JN, Peng C, Li X, Shen J, et al. Exercise rehabilitation immediately following ischemic stroke exacerbates inflammatory injury. *Neurol Res*. (2017) 39:530–7. doi: 10.1080/01616412.2017.1315882
8. Ho E, Cheung SHC, Denton M, Kim BDH, Stephenson F, Ching J, et al. The practice and predictors of early mobilization of patients post-acute admission to a specialized stroke center. *Top Stroke Rehabil*. (2018) 15:1–7. doi: 10.1080/10749357.2018.1507308
9. Prakash V, Shah MA, Hariohm K. Family's presence associated with increased physical activity in patients with acute stroke: an observational study. *Braz J Phys Ther*. (2016) 20:306–11. doi: 10.1590/bjpt-rbf.2014.0172
10. Åstrand A, Saxin C, Sjöholm A, Skarin M, Linden T, Stoker A, et al. Poststroke physical activity levels no higher in rehabilitation than in the acute hospital. *J Stroke Cerebrovasc*. (2016) 25:938–45. doi: 10.1016/j.jstrokecerebrovasdis.2015.12.046
11. Norvang OP, Hokstad A, Taraldsen K, Tan X, Lydersen S, Indredavik B, et al. Time spent lying, sitting, and upright during hospitalization after stroke: a prospective observation study. *BMC Neurol*. (2018) 18:138. doi: 10.1186/s12883-018-1134-0
12. Nathoo C, Buren S, El-Haddad R, Feldman K, Schroeder E, Brooks D, et al. Aerobic training in canadian stroke rehabilitation programs. *J Neurol Phys Ther*. (2018) 42:248–55. doi: 10.1097/NPT.0000000000000237
13. Boyne P, Billinger S, MacKay-Lyons M, Barney B, Khoury J, Dunning K. Aerobic exercise prescription in stroke rehabilitation: a web-based survey of us physical therapists. *JNPT*. (2017) 41:119–28. doi: 10.1097/NPT.0000000000000177
14. Hasan SMM, Rancourt SN, Austin MW, Ploughman M. Defining optimal aerobic exercise parameters to affect complex motor and cognitive outcomes after stroke: a systematic review and synthesis. *Neural Plast*. (2016) 2016:12. doi: 10.1155/2016/2961573
15. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. (2018) 49:e46–99. doi: 10.1161/STR.0000000000000172
16. (Australian) Clinical Guidelines for Stroke Management 2017 v5.2. Available online at: https://app.magicapp.org/app#/guideline/2282
17. Intercollegiate Stroke Working Party. *National Clinical Guideline for Stroke*. 5th ed. London: Royal College of Physicians (2016).
18. Hebert D, Lindsay MP, McIntyre A, Kirton A, Rumney PG, Bagg S, et al. Canadian stroke best practice recommendations: stroke rehabilitation practice guidelines, update 2015. *Int J Stroke*. (2016) 11:459–84. doi: 10.1177/1747493016643553
19. Küçükdeveci AA, Sunnerhagen KS, Golyk V, Delarque A, Ivanova G, Zampolini M, et al. Evidence based position paper on physical and rehabilitation medicine (prm) professional practice for persons with stroke. The european prm position (uems prm section). *Eur J Phys Rehabil Med*. (2018) 54:957–70. doi: 10.23736/S1973-9087.18.05501-6
20. Bernhardt J, Langhorne P, Lindley RI, Ellery F, Collier J, Churilov L, et al. Efficacy and safety of very early mobilisation within 24 h of stroke onset (avert): a randomised controlled trial. *Lancet*. (2015) 386:46–55. doi: 10.1016/S0140-6736(15)60690-0
21. National Guideline Centre. *Stroke and Transient Ischaemic Attack in Over 16s: Diagnosis and Initial Management*. London: National Institue for Health and Care Excellence (2019).
22. Mackay-Lyons M, Billinger CJ, Eng J, Dromerick A, Firth W, Giacomantonio N, et al. Aerobic exercise recommendations to optimize best practices in care after stroke (aerobics). *Stroke*. (2019) 2019:pzz153. doi: 10.1093/ptj/pzz153
23. Podolin DA, Munger PA, Mazzeo RS. Plasma catecholamine and lactate response during graded exercise with varied glycogen conditions. *J Appl Physiol*. (1991) 71:1427–33. doi: 10.1152/jappl.1991.71.4.1427
24. Stratton JR, Halter JB, Hallstrom AP, Caldwell JH, Ritchie JL. Comparative plasma catecholamine and hemodynamic responses to handgrip, cold pressor and supine bicycle exercise testing in normal subjects. *J Am Coll Cardiol*. (1983) 2:93–104. doi: 10.1016/S0735-1097(83)80381-7
25. Vlcek M, Radikova Z, Penesova A, Kvetnansky R, Imrich R. Heart rate variability and catecholamines during hypoglycemia and orthostasis. *Auton Neurosci Basic*. (2008) 143:53–7. doi: 10.1016/j.autneu.2008.08.001
26. Castro P, Serrador JM, Rocha I, Sorond F, Azevedo E. Efficacy of cerebral autoregulation in early ischemic stroke predicts smaller infarcts and better outcome. *Front Neurol*. (2017) 8:113. doi: 10.3389/fneur.2017.00113
27. Reinhard M, Rutsch S, Hetzel A. Cerebral autoregulation in acute ischemic stroke. *Persp. Med*. (2012) 1:194–7. doi: 10.1016/j.permed.2012.02.028
28. Castro P, Azevedo E, Serrador J, Rocha I, Sorond F. Hemorrhagic transformation and cerebral edema in acute ischemic stroke: link to cerebral autoregulation. *J Neurol Sci*. (2017) 372:256–61. doi: 10.1016/j.jns.2016.11.065
29. Tzeng Y-C, Ainslie PN. Blood pressure regulation ix: cerebral autoregulation under blood pressure challenges. *Euro J Appl Physiol*. (2014) 114:545–59. doi: 10.1007/s00421-013-2667-y
30. Zhang R, Zuckerman JH, Iwasaki K, Wilson TE, Crandall CG, Levine BD. Autonomic neural control of dynamic cerebral autoregulation in humans. *Circulation*. (2002) 106:1814–20. doi: 10.1161/01.CIR.0000031798.07790.FE
31. Ma H, Guo Z-N, Liu J, Xing Y, Zhao R, Yang Y. Temporal course of dynamic cerebral autoregulation in patients with intracerebral hemorrhage. *Stroke*. (2016) 47:674–81. doi: 10.1161/STROKEAHA.115.011453
32. Xiong L, Tian G, Lin W, Wang W, Wang L, Leung T, et al. Is dynamic cerebral autoregulation bilaterally impaired after unilateral acute ischemic stroke? *J Stroke Cerebrovasc*. (2017) 26:1081–7. doi: 10.1016/j.jstrokecerebrovasdis.2016.12.024
33. Otite F, Mink S, Tan CO, Puri A, Zamani AA, Mehregan A, et al. Impaired cerebral autoregulation is associated with vasospasm and delayed cerebral ischemia in subarachnoid hemorrhage. *Stroke*. (2014) 45:677–82. doi: 10.1161/STROKEAHA.113.002630
34. Dawson SL, Panerai RB, Potter JF. Serial changes in static and dynamic cerebral autoregulation after acute ischaemic stroke. *Cerebrovasc Dis*. (2003) 16:69–75. doi: 10.1159/000070118
35. Salinet ASM, Panerai RB, Robinson TG. The longitudinal evolution of cerebral blood flow regulation after acute ischaemic stroke. *Cerebrovasc Dis Extra*. (2014) 4:186–97. doi: 10.1159/000366017
36. Petersen NH, Ortega-Gutierrez S, Reccius A, Masurkar A, Huang A, Marshall RS. Dynamic cerebral autoregulation is transiently impaired for one week after large-vessel acute ischemic stroke. *Cerebrovasc Dis*. (2015) 39:144–50. doi: 10.1159/000368595
37. Eames P, Blake M, Dawson S, Panerai R, Potter J. Dynamic cerebral autoregulation and beat to beat blood pressure control are impaired in acute ischaemic stroke. *J Neurol Neurosur PS*. (2002) 72:467–72. doi: 10.1136/jnnp.72.4.467
38. Lam JM, Smielewski P, Czosnyka M, Pickard JD, Kirkpatrick PJ. Predicting delayed ischemic deficits after aneurysmal subarachnoid hemorrhage using a transient hyperemic response test of cerebral autoregulation. *Neurosurgery*. (2000) 47:819–26. doi: 10.1097/00006123-200010000-00004
39. Lang EW, Diehl RR, Mehdorn HM. Cerebral autoregulation testing after aneurysmal subarachnoid hemorrhage: the phase relationship between arterial blood pressure and cerebral blood flow velocity. *Crit Care Med*. (2001) 29:158–63. doi: 10.1097/00003246-200101000-00031
40. Soehle M, Czosnyka M, Pickard JD, Kirkpatrick PJ. Continuous assessment of cerebral autoregulation in subarachnoid hemorrhage. *Anesth Analg*. (2004) 98:1133–9. doi: 10.1213/01.ANE.0000111101.41190.99
41. Mitchell GF, Vita JA, Larson MG, Parise H, Keyes MJ, Warner E, et al. Cross-sectional relations of peripheral microvascular function, cardiovascular disease risk factors, and aortic stiffness the framingham heart study. *Circulation*. (2005) 112:3722–8. doi: 10.1161/CIRCULATIONAHA.105.551168

42. Attwell D, Buchan AM, Charpak S, Lauritzen M, MacVicar BA, Newman EA. Glial and neuronal control of brain blood flow. *Nature*. (2010) 468:232. doi: 10.1038/nature09613
43. Stead LG, Gilmore RM, Decker WW, Weaver AL, Brown RD. Initial emergency department blood pressure as predictor of survival after acute ischemic stroke. *Neurology*. (2005) 65:1179–83. doi: 10.1212/01.wnl.0000180939.24845.22
44. Castro P, Azevedo E, Sorond F. Cerebral autoregulation in stroke. *Curr Atheroscler Rep*. (2018) 20:37. doi: 10.1007/s11883-018-0739-5
45. Schmidt B, Czosnyka M, Klingelhöfer J. Asymmetry of cerebral autoregulation does not correspond to asymmetry of cerebrovascular pressure reactivity. *Persp Med*. (2012) 1:285–9. doi: 10.1016/j.permed.2012.02.026
46. Schmidt B, Klingelhöfer J, Perkes I, Czosnyka M. Cerebral autoregulatory response depends on the direction of change in perfusion pressure. *J Neurotraum*. (2009) 26:651–6. doi: 10.1089/neu.2008.0784
47. Aaslid R, Blaha M, Sviri G, Douville CM, Newell DW. Asymmetric dynamic cerebral autoregulatory response to cyclic stimuli. *Stroke*. (2007) 38:1465–9. doi: 10.1161/STROKEAHA.106.473462
48. Tzeng Y-C, Willie CK, Atkinson G, Lucas SJ, Wong A, Ainslie PN. Cerebrovascular regulation during transient hypotension and hypertension in humans. *Hypertension*. (2010) 56:268–73. doi: 10.1161/HYPERTENSIONAHA.110.152066
49. Aries MJH, Elting JW, De Keyser J, Kremer BPH, Vroomen PCAJ. Cerebral autoregulation in stroke: a review of transcranial doppler studies. *Stroke*. (2010) 41:2697–704. doi: 10.1161/STROKEAHA.110.594168
50. Leigh R, Knutsson L, Zhou J, Zijl PCv. Imaging the physiological evolution of the ischemic penumbra in acute ischemic stroke. *J Cerebr Blood F Met*. (2018) 38:1500–16. doi: 10.1177/0271678X17700913
51. Baron JC. How healthy is the acutely reperfused ischemic penumbra? *Cerebrovasc Dis*. (2005) 20(suppl 2):25–31. doi: 10.1159/000089354
52. Dani KA, Warach S. Metabolic imaging of ischemic stroke: the present and future. *Am J Neuroradiol*. (2014) 35:S37–43. doi: 10.3174/ajnr.A3789
53. Jørgensen H, Sperling B, Nakayama H, Raaschou H, Olsen T. Spontaneous reperfusion of cerebral infarcts in patients with acute stroke: incidence, time course, and clinical outcome in the copenhagen stroke study. *Arch Neurol*. (1994) 51:865–73. doi: 10.1001/archneur.1994.00540210037011
54. Figoni SF. Cardiovascular and haemodynamic responses to tilting and to standing in tetraplegic patients: a review. *Spinal Cord*. (1984) 22:99. doi: 10.1038/sc.1984.18
55. He M, Wang Je, Liu N, Xiao X, Geng S, Meng P, et al. Effects of blood pressure in the early phase of ischemic stroke and stroke subtype on poststroke cognitive impairment. *Stroke*. (2018) 49:1610–7. doi: 10.1161/STROKEAHA.118.020827
56. Gibbons CH, Schmidt P, Biaggioni I, Frazier-Mills C, Freeman R, Isaacson S, et al. The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension. *J Neurol*. (2017) 264:1567–82. doi: 10.1007/s00415-016-8375-x
57. Jansen S, Bhangu J, de Rooij S, Daams J, Kenny RA, van der Velde N. The association of cardiovascular disorders and falls: a systematic review. *J Am Med Dir Assoc*. (2016) 17:193–9. doi: 10.1016/j.jamda.2015.08.022
58. Rocca A, Pignat J-M, Berney L, Jöhr J, Van de Ville D, Daniel R, et al. Sympathetic activity and early mobilization in patients in intensive and intermediate care with severe brain injuries: a preliminary prospective randomized study. *BMC Neurol*. (2016) 16:169. doi: 10.1186/s12883-016-0684-2
59. Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. *Am J Med*. (2007) 120:841–7. doi: 10.1016/j.amjmed.2007.02.023
60. Peters R, Anstey KJ, Booth A, Beckett N, Warwick J, Antikainen R, et al. Orthostatic hypotension and symptomatic subclinical orthostatic hypotension increase risk of cognitive impairment: an integrated evidence review and analysis of a large older adult hypertensive cohort. *Eur Heart J*. (2018) 39:3135–43. doi: 10.1093/eurheartj/ehy418
61. Kong K-H, Chuo AM. Incidence and outcome of orthostatic hypotension in stroke patients undergoing rehabilitation. *Arch Phys Med Rehabil*. (2003) 84:559–62. doi: 10.1053/apmr.2003.50040
62. Ainslie PN, Murrell C, Peebles K, Swart M, Skinner MA, Williams MJA, et al. Early morning impairment in cerebral autoregulation and cerebrovascular CO_2 reactivity in healthy humans: relation to endothelial function. *Exp Physiol*. (2007) 92:769–77. doi: 10.1113/expphysiol.2006.036814
63. de Brito LC, Rezende RA, da Silva Junior ND, Tinucci T, Casarini DE, Cipolla-Neto J, et al. Post-exercise hypotension and its mechanisms differ after morning and evening exercise: a randomized crossover study. *PLoS ONE*. (2015) 10:e0132458. doi: 10.1371/journal.pone.0132458
64. Robert Carter I, Cheuvront SN, Vernieuw CR, Sawka MN. Hypohydration and prior heat stress exacerbates decreases in cerebral blood flow velocity during standing. *J Appl Physiol*. (2006) 101:1744–50. doi: 10.1152/japplphysiol.00200.2006
65. Privett SE, George KP, Whyte GP, Cable NT. The effectiveness of compression garments and lower limb exercise on post-exercise blood pressure regulation in orthostatically intolerant athletes. *Clin J Sport Med*. (2010) 20:362–7. doi: 10.1097/JSM.0b013e3181f20292
66. Dorey TW, O'Brien MW, Robinson SA, Kimmerly DS. Knee-high compression socks minimize head-up tilt-induced cerebral and cardiovascular responses following dynamic exercise. *Scand J Med Sci Sports*. (2018) 28:1766–74. doi: 10.1111/sms.13084
67. Ogoh S, Fisher JP, Purkayastha S, Dawson EA, Fadel PJ, White MJ, et al. Regulation of middle cerebral artery blood velocity during recovery from dynamic exercise in humans. *J Appl Physiol*. (2007) 102:713–21. doi: 10.1152/japplphysiol.00801.2006
68. Sochart D, Hardinge K. The relationship of foot and ankle movements to venous return in the lower limb. *J Bone Joint Surg Br*. (1999) 81:700–4. doi: 10.1302/0301-620X.81B4.0810700
69. Zazulia AR, Diringer MN, Videen TO, Adams RE, Yundt K, Aiyagari V, et al. Hypoperfusion without ischemia surrounding acute intracerebral hemorrhage. *J Cerebr Blood F Met*. (2001) 21:804–10. doi: 10.1097/00004647-200107000-00005
70. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. (1997) 28:1–5. doi: 10.1161/01.STR.28.1.1
71. Anderson CS, Huang Y, Arima H, Heeley E, Skulina C, Parsons MW, et al. Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: the intensive blood pressure reduction in acute cerebral haemorrhage trial (interact). *Stroke*. (2010) 41:307–12. doi: 10.1161/STROKEAHA.109.561795
72. Reinhard M, Neunhoeffer F, Gerds TA, Niesen W-D, Buttler K-J, Timmer J, et al. Secondary decline of cerebral autoregulation is associated with worse outcome after intracerebral hemorrhage. *Intensive Care Med*. (2010) 36:264–71. doi: 10.1007/s00134-009-1698-7
73. Rätsep T, Eelmäe J, Asser T. Routine utilization of the transient hyperaemic response test after aneurysmal subarachnoid haemorrhage. *Acta Neurochir Suppl*. (2002) 81:121–4. doi: 10.1007/978-3-7091-6738-0_31
74. Zweifel C, Castellani G, Czosnyka M, Carrera E, Brady KM, Kirkpatrick PJ, et al. Continuous assessment of cerebral autoregulation with near-infrared spectroscopy in adults after subarachnoid hemorrhage. *Stroke*. (2010) 41:1963–8. doi: 10.1161/STROKEAHA.109.577320
75. Schmieder K, Möller F, Engelhardt M, Scholz M, Schregel W, Christmann A, et al. Dynamic cerebral autoregulation in patients with ruptured and unruptured aneurysms after induction of general anesthesia. *Zbl Neurochir*. (2006) 67:81–7. doi: 10.1055/s-2006-933374
76. Calviere L, Nasr N, Arnaud C, Czosnyka M, Viguier A, Tissot B, et al. Prediction of delayed cerebral ischemia after subarachnoid hemorrhage using cerebral blood flow velocities and cerebral autoregulation assessment. *Neurocrit Care*. (2015) 23:253–8. doi: 10.1007/s12028-015-0125-x
77. Jaeger M, Schuhmann MU, Soehle M, Nagel C, Meixensberger J. Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. *Stroke*. (2007) 38:981–6. doi: 10.1161/01.STR.0000257964.65743.99
78. Budohoski KP, Czosnyka M, Smielewski P, Kasprowicz M, Helmy A, Bulters D, et al. Impairment of cerebral autoregulation predicts delayed cerebral ischemia after subarachnoid hemorrhage: a prospective observational study. *Stroke*. (2012) 43:3230–7. doi: 10.1161/STROKEAHA.112.669788
79. Budohoski KP, Czosnyka M, Kirkpatrick PJ, Reinhard M, Varsos GV, Kasprowicz M, et al. Bilateral failure of cerebral autoregulation is related to

unfavorable outcome after subarachnoid hemorrhage. *Neurocrit Care*. (2015) 22:65–73. doi: 10.1007/s12028-014-0032-6
80. Bederson JB, Connolly ES Jr, Batjer HH, Dacey RG, Dion JE, Diringer MN, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the stroke council, American Heart Association. *Stroke*. (2009) 40:994–1025. doi: 10.1161/STROKEAHA.108.191395
81. Kassell N, Sasaki T, Colohan A, Nazar G. Cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *Stroke*. (1985) 16:562–72. doi: 10.1161/01.STR.16.4.562
82. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood–brain barrier. *Neurobiol Dis*. (2010) 37:13–25. doi: 10.1016/j.nbd.2009.07.030
83. Latour LL, Kang D-W, Ezzeddine MA, Chalela JA, Warach S. Early blood–brain barrier disruption in human focal brain ischemia. *Ann Neurol*. (2004) 56:468–77. doi: 10.1002/ana.20199
84. Jickling GC, Liu D, Stamova B, Ander BP, Zhan X, Lu A, et al. Hemorrhagic transformation after ischemic stroke in animals and humans. *J Cerebr Blood F Met*. (2014) 34:185–99. doi: 10.1038/jcbfm.2013.203
85. Kuroiwa T, Ting P, Martinez H, Klatzo I. The biphasic opening of the blood-brain barrier to proteins following temporary middle cerebral artery occlusion. *Acta Neuropathol*. (1985) 68:122–9. doi: 10.1007/BF00688633
86. Brouns R, Wauters A, De Surgeloose D, Mariën P, De Deyn PP. Biochemical markers for blood-brain barrier dysfunction in acute ischemic stroke correlate with evolution and outcome. *Euro Neurol*. (2011) 65:23–31. doi: 10.1159/000321965
87. Hamann GF, Okada Y, Fitridge R, Del Zoppo GJ. Microvascular basal lamina antigens disappear during cerebral ischemia and reperfusion. *Stroke*. (1995) 26:2120–6. doi: 10.1161/01.STR.26.11.2120
88. Merten C, Knitelius H, Assheuer J, Bergmann-Kurz B, Hedde J, Bewermeyer H. Mri of acute cerebral infarcts: increased contrast enhancement with continuous infusion of gadolinium. *Neuroradiology*. (1999) 41:242–8. doi: 10.1007/s002340050740
89. Liu H-S, Chung H-W, Chou M-C, Liou M, Wang C-Y, Kao H-W, et al. Effects of microvascular permeability changes on contrast-enhanced t1 and pharmacokinetic mr imagings after ischemia. *Stroke*. (2013) 44:1872–7. doi: 10.1161/STROKEAHA.113.001558
90. Lin C-Y, Chang C, Cheung W-M, Lin M-H, Chen J-J, Hsu CY, et al. Dynamic changes in vascular permeability, cerebral blood volume, vascular density, and size after transient focal cerebral ischemia in rats: evaluation with contrast-enhanced magnetic resonance imaging. *J Cerebr Blood F Met*. (2008) 28:1491–501. doi: 10.1038/jcbfm.2008.42
91. Moisan A, Favre IM, Rome C, Grillon E, Naegele B, Barbieux M, et al. Microvascular plasticity after experimental stroke: a molecular and mri study. *Cerebrovasc Dis*. (2014) 38:344–53. doi: 10.1159/000368597
92. Strbian D, Durukan A, Pitkonen M, Marinkovic I, Tatlisumak E, Pedrono E, et al. The blood–brain barrier is continuously open for several weeks following transient focal cerebral ischemia. *Neuroscience*. (2008) 153:175–81. doi: 10.1016/j.neuroscience.2008.02.012
93. Bailey DM, Evans KA, McEneny J, Young IS, Hullin DA, James PE, et al. Exercise-induced oxidative–nitrosative stress is associated with impaired dynamic cerebral autoregulation and blood–brain barrier leakage. *Exp Physiol*. (2011) 96:1196–207. doi: 10.1113/expphysiol.2011.060178
94. Roh H-T, Cho S-Y, So W-Y. Obesity promotes oxidative stress and exacerbates blood-brain barrier disruption after high-intensity exercise. *J Sport Health Sci*. (2017) 6:225–30. doi: 10.1016/j.jshs.2016.06.005
95. Koh SX, Lee JK. S100b as a marker for brain damage and blood–brain barrier disruption following exercise. *Sports Med*. (2014) 44:369–85. doi: 10.1007/s40279-013-0119-9
96. Keep RF, Zhou N, Xiang J, Andjelkovic AV, Hua Y, Xi G. Vascular disruption and blood–brain barrier dysfunction in intracerebral hemorrhage. *Fluids Barriers CNS*. (2014) 11:18. doi: 10.1186/2045-8118-11-18
97. Qureshi AI. Acute hypertensive response in patients with stroke: pathophysiology and management. *Circulation*. (2008) 118:176–87. doi: 10.1161/CIRCULATIONAHA.107.723874
98. Wallace JD, Levy LL. Blood pressure after stroke. *JAMA*. (1981) 246:2177–80. doi: 10.1001/jama.1981.03320190035023
99. Qureshi AI, Ezzeddine MA, Nasar A, Suri MF, Kirmani JF, Hussein HM, et al. Prevalence of elevated blood pressure in 563704 adult patients with stroke presenting to the ed in the united states. *Am J Emerg Med*. (2007) 25:32–8. doi: 10.1016/j.ajem.2006.07.008
100. Fischer U, Cooney MT, Bull LM, Silver LE, Chalmers J, Anderson CS, et al. Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study. *Lancet Neurol*. (2014) 17:374–84. doi: 10.1016/S1474-4422(14)70031-6
101. Sandset EC, Bath PMW, Boysen G, Jatuzis D, Kõrv J, Lüders S, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (scast): a randomised, placebo-controlled, double-blind trial. *Lancet*. (2011) 377:741–50. doi: 10.1016/S0140-6736(11)60104-9
102. Morrison SA, Cheung SS, Hurst RD, Cotter JD. Cognitive function and blood-brain barrier permeability during exercise in the heat: effect of fitness and bovine colostrum supplementation. *J Therm Biol*. (2013) 38:374–83. doi: 10.1016/j.jtherbio.2013.05.002
103. Watson P, Black KE, Clark SC, Maughan RJ. Exercise in the heat: effect of fluid ingestion on blood-brain barrier permeability. *Med Sci Sport Exer*. (2006) 38:2118–24. doi: 10.1249/01.mss.0000235356.31932.0a
104. Watson P, Shirreffs SM, Maughan RJ. Blood-brain barrier integrity may be threatened by exercise in a warm environment. *Am J Physiol-Reg I*. (2005) 288:R1689–94. doi: 10.1152/ajpregu.00676.2004
105. Rabinstein AA, Albers GW, Brinjikji W, Koch S. Factors that may contribute to poor outcome despite good reperfusion after acute endovascular stroke therapy. *Int J Stroke*. (2019) 14:23–31. doi: 10.1177/1747493018799979
106. Corbett D, Thornhill J. Temperature modulation (hypothermic and hyperthermic conditions) and its influence on histological and behavioral outcomes following cerebral ischemia. *Brain Pathol*. (2000) 10:145–52. doi: 10.1111/j.1750-3639.2000.tb00251.x
107. Liesz A, Hu X, Kleinschnitz C, Offner H. Functional role of regulatory lymphocytes in stroke: facts and controversies. *Stroke*. (2015) 46:1422–30. doi: 10.1161/STROKEAHA.114.008608
108. Li P, Gan Y, Sun B-L, Zhang F, Lu B, Gao Y, et al. Adoptive regulatory T-cell therapy protects against cerebral ischemia. *Ann Neurol*. (2013) 74:458–71. doi: 10.1002/ana.23815
109. Goekint M, Roelands B, Heyman E, Njemini R, Meeusen R. Influence of citalopram and environmental temperature on exercise-induced changes in bdnf. *Neurosci Lett*. (2011) 494:150–4. doi: 10.1016/j.neulet.2011.03.001
110. Prosser J, MacGregor L, Lees KR, Diener H-C, Hacke W, Davis S. Predictors of early cardiac morbidity and mortality after ischemic stroke. *Stroke*. (2007) 38:2295–302. doi: 10.1161/STROKEAHA.106.471813
111. Tanne D, Molshatzki N, Merzeliak O, Tsabari R, Toashi M, Schwammenthal Y. Anemia status, hemoglobin concentration and outcome after acute stroke: a cohort study. *BMC Neurol*. (2010) 10:22. doi: 10.1186/1471-2377-10-22
112. Bovim MR, Askim T, Lydersen S, Fjærtoft H, Indredavik B. Complications in the first week after stroke: a 10-year comparison. *BMC Neurol*. (2016) 16:133. doi: 10.1186/s12883-016-0654-8
113. Langhorne P, Stott DJ, Robertson L, MacDonald J, Jones L, McAlpine C, et al. Medical complications after stroke: a multicenter study. *Stroke*. (2000) 31:1223–9. doi: 10.1161/01.STR.31.6.1223
114. Weiss A, Grossman E, Beloosesky Y, Grinblat J. Orthostatic hypotension in acute geriatric ward: is it a consistent finding? *Arch Intern Med*. (2002) 162:2369–74. doi: 10.1001/archinte.162.20.2369
115. Chang SW, Huang YC, Lin LC, Yang JT, Weng HH, Tsai YH, et al. Effect of dehydration on the development of collaterals in acute middle cerebral artery occlusion. *Eur J Neurol*. (2016) 23:494–500. doi: 10.1111/ene.12841
116. Mankovsky B, Piolot R, Mankovsky O, Ziegler D. Impairment of cerebral autoregulation in diabetic patients with cardiovascular autonomic neuropathy and orthostatic hypotension. *Diabetic Med*. (2003) 20:119–26. doi: 10.1046/j.1464-5491.2003.00885.x
117. Kim YS, Immink RV, Stok WJ, Karemaker JM, Secher NH, Van Lieshout JJ. Dynamic cerebral autoregulatory capacity is affected early in type 2 diabetes. *Clin Sci*. (2008) 115:255–62. doi: 10.1042/CS20070458
118. Candelise L, Landi G, Orazio EN, Boccardi E. Prognostic significance of hyperglycemia in acute stroke. *Arch Neurol*. (1985) 42:661–3. doi: 10.1001/archneur.1985.04060070051014
119. Masrur S, Cox M, Bhatt DL, Smith EE, Ellrodt G, Fonarow GC, et al. Association of acute and chronic hyperglycemia with acute ischemic stroke

outcomes post-thrombolysis: findings from get with the guidelines-stroke. *J Am Heart Assoc*. (2015) 4:e002193. doi: 10.1161/JAHA.115.002193
120. Hemphill JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. (2015) 46:2032–60. doi: 10.1161/STR.0000000000000069
121. Oliveira-Filho J, Silva S, Trabuco C, Pedreira B, Sousa E, Bacellar A. Detrimental effect of blood pressure reduction in the first 24 hours of acute stroke onset. *Neurology*. (2003) 61:1047–51. doi: 10.1212/01.WNL.0000092498.75010.57
122. Wang Y, Wang Je, Meng P, Liu N, Ji N, Zhang G, et al. Mid-term blood pressure variability is associated with clinical outcome after ischemic stroke. *Am J Hypertens*. (2017) 30:968–77. doi: 10.1093/ajh/hpx083
123. Stead LG, Gilmore RM, Vedula KC, Weaver AL, Decker WW, Brown RD. Impact of acute blood pressure variability on ischemic stroke outcome. *Neurology*. (2006) 66:1878–81. doi: 10.1212/01.wnl.0000219628.78513.b5
124. Shi Z, Li ES, Zhong JS, Yuan JL, Li LR, Zheng CW. Predictive significance of day-to-day blood pressure variability in acute ischemic stroke for 12-month functional outcomes. *Am J Hypertens*. (2017) 30:524–31. doi: 10.1093/ajh/hpx005
125. Vernino S, Brown RD, Sejvar JJ, Sicks JD, Petty GW, O'Fallon WM. Cause-specific mortality after first cerebral infarction: a population-based study. *Stroke*. (2003) 34:1828–32. doi: 10.1161/01.STR.0000080534.98416.A0
126. Hartmann A, Rundek T, Mast H, Paik M, Boden–Albala B, Mohr J, et al. Mortality and causes of death after first ischemic stroke the northern manhattan stroke study. *Neurology*. (2001) 57:2000–5. doi: 10.1212/WNL.57.11.2000
127. Chen Z, Venkat P, Seyfried D, Chopp M, Yan T, Chen J. Brain–heart interaction: cardiac complications after stroke. *Circ Res*. (2017) 121:451–68. doi: 10.1161/CIRCRESAHA.117.311170
128. Naredi S, Lambert G, Edén E, Zäll S, Runnerstam M, Rydenhag B, et al. Increased sympathetic nervous activity in patients with nontraumatic subarachnoid hemorrhage. *Stroke*. (2000) 31:901–6. doi: 10.1161/01.STR.31.4.901
129. Banki NM, Kopelnik A, Dae MW, Miss J, Tung P, Lawton MT, et al. Acute neurocardiogenic injury after subarachnoid hemorrhage. *Circulation*. (2005) 112:3314–9. doi: 10.1161/CIRCULATIONAHA.105.558239
130. Masuda T, Sato K, Yamamoto S-i, Matsuyama N, Shimohama T, Matsunaga A, et al. Sympathetic nervous activity and myocardial damage immediately after subarachnoid hemorrhage in a unique animal model. *Stroke*. (2002) 33:1671–6. doi: 10.1161/01.STR.0000016327.74392.02
131. van der Bilt IA, Vendeville J-P, van de Hoef TP, Begieneman MP, Lagrand WK, Kros JM, et al. Myocarditis in patients with subarachnoid hemorrhage: a histopathologic study. *J Crit Care*. (2016) 32:196–200. doi: 10.1016/j.jcrc.2015.12.005
132. Tranmer BI, Keller TS, Kindt GW, Archer D. Loss of cerebral regulation during cardiac output variations in focal cerebral ischemia. *J Neurosurg*. (1992) 77:253–9. doi: 10.3171/jns.1992.77.2.0253
133. Koike A, Itoh H, Oohara R, Hoshimoto M, Tajima A, Aizawa T, et al. Cerebral oxygenation during exercise in cardiac patients. *Chest*. (2004) 125:182–90. doi: 10.1378/chest.125.1.182
134. Powers WJ. Cerebral blood flow and metabolism: regulation and pathophysiology in cerebrovascular disease. *Stroke*. (2016) 2016:28–46.e27. doi: 10.1016/B978-0-323-29544-4.00003-7
135. Wira III CR, Rivers E, Silver B, Lewandowski C. The impact of cardiac contractility on cerebral blood flow in ischemia. *West J Emerg Med*. (2011) 12:227. doi: 10.5811/westjem.2011.2.1765
136. Treib J, Haass A, Koch D, Stoll M, Ohlmann D, Schimrigk K. Transcranial doppler examination on effect of hemodynamics on cerebral autoregulation in acute cerebral infarct. *Ultraschall Med*. (1996) 17:64–7. doi: 10.1055/s-2007-1003148
137. Caldas JR, Panerai RB, Haunton VJ, Almeida JP, Ferreira GS, Camara L, et al. Cerebral blood flow autoregulation in ischemic heart failure. *Am J Physiol-Reg I*. (2016) 312:R108–13. doi: 10.1152/ajpregu.00361.2016
138. Fraser KS, Heckman GA, McKelvie RS, Harkness K, Middleton LE, Hughson RL. Cerebral hypoperfusion is exaggerated with an upright posture in heart failure: impact of depressed cardiac output. *J Am Coll Cardiol*. (2015) 3:168–75. doi: 10.1016/j.jchf.2014.07.017
139. Cremers CHP, van der Bilt IAC, van der Schaaf IC, Vergouwen MDI, Dankbaar JW, Cramer MJ, et al. Relationship between cardiac dysfunction and cerebral perfusion in patients with aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. (2016) 24:202–6. doi: 10.1007/s12028-015-0188-8
140. Wira CR, Rivers E, Martinez-Capolino C, Silver B, G. I, Sherwin R, et al. Cardiac complications in acute ischemic stroke. *West J Emerg Med*. (2011) 12:414–20. doi: 10.5811/westjem.2011.2.1785
141. Stouffer GA, Sheahan RG, Sorescu D, Turk RJ, Cain M, Lerakis S. Clinical and transthoracic echocardiographic predictors of abnormal transesophageal findings in patients with suspected cardiac source of embolism. *Am J Med Sci*. (2003) 326:31–4. doi: 10.1097/00000441-200307000-00005
142. Rauh G, Fischereder M, Spengel FA. Transesophageal echocardiography in patients with focal cerebral ischemia of unknown cause. *Stroke*. (1996) 27:691–4. doi: 10.1161/01.STR.27.4.691
143. Banki N, Kopelnik A, Tung P, Lawton MT, Gress D, Drew B, et al. Prospective analysis of prevalence, distribution, and rate of recovery of left ventricular systolic dysfunction in patients with subarachnoid hemorrhage. *J Neurosurg*. (2006) 105:15–20. doi: 10.3171/jns.2006.105.1.15
144. Kothavale A, Banki NM, Kopelnik A, Yarlagadda S, Lawton MT, Ko N, et al. Predictors of left ventricular regional wall motion abnormalities after subarachnoid hemorrhage. *Neurocrit Care*. (2006) 4:199–205. doi: 10.1385/NCC:4:3:199
145. Jangra K, Grover VK, Bhagat H, Bhardwaj A, Tewari MK, Kumar B, et al. Evaluation of the effect of aneurysmal clipping on electrocardiography and echocardiographic changes in patients with subarachnoid hemorrhage: a prospective observational study. *J Neurosurg Anesth*. (2017) 29:335–40. doi: 10.1097/ANA.0000000000000318
146. Van der Bilt I, Hasan D, Vandertop W, Wilde A, Algra A, Visser F, et al. Impact of cardiac complications on outcome after aneurysmal subarachnoid hemorrhage a meta-analysis. *Neurology*. (2009) 72:635–42. doi: 10.1212/01.wnl.0000342471.07290.07
147. Deibert E, Barzilai B, Braverman AC, Edwards DF, Aiyagari V, Dacey R, et al. Clinical significance of elevated troponin i levels in patients with nontraumatic subarachnoid hemorrhage. *J Neurosurg*. (2003) 98:741–6. doi: 10.3171/jns.2003.98.4.0741
148. Mayer SA, Lin J, Homma S, Solomon RA, Lennihan L, Sherman D, et al. Myocardial injury and left ventricular performance after subarachnoid hemorrhage. *Stroke*. (1999) 30:780–6. doi: 10.1161/01.STR.30.4.780
149. Bieber M, Werner RA, Tanai E, Hofmann U, Higuchi T, Schuh K, et al. Stroke-induced chronic systolic dysfunction driven by sympathetic overactivity. *Ann Neurol*. (2017) 82:729–43. doi: 10.1002/ana.25073
150. Van Der Bilt IA, Hasan D, Van Den Brink RB, Cramer MJ, Van Der Jagt M, Van Kooten F, et al. Time course and risk factors for myocardial dysfunction after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. (2015) 76:700–6. doi: 10.1227/NEU.0000000000000699
151. Casaubon LK, Boulanger J-M, Glasser E, Blacquiere D, Boucher S, Brown K, et al. Canadian stroke best practice recommendations: acute inpatient stroke care guidelines, update 2015. *Int J Stroke*. (2016) 11:239–52. doi: 10.1177/1747493015622461
152. Kerr G, Ray G, Wu O, Stott DJ, Langhorne P. Elevated troponin after stroke: a systematic review. *Cerebrovasc Dis*. (2009) 28:220–6. doi: 10.1159/000226773
153. Naidech AM, Kreiter KT, Janjua N, Ostapkovich ND, Parra A, Commichau C, et al. Cardiac troponin elevation, cardiovascular morbidity, and outcome after subarachnoid hemorrhage. *Circulation*. (2005) 112:2851–6. doi: 10.1161/CIRCULATIONAHA.105.533620
154. Darki A, Schneck MJ, Agrawal A, Rupani A, Barron JT. Correlation of elevated troponin and echocardiography in acute ischemic stroke. *J Stroke Cerebrovasc*. (2013) 22:959–61. doi: 10.1016/j.jstrokecerebrovasdis.2011.12.004
155. Wrigley P, Khoury J, Eckerle B, Alwell K, Moomaw CJ, Woo D, et al. Prevalence of positive troponin and echocardiogram findings and association with mortality in acute ischemic stroke. *Stroke*. (2017) 48:1226–32. doi: 10.1161/STROKEAHA.116.014561

156. Sörös P, Hachinski V. Cardiovascular and neurological causes of sudden death after ischaemic stroke. *Lancet Neurol*. (2012) 11:179–88. doi: 10.1016/S1474-4422(11)70291-5
157. Daniele O, Caravaglios G, Fierro B, Natalè E. Stroke and cardiac arrhythmias. *J Stroke Cerebrovasc*. (2002) 11:28–33. doi: 10.1053/jscd.2002.123972
158. Goldstein DS. The electrocardiogram in stroke: relationship to pathophysiological type and comparison with prior tracings. *Stroke*. (1979) 10:253–9. doi: 10.1161/01.STR.10.3.253
159. Morris JJ, Entman M, North WC, Kong Y, Mcintosh H. The changes in cardiac output with reversion of atrial fibrillation to sinus rhythm. *Circulation*. (1965) 31:670–8. doi: 10.1161/01.CIR.31.5.670
160. Clark DM, Plumb VJ, Epstein AE, Kay GN. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. *J Am Coll Cardiol*. (1997) 30:1039–45. doi: 10.1016/S0735-1097(97)00254-4
161. Ide, Gulløv, Pott, Van LJJ, Koefoed, Petersen, et al. Middle cerebral artery blood velocity during exercise in patients with atrial fibrillation. *Clin Physiol*. (1999) 19:284–9. doi: 10.1046/j.1365-2281.1999.00178.x
162. LIESHOUT JV. Middle cerebral artery blood velocity depends on cardiac output during exercise with a large muscle mass. *Acta Physiol Scand*. (1998) 162:13–20. doi: 10.1046/j.1365-201X.1998.0280f.x
163. Contijoch F, Rogers K, Rears H, Shahid M, Kellman P, Gorman J, et al. Quantification of left ventricular function with premature ventricular complexes reveals variable hemodynamics. *Circ-Arrhythmia Elec*. (2016) 9:e003520. doi: 10.1161/CIRCEP.115.003520
164. Fernández-Menéndez S, García-Santiago R, Vega-Primo A, González Nafría N, Lara-Lezama LB, Redondo-Robles L, et al. Cardiac arrhythmias in stroke unit patients. Evaluation of the cardiac monitoring data. *Neurología*. (2016) 31:289–95. doi: 10.1016/j.nrleng.2015.03.007
165. Kallmünzer B, Breuer L, Kahl N, Bobinger T, Raaz-Schrauder D, Huttner HB, et al. Serious cardiac arrhythmias after stroke: incidence, time course, and predictors—a systematic, prospective analysis. *Stroke*. (2012) 43:2892–7. doi: 10.1161/STROKEAHA.112.664318
166. Jensen JK, Atar D, Mickley H. Mechanism of troponin elevations in patients with acute ischemic stroke. *Am J Cardiol*. (2007) 99:867–70. doi: 10.1016/j.amjcard.2006.10.052
167. Zaroff JG, Rordorf GA, Ogilvy CS, Picard MH. Regional patterns of left ventricular systolic dysfunction after subarachnoid hemorrhage: evidence for neurally mediated cardiac injury. *J Am Soc Echocardiog*. 13:774–9. doi: 10.1067/mje.2000.105763
168. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. *Circulation*. (2012) 126:2020–35. doi: 10.1161/CIR.0b013e31826e1058
169. Sandhu R, Aronow WS, Rajdev A, Sukhija R, Amin H, D'aquila K, et al. Relation of cardiac troponin i levels with in-hospital mortality in patients with ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. *Am J Cardiol*. (2008) 102:632–4. doi: 10.1016/j.amjcard.2008.04.036
170. Hays A, Diringer MN. Elevated troponin levels are associated with higher mortality following intracerebral hemorrhage. *Neurology*. (2006) 66:1330–4. doi: 10.1212/01.wnl.0000210523.22944.9b
171. Zhang L, Wang Z, Qi S. Cardiac troponin elevation and outcome after subarachnoid hemorrhage: a systematic review and meta-analysis. *J Stroke Cerebrovasc*. (2015) 24:2375–84. doi: 10.1016/j.jstrokecerebrovasdis.2015.06.030
172. Barber M, Morton JJ, Macfarlane PW, Barlow N, Roditi G, Stott DJ. Elevated troponin levels are associated with sympathoadrenal activation in acute ischaemic stroke. *Cerebrovasc Dis*. (2007) 23:260–6. doi: 10.1159/000098325
173. Su YC, Huang KF, Yang FY, Lin SK. Elevation of troponin i in acute ischemic stroke. *PeerJ*. (2016) 4:e1866. doi: 10.7717/peerj.1866
174. Tung P, Kopelnik A, Banki N, Ong K, Ko N, Lawton MT, et al. Predictors of neurocardiogenic injury after subarachnoid hemorrhage. *Stroke*. (2004) 35:548–51. doi: 10.1161/01.STR.0000114874.96688.54
175. Hravnak M, Frangiskakis JM, Crago EA, Chang Y, Tanabe M, Gorcsan J, et al. Elevated cardiac troponin I and relationship to persistence of electrocardiographic and echocardiographic abnormalities after aneurysmal subarachnoid hemorrhage. *Stroke*. (2009) 40:3478–84. doi: 10.1161/STROKEAHA.109.556753
176. Ay H, Koroshetz WJ, Benner T, Vangel MG, Melinosky C, Arsava EM, et al. Neuroanatomic correlates of stroke-related myocardial injury. *Neurology*. (2006) 66:1325–9. doi: 10.1212/01.wnl.0000206077.13705.6d
177. Rincon F, Dhamoon M, Moon Y, Paik MC, Boden-Albala B, Homma S, et al. Stroke location and association with fatal cardiac outcomes: Northern manhattan study (nomas). *Stroke*. (2008) 39:2425–31. doi: 10.1161/STROKEAHA.107.506055
178. Min J, Farooq MU, Greenberg E, Aloka F, Bhatt A, Kassab M, et al. Cardiac dysfunction after left permanent cerebral focal ischemia: the brain and heart connection. *Stroke*. (2009) 40:2560–3. doi: 10.1161/STROKEAHA.108.536086
179. Laowattana S, Zeger S, Lima J, Goodman S, Wittstein I, Oppenheimer S. Left insular stroke is associated with adverse cardiac outcome. *Neurology*. (2006) 66:477–83. doi: 10.1212/01.wnl.0000202684.29640.60
180. Abdi S, Oveis-Gharan S, Sinaei F, Ghorbani A. Elevated troponin T after acute ischemic stroke: association with severity and location of infarction. *Iran J Neurol*. (2015) 14:35.
181. Chalela JA, Ezzeddine MA, Davis L, Warach S. Myocardial injury in acute stroke. *Neurocrit Care*. (2004) 1:343–6. doi: 10.1385/NCC:1:3:343
182. Apak I, Iltumur K, Tamam Y, Kaya N. Serum cardiac troponin T levels as an indicator of myocardial injury in ischemic and hemorrhagic stroke patients. *Tohoku J Exp Med*. (2005) 205:93–101. doi: 10.1620/tjem.205.93
183. Kolin A, Norris JW. Myocardial damage from acute cerebral lesions. *Stroke*. (1984) 15:990–3. doi: 10.1161/01.STR.15.6.990
184. Parekh N, Venkatesh B, Cross D, Leditschke A, Atherton J, Miles W, et al. Cardiac troponin i predicts myocardial dysfunction in aneurysmal subarachnoid hemorrhage. *J Am Coll Cardiol*. (2000) 36:1328–35. doi: 10.1016/S0735-1097(00)00857-3
185. Yarlagadda S, Rajendran P, Miss JC, Banki NM, Kopelnik A, Wu AH, et al. Cardiovascular predictors of in-patient mortality after subarachnoid hemorrhage. *Neurocrit Care*. (2006) 5:102–7. doi: 10.1385/NCC:5:2:102
186. Riebe D, Ehrman JK, Liguori G, Magal M, editors. *ACSM's Guidelines for Exercise Testing and Prescription*. 10th ed. Philadelphia, PA: Wolters Kluwer (2018).
187. Amarenco P, Lavallee PC, Labreuche J, Ducrocq G, Juliard J, Feldman L, et al. Prevalence of coronary atherosclerosis in patients with cerebral infarction. *Stroke*. (2011) 42:22–9. doi: 10.1161/STROKEAHA.110.584086
188. Di Pasquale G, Pinelli G, Grazi P, Andreoli A, Corbelli C, Manini GL, et al. Incidence of silent myocardial ischaemia in patients with cerebral ischaemia. *Eur Heart J*. (1988) 9:104–7. doi: 10.1093/eurheartj/9.suppl_N.104
189. Xu T, Yu X, Ou S, Liu X, Yuan J, Chen Y. Efficacy and safety of very early mobilization in patients with acute stroke: a systematic review and meta-analysis. *Sci Rep*. (2017) 7:6550. doi: 10.1038/s41598-017-06871-z
190. Sundseth A, Thommessen B, Rønning OM. Outcome after mobilization within 24 hours of acute stroke: a randomized controlled trial. *Stroke*. (2012) 43:2389–94. doi: 10.1161/STROKEAHA.111.646687
191. Yelnik AP, Quintaine V, Andriantsifanetra C, Wannepain M, Reiner P, Marnef H, et al. Amobes (active mobility very early after stroke): a randomized controlled trial. *Stroke*. (2017) 48:400–5. doi: 10.1161/STROKEAHA.116.014803
192. Bernhardt J, Churilov L, Ellery F, Collier J, Chamberlain J, Langhorne P, et al. Prespecified dose-response analysis for a very early rehabilitation trial (avert). *Neurology*. (2016) 86:2138–45. doi: 10.1212/WNL.0000000000002459
193. Strømmen AM, Christensen T, Jensen K. Intensive treadmill training in the acute phase after ischemic stroke. *Int J Rehabil Res*. (2016) 39:145–52. doi: 10.1097/MRR.0000000000000158
194. Flöel A, Werner C, Grittner U, Hesse S, Jöbges M, Knauss J, et al. Physical fitness training in subacute stroke (phys-stroke)-study protocol for a randomised controlled trial. *Trials*. (2014) 15:45. doi: 10.1186/1745-6215-15-45
195. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Auton Neurosci-Basic*. (2011) 161:46–8. doi: 10.1016/j.autneu.2011.02.004
196. van Lieshout JJ, Wieling W, Karemaker JM, Eckberg DL. The vasovagal response. *Clin Sci*. (1991) 81:575–86. doi: 10.1042/cs0810575

197. Gibbons CH, Freeman R. Orthostatic dyspnea: a neglected symptom of orthostatic hypotension. *Clin Auton Res*. (2005) 15:40–4. doi: 10.1007/s10286-005-0227-1
198. Lipsitz LA. Orthostatic hypotension in the elderly. *New Engl J Med*. (1989) 321:952–7. doi: 10.1056/NEJM198910053211407
199. Mattace-Raso FU, van der Cammen TJ, Knetsch AM, van den Meiracker AH, Schalekamp MA, Hofman A, et al. Arterial stiffness as the candidate underlying mechanism for postural blood pressure changes and orthostatic hypotension in older adults: the rotterdam study. *J Hypertens*. (2006) 24:339–44. doi: 10.1097/01.hjh.0000202816.25706.64
200. Mattace-Raso FU, van den Meiracker AH, Bos WJ, van der Cammen TJ, Westerhof BE, Elias-Smale S, et al. Arterial stiffness, cardiovagal baroreflex sensitivity and postural blood pressure changes in older adults: the rotterdam study. *J Hypertens*. (2007) 25:1421–6. doi: 10.1097/HJH.0b013e32811d6a07
201. Metzler M, Duerr S, Granata R, Krismer F, Robertson D, Wenning GK. Neurogenic orthostatic hypotension: pathophysiology, evaluation, and management. *J Neurol*. (2013) 260:2212–9. doi: 10.1007/s00415-012-6736-7
202. Carlsson A, Britton M. Blood pressure after stroke. A one-year follow-up study. *Stroke*. (1993) 24:195–9. doi: 10.1161/01.STR.24.2.195
203. Treger I, Shafir O, Keren O, Ring H. Orthostatic hypotension and cerebral blood flow velocity in the rehabilitation of stroke patients. *Int J Rehabil Res*. (2006) 29:339–42. doi: 10.1097/MRR.0b013e328010c87d
204. Panayiotou B, Reid J, Fotherby M, Crome P. Orthostatic haemodynamic responses in acute stroke. *Postgrad Med J*. (1999) 75:213–8. doi: 10.1136/pgmj.75.882.213
205. Langhorne P, Stott D, Knight A, Bernhardt J, Barer D, Watkins C. Very early rehabilitation or intensive telemetry after stroke: a pilot randomised trial. *Cerebrovasc Dis*. (2010) 29:352–60. doi: 10.1159/000278931
206. Hamrefors V, Fedorowski A, Strandberg K, Sutton R, Isma N. Procoagulatory changes induced by head-up tilt test in patients with syncope: observational study. *Thromb J*. (2017) 15:16. doi: 10.1186/s12959-017-0139-z
207. Isma N, Sutton R, Hillarp A, Strandberg K, Melander O, Fedorowski A. Higher levels of von willebrand factor in patients with syncope due to orthostatic hypotension. *J Hypertens*. (2015) 33:1594–601. doi: 10.1097/HJH.0000000000000595
208. Cvirn G, Schlagenhauf A, Leschnik B, Koestenberger M, Roessler A, Jantscher A, et al. Coagulation changes during presyncope and recovery. *PLoS ONE*. (2012) 7:e42221. doi: 10.1371/journal.pone.0042221
209. Olavarría VV, Arima H, Anderson CS, Brunser AM, Muñoz-Venturelli P, Heritier S, et al. Head position and cerebral blood flow velocity in acute ischemic stroke: a systematic review and meta-analysis. *Cerebrovasc Dis*. (2014) 37:401–8. doi: 10.1159/000362533
210. Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of body position on intracranial pressure and cerebral perfusion in patients with large hemispheric stroke. *Stroke*. (2002) 33:497–501. doi: 10.1161/hs0202.102376
211. Wu J-S, Yang Y-C, Lu F-H, Wu C-H, Wang R-H, Chang C-J. Population-based study on the prevalence and risk factors of orthostatic hypotension in subjects with pre-diabetes and diabetes. *Diabetes Care*. (2009) 32:69–74. doi: 10.2337/dc08-1389
212. Scuteri A, Tesauro M, Guglini L, Lauro D, Fini M, Di Daniele N. Aortic stiffness and hypotension episodes are associated with impaired cognitive function in older subjects with subjective complaints of memory loss. *Int J Cardiol*. (2013) 169:371–7. doi: 10.1016/j.ijcard.2013.09.009
213. Anderson CS, Arima H, Lavados P, Billot L, Hackett ML, Olavarría VV, et al. Cluster-randomized, crossover trial of head positioning in acute stroke. *New Engl J Med*. (2017) 376:2437–47. doi: 10.1056/NEJMoa1615715
214. Teasell R, McRae M, Foley N, Bhardwaj A. The incidence and consequences of falls in stroke patients during inpatient rehabilitation: factors associated with high risk. *Arch Phys Med Rehabil*. (2002) 83:329–33. doi: 10.1053/apmr.2002.29623
215. Czernuszenko A, Czlonkowska A. Risk factors for falls in stroke patients during inpatient rehabilitation. *Clin Rehabil*. (2009) 23:176–88. doi: 10.1177/0269215508098894
216. Cox R, Buckholz B, Bradas C, Bowden V, Kerber K, McNett MM. Risk factors for falls among hospitalized acute post–ischemic stroke patients. *J Neurosci Nurs*. (2017) 49:355–60. doi: 10.1097/JNN.0000000000000322
217. Holloway RG, Tuttle D, Baird T, Skelton WK. The safety of hospital stroke care. *Neurology*. (2007) 68:550–5. doi: 10.1212/01.wnl.0000254992.39919.2e
218. Walsh ME, Horgan NF, Walsh CD, Galvin R. Systematic review of risk prediction models for falls after stroke. *J Epidemiol Community Health*. (2016) 70:513–9. doi: 10.1136/jech-2015-206475
219. Hagan R, Diaz F, Horvath S. Plasma volume changes with movement to supine and standing positions. *J Appl Physiol*. (1978) 45:414–7. doi: 10.1152/jappl.1978.45.3.414
220. Masoud M, Sarig G, Brenner B, Jacob G. Orthostatic hypercoagulability: a novel physiological mechanism to activate the coagulation system. *Hypertension*. (2008) 51:1545–51. doi: 10.1161/HYPERTENSIONAHA.108.112003
221. Cvirn G, Kneihsl M, Rossmann C, Paar M, Gattringer T, Schlagenhauf A, et al. Orthostatic challenge shifts the hemostatic system of patients recovered from stroke toward hypercoagulability. *Front Physiol*. (2017) 8:12. doi: 10.3389/fphys.2017.00012
222. Schobersberger W, Mittermayr M, Innerhofer P, Sumann G, Schobersberger B, Klingler A, et al. Coagulation changes and edema formation during long-distance bus travel. *Blood Coagul Fibrinolysis*. (2004) 15:419–25. doi: 10.1097/01.mbc.0000114438.81125.cf
223. Smit AA, Halliwill JR, Low PA, Wieling W. Pathophysiological basis of orthostatic hypotension in autonomic failure. *J Physiol-London*. (1999) 519:1–10. doi: 10.1111/j.1469-7793.1999.0001o.x
224. Faghri PD, Yount J. Electrically induced and voluntary activation of physiologic muscle pump: a comparison between spinal cord-injured and able-bodied individuals. *Clin Rehabil*. (2002) 16:878–85. doi: 10.1191/0269215502cr570oa
225. Carpio-Rivera E, Moncada-Jiménez J, Salazar-Rojas W, Solera-Herrera A. Acute effects of exercise on blood pressure: a meta-analytic investigation. *Arq Bras Cardiol*. (2016) 106:422–33. doi: 10.5935/abc.20160064
226. Brito LC, Fecchio RY, Peçanha T, Andrade-Lima A, Halliwill JR, Forjaz CL. Post-exercise hypotension as a clinical tool: a "single brick" in the wall. *J Am Soc Hypertens*. (2018) 12:e59–64. doi: 10.1016/j.jash.2018.10.006
227. Kenney MJ, Seals DR. Postexercise hypotension. Key features, mechanisms, and clinical significance. *Hypertension*. (1993) 22:653–64. doi: 10.1161/01.HYP.22.5.653
228. Boeno FP, Ramis TR, Farinha JB, Moritz C, Santos VPd, Oliveira ARd, et al. Hypotensive response to continuous aerobic and high-intensity interval exercise matched by volume in sedentary subjects. *Int J Cardiovasc Sci*. (2018) 32:48–54. doi: 10.5935/2359-4802.20180084
229. Mündel T, Perry BG, Ainslie PN, Thomas KN, Sikken EL, Cotter JD, et al. Postexercise orthostatic intolerance: influence of exercise intensity. *Exp Physiol*. (2015) 100:915–25. doi: 10.1113/EP085143
230. MacDonald JR. Potential causes, mechanisms, and implications of post exercise hypotension. *J Hum Hypertens*. (2002) 16:225. doi: 10.1038/sj.jhh.1001377
231. Halliwill JR, Buck TM, Lacewell AN, Romero SA. Postexercise hypotension and sustained postexercise vasodilatation: what happens after we exercise? *Exp Physiol*. (2013) 98:7–18. doi: 10.1113/expphysiol.2011.058065
232. Halliwill JR. Mechanisms and clinical implications of post-exercise hypotension in humans. *Exerc Sport Sci Rev*. (2001) 29:65–70. doi: 10.1249/00003677-200104000-00005
233. Halliwill JR, Sieck DC, Romero SA, Buck TM, Ely MR. Blood pressure regulation x: what happens when the muscle pump is lost? Post-exercise hypotension and syncope. *Eur J Appl Physiol*. (2014) 114:561–78. doi: 10.1007/s00421-013-2761-1
234. Hiura M, Nariai T, Sakata M, Muta A, Ishibashi K, Wagatsuma K, et al. Response of cerebral blood flow and blood pressure to dynamic exercise: a study using pet. *Int J Sport Med*. (2018) 39:181–8. doi: 10.1055/s-0043-123647
235. Eicher JD, Maresh CM, Tsongalis GJ, Thompson PD, Pescatello LS. The additive blood pressure lowering effects of exercise intensity on post-exercise hypotension. *Am Heart J*. (2010) 160:513–20. doi: 10.1016/j.ahj.2010.06.005
236. Williamson JW, McColl R, Mathews D. Changes in regional cerebral blood flow distribution during postexercise hypotension in humans. *J Appl Physiol*. (2004) 96:719–24. doi: 10.1152/japplphysiol.00911.2003
237. Billinger SA, Arena R, Bernhardt J, Eng JJ, Franklin BA, Johnson CM, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American

Heart Association/American Stroke Association. *Stroke*. (2014) 45:2532–53. doi: 10.1161/STR.0000000000000022
238. Gormley SE, Swain DP, High R, Spina RJ, Dowling EA, Kotipalli EA, et al. Effect of intensity of aerobic training on vo_{2max}. *Med Sci Sport Exer*. (2008) 40:1336–43. doi: 10.1249/MSS.0b013e31816c4839
239. Ivey FM, Stookey AD, Hafer-Macko CE, Ryan AS, Macko RF. Higher treadmill training intensity to address functional aerobic impairment after stroke. *J Stroke Cerebrovasc*. (2015) 24:2539–46. doi: 10.1016/j.jstrokecerebrovasdis.2015.07.002
240. Swain DP, Franklin BA. Vo_2 reserve and the minimal intensity for improving cardiorespiratory fitness. *Med Sci Sport Exer*. (2002) 34:152–7. doi: 10.1097/00005768-200201000-00023
241. Wenger HA, Bell GJ. The interactions of intensity, frequency and duration of exercise training in altering cardiorespiratory fitness. *Sports Med*. (1986) 3:346–56. doi: 10.2165/00007256-198603050-00004
242. Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, et al. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation*. (2002) 106:666–71. doi: 10.1161/01.CIR.0000024413.15949.ED
243. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing *N Engl J Med*. (2002) 346:793–801. doi: 10.1056/NEJMoa011858
244. Artero EG, Jackson AS, Sui X, Lee DC, O'Connor DP, Lavie CJ, et al. Longitudinal algorithms to estimate cardiorespiratory fitness: associations with nonfatal cardiovascular disease and disease-specific mortality. *J Am Coll Cardiol*. (2014) 63:2289–96. doi: 10.1016/j.jacc.2014.03.008
245. Laukkanen JA, Rauramaa R, Salonen JT, Kurl S. The predictive value of cardiorespiratory fitness combined with coronary risk evaluation and the risk of cardiovascular and all-cause death. *J Intern Med*. (2007) 262:263–72. doi: 10.1111/j.1365-2796.2007.01807.x
246. Dhamoon MS, Sciacca RR, Rundek T, Sacco RL, Elkind MS. Recurrent stroke and cardiac risks after first ischemic stroke: the northern manhattan study. *Neurology*. (2006) 66:641–6. doi: 10.1212/01.wnl.0000201253.93811.f6
247. Sacco R, Wolf PA, Kannel W, McNamara P. Survival and recurrence following stroke. the Framingham study. *Stroke*. (1982) 13:290–5. doi: 10.1161/01.STR.13.3.290
248. Kokkinos PF, Faselis C, Myers J, Panagiotakos D, Doumas M. Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidaemia: a cohort study. *Lancet*. (2013) 381:394–9. doi: 10.1016/S0140-6736(12)61426-3
249. Myers J, McAuley P, Lavie CJ, Despres JP, Arena R, Kokkinos P. Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status *Prog Cardiovasc Dis*. (2015) 57:306–14. doi: 10.1016/j.pcad.2014.09.011
250. Kodama S, Saito K, Tanaka S, Yachi Y, Asumi M, Sugawara A, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*. (2009) 301:2024–35. doi: 10.1001/jama.2009.681
251. Fogelholm M. Physical activity, fitness and fatness: relations to mortality, morbidity and disease risk factors: a systematic review *Obes Rev*. (2010) 11:202–21. doi: 10.1111/j.1467-789X.2009.00653.x
252. Forman DE, Arena R, Boxer R, Dolansky MA, J.J. E, Fleg JL, et al. Prioritizing functional capacity as a principal end point for therapies oriented to older adults with cardiovascular disease: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. (2017) 135:e894–918. doi: 10.1161/CIR.0000000000000483
253. Lau KWK, Mak MKY. Speed-dependent treadmill training is effective to improve gait and balance performance in patients with sub-acute stroke. *J Rehabil Med*. (2011) 43:709–13. doi: 10.2340/16501977-0838
254. Pohl M, Mehrholz J, Ritschel C, Ruckriem MA. Speed-dependent treadmill training in ambulatory hemiparetic stroke patients: a radnomized controlled trial. *Stroke*. (2002) 33:553–8. doi: 10.1161/hs0202.102365
255. Angevarena M, Vanheesa L, Wendel-Vosc W, Verhaarb HJJ, Aufdemkampea G, Alemand A, et al. Intensity, but not duration, of physical activities is related to cognitive function. *Eur J Cardiovasc Prev Rehabil*. (2007) 14:825–30. doi: 10.1097/HJR.0b013e3282ef995b
256. Brown BM, Peiffer JJ, Sohrabi HR, Mondal A, Gupta VB, Rainey-Smith SR, et al. Intense physical activity is associated with cognitive performance in the elderly. *Transl Psychiatry*. (2012) 2:e191. doi: 10.1038/tp.2012.118
257. Ferris lT, Williams JS, Shen CL. The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Med. Sci Sports Exerc*.39:728–34. doi: 10.1249/mss.0b013e31802f04c7
258. Kluding PM, Tseng BY, Billinger SA. Exercise and executive function in individuals with chronic stroke: a pilot study. *J Neurol Phys Ther*. (2011) 35:11–7. doi: 10.1097/NPT.0b013e318208ee6c
259. Marzolini S, Oh PI, McIlroy W, Brooks D. The effects of an aerobic and resistance exercise training program on cognition following stroke. *Neurorehab Neural Repair*. (2013) 27:392–402. doi: 10.1177/1545968312465192
260. van Gelder BM, Tijhuis MA, Kalmijn S, Giampaoli S, Nissinen A, Kromhout D. Physical activity in relation to cognitive decline in elderly men: the fine study. *Neurology*. (2004) 63:2316–21. doi: 10.1212/01.WNL.0000147474.29994.35
261. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol*. (2001) 58:498–504. doi: 10.1001/archneur.58.3.498
262. Ogoh S, Dalsgaard MK, Yoshiga CC, Dawson EA, Keller DM, Raven PB, et al. Dynamic cerebral autoregulation during exhaustive exercise in humans. *Am J Physiol-Heart C*. (2005) 288:H1461–7. doi: 10.1152/ajpheart.00948.2004
263. Zhang Y, Zhang P, Shen X, Tian S, Wu Y, Zhu Y, et al. Early exercise protects the blood-brain barrier from ischemic brain injury via the regulation of mmp-9 and occludin in rats. *Int J Mol Sci*. (2013) 14:11096–112. doi: 10.3390/ijms140611096
264. Smith KJ, Ainslie PN. Regulation of cerebral blood flow and metabolism during exercise. *Exp Physiol*. (2017) 102:1356–71. doi: 10.1113/EP086249
265. Olson TP, Tracy J, Dengel DR. Relationship between ventilatory threshold and cerebral blood flow during maximal exercise in humans. *Open Sports Med J*. (2009) 3:9–13. doi: 10.2174/1874387000903010009
266. Moraine JJ, Lamotte M, Berré J, Niset G, Leduc A, Naeijel R. Relationship of middle cerebral artery blood flow velocity to intensity during dynamic exercise in normal subjects. *Eur J Appl Physiol O*. (1993) 67:35–8. doi: 10.1007/BF00377701
267. Burnley M, Jones AM. Oxygen uptake kinetics as a determinant of sports performance. *Eur J Sport Sci*. (2007) 7:63–79. doi: 10.1080/17461390701456148
268. Brawner CA, Vanzant MA, Ehrman JK, Foster C, Porcari JP, Kelso AJ, et al. Guiding exercise using the talk test among patients with coronary artery disease. *J Cardiopulm Rehabil*. (2006) 26:72–5. doi: 10.1097/00008483-200603000-00002
269. Ballweg J, Foster C, Porcari J, Haible S, Aminaka N, Mikat RP. Reliability of the talk test as a surrogate of ventilatory and respiratory compensation thresholds. *J Sport Sci Med*. (2013) 12:610–1.
270. Marzolini S, Oh P, Corbett D, Dooks D, Calouro M, Macintosh BJ, et al. Prescribing aerobic exercise intensity without a cardiopulmonary exercise test post stroke: utility of the six-minute walk test. *J Stroke Cerebrovasc*. (2016) 25:2222–31. doi: 10.1016/j.jstrokecerebrovasdis.2016.04.016
271. Rattray B, Argus C, Martin K, Northey J, Driller M. Is it time to turn our attention toward central mechanisms for post-exertional recovery strategies and performance? *Front Physiol*. (2015) 6:79. doi: 10.3389/fphys.2015.00079
272. Lee M-J, Kilbreath SL, Fiatarone Singh M, Zeman B, Lord SR, Raymond J, et al. Comparison of effect of aerobic cycle training and progressive resistance training on walking ability after stroke: a randomized sham exercise–controlled study. *J Am Geriatr Soc*. (2008) 56:976–85. doi: 10.1111/j.1532-5415.2008.01707.x
273. Severinsen K, Jakobsen JK, Pedersen AR, Overgaard K, Andersen H. Effects of resistance training and aerobic training on ambulation in chronic stroke. *Am J Phys Med Rehabil*. (2014) 93:29–42. doi: 10.1097/PHM.0b013e3182a518e1
274. Marzolini S, Tang A, McIlroy W, Oh PI, Brooks D. Outcomes in people after stroke attending an adapted cardiac rehabilitation exercise program: does time from stroke make a difference?. *J Stroke Cerebrovasc*. (2014) 23:1648–56. doi: 10.1016/j.jstrokecerebrovasdis.2014.01.008
275. Ide K, Boushel R, Sørensen H, Fernandes A, Cai Y, Pott F, et al. Middle cerebral artery blood velocity during exercise with beta-1 adrenergic and

unilateral stellate ganglion blockade in humans. *Acta Physiol Scand*. (2000) 170:33–8. doi: 10.1046/j.1365-201x.2000.00757.x

276. Pott F, Jensen K, Hansen H, Christensen N, Lassen N, Secher N. Middle cerebral artery blood velocity and plasma catecholamines during exercise. *Acta Physiol Scand*. (1996) 158:349–56. doi: 10.1046/j.1365-201X.1996.564325000.x
277. Pott F, Knudsen L, Nowak M, Nielsen H, Hanel B, Secher N. Middle cerebral artery blood velocity during rowing. *Acta Physiol Scand*. (1997) 160:251–5. doi: 10.1046/j.1365-201X.1997.00144.x
278. Atkinson G, Jones H, Ainslie PN. Circadian variation in the circulatory responses to exercise: relevance to the morning peaks in strokes and cardiac events. *Eur J Appl Physiol*. (2010) 108:15–29. doi: 10.1007/s00421-009-1243-y
279. Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson JL Jr. Responses of cerebral arteries and arterioles to acute hypotension and hypertension. *Am J Physiol Heart C*. (1978) 234:H371–83. doi: 10.1152/ajpheart.1978.234.4.H371
280. Pstras L, Thomaseth K, Waniewski J, Balzani I, Bellavere F. The valsalva manoeuvre: physiology and clinical examples. *Acta Physiol*. (2016) 217:103–19. doi: 10.1111/apha.12639
281. Perry BG, Cotter JD, Mejuto G, Mündel T, Lucas SJ. Cerebral hemodynamics during graded valsalva maneuvers. *Front Physiol*. (2014) 5:349. doi: 10.3389/fphys.2014.00349
282. Ogoh S, Brothers RM, Barnes Q, Eubank WL, Hawkins MN, Purkayastha S, et al. The effect of changes in cardiac output on midle cerebral artery mean blood velocity at rest and during exercise. *J Physiol*. (2005) 569:697–704. doi: 10.1113/jphysiol.2005.095836

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CLINICAL TRIAL
published: 28 February 2020
doi: 10.3389/fneur.2020.00104

Effectiveness of AbobotulinumtoxinA in Post-stroke Upper Limb Spasticity in Relation to Timing of Treatment

Jörg Wissel[1†], *Klemens Fheodoroff*[2*†], *Maurits Hoonhorst*[3], *Martina Müngersdorf*[4], *Philippe Gallien*[5], *Niklaus Meier*[6], *Jürgen Hamacher*[7], *Harald Hefter*[8], *Pascal Maisonobe*[9] *and Manuel Koch*[10]

[1] Vivantes Hospital Spandau, Berlin, Germany, [2] Gailtal-Klinik, Hermagor-Pressegger See, Austria, [3] Center for Rehabilitation Vogellanden, Zwolle, Netherlands, [4] Neurologisches Zentrum für Bewegungsstörungen und Diagnostik, Berlin, Germany, [5] Pôle Saint Hélier, Rennes, France, [6] Department of Neurology, University Hospital Bern and University of Bern, Bern, Switzerland, [7] Praxis für Neurochirurgie, Essen, Germany, [8] Department of Neurology, University of Düsseldorf, Düsseldorf, Germany, [9] Ipsen Pharma, Boulogne-Billancourt, France, [10] IPSEN PHARMA GmbH, Munich, Germany

OPEN ACCESS

Edited by:
Stefano Tamburin,
University of Verona, Italy

Reviewed by:
Domenico Antonio Restivo,
Ospedale Garibaldi, Italy
Alessio Baricich,
Università degli Studi del Piemonte Orientale, Italy

***Correspondence:**
Klemens Fheodoroff
klemens.fheodoroff@me.com

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 13 December 2019
Accepted: 30 January 2020
Published: 28 February 2020

Citation:
Wissel J, Fheodoroff K, Hoonhorst M, Müngersdorf M, Gallien P, Meier N, Hamacher J, Hefter H, Maisonobe P and Koch M (2020) Effectiveness of AbobotulinumtoxinA in Post-stroke Upper Limb Spasticity in Relation to Timing of Treatment. Front. Neurol. 11:104. doi: 10.3389/fneur.2020.00104

Background: Recent studies of botulinum toxin for post-stroke spasticity indicate potential benefits of early treatment (i. e., first 6 months) in terms of developing hypertonicity, pain and passive function limitations. This non-interventional, longitudinal study aimed to assess the impact of disease duration on the effectiveness of abobotulinumtoxinA treatment for upper limb spasticity.

Methods: The early-BIRD study (NCT01840475) was conducted between February 2013 and 2018 in 43 centers across Germany, France, Austria, Netherlands and Switzerland. Adult patients with post-stroke upper limb spasticity undergoing routine abobotulinumtoxinA treatment were followed for up to four treatment cycles. Patients were categorized by time from stroke event to first botulinum toxin-A treatment in the study (as defined by the 1st and 3rd quartiles time distribution) into early-, medium- and late- start groups. We hypothesized that the early-start group would show a larger benefit (decrease) as assessed by the modified Ashworth scale (MAS, primary endpoint) on elbow plus wrist flexors compared with the late-start group.

Results: Of the 303 patients enrolled, 292 (96.4%) received ≥1 treatment and 186 (61.4%) received 4 injection cycles and completed the study. Patients in all groups showed a reduction in MAS scores from baseline over the consecutive injection visits (i.e., at end of each cycle). Although reductions in MAS scores descriptively favored the early treatment group, the difference compared to the late group did not reach statistical significance at the last study visit (ANCOVA: difference in adjusted means of 0.15, $p = 0.546$).

Conclusions: In this observational, routine-practice study, patients in all groups displayed a benefit from abobotulinumtoxinA treatment, supporting the effectiveness of treatment for patients at various disease stages. Although the data revealed some trends in favor of early vs. late treatment, we did not find strong evidence for a significant benefit of early vs. late start of treatment in terms of reduction in MAS scores.

Keywords: abobotulinumtoxinA, botulinum toxin, Dysport, spasticity, stroke

INTRODUCTION

A significant percentage of patients develop upper limb spasticity after stroke. In general, upper limb muscles are more affected than lower limb muscles, with the arm being severely affected in about 30% of stroke survivors (1–3). Spasticity interferes with routine task performance, contributes to the development of joint contractures and pain, makes hygiene, and self-care difficult and ultimately has great impact on patient and caregiver quality of life (QoL) (4–7). Spasticity may evolve early in the post-stroke period, with one in five patients developing spasticity within 3 months of the stroke event (8, 9). Some studies have demonstrated muscle tone changes in the affected limbs within just 3 weeks after the stroke event (10–12).

Botulinum neurotoxin A (BoNT-A), including abobotulinumtoxinA (Dysport®, Ipsen Pharma, Wrexham UK), is recommended as a first-line pharmacological treatment option for spasticity (13, 14), but is not typically initiated until spasticity is well-established, and often much later (15). Systematic reviews based on randomized, controlled trial evidence have confirmed that BoNT-A is well-tolerated and effective for the treatment of upper limb spasticity (16, 17). However, to date, most interventional studies have been restricted to patient cohorts with chronic spasticity (i.e., at least 6 months, and an average of 2.5 years post-stroke) (16–18). This limited evidence-base has influenced current guidelines remaining unclear about treatment goals considering different stages and severity of spasticity. AbobotulinumtoxinA is approved for the management of adult upper (and lower) limb spasticity. Recent randomized, placebo-controlled data indicate potential benefits of early treatment with abobotulinumtoxinA in terms of delaying development of hypertonicity, reducing pain and passive function limitations (18–20), and it has further been suggested that early injections may be helpful in preventing contracture development, with potential to unmask active functional improvement (18, 21). Indeed, exploratory analyses of studies of abobotulinumtoxinA in upper limb spasticity management have suggested that the most influential factors predicting goal achievement are previous treatment status (whether the patients were *de novo* or had been previously treated with BoNT-A) and time since spasticity onset as well as the spasticity pattern, and overall injection dose (22).

The aim of the early-BIRD (early Botulinum toxin treatment: Initial and Repeated Documentation) study was to evaluate the real-world effectiveness of abobotulinumtoxinA on the evolution of spasticity in patients with post-stroke upper limb spasticity according to the time from stroke to start of BoNT-A treatment. We hypothesized that patients who start treatment with abobotulinumtoxinA early in their treatment journey will show a larger effect (i.e., reduction in spasticity from baseline) as assessed by the composite sum of the modified Ashworth scale (MAS) at the elbow and wrist flexors when compared to those who start treatment later in their disease course.

METHODS

Study Setting

The early-BIRD study was an international, multicenter, non-interventional, prospective, longitudinal study conducted in 303 post-stroke survivors undergoing treatment in 43 centers specializing in outpatient spasticity treatment across Germany, France, Austria, Netherlands and Switzerland. The study began in February 2013, recruitment continued until February 2016, and the study completed in February 2018. The study was conducted in compliance with the Declaration of Helsinki, the International Ethical Guidelines for Epidemiological Studies and the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP); it was registered at clinicaltrials.gov as NCT01840475. Ethics approval was obtained from the relevant independent ethics committee at each study center. All patients provided written informed consent for trial participation, including specific consent that they were willing to fill in the QoL questionnaire (EQ-5D-3L) at three visits.

Since this was a non-interventional study, investigators were asked to report adverse events (AEs) to the safety department of the drug manufacturer using the usual local process for such reactions.

Patients

Patients were recruited on an out-patient basis through the participating specialist centers (BoNT-A clinics, rehabilitation clinics, or neurological practices) where they were undergoing routine assessment and treatment. Investigators recruited all adult patients (aged at least 25 years old) with hemiparesis and clinically relevant post-stroke upper limb spasticity who consented to study participation during a pre-defined time-frame. Eligible patients were either currently being treated with a BoNT-product or considering starting treatment in line with the local prescribing information and usual medical practice. The decision to prescribe abobotulinumtoxinA was made prior to and independently from the decision to enroll the patient in this non-interventional study. Out-of-routine diagnostic or therapeutic interventions were not permitted during this study. Key exclusion criteria included: recurrent stroke, sensitivity to abobotulinumtoxinA, or its excipients, any contraindications as given in the local SmPC for Dysport®, and current participation in an interventional trial.

The maximum number of patients per center was 20. Investigators were permitted to space the inclusions (e.g., inclusion of 1 patient after every 2, or 3, etc. patients) but had to follow the same recruitment frequency until achievement of the recruitment target.

Assessments

Study data collected as part of routine medical care were captured using an electronic Case Report Form (eCRF). Aside from the EQ-5D-3L which was self-completed by the patients (with or without caregiver assistance), investigators were only required to record outcome assessments they routinely perform in their clinical practice. Thus, some sites did not complete all sections contained within the eCRF. Patients were followed for a maximum of 4 routine abobotulinumtoxinA treatment cycles. The timing of assessments was in accordance with routine medical practice for the investigator. Other than this, no specific instructions on the timing of treatment were given in the study protocol.

The primary measurement of effectiveness was the modified Ashworth Scale (23) (composite sum of elbow and wrist flexors; MAS_{EWF}) at the end of treatment cycle 4 (visit 5) or last study visit. The composite MAS_{EWF} is the sum of the MAS measured at the elbow and at the wrist, which was chosen for this routine practice study because is easier to perform than determining a primary targeted muscle group. Other routine assessments included demographics and relevant medical history, date of stroke event, use of physical and occupational therapy, pattern of upper limb spasticity involvement (24), passive and active Range of Motion (PROM and AROM) assessments, pain assessment [on a visual analog scale [VAS] at rest], and treatment satisfaction, as well as injection details (dose, muscles injected etc.). In addition, many specialist centers routinely use a goal setting approach, including Goal Attainment Scaling (GAS) to assess effectiveness of the treatment (25, 26). Investigators negotiated and agreed the main treatment goal(s) with the patient at the baseline visit. As previously suggested (27), goals were categorized under the following six domains: improvement of mobility, pain reduction, ease of care and hygiene, support and ease of physiotherapy (PT) and/or occupational therapy (OT), functional improvement (with definition of individual functional goal) and other (to be specified). Goal attainment was rated as "fully achieved," "partly achieved," or "not achieved" at each visit. Investigators were asked to report adverse drug reactions directly to the safety department of the study sponsor.

Statistical Analyses

The study population included all patients who received ≥1 injection of abobotulinumtoxinA and had ≥1 valid MAS measurement post-baseline. For the primary effectiveness endpoint, patients were categorized into sub-groups (early-start, medium-start or late-state) according to the first and third quartiles time distribution (first quartile = early group; final quartile = late group) since the stroke event until start of BoNT treatment.

The primary effectiveness assessment (MAS) was analyzed with an analysis of covariance (ANCOVA) where the model included a start of treatment group (early/medium/late), and baseline MAS value. Other potential prognostic factors/covariates were tested for inclusion in the model in a stepwise selection process. The first step was based on univariate testing of candidate prognostic factors/covariates (full list provided in the **Table e1**). All factors with a critical significance level of 0.20 were included in the second step that compared each retained variable against the other retained variables (at the 0.001 level using Pearson correlation for continuous variables, Chi-square test/Fisher's exact test for categorical variables and Kruskal–Wallis for mixed categorical and continuous variables) to confirm that there was no strong link between them. If independence was not met for two variables ($p < 0.001$), the choice was done according to clinical relevance. Retained variables after step 2 were included in the stepwise multivariate model and kept if the $p < 0.2$. Patients categorized as medium-start were included in the model, but the primary comparison was between early-start and late-start.

Comparisons of (i) MAS_{EWF} at each study visit (Visits 2, 3, 4 and 5) and (ii) change in MAS_{EWF} scores at study Visit 5, between early-start and late-start patients (with and without stratification by previous BoNT exposure) were analyzed as secondary effectiveness variables using a similar model (ANCOVA including start-of-treatment group and baseline MAS) as the primary effectiveness endpoint. Other endpoints included descriptive analyses of MAS_{EWF} scores in the early, medium and late group with (exploratory) and without (secondary) stratification by BoNT exposure.

Between group differences in goal attainment and treatment satisfaction were analyzed using proportional odds models including treatment group as fixed effects. Changes in AROM, PROM and pain from Visit 1 to Visit 5 were analyzed using an ANCOVA where the model included start of treatment group and baseline values. Finally, changes from baseline in MAS and other endpoints, including EQ-5D-3L, were summarized descriptively by start of treatment group.

Sample Size Estimation

It was estimated that a total of 150 patients was required to achieve 80% power in detecting an effect size of 0.5 on the composite MAS between the early-start and late-start groups at the 2-sided 5% significance level. To achieve a sample size of 150 patients in the early-start and late-start groups (75 in each group), a total of 300 patients was required.

RESULTS

Patient Disposition and Baseline Characteristics

Of the 303 patients enrolled, 257 (84.8%) received treatment and had one post-baseline measurement of MAS, and 186 (61.4%) received 4 injection cycles and completed the study. The most common reason for early discontinuation was loss to follow-up (**Figure 1**). Per protocol, the study population was categorized into treatment groups: early-start $n = 63$, medium-start $n = 126$ and late-start $n = 63$; five patients were not categorized due to lack of information. Baseline characteristics are given in **Table 1**, overall 147 patients were previously-treated with a BoNT and 110 patients were naïve to BoNT treatment. Of note, the mean age at inclusion was higher and the mean age at stroke was lower in the late-start group vs. the other groups.

Treatment Exposure

The mean ± SD time from stroke until start of first BoNT-A treatment was 3.74 ± 1.75 months in the early-start group, 20.11 ± 11.08 months in the medium-start group and 144.24 ± 90.85 in the late-start group. The time from documented onset of spasticity to start of first BoNT-A treatment was 1–5 months shorter than time since stroke; mean ± SD times since onset of spasticity were 2.60 ± 1.96, 17.20 ± 11.76, and 138.63 ± 91.82 months, respectively.

Most patients ($n = 190$, 73.9%) received 4 injections of abobotulinumtoxinA during the study period. Taken overall, the mean total dose of abobotulinumtoxinA over the study was 743.08 ± 356.60 U and the mean time between injections was

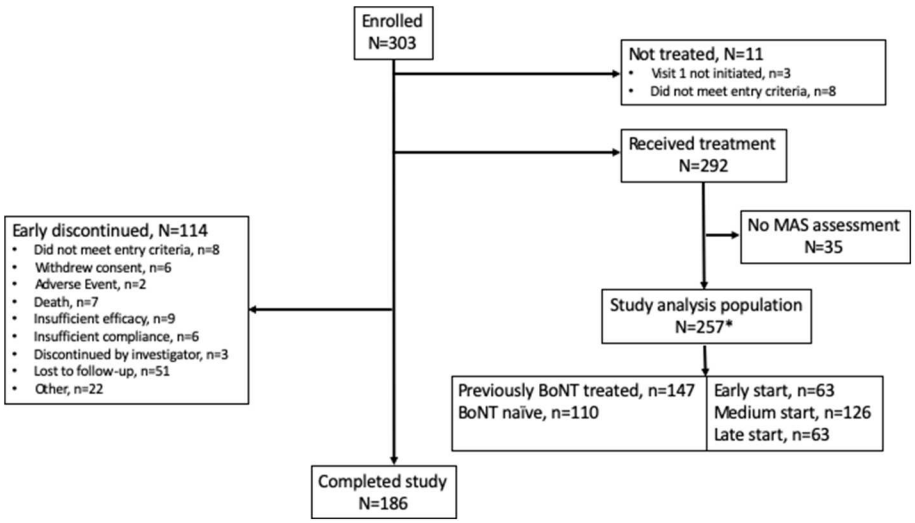


FIGURE 1 | Patient disposition. *Five subjects in the study analysis population were not categorized in the start of treatment groups due to lack of information reported in the eCRF.

TABLE 1 | Baseline (Visit 1) characteristics.

	Early-start *N* = 63	Medium-start *N* = 126	Late-start *N* = 63
Age (years); mean (*SD*)	59.70 (10.98)	60.58 (10.94)	62.25 (13.35)
Sex; *n*(%) male	41 (65.1)	89 (70.6)	30 (47.6)
Time since stroke event to first treatment (months); *N*, mean (*SD*) [95%CI]	*N* = 62 3.74 (1.75) [3.29, 4.18]	*N* = 126 20.11 (11.08) [18.16, 22.06]	*N* = 63 144.24 (90.85) [121.36, 167.12]
Time since arm spasticity onset to first treatment (months); N, mean (SD), [95%CI]	*N* = 59 2.60 (1.96) [2.09, 3.11]	*N* = 114 17.20 (11.76) [15.02, 19.38]	*N* = 59 138.63 (91.82) [114.70, 162.56]
Arm pattern; *n* (%)			
Type I	11 (17.5)	16 (13.2)	4 (6.3)
Type II	0	3 (2.5)	4 (6.3)
Type III	24 (38.1)	52 (43.0)	23 (36.5)
Type IV	27 (42.9)	40 (33.1)	30 (47.6)
Type V	1 (1.6)	10 (8.3)	2 (3.2)
Missing	0	5	0
MAS_{EWF} score*	4.82 (1.39)	4.53 (1.55)	4.83 (1.36)
Pain on VAS	3.92 (3.05)	2.80 (2.83)	2.30 (2.81)

*All available data is presented, including the number of patients who had available data for each individual outcome. *Composite Modified Ashworth Scale (MAS) score = sum of elbow and wrist flexors (MAS_{EWF}). VAS, visual analog scale.*

TABLE 2 | AbobotulinumtoxinA exposure.

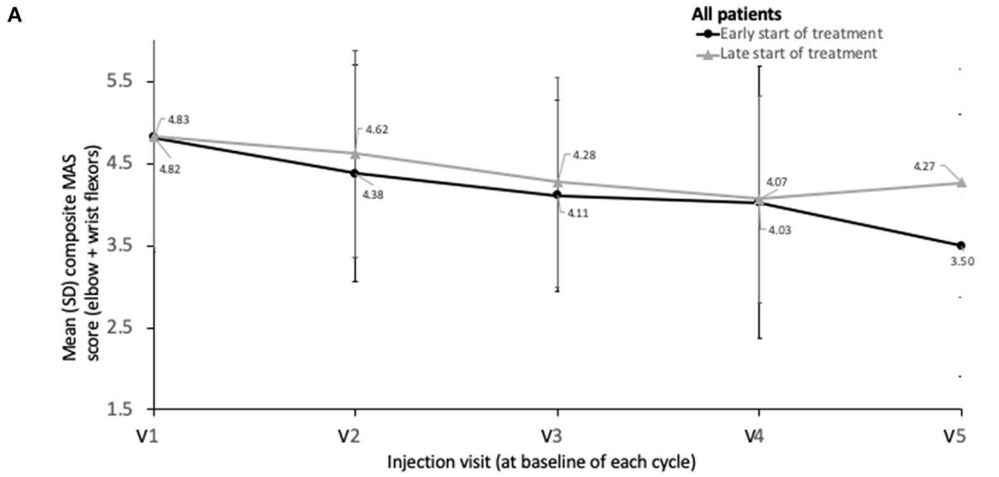
	Early-start *N* = 63	Medium-start *N* = 126	Late-start *N* = 63
Total dose (U) throughout study;	*N* = 63	*N* = 125	*N* = 62
Mean (SD)	719.32 (338.5)	714.23 (342.2)	807.45 (402.7)
Median [range]	645.0 [150.0–1833.7]	655.0 [220.0–2112.5]	780.0 [100.0–1800.0]
Time between study injections; (M)	*N* = 60	*N* = 125	*N* = 63
Mean (SD)	3.70 (1.2)	3.78 (1.5)	3.46 (0.8)
Median [range]	3.2 [2.1–7.4]	3.3 [1.5–13.4]	3.2 [2.7–6.1]
Length of exposure (days)	*N* = 63	*N* = 126	*N* = 63
Mean (SD)	375.3 (169.6)	402.9 (140.1)	390.6 (136.7)
Median [range]	387.0 [58.0–1018.0]	381.5 [92.0–1113.0]	386.0 [87.0–1029.0]

3.69 ± 1.27 months. Overall dose exposure per cycle by groups is presented in **Table 2**. Mean ± SD total doses increased over the course of the study; from 675.7 ± 308.6 U to 718.9 ± 473.8 U in the early-start group, and from 745.3 U ± 402.6 U to 861.9 U ± 401.6 U in the late-start group. The overall (averaged) time between study injections was longer in the early-start vs. late-start group (3.70 ± 1.16 months vs. 3.46 ± 0.76 months).

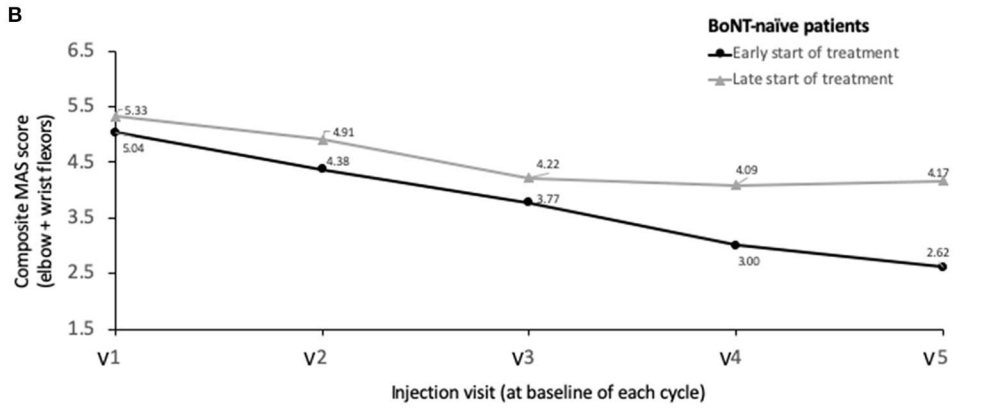
Modified Ashworth Scale

Patients in all groups showed a reduction in MAS_{EWF} scores from baseline over the consecutive injection visits (i.e., at the end of each cycle) (**Figure 2A**). Although the primary analysis showed a numerically lower MAS_{EWF} score (LS mean) for the early- compared to the late- start treatment group (3.72 ± 0.28 vs. 3.87 ± 0.28), the difference at V5/last observed visit did not reach statistical significance (ANCOVA, $p = 0.5465$) (**Table 3**).

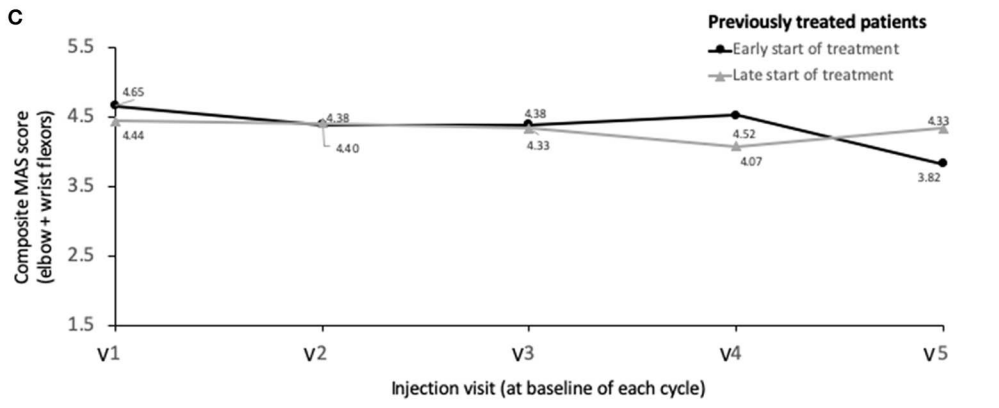
Analysis by prior treatment showed that for the patients who were previously BoNT-naïve, there was a numerically larger reduction in the mean MAS_{EWF} scores in the early-start (despite a slightly lower baseline) vs. late-start patients from Visits 2 to 5 **(Figure 2B)**; however differences were not statistically significant in the ANCOVA model (*p*-values ranged from 0.4788 to 0.8150). This clear pattern was not apparent in those patients who had been previously treated with a BoNT prior to study entry **(Figure 2C)**. Previously treated patients showed



Early-start	n=62	n=60	n=50	n=37	n=32
Late start	n=62	n=62	n=58	n=47	n=44



Early-start	n=28	n=28	n=22	n=12	n=13
Late start	n=27	n=27	n=23	n=17	n=15



Early-start	n=34	n=32	n=28	n=25	n=19
Late start	n=35	n=35	n=35	n=30	n=29

FIGURE 2 | Descriptive statistics for MAS_{EWF} by study visit, early-start vs. delayed start subgroups **(A)** overall population, **(B)** BoNT-naïve population, and **(C)** previously treated population. Study visits were at end of treatment cycle.

TABLE 3 | Primary ANCOVA analysis.

	Early-start group ($N = 52$)	Late-start group ($N = 54$)
Least square mean (SE) MAS_{EWF} score	3.72 (0.28)	3.87 (0.28)
Difference in Least square means		0.15
95% Confidence interval for the difference		[−0.34, 0.64]
p-value		0.55

The final ANCOVA model included the following covariates: start of treatment group, baseline MAS score, time since last injection before MAS assessment at V5 (days), spasticity pattern at baseline, overall achievement of individual treatment goals, concomitant therapy and average total dose (U).

lower MAS_{EWF} scores at baseline in both groups compared to BoNT-naïve patients.

Goal Achievement

Analysis of baseline goal choice revealed that patients in the early-start group appeared more likely to list pain reduction as a key goal than those in the late-start group (54.0 vs. 39.7%, respectively) and functional improvement (38.1 vs. 27.0%, respectively). Conversely, improving ease of care and/or hygiene and supporting ease of PT and/or OT appeared to be chosen more frequently by patients with a longer duration of spasticity until BoNT treatment. Similar proportions of patients in all groups selected improvement of mobility as a treatment goal.

Overall at Visit 5, treatment goals were at least partially achieved for all groups (**Table 4**). At most visits, there were no significant differences in goal achievement between the early and late-start groups. However, at Visits 2 and 3, the treatment goal "functional improvement" was significantly better achieved in the late than in the early-start group ($p = 0.0179$ and 0.0312, respectively). At Visit 5, the treatment goals "Improvement of mobility/flexibility" and "Support and ease of PT/OT" were significantly better achieved in the early than in the late start of treatment group (both $p = 0.04$). Whereas, the mean number of hours per week for subjects using PT and/or OT decreased by about an hour in the early start of treatment group (from 3.49 ± 3.23 h at baseline to 2.34 ± 1.41 h at Visit 5), it increased by over an hour in the late start of treatment group (from 2.06 ± 1.37 h at baseline to 3.30 ± 7.08 h at Visit 5).

Pattern of Upper Limb Spasticity Involvement and Range of Motion

In terms of spasticity pattern, Types III and IV predominated at each visit. There were no significant differences at Visits 3 ($p = 0.18$) or 5 ($p = 0.06$) in the type of spasticity pattern between early-start and delayed-start groups.

Descriptive data for PROM and AROM at each visit are given in **Table 5.** The only significant difference between groups was PROM at the wrist joint at Visit 5, where the LS mean PROM was significantly higher in the early-start group vs. the late-start group (difference in LS mean −21.1 [95%CI: −38.7, −3.47],

TABLE 4 | Goal achievement.

Goal type	Visit	Early-start	Medium-start	Late-start
Improvement of mobility/flexibility; *n* (%)	**Visit 2**			
	Fully achieved	8 (22.9%)	19 (22.1%)	7 (16.7%)
	Partially achieved	20 (57.1%)	58 (67.4%)	31 (73.8%)
	Not achieved	7 (20.0%)	9 (10.5%)	4 (9.5%)
	Missing	11	8	6
	Visit 5			
	Fully achieved	9 (47.4%)	22 (34.4%)	6 (18.2%)
	Partially achieved	9 (47.4%)	38 (59.4%)	25 (75.8%)
	Not achieved	1 (5.3%)	4 (6.3%)	2 (6.1%)
	Missing	0	4	3
Pain reduction; *n* (%)	**Visit 2**			
	Fully achieved	8 (32.0%)	16 (41.0%)	7 (33.3%)
	Partially achieved	14 (56.0%)	21 (53.8%)	11 (52.4%)
	Not achieved	3 (12.0%)	2 (5.1%)	3 (14.3%)
	Missing	8	12	4
	Visit 5			
	Fully achieved	3 (37.5%)	9 (30.0%)	7 (38.9%)
	Partially achieved	4 (50.0%)	17 (56.7%)	9 (50.0%)
	Not achieved	1 (12.5%)	4 (13.3%)	2 (11.1%)
	Missing	1	3	2
Ease of care and hygiene; *n* (%)	**Visit 2**			
	Fully achieved	8 (30.8%)	22 (38.6%)	13 (32.5%)
	Partially achieved	16 (61.5%)	30 (52.6%)	26 (65.0%)
	Not achieved	2 (7.7%)	5 (8.8%)	1 (2.5%)
	Missing	6	9	5
	Visit 5			
	Fully achieved	9 (64.3%)	20 (45.5%)	15 (50.0%)
	Partially achieved	4 (28.6%)	22 (50.0%)	14 (46.7%)
	Not achieved	1 (7.1%)	2 (4.5%)	1 (3.3%)
	Missing	0	2	3
Support and ease of PT/OT; *n* (%)	**Visit 2**			
	Fully achieved	9 (33.3%)	21 (35.0%)	9 (27.3%)
	Partially achieved	17 (63.0%)	37 (61.7%)	22 (66.7%)
	Not achieved	1 (3.7%)	2 (3.3%)	2 (6.1%)
	Missing	5	6	4
	Visit 5			
	Fully achieved	12 (75.0%)	24 (50.0%)	11 (39.3%)
	Partially achieved	3 (18.8%)	23 (47.9%)	17 (60.7%)
	Not achieved	1 (6.3%)	1 (2.1%)	0
	Missing	0	2	1
Functional improvement; *n* (%)	**Visit 2**			
	Fully achieved	2 (10.5%)	5 (12.5%)	1 (7.1%)
	Partially achieved	8 (42.1%)	29 (72.5%)	13 (92.9%)
	Not achieved	9 (47.4%)	6 (15.0%)	0
	Missing	5	8	3
	Visit 5			
	Fully achieved	1 (9.1%)	2 (7.1%)	2 (16.7%)
	Partially achieved	5 (45.5%)	21 (75.0%)	7 (58.3%)
	Not achieved	5 (45.5%)	5 (17.9%)	3 (25.0%)
	Missing	0	3	1
Other; *n* (%)	**Visit 2**			
	Fully achieved	0	4 (66.7%)	1 (50.0%)
	Partially achieved	2 (100.0%)	1 (16.7%)	1 (50.0%)
	Not achieved	0	1 (16.7%)	0
	Missing	0	0	0
	Visit 5			
	Fully achieved	1 (100.0%)	3 (60.0%)	2 (66.7%)
	Partially achieved	0 0	2 (40.0%)	1 (33.3%)
	Not achieved	0	0	0
	Missing		0	0

TABLE 5 | Passive and active range of motion by visit.

	Early-start	Medium-start	Late-start
ELBOW			
PROM; *N*, Mean (SD)			
Visit 1	40 105.63 (40.16)	79 107.25 (37.86)	42 105.07 (34.53)
Visit 3	32 112.50 (39.72)	69 109.20 (35.04)	36 103.75 (35.68)
Visit 5	20 107.50 (36.58)	58 118.36 (38.22)	29 102.24 (38.44)
AROM; *N*, Mean (SD)			
Visit 1	25 66.20 (41.91)	52 70.19 (41.79)	30 68.87 (39.25)
Visit 3	21 70.00 (38.57)	50 68.50 (39.96)	24 78.42 (33.93)
Visit 5	12 66.67 (32.64)	35 72.29 (44.58)	18 63.33 (39.33)
WRIST			
PROM; N, Mean (SD)			
Visit 1	43 88.07 (38.22)	87 84.74 (36.01)	46 88.65 (34.81)
Visit 3	33 97.88 (31.08)	76 93.49 (33.33)	32 91.88 (35.05)
Visit 5	24 110.83 (37.41)	60 103.25 (33.02)	30 95.00 (37.55)
AROM; *N*, Mean (SD)			
Visit 1	30 46.33 (31.10)	53 45.28 (29.03)	24 43.50 (27.86)
Visit 3	21 41.90 (21.12)	44 43.64 (24.50)	18 46.50 (29.90)
Visit 5	19 49.21 (38.12)	35 45.29 (31.53)	17 50.24 (44.56)

$p = 0.02$). Other changes in AROM and PROM at the wrist joint were not significantly different between groups.

Pain

Patients in the early-start group reported higher pain scores than those in the late-start group at baseline (3.92 vs. 2.30, respectively). Whereas, patients in the early-start group showed a trend to reduced pain, and particularly over the first injection cycle, patients in the late-start group reported relatively stable pain scores over time (**Figure 3A**). However, while LS mean of pain scores tended to be lower in the early-start vs. late-start group from Visits 3 to 5, the differences were not significant in the ANCOVA model (p-value ranged from 0.055 to 0.196).

Quality of Life and Treatment Satisfaction

Stronger increases in the mean quality of life EQ-5D index scores were observed in the early start of treatment group compared to the late start of treatment group. In the early-start group, mean EQ-5D index scores continuously increased from 0.54 ± 0.26 at baseline to 0.72 ± 0.18 at Visit 5. Although mean EQ-5D index scores in the late-start group also increased from 0.61 ± 0.31 at baseline to 0.65 ± 0.26 at Visit 5, the increase was not continuous. Overall, in all 5 dimensions, the percentage of subjects having no problems increased for all dimensions between Visit 1 and Visit 5 in the early-start group. By contrast, the percentage of subjects having no problems tended to remain similar in the late-start group (**Figure e1**). The main exception to this rule was pain, which tended to improve in all groups, and particularly in the early-start group. By Visit 5, no patient reported extreme pain in the early-start group (vs. 15.9% at visit 1) (**Figure 3B**).

Satisfaction with treatment was good across treatment groups; patients, investigators and caregivers were generally satisfied with the treatment at Visits 3 and 5 (**Figure 4**). There were generally no significant differences in treatment satisfaction between the early-start and delayed-start groups, except for the investigator's satisfaction at Visit 3 which was significantly better for the late-start group than for the early-start group ($p = 0.047$).

Safety

No new safety issues arose from the study. A total of 47 AEs were reported, including 39 serious AEs in 21 patients. There were 7 deaths (myocardial infarction =1, cardiac arrest =1, cholangitis =1, lung cancer progression =1, cause not reported =3), none were considered treatment-related. Four of the 39 serious AEs were considered potentially related to treatment (listlessness, muscular weakness and two events of fall).

DISCUSSION

The results of this open-label, routine practice study did not show an overall significant difference in tone when abobotulinumtoxinA was started earlier (0–7 months) compared to later (36–443 months) in the patient treatment journey. Treatment with abobotulinumtoxinA was consistently effective in reducing spasticity as well as spasticity/stretch- related pain, whether started early after the stroke event or later, indicating a continued benefit of repeated abobotulinumtoxinA injections regardless of chronicity. MAS_{EWF} scores were, however, descriptively lower in the early-start group than the late-start group at each retreatment visit and at the end of study, and this trend was particularly apparent in patients who were new to BoNT-A treatment. No new safety findings emerged from this study with doses up to 2,000 U.

Clinical guidelines recommend that spasticity is treated when it becomes troublesome and impacts the patient's life (14). The similarity of baseline MAS scores between the three groups confirm prior observations that clinically relevant spasticity (as measured by muscle tone) develops in the first 3 months after stroke (10, 11, 18). Our definition of the "early-start" group generally aligns with the recently agreed definition of the "subacute phase" as proposed by The Stroke Recovery and Rehabilitation Roundtable taskforce (9). Most patients in the early-start group were either in the "early subacute" phase (1 week to 3 months) or the "late subacute" phase (3–6 months). Our findings show that patients treated in the subacute phase experience at least a similar (and a tendency for better) benefit than those treated in the chronic stages after stroke. Importantly, we observed continued effectiveness and safety with repeat treatments. Thus, as suggested by Rosales and colleagues (20), it follows that patients who receive early treatment will gain more

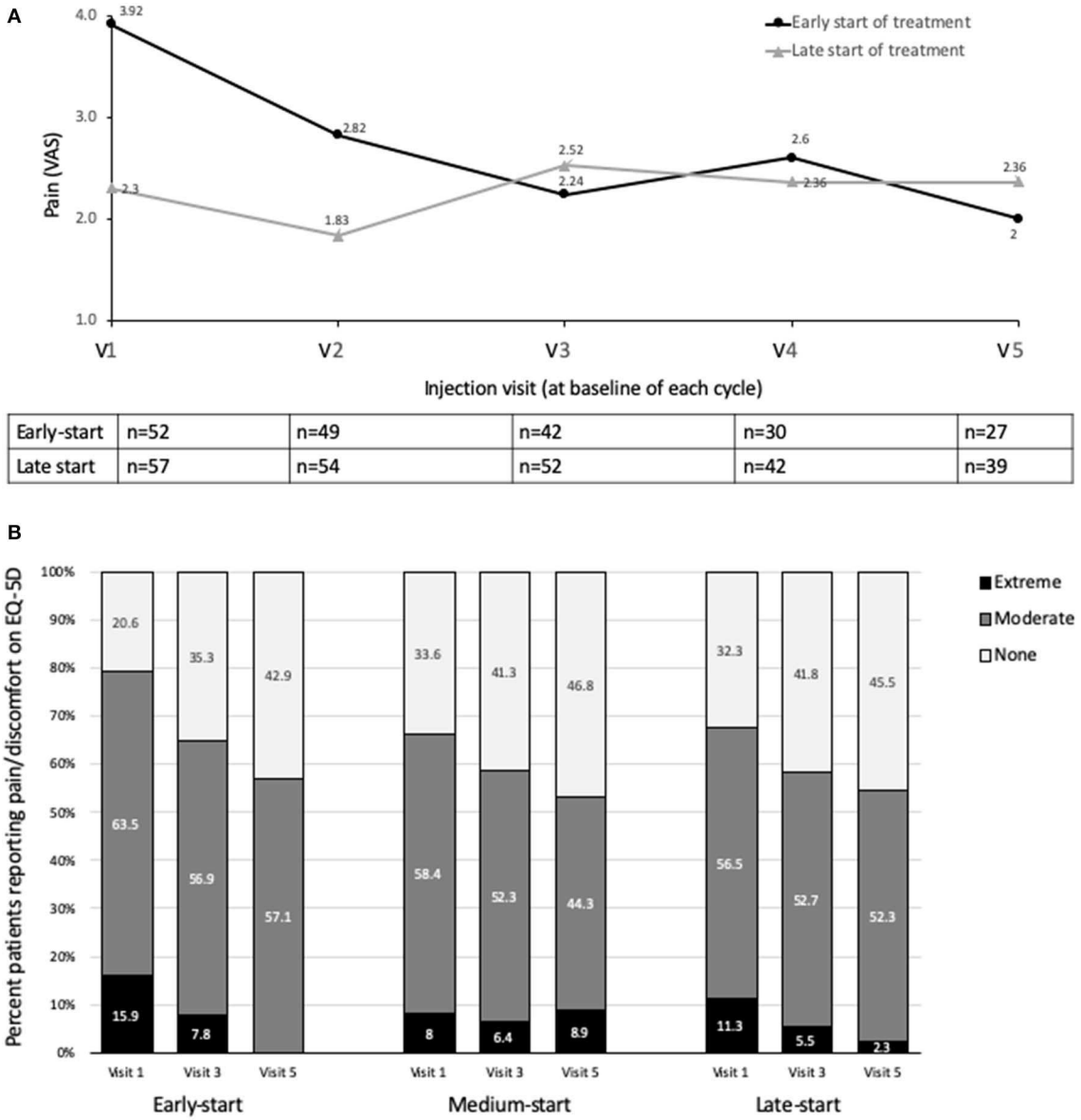


FIGURE 3 | Effects on pain **(A)** Descriptive statistics for pain score (VAS), early-start vs. delayed start subgroups **(B)** Patient quality of life (EQ-5D pain/discomfort domain). Study visits were at end of treatment cycle. VAS, visual analog scale.

time living with reduced spasticity than if they were treated later in their lifetime. In addition, the conditions for rehabilitation are typically better in the subacute vs. the chronic phase. There is evidence of continued neuroplasticity in the subacute phase, and it is intuitively easier to treat a patient before the development of intrinsic muscle changes and contractures that can worsen the severity of spasticity (9, 11, 28–30). Indeed, we saw a significant difference in PROM at the wrist joint between the early- and late-start groups. This is of direct practical importance because many of our patients were at risk of palmar flexion, which once the wrist goes beyond 70°, is hard to treat except by surgery. Further, it has been suggested that starting treatment early may *prevent* the development of secondary complications, allowing the spasticity to be effectively managed with lower doses of BoNT (18). Our findings support this concept of lower dosing in the subacute phase and also indicate that the time between injections may be longer in the earlier stages than the late stages.

The impact of previous treatment was highlighted by the descriptive results when analyzed by prior exposure to BoNT therapy. While there was a numerically larger reduction in mean MAS_{EWF} scores in the early-start vs. late-start BoNT-naïve patients, this pattern was not apparent in the previously-treated patients, again supporting the effectiveness of an early-start. Recent Phase III studies of repeat treatment with

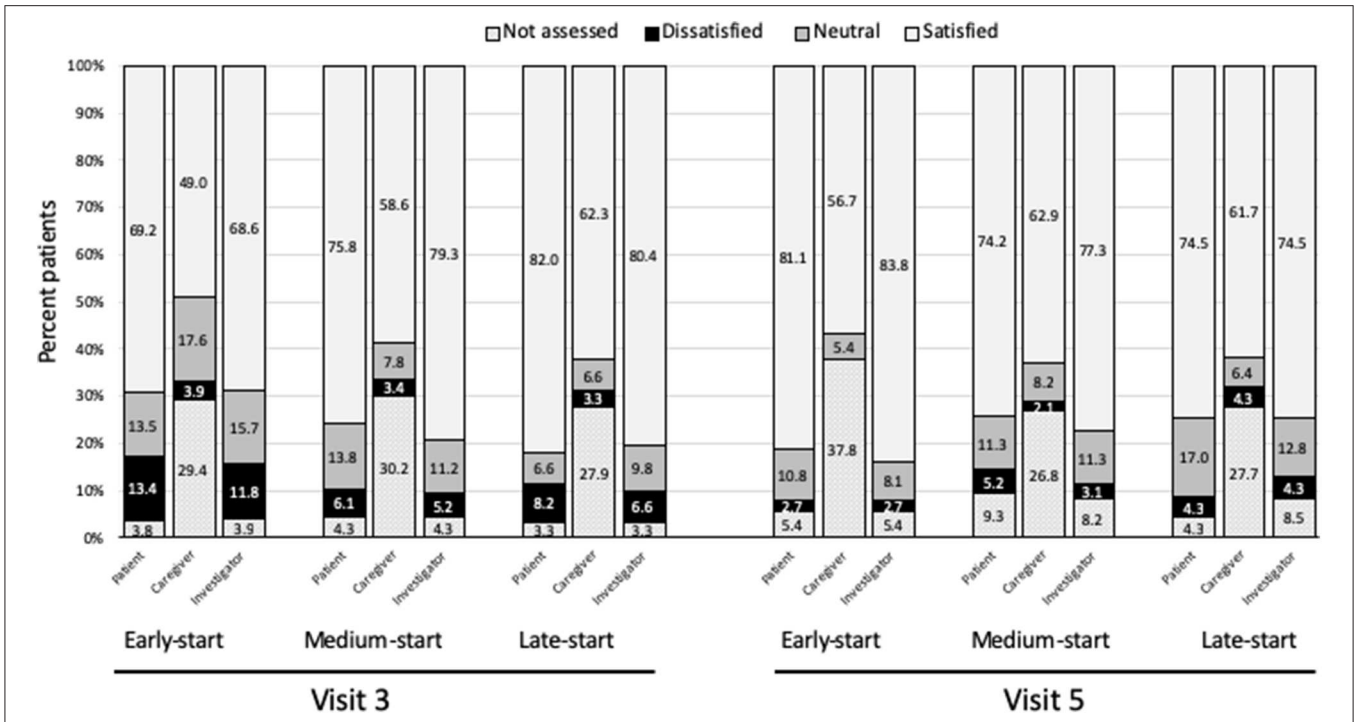


FIGURE 4 | Satisfaction with treatment. Study visits were at end of treatment cycle. Satisfied = satisfied + very satisfied; Dissatisfied = unsatisfied + very unsatisfied.

abobotulinumtoxinA have shown that spasticity parameters continue to improve with repeat treatments (31), and our observations in the treatment naïve patients suggest this may be especially true in the earlier (i.e., first three or four) treatment cycles where we saw a continual reduction in MAS scores–in both the early and late start groups. MAS scores for the previously treated patients were lower than for the BoNT-naïve group and were relatively stable, indicating that they were already well-managed. However, statistical significance between early- and late- start of treatment in the ANCOVA model was not achieved for BoNT-naïve patients, although this may also reflect the much reduced sample size. Another limitation is that, in line with its real-life design, we assessed MAS scores at end of treatment cycle, rather than at peak effect. It is likely that measuring the MAS and other parameters 3–4 months after injection when the pharmacological effect is expected to be waning, might hide a stronger effect of BoNT-A treatment *during* the treatment cycle.

Goal achievement was generally good in this study. Since treatment goals are necessarily tailored to be appropriate for the individual needs of the patient at the time of treatment, it is perhaps to be expected that there were no significant differences in goal achievement between the early- and late- start treatment groups. Of interest, patients in the early-start group reported higher pain scores and more frequently chose reduced pain as a treatment goal than those in the late-start group. This is noteworthy as pain in poststroke patients is often only associated with contractures and painful postures in chronic spasticity, which is less likely to be the cause of pain in the early-start group. This is an important observation as stretch-related pain is a common barrier to patient adherence with home-based physiotherapy (32). Previous studies have shown beneficial effects of BoNT-A on post-stroke pain (22, 33, 34), and our data extends this finding to patients with early post-stroke spasticity and particularly in the first abobotulinumtoxinA treatment cycle. The reasons for this better effect in the first cycle merit further exploration, but may include an indirect effect through reduction of painful spasms (33).

A common indication for BoNT-A therapy is to reduce tone in order to permit more effective OT and PT with respect to gaining function (26). While the goal of improving ease of PT or OT appeared to be more relevant for patients in the late-start group, it is pertinent to note that this goal was significantly better achieved in the early- than in the late-start of treatment group ($p = 0.04$). There is some limited evidence that certain task-based PT and OT approaches are more effective when started earlier post-stroke than later, and it may be that earlier use of BoNT-A may help patients make the most of an early window of opportunity (35, 36). Moreover, the number of hours spent at PT/OT reduced in the early compared to late group (mean decrease of almost 1 h vs. an increase of almost 1 h). It may be that BoNT-A injection (and study participation) caused some re-energization in late-start patients to participate in OT and PT programs. A limitation of this study is that we only considered hours of therapy, and not type of therapy. Other ongoing studies, such as the ULIS III program are currently collecting data to address this important issue (37).

Satisfaction with treatment was generally good across the whole patient cohort with few significant differences between groups. Ratings of treatment satisfaction were generally similar for patients, investigators and caregivers, although many

caregivers were not assessed. This highlights the need for including the caregivers in discussing treatment expectations as well as providing caregiver support. Taken overall, we observed a generally stronger increase in quality of life scores in the early-start compared to the late-start group. In particular, patients in the early-start group showed good improvements in self-care and usual activities, whereas these domains remained more stable in the middle and late-start groups. Quality of life in terms of anxiety and depression domain scores improved in all patients during the study; here a limitation of this routine-practice study is that we cannot tease out the effects of the treatment from external factors such as acceptance and learning to cope with having spasticity. Other studies have found spasticity and social needs to have the strongest impact on quality of life following a stroke (38).

To our knowledge, this is the first prospective evaluation of the long-term effectiveness of routine botulinum toxin treatment on the recovery of upper limb spasticity in relation to the time since stroke. Limitations of the study include the high dropout rate primarily driven by loss to follow-up, with the consequence of relatively small patient numbers, especially at the later visits. As seen in the various analyses, prior exposure to BoNT therapy appears to be an important confounder of results. The study originally planned to primarily enroll BoNT naive patients, but problems with recruitment meant that the study had to be opened up to patients already under treatment. Since this was an observational study, we did not have complete datasets for each variable evaluated and it would have also been valuable to include more patient reported outcomes (as well as satisfaction with treatment) to give the patients perspective on their spasticity management. Finally, another important limitation is our quartile-based definition of early-start treatment, where the mean time since stroke was 3.2 months. This is just on the upper limits of the study-based definitions for "very early intervention" where botulinum toxin has been given within 2–12 weeks of the event to try and target neutrally mediated spasticity (18–20). Other factors having influenced the outcome might be the measurement not at peak effect, but rather at the end of the treatment effect and the shorter intervals and higher dose in the late compared to the early group. This is an interesting finding in itself, as it suggests similar or slightly better effects can be obtained when treating early–even when saving toxin and intervals.

CONCLUSION

Taken overall, the results of this study confirm the utility of abobotulinumtoxinA injections at all stages of disease and support the idea that all patients whose spasticity is troublesome merit goal-directed treatment, regardless of whether it is started in the early or latter stages of the patients disease journey. Continuous treatment should be offered to patients where their treatment goals are considered amenable to BoNT-A treatment. Although our primary effectiveness analyses did not show a significant difference between early- and late- start of treatment, exploratory analyses in BoNT-naive patients showed a trend in favor of early treatment that merits further exploration.

DATA AVAILABILITY STATEMENT

Where patient data can be anonymized, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the relevant independent ethics committee at each study center. The patients/participants provided their written informed consent to participate in this study. The study centers are as follows: Medizinische Universität Graz, Kantonale Ethikkommission Bern, Ordre National de Medicine, ISALA hospital, Universitätsklinikum Tübingen, Universitätsklinikum TU München, and Universitätsklinikum Düsseldorf.

AUTHOR CONTRIBUTIONS

JW and KF were involved in protocol development and wrote the first draft of the manuscript. JW, MH, MM, PG, NM, and KF were involved in patient recruitment and treatment. MK and PM were involved in data analysis. All authors contributed to the interpretation of results and approved the final version of the article.

FUNDING

This work was funded by Ipsen Pharma.

ACKNOWLEDGMENTS

The authors wish to thank all participating sites, their principal investigators, sub-investigators, study coordinators as well as patients who contributed their data. We thank Anita Chadha-Patel, Ph.D., of ACP Clinical Communications Ltd. (Hertfordshire, UK) for providing medical writing support, which was funded by Ipsen (Paris, France) in accordance with Good Publication Practice guidelines.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00104/full#supplementary-material

REFERENCES

1. Watkins CL, Leathley MJ, Gregson JM, Moore AP, Smith TL, Sharma AK. Prevalence of spasticity post stroke. *Clin Rehabil*. (2002) 16:515–22. doi: 10.1191/0269215502cr512oa
2. Hesse S, Mach H, Frohlich S, Behrend S, Werner C, Melzer I. An early botulinum toxin a treatment in subacute stroke patients may prevent a disabling finger flexor stiffness six months later: a randomized controlled trial. *Clin Rehabil*. (2012) 26:237–45. doi: 10.1177/0269215511421355
3. Urban PP, Wolf T, Uebele M, Marx JJ, Vogt T, Stoeter P, et al. Occurence and clinical predictors of spasticity after ischemic stroke. *Stroke*. (2010) 41:2016–20. doi: 10.1161/STROKEAHA.110.581991
4. Doan QV, Brashear A, Gillard PJ, Varon SF, Vandenburgh AM, Turkel CC, et al. Relationship between disability and health-related quality of life and caregiver burden in patients with upper limb poststroke spasticity. *Randomized Control Trial*. (2012) 4:4–10. doi: 10.1016/j.pmrj.2011.10.001
5. Barnes M, Kocer S, Murie Fernandez M, Balcaitiene J, Fheodoroff K. An international survey of patients living with spasticity. *Disabil Rehabil*. (2017) 39:1428–34. doi: 10.1080/09638288.2016.1198432
6. Zorowitz RD, Gillard PJ, Brainin M. Poststroke spasticity: sequelae and burden on stroke survivors and caregivers. *Neurology*. (2013) 80(3 Suppl. 2):S45–52. doi: 10.1212/WNL.0b013e3182764c86
7. Esquenazi A. The human and economic burden of post stroke spasticity and muscle overactivity. *J Clin Outcomes Manage*. (2011) 18:607–14.
8. Sommerfeld DK, Eek EU, Svensson AK, Holmqvist LW, von Arbin MH. Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. *Stroke*. (2004) 35:134–9. doi: 10.1161/01.STR.0000105386.05173.5E
9. Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: the stroke recovery and rehabilitation roundtable taskforce. *Int J Stroke*. (2017) 12:444–50. doi: 10.1177/1747493017711816
10. Wissel J, Schelosky LD, Scott J, Christe W, Faiss JH, Mueller J. Early development of spasticity following stroke: a prospective, observational trial. *J Neurol*. (2010) 257:1067–72. doi: 10.1007/s00415-010-5463-1
11. Welmer AK, Widen Holmqvist L, Sommerfeld DK. Location and severity of spasticity in the first 1–2 weeks and at 3 and 18 months after stroke. *Eur J Neurol*. (2010) 17:720–5. doi: 10.1111/j.1468-1331.2009.02915.x
12. Malhotra S, Cousins E, Ward A, Day C, Jones P, Roffe C, et al. An investigation into the agreement between clinical, biomechanical and neurophysiological measures of spasticity. *Clin Rehabil*. (2008) 22:1105–15. doi: 10.1177/0269215508095089
13. Simpson DM, Hallett M, Ashman EJ. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache. *Neurology*. (2016) 86:1–9. doi: 10.1212/WNL.0000000000002560
14. RCP. *Spasticity in Adults: Management Using Botulinum Toxin. National Guidelines 2018*. (2018). Available online at: https://www.rcplondon.ac.uk/guidelines-policy/spasticity-adults-management-using-botulinum-toxin (accessed February 11, 2020).
15. Bowers D, Fheodoroff K, Khan P, Harriss J, Dashtipour K, Bahroo LB, et al. Spastic Paresis and Rehabilitation – The Patient Journey. *Eur Neurol Rev*. (2016) 11:87–95. doi: 10.17925/ENR.2016.11.02.87
16. Rosales RL, Chua-Yap AS. Evidence-based systematic review on the efficacy and safety of botulinum toxin-A therapy in post-stroke spasticity. *J Neural Transm*. (2008) 115:617–23. doi: 10.1007/s00702-007-0869-3
17. Baker JA, Pereira G. The efficacy of Botulinum Toxin A on improving ease of care in the upper and lower limbs: a systematic review and meta-analysis using the grades of recommendation, assessment, development and evaluation approach. *Clin Rehabil*. (2015) 29:731–40. doi: 10.1177/0269215514555036
18. Rosales RL, Efendy F, Teleg ES, Delos Santos MM, Rosales MC, Ostrea M, et al. Botulinum toxin as early intervention for spasticity after stroke or non-progressive brain lesion: a meta-analysis. *J Neurol Sci*. (2016) 371:6–14. doi: 10.1016/j.jns.2016.10.005
19. Rosales RL, Kong KH, Goh KJ, Kumthornthip W, Mok VC, Delgado-De Los Santos MM, et al. Botulinum toxin injection for hypertonicity of the upper extremity within 12 weeks after stroke: a randomized controlled trial. *Neurorehabil Neural Repair*. (2012) 26:812–21. doi: 10.1177/1545968311430824
20. Rosales RL, Balcaitiene J, Berard H, Maisonobe P, Goh KJ, Kumthornthip W, et al. Early abobotulinumtoxinA (Dysport((R))) in post-stroke adult upper limb spasticity: ONTIME pilot study. *Toxins*. (2018) 10:253. doi: 10.3390/toxins10070253
21. Sheean G, Lannin NA, Turner-Stokes L, Rawicki B, Snow BJ. Botulinum toxin assessment, intervention and after-care for upper limb hypertonicity in adults: international consensus statement. *Eur J Neurol*. (2010) 17 (Suppl. 2):74–93. doi: 10.1111/j.1468-1331.2010.03129.x
22. Jost WH, Hefter H, Reissig A, Kollewe K, Wissel J. Efficacy and safety of botulinum toxin type A (Dysport) for the treatment of post-stroke arm spasticity: results of the German-Austrian open-label post-marketing surveillance prospective study. *J Neurol Sci*. (2014) 337:86–90. doi: 10.1016/j.jns.2013.11.022
23. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther*. (1987) 67:206–7. doi: 10.1093/ptj/67.2.206
24. Hefter H, Jost WH, Reissig A, Zakine B, Bakheit AM, Wissel J. Classification of posture in poststroke upper limb spasticity: a potential decision tool for botulinum toxin a treatment? *Int J Rehabil Res*. (2012) 35:227–33. doi: 10.1097/MRR.0b013e328353e3d4
25. Turner-Stokes L. Goal attainment scaling (GAS) in rehabilitation: a practical guide. *Clin Rehabil*. (2009) 23:362–70. doi: 10.1177/0269215508101742
26. Turner-Stokes L, Ashford S, Esquenazi A, Wissel J, Ward AB, Francisco G, et al. A comprehensive person-centered approach to adult spastic paresis: a consensus-based framework. *Eur J Phys Rehabil Med*. (2018) 54:605–17. doi: 10.23736/S1973-9087.17.04808-0
27. Ashford S, Fheodoroff K, Jacinto J, Turner-Stokes L. Common goal areas in the treatment of upper limb spasticity: a multicentre analysis. *Clin Rehabil*. (2016) 30:617–22. doi: 10.1177/0269215515593391
28. Wissel J, Manack A, Brainin M. Toward an epidemiology of poststroke spasticity. *Neurology*. (2013) 80(3 Suppl. 2):S13–9. doi: 10.1212/WNL.0b013e3182762448
29. Thilmann AF, Fellows SJ, Garms E. The mechanism of spastic muscle hypertonus. Variation in reflex gain over the time course of spasticity. *Brain*. (1991) 114:233–44.
30. Thilmann AF, Fellows SJ, Ross HF. Biomechanical changes at the ankle joint after stroke. *J Neurol Neurosurg Psychiatry*. (1991) 54:134–9. doi: 10.1136/jnnp.54.2.134
31. Gracies JM, O'Dell M, Vecchio M, Hedera P, Kocer S, Rudzinska-Bar M, et al. Effects of repeated abobotulinumtoxinA injections in upper limb spasticity. *Muscle Nerve*. (2018) 57:245–54. doi: 10.1002/mus.25721
32. Kuno Y, Morino A, Takamatsu Y. Upper extremities pain relates to adherence to home-based exercise in patients with stroke. *Physiotherapy*. (2015) 101:e800–e1. doi: 10.1016/j.physio.2015.03.3683
33. Wissel J, Ganapathy V, Ward AB, Borg J, Ertzgaard P, Herrmann C, et al. Onabotulinumtoxina improves pain in patients with post-stroke spasticity: findings from a randomized, double-blind, placebo-controlled trial. *J Pain Symptom Manage*. (2016) 52:17–26. doi: 10.1016/j.jpainsymman.2016.01.007
34. Turner-Stokes L, Fhedoroff K, Jacinto J, Maisonobe P. Results from the upper limb international spasticity study-II (ULIS- II): a large, international, prospective cohort study investigating practice and goal attainment following treatment with botulinum toxin a in real-life clinical management. *BMJ Open*. (2013) 3:e002771. doi: 10.1136/bmjopen-2013-002771
35. Van Peppen RP, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? *Clin Rehabil*. (2004) 18:833–62. doi: 10.1191/0269215504cr843oa
36. Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M, et al. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. *PLoS ONE*. (2014) 9:e87987. doi: 10.1371/journal.pone.0087987
37. Turner-Stokes L, Ashford SA, Jacinto J, Maisonobe P, Balcaitiene J, Fheodoroff K. Impact of integrated upper limb spasticity management including botulinum toxin a on patient-centred goal attainment: rationale and protocol for an international, prospective, longitudinal cohort study (ULIS-III). *BMJ Open*. (2016) 6:e011157. doi: 10.1016/j.toxicon.2016.11.224

38. Hotter B, Padberg I, Liebenau A, Knispel P, Heel S, Steube D, et al. Identifying unmet needs in long-term stroke care using in-depth assessment and the post-stroke checklist - the managing aftercare for stroke (MAS-I) study. *Eur Stroke J.* (2018) 3:237–45. doi: 10.1177/2396987318771174

Conflict of Interest: Authors employed by Ipsen participated in designing the questionnaire and study; in analysis and interpretation of the data; and in review, approval of, and decision to submit the manuscript. JW has received honoraria for being on the Speakers' Bureau for Allergan, Ipsen, Merz, and for his role on advisory boards at Allergan, Ipsen, Merz. He also received an unrestricted research grant from Allergan and Merz. JH has received consultancy fees and speaker honorarium from Allergan, Ipsen, and Merz. He is also an investigator in an Ipsen study. HH has received consultancy fees and speaker honorarium from Allergan, Ipsen, and Merz. He is also an investigator in an Ipsen study. MH is an investigator in an Ipsen study. MK is employed by Ipsen. PM is employed by Ipsen. NM is an investigator in an Ipsen study. MM has received speaker honorarium from Ipsen and Merz. She is also an investigator in an Ipsen study. PG is an investigator in an Ipsen study. KF has received consultancy fees and speaker honorarium from Allergan, Ipsen, and Merz. He is also an investigator in an Ipsen study.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 02 April 2020
doi: 10.3389/fneur.2020.00155

Synergistic Effect of Combined Mirror Therapy on Upper Extremity in Patients With Stroke: A Systematic Review and Meta-Analysis

Zhonghua Luo[1†], Yuqing Zhou[2†], He He[2], Shanshan Lin[3], Rui Zhu[2], Zhen Liu[4], Jiemei Liu[5], Xiaoli Liu[2], Shuping Chen[2,6], Jihua Zou[2,6] and Qing Zeng[2,6*]*

[1] First Clinical Medical College, Southern Medical University, Guangzhou, China, [2] Department of Rehabilitation Medicine, Zhujiang Hospital, Southern Medical University, Guangzhou, China, [3] Department of Rehabilitation Medicine, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China, [4] Department of Rehabilitation Medicine, The First People's Hospital of Foshan, Foshan, Guangdong, China, [5] Department of Rehabilitation Medicine, Shunde Hospital, Southern Medical University, Guangzhou, China, [6] School of Rehabilitation Medicine, Southern Medical University, Guangzhou, China

OPEN ACCESS

Edited by:
Mariella Pazzaglia,
Sapienza University of Rome, Italy

Reviewed by:
Laura Mori,
University of Genoa, Italy
Giulia Galli,
Santa Lucia Foundation (IRCCS), Italy

***Correspondence:**
Qing Zeng
zengqingyang203@126.com
Jihua Zou
zoujihua@i.smu.edu.cn

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 02 December 2019
Accepted: 18 February 2020
Published: 02 April 2020

Citation:
Luo Z, Zhou Y, He H, Lin S, Zhu R, Liu Z, Liu J, Liu X, Chen S, Zou J and Zeng Q (2020) Synergistic Effect of Combined Mirror Therapy on Upper Extremity in Patients With Stroke: A Systematic Review and Meta-Analysis. Front. Neurol. 11:155. doi: 10.3389/fneur.2020.00155

Background: There is an increasing trend for researchers to combine mirror therapy with another rehabilitation therapy when treating the upper extremity of patients with stroke.

Objective: To evaluate the synergistic effect of combined mirror therapy (MT) on the upper extremity in patients with stroke and to judge efficacies of four combined mirror therapy subgroups [EMGBF group: electromyographic biofeedback (EMGBF) + MT; MG group: mesh glove (MG) + MT; AT group: acupuncture (AT) + MT; ES group: EMG-triggered electrical stimulation (ES) + MT].

Methods: CNKI, Wan Fang, VIP, Web of Science, ScienceDirect, PubMed, OVID LWW, and Cochrane were used. We searched these databases for randomized controlled trials published from January 2013 to August 2019, which presented results of combining mirror therapy with other rehabilitation therapies. Quality assessments were performed using the Cochrane Handbook criteria in order to accurately review interventions. The primary outcomes were measured by the Fugl–Meyer Assessment—upper extremity (FMA-UE).

Results: Ten trials, with a total of 444 patients whose upper limb functions were damaged after stroke, were included in the meta-analysis. Compared with the control group, a remarkable effect of combined mirror therapy [all: weight mean difference in random effects model (WMD): 8.07, 95% confidence interval (CI) 5.87, 10.26] on functional recovery of the upper limb was detected. However, a high value of heterogeneity ($\chi 2 = 20.09$, df = 9; $I^2 = 55\%$) was found. The subgroup analysis (EMGBF group: WMD = 8.95, 95% CI 6.33, 11.58; ES group: WMD = 10.14, 95% CI: 5.67, 15.01) showed moderate improvement in functional recovery of the upper extremity in patients with stroke when mirror therapy was combined with conventional therapy. Furthermore, no difference in efficacy on upper extremity in patients with stroke was observed between the EMGBF group and the ES group.

Conclusion: Despite the heterogeneity, the results indicate that combining mirror therapy with another rehabilitation therapy on the upper extremity in patients with stroke

is better than single rehabilitation therapy. However, more randomized controlled clinical trials and larger sample sizes are required for an in-depth meta-analysis.

Keywords: mirror therapy, combined therapy, upper limb, stroke, functional recovery

INTRODUCTION

Stroke is one of the primary causes of disability not only in middle-aged but also elderly people worldwide (1). Stroke survival is often accompanied by paralysis of the upper and lower limbs, which seriously affects the quality of life of patients (2, 3). Therefore, rehabilitation therapy after stroke is very important.

Several current interventions are used to improve upper limb function, including mirror therapy (MT) (4, 5), constraint-induced movement therapy (6, 7), acupuncture (8), electromyographic biofeedback (EMGBF) (9), afferent stimulation (10), and robot-assisted therapy (11). Recently, the promising therapy, MT, is popular with researchers due to it being simple, cheap, and maneuverable. Among them, MT refers to the application of a simple device, called a "mirror box," which uses the principles of the same object image and distance reflected by the plane mirror to replace the normal limb image, which achieves the rehabilitation goal of eliminating abnormal sensation and restoring motor function (12). For example, Ramachandran et al. first discovered that the mirror box could provide a useful new tool to reconstruct the sensory circuitry of phantom limbs (13). Stevens and Zeng et al. further found that in hemiplegia, the function of the damaged limb significantly improved within 3 months in hemiplegia, indicating the potential of using mirror therapy as a cognitive strategy for upper extremity functional recovery (14, 15). Yavuzer and Rothgangel et al. reported that the improvement of upper extremity with mirror therapy was obvious than with conventional treatment program (16, 17). To further improve treatment effect, researchers combined mirror therapy with another rehabilitation therapy on upper extremity in patients with stroke and found preliminary evidence that combined mirror therapy is more effective than pure rehabilitation therapy (18, 19). Therefore, in recent studies, researchers are focusing more on mirror therapy with the combination of electromyographic biofeedback, mesh glove, acupuncture, or EMG-triggered electrical stimulation applied for the rehabilitation of the upper extremity.

EMG-BF has been established as a significant treatment for all kinds of peripheral nerve injuries (PNI) (20, 21). It improves motor function by promoting proprioceptive feedback caused by cortical recombination and muscle contraction through sensory stimulation (22). As early as 1982, Basmajian et al. found that the myoelectric biofeedback treatment for stroke patients with hemiplegia can significantly improve the recovery of upper limb motor function in stroke patients with hemiplegia (23, 24). Mesh glove (MG), a type of whole-hand electrical afferent stimulation, has been demonstrated to reduce muscle hypertonia and modify voluntary motor control as well as increase wrist extension motion. Therefore, it is expected to improve the daily life ability of stroke patients with a chronic neurological deficit (25, 26). Studies have shown that MG is likely to play an important role in plastic changes in the primary motor cortex and have a long-term influence on motor cortical excitability (26, 27). Acupuncture (AT) plays an irreplaceable role in traditional Chinese medicine and has a history of more than 3,000 years of use in China (28). As a unique Chinese medicine treatment, it is widely used to improve movement, sensation, speech, and other neurological functions in stroke patients (29, 30). EMG-triggered electrical stimulation (EMG-ES) is a process to increase electrical stimulation, starting with stimulation of a specific motor and reaching a threshold for muscular contraction. In the EMG method, when activity reaches the threshold for muscular contraction, the patient receives an additional electrical stimulus until there is maximum extension of the wrist several times to determine the target stimulation (18, 31). These four treatments have respective advantages and complement each other. Thus, the mirror therapy combination is regarded as a promising strategy for the treatment of the upper extremity in patients with stroke.

However, data is still not completely accurate, and further studies are still necessary. The aim of this meta-analysis is to investigate the synergistic effect of mirror therapy combined with other rehabilitation therapies on the upper extremity in patients with stroke, to screen for more effective rehabilitation methods for patients.

METHODS

Data Sources and Search Strategy

According to the guidelines for randomized controlled trials provided by the Cochrane systematic evaluation of interventions, we systematically searched for studies published from January 2013 to August 2019 in the following databases: CNKI, VIP, Wan Fang, Web of Science, ScienceDirect, PubMed, OVID LWW, and Cochrane library.

Quality Appraisal

To ensure the reliability of the included studies, two independent authors screened each study to assess quality using the criteria of the Cochrane Handbook (update 15.1.0) and the PEDro scale for reviewing interventions. The risk assessment criteria in the Cochrane Handbook are as follows (32): random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attribution bias), selective outcome reporting (reporting bias), and other source of bias. The PEDro scale contains 11 items: inclusion criteria, random allocation, allocation concealment, baseline similarity, blinded subjects, therapist and referees, recording the key findings of 85% of the subjects, completing the target therapy, intergroup analysis, and primary outcome. Before the two authors evaluated the quality of

studies, they studied the manuals, discussed differences in their views, and reached a consensus. When the two authors finished quality appraisal, a third professor made the final evaluation.

Inclusion and Exclusion Criteria

Types of Studies

Randomized controlled clinical trials (RCTs) that combined mirror therapy with another rehabilitation therapy on the upper extremity in patients with stroke were examined.

Types of Participants

The enrolled patients were not restricted by age, gender, or area of limb hemiplegia (**Tables 1**, **2**). Patients were eligible for inclusion if they (i) suffered from stroke in subacute or chronic phases according to diagnostic guidelines updated by the American Heart Association/American Stroke Association (38); (ii) had ≤to 46 points according to the Fugl–Meyer Assessment—upper extremity (FMA-UE) (39, 40); (iii) were able to comprehend and execute the therapeutic schedules; and (iv) were diagnosed with ischemic or hemorrhagic stroke for the first time. They were excluded if they (i) were diagnosed with severe cognitive impairment; (ii) suffered from other severe diseases such as brain tumor or brain trauma; or (iii) were also involved in other trials.

Types of Intervention

Combined mirror therapy was compared with single rehabilitation therapy, and all the patients received conventional therapy. There are four combined therapies such as EMGBF + MT, AT + MT, ES + MT, and MG + MT. Since the experimental scheme of each combined method is different, the strategies of classifying it into a class of the same methods are (i) the same principle of experiment; (ii) target group consistency; (iii) using an identical single-blind method; (iv) had initiative in moving their impaired upper extremity or moved assisted by therapist in order to be in line with unaffected extremity.

Outcome Measures

FMA-UE, as a professional assessment, was used to measure the outcome in the upper limb's functional recovery in terms of reflex ability, synergic movement, wrist stability, and hand grip strength.

Search Strategies

All the searches were performed in electronic databases published in English or Chinese, specifically CNKI (publication year: 2013.01.01–2019.08.01; language: Chinese and English; all types of literature), PubMed (publication date: 2013.01.01–2019.08.01; language: English; all types of literature); Wan Fang (date of publication: 2013–2019; article types: paper), Web of Science (time span: 2013–2019), ScienceDirect (years: 2013–2019; all types of articles), SpringerLink (show documents published: between 2013 and 2019), OVID LWW (publication year: 2013.2018), Cochrane library (trials; publication year: between 2013 and 2018). There were three key words used to search the literature, namely ("upper limb" or "upper extremity" or "membrum superius" or "pectoral limb") AND ("stroke" or "cerebrovascular stroke" or "cerebrovascular accident") AND ("mirror therapy").

TABLE 1 | Detailed description of 10 studies.

References	ALL_n	Age, years, mean (SD)(E/C)	Paretic side (n: right/left)(E/C)	Time since stroke onset, day, mean (SD)(E/C)	Clinical stage	Severity (Brunnstrom stages) (E/C)	Type	Interventions(E/C)
Wang and Chen (33)	60	47.02 ± 9.1/48.08 ± 10.2	11/19 10/20	119.26 ± 41.08/120.37 ± 39.4	Subcute	Unclear	EMGBF	EMGBF+MT+CT/EMGBT+CT
Xu (34)	40	62.40 ± 8.61/60.65 ± 8.80	13/7 12/8	17.61 ± 7.63/15.36 ± 8.19	Subcute	1.15 ± 0.37/1.20 ± 0.41	EMGBF	EMGBF+MT+CT/EMGBF+CT
Yao (21)	60	57.40 ± 7.323/57.07 ± 6.181	14/16 14/16	18.03 ± 5.654/21.23 ± 8.365	Subcute	2.93 ± 1.0065/2.67 ± 1.011	EMGBF	EMGBF+MT+CT/EMGBF+CT
Xie et al. (35)	90	56 ± 8/54 ± 6	27/18 21/24	40.73 ± 6.75/42.69 ± 7.42	Subcute	Unclear	AT	AT+MT+CT /MT+CT
Zhang et al. (36)	40	55.2 ± 10.9/54.9 ± 11.3	11/9 8/12	19.6 ± 20.3/30.8 ± 28.7	Subcute	2.15 ± 0.726/1.9 ± 0.70	AT	AT+MT+CT /MT+CT
Zhou and Ye (30)	40	57.22 ± 6.15/54.20 ± 5.03	unclear	<8 weeks	Subcute	Unclear	AT	AT+MT+CT /MT+CT
Lin et al. (37)	28	55.79 ± 14.59 /56.01+12.53	8/6 6/8	158.97 ± 95.34/129.5 ± 81.27	Chronic	4.25 ± 0.64 /4.25 ± 0.64	MG	MG+MT+CT/MT+CT
Lee et al. (10)	32	52.50+13.24 /56.64+9.43	7/8 7/10	660 ± 421.2 /531.3 ± 397.2	Chronic	Unclear	MG	MG+MT+CT /MT+CT
Kim et al. (31)	23	55.92 ± 11.75/55.64 ± 12.61	4/8 6/5	34.06 ± 1.65/35.00 ± 15.05	Subcute	3.5 ± 0.97/3.28 ± 1.051	ES	ES+MT +CT /ES+CT
Schick et al. (18)	32	62 ± 19.6 /63 ± 11.5	7/8 8/9	1–6 months	Subcute	Unclear	ES	ES+MT+CT/ES+CT

TABLE 2 | Detailed description of 10 studies (continued **Table 1**).

Duration	Case_n	Case_mean	Case_SD	Control_n	Control_mean	Control_SD	Duration(min)	Outcome measures
5 × 30 min sessions over a 4-week period	30	38.97	10.06	30	33.17	10.49	600	FMA;AROM;IEMG;
6 × 40 min sessions over a 8-week period	20	34.3	6.31	20	23.8	5.09	1920	BN;FMA;MAS;
6 × 20 min sessions over a 4-week period	30	51.2	7.871	30	42.23	11.316	480	BN;FMA;FIM;
MT:5 × 30 min sessions over a 4-week period AT:5 × 30 min sessions over a 4-week period	45	45.96	4.03	45	38.58	1.98	900	FMA;BI;STEF;
AT:6 × 20 min sessions over a 4-week period AT+MT: 6 × 20 min sessions over a 4-weekperiod	20	47.7	9.71	20	32.7	8.73	480	FMA;AROM;BI;BN;
5 × 30 min sessions over a 12-week period	20	34.97	7.85	20	25.71	9.45	1800	FMA;BI;
5 × 90min sessions over a 4-week period	14	50.93	9.41	14	49.86	8.97	1800	FMA;Myoton;BBT;10 MWT;MAL;
5 × 90 min sessions over a 4-week period	15	43.6	9.76	16	43.56	8.73	1800	FMA; FIM; rNSA; BBT;
5 × 40 min sessions over a 3-week period	12	26.67	8.68	11	17.45	5.69	600	BBT;FMA;BN;MFT;
5 × 30 min sessions over a 3-week period	15	29.73	14.4	17	17.73	9.1	450	FMA;

E, experimental group; C, control group; EMGBF, Electromyographic biofeedback; AT, Acupuncture; MG, Mesh glove; ES, EMG-triggered electrical stimulation; CT, Conventional therapy; MT, mirror therapy; FMA, Fugl-Meyer Assessment; AROM, active range of motion; IEMG, Imaging electromyography; BN, Brunnstrom stage; MAS, motor assessment scale; FIM, Function Independence Measure; MBI, Modified Barthel Index; STEF, simple test for evaluating hand function; BI, Barthel Index; BBT, Box and Block Test; 10MWT, 10-Meter Walk Test; MAL, MAL, Motor Activity Log.; rNSA, revised Nottingham Sensory Assessment; MFT, Manual Function Test; n, number; mean, average number; SD, standard difference.

Data Collection and Exclusion

The results of the literature search were brought into the CNKI E-study, and duplicate records were removed. One author reviewed and assessed the title, abstract, and purpose of the document to remove irrelevant studies. After this preliminary screening, two independent authors filtered the remaining results according to (i) clear outcome; (ii) combined therapy; (iii) completed data; (iv) outcome assessment of FMA-UE; (v) randomized controlled trial; and (vi) single blind or double blind. After discussion and negotiation, 10 studies were included in the quantitative synthesis (meta-analysis).

Data Extraction

Blinded to the journal, we made a detailed form (**Tables 1**, **2**) based on PRISMA that described the enrolled studies' characteristics in terms of publication year, sample size, author, and patient characteristics [i.e., age, paretic side, severity (Brunnstrom stages), time when patient was diagnosed with a stroke, interventions (i.e., intervention types and duration), outcome measures and statistic data (i.e., case group's number (n); case group's mean; case group's standard difference (SD); control group's n; control group's mean; control group's SD)]. When we encounter problems, we contacted the first author by email as much as possible.

Data Analysis

To accurately infer the synergistic effect of combined mirror therapy for functional recovery in a stroke patient's upper limb, raw data from research materials were processed using Review Manager 5.3 and Stata 12.0 to calculate weight mean difference (WMD) with a confidence interval of 95% (95% CI). Given the continuity of the data, the best methods random effects model and the statistical method of inverse variance were, respectively, used to compare combined therapy with single rehabilitation therapy. The weight mean difference (WMD) and 95% confidence intervals (95% CI) were used to assess the mean effect size of therapy. Heterogeneity among studies was assessed using I^2 tests (a value of $p < 0.1$ was considered to indicate the existence of significant heterogeneity) and chi-square (0–40% low; 40–60% moderate; 60–100% high heterogeneity). Subgroup analysis (1) combined therapy subgroup: EMGBF group, ES group, AT group, and MG group, and (2) the subgroup's control method: (i) adding mirror therapy to rehabilitation therapy in the experimental group. (ii) adding rehabilitation therapy to mirror therapy in the experimental group) was performed using Review Manager 5.3. In order to investigate the sources of heterogeneity, we rigorously applied moderator analyses using Stata12.0 (i.e., meta-regression and publication bias) (41). Differences were considered statistically significant when the $p < 0.05$.

RESULTS

Nine hundred sixty-one records were identified through database searching, and 761 records were retained after removal of duplicates. In the end, 10 studies (10, 21, 31–33, 43–47) were included in the quantitative synthesis (meta-analysis). The detailed process for selecting studies is demonstrated in **Figure 1**. Studies published between 2013 and 2019 were included in the meta-analysis. A total of 444 patients were studied, with 221 patients in the experimental group and 223 patients in the control group. **Tables 1**, **2** summarize the 10 studies in detail. The average age of the patients ranged from 47.02 to 63.00 years. The mean time since stroke onset was 15.36 to 6 months except for two studies (10, 47) whose onset time of stroke was more than 6 months. Five studies (21, 32, 44, 46, and 47) precisely described the average Brunnstrom stages, which ranged from 1.15 to 4.25. The duration of interventions was from 450 to

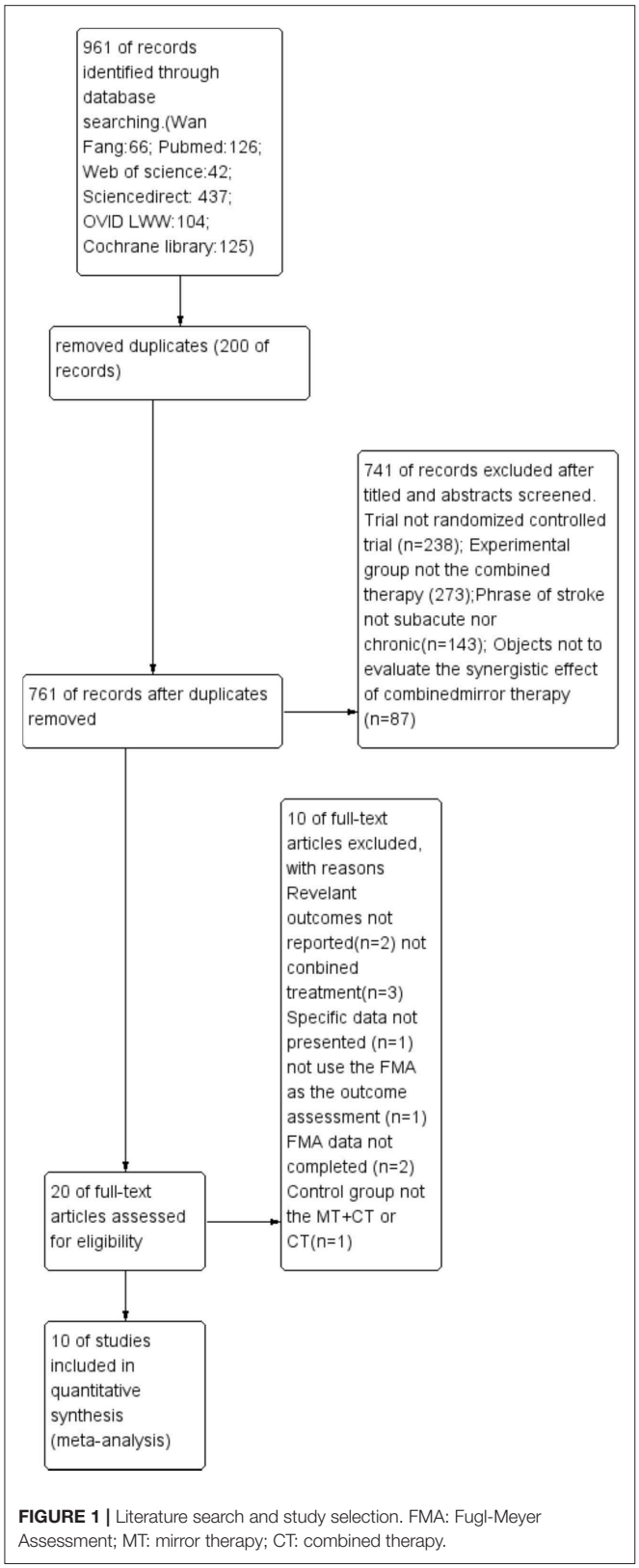


FIGURE 1 | Literature search and study selection. FMA: Fugl-Meyer Assessment; MT: mirror therapy; CT: combined therapy.

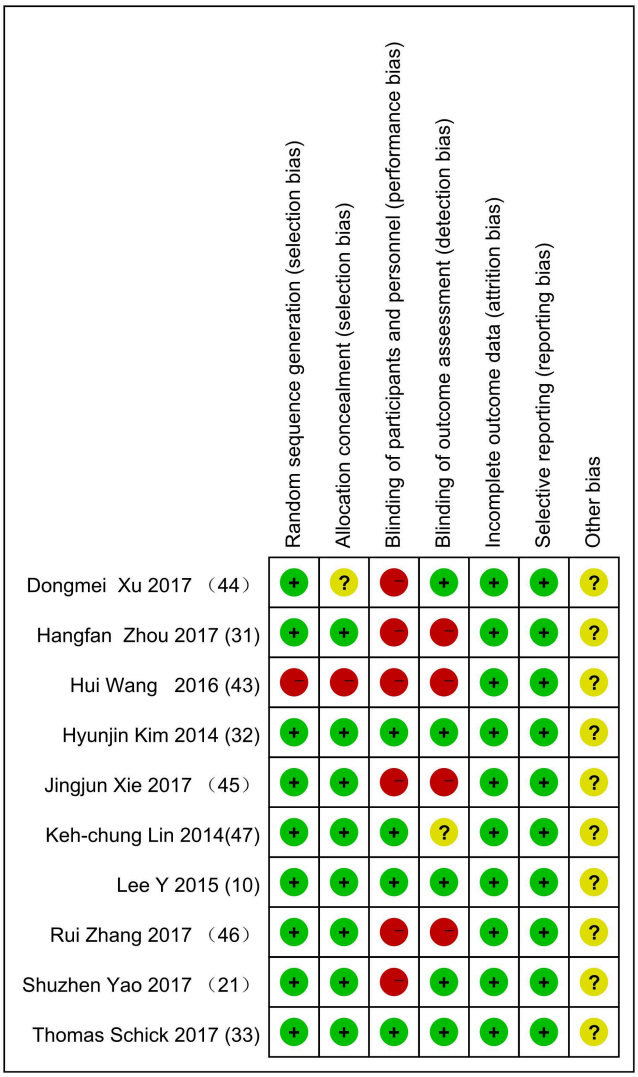


FIGURE 2 | Authors' judgments about each risk of bias item for included studies.

1,920 min. **Figure 2** presents the authors' judgments about the risks of bias for the included studies. All studies (10, 21, 31–33, 43–47) described the methods used to generate the allocation sequence in sufficient detail, and all studies had complete data. The risk of selection bias (allocation concealing) was obscure in five studies (21, 31, 32, 43, and 46) because of insufficient information, and the selection bias (allocation concealing) of Xu (44) was considered high due to the allocation sequence being generated by date of admission. Performance bias (blinding of participants and personnel) was low in six studies (10, 21, 33, 44, 46, and 47) because reliable blinding methods were implemented for both participants and study personnel, while these factors were obscure in four studies (31, 32, 43, and 45). Detection biases (detection of outcome assessment) were not able to be estimated for three studies (32, 43, and 45) as no information was given. **Table 3** shows the gross score for each study in the internal validity analysis carried out using the PEDro scale: four studies were excellent (>8), five studies were good (≥6, ≤8), and one study was fair (≥4, ≤5).

Figure 3 presents the random effects meta-analysis of mirror therapy (MT) combined with another rehabilitation therapy and applied to functional recovery of a stroke patient's upper limb. Using the standard chi square test, the heterogeneity statistic ($\chi^2 = 20.09$, $p = 0.02$; $I^2 = 55\%$) was significant. The value for overall effect is 7.20 ($p < 0.00001$) in random mode due to the existence of substantial heterogeneity, and the total weight mean difference were 8.07 (95% CI: 8.07, 10.26). Meanwhile, a subgroup analysis (**Figure 4**) was applied to detect the cause of high heterogeneity, and this revealed that the AT group ($I^2 = 70\%$) was the important factors. **Figure 4** shows that the EMGBF group (WMD = 8.95, 95% CI: 6.33, 11.58) and ES group (WMD = 10.14 95% CI: 5.67, 15.01) showed moderate improvement in functional recovery on upper extremity in patients with stroke, but no difference was witnessed in the MG group (WMD = 0.53, 95% CI −4.18, 5.25, Z = 0.22, $p = 0.82$). The difference between the subgroup analysis in **Figures 5**, **6** is the interventional method adding mirror therapy to rehabilitation therapy in the experimental group (**Figure 5**) or adding rehabilitation therapy to mirror therapy in the experimental group (**Figure 6**). No difference in efficacy on upper extremity in patients with stroke was observed between the EMGBF group and ES group in **Figure 5**. **Figure 6** shows that there is a substantial heterogeneity ($\chi^2 = 15.42$, $I^2 = 74\%$) and a subgroup difference ($\chi^2 = 8.18$, $I^2 = 87.8\%$) between the AT group and MG group. Meta-analysis regression (**Table 4**) was used to examine the cause of high heterogeneity, with inconclusive results: the covariate sample size ($p > 0.352$) and during treatment ($p > 0.782$) showed significant correlation with high heterogeneity. Finally, an Egger test (coefficient = 0.2267264; 95% CI: −1.687296, 2.140749; $p = 0.792$) showed no sign of publication bias among the 10 studies (**Table 5**). The subgroup analysis (**Figure 7**) was applied to analyze the relationship between the time elapsed since stroke onset and the high heterogeneity. **Figure 7** shows that there is a substantial subgroup difference ($\chi^2 = 10.86$, $I^2 = 90.8\%$) between the chronic group and subacute group.

TABLE 3 | Internal validity analysis.

References	2	3	4	5	6	7	8	9	10	11	Total
Wang and Chen (33)	-	-	•	-	-	-	•	•	•	•	5
Xu (34)	•	•	•	-	-	-	•	•	•	•	7
Yao (21)	•	•	•	-	-	•	•	•	•	•	8
Xie et al. (35)	•	•	•	-	-	-	•	•	•	•	7
Zhang et al. (36)	•	•	•	-	-	-	•	•	•	•	7
Zhou and Ye (30)	•	•	•	-	-	-	•	•	•	•	7
Lin et al. (37)	•	•	•	•	-	•	•	•	•	•	9
Lee et al. (10)	•	•	•	•	-	•	•	•	•	•	9
Kim et al. (31)	•	•	•	•	•	•	•	•	•	•	10
Schick et al. (18)	•	•	•	•		•	•	•	•	•	9

DISCUSSION

This is the first meta-analysis probing the synergistic effect of combined mirror therapy on the upper extremity in patients with stroke. Some preliminary conclusions can be drawn from this meta-analysis. First and foremost, this meta-analysis of 10 RCTs including 444 patients showed that combined mirror therapy (mirror therapy mixed with other rehabilitation therapies) was superior to single rehabilitation therapy to promote upper limb motor function of stroke patients (WMD 8.07, 95% CI 5.87, 10.26) in terms of muscle reflex ability, coordinated movement, and accurate operation in the Fugl–Meyer Assessment (FMA). However, heterogeneity ($\chi^2 = 20.09$, $p < 0.00001$; $I^2 = 55\%$) was high, and one study [Lee (10)] did not draw a precise conclusion about whether combined mirror therapy (mirror therapy with MG therapy) was better than pure mirror therapy in promoting upper limb motor function. The difference between Lee's study and the other studies is that the stimulation intensity—other studies (37) were at the sensory threshold of the non-operatic

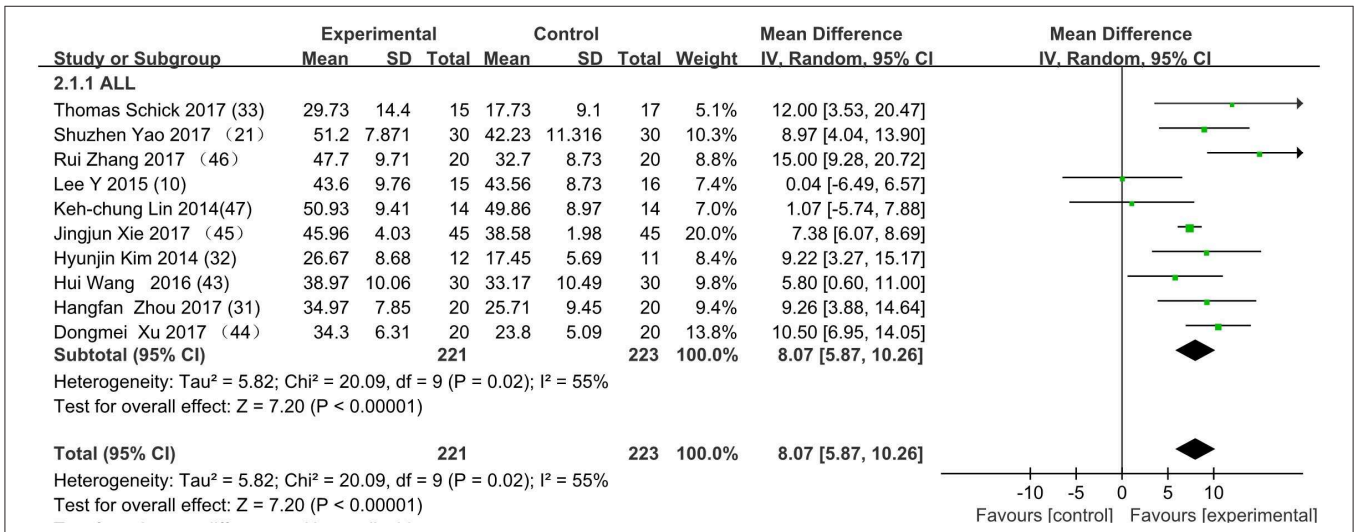


FIGURE 3 | Forest plot of the random effects meta-analysis of CT and MT on motor function of the upper extremity. SD: standard deviation; 95% CI: 95% confidence interval.

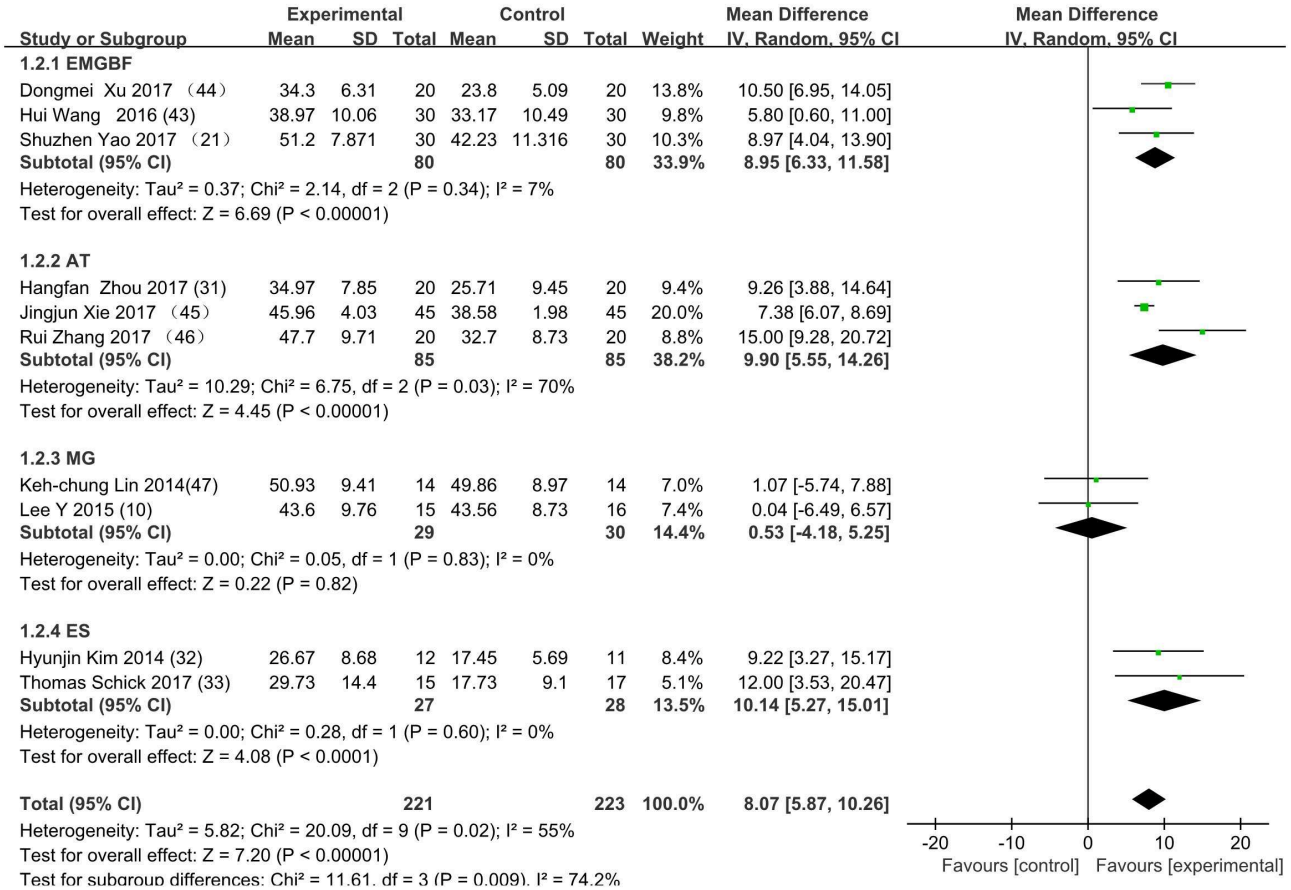


FIGURE 4 | Subgroup analysis for the high heterogeneity. SD: standard deviation; 95% CI: 95% confidence interval. EMGBF: Electromyographic biofeedback; AT: Acupuncture; MG: mesh glove; ES: electrical stimulation.

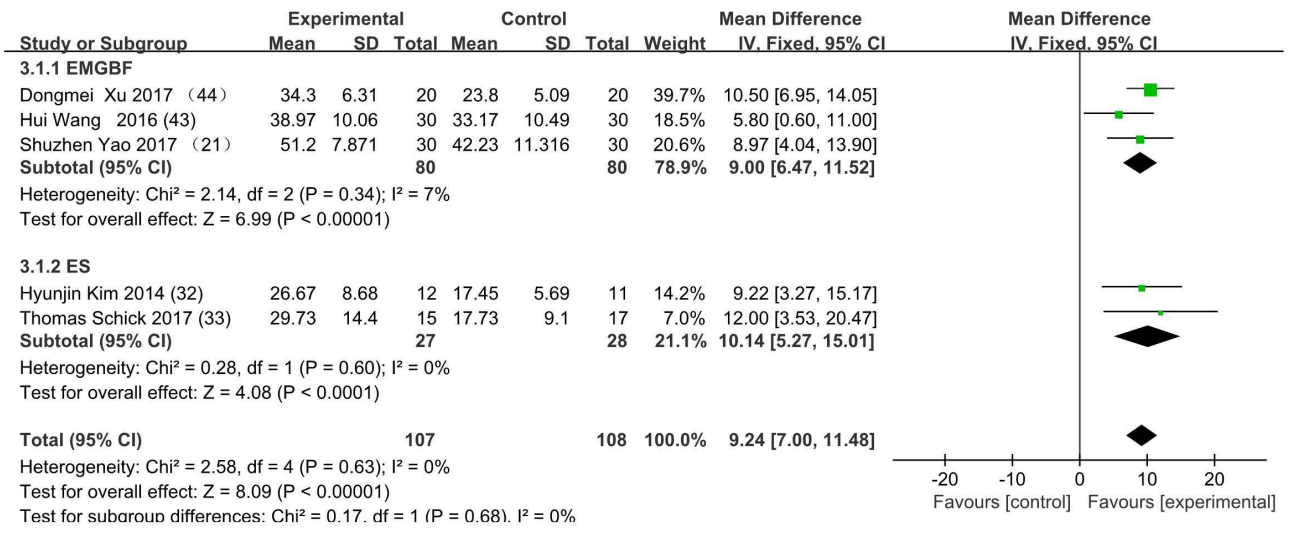


FIGURE 5 | The subgroup's control method is adding MT to rehabilitation therapy in experimental group. EMGBF group: (E: EMGBF+MT/C: EMGBT); ES group: (E: ES+MT/C: ES) E: experimental group; C: control group.

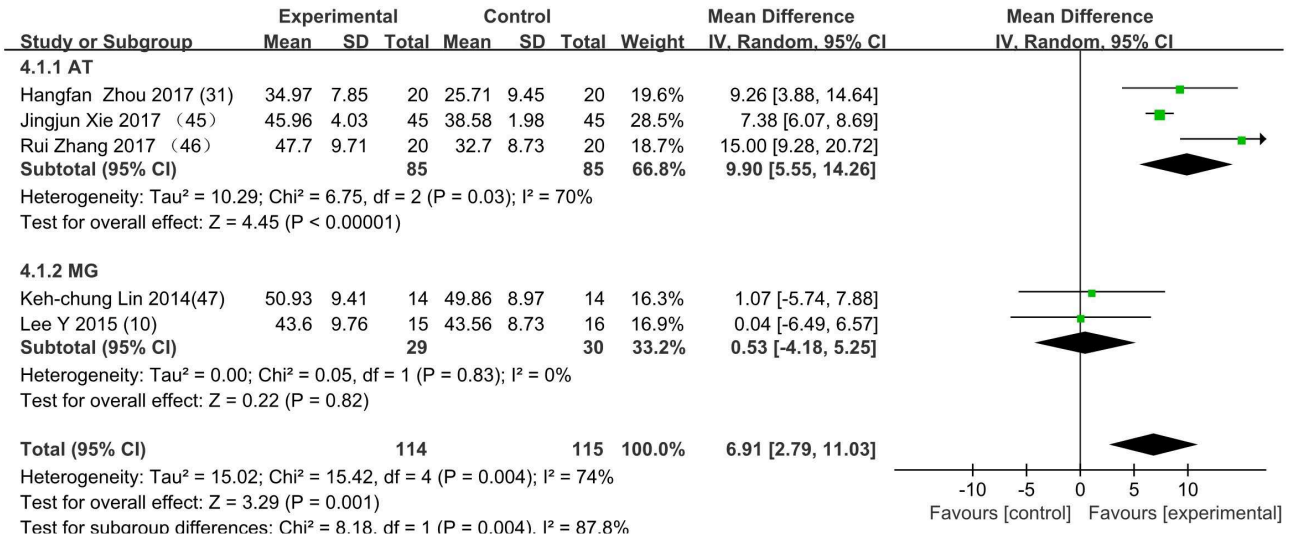


FIGURE 6 | The subgroup's control method is adding rehabilitation therapy to MT in experimental group. AT group: (E: AT+MT/C: MT); MG group: (E: MG+MT/C: MT); E: experimental group; C: control group.

hand (20 Hz, with pulse rate of 300 μs), but the MG intensity in this study was set at the sensory threshold of the paretic hand (50 Hz, with a pulse rate of 300 μs). Further evidence is needed to determine whether sensory threshold leads to significant differences. From the subgroup analysis (I^2: EMGBF group 7%; AT group 70; MG group 0%; ES0%), it is clear that the high heterogeneity came from the AT group as expected. A further subgroup analysis separated interventional methods: adding mirror therapy to rehabilitation therapy in the experimental group (**Figure 5**) and adding rehabilitation therapy to mirror therapy in the experimental group (**Figure 6**). **Figure 5** showed that the synergistic effect of combining mirror therapy with EMGBF was the same as that of combining mirror therapy with ES. In **Figure 6**, it is difficult to judge whether AT + MT has an advantage over single treatment due to the high heterogeneity. The time since stroke onset is likely to cause the high heterogeneity because the mean time in the Xie study (40.73 ± 6.75/42.69 ± 7.42 days) was longer than in the Zhang study (19.6 ± 20.3/30.8 ± 28.7 days). It is likely that the more early patients received AT + MT, the upper limb function will be more effectively improved. A large sample size is necessary to verify this hypothesis. Meanwhile, MG + MT, a popular treatment abroad, showed no significant effect in promoting upper limb motor function in stroke patients in this meta-analysis. This finding is inconsistent with those of Peurala et al. (25) and Dimitrijevic, wherein MT combined with MG stimulation provided additional benefits for manual dexterity when compared with MT alone. Because a string of studies had demonstrated that MG could effectively improve upper limb motor function in stroke patients, meta-analysis regression was applied to detect the reason for this discrepancy. However, neither sample size ($p > 0.186$) nor duration of treatment ($p > 0.787$) could be regarded as the cause of high heterogeneity. The result was discussed in correspondence with Wen Zeng (15) whose meta-analysis mainly explored mirror therapy on motor function of the upper extremity in patients with stroke. From this discussion, the conclusion that two factors (sample size and duration of treatment) were regarded as the cause of high heterogeneity can be reached. **Figure 7** shows the significant effect of sample size and duration of treatment on the subacute group compared with that on the chronic group, and the high heterogeneity found in the subgroup analysis was related to the time elapsed since stroke onset.

TABLE 4 | Results of meta-analysis regression.

Covariance	Coefficients	Standard error	*t*	P>|t|	95% CI
ALL_n	0.0294893	0.292273	1.01	0.352	(−0.0420273,0.1010059)
duration	−0.0004548	0.0015713	0.29	0.782	(−0.0033899,0.0042995)
_cons:	0.7778708	3.402441	−0.23	0.827	(−9.103343,7.547602)

TABLE 5 | Results of publication bias.

Std_Eff	Coefficients	Standard error	*t*	P>|t|	95% CI
Slope	7.474338	1.419139	5.27	0.001	(4.201797,10.74689)
Bias	0.2267264	0.830017	0.27	0.792	(−11.46154,2.140749)

There were many factors not detected in the studies included in this meta-analysis, such as paretic side, severity (Brunnstrom stages), age, and sex, resulting in incomplete data in **Table 1**. For instance, the details of the paretic side were not described in Hangfan Zhou (31). No evidence in recent years has demonstrated a relationship between paretic side and treatment, and this unknown area should be explored by researchers. **Table 1** also shows that Wang (43), Xie (45), Zhou (31), Lee (10), and Schick (33) did not describe the details of severity (Brunnstrom stages), which limited the quality of the articles. Safaz (42) and Watanabe (43) had confirmed that BRS (Brunnstrom stages)

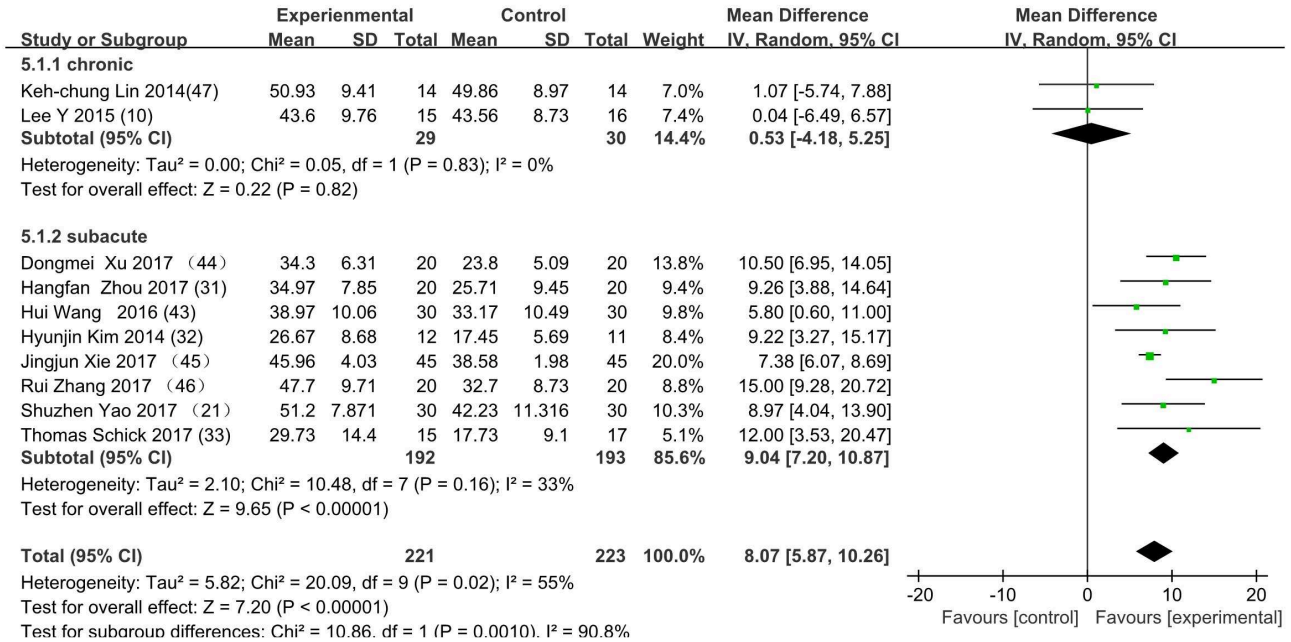


FIGURE 7 | Subgroup analysis for discriminating between subacute or chronic stroke.

is a convenient and effective tool for the evaluation of UEs in early stage stroke patients. Besides these factors, there may be unknown elements contributing to the high level of heterogeneity in publication bias. Wang (43) and Xu (44) did not describe the details of allocation group concealing, which can lead to selection bias. In addition, Yao (21), Zhou (31), Wang (43), Xie (45), and Zhang (46) did not describe the details of blinding of participants and personnel, and implementation bias can arise when participants and implementers are aware of the interventions. Further, Zhou (31), Wang (43), Xie (45), Zhang (46), and Lin (47) did not describe the details of blinding of intervention allocation in outcome assessment, which can lead to measurement bias.

There are several limitations of this study that should be taken into account. First, the number of studies included in meta-analysis was limited, reducing the representativeness of the article. This was unavoidable due to the particularity of topic selection, the limitation of resources, and the rigor of the article. Second, the high heterogeneity of the studies partly limits the impact of this paper. The objective of this meta-analysis is to study combined therapy, focusing on mirror therapy mixed with other therapies such as AT, ES, EMBGF, and MG, so the high heterogeneity is unavoidable. Third, studies published in English and Chinese were included in the analysis, but studies in other languages were not included. Fourth, all articles were randomized controlled trials, but there is a belief that non-randomized controlled trials should also be taken into account when RCTs are unfeasible or unethical.

From a patient's perspective, we must take expense and time spent on combined mirror therapy into consideration. If there is a directly proportional relationship between expense and efficacy on recovery, we might as well take combined therapy as first choice for patients after stroke. In summary, combining mirror therapy with another rehabilitation therapy (especially electromyographic biofeedback and EMG-triggered electrical stimulation) is better than single rehabilitation therapy on upper extremity in patients with stroke. In the future, there should be considerable work applied by researchers to more deeply probe the optimal specific combination therapy.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

AUTHOR CONTRIBUTIONS

JZ and QZ: conception and design, drafting the article. HH, SL, and RZ: acquisition of data. ZL and YZ: analysis and interpretation of data, editing the article. JL, XL, and SC: study supervision and revising the article. ZL and YZ contributed equally to this work and should be considered co-first authors. All authors proofed and approved the submitted version of the article.

FUNDING

This work was supported by grants from the Medical Science and Technology Research Fund Project of Guangdong Province (no. 20161198360341) and College Student's Innovative Entrepreneurial Training Plan Program in school level.

REFERENCES

1. Dennis MS, Burn JP, Sanderrock PA, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke*. (1993) 24:796–800. doi: 10.1161/01.STR.24.6.796
2. Samuelkamaleshkumar S, Reethajanetsureka S, Pauljebaraj P, Benshamir B, Padankatti S, David J. Mirror therapy enhances motor performance in the paretic upper limb after stroke: a pilot randomized controlled trial. *Arch Phys Med Rehabil*. (2014) 95:2000–5. doi: 10.1016/j.apmr.2014.06.020
3. Lim KB, Lee HJ, Yoo J, Yun HJ, Hwang HJ. Efficacy of mirror therapy containing functional tasks in poststroke patients. *Ann Rehabil Med*. (2016) 40:629–36. doi: 10.5535/arm.2016.40.4.629
4. Altschuler EL, Wisdom SB, Stone L, Foster C, Galasko D, Llewellyn DM, et al. Rehabilitation of hemiparesis after stroke with a mirror. *Lancet*. (1999) 353:2035–6. doi: 10.1016/S0140-6736(99)00920-4
5. Hartman K, Altschuler EL. Mirror therapy for hemiparesis following stroke: a review. *Curr Phys Med Rehabil Rep*. (2016) 4:237–48. doi: 10.1007/s40141-016-0131-8
6. Sirtori V, Corbetta D, Moja L, Gatti R. Constraint-induced movement therapy for upper extremities in stroke patients. *Cochrane Database Syst Rev*. (2009) CD004433. doi: 10.1002/14651858.CD004433
7. Taub E, Uswatte G, King DK, Morris D, Crago JE, Chatterjee A. A placebo-controlled trial of constraint induced movement therapy for upper extremity after stroke. *Stroke*. (2006) 37:1045–9. doi: 10.1161/01.STR.0000206463.66461.97
8. Schaechter JD, Ph D, Connell BD, Kaptchuk TJ, Krebs DE, Macklin EA, et al. Correlated change in upper limb function and motor cortex activation after verum and sham acupuncture in patients with chronic stroke. *J Altern Complement Med*. (2007) 13:527–32. doi: 10.1089/acm.2007.6316
9. Rayegani SM, Raeissadat SA, Rezazadeh IM, Bahrami MH, Eliaspour D, Khosrawi. Effect of neurofeedback and electromyographic-biofeedback therapy on improving hand function in stroke patients. *Top Stroke Rehabil*. (2014) 21:137–51. doi: 10.1310/tsr2102-137
10. Lee Y, Lin K, Wu C, Liao C, Lin J, Chen C. Combining afferent stimulation and mirror therapy for improving muscular, sensorimotor, and daily functions after chronic stroke a randomized, placebo-controlled study. *Am J Phys Med Rehabil*. (2015) 94:859–68. doi: 10.1097/PHM.0000000000000271
11. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. *N Engl J Med*. (2010) 362:1772–83. doi: 10.1056/NEJMoa0911341
12. Thieme H, Morkisch N, Mehrholz J, Pohl M, Behrens J, Borgetto B, et al. Mirror therapy for improving motor function after stroke. *Cochrane Database Syst Rev*. (2018) 7:CD008449. doi: 10.1002/14651858.CD008449.pub3
13. Ramachandran VS, Rogers-Ramachandran D. Synaesthesia in phantom limbs induced with mirrors. *Proc Biol Sci*. (1996) 263:377–86. doi: 10.1098/rspb.1996.0058
14. Stevens JA, Stoykov ME. Using motor imagery in the rehabilitation of hemiparesis. *Arch Phys Med Rehabil*. (2003) 84:1090–2. doi: 10.1016/S0003-9993(03)00042-X
15. Zeng W, Guo Y, Wu G, Liu X, Fang Q. Mirror therapy for motion function of the upper extremity in patient with stroke: a meta-analysis. *J Rehabil Med*. (2018) 50:8–15. doi: 10.2340/16501977-2287
16. Rothgangel AS, Braun SM, Beurskens AJ, Seitz RJ, Wade DT. The clinical aspects of mirror therapy in rehabilitation: a systematic review of the literature. *Int J Rehabil Res Mar*. (2011) 34:1–13. doi: 10.1097/MRR.0b013e3283441e98
17. Yavuzer G, Selles R, Sezer N, Sutbeyaz S, Bussmann JB, Koseoglu F, et al. Mirror therapy improves hand function in subacute stroke: a randomized controlled trial. *Arch Phys Med Rehabil*. (2008) 89:393. doi: 10.1016/j.apmr.2007.08.162
18. Schick T, Schlake HP, Kallusky J, Kallusky J, Hohlfeld G, Steinmetz M, et al. Synergy effects of combined multichannel EMG-triggered electrical stimulation and mirror therapy in subacute stroke patients with severe or very severe arm/hand paresis. *Restor Neurol Neurosci*. (2017) 35:319–32. doi: 10.3233/RNN-160710
19. Amasyali SY, Yaliman A. Comparison of the effects of mirror therapy and electromyography-triggered neuromuscular stimulation on hand functions in stroke patients: a pilot study. *Int J Rehabil Res*. (2016) 39:302–7. doi: 10.1097/MRR.0000000000000186
20. Duarte-Moreira RJ, Castro KV, Luz-Santos C, Martins JVP, Sa KN, Baptista AF. Electromyographic biofeedback in motor function recovery after peripheral nerve injury: an integrative review of the literature. *Appl Psychophysiol Biofeedback*. (2018) 43:247–57. doi: 10.1007/s10484-018-9403-7
21. Yao S. *Mirror Therapy Combined With Electromyographic Biofeedback Therapy on the Reconstruction of Upper Extremity Function in Hemiplegics After Stroke: A Clinical Research*. Chengde: Chengde Medical College (2017). p. 1–42.
22. Arya KN, Pandian S, Kumar D, Puri V. Task-based mirror therapy a ugmenting motor recovery in poststroke hemiparesis: a randomized controlled trial. *J Stroke Cerebrovasc Dis*. (2015) 24:1738–48. doi: 10.1016/j.jstrokecerebrovasdis.2015.03.026
23. Basmajian JV. Research foundations of EMG biofeedback in rehabilitation. *Biofeedback Self Regul*. (1988) 13:275–98. doi: 10.1007/BF00999085
24. Bolton DA, Cauraugh JH, Hausenblas HA. Electromyogram-triggered neuromuscular stimulation and stroke motor recovery of arm/hand functions: a meta-analysis. *J Neurol Sci*. (2004) 223:121–7. doi: 10.1016/j.jns.2004.05.005
25. Peurala SH, Pitkanen K, Sivenius J, Tarkka IM. Cutaneous electrical stimulation may enhance sensorimotor recovery in chronic stroke. *Clin Rehabil*. (2002) 16:709–16. doi: 10.1191/0269215502cr543oa
26. Dimitrijević MM, Stokić DS, Wawro AW, Wun CC. Modification of motor control of wrist extension by mesh-glove electrical afferent stimulation in stroke patients. *Arch Phys Med Rehabil*. (1996) 77:252–8. doi: 10.1016/S0003-9993(96)90107-0
27. Golaszewski SM, Bergmann J, Christova M, Nardone R, Kronbichler M, Rafolt D, et al. Increased motor cortical excitability after whole-hand electrical stimu-lation: a TMS study. *Clin Neurophysiol*. (2010) 121:248–54. doi: 10.1016/j.clinph.2009.09.024
28. Huang Y, Tang CZ, Wang SX, Lu YJ, Shen W, Yang JJ, et al. Acupuncture regulates the glucose metabolism in cerebral functional regions in chronic stage ischemic stroke patients—a PET-CT cerebral functional imaging study. *BMC Neurosci*. (2012) 13:75. doi: 10.1186/1471-2202-13-75
29. Zhuang LX, He J, Zhuang X, Lu LM. Quality of reporting on randomized controlled trials of acupuncture for stroke rehabilitation. *BMC Complement Altern Med*. (2014) 14:151. doi: 10.1186/1472-6882-14-151
30. Zhou H, Ye H. Effect of mirror therapy combined with acupuncture in restoring the upper limbs of patients with early hemiplegia. *Health Res*. (2017) 37:427–9. doi: 10.3969/j.issn.1674-6449.2017.04.020
31. Kim H, Lee G, Song C. Effect of functional electrical stimulation with mirror therapy on upper extremity motor function in poststroke patients. *J Stroke Cerebrovasc Dis*. (2014) 23:655–61. doi: 10.1016/j.jstrokecerebrovasdis.2013.06.017
32. Higgins JP, Green S, editors. *Cochrane Handbook for Systematic Reviews of interventions version 5.1.0*. John Wiley & Sons (2011).
33. Wang H, Chen H. Effects of mirror therapy combined with electromyobiofeedback on stroke patients. *Chin Manipulat Rehabil Med*. (2017) 8:28–30.
34. Xu D. *The Clinical Study of Biofeedback Therapy and Mirror Image Therapy in Upper Limb Disorder After Stroke*. Nanchang University (2017).
35. Xie J, Li J, Sun Q, Ma Y. Therapeutic observation of acupuncture plus mirror therapy for upper-limb dysfunction of post-stroke hemiplegia Shanghai. *J Acu Mox*. (2018) 37:494–98. doi: 10.13460/j.issn.1005-0957.2018.13.0052
36. Zhang R, Zhang M, Liu B, Wu L. Mirror therapy combined with acupuncture can improve the upper extremity function of stroke survivors. *Chin J Phys Rehabil*. (2017) 39–8. doi: 10.3760/cma.j.issn.0254-1424.2017.08.006
37. Lin KC, Huang PC, Chen YT, Wu CY, Huang WL. Combining afferent stimulation and mirror therapy for rehabilitating motor function, motor control, ambulation, and daily functions after stroke. *Neurorehabil Neural Repair*. (2014) 28:153–62. doi: 10.1177/1545968313508468

38. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Buddy Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century. *J Neurol Neurorehabil*. (2013) 44:2064–89. doi: 10.1161/STR.0b013e318296aeca
39. Deakin A, Hill H, Pomeroy VM. Rough guide to the Fugl-Meyer assessment: upper limb section. *Physiotherapy*. (2003) 89:751–63. doi: 10.1016/S0031-9406(05)60502-0
40. Berglund K, Fugl-Meyer AR. Upper extremity function in hemiplegia: a cross-validation study of two assessment methods. *Scand J Rehabil Med*. (1985) 18:155–7.
41. Card NA. *Applied Meta-Analysis for Social Science Research*. New York, NY: Guilford Publications (2012).
42. Safaz I, Yilmaz B, Yaşar E, Alaca R. Brunnstrom recovery stage and motricity index for the evaluation of upper extremity in stroke: analysis for correlation and responsiveness. *Int J Rehabil Res*. (2009) 32:228–31. doi: 10.1097/MRR.0b013e32832a62ad
43. Watanabe H, Tashiro K. Brunnstrom stages and Wallerian degenerations: a study using MRI. *Tohoku J Exp Med*. (1992) 166:471–3. doi: 10.1620/tjem.166.471

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

SPECIALTY GRAND CHALLENGE
published: 22 May 2020
doi: 10.3389/fneur.2020.00349

Specialty Grand Challenge for NeuroRehabilitation Research

Thomas Platz[1,2,3]* *and Giorgio Sandrini*[4,5]

[1] BDH-Klinik Greifswald, Centre for Neurorehabilitation, Intensive and Ventilation Care, Spinal Cord Injury Unit, University of Greifswald, Greifswald, Germany, [2] Neurorehabilitation Research Group, University Medical Centre, Greifswald, Germany, [3] Special Interest Group Clinical Pathways, World Federation for NeuroRehabilitation, North Shields, United Kingdom, [4] Neurorehabilitation Unit, IRCCS Mondino Foundation, Pavia, Italy, [5] Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

Keywords: rehabilitation, research, evidence, knowledge, guideline

GLOBAL BURDEN OF DISEASE AND NEURO-DISABILITIES

One of the great challenges the world faces in terms of health care is the increasing number of people living with neuro-disabilities that affect their ability to participate in societal activities. Various neurological conditions such as stroke, multiple sclerosis, or Parkinson's disease, to name just a few, change cognitive, sensory, or motor capacities, alter the emotional well-being of those affected, and lead to disability in their everyday lives.

Over the last few decades, aging populations and reduced mortality in many regions of the world have increased the number of people living with neuro-disabilities considerably, an effect that is still ongoing (1): for 2017, the worldwide prevalence of stroke (thousands) has been estimated to be as high as 104178.7 (95% confidence interval, 95% CI 98454.0–110125.0), and years lived with disabilities (YLD) (counts in thousands) caused by stroke were reported to amount to 18695.4 (95% CI 13,574–23686.9). The stroke-related increase in YLD (percentage change in counts) was 40% (95% CI 38.4–41.4) from 1990 to 2007 and another 43.6% (39.6–47.8) during only 10 years from 2007 to 2017. The numbers are similarly impressive for other neurological disorders (i.e., dementias, Parkinson's disease, epilepsy, multiple sclerosis, motor neuron disease, headache disorders, and others). Taken together, their worldwide prevalence (in thousands) in 2017 was 3121435.3 (95% CI 2951124.5–3316268.0), while YLD (thousands) in 2017 were 3121435.3 (95% CI 2951124.5–3316268.0), with an increase in YLD by 35.1% (95% CI 31.9–38.1) from 1990 to 2007 and by a further 17.8% (95% CI 15.8–20.2) from 2007 to 2017.

These numbers not only demonstrate the huge global burden of disease and prevailing neuro-disabilities, but they indicate a considerable increase in the number of people living with neuro-disabilities with an accelerating dynamic over time (for stroke).

CLINICAL RESEARCH TO INDICATE THE OVERALL BENEFIT OF NEUROREHABILITATION

Neuro-disabilities cannot be avoided, in spite of great advances that have more recently been achieved in acute medical care. The increase in their prevalence is rather a consequence of more effective health care management, reducing mortality (but not necessarily morbidity), and of aging populations around the globe.

Morbidity and disability are, however, not an inevitable union. Even when organic brain damage cannot be prevented or cured altogether, neurorehabilitation as a specialized form of rehabilitation care can effectively (while most frequently not completely) reduce the burden of disability by promoting functional recovery, compensation of body dysfunction, and/or adaptations, e.g., by the provision of adaptive technology.

OPEN ACCESS

Edited and reviewed by:
Sheng Li,
University of Texas Health Science Center at Houston, United States

***Correspondence:**
Thomas Platz
t.platz@bdh-klinik-greifswald.de

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *12 February 2020*
Accepted: *08 April 2020*
Published: *22 May 2020*

Citation:
Platz T and Sandrini G (2020) Specialty Grand Challenge for NeuroRehabilitation Research. Front. Neurol. 11:349. doi: 10.3389/fneur.2020.00349

Neurorehabilitation is mostly structured as a multi-professional physician-led team approach to health care and has been shown to reduce disability effectively (2).

A Cochrane review with a meta-analysis including 21 randomized controlled trials (RCTs) with a total of 39,994 participants showed a reduced rate of death or institutionalized care (odds ratio, OR 0.78, 95% CI 0.68–0.89) and death or dependence (OR 0.79, 95% CI 0.68–0.90) after multi-disciplinary stroke unit care compared to care in general wards post stroke without significantly increasing length of stay, and independent of age, sex, or stroke severity (3). The situation in low and middle countries (LMIC) with a large diversity of stroke rehabilitation structures sadly supports the notion that adequate rehabilitation efforts effectively reduce disability (4): with better structure and processes of care such as the availability of multi-disciplinary stroke care units, patients were more likely to be alive, independent, and living at home 1 year after stroke; absence of rehabilitation, on the other hand, was associated with a higher level of disability.

A COMPLEX PATTERN OF RESEARCH IS REQUIRED TO PROMOTE NEUROREHABILITATION AS A MEDICAL SPECIALTY

Neurorehabilitation is a medical discipline that, for its scientific advancement, necessitates a complex pattern of research. Brain functions and their dysfunctions are complex issues, as are any interventions that intend to promote functional recovery after brain damage and hence to improve brain function. Such interventions target specific brain network activities and functions and can include training procedures ("therapy"), electrical or magnetic stimulation of the brain or body limbs, and medication targeting the brain and its transmitter systems.

"From bench to bedside" involves a multitude of research avenues for neurorehabilitation: basic research, translational research, clinical trials (pilot and confirmatory), collating evidence across clinical trials and providing an evidence synthesis by systematic reviews and meta-analyses, the systematic generation of evidence-based practice guidelines, and finally their regional adaption into clinical pathways (5). All of these research areas need to be addressed for such diverse neurological conditions as stroke, multiple sclerosis, or Parkinson's disease, with their distinct neuropathologies and different patterns of cognitive, sensory, and motor dysfunctions as well as emotional disorders.

In addition, there is a great need to perform research from a global health perspective. Technologies that generate a clinical benefit in neurorehabilitation, e.g., arm rehabilitation robots (6), electromechanical gait training (7), virtual reality applications (8), tele-rehabilitation (9), or non-invasive brain stimulation (10), might be considered candidates for an adaptation for low- and middle-income countries (LMIC); low-cost technologies could be developed for a broader international distribution and clinically evaluated.

Furthermore, priority research is necessary to elaborate rehabilitative needs and therapeutic options when new challenges like the current novel coronavirus (2019-nCoV) pandemic manifest themselves. Most people affected by the Coronavirus Disease 2019 (COVID-19) have mild symptoms and recover, while 6.1% become critically ill (respiratory failure, septic shock, and/or multiple organ dysfunction/failure) (11) and might develop a post-intensive care syndrome, PICS, with motor, cognitive, and emotional disorders necessitating intensive rehabilitation (12, 13). Research has to document the epidemiology and rehabilitation needs of COVID-19 cases and their clinical course. It should further address the effectiveness of neurorehabilitation treatment including the use of new technologies for home care purposes (e.g., use of low-cost technologies such as smartphones or tablets for virtual medical examination, counseling, and tele-rehabilitation), as well as health care system questions (e.g., how rapidly increasing demands for services should be coped with), and guidance (practice recommendations).

THE CONTINUUM OF CARE IN NEUROREHABILITATION AND ITS RESEARCH

Another specific aspect of neurorehabilitation for people with neuro-disabilities is that we do not have a single "phase" of disease and do not need to take care of people affected at a given point in time only when the disease becomes evident. On the contrary, the care of people with neuro-disabilities frequently involves a lifetime perspective.

For example, for people with stroke, it is well-understood that the best outcome is achieved with a multi-stage rehabilitation pathway (14–16). Such a dedicated pathway starts with acute rehabilitation and post-acute rehabilitation (usually inpatient services), and continues with out-patient rehabilitation, home-based rehabilitation, community-based rehabilitation, and long-term and sustained rehabilitation.

Accordingly, research and knowledge management in neurorehabilitation need to take the continuum of care for people with neuro-disabilities into consideration.

THE NEED FOR EDUCATION AND KNOWLEDGE DISSEMINATION

Neurorehabilitation teams frequently include physicians, physiotherapists, occupational therapists, speech and language therapists, psychologists, nurses, and social workers trained in neurorehabilitation as a "core set" of involved disciplines. The reason is two-fold. For one, all of their specialized professional knowledge and therapeutic skills are essential to treat people with neuro-disabilities. Secondly, it is the team approach itself that contributes essentially to the overall clinical benefit and not just the availability of diverse professions, each working on its own (2, 3).

These affordances can, however, not be met in many regions of the world, especially in many low- and middle-income

countries (LMIC). There is a substantial lack in the number of health care professionals for rehabilitation in LMICs, and, frequently, the types of health care professionals needed for rehabilitation teams are not at all available. A few examples (17): high-income countries have, on average, more than 900 physiotherapists per million inhabitants; the corresponding number is <10 physiotherapists in many countries in Sub-Saharan Africa and the South-East Asia Region. Further, high-income countries have more than 300 speech and language therapists per 1 million inhabitants, while some low-income countries in the African region have no speech and language therapists for the entire population.

There is thus a huge demand for education in neurorehabilitation. The need includes (a) the establishment of qualifying program for various disciplines in many countries, (b) specialized training in neurorehabilitation for health care professionals holding their basic professional qualification (physicians and allied health professionals), (c) continued medical education for those who have received specialized training, and (d) fast knowledge distribution in new challenging situations or "game-changing" opportunities for clinical practice.

Initiatives to address these needs are far from being sufficient. An example for (b) is the core curriculum for neurorehabilitation developed by the European Federation for Neurorehabilitation (18), and an example for (c) are the summer schools on neurorehabilitation organized by the Word Federation for NeuroRehabilitation (19). For the transnational harmonization of education initiatives, it could be useful to start in countries with similar health care systems (e.g., in Europe) while being accessible for international attendees.

KNOWLEDGE MANAGEMENT PLATFORMS AS KEY STRUCTURES

With all the complexity of neurorehabilitation in terms of the diversity of health conditions leading to neuro-disabilities, the research avenues involved, the multitude of healthcare professions and settings from inpatient to community rehabilitation (compare **Figure 1**), and the lack of human resources and knowledge hubs in many regions of the world, there is a great need for knowledge management platforms that host high-quality up-to-date research across this wide spectrum and make that knowledge publically available, not only to those who can afford to pay for it but especially to those who are put at a disadvantage both by their limited regional professional

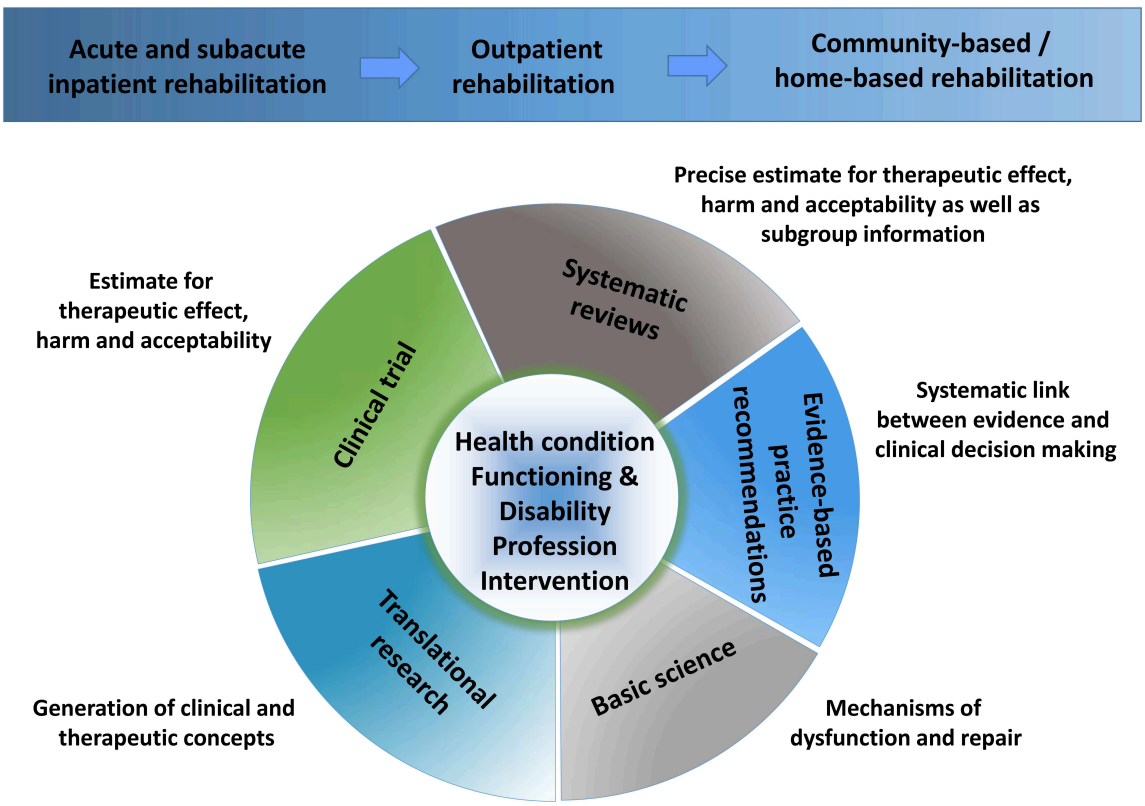


FIGURE 1 | Neurorehabilitation research perspectives. The figure shows the complexity of the background to research in neurorehabilitation. The complexity is caused by the multitude of health conditions, alterations of functioning and disabilities, and of respective interventions as provided by different health care professions along a continuum of health care from acute rehabilitation to community-based rehabilitation. The diversity of research focuses is further enlarged by a necessity to engage in both basic and translational research, clinical trials, and synthesis of the evidence in systematic reviews with meta-analyses and by a methodologically sound link from evidence to the clinical decision via evidence-based practice recommendations.

resources and by any financially restricted access to high-quality professional knowledge sources.

Such platforms provide an opportunity to advance the science in the field by providing a possibility to collate and synthesize research knowledge across the boundaries of individual research cluster and professions (20, 21) as well as for various health care situations, be it in high- or low- and middle-income countries.

CONCLUSIONS

Frontiers in Neurology is a leading journal in its field, publishing rigorously peer-reviewed articles across a wide spectrum of basic, translational, and clinical research that help improve patient care. Its *Neurorehabilitation section* provides an interdisciplinary platform for new developments in this highly complex field that demands the involvement of a broad range of professionals and to create a forum for the exchange of knowledge among these different specialists.

The *Neurorehabilitation section* focuses primarily on clinical studies, though it also attracts papers dealing with basic and translational research relevant to clarifying mechanisms or scientifically addressing new therapeutic concepts for neurorehabilitation. Systematic reviews that synthesize evidence from clinical practice and provide more precise estimates for the evaluation of benefit-risk ratios and the acceptability of interventions together with subgroup information are highly welcome, as are reviews that systematically link evidence syntheses to evidence-based practice recommendations. In addition, the section wants to promote scientific exchange for the adaptation of therapeutic concepts and technology to the diverse health care backgrounds that exist at an international level.

The section equally wants to promote health care in neurorehabilitation by serving as a platform for *Research Topics* with the collation of research papers on topics of great interest to the scientific and/or clinical community.

Taken together, the *Neurorehabilitation section,* which is driven by academic standards and makes its publications freely available for a worldwide readership, makes a significant contribution to quality in neurorehabilitation research and healthcare with a global perspective for the ultimate sake of those affected by neuro-disabilities and in need of the best possible professional help.

AUTHOR CONTRIBUTIONS

TP designed and wrote the manuscript, and GS revised it critically for intellectual content.

FUNDING

This work was supported by BDH Bundesverband Rehabilitation e.V. (a charity for neuro-disabilities) by a non-restricted personal grant to TP. The sponsor had no role in the decision to publish or any content of the publication.

REFERENCES

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. (2018) 392:1789–858. doi: 10.1016/S0140-6736(18)32279-7
2. Clarke DJ. The role of multidisciplinary team care in stroke rehabilitation. *Prog Neurol Psychiatry*. (2013) 17:5–8. doi: 10.1002/pnp.288
3. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev*. (2013) 2013:CD000197. doi: 10.1002/14651858.CD000197.pub3
4. Chimatiro GL, Rhoda AJ. Scoping review of acute stroke care management and rehabilitation in low and middle-income countries. *BMC Health Serv Res*. (2019) 19:789. doi: 10.1186/s12913-019-4654-4
5. Platz T. Evidence-based guidelines and clinical pathways in stroke rehabilitation — an international perspective. *Front Neurol*. 10:200. doi: 10.3389/fneur.2019.00200
6. Mehrholz J, Pohl M, Platz T, Kugler J, Elsner B. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. *Cochrane Database Syst Rev*. (2018) 9:CD006876. doi: 10.1002/14651858.CD006876.pub5
7. Mehrholz J, Thomas S, Werner C, Kugler J, Pohl M, Elsner B. Electromechanical-assisted training for walking after stroke. *Cochrane Database Syst Rev*. (2017) 5:CD006185. doi: 10.1002/14651858.CD006185.pub4
8. Laver KE, Lange B, George S, Deutsch JE, Saposnik G, Crotty M. Virtual reality for stroke rehabilitation. *Cochrane Database Syst Rev*. (2017) 11:CD008349. doi: 10.1002/14651858.CD008349.pub4
9. Laver KE, Adey-Wakeling Z, Crotty M, Lannin NA, George S, Sherrington C. Telerehabilitation services for stroke. *Cochrane Database Syst Rev*. (2020) 1:CD010255. doi: 10.1002/14651858.CD010255.pub3
10. Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving aphasia in adults with aphasia after stroke. *Cochrane Database Syst Rev*. (2019) 5:CD009760. doi: 10.1002/14651858.CD009760.pub4
11. World Health Organization. *Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)*. (2020). Available online at: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf (accessed 31 March, 2020)
12. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med*. (2012) 40:502–9. doi: 10.1097/CCM.0b013e318232da75
13. Bryant SE, McNabb K. Postintensive care syndrome. *Crit Care Nurs Clin North Am*. (2019) 31:507–16. doi: 10.1016/j.cnc.2019.07.006
14. NICE. *Stroke Rehabilitation in Adults Guidance and Guidelines, Clinical Guideline CG162*. (2013). Available online at: https://www.nice.org.uk/guidance/cg162/resources/stroke-rehabilitation-in-adults-pdf-35109688408261 (accessed 06 February, 2020)
15. Teasell R, Foley N, Hussein N, Speechley M. *'The Elements of Stroke Rehabilitation', Evidence-Based Review of Stroke Rehabilitation*. Available online at: http://www.ebrsr.com/evidence-review/6-elements-stroke-rehabilitation (accessed 6 February, 2020)
16. Stroke Foundation. *(Australian) Clinical Guidelines for Stroke Management 2017*. - Chapter 5 of 8: Rehabilitation (update published on 21.11.2019). Available online at: https://app.magicapp.org/app#/guideline/3973 (accessed 6 February, 2020)
17. WHO Rehabilitation 2030. *A Need to Scale Up Rehabilitation*. Geneva: WHO (2018). Available online at: http://www.who.int/disabilities/care/Need-to-scale-up-rehab-July2018.pdf (accessed 6 February, 2020)
18. Sandrini G, Binder H, Hömberg V, Saltuari L, Tarkka I, Smania N, et al. European core curriculum in neurorehabilitation.

Funct Neurol. (2017) 32:63–8. doi: 10.11138/FNeur/2017.32.2.063

19. Platz T. Summer school neurorehabilitation (SSNR) vom 13. bis 16. Juni 2018 in Greifswald. Ein Update zur Neurorehabilitation in 3 Tagen – dicht gepackt und trotzdem aufgelockert. *Neuroreha*. (2018) 10:149–51. doi: 10.1055/a-0640-2127
20. Crosson B, Hampstead BM, Krishnamurthy LC, Krishnamurthy V, McGregor KM, Nocera JR, et al. Advances in neurocognitive rehabilitation research from 1992 to 2017: The ascension of neural plasticity. *Neuropsychology*. (2017) 31:900–20. doi: 10.1037/neu0000396
21. Carey L, Walsh A, Adikari A, Goodin P, Alahakoon D, De Silva D, et al. Finding the intersection of neuroplasticity, stroke recovery, and learning: scope and contributions to stroke rehabilitation. *Neural Plast*. (2019) 2019:5232374. doi: 10.1155/2019/5232374

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 02 September 2020
doi: 10.3389/fneur.2020.00875

Consensus-Based Core Set of Outcome Measures for Clinical Motor Rehabilitation After Stroke—A Delphi Study

Johannes Pohl[1,2], Jeremia Philipp Oskar Held[1], Geert Verheyden[2], Margit Alt Murphy[3], Stefan Engelter[4,5], Agnes Flöel[6,7], Thierry Keller[8], Gert Kwakkel[9,10], Tobias Nef[11,12], Nick Ward[13,14], Andreas Rüdiger Luft[1,15] and Janne Marieke Veerbeek[1]**

[1] Department of Neurology, University of Zurich and University Hospital Zurich, Zurich, Switzerland, [2] Department of Rehabilitation Sciences, KU Leuven—University of Leuven, Leuven, Belgium, [3] Institute of Neuroscience and Physiology, Clinical Neuroscience, University of Gothenburg, Gothenburg, Sweden, [4] Department of Neurology and Department of Clinical Research, University of Basel, Basel, Switzerland, [5] Neurorehabilitation Unit and University Center for Medicine of Aging and Rehabilitation, Felix Platter Hospital, University of Basel, Basel, Switzerland, [6] Department of Neurology, University of Greifswald, Greifswald, Germany, [7] German Center for Neurodegenerative Diseases, Greifswald, Germany, [8] TECNALIA, Basque Research and Technology Alliance (BRTA), Neurorehabilitation Area at the Health Division, Donostia-San Sebastian, Spain, [9] Department of Rehabilitation Medicine, Amsterdam Neuroscience and Amsterdam Movement Sciences, Amsterdam University Medical Centre, Amsterdam, Netherlands, [10] Department Non-acquired-brain Injuries, Amsterdam Rehabilitation Centre Reade, Amsterdam, Netherlands, [11] Gerontechnology and Rehabilitation Group, University of Bern, Bern, Switzerland, [12] Artorg, Center for Biomedical Engineering Research, University of Bern, Bern, Switzerland, [13] Department of Movement and Clinical Neuroscience, UCL Queen Square Institute of Neurology, London, United Kingdom, [14] The National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom, [15] cereneo, Center for Neurology and Rehabilitation, Vitznau, Switzerland

OPEN ACCESS

Edited by:
Stefano Tamburin,
University of Verona, Italy

Reviewed by:
Ning Cao,
Moss Rehabilitation Hospital, United States
Alessandro Giustini,
Istituto di Riabilitazione Santo Stefano, Italy
Catherine E. Lang,
Santo Stefano Rehabilitation Group, Italy

***Correspondence:**
Janne Marieke Veerbeek
janne.veerbeek@usz.ch
Johannes Pohl
johannes.pohl@usz.ch

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 17 January 2020
Accepted: 09 July 2020
Published: 02 September 2020

Citation:
Pohl J, Held JPO, Verheyden G, Alt Murphy M, Engelter S, Flöel A, Keller T, Kwakkel G, Nef T, Ward N, Luft AR and Veerbeek JM (2020) Consensus-Based Core Set of Outcome Measures for Clinical Motor Rehabilitation After Stroke—A Delphi Study. Front. Neurol. 11:875. doi: 10.3389/fneur.2020.00875

Introduction: Outcome measures are key to tailor rehabilitation goals to the stroke patient's individual needs and to monitor poststroke recovery. The large number of available outcome measures leads to high variability in clinical use. Currently, an internationally agreed core set of motor outcome measures for clinical application is lacking. Therefore, the goal was to develop such a set to serve as a quality standard in clinical motor rehabilitation poststroke.

Methods: Outcome measures for the upper and lower extremities, and activities of daily living (ADL)/stroke-specific outcomes were identified and presented to stroke rehabilitation experts in an electronic Delphi study. In round 1, clinical feasibility and relevance of the outcome measures were rated on a 7-point Likert scale. In round 2, those rated at least as "relevant" and "feasible" were ranked within the body functions, activities, and participation domains of the *International Classification of Functioning, Disability, and Health* (*ICF*). Furthermore, measurement time points poststroke were indicated. In round 3, answers were reviewed in reference to overall results to reach final consensus.

Results: In total, 119 outcome measures were presented to 33 experts from 18 countries. The recommended core set includes the Fugl–Meyer Motor Assessment and Action Research Arm Test for the upper extremity section; the Fugl–Meyer Motor Assessment, 10-m Walk Test, Timed-Up-and-Go, and Berg Balance Scale for the lower extremity section; and the National Institutes of Health Stroke Scale, and Barthel

Index or Functional Independence Measure for the ADL/stroke-specific section. The Stroke Impact Scale was recommended spanning all *ICF* domains. Recommended measurement time points are days 2 ± 1 and 7; weeks 2, 4, and 12; 6 months poststroke and every following 6th month.

Discussion and Conclusion: Agreement was found upon a set of nine outcome measures for application in clinical motor rehabilitation poststroke, with seven measurement time points following the stages of poststroke recovery. This core set was specifically developed for clinical practice and distinguishes itself from initiatives for stroke rehabilitation research. The next challenge is to implement this clinical core set across the full stroke care continuum with the aim to improve the transparency, comparability, and quality of stroke rehabilitation at a regional, national, and international level.

Keywords: stroke, motor rehabilitation, clinical, outcome measures, Delphi study

INTRODUCTION

Despite the advances of primary and secondary prevention and the availability of acute medical interventions, stroke remains the second most common cause of disability worldwide (1). Because of an aging population and increasing rates of stroke in younger adults, the number of stroke cases is most likely to increase to 1.5 million cases by the year 2025 (2). In respect to resulting challenges to national health systems and social economy, a European Stroke Action Plan was formulated and includes the domains *primary prevention*, *organization of stroke services*, *management of acute stroke*, *secondary prevention*, *rehabilitation*, *evaluation of stroke outcome/quality assessment*, and *life after stroke* (3). As motor deficits due to stroke lead to limitations in the performance of activities of daily living (ADL), reduced societal participation, and a lower quality of life (4), outcome measures (OMs) in the motor domain comprise a key role in optimizing and monitoring attainable treatment goals and providing transparency regarding the quality along the stroke care continuum (5). An early and systematic administration of OMs could have multiple benefits for clinicians and patients, such as objective monitoring of the recovery process and the facilitation of goal-oriented interprofessional collaboration, and to support the stroke survivor's education. Currently, a significant number of OMs are available for different clinical settings and stages poststroke (6). Consequently, there is a large variability in clinical use, which hampers transparency and the comparability of motor rehabilitation within and across countries.

Clinical guidelines for evidence-based practice regarding stroke operate on a national level and lack international consensus regarding the use of OMs and, more importantly, the timing of measurements. Despite attempts of implementing the evidence resulting from stroke rehabilitation research into clinical stroke rehabilitation by specific clinical guidelines, the adherence across Europe is often insufficient (7). Standards for OMs to use are not commonly practiced, and the administration of OMs in the field of stroke rehabilitation and other areas is surprisingly low (8). Recently, an international group of researchers systematically reviewed existing clinical guidelines on recommendations for upper extremity assessments and concluded that there is a lack of explicit recommendations on OMs in most of the guidelines (9).

Specifically for research purposes, consensus-based recommendations for sensorimotor measurements in stroke rehabilitation trials were developed by the international Stroke Recovery and Rehabilitation Roundtable (SRRR) to set standards for methodological quality for clinical trials on the body functions and activities domains of the *International Classification of Functioning, Disability, and Health* (*ICF*) (10). Also, local and national research groups recommended OMs for stroke research (11–13), including specific interventions such as robotics (14), a single poststroke recovery stage (15), and patient-reported outcomes only (16, 17). Although these efforts are very valuable for stroke rehabilitation research, the recommendations cannot be translated one to one into clinical practice, as the requirements on OMs for clinical use might differ by aspects of the administration time, the number of measurement time points, and the length of follow-up. It is also likely that, for clinical practice, a broader spectrum in terms of impairment and disability levels as well as body sections is relevant, when compared to those covered by various research initiatives. Furthermore, the clinical core set should incorporate the patient's multidomain perspective (18) that was not covered by the SRRR research recommendations, and an international group of clinical stakeholders should be involved.

Therefore, the aim of the present study was to develop an international consensus-based core set of OMs with fixed measurement time points for clinical use in motor rehabilitation after stroke, which is relevant for the full stroke rehabilitation pathway. This set is a key ingredient for transparent stroke rehabilitation and allows alignment between regions and countries with the ultimate goal to improve stroke patients' motor outcomes.

MATERIALS AND METHODS

Identification of Outcome Measures

An initial collection of sensorimotor OMs was compiled based on an extensive search in relevant systematic reviews (6, 10–27),

clinical guidelines (28, 29), and electronic rehabilitation measurement databases [e.g., StrokEngine (30) and Shirley Ryan Ability Lab (31)] by two researchers (JP, JV). The OMs had to meet the following inclusion criteria: (1) assess the motor domain, (2) validated for use in stroke patients, and (3) have a good reliability for the stroke population (intraclass correlation coefficient > 0.7). Eligible OMs were allocated to one of the following three sections: the upper extremity, lower extremity, or ADL/stroke-specific section. The constructs of trunk control, balance, and mobility were assigned to the lower extremity section. The ADL/stroke-specific section included a broader variety of constructs, assessing stroke-specific motor-related functions, activities, and participation. Within each section, OMs were classified according to the *ICF* domains body structure and function, activities, and participation (18).

Delphi Study Design

A Delphi study design was used to develop the consensus-based core set. The three-round Delphi study was conducted from November 2018 until April 2019. Per section, we aimed to have one OM in each *ICF* domain that could be applied, regardless of stroke severity. In the lower extremity section, one OM per *ICF* domain had to be applicable for both patients with and without walking ability.

After each round, each expert received an individualized feedback report with details of the previous round's results in reference to their personal rating. In round 1, each OM was presented with details of the measure's construct, costs, time to administer, and clinimetric properties [validity, reliability, and minimal clinically important difference (MCID)] in line with COSMIN recommendations (**Figure 1**) (32). For each OM, experts had to rate on a 7-point Likert scale: (1) how familiar they were with that measure, (2) its relevance for clinical practice, and (3) its clinical feasibility. The initial set of OMs was then reduced to those, rated with scores of at least five of seven points for both clinical relevance and clinical feasibility. In round 2, the reduced set of OMs had to be prioritized for each section and *ICF* domain by assigning ranks in ascending order. As for some lower extremity OMs, patients need to be able to walk; a second measure was allowed if the OM ranked first requires walking ability. For each section, the highest-ranked OM within each *ICF* domain was included in a preliminary core set for the third round. Additionally, the experts designed a specific measurement scheme, indicating their preferred measurement time points poststroke: Within the acute phase (days 1, 3, and 7), early subacute phase (weeks 2, 4, 6, and 10), the late subacute phase (weeks 12, 16, and 20 and month 6) and for the chronic phase (every 3rd and 6th month following). The minimal agreement rate on measurement timing in round 2 was set to at least $50\% \pm 2\%$. In round 3, the experts reviewed the aggregated results presented next to their individual rankings and suggested time points and confirmed their agreement. The cutoff rate for minimal agreement on measurement time points in round 3 was $70 \pm 5\%$.

A clearance certificate for this study was provided by the cantonal ethics committee Zurich (BASEC Nr. Req-2018-00601). Informed consent of the participating experts was not needed.

Rehabilitation Experts

From September to October 2018, personal enquiries were sent to renowned experts of stroke rehabilitation research and with a networking approach via the following organizations: European Stroke Organization, Council of Occupational Therapists in European Countries, Research in Occupational Therapy and Occupational Science, European Network Occupational Therapy, and the European Network of Physiotherapy in Higher Education. It was our goal to recruit a balanced group of international experts with different clinical backgrounds, including medical doctors, physical therapists, occupational therapists, and rehabilitation engineers. Persons were considered eligible if they had expertise in clinical stroke rehabilitation and clinical research or rehabilitation engineering research and hold at least a master of science degree. The experts were kept ignorant about the other participating experts and received no compensation.

Data Collection and Analysis

The participants received detailed information and instructions on a website with access to the first round's electronic survey created with Research Electronic Data Capture (REDCap, Vanderbilt University Medical Center, USA). Rounds 2 and 3 were carried out via personalized electronic forms, sent and responded via email. Responses were filed by hand (JP) and cross-checked for insertion errors (JH, JV). Feedback of results was given after each round, and equivocal responses were followed up by inquiries via email. Rankings and ratings were analyzed as medians and interquartile ranges. The data were analyzed after each round and presented for the next round. Data analysis and visualization were conducted with Microsoft Office Professional Plus 2016 (Microsoft Cooperation, Redmond, WA, USA).

RESULTS

Participants

Written inquiries yielded 46 eligible experts of whom 33 experts from 18 countries participated and completed the first round of the Delphi study with a response rate of 72% (**Table 1**). Final agreement was given by 27 experts with three participants lost after the first round and three after the second round.

Development of the Core Set for Clinical Motor Rehabilitation After Stroke

In total, 177 OMs were identified, of which 119 met the inclusion criteria and were presented to the experts. Fifty-nine OMs were rated as being relevant and feasible and were consecutively ranked in round 2. In round 3, final agreement for a core set of nine OMs was given (**Figure 2**, **Table 2**).

The highest ranking in the upper extremity section was given to the Upper Extremity Subscale of the Fugl–Meyer Motor Assessment (FMA-UE) in the body functions domain and the Action Research Arm Test (ARAT) for the activities domain. In the lower extremity section, the two OMs with the highest rankings in the body functions domain were the Fugl–Meyer Motor Assessment Lower Extremity Subscale (FMA-LE) and the 10-m Walk Test (10 MWT); for the activities domain, the

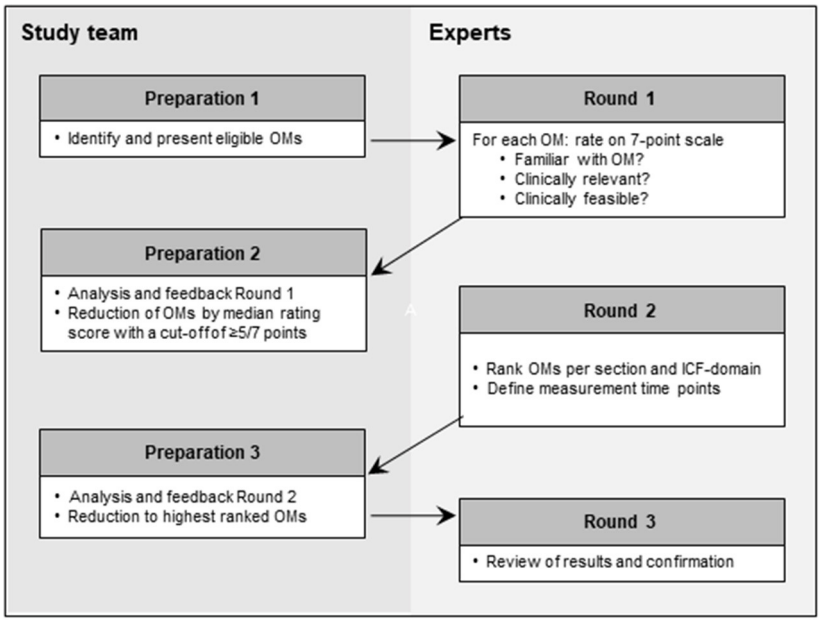


FIGURE 1 | Overview of the Delphi process. *ICF*, *International Classification of Functioning, Disability, and Health*; OMs, outcome measures.

TABLE 1 | Participant characteristics.

Characteristic	*N* = 33
Profession, *n* (%)	
Medical doctor	12 (36.4)
Occupational therapist	8 (24.2)
Physical therapist	11 (33.3)
Rehabilitation engineer	2 (6.1)
Experience, Median (IQR), Years	
Clinical	15 (9)
Research	15 (14)
Region of practice	Austria, Belgium, Czech Republic, Cyprus, Denmark, Finland, Germany, Italy, Latvia, Lithuania, the Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland, United Kingdom

IQR, interquartile range.

Timed-Up-and-Go (TUG) and the Berg Balance Scale (BBS) were indicated. Regarding the ADL/stroke-specific section, the highest ranks were given to the National Institutes of Health Stroke Scale for the body functions domain, and the Barthel Index (BI) or Functional Independent Measure (FIM) for the activities domain. Within all sections, the Stroke Impact Scale (SIS) was prioritized first for the participation domain. However, it should be noted that the SIS also provides the patient's perspective on the body functions and activities domains of the *ICF*. Subsections of the SIS (hand function, mobility, strength) were presented separately for the upper extremity and lower extremity sections and the whole SIS for the ADL/stroke-specific section. Detailed rankings of the OMs per section and *ICF* domain and details of the OMs, such as clinimetric properties with references and measurement protocols, can be found in the online supplement (**Tables S1**–**S3**, **S6**–**S8**, respectively).

Measurement Time Points

In round 2, between three and eight measurement time points per OM within *ICF* domains were proposed by the experts showing consistent agreement in a range from 48 to 90%. Agreement rates for measurements at 6, 10, 12, and 20 weeks were below 50 ± 2% and were not presented in the last round. Because of expert comments, the first two time points were combined and presented in the final round as one measurement to be administered within the first 3 days. Final agreement was given, with agreement rates ranging from 65.2 to 91.3% for a maximum of seven measurement time points for the upper and lower extremity body functions domain to be taken between days 1 and 3; at day 7; at weeks 2, 4, and 12; at 6 months; and every following 6th month. In the activities domain of the upper and lower extremity sections, agreement of measurement time points followed the same scheme but starting at day 7. A deviating scheme was compiled for the ADL/stroke-specific OMs (**Table 3**). Final agreement rates can be found in the online supplement (**Tables S4**, **S5**).

DISCUSSION

The goal of this Delphi study was to develop a core set of OMs for clinical motor rehabilitation after stroke as a tool to evaluate the quality of stroke rehabilitation at a local, national, and international level. The consensus-based core set contains nine OMs that cover a wide range of measurement constructs

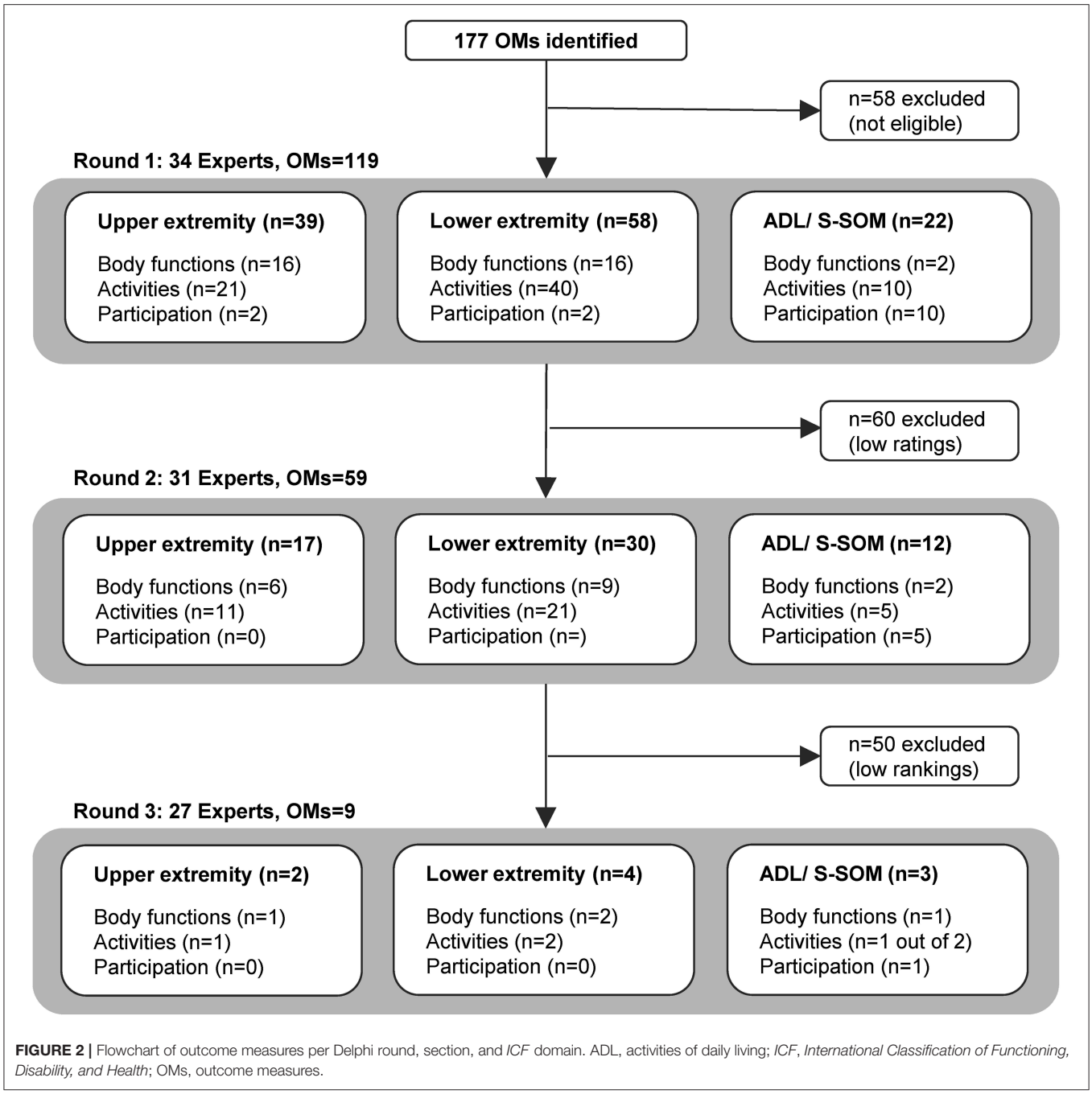


FIGURE 2 | Flowchart of outcome measures per Delphi round, section, and *ICF* domain. ADL, activities of daily living; *ICF*, *International Classification of Functioning, Disability, and Health*; OMs, outcome measures.

within all *ICF* domains that are applicable to patients with different stroke severity levels. In addition, a framework with fixed measurement time points was established, following a non-linear pattern (33), with more frequent measurements within the first 3 months after stroke and larger measurement intervals in the chronic phase. The core set was developed on the basis of independent opinions of international experts of different health care professions. All experts have comprehensive experience in clinical stroke rehabilitation. This active involvement of clinical stakeholders ensures the set's clinical relevance, feasibility, and applicability.

Core Set for Clinical Motor Rehabilitation After Stroke

The FMA-UE and ARAT are the selected OMs for the upper extremity section and are in line with the minimal set developed for stroke rehabilitation trials (10). Both instruments have excellent clinimetric properties and therefore

TABLE 2 | Core set of outcome measures for clinical motor rehabilitation after stroke.

	Body functions	Activities	Participation
Upper extremity	FMA	ARAT	SIS
Lower extremity	FMA & 10MWT*	TUG* & BBS	SIS
ADL/ stroke-specific	NIHSS	BI/ FIM	SIS

**Measure only required for patients with a Functional Ambulation Categories score of ≥3/5.*
ADL, activities of daily living; ICF, International Classification of Functioning, Disability, and Health.

TABLE 3 | Measurement time points of the core set for clinical motor rehabilitation after stroke.

	d 2±1	d 7	wk 2	wk 4	wk 12	wk 26	+26 wks
Body functions	✓ (1)	✓ (1)	✓	✓	✓	✓	✓
Activities		✓ (2)	✓	✓	✓ (2)	✓	✓ (2)
Participation					✓		✓

✓, recommended time point for assessment; d, day; m, month; wk, week; (1) exceptional time points for the National Institutes of Health Stroke Scale, only indicated at these time points; (2) exceptional time points for the Barthel Index/Functional Independence Measure, only indicated at these time points.

demonstrate a high measurement quality for clinical stroke rehabilitation (6, 11). In order to guarantee consistent measurements that allow comparing clinical and research findings, standardized measurement procedures should be followed.

The lower extremity section of the core set covers a large variety of constructs within the spectrum of body functions and activities: motor function, gait speed, functional mobility, and balance in sitting and standing. The OMs are feasible and relevant for stroke patients with and without walking ability. Outcome measures on the activities domain are discriminated by the Functional Ambulation Categories (FAC). Hence, the FAC is not *per se* included as one of the core set's OMs, but it is a screening tool to determine which OMs should at least be applied. The constructs of motor function (FMA-LE) and balance (BBS) should be evaluated in all patients, whereas walking speed (10 MWT) and functional mobility (TUG) should only be assessed in patients with an FAC score of at least three out of five. Comparing these OMs for the lower extremity with those recommended for stroke rehabilitation research (10) clearly shows that although the constructs of functional balance and mobility were not recommended for research, they are found to be relevant for the clinical setting.

The ADLs/stroke-specific OMs section covers the constructs stroke severity (body functions domain) and basic ADLs (activities domain). Within the activities domain, the highest rank is shared by the BI and FIM, which are highly correlated ($r = 0.92–0.99$) (34). These OMs can be chosen upon individual considerations within stroke services. The FIM requires annual license fees and provides chargeable access to training materials, offers data services, and contains additional socio-cognitive items. The BI might be favorable regarding time and financial resources (online supplement, **Table S8**).

The majority of the recommended OMs are designed to objectify the patient's observed functional impairment or to evaluate motor capacity in a standardized test environment, which is defined as the "maximum potential of an individual to succeed in the performance of a motor skill" (35). The included capacity measures are complemented by the patient-reported SIS, which is sensitive to change (36). The SIS not only covers the participation domain of the *ICF*, but also provides the patient's perspective on the body functions and activities domain. With that, it adds an important multidomain perspective to this clinical core set, a perspective on which no consensus was found for stroke rehabilitation research (10).

The core set's OMs are part of the few clinical guidelines that gave specific recommendations on OMs (9), which potentially facilitates implementation at a national level. The responsibility of clinical assessments should be shared by the involved health care professions according to their specialization. The total time to complete the core set lies between 60 and 75 min, depending on the patient's ability to understand and answer questions or to perform the required tasks of the BI or FIM.

Measurement Time Points

The core set provides a refined framework of fixed measurement time points poststroke, with more frequent measurements early after symptom onset and a low frequent monitoring pattern in the chronic phase. This is in accordance with the logarithmic pattern of sensorimotor recovery after stroke, in which the greatest changes on the body functions and activities domains occur within the first 12 weeks after symptom onset (37, 38). In this period, behavioral restitution takes place, and thereafter, changes occur predominantly due to compensational mechanisms, reaching a plateau between ∼3 and 6 months poststroke (33). Low-frequent assessment in the chronic phase allows for monitoring the patient's impairments and disabilities. In case of presence or lack of clinically relevant changes, rehabilitation can be restarted, continued, adapted, or completed (29).

The core set's seven consensus-based measurement time points are in line with existing recommendations in national clinical guidelines (29, 39) and stroke rehabilitation research guidelines (10) to assess in all four recovery phases poststroke (40). However, the experts recommended more measurement time points in the subacute phase, when compared to research recommendations. This will provide more detail about the individual motor recovery pattern across different *ICF* domains and therefore promote personalized rehabilitation and support appropriate discharge and adaptive planning regarding the home environment. The experts did not select admission and discharge as recommended measurement time points. Although we did not investigate the reason for not selecting specific time points by the experts, we hypothesize that this could

be explained by the large international variability in both the length of stay and the accessibility to acute clinics and rehabilitation facilities (41). These arbitrary time points impede the comparability on a regional, national, and international level. As the consensus-based time points are a minimum number of required measurement time points, measurements at admission and discharge could be optionally implemented in the local framework to facilitate rehabilitation goal setting and evaluation.

For clinical practice, an important clinimetric requirement of OMs is their responsiveness to clinically meaningful differences. As it is known that these differences depend on the recovery phase poststroke (42), changes between measurements should be related to the poststroke phase-specific MCID. Although results of anchor-based MCIDs were no inclusion criterion for the preselection of OMs in the Delphi study, MCIDs are available from the acute to the chronic stage for most OMs (online supplement **Tables S6–S8**).

The experts' consensus resulted in a clear measurement pattern for upper and lower extremity body functions and activities. They proposed a scheme with less measurement time points for the ADL/stroke specific section, possibly because these OMs are not valid and responsive at all time points.

Limitations

There are considerations to be made regarding the developed core set for clinical motor rehabilitation after stroke. First, the availability of validated translations and transcultural validations was no inclusion criterion for OMs. However, with the call for international quality standards in stroke care (3), it should be the interest of stroke services on a regional and national level, to allow for translated and validated versions of the core set's OMs. Second, although we aimed for a well-balanced group of experts in terms of clinical background, occupational therapists were underrepresented. It is unlikely that this influenced the final core set, as there were only marginal variations in the rankings between professions. Regarding the balance by regions of practice, Eastern European countries were underrepresented. Third, there is variability in agreement rates of measurement time points after rounds 2 and 3. However, there was a clear difference in agreement rates between the excluded and final recommended measurement time points. Finally, although most of the experts are still clinically active in stroke rehabilitation, many of them are also involved in research, and they may have ranked OMs using both their clinical and research experiences.

Future Directions

In a next step, the core set for clinical motor rehabilitation after stroke should be implemented across the whole stroke care pathway, including stroke units and acute hospitals, rehabilitation facilities, and outpatient centers or private practices. It should be acknowledged that the implementation of standardized tests in the clinic is challenging. Bland and colleagues (43) demonstrated differences in adherence between settings and professions. Especially in the outpatient facilities, standardized assessments were less frequently applied. However, implementation projects have demonstrated that educational programs and assessment training leads to a successful implementation of stroke OMs in clinical practice (44), and these should be taken as a good example. Routinely scheduled time slots for fixed measurement time points could support time and resource efficiency. A reevaluation of the core set's OMs and the adherence of health care professionals to apply this set should be initiated in 5 years. The measurements' results should be fed to national registries to gain insight into the quality of clinical motor rehabilitation in the acute, subacute, and chronic phase poststroke and provide input for actions for improvement. Last but not least, a collaboration of clinicians and researchers should aim for the development of a minimal set of OMs for other important domains in clinical stroke rehabilitation, such as cognition and speech.

CONCLUSION

The consensus-based core set of OMs for clinical motor rehabilitation after stroke contains nine OMs that cover the main impairments in body functions, activities, and participation on the motor domain and is complementary to recommendations for stroke rehabilitation research. Measurements should be performed at six time points within the first 6 months poststroke, and consecutive monitoring should take place every 6th month in the chronic stage. The core set and its measurement framework should be implemented throughout the whole stroke care continuum and allows benchmarking, with the long-term goal to optimize the quality of poststroke rehabilitation.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements (BASEC Nr. Req-2018-00601). Written informed consent from the participants was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

The idea was conceived by AL, JH, and JV. JV designed the study. JP and JV searched the literature for relevant OMs and designed the electronic survey and forms. JP analyzed the responses, drafted, and edited the manuscript that was critically reviewed by JH, GV, AL, and JV. JH and JV reviewed the data entry and analysis done by JP. MA, SE, AF, TK, GK, and TN also participated in the study. All authors approved the study plan, methods, study design, critically read, and approved the final version.

FUNDING

This work was financially supported by the P & K Pühringer Foundation.

ACKNOWLEDGMENTS

We would like to thank all experts for their participation: MA, Dr. Guna Berzina, Dr. Iris Brunner, Professor Dr. Jane Burridge, Dr. Lina Butenaite, Dr. David Cioncoloni, SE, Dr. Beatriz Fernandes, AF, Professor Dr. Friedhelm Hummel, MSc. Jip Kamphuis, Dr. Samuel Knobel, Dr. Jan Kool, Professor Dr. Hanne Kaae Kristensen, GK, Professor Dr. Birgitta Langhammer, AL, Professor Dr. Habil Jan Mehrholz, Dr. Illa Mihejeva, Professor Dr. Karel Moses, TN, Professor Dr. Hab Józef Opara, MSc. Beatrice Ottiger, Professor Dr. Valerie Pomeroy, Dr. Pavlin Psychouli, MSc. José López Sánchez, Professor Dr. Blanche Staes, Dr. Esther Steultjens, Professor Dr. Katharina Sunnerhagen, Dr. Ina Tarkka, Dr. Annick van Gils, GV, and Dr. Andreas Winkler. Furthermore, we thank Dr. Shehab Anwer for creating the website and providing technical support.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00875/full#supplementary-material

REFERENCES

1. Feigin VL, Nichols E, Alam T, Bannick MS, Beghi E, Blake N, et al. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* (2019) 18:459–80. doi: 10.1016/S1474-4422(18)30499-X
2. Béjot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in Europe and trends for the 21st century. *La Presse Médicale.* (2016) 45:e391–8. doi: 10.1016/j.lpm.2016.10.003
3. Norrving B, Barrick J, Davalos A, Dichgans M, Cordonnier C, Guekht A, et al. Action plan for stroke in Europe 2018–2030. *Eur Stroke J.* (2018) 3:309–36. doi: 10.1177/2396987318808719
4. Franceschini M, Porta FL, Agosti M, Massucci M. Is health-related-quality of life of stroke patients influenced by neurological impairments at 1 year after stroke? *Eur J Phys Rehabil Med.* (2010) 46:11.
5. Grube MM, Dohle C, Djouchadar D, Rech P, Bienek K, Dietz-Fricke U, et al. Evidence-based quality indicators for stroke rehabilitation. *Stroke.* (2012) 43:142–6. doi: 10.1161/strokeAHA.111.627679
6. Sullivan JE, Crowner BE, Kluding PM, Nichols D, Rose DK, Yoshida R, et al. Outcome measures for individuals with stroke: process and recommendations from the American Physical Therapy Association Neurology Section Task Force. *Phys Ther.* (2013) 93:1383–96. doi: 10.2522/ptj.20120492
7. Legido-Quigley H, Panteli D, Brusamento S, Knai C, Saliba V, Turk E, et al. Clinical guidelines in the European Union: mapping the regulatory basis, development, quality control, implementation and evaluation across member states. *Health Policy.* (2012) 107:146–56. doi: 10.1016/j.healthpol.2012.08.004
8. Haigh R, Tennant A, Biering-Sørensen N, Gimby G, Marinček C, Phillips S, et al. The use of outcome measures in physical medicine and rehabilitation within Europe. *J Rehabil Med.* (2001) 33:273–8.doi: 10.1080/165019701753236464
9. Burridge J, Alt Murphy M, Buurke J, Feys P, Keller T, Klamroth-Marganska V, et al. A systematic review of international clinical guidelines for rehabilitation of people with neurological conditions: what recommendations are made for upper limb assessment? *Front Neurol.* (2019) 10:567. doi: 10.3389/fneur.2019.00567
10. Kwakkel G, Lannin NA, Borschmann K, English C, Ali M, Churilov L, et al. Standardized measurement of sensorimotor recovery in stroke trials: consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. *Int J Stroke.* (2017) 12:451–61. doi: 10.1177/1747493017711813
11. Alt Murphy M, Resteghini C, Feys P, Lamers I. An overview of systematic reviews on upper extremity outcome measures after stroke. *BMC Neurol.* (2015) 15:6. doi: 10.1186/s12883-015-0292-6
12. Sullivan KJ, Tilson JK, Cen SY, Rose DK, Hershberg J, Correa A, et al. Fugl-Meyer Assessment of sensorimotor function after stroke: standardized training procedure for clinical practice and clinical trials. *Stroke.* (2011) 42:427–32. doi: 10.1161/STROKEAHA.110.592766
13. Moore JL, Potter K, Blankshain K, Kaplan SL, O'Dwyer LC, Sullivan JE. A core set of outcome measures for adults with neurologic conditions undergoing rehabilitation: a clinical practice guideline. *J Neurol Phys Ther.* (2018) 42:174–220. doi: 10.1097/NPT.0000000000000229
14. Baker K, Cano SJ, Playford ED. Outcome measurement in stroke: a scale selection strategy. *Stroke.* (2011) 42:1787–94. doi: 10.1161/STROKEAHA.110.608505
15. Bushnell C, Bettger JP, Cockroft KM, Cramer SC, Edelen MO, Hanley D, et al. Chronic stroke outcome measures for motor function intervention trials: expert panel recommendations. *Circ Cardiovasc Qual Outcomes.* (2015) 8:S163–9. doi: 10.1161/CIRCOUTCOMES.115.002098
16. Reeves M, Lisabeth L, Williams L, Katzan I, Kapral M, Deutsch A, et al. Patient-reported outcome measures (PROMs) for acute stroke: rationale, methods and future directions. *Stroke.* (2018) 49:1549–56. doi: 10.1161/STROKEAHA.117.018912
17. Katzan IL, Thompson NR, Lapin B, Uchino K. Added value of patient-reported outcome measures in stroke clinical practice. *J Am Heart Assoc.* (2017) 6:5356. doi: 10.1161/JAHA.116.005356
18. World Health Organization. *International Classification of Functioning, Disability and Health: ICF*. Geneva: World Health Organization (2001).
19. Simpson LA, Eng JJ. Functional Recovery Following Stroke: capturing changes in upper-extremity function. *Neurorehabil Neural Repair.* (2013) 27:240–50. doi: 10.1177/1545968312461719
20. Lang CE, Bland MD, Bailey RR, Schaefer SY, Birkenmeier RL. Assessment of upper extremity impairment, function, and activity after stroke: foundations for clinical decision making. *J Hand Ther.* (2013) 26:104–15. doi: 10.1016/j.jht.2012.06.005
21. Santisteban L, Térémetz M, Bleton J-P, Baron J-C, Maier MA, Lindberg PG. Upper limb outcome measures used in stroke rehabilitation studies: a systematic literature review. *PLoS ONE.* (2016) 11:e0154792. doi: 10.1371/journal.pone.0154792
22. Lemmens RJ, Timmermans AA, Janssen-Potten YJ, Smeets RJ, Seelen HA. Valid and reliable instruments for arm-hand assessment at ICF activity level in persons with hemiplegia: a systematic review. *BMC Neurol.* (2012) 12:21. doi: 10.1186/1471-2377-12-21
23. Ashford S, Brown S, Turner-Stokes L. Systematic review of patient-reported outcome measures for functional performance in the lower limb. *J Rehabil Med.* (2015) 47:9–17. doi: 10.2340/16501977-1889
24. Tyson S, Connell L. How to measure balance in clinical practice. A systematic review of the psychometrics and clinical utility of measures of balance activity for neurological conditions. *Clin Rehabil.* (2009) 23:824–40. doi: 10.1177/0269215509335018
25. Van Bloemendaal M, Van de Water ATM, Van de Port IGL. Walking tests for stroke survivors: a systematic review of their measurement properties. *Disabil Rehabil.* (2012) 34:2207–21. doi: 10.3109/09638288.2012.680649
26. Kelly-Hayes PM, Robertson JT, Broderick JP, Duncan PW, Hershey LA, Roth EJ, et al. The American Heart Association stroke outcome classification. *Stroke.* (1998) 29:1274–80. doi: 10.1161/01.STR.29.6.1274

27. Van Peppen RPS, Hendriks HJM, Van Meeteren NLU, Helders PJM, Kwakkel G. The development of a clinical practice stroke guideline for physiotherapists in The Netherlands: a systematic review of available evidence. *Disabil Rehabil.* (2007) 29:767–83. doi: 10.1080/09638280600919764
28. National Institute of Health and Care Excellence. *Stroke Rehabilitation in Adults* (2013). Available online at: https://www.nice.org.uk/guidance/cg162
29. Veerbeek JM, Van Wegen EE, Van Peppen RPS, Hendriks HJM, Rietberg M, Van derWees PhJ, et al. *KNGF Clinical Practice Guideline for Physical Therapy in PatientsWith Stroke Practice Guidelines.* Amersfoort: KNGF (2014).
30. Heart and Stroke Foundation. *Stroke Engine*. Available online at: https://www.strokengine.ca/en/find-assessment/ (accessed October 30, 2018).
31. Shirley Ryan Ability Lab. *Rehabilitation Measure Data Base*. Available online at: https://www.sralab.org/rehabilitation-measures/ (accessed October 30, 2018).
32. Mokkink LB, Prinsen CAC, Bouter LM, Vet HCW de, Terwee CB. The Consensus-based Standards for the Selection of health Measurement Instruments (COSMIN) and how to select an outcome measurement instrument. *Braz J Phys Ther.* (2016) 20:105–13. doi: 10.1590/bjpt-rbf.2014.0143
33. Kwakkel G, Kollen B, Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. *Restor Neurol Neurosci.* (2004) 22:281–99. doi: 10.1017/CBO9780511995590.004
34. Hsueh I-P, Lin J-H, Jeng J-S, Hsieh C-L. Comparison of the psychometric characteristics of the Functional Independence Measure, 5-item Barthel Index, and 10-item Barthel Index in patients with stroke. *J Neurol Neurosurg Psychiatry.* (2002) 73:188–90. doi: 10.1136/jnnp.73.2.188
35. Oxford University Press. *The Oxford Dictionary of Sports Science and Medicine*. 3rd ed. Oxford University Press (2006). doi: 10.1093/acref/9780198568506.001.0001
36. Lin K, Fu T, Wu C, Hsieh C. Assessing the Stroke-Specific Quality of Life for outcome measurement in stroke rehabilitation: minimal detectable change and clinically important difference. *Health Qual Life Outcomes.* (2011) 9:5. doi: 10.1186/1477-7525-9-5
37. Persson HC, Opheim A, Lundgren-Nilsson Å, Alt Murphy M, Danielsson A, Sunnerhagen KS. Upper extremity recovery after ischaemic and haemorrhagic stroke: part of the SALGOT study. *Eur Stroke J.* (2016) 1:310–9. doi: 10.1177/2396987316672809
38. Persson CU, Danielsson A, Sunnerhagen KS, Grimby-Ekman A, Hansson P-O. Timed Up and Go as a measure for longitudinal change in mobility after stroke–Postural Stroke Study in Gothenburg (POSTGOT). *J NeuroEngineering Rehabil.* (2014) 11:83. doi: 10.1186/1743-0003-11-83
39. Teasell RW, Foley NC, Bhogal SK, Speechley MR. An Evidence-Based Review of Stroke Rehabilitation. *Top Stroke Rehabil.* (2003) 10:29–58. doi: 10.1310/8YNA-1YHK-YMHB-XTE1
40. Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: the Stroke Recovery and Rehabilitation Roundtable taskforce. *Int J Stroke.* (2017) 12:444–50. doi: 10.1177/1747493017711816
41. Langhorne P, Baylan S. Early supported discharge services for people with acute stroke. *Cochrane Database Syst Rev.* (2017) doi: 10.1002/14651858.CD000443.pub4
42. Lang CE, Edwards DF, Birkenmeier RL, Dromerick AW. Estimating minimal clinically important differences of upper-extremity measures early after stroke. *Arch Phys Med Rehabil.* (2008) 89:1693–700. doi: 10.1016/j.apmr.2008.02.022
43. Bland MD, Sturmoski A, Whitson M, Harris H, Connor LT, Fucetola R, et al. Clinician adherence to a standardized assessment battery across settings and disciplines in a poststroke rehabilitation population. *Arch Phys Med Rehabil.* (2013) 94:1048–53.e1. doi: 10.1016/j.apmr.2013.02.004
44. Van Peppen R, Schuurmans M, Stutterheim E, Lindeman E, Van Meeteren N. Promoting the use of outcome measures by an educational programme for physiotherapists in stroke rehabilitation: a pilot randomized controlled trial. *Clin Rehabil.* (2009) 23:1005–17. doi: 10.1177/0269215509338999

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 18 September 2020
doi: 10.3389/fneur.2020.01025

Characterization of Post–exertional Malaise in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Barbara Stussman[1], Ashley Williams[2], Joseph Snow[3], Angelique Gavin[4], Remle Scott[1], Avindra Nath[4] and Brian Walitt[5]*

[1] National Center for Complementary and Integrative Health (NCCIH), National Institutes of Health (NIH), Bethesda, MD, United States, [2] Oakland University William Beaumont School of Medicine, Rochester, MI, United States, [3] National Institute of Mental Health, National Institutes of Health (NIH), Bethesda, MD, United States, [4] National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), Bethesda, MD, United States, [5] National Institute of Nursing Research (NINR), National Institutes of Health (NIH), Bethesda, MD, United States

Background: Myalgic encephalomyelitis/chronic fatigue syndrome is characterized by persistent and disabling fatigue, exercise intolerance, cognitive difficulty, and musculoskeletal/joint pain. Post–exertional malaise is a worsening of these symptoms after a physical or mental exertion and is considered a central feature of the illness. Scant observations in the available literature provide qualitative assessments of post–exertional malaise in patients with myalgic encephalomyelitis/chronic fatigue syndrome. To enhance our understanding, a series of outpatient focus groups were convened.

Methods: Nine focus groups totaling 43 patients who reported being diagnosed with myalgic encephalomyelitis/chronic fatigue syndrome were held between November 2016 and August 2019. Focus groups queried post–exertional malaise in daily life and participants' retrospective memory of post–exertional malaise that followed an exercise provocation with a cardiopulmonary exercise test. Data analysis followed the grounded theory method to systematically code and categorize the data to find meaningful patterns. A qualitative software package was used to move text into categories during data coding.

Results: A wide range of symptoms were attributed to exertion both in daily lives and following cardiopulmonary exercise testing. While three core symptoms emerged (exhaustion, cognitive difficulties, and neuromuscular complaints), participants' descriptions were notable for their unique individual variations. Of 18 participants who responded to questions centered around symptoms following a cardiopulmonary exercise test, 17 reported that symptoms started within 24 h and peaked in severity within 72 h following the cardiopulmonary exercise test. Patients described post–exertional malaise as interfering with their ability to lead a "normal" life.

Conclusion: The experience of post–exertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome varies greatly between individuals and leads to a diminished quality of life. myalgic encephalomyelitis/chronic fatigue syndrome

OPEN ACCESS

Edited by:
Stefano Tamburin, University of Verona, Italy

Reviewed by:
Meg E. Morris, La Trobe University, Australia
Eliana Mattos Lacerda, University of London, United Kingdom

***Correspondence:**
Barbara Stussman
stussmanbj@mail.nih.gov

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *02 March 2020*
Accepted: *05 August 2020*
Published: *18 September 2020*

Citation:
Stussman B, Williams A, Snow J, Gavin A, Scott R, Nath A and Walitt B (2020) Characterization of Post–exertional Malaise in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Front. Neurol. 11:1025. doi: 10.3389/fneur.2020.01025

patients describe post–exertional malaise as all-encompassing with symptoms affecting every part of the body, difficult to predict or manage, and requiring complete bedrest to fully or partially recover. Given the extensive variability in patients, further research identifying subtypes of post–exertional malaise could lead to better targeted therapeutic options.

Keywords: myalgic encephalitis, chronic fatgue syndrome, post-exertional malaise, exhaustion, cardiopulmonary exercise testing, exercise intolerance

INTRODUCTION

Persistent and disabling fatigue, exercise intolerance, cognitive difficulties, and musculoskeletal/joint pain are characteristic of a disorder that has been referred to as the Royal Free Disease, benign myalgic encephalomyelitis, chronic fatigue syndrome (CFS), myalgic encephalomyelitis (ME), and systemic exertion intolerance disease at various times in history (1). The term *myalgic encephalomyelitis/chronic fatigue syndrome* is currently the most common term used in diagnostic criteria, by advocates, and by the US Federal Government to refer to the illness (2). Post–exertional malaise (PEM) is a worsening of these symptoms after minimal physical or mental exertion (3). PEM is considered a central feature of ME/CFS (4). The cause of ME/CFS remains unknown, and there are no approved diagnostic tests or treatments (5). Historically, measurement of PEM has had considerable controversy, and patient groups have felt left out of the process by which policy makers develop definitions of ME/CFS (6, 7). Qualitative research affords patients an opportunity to discuss their experiences with researchers at length and inform patient-focused clinical decision making (8).

Previous qualitative assessments of ME/CFS have shown a significant and debilitating effect on the lives of patients. ME/CFS patients have described the fatigue experience as all-encompassing and debilitating, fluctuating, unpredictable, often triggered by minor activities, and causing a significant impediment to daily functioning (7). A previous study using qualitative telephone interviews found the lessening ability to independently perform daily tasks had a significant impact on psychological well-being of ME/CFS patients (9). The one study of which we are aware that employed focus groups to explore PEM in individuals with ME/CFS (10) queried patients about different dimensions of fatigue and found distinct physical and cognitive dimensions, including five key themes: exhausted, drained of energy, heavy feeling, cognitive fog, and muscle weakness.

Previous quantitative studies looking at PEM in ME/CFS patients have shown a wide range of physical and cognitive symptoms affecting every part of the body (6, 11–13). These studies have detailed common PEM symptoms (e.g., physical fatigue, cognitive exhaustion, muscle pain, unrefreshed sleep, and headaches) and timeframes for symptom onset and duration. A recent study (11) used survey data to summarize symptoms, triggers, and time patterns for onset and duration of PEM and found most patients experienced several cognitive and physical symptoms and that triggers of PEM can be physical, cognitive, and emotional. That study also found that onset relative to exertion ranged from immediate to more than 24 h, and duration ranged from <1 h to years.

Although the scientific literature provides few qualitative assessments of PEM in ME/CFS patients, qualitative descriptions of chronic fatigue have been made in other health disorders. A metasynthesis of fatigue across several long-term conditions such as cancer and stroke, not including ME/CFS, produced some commonalities in the fatigue experience (14). For instance, participants described fatigue as unpredictable in occurrence, intensity, and duration and feeling a loss of control of the body. Patients with whiplash-associated disorders suffer from fatigue, sleep disturbance, and cognitive deficits similar to ME/CFS patients (15). Chronic fatigue can be unpredictable and triggered by anxiety and emotional trauma (16). Using the DePaul PEM Questionnaire, one study found the fatigue experience in a subset of cancer patients was similar to PEM in ME/CFS patients (17). However, unlike ME/CFS patients, many patients with fatiguing conditions such as multiple sclerosis and post-polio syndrome are able to exercise without experiencing PEM (13).

Because PEM in ME/CFS patients is still underexplored, especially through purely qualitative methods, the aim of the current study was to expand the knowledge base on the symptoms; manner of onset; timeframes for onset, peak, and duration of PEM; and impact on day-to-day lives of patients. We aimed to understand how ME/CFS is impacted by exertion in day-to-day life and how this compares to the impact after cardiopulmonary exercise testing (CPET). Additionally, we wanted to delve deeper into the experience of PEM following CPET, a gap in the current research. Based on the literature we expected to find a feeling of loss of control and unpredictability to PEM. We also expected to find physical, cognitive, and emotional aspects.

We present results from nine focus groups conducted to better understand PEM experiences from the perspective of ME/CFS patients. Focus groups were centered on ME/CFS patients' usual daily symptoms and how these changed or worsened following exertion. Additionally, for five of the nine focus groups, we recruited ME/CFS patients who had undergone a CPET evaluation and prompted them to report their memory of the symptoms following the CPET evaluation. The primary purpose of the focus groups was to provide a richer and more nuanced understanding of how ME/CFS patients experience their illness. Secondarily, results from the current study were used

Abbreviations: ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; PEM, post–exertional malaise; CPET, cardiopulmonary exercise test.

to inform the design of an exploratory ME/CFS study at the National Institutes of Health (18). We present these findings to aid physicians who provide care to these patients and other investigators interested in designing mechanistic studies of PEM.

MATERIALS AND METHODS

We chose to conduct a qualitative assessment through the collection and analyses of rich textual data enabling depth and nuance of discovery not possible via purely quantitative methods. For example, while surveys may produce a comprehensive list of symptoms, focus groups can capture the personal experiences and importance of specific symptoms from the perspective of individual ME/CFS patients. A qualitative exploratory focus group approach was chosen because of its known benefit for underexplored topic areas and disabled populations (19, 20, 23). Focus groups offers the ability to understand the unique experiences of patients and provide a deep, more nuanced understanding of the PEM experience within their social worlds. Focus groups have the further benefit of allowing participants to compare and contrast their experiences, which is particularly helpful when exploring a relatively unknown area. Focus group participants were queried about PEM in their daily lives and in relation to previous CPET tests in which they had participated. Nine focus groups were conducted between November 2016 and August 2019. They ranged from 4 to 7 participants per group for a total of 43 participants and ranged in length from 103 to 120 min. All focus groups were conducted over the telephone to enable geographic diversity without travel burden for the ME/CFS participants.

Data analysis followed the grounded theory method first developed by Glaser and Strauss (21). This approach was chosen to generate a theoretical understanding of the experience of PEM within the social context of persons with ME/CFS. Grounded theory is an inductive, iterative method of conducting qualitative research in which theory is built from the data. Focus group scripts were iteratively modified to further explore emergent categories identified during data analysis. Consistent with the grounded theory approach, data were analyzed using the constant comparative method (22). The constant comparative method is the process of generating conceptual categories from uncategorized data. This involves comparing each piece of data so that similar pieces of data are labeled and grouped to form categories. Every new piece of data is then compared to this categorical structure, and the structure is reconstructed in an iterative manner until no new piece of data challenges the structure's ability to account for all pieces of data (22).

Participants

Participants were recruited using purposeful sampling, a qualitative sampling procedure in which investigators intentionally recruit participants who have experienced the phenomenon being explored (23). Specifically, 257 potential participants were interviewed by members of the study team. Recruitment solicitations were posted on ME/CFS advocacy websites and were emailed to persons willing to be contacted for research from the practices of health professionals specializing in the evaluation of ME/CFS patients. The majority of these participants were ME/CFS patients in the community and referred by physicians to exercise physiologists for clinical CPET evaluations. All focus group participants reported having received an ME/CFS diagnosis by a health care provider; an independent verification of medical records was not performed.

Within the pool of individuals who expressed interest in participating, we sought to maximize variability with respect to age, gender, race, ethnicity, marital status, education, employment status, severity of impairment (in bed most of the time or not), years since symptoms onset, and geographic location to gain a wide representation. The study was approved by the Combined NeuroScience Institutional Review Board. Informed consent was obtained from all participants using a witnessed telephone consenting process.

Cardiopulmonary Exercise Testing

CPET is an exercise physiology protocol that is typically used to measure exercise performance and tolerance. It typically involves performing exercise on a cycle ergometer that starts off being easy and steadily becomes harder over time. Participants are instructed to exercise until they reach subjective exhaustion and cannot continue to exercise further (24). Small studies report that a single CPET session (1-day CPET) is a reliable way to induce PEM in ME/CFS patients (25). Single-session CPET is being used as a method to induce PEM for scientific inquiry (26). Some ME/CFS patients undergo an exercise protocol that has them perform two CPET evaluations on sequential days (2-days CPET) as an evaluation of ME/CFS status (27).

As we were interested in learning more about PEM following CPET, five of the nine focus groups were restricted to ME/CFS patients who had undergone CPET to probe them about their experiences with PEM following the test. Of the 18 participants who reported on the timeframe for PEM following CPET, half underwent the 2-days CPET, and half underwent the 1-day CPET. Participants who underwent 2-days CPETs were asked to describe symptoms following Day 1, while also explaining any compounding effects from Day 2.

Data Collection

All focus groups were conducted by an experienced focus group moderator who had no prior experience with the study population or ME/CFS to ensure impartiality. The semistructured focus group script included broad questions aimed to explore patients' experiences of having PEM, both in their daily lives and in response to the CPET test. Discussion questions centered around activities that can trigger PEM, specific symptoms of PEM, how long after exertion symptoms began, how long the symptoms lasted, and at what point the symptoms were at their worst. Participants were also asked about strategies they employed to try to alleviate symptoms of PEM. With respect to the discussion questions related to the CPET test, we sought to gain a complete picture of how patients felt before the test, during the test, and following the test, including a better understanding of the experience of the onset and course of symptoms. **Table 1** shows the final version of discussion questions.

TABLE 1 | Focus group discussion questions.

Focus group discussion questions
Daily post–exertional malaise discussion questions:
• We are interested in learning about how you have felt after exertion in your day to day life. We want to hear about any physical, cognitive, or emotional symptoms that you may have experienced after exertion. It may be helpful to use a specific example. Probe: Physical, cognitive, and emotional Probe: We are interested in how you felt throughout your whole body
• How long after the exertion in your daily life do your symptoms usually first begin or start to come on?
• Please describe the transition from before exertion to having PEM symptoms. Probe: Was it more gradual or more sudden?
• When are your symptoms at the worst, or the peak of PEM following exertion in your daily life? Probe: How many hours or days after the exertion?
• We would like to get a sense of how long after exertion in your daily life until you felt that you had recovered, that is, went back to feeling the same as you did at your usual baseline?
Cardiopulmonary exercise test discussion questions:
• We are interested in learning about your experiences before, during, and after the CPET test. We want to get a sense of how you were feeling *before* you got on the bike or treadmill, how you felt *while on* the bike or treadmill, and *finally* what you experienced several hours and days later. Please describe what this was like physically, cognitively, and emotionally. Probe: Physical, cognitive, and emotional. Probe: We are interested in how you felt throughout your whole body.
• How long after the CPET test did your symptoms first begin or start to come on?
• Please describe the transition from before the CPET to having PEM symptoms. Probe: Was it more gradual or more sudden?
• When were your symptoms at the worst, or the peak following the CPET test? Probe: How many hours or days after the CPET?
• We would like to get a sense of how long it took after the CPET test until you felt that you had recovered from the test, that is, went back to feeling the same as you did before the test, or at your usual baseline? Probe: How many hours or days after the CPET?
• Please compare the physical, cognitive, and emotional symptoms following CPET with those that occur after exertion in your daily life. In what ways are symptoms after CPET similar or different from symptoms after exertion in your daily life?
• Can you describe how it felt as you recovered from the C-PET test? Was it a gradual or more sudden recovery?
General questions about post–exertional malaise:
• The next question is about any strategies you may have tried to feel better after experiencing symptoms of post–exertional malaise or PEM. Please tell us about anything that you've tried that has or has not helped. Probe: What does "complete rest" mean? Do you get up for the toilet or to eat? For any other reason?
• Have you modified your activities because of anticipation of feeling poorly after exertion? Probe: What kinds of thoughts go through your mind when deciding whether to exert yourself?
• Anything else you would like to add to help us better understand your experiences with PEM related to exertion in your daily life or from the C-PET test?
• Any final thoughts or questions before we end today?

At the start of each focus group, participants were given information about the purpose of the discussion and basic ground rules for the discussion such as giving everyone a chance to speak and that there were no right or wrong answers. As is usual during the conduct of focus groups, some participated more than others. However, the moderator systematically solicited participation from each participant and intervened when the discussion veered off topic. Participants often "fed off" each other generating broad and comprehensive discussions. Based on the potential for overexertion, focus groups were limited to 2 h, which allowed for most participants to answer every question; occasionally, not every participant responded to all discussion questions.

Data Analysis

For reasons explained above, we chose the grounded theory approach and, within that approach, the constant comparative method to analyze our data. Data analysis began after the first focus group and continued iteratively throughout the study. Three researchers developed the coding scheme individually and through team meetings and discussions. In-depth meetings were held to discuss coding differences at length and reach consensus. By the completion of the ninth focus group, salient themes were confirmed and repeated with no new themes emerging (i.e., saturation), signaling an end for the need for further participant recruitment (28). A qualitative software package (29) was used that automated the analysis process described above by allowing the researchers to electronically highlight words or phrases from each transcript and drag them into folders labeled for each theme and subtheme. The software package also allowed for easily combining or separating categories as needed based on analysis.

RESULTS

Forty-three participants with ME/CFS participated in nine focus groups. Participant demographics are shown in **Table 2**. Eight overarching themes emerged with salience to ME/CFS patients' experiences with PEM. Themes included the following: (1) PEM was triggered by three broad categories of events; (2) effects of PEM were impacted by baseline pre-exertional symptoms; (3) PEM had a wide symptom range with few differences between daily PEM and PEM following CPET, with three core symptoms (exhaustion, cognitive difficulties, and neuromuscular complaints); (4) PEM following CPET was more immediate and of longer duration than PEM in daily life; (5) the manner of onset of PEM symptoms varied; (6) complete rest was necessary to gain any relief in PEM symptoms; (7) planning and moderation of energy expenditure were seen as essential to avoiding PEM; and (8) the uncertainty and debility of PEM created despair.

Theme 1. PEM Was Triggered by Three Broad Categories of Events

We asked focus group participants to give examples of activities that caused them to have PEM. Notably, there were three broad categories of activities: physical activity, cognitive effort, and emotion precipitated, although there was overlap across the three groups. These categories included triggers such as household chores, social activities, errands outside of the home, physical exercise, cognitive activities, and emotional moments (**Figure 1**).

One participant explained how a trip to the grocery store can cause PEM:

TABLE 2 | Demographic characteristics of focus group participants ($n = 43$).

Characteristic	Percent (%)
Sex	
Male	20.9
Female	79.1
Race	
White	90.7
Black	4.6
Asian	2.3
Native American	2.3
Ethnicity	
Hispanic	9.3
Non-Hispanic	90.7
Age (years)	
18–29	2.3
30–39	20.1
40–49	18.6
50–59	37.2
60–69	16.3
≥70	4.7
Marital status	
Married	48.8
Divorced	14
Living with a partner	9.3
Never married	11.6
Unknown	
Education	16.3
High school	4.7
Some college	2.4
Bachelor's degree	48.8
Graduate degree	27.9
Unknown	16.3
Employment	
Full-time	2.3
Part-time	9.3
Disabled	67.4
Retired	4.7
Unknown	16.3
In bed most of the time	
Yes	42
No	39.5
Unknown	18.6
Years since symptom onset	
<5	25.6
5–9	25.6
10–14	18.6
≥15	30.2
Area of country	
West	25.6
Midwest	20.9
South	30.2
East	23.3

"I can go grocery shopping 1 day and I am completely spent for 2 or 3 days."

Another participant described how a trip to Walmart can cause PEM:

"I'm walking through Walmart to get my prescriptions but I'll feel ok, but then as soon as I get home it's like flipping a switch, and I just immediately have no energy."

Participants frequently described how cognitive effort can cause PEM symptoms, as this participant described:

"I specifically notice it if I've had a one-on-one conversation with a friend. After about anywhere from 30 min to an hour, my brain literally starts to shut down, and I can't think clearly and I can't pay attention anymore."

Another cognitive trigger example was described:

"Yesterday I was doing some sorting of a folder trying to clean some things out not even like processing just keeping this, throwing out that, and like an hour of that really burned my brain. I could feel that immediately after."

Many participants also described how PEM can be caused by social or emotional stress. One participant described the effect of having her parents visit on a Saturday:

"Compared to a normal Saturday for me, which is just having my son at home with my husband, I engaged in several hours of social interaction, which I normally don't do. I have all this extra stress of parents coming. It's unexpected and other people in my house and all of that. So the next day midmorning, I start feeling bad and I know I definitely need to rest. So I start feeling bad and I lay down. I am basically in bed for 4 h."

Another participant explained how stress can be a trigger for PEM:

"Stress is a big trigger. If I have a lot of things going on, a lot of things I need to do, or a lot of things I need to accomplish, and/or feel like I need to accomplish, it's hard for me to let go of those things. And I don't get better as quickly if I don't recognize it."

Theme 2. Effects of PEM Were Impacted by Baseline Pre-exertional Symptoms

When focus group participants were asked to describe PEM following exertion, many expressed the importance of understanding their "starting point" or "baseline." Participants described the pliable nature of symptoms and how successive exertion can compound symptoms. One participant explained this compounding effect:

"Two days after going to the doctor, my baseline was now exacerbated. It took much less [to cause PEM]. It could now be just having to get in the car and go get my kids, which I do every single

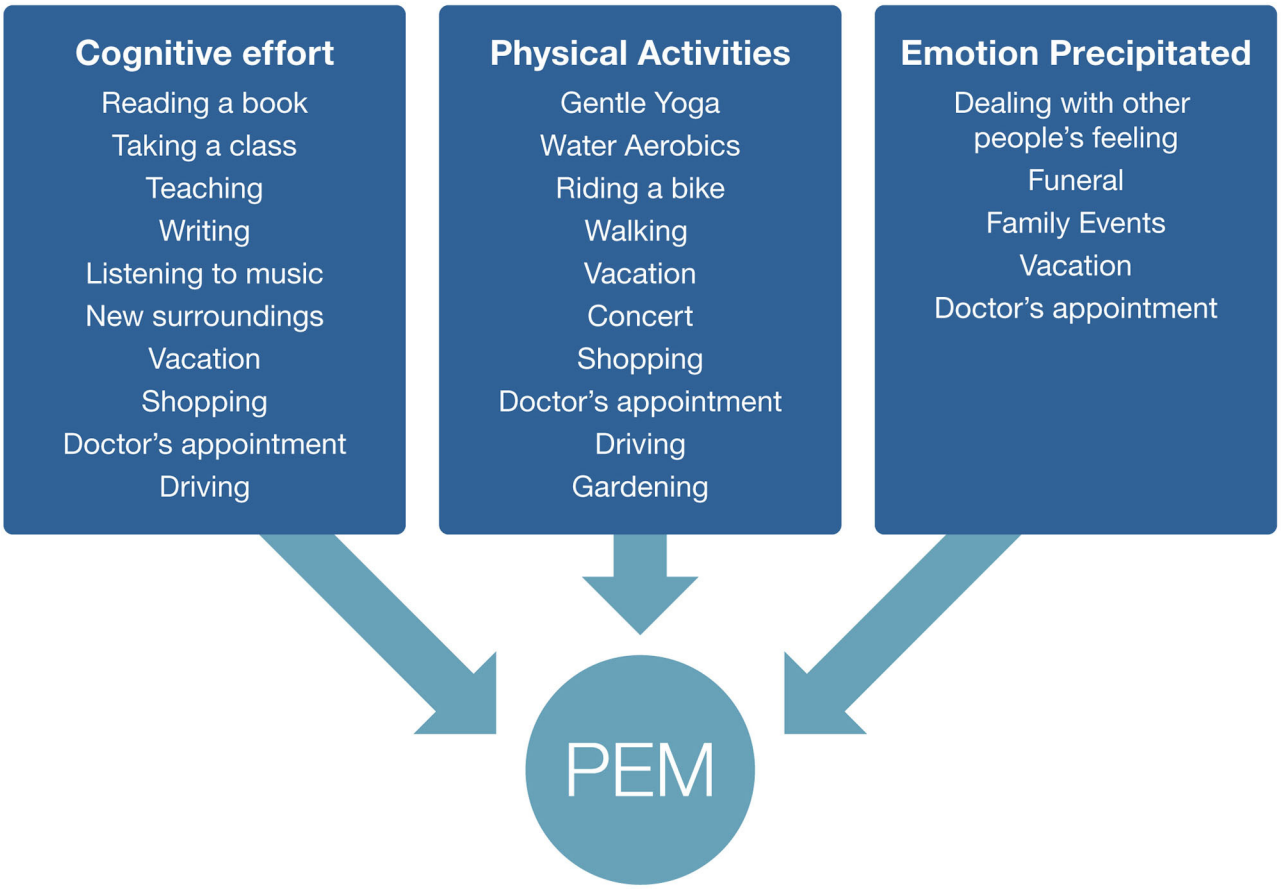


FIGURE 1 | Examples of post–exertional malaise triggers given by focus group respondents. Some triggers fall into multiple categories.

day. I'm now unable to do because of that doctor appointment 2 days prior."

Having an accurate assessment of baseline was particularly important for PEM following CPET evaluation. Many patients had to travel a long way to get to the site where the CPET was performed. These participants explained that PEM can be compounded by back-to-back exertion and that travel was a trigger for PEM. One participant explained:

"I had to travel several days across a number of states and I had to fly and all that, so it took a lot out of me just to get to the site of the testing, so I was feeling worse than a typical day for me by the time I got to the test site."

Another participant described the effect of the travel to get to the CPET:

"Flying from Illinois to California and all the traveling, even with having a wheelchair, there was still walking and stress of traveling. I was going in already at a low baseline."

Because ME/CFS symptoms can vary widely based on exertion in daily living, to accurately detect changes in symptoms from before to after CPET, it is imperative to obtain a thorough pre-CPET assessment.

This concept was not limited to CPET evaluation, but also was frequently mentioned in relation to daily PEM. Participants emphasized that when they overexert while already in an episode of PEM, the result was amplified.

This participant described how PEM symptoms can compound:

"If I do make it to the point where I almost faint, it is harder to recover from. Those situations for me are only happening if I just keep letting it compound, if this is several weeks of overexertion or having a cold or another issue."

This compounding effect has implications for the management of PEM as described in a later section.

Theme 3. PEM Had a Wide Symptom Range With Few Differences Between Daily PEM and Following CPET, With Three Core Symptoms (Exhaustion, Cognitive Difficulties, and Neuromuscular Complaints)

During focus groups, we asked participants to describe symptoms they have experienced following exertion, both in their daily lives and following a CPET evaluation. We purposely did not query participants about specific symptoms, but rather asked a general open-ended question, "We'd like to hear some specific examples of how you feel throughout your entire body after exertion." The purpose of this inquiry was to capture these complaints in the participant's own words. As such, no attempt was made to verify medical symptoms or diagnosis. Additionally, the intention of asking participants about symptoms was to determine the range and most commonly reported symptoms, but it was not feasible in the limited time to query each participant about every potential symptom. Furthermore, the benefit of using focus groups was to capture the most salient symptoms to participants without medical jargon or predetermined categories. **Table 3** and **Figures 2**, **3** present the range and frequency of symptoms reported during focus groups, both for daily PEM and following CPET evaluation. Similar symptoms were reported for daily PEM and PEM following CPET evaluation. In response to this general question, nearly all participants described three core symptoms (exhaustion, cognitive difficulties, and neuromuscular complaints), both for daily PEM and PEM following CPET evaluation.

Theme 3a. Exhaustion

Participants explained that the exhaustion from PEM is different than what they experienced before having ME/CFS. One participant put it this way:

> *"And it's a flulike exhaustion, really tiring. I used to be an athlete. I had a very intense job. So I would feel a lot of fatigue from those activities. But this is not that type of fatigue. This is a type of fatigue I felt when I rarely got the flu, years ago. Only that flu lasted for a few days and not for the years they have now."*

For some participants, the exhaustion from PEM was severe as explained by a participant:

> *"On some days, just walking from my bed to the bathroom was exhausting"*

Another participant explained how PEM:

> *"Feels like you've had the flu, and you're just so weak and everything hurts, and you're exhausted trying to take a shower."*

Another participant described exhaustion following CPET as:

> *"I was exhausted. My arms and legs felt like Jell-O. Like they didn't want to do things."*

TABLE 3 | Number of focus group participants with self-described post–exertional malaise symptoms.

Category	Symptom	Daily PEM ($n = 30$)	CPET PEM ($n = 21$)
General			
	Exhaustion	30	20
	Difficulty sleeping/insomnia	8	3
	"Flulike" unspecified	6	2
	Chills	5	1
	Feverish feeling or low-grade fever	3	6
	Drop in temperature	1	—
Cognitive			
	Difficulty thinking clearly or paying attention	24	10
	Memory problems	8	2
	Difficulty finding words when speaking	12	5
Neuromuscular complaints			
	Muscle pain/aches	20	8
	Muscle weakness	10	5
	Joint pain	5	5
	Muscle stiffness	—	2
	Clumsy in movements	4	2
	Muscle convulsions/twitching/spasms	3	3
	Widespread body pain	2	2
Sensory			
	Sensitive to light, sound, smell	11	4
	Blurry vision	—	1
Affect			
	Depression/despair/hopelessness	9	2
	Short temper/irritability	3	—
	Anxiety	3	—
Ear, nose, throat			
	Sore throat	7	3
	"Sore glands" /lymph nodes	1	2
	Sinus pain	1	—
	Congestion	—	1
	Heavy eyes	1	—
Cardiovascular			
	Low blood pressure/near fainting/drop in heart rate	7	2
	Heart racing or pounding	6	4
	Sweating	2	—
Neurological			
	Dizziness/vertigo	6	3
	Headache/migraine	7	6
	Burning pain	5	2
	Tingling/numbness	3	—
	Tremors	2	2
	Slurred speech	1	—
	Blurry vision	1	—

(Continued)

TABLE 3 | Continued

Category	Symptom	Daily PEM ($n = 30$)	CPET PEM ($n = 21$)
Gastrointestinal			
	Nausea	4	4
	Diarrhea	2	1
	Can't control bowels	2	—
	Constipation	2	—
	Cramping	1	—
	Loss of appetite	1	2
	Unspecified	2	—
Pulmonary			
	Difficulty breathing/short on breath	3	5
	Chest pain	3	—
Bladder control		2	—
Dermatologic			
	Hives	1	—

The medical groupings listed on this table are based on the participant's own description of the symptoms. No medical examination was given, nor was there an attempt to verify or qualify self-report symptom.

Similarly, another explained that after CPET:

> *"They just had to pick me up and toss me on the bed that they keep next to the bike. I couldn't even get off the bike and onto the bed myself because I was so exhausted."*

Theme 3b. Cognitive Difficulties

Cognitive difficulties were described as both difficulty thinking clearly/paying attention and difficulty speaking or finding words.

One participant described cognitive difficulties as:

> *"I get what I call molasses-type thinking. So I can still think, but it's harder to think and harder to put ideas together. And sometimes I have to read things over a few times to make them stick in my brain."*

Another explained:

> *"I can't think clearly. I'm unable to make any decisions about anything. Numbers, I feel almost like they're Greek, and they just don't make sense to me anymore at all."*

Thinking clearly was a common complaint as another described:

> *"I can be in a complete fog for a couple of days, and it is hard to make any decisions or remember basic things."*

Similarly, another participant described:

> *"I find it much harder to follow a conversation or a story."*

When describing the difficulty talking or finding words, one participant described:

> *"With speaking verbally, with words that I have known forever. The words weren't there anymore."*

Theme 3c. Neuromuscular Complaints

Patients often complained of neuromuscular symptoms, which included muscle pain/aches and muscle weakness. One participant described the overall muscle pain as:

> *"It's like pain has suddenly flared. They'll just be days that are like every exercise in any position I do just hurts. And I try something different, and it hurts and it hurts, and everything is just very irritated and I just have to stop, you know, I can't keep going."*

When describing muscle weakness, a participant talked about a three-block walk:

> *"I walked three blocks to a CVS and we were in there for maybe 10 min. And I had to leave; my legs were getting so weak they were shaky as if I had just run 10 miles. I had to go out and sit down. We had to go to a coffee place and sit for 20 to 30 min before I could move again to go three blocks back."*

Another participant compared muscle weakness to falling out of a truck:

> *"Like having glue between my muscles and feeling bruised all over, like I fell out of a truck."*

In addition to the three core symptoms, participants described a wide range of other symptoms including sensory sensitivity, feelings of despair, difficulty sleeping, headaches, nausea, and sore throat, among others (**Table 3**). Furthermore, no obvious symptom patterns or subsets emerged, but rather PEM symptoms were very specific to the individual. Additionally, patients reported several individual subcategories of major symptoms. For example, within the musculoskeletal subcategory, participants separately described muscle pain and muscle weakness, and as noted above, within cognitive difficulties, participants saw a distinction between difficulty focusing/thinking clearly and difficulty finding words/delayed talking. Participants also told us they view their physical, cognitive, and emotional symptoms as separate. As one participant explained:

> *"A physical reaction and emotional reaction are just so separate."*

Others explained how the emotional aspects can be tied to the unpredictability of PEM. One participant explained:

> *"You're questioning what awaits you. It's daily and in every single thing you do, everything you commit to. It's hard."*

While not as commonly mentioned as the three core symptoms, many participants described sensitivity to light, sound, and smell as part of PEM. One participant explained:

> *"I have to put on earphones. I need to block the sound. I wear a mask to block the light, wear sunglasses."*

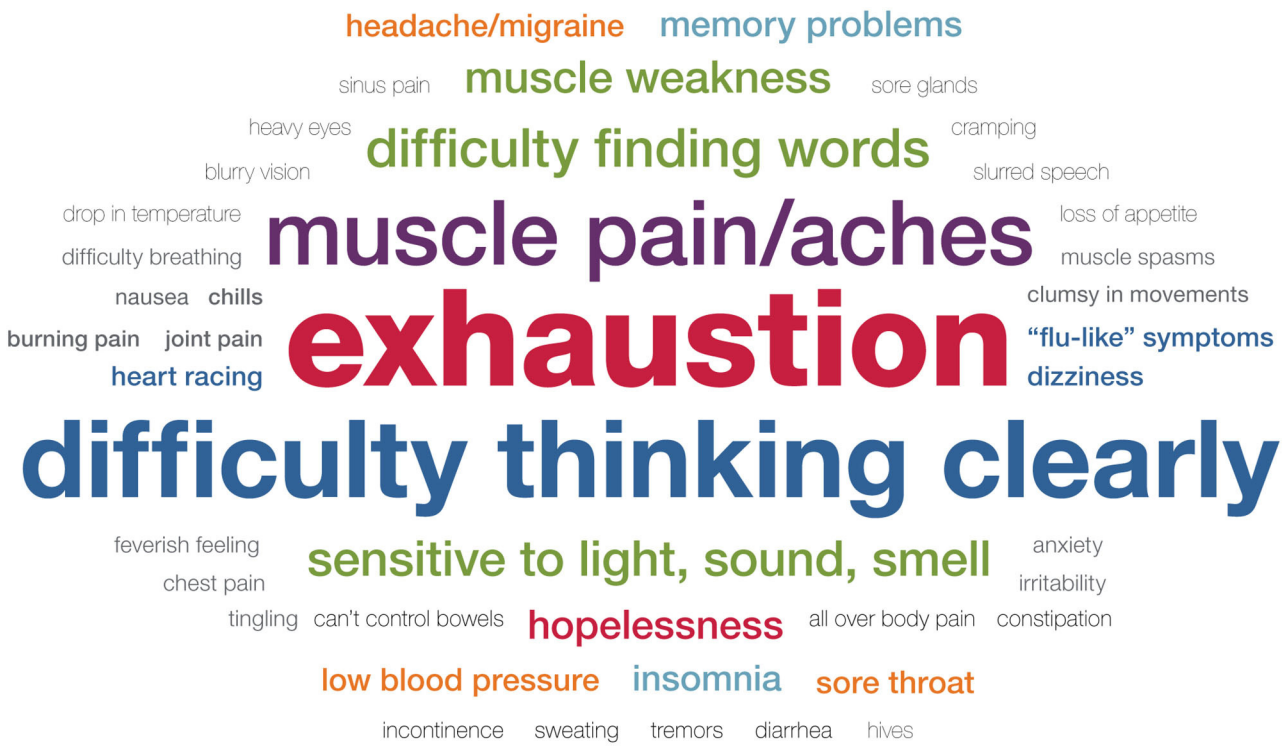


FIGURE 2 | Symptoms of daily post–exertional malaise.

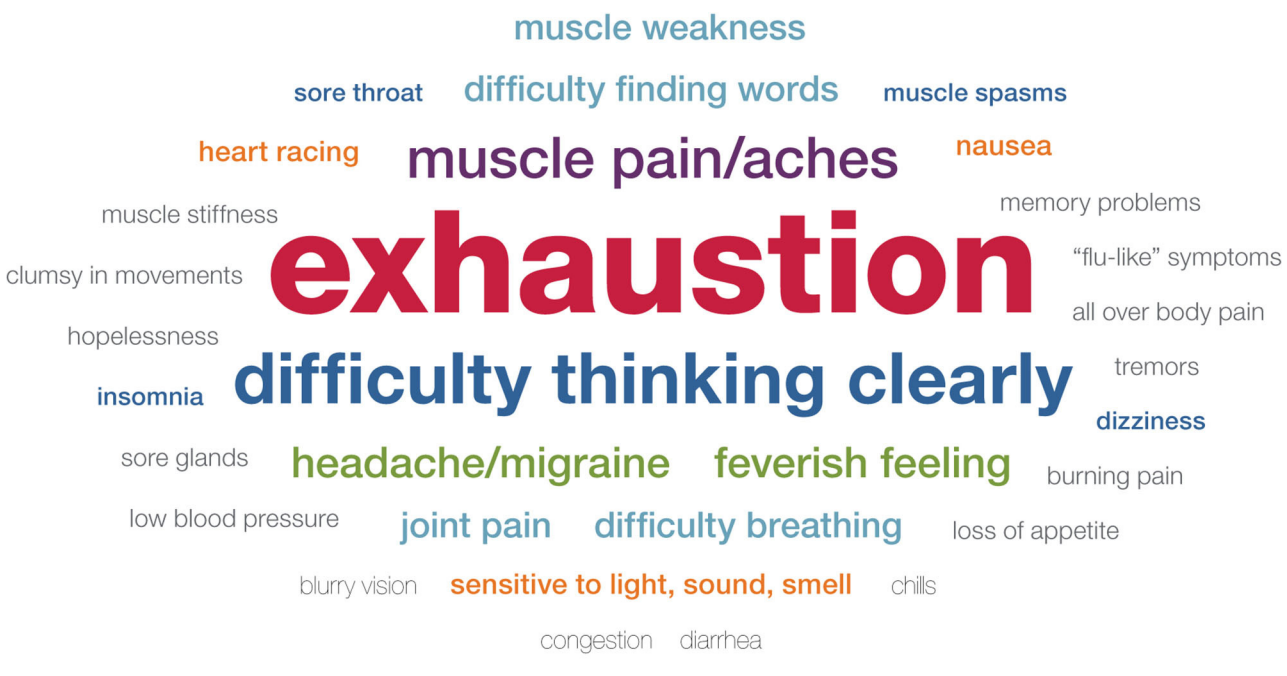


FIGURE 3 | Symptoms of post–exertional malaise following cardiopulmonary exercise test.

When describing sensory sensitivity another participant said:

> *"I have to keep my room dark and noise to a minimum. If that's not good enough, then I have to wear an eye mask and earplugs to decrease the noise."*

Another talked about her sensitivity to noise:

> *"Even what's normal noise for people was painful to me. It would make me cry."*

Theme 4. PEM Following CPET Was More Immediate and of Longer Duration Than PEM in Daily Life

Focus group participants were asked about the timeframes for PEM symptoms, both after exertion in their daily lives and following CPET. We wanted to better understand when PEM symptoms began, peaked, and subsided. Open-ended questions were asked about PEM with no predetermined time frame provided to participants. We analyzed data for post–daily exertion and post-CPET separately (**Figures 4**, **5**). For daily PEM, most participants perceived a delayed onset of symptoms, with nearly half reporting symptoms beginning 12–48 h after exertion. In contrast, more than three-quarters of participants reporting the onset of symptoms following CPET said they began immediately or within several hours. For participants who gave a timeframe for when symptoms of daily PEM peaked, nearly all agreed they peaked within 48 h after exertion, whereas peak in symptoms following CPET was reported sooner, with more than half saying they peaked within 24 h following the test. Approximately half of participants describing PEM from typical daily activities said that symptoms lasted between 2 and 7 days. Half of participants who described PEM symptoms following CPET said the duration was 48–96 h.

Focus group participants contrasted PEM following CPET with PEM in their daily lives. This enabled participants to illustrate how the test pushed them beyond their usual activities. In particular, for many participants PEM following CPET was more immediate than PEM in their daily lives. Fourteen of 18 participants described having symptoms immediately or within a few hours following CPET compared to less than half of participants describing daily PEM. Many participants described sudden and immediate symptoms following the CPET, and for some, these began while still exercising on the bike, as described by this participant:

> *"During the test and right after I felt terrible. I felt I was going to pass out and very out of breath. I felt extremely nauseous like I was going to throw up. I felt very weak, and I was shaking, and they had to help get me off the bike."*

Another participant explained:

> *"As soon as I got off of the bike, I was incredibly wobbly. My muscles weren't working right, like I couldn't get them to work well. So they had me lie flat immediately for about an hour. During that time I started to feel sick. And by the time I got back to the hotel, I was in bed for the rest of the day."*

In addition to having more immediate symptoms following CPET, many also talked about how the CPET symptoms were more severe than PEM symptoms in daily life. As one participant told us:

> *"It was radically different than what normal life is because a lot of energy was expended in a short period of time… My day to day life is much different than that. I don't normally use energy that quickly and in that quantity. It's usually more of a gradual pronounced thing, whether it's working around the house a little bit, doing different chores… Normally that buildup of energy happens over a longer period of time."*

Another explained that:

> *"The symptoms [following CPET] were similar to PEM in day to day life, but they're multiplied by a factor of five, every one of them."*

Another participant agreed the symptoms were similar but more intense:

> *"I'm not sure the symptoms were a whole lot different than what I normally experience. It was just so much all at once."*

Reinforcing that PEM following CPET was more severe than daily PEM, this participant described how she still has not fully recovered:

> *"By the time I got home, I was pretty much a wreck. I was able to walk into the house on my own with my husband helping hold me up but I was unable to function at all. I wasn't brushing my teeth. I was just focused on getting to the bathroom. And I would say it took 4 months before I came back to close to my baseline. I don't think I've ever returned back to what I was before I walked into that test."*

Theme 5. The Manner of Onset of PEM Symptoms Varied

Separate from when PEM began (as shown in **Figures 4**, **5**), we also determined whether participants perceived the onset of symptoms as sudden or gradual. We asked them to describe the transition from before exertion to experiencing symptoms of PEM. Many participants explained that it varied such that some symptoms came on suddenly and other symptoms were more gradual. As one participant explained:

> *"The hand tremors were sudden. The other symptoms I would say were more gradual. The other symptoms being the body pain, the diarrhea, the low-grade fever."*

For participants who reported their symptoms to have a usual onset, they were nearly evenly split between gradual and sudden onset. One participant described the gradual onset of symptoms as:

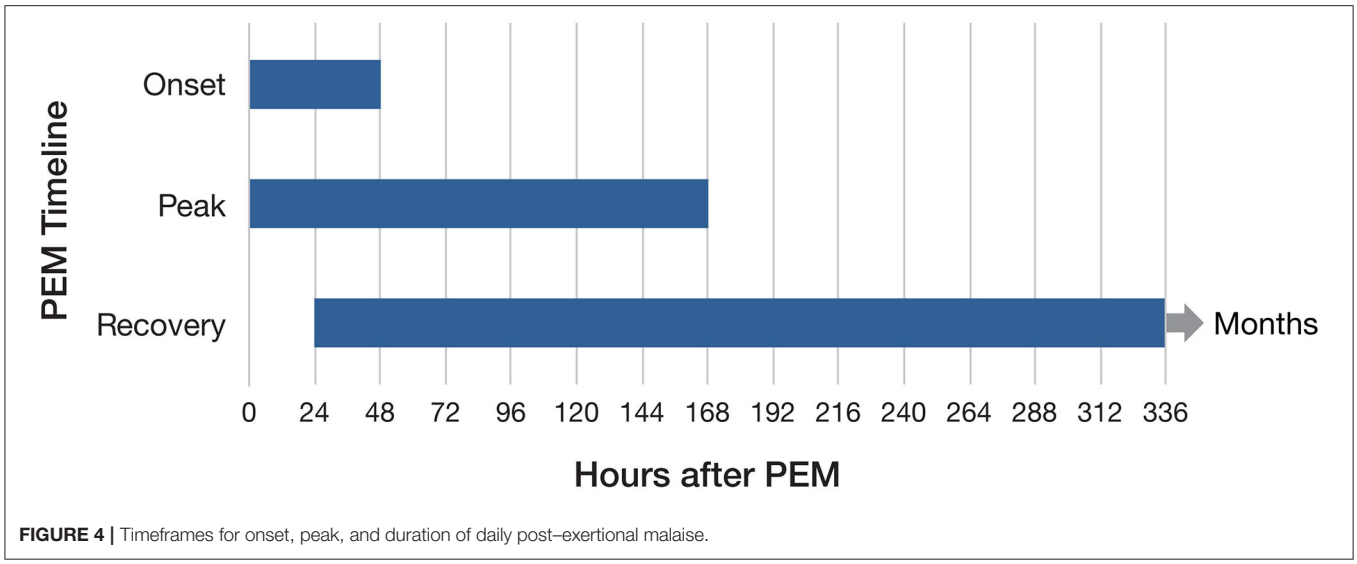


FIGURE 4 | Timeframes for onset, peak, and duration of daily post–exertional malaise.

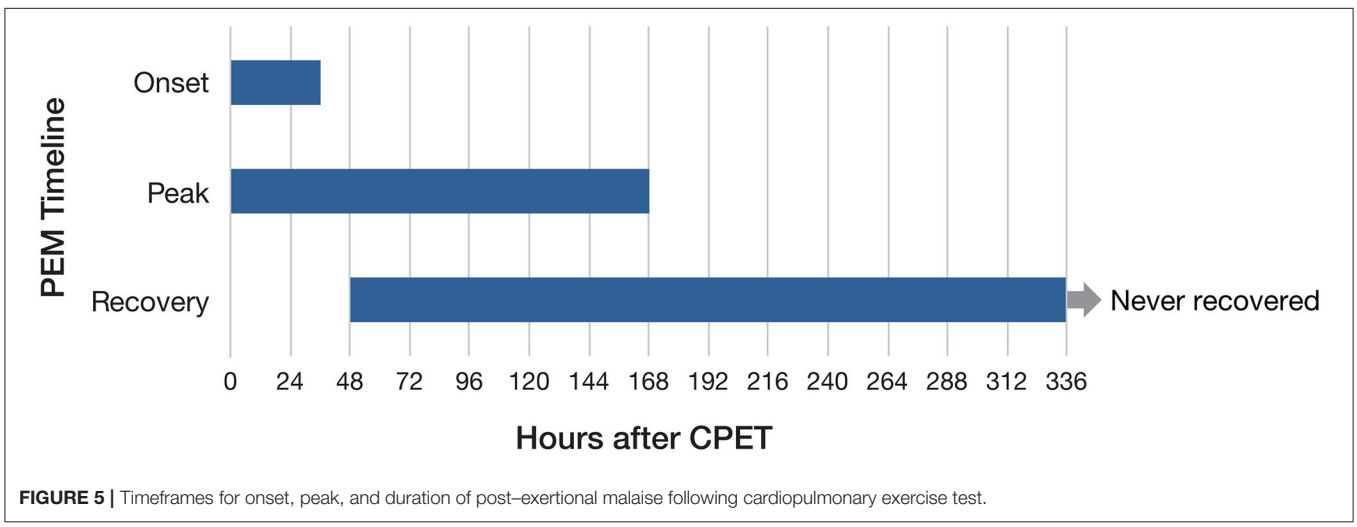


FIGURE 5 | Timeframes for onset, peak, and duration of post–exertional malaise following cardiopulmonary exercise test.

"It was gradual. The symptoms just started coming on, and they just kept getting a little bit worse and a little bit worse and a little bit worse."

Another participant said that for her the onset is usually sudden. She explained:

"The symptoms often happen with an episode of low blood pressure, near fainting experience. And so, when they're combined, it's very sudden. And I can have an episode of almost fainting that comes on within minutes."

Interestingly, 11 focus group participants described experiencing an adrenaline rush while doing an activity before the PEM symptoms came on, both in daily activities and during the CPET. These participants described experiencing "adrenaline," "endorphins," and "euphoria." One participant described this feeling after CPET as:

"I get that high of feeling like, wow, I can do anything…"

Another explained:

"Emotionally right after my test I felt elated."

Another said,

"I had a surge of endorphins and adrenaline during the test."

Theme 6. Complete Rest Was Necessary to Gain Any Relief in PEM Symptoms

When asked what could alleviate PEM symptoms, virtually every participant agreed that while in an episode of PEM, complete rest was absolutely necessary to reduce symptoms. Many participants emphasized that this was not a strategy so much as an outcome. For these participants, complete rest was a "demand from the body." One participant described it as:

"I have to say that the only thing that helps me, that helps those symptoms start to subside is complete rest. There is not a drug, there is nothing. It is complete rest"

Another participant elaborated,

"Complete rest is really the only thing that can facilitate a recovery for me. Basically, I have to stop and put things on hold because I realize when I am weakened with PEM, if I push through… I will end up making the symptoms worse, like going downhill really fast."

Another described:

"It feels like life has all but shut down. It's such a profound undercutting of everything that feels positive, everything that feels like you can make a movement out or forward or up. Somebody was talking about the need to lie down. It's not even just a need. It's an absolute necessity. And I think that PEM just courses through your body and steals everything away that you think of as lively."

When asked to describe what "complete rest" entails, most participants described lying down "absolutely flat" and with as little sensory input as possible. For many, this included ear plugs, darkness, and solitude. Some participants minimized going to the bathroom or had a bedside toilet option. In addition to complete rest, participants described a wide array of practices including over-the-counter and prescription medications, relaxation techniques, special diets, and professional counseling.

Theme 7. Planning and Moderation of Energy Expenditure Was Essential to Avoiding PEM

An interesting theme that emerged during focus group discussions centered around the steps taken by participants to manage activity levels in their daily lives to minimize the effects of PEM. This evolved into an in-depth discussion of pacing and its importance to ME/CFS patients in coping with the illness. Many participants described months or years of learning strategies for mitigating PEM. One participant explained:

"Now that I know how to manage my illness better and I know to always rest more than I need to, I don't have big crashes very often. I'm able to maintain a certain equilibrium as long as I stay within my energy envelope, and I have to be very strict about it. I've missed weddings and funerals and births and birthdays, and I have to be very, very careful, but I'm doing better overall, and my quality of life from day to day is better. And, so, I don't have very many crashes. So, I've kind of finally figured out how to keep that equilibrium, but it's very tentative."

Another participant described the importance of planning ahead:

"If it's a really big thing, say I know that I've got to run a lot of errands that are unavoidable, I will actually look at the calendar and make sure that I don't have anything back to back, there's nothing going on for days after."

Calendar management was an important aspect as a participant described:

"The other part of it is really, really managing my calendar. If I have a doctor's appointment, there is literally nothing else that I can get done that day and I have in my head to be prepared for it. So, I keep lots of tasks lists and things that need to get done, and during the week, I sort of move things around or, you know, change things."

Along with learning to pace themselves, many participants described the compounding aspect of PEM. One participant explained:

"*If I'm already in PEM and overexert, I feel the effects instantly and more intensely, and it lasts deeper and longer*."

Another explained:

"*It's not just an add-on it's a multiplier. It's like an exponential effect on it. So to overdo while you're having PEM is much worse than overdoing when you're not in PEM*."

Although participants talked at length about the importance of moderating activities, many also emphasized that it is not easy, and PEM can be unpredictable. As one participant explained:

"One of the confusing things about symptoms is that they sometimes respond to behavioral changes, so, e.g., not doing certain things in order to not trigger the symptoms. And yet, other times is seems to happen no matter what you try to do differently. It's just not easy to predict or mange."

Finally, many participants talked about the "learning curve" involved in managing activities in order to avoid PEM. Many took years of overexerting and "crashing" before learning better how to manage having ME/CFS. One participant put it this way:

"When I first got sick, I wasn't even familiar with the concept of pacing. So I was constantly in the cycle of overdoing it and crashing and overdoing it and crashing."

Theme 8. The Uncertainty and Debility of PEM Created Despair

We asked focus group participants to describe the emotional aspects of having ME/CFS and PEM in particular. Participants talked at length about living with the unpredictability of PEM and having to adjust their lives to try to avoid severe PEM. Participants described the anxiety of not knowing how long the PEM would last and if they would ever return to their pre-PEM state. One participant summed it up as,

"*I have a kind of post exertional despair that maybe I'll never get better*."

Other respondents described the difficulty in having ME/CFS symptoms on a daily basis and knowing that PEM could occur at any time, such as a participant who said:

"*The real hard part is that you have to choose. You can't just do this. My life is never going to be complete.*"

Another participant explained the unpredictability of PEM:

"It seems unpredictable in my case because I could do the same thing two different days, and 1 day it affects me a lot more than the other day."

Another explained the despair in living with PEM:

"*I have been sick so long that I really don't have a life. I would give anything to have just some part of my life back.*"

Another participant explained the toll PEM has taken on her life,

"*It's substantially different than my life was before, and it's debilitating to my life.*"

PATIENT'S EXPERIENCES OF PEM

Figure 6 diagrams the overall experience of PEM described by focus group participants. Focus group analysis revealed an inability to live a "normal" life as a core aspect of the PEM experience as described by patients. The widespread mind and body symptoms coupled with the unpredictability of triggering events and the timing of onset and recovery of PEM create disabling consequences for ME/CFS patients. While many patients have found some success in managing PEM through pacing and forgoing previously joyful activities, our analyses nevertheless revealed a profound sense of loss and hopelessness in several participants. When describing the symptoms, timeframe, and experience of PEM, many found it helpful to contrast PEM to how "normal" people experience energy. An example is a participant describing her lack of energy throughout the day,

"A normal person's energy is almost energy on demand throughout the day aside from resting every 24 h, but for us, it is such a lag for recuperating energy."

Another explained:

"I feel like I'm just constantly assessing my energy level, and normal people don't do that. They get up in the morning and they pretty much know that they can get through a list of things to do, whereas it can take me weeks to get two or three things done, sometimes none at all."

Focus group participants similarly contrasted their cognitive fatigue with "normal" people as this participant explained:

"You cannot focus on simple things like remembering the name of a lamp… the word won't come. I can't balance a checkbook, can't do any kind of math, can't absorb information. People will be explaining something to you, and it's like they're speaking another language, and my mind will not focus on what they're saying. Those are times I stay home because I shouldn't be driving. I shouldn't be operating any kind of machinery. I shouldn't be cooking because I'm not able to function on a 'normal' basis like everybody else does."

Participants also described the inability to live a "normal" life due to the compounding effect of PEM. One participant explained this in relation to a visit from relatives,

"So my parents decide to come, and it immediately becomes this stressful situation because my mom is a delegator, and she's saying we need to bring our dog and start looking for a dog-friendly hotel and a place to stay with her RV, and she's already delegating and putting this stuff on me without realizing what she's doing. So all of that may not seem like much to a normal healthy person, but that starts building throughout the day."

This lack of living a normal life came up related to adjustments people have made in their daily lives to try to minimize PEM. As one participant described:

"There are all sorts of things we do to try to minimize PEM. I used to listen to music and I don't do that anymore. And there are all sorts of things that when anyone sees me doing this, I look pretty normal. But they don't see all the planning and all the changes I've made in order to do something. Like going outside, I used to hike. I can't do that anymore. But I can still sit down and picnic, and that looks normal to someone else."

DISCUSSION

Focus groups analyses found that PEM is significantly disruptive to the lives of ME/CFS patients, often being unpredictable and difficult to control. Day-to-day activities such as going to the grocery store or having a family member visit can cause PEM, and symptoms are wide ranging with every part of the body affected. This is the first in the literature using purely qualitative methods to study PEM following CPET, and findings point to more immediate and longer-lasting PEM than occurring in patients' day-to-day lives. Participants also described the necessity of lying flat and minimizing sensory input to recover from PEM and tedious planning to try to avoid episodes of PEM. The PEM experience for ME/CFS patients can create a significant emotional impact.

The wide range of symptoms found in the current study has been found in previous research. For instance, a previous review article found that symptoms affect every part of the body (30). Similarly, Chu et al. (11) found over a dozen PEM symptoms affecting all parts of the body and also noted a different cluster of symptoms among men and older patients vs. women. The current study found no discrete symptom groups, and in fact, many individual symptoms were reported by only one or two participants.

In addition to wide-ranging symptoms, the current study found three core PEM symptoms: exhaustion, cognitive difficulties, and neuromuscular complaints. While several studies have found core PEM symptoms, the exact set differs across studies, although nearly all have found some form of physical fatigue, cognitive difficulties, and pain as core symptoms. A recent study (31) used open-ended questionnaire data and

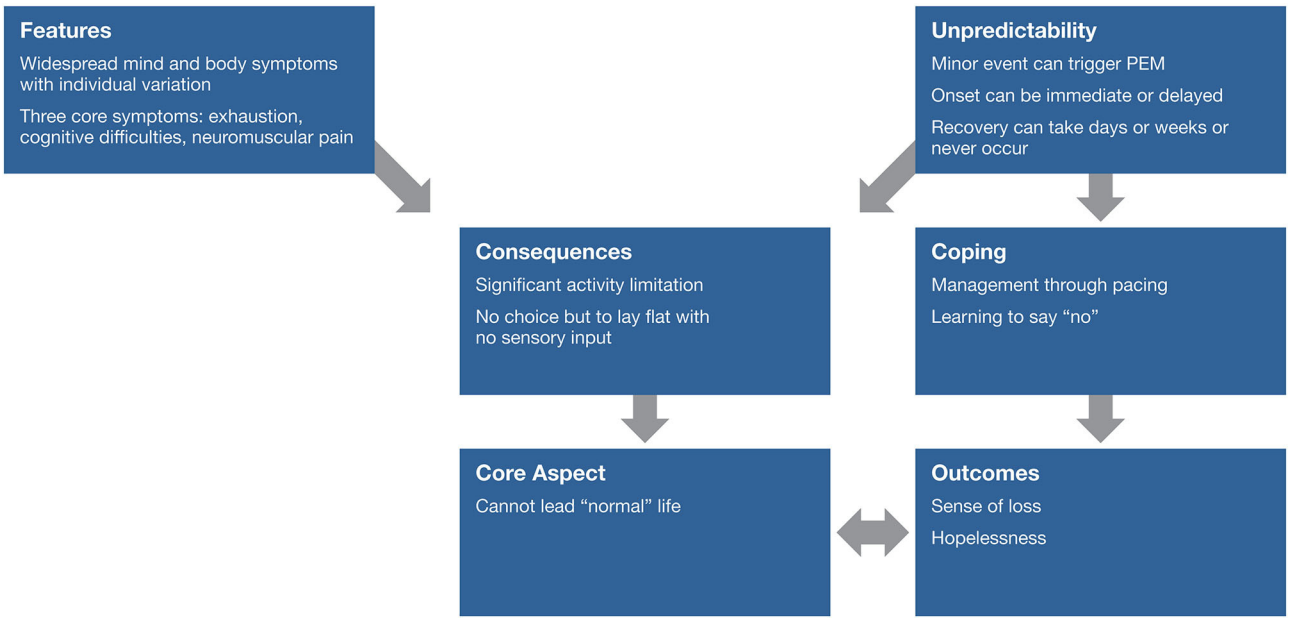


FIGURE 6 | Experience of post–exertional malaise.

predefined symptom categories to determine PEM symptoms in ME/CFS patients following CPET testing. That study found fatigue, muscle/joint pain, and cognitive dysfunction occurred with greatest frequency, overlapping substantially with the current findings. A previous study examining PEM across several countries found fatigue, cognitive dysfunction, disturbed/unrefreshed sleep, and pain presenting as common symptoms across patients (32). Another study found fatigue, difficulty concentrating, difficulty thinking, and muscle pain as the top four PEM symptoms in ME/CFS patients (11), and another found reduced stamina, physical fatigue, cognitive exhaustion, and problems thinking to be the most common PEM symptoms (6). Several studies have found unrefreshed sleep/sleep disturbance as a core PEM symptom reported via questionnaire data (6, 11). Sleep disturbances or unrefreshed sleep was reported by about one-quarter of participants in the current study. One-third of participants in the current study reported sensory sensitivity, higher in frequency than previous studies using questionnaire data (11, 12). Differences across studies may be due to differences in data collection methods and/or differences in the demographics of the study populations. None used a random sample of patients, and most used an exhaustive list of symptoms rather than the open-ended approach used in the current study.

Our findings overlap substantially with a previous focus group study of PEM in ME/CFS patients. That study found five main themes related to symptoms: feeling exhausted or tired, feeling heaviness in the limbs or whole body, sensing fogginess in the head, feeling weakness in the muscles, and feeling drained of energy (10). These findings overlap with the three core symptoms that emerged from the current study. "Cognitive difficulties" is comparable to "sensing fogginess in the head," "muscle pain and weakness" is akin to "feeling weakness in the muscles," and "exhaustion" overlaps with "feeling drained of energy" and "feeling exhausted or tired (11)." This previous study found that physical or cognitive exertion can cause PEM, and basic daily activities such as bathing, dressing, toileting, and reading can be triggers. The current study similarly found a wide range of physical and cognitive activities can trigger PEM, but also found that emotional events are common triggers. Focus group participants described how the emotional stress from family visits or funerals can trigger PEM symptoms. Previous studies using questionnaires have similarly found that emotional distress can cause PEM (6, 11, 33).

The current findings in conjunction with previous studies presenting descriptors of PEM symptoms have translated into multiple labels used for similar symptoms. For example, Chu et al. (11) list "poor concentration" and "difficulty thinking" separately among the top symptoms, whereas Holtzman et al. (6) list "cognitive exhaustion" and "problems thinking" separately. The current study found differences reported by participants between "difficulty focusing or thinking clearly," "memory problems," and "delayed speech or difficulty finding words." These cognitive symptoms may correspond to the neurocognitive domains of attention/executive functioning, memory, and language functioning, although it is also possible that cognitive symptoms that appear to be describing deficits in one domain (e.g., language) are actually the downstream effect of disruption of another domain (e.g., attention/executive functioning). Regardless, in conducting neurocognitive and neuroimaging studies of ME/CFS, the current study may suggest focused assessment of those three cognitive domains and the brain networks that subserve them. The wide variety of ways in which people describe the same experience may cause inconsistencies

in the performance of patient outcome questionnaires used to measure PEM symptoms. Underreporting of symptoms with PEM symptom questionnaires has been previously observed (34). Open-ended questions to allow research participants to express their personal nuances of PEM may be needed in addition to standardized instruments, to accurately discern the onset and severity of PEM in an experimental setting.

PEM in the current study was similar to PEM found in veterans with Gulf War syndrome who rated exercise as painful and fatiguing (35). However, prolonged effects from PEM occurred more often and with greater duration among ME/CFS (13) patients than patients with multiple sclerosis and postpolio syndrome, suggesting that the fatigue experience is multifaceted with variation across patient groups.

The current study is the first in the available literature using qualitative methods to compare daily PEM and PEM following CPET evaluation. Patients emphasized the importance of understanding pre-exertion state to fully assess the effects of PEM. Furthermore, current findings highlight that PEM following CPET was more immediate and of longer duration than PEM in daily life. For both daily and following CPET, participants said recovery took several days to several weeks or even months with more variation seen for daily PEM. These findings are in keeping with the literature. Jason et al. (34) found variability in the duration or onset of fatigue after activity, from an hour to over a day. Another ME/CFS study (10) found PEM came on immediately for some, and for others, it was delayed and that it often depended on the intensity of activity. Many of the current participants also described variability based on the intensity of activity and whether they were already in the midst of a PEM episode.

Also unique to the current study is querying patients about whether they perceived a sudden or gradual onset of PEM symptoms. Like other aspects of ME/CFS, no clear pattern was seen. Regardless of specific symptoms, timing, and onset of PEM, participants nearly all agreed that recovery from PEM required complete rest, and this rest must include as little sensory input as possible.

The need on the part of ME/CFS patients for calendar management and pacing has been seen in several prior studies (36–38). A prior focus group study found that patients can benefit by learning their body signals and by individually tailored activities (36). Clinical and experimental studies should consider providing schedules to participants prior to the study to enable alterations to be made to aid in participant pacing. Likewise, every attempt should be made to allow ME/CFS participants to have complete rest to recover from PEM. Studies of PEM should be cognizant of this need in providing after CPET care for ME/CFS participants. Pacing has also been found as beneficial with postpolio syndrome (39) and chronic pain and fatigue (40).

The current study touched upon the emotional toll of coping with ME/CFS. Researchers and clinicians should take care to appreciate and address the deep despair conveyed by ME/CFS patients. For some, the daily toll of living with ME/CFS has been devastating. There currently exist few treatments for ME/CFS and current clinical protocols focus on management. A previous study found that stress management interventions might alleviate PEM in some patients (41). The current finding that emotional triggers can cause PEM adds additional evidence that stress management could be beneficial.

STUDY LIMITATIONS

There are several limitations to this study. First, responses were dependent on retrospective recall of participant experiences with CPET evaluation. Second, all of the participants provided their diagnostic information strictly through self-report. No attempt to understand whether participants would fulfill a criteria-based diagnosis was made as part of this study. These participants are best described as persons who reported a medical diagnosis of ME/CFS and had a physician refer them for ME/CFS specific CPET testing in the community. The current research team has had extensive experience with review of medical records for ME/CFS; the vast majority of diagnoses are made by practitioner gestalt rather than by published diagnostic criteria. These results reflect how PEM is described by persons in the general ME/CFS community. Third, focus groups were conducted over the telephone, making it more difficult for the moderator to control and manage discussions. Some participants may not have fully engaged with the focus group, and at times, discussions went on tangents unrelated to the original query. Despite these limitations, almost all participants contributed substantially to discussions, and the moderator was able, to a large extent, to keep discussions focused and on track.

IMPLICATIONS FOR FUTURE RESEARCH AND CLINICAL APPLICATION

The current study points to several areas that warrant further exploration. One such area is determining the most effective tools clinicians can provide to patients for managing PEM. Because of the lack of effective treatments for PEM, some ME/CFS researchers have suggested pacing as a therapeutic option to be used by practitioners (42). Focus group participants in the current study talked at length about the importance of planning and moderation of energy expenditure to avoid PEM, and many described a long period of trial and error before gaining any success with moderating PEM. Although widely discussed in patient forums, this topic has little empirical research and should be studied further. In particular, future research could identify specific pacing regimens that prove most beneficial to specific subtypes of PEM.

The current study also points to the need for researchers studying PEM in ME/CFS patients to be cognizant of the effects of travel on PEM. For example, patients should arrive several days prior to starting participation to foster recovery from travel. Additionally, it is important to fully understanding a patient's pre-CPET state to accurately assess the effects of the test on PEM symptoms. ME/CFS patients described a fluid baseline, which could change quickly and was difficult to anticipate. Assessments should be performed before the patient travels to get an accurate

understanding of the patient's physical, cognitive, and emotional state prior to the experiment. Researchers should also note that PEM induced by CPET differs from daily PEM, and symptoms and timeframes from the experimental setting might not fully correspond with those found in daily PEM.

CONCLUSION

ME/CFS patients describe PEM as all-encompassing with symptoms affecting every part of the body, difficult to predict or manage, and requiring complete bedrest to fully or partially recover. Through in-depth focus group discussions, ME/CFS patients describe PEM as disruptive to living a self-described "normal" life, sometimes leading to hopelessness or despair. Given the extensive variability in PEM symptoms and timeframes for onset, peak, and recovery, further research identifying subtypes of PEM could lead to better targeted therapeutic options.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available The data are all textual and cannot be provided without breaching confidentiality.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by NIH Combined NeuroScience Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BS designed the study, collected and analyzed the data, wrote, and edited the manuscript. AW, AG, and RS collected and analyzed the data and edited the manuscript. JS participated in writing and editing the paper and approved of the final version. AN contributed to supervision of the work, participated in writing and editing the paper, and approved the final version. BW contributed to supervision of the work, data collection, data analysis, writing and editing the paper, and approved the final version. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported (in part) by the Intramural Research Program of the NIH, National Center for Complementary and Integrative Health, National Institute of Nursing Research, National Institute of Neurological Diseases and Stroke, and National Institute of Mental Health.

ACKNOWLEDGMENTS

We would like to thank Staci Stevens and Mark Van Ness for sharing their experiences with cardiopulmonary exercise testing and aiding us in finding appropriate focus group participants. We would also like to thank Christine Wishnoff for her assistance with focus groups, Bryan Ewsichek for his assistance with graphics, and Richard Nahin for comments on a previous draft. Finally, we would like to thank the entire NIH ME/CFS Study Group.

REFERENCES

1. Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner AM, et al. Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatments protocols. *J Chron Fatig Syndr.* (2003) 11:7–115 doi: 10.1300/J092v11n01_02
2. Clayton EW. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: an IOM report on redefining an illness. *JAMA*. (2015) 313:1101–2. doi: 10.1001/jama.2015.1346
3. Unger ER, Lin JS, Brimmer DJ, Lapp CW, Komaroff AL, Nath A, et al. CDC grand rounds: chronic fatigue syndrome advancing research and clinical education. *MMWR Morb Mortal Wkly Rep.* (2016) 65:1434. doi: 10.15585/mmwr.mm655051a4
4. *IOM Report*: Available online at: https://www.ncbi.nlm.nih.gov/books/NBK274235/
5. *(CFSAC 2015)* Available online at: http://www.hhs.gov/advcomcfs/recommendations/2015 08 18 19 recommendations.pdfCFSAC recommendations (*http://www.hhs.gov/advcomcfs/recommendations/2015 08 18 19 recommenda*tions.pdf)
6. Holtzman CS, Bhatia S, Cotler J, Jason LA. assessment of post exertional malaise (pem) in patients with myalgic encephalomyelitis (me) and chronic fatigue syndrome (cfs): a patient driven survey. *Diagnostics.* (2019) 9:10026. doi: 10.3390/diagnostics9010026
7. Stormorken E, Jason LA, Kirkevold M. Fatigue in adults with post-infectious fatigue syndrome: a qualitative content analysis. *BMC Nurs.* (2015) 14:64. doi: 10.1186/s12912-015-0115-5
8. Tong A, Craig JC. Tuning into qualitative research-a channel for the patient voice. clin j am soc nephrol. (2016). 11:1128–30. doi: 10.2215/CJN.05110516
9. Williams AM, Christopher G, Jenkinson E. The psychological impact of dependency in adults with chronic fatigue syndrome/myalgic encephalomyelitis: a qualitative exploration. *J Health Psychol.* (2019) 24:264–275. doi: 10.1177/1359105316643376
10. Keech A, Sandler CX, Vollmer Conna U, Cvejic E, Lloyd AR, Barry BK. Capturing the post exertional exacerbation of fatigue following physical and cognitive challenge in patients with chronic fatigue syndrome. *J Psychosom Res.* (2015) 79:537–49. doi: 10.1016/j.jpsychores.2015.08.008
11. Chu L, Valencia IJ, Garvert DW, Montoya JG. Deconstructing post exertional malaise in myalgic encephalomyelitis/ chronic fatigue syndrome: a patient centered, cross sectional survey. *PLoS ONE.* (2018) 13:e0197811. doi: 10.1371/journal.pone.0197811
12. McManimen SL, Jason LA. Post exertional malaise in patients with me and cfs with comorbid fibromyalgia. *SRL Neurol Neurosurg.* (2017) 3:22–7.
13. Cotler J, Holtzman C, Dudun C, Jason LA. A brief questionnaire to assess post exertional malaise. *Diagnostics.* (2018) 8:30066. doi: 10.3390/diagnostics8030066
14. Whitehead LC, Unahi K, Burrell B, Crowe MT. The experience of fatigue across long-term conditions: a qualitative meta-synthesis. *J Pain Symptom Manage.* (2016) 52:131–43.e1. doi: 10.1016/j.jpainsymman.2016.02.013
15. Tjell C, Iglebekk W, Borenstein P. Can a chronic BPPV with a history of trauma be the trigger of symptoms in vestibular migraine, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and Whiplash Associated Disorders (WAD)? A retrospective cohort study. *Otol Neurotol.* (2019) 40:96–102. doi: 10.1097/MAO.0000000000002020

16. Watson A, van Kessel K. Cancer survivors' experiences and explanations of postcancer fatigue: an analysis of online blogs. *Cancer Nurs*. (2018). 41:117–23. doi: 10.1097/NCC.0000000000000460
17. Twomey R, Yeung ST, Wrightson JG, Millet GY, Culos-Reed SN. Post-exertional malaise in people with chronic cancer-related fatigue. *J Pain Symptom Manage*. (2020) 60:407–16. doi: 10.1101/2019.12.12.19014829
18. ClinicalTrials.gov [Internet]. (2017). *Identifier NCT02669212, Myalgic Encephalomyelitis Chronic Fatigue at the National Institutes of Health)* Bethesda, MD: National Library of Medicine (US) (2017). [about 4 screens]. Available online at: http://clinicaltrials.gov/ct/show/NCT00287391?order=1 (accessed March 22, 2018).
19. Kroll T, Barbour R, Harris J. Using focus groups in disability research. *Qual Health Res*. (2007). 17:690–8. doi: 10.1177/1049732307301488
20. Stebbins RA. *Exploratory Research in the Social Sciences*. Thousand Oaks, CA: Sage (2001) doi: 10.4135/9781412984249
21. Glaser BG, Strauss AL. *The Discovery of Grounded Theory: Strategies for Qualitative Research.* New York: Aldine. (1967) doi: 10.1097/00006199-196807000-00014
22. Strauss A. Corbin J. *Basics of Qualitative Research: Grounded Theory Procedures and Techniques*. Newbury Park: Sage Publications. (1990)
23. Creswell C. *Designing and Conducting Mixed Methods Research.* Los Angeles: Sage (2011).
24. Mezzani A. Cardiopulmonary exercise testing: basics of methodology and measurements. *Ann Am Thorac Soc.* (2017) 14(Suppl. 1):S3–S11. doi: 10.1513/AnnalsATS.201612-997FR
25. VanNess JM, Stevens SR, Bateman L, Stiles TL, Snell CR. Postexertional malaise in women with chronic fatigue syndrome. *J Womens Health*. (2010) 19:239–44. doi: 10.1089/jwh.2009.1507
26. Broderick G, Ben Hamo R, Vashishtha S, Efroni S, Nathanson L, Barnes Z, et al. Altered immune pathway activity under exercise challenge in gulf war illness: an exploratory analysis. *Brain Behav Immun.* (2013) 28:159–69. doi: 10.1016/j.bbi.2012.11.007
27. Snell CR, Stevens SR, Davenport TE, Van Ness JM. Discriminative validity of metabolic and workload measurements for identifying people with chronic fatigue syndrome. *Phys Ther*. (2013) 93:1484–92. doi: 10.2522/ptj.20110368
28. Saunders B, Sim J, Kingstone T, Baker S, Waterfield J, Bartlam B, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. *Qual Quant*. (2018) 52:1893. doi: 10.1007/s11135-017-0574-8
29. VERBI Software. *MAXQDA*. (2020). Berlin: VERBI Software. (2019). Available online at: maxqda.com.
30. Bested AC, Marshall LM. Review of myalgic encephalomyelitis/chronic fatigue syndrome: an evidence-based approach to diagnosis and management by clinicians. *Rev Environ Health*. (2015). 30:223–49. doi: 10.1515/reveh-2015-0026
31. Mateo LJ, Chu L, Stevens S, Stevens J, Snell CR, Devanport T, et al. Post-exertional symptoms distinguish myalgic encephalomyelitis/chronic fatigue syndrome subjects from healthy controls. *Work*. (2020). 66:265–75. doi: 10.3233/WOR-203168
32. Collin SM, Heron J, Nikolaus S, Knoop H, Crawley E. Chronic fatigue syndrome (CFS/ME) symptom-based phenotypes and 1-year treatment outcomes in two clinical cohorts of adult patients in the UK and the Netherlands. *J Psychosom Res*. (2018). 104:29–34. doi: 10.1016/j.jpsychores.2017.11.007
33. May M, Milrad SF, Perdomo DM, Czaja SJ, Fletcher MA, Jutagir DR, et al. Post-exertional malaise is associated with greater symptom burden and psychological distress in patients diagnosed with chronic fatigue syndrome. *J Psychosom Res*. (2020). 129:109893. doi: 10.1016/j.jpsychores.2019.109893
34. Jason LA, Evans M, So S, Scott J, Brown A. Problems in defining post exertional malaise. *J Prev Interv Commun.* (2015) 43:20–31 doi: 10.1080/10852352.2014.973239
35. Lindheimer JB, Stegner AJ, Wylie GR, Klein-Adams JC, Almassi NE, Ninneman JV, et al. Post-exertional malaise in veterans with gulf war illness. *Int J Psychophysiol*. (2020). 147:202–12. doi: 10.1016/j.ijpsycho.2019.11.008
36. Larun L, Malterud K. Finding the right balance of physical activity: a focus group study about experiences among patients with chronic fatigue syndrome. *Patient Educ Couns*. (2011) 83:222–6. doi: 10.1016/j.pec.2010.05.027
37. Jason LA, Brown M, Brown A, Evans M, Flores S, Grant-Holler E, et al. Energy conservation/envelope theory interventions to help patients with myalgic encephalomyelitis/chronic fatigue Syndrome. *Fatigue*. (2013) 1:27–42. doi: 10.1080/21641846.2012.733602
38. Brown AA, Evans MA, Jason LA. Examining the energy envelope and associated symptom patterns in chronic fatigue syndrome: does coping matter?. *Chronic Illn*. (2013) 9:302–11. doi: 10.1177/1742395313478220
39. Jubelt B. Post-polio syndrome. *Curr Treat Options Neurol*. (2004) 6:87–93. doi: 10.1007/s11940-004-0018-3
40. Antcliff D, Keenan AM, Keeley P, Woby S, McGowan L. Survey of activity pacing across healthcare professionals informs a new activity pacing framework for chronic pain/fatigue. *Musculoskeletal Care*. (2019) 17:335–345. doi: 10.1002/msc.1421
41. Hall DL, Lattie EG, Antoni MH, Fletcher MA, Czaja S, Perdomo D, et al. Stress management skills, cortisol awakening response, and post-exertional malaise in chronic fatigue syndrome. *Psychoneuroendocrinology*. (2014) 49:26–31. doi: 10.1016/j.psyneuen.2014.06.021
42. Goudsmit EM, Nijs J, Jason LA, Wallman KE. Pacing as a strategy to improve energy management in myalgic encephalomyelitis/chronic fatigue syndrome: a consensus document. Disabil Rehabil. (2012). 34:1140–7. doi: 10.3109/09638288.2011.635746

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership