INTEGRITY OF THE AUTONOMIC NERVOUS SYSTEM IN PSYCHIATRIC AND NEUROLOGICAL DISORDERS

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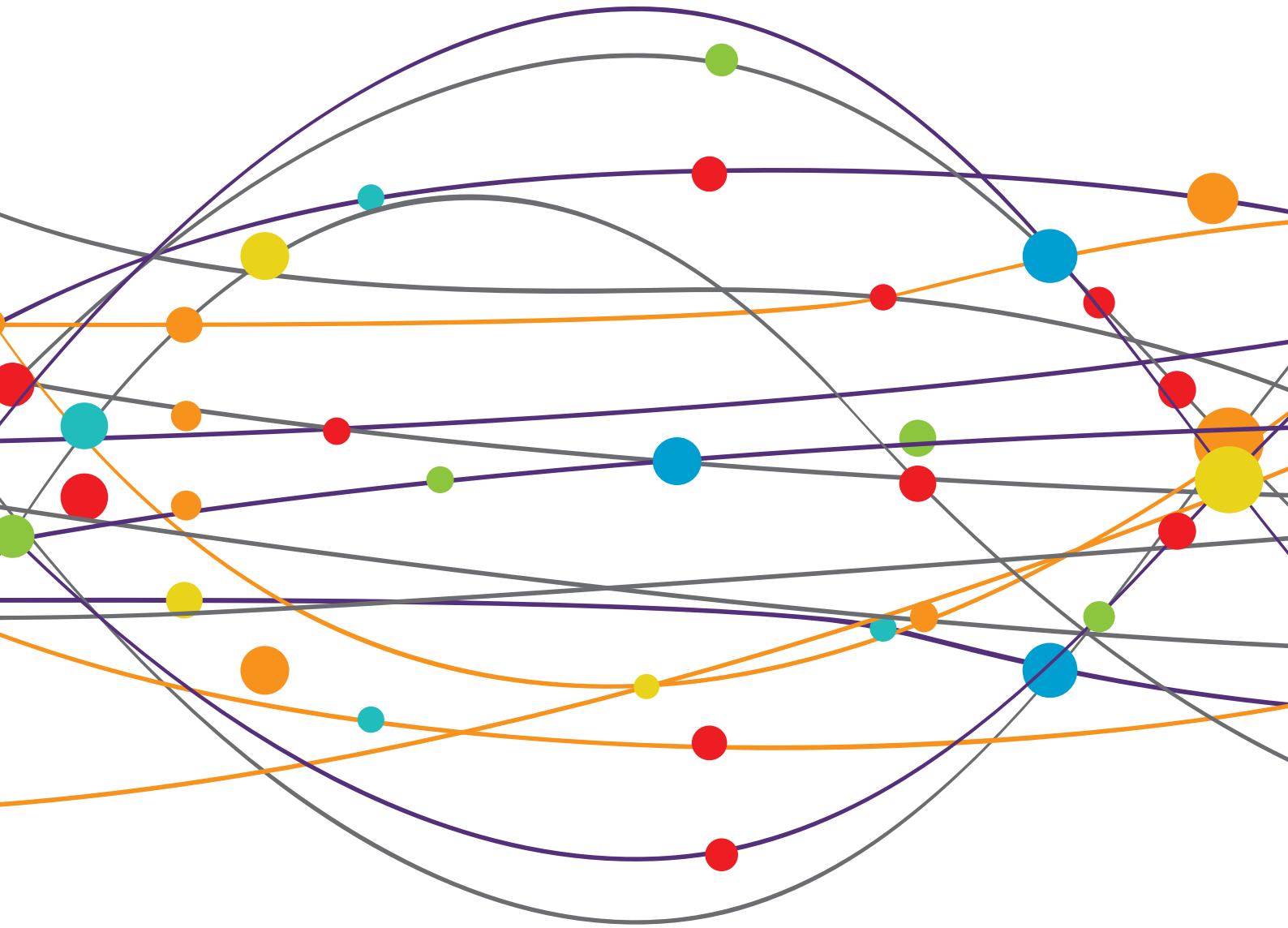

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INTEGRITY OF THE AUTONOMIC NERVOUS SYSTEM IN PSYCHIATRIC AND NEUROLOGICAL DISORDERS

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EDITORIAL
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Editorial: Integrity of the Autonomic Nervous System in Psychiatric and Neurological Disorders

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Keywords: autonomic, psychiatry, neurology, assessment, treatment

Editorial on the Research Topic

Integrity of the Autonomic Nervous System in Psychiatric and Neurological Disorders

The autonomic nervous system is an essential neural control network of the human body that maintains physiologic balance. It regulates function of vital systems such as the cardiovascular system, the gastrointestinal system, and the skin. Autonomic neuronal structures permeate and innervate the entire human organism, managing its autonomic functions largely independent from consciousness and thereby securing its survival. Professor Phillip Low, a pioneer of autonomic neurology, has once referred to the autonomic nervous system as the "Cinderella of Medicine," a field of science, which attracted distinct interest in the scientific community but was limited by a substantial lack of coherent knowledge (1). When Low and a handful of out-of-the-box-thinking scientists such as Sir Roger Bannister from London, a famous neurologist and record-breaking middle-distance athlete, as well as David Robertson from Nashville, a distinguished neurologist and space physiologist, first embarked on the endeavor to explore the autonomic nervous system in the 1960s and 1970s, they could probably not foresee the future impact of their research. Nowadays, their observations provide a basis for diagnosis and treatment of highly prevalent and debilitating disorders, including metabolic disorders such as diabetes and neurodegenerative disorders such as Parkinson's disease.

Over the past decades, techniques to assess structural and functional integrity of the autonomic nervous system have become paramount in understanding the pathophysiology of these diseases (2–4). Functional integrity of the sudomotor and cardiovascular autonomic nervous system can be tested non-invasively using well-established techniques such as quantitative sudomotor axon-reflex test, heart rate variability assessment and tilt table test (5). Structural integrity of the autonomic nervous system can be assessed using imaging of autonomic cerebral control centers such as the insular cortex as well as by immunohistochemical analysis of small nerve fibers in cutaneous punch biopsies (6, 7). Designing and further advancing these techniques helped improving our pathophysiological understanding of autonomic nervous system disorders and allowed identification of novel diagnostic and therapeutic targets. For example, Parkinson's disease has long been believed to be a primarily central synucleinopathy that affects brain regions of motor control. However, recent research has provided evidence that the peripheral autonomic nervous system is affected by deposition of misfolded alpha-synuclein long before motor control is clinically impaired. In these premotor disease stages the pathological form of alpha-synuclein can be detected in peripheral small autonomic nerve fibers of the skin, introducing a potential target for immunotherapy and other forms of targeted diagnostic and therapeutic approaches (8–10). As part of this article collection, Hong et al. reported an increased risk for atrial fibrillation in Parkinson's disease highlighting the significance of cardiac dysautonomia in these patients. In this

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population-based study in 15,434 newly diagnosed patients with Parkinson's disease, the authors observed a significant predictive association between atrial fibrillation and Parkinson's disease in premotor and early but not in later disease stages. This observation highlights the potential diagnostic value of atrial fibrillation in prodromal and early Parkinson's disease as well as the potential impact of cardiac dysautonomia on cardiovascular risk in these patients.

While neurodegenerative synucleinopathies have recently been in the spotlight of autonomic neuroscience, autonomic dysfunction can in fact occur in a variety of neurological disorders such as diabetic or amyloidosis-related neuropathies, acute ischemic stroke, multiple sclerosis, neuroinflammatory diseases as well as psychiatric disorders such as anxiety and depression. This is of high clinical relevance as autonomic dysfunction can reduce quality of life, increase mortality, and increase cardiovascular risk. For example, autonomic impairment has been shown to independently increase mortality in patients with diabetic autonomic neuropathy and increase risk for cardiovascular disease in patients with depression (11, 12). Moreover, autonomic dysfunction seems to be associated with cognitive impairment as reported by Forte et al. in their systematic review, which is part of this article collection. In 20 studies comprising data from 19,431 study participants, they found that both increased sympathetic activity and decreased parasympathetic activity are associated with cognitive impairment. Notably, in the majority of included studies these associations were independent from demographic and clinical characteristics supporting a direct link between impairment of autonomic and cognitive functional integrity. Viewed in conjunction with the complex etiopathogenesis of autonomic dysfunction these observations highlight the need for personalized diagnostic and therapeutic strategies for disorders of the autonomic nervous system. Possible keys to improve early detection and personalized treatment of autonomic dysfunction comprise interdisciplinary symptom-driven clinical management strategies, advancement of assessment and further elucidation of the pathophysiological pathways leading to dysautonomia. Thus, interdisciplinary research on the autonomic nervous system has the potential to help improve quality of life, reduce mortality, and improve cardiovascular health. This would have implications for diseases that extend far beyond classic autonomic disorders such as diabetic neuropathy. Our article collection aims to provide a platform to foster autonomic neuroscience.

AUTHOR CONTRIBUTIONS

TS drafted the first version of the manuscript. BM-W and KB revised the manuscript for intellectual content.

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In our capacity as guest editors we would like to express our sincere appreciation to the authors of this Research Topic.

REFERENCES

1. Morgan J. Phillip Low: the autonomic expert. *Lancet Neurol.* (2018) 17:743. doi: 10.1016/S1474-4422(17)30287-9
2. Freeman R. Autonomic peripheral neuropathy. *Lancet*. (2005) 365:1259–70. doi: 10.1016/s0140-6736(05)74815-7
3. Braak H, Sastre M, Bohl JR, de Vos RA, Del Tredici K. Parkinson's disease: lesions in dorsal horn layer I, involvement of parasympathetic and sympathetic pre- and postganglionic neurons. *Acta Neuropathol.* (2007) 113:421–9. doi: 10.1007/s00401-007-0193-x
4. Tsukita K, Sakamaki-Tsukita H, Tanaka K, Suenaga T, Takahashi R. Value of *in vivo* α-synuclein deposits in Parkinson's disease: a systematic review and meta-analysis. *Mov Disord.* (2019) 34:1452–63. doi: 10.1002/mds.27794
5. Ziemssen T, Siepmann T. The investigation of the cardiovascular and sudomotor autonomic nervous system-a review. *Front Neurol.* (2019) 10:53. doi: 10.3389/fneur.2019.00053
6. Low PA. Testing the autonomic nervous system. *Semin Neurol*. (2003) 23:407–21. doi: 10.1055/s-2004-817725
7. Siepmann T, Illigens BM, Barlinn K. Alpha-synuclein in cutaneous small nerve fibers. *Neuropsychiatr Dis Treat*. (2016) 12:2731–5. doi: 10.2147/NDT.S117423
8. Wang N, Gibbons CH, Lafo J, Freeman R. α-Synuclein in cutaneous autonomic nerves. *Neurology*. (2013) 81:1604–10. doi: 10.1212/WNL.0b013e3182a9f449
9. Doppler K, Ebert S, Üçeyler N, Trenkwalder C, Ebentheuer J. Volkmann J, et al. Cutaneous neuropathy in Parkinson's disease: a window into brain pathology. *Acta Neuropathol.* (2014) 128:99–109. doi: 10.1007/s00401-014-1284-0
10. Zella, S.M.A., Metzdorf J, Ciftci E, Ostendorf F, Muhlack S, Gold R, et al. Emerging immunotherapies for Parkinson disease. *Neurol Ther*. (2019) 8:29–44. doi: 10.1007/s40120-018-0122-z
11. Pop-Busui R, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, et al. Effects of Cardiac Autonomic Dysfunction on Mortality Risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care.* (2010) 33:1578–84. doi: 10.2337/dc10-0125
12. Fiedorowicz JG. Depression and cardiovascular disease: an update on how course of illness may influence risk. *Curr Psychiatry Rep.* (2014) 16:492. doi: 10.1007/s11920-014-0492-6

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ORIGINAL RESEARCH
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Reduction in Parasympathetic Tone During Sleep in Children With Habitual Snoring

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Introduction: Changes in the autonomic nervous system due to Obstructive Sleep Apnea (OSA) during the life span have been described. Some pediatric studies have shown cardiovascular effects in children who do not fit the criteria for OSA; namely children with mild sleep disordered breathing.

Objective: We investigated heart rate variability (HRV) during sleep in children with chronic snoring and flow limitation events during sleep.

Methods: Ten children and adolescents with chronic snoring and an apnea hypopnea index < 1, associated to high Respiratory Index, and 10 controls matched for age, gender, and Tanner stage were monitored following one night of habituation in the sleep laboratory. HRV was studied at each sleep stage. The time and frequency domains were calculated for each 5-min period.

Results: All patients were chronic heavy snorers. They presented an apnea hypopnea index $= 0.8$, respiratory disturbance index $= 10.2$/h with lowest O2 saturation 96.1 $\pm$ 2.4%. The total power of HRV was decreased in all stages ($p < 0.05$). There was also a decrease in NN50 and pNN50 during all sleep stages compared to healthy controls ($p = 0.0003$ and $p = 0.03$, respectively).

Conclusion: A reduction in parasympathetic tone was found in the patient group. This may represent an autonomic impairment during sleep in children with mild SDB. A reduction in HRV in children with habitual snoring could be associated with possible increases in cardiovascular risk in adulthood.

Significance: The study indicates that children with habitual snoring have important parasympathetic tone changes during sleep.

Keywords: children, sleep-disordered-breathing, habitual snoring, Parasympatethic tone, heart-rate-variability, sleep, snoring

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INTRODUCTION

Sleep disordered breathing (SDB) in children is associated with abnormal daytime behavior (Guilleminault et al., 1982) and neurobehavioral morbidity such as behavior problems (Ali et al., 1993; Chervin et al., 2006), cognitive deficits (Blunden et al., 2000; Halbower et al., 2006), and poor academic performance (Gozal, 1998; Urschitz et al., 2003). Behavior problems also include

attentional regulation, affective information processing, and behavioral and physiological flexibility (Thayer and Lane, 2000). Moreover, according to Jackman et al. (2012), there is a window of opportunity when children just have behavior changes without cognitive deficits. It has been shown that these symptoms may also occur with low apnea hypopnea index (AHI) (O'Brien et al., 2004). Snoring associated with flow limitation and increased respiratory rate during sleep in children might also be associated with similar complaints (Guilleminault et al., 2004). A sign of abnormal sleep is the increase in cyclic alternating pattern (CAP) rate in these cases, even if the AHI is lower than 1 event/h (Lopes and Guilleminault, 2006). Unlike adults, children with obstructive sleep apnea (OSA) do not usually develop high blood pressure (BP), (Guilleminault et al., 2004) although the levels of overnight urinary noradrenaline and adrenaline are increased and changes occur in the sympathetic tone that may contribute to the cardiovascular consequences of the condition (O'Driscoll et al., 2011). Children with high BP usually have a co-morbid condition such as obesity (Horne et al., 2018; Walter et al., 2018) that may lead to both abnormal breathing during sleep and even higher BP. A subgroup of normal-weight children with SDB may even present low BP (Guilleminault et al., 2004).

There has been some interest in evaluating the autonomic sympathovagal balance in subjects with OSA by heart rate variability (HRV). Investigations were previously performed in adults (Somers et al., 1995) and also in children with severe OSA (Baharav et al., 1999). The authors have been developing studies in which they investigated autonomic balance in children with snoring and low AHI (Kwok et al., 2011; Walter et al., 2013; Nisbet et al., 2014). However, upper-area resistance can be detected by **esophageal pressure** monitoring, which is an indirect measurement of **upper** airway collapse. We hypothesize that children who do not fit the criteria for OSA (AHI < 1) but have chronic snoring and flow limitation due to upper airway collapse in events during sleep can show reduced HRV.

METHODS

Sample

Ten children (7 boys) with chronic snoring and flow limitation during nocturnal sleep between 8 and 16 years of age and 10 individually matched controls were studied.

Patients had been referred to a sleep disorders clinic for daytime complaints that varied from fatigue, tiredness, sleepiness, and reported nocturnal sleep disruption with variable difficulties in going back to sleep. Children, with parental help, responded to the "Pediatric Sleep Questionnaire" (Chervin et al., 2000). Seven days of sleep diaries indicating bedtime, nocturnal events and daytime activities were collected according to child activity (Spruyt and David Gozal, 2011). All patients and members of the control group underwent nocturnal polysomnography.

Inclusion criteria: All children whose parents had consented to their participation and agreed to the anonymous use of their polysomnographic data, exhibiting the presence of regular snoring during sleep associated with flow limitation that did not meet the criteria of hypopnea as defined by the International Classification of Sleep Disorders 3rd edition (2014), (American Academy of Sleep Medicine, 2014) but with respiratory disturbance index (RDI) >2 events/h based on nasal cannula-pressure transducer or esophageal pressure monitoring. Children were recruited during a 2-month period. These children were followed up in order to properly treat their SDB.

Exclusion criteria: Use of medication of any type in the last 3 months, presence of restless-leg syndrome or parasomnia such as night terrors, sleep walking, bruxism, as shown by interview or questionnaire, and a reported associated disorder including migraine headache in the morning. Obesity, as determined by body mass index (BMI) adjusted for ethnicity, history of premature birth, and periodic leg movement score$>$ 5 event/hour were also criteria for exclusion.

Controls were recruited from the general community by local advertisement and word of mouth. They were age (13 $\pm$ 4 months), gender, and ethnicity matched. They underwent similar clinical and pediatric sleep questionnaire evaluation and completed sleep logs. They had no sleep complaints, normal health, and had normal sleep habits. They underwent the same polysomnography setting and scoring.

Polysomnography

The following variables were monitored during nocturnal sleep, with lights out time based on 7 days of sleep logs: electroencephalogram (EEG) of C3/A2, C4/A1, Fz/A1-A2, O1/A2 (band pass filtered at 0.3 to 40 Hz), electrooculogram (EOG) of both eyes, chin and leg electromyograms (EMGs), electrocardiogram (ECG) with two electrodes placed laterally below the two clavicles equidistant from the sternum, and respiration, using nasal cannula pressure transducer, oral airflow (by thermocouple measurement), thoracic and abdominal expansion (with piezoelectric bands), (one out of two nights of recording included Pes monitoring, but the study night without such measurement was selected to avoid any question of possible sleep disturbance related to equipment), breath-sound intensity with a microphone (anterior neck), and arterial oxygen saturation (SaO2) via pulse oximetry (Nellcor Inc., Oakland, CA). Recordings were performed on computerized polygraphic sleep systems (Sandman^{TM}, Ottawa, ON, Canada). The sampling rate of the recorded EEG was 128 Hz with the Sandman system and 256 Hz for heart rate. Anonymized recording data were transferred to CD-ROM.

Analysis

Polysomnography Analysis

All anonymized CD-ROM data were rescored for research purpose, scorers were blind to the condition of the subject. Each sleep recording was exported in the European Data Format, and the Somnologica TM (Flagra-Medcare, Reykjavík, Iceland) program was used for the HRV data. Patients were resting in a supine position during all epochs chosen for HRV analysis. In order to record sleep-stage related HRV a series of 5-min epochs were chosen in the first two cycles. In each 5-min period, ECG signals were analyzed for automatic detection of R waves. We used a minimum sampling frequency of 250 Hz for HRV analysis

in accordance with the Task Force of the European Society of Cardiology (1996).

The subsequent tabulations were performed following pre-determined criteria. Sleep/wake was analyzed using the international criteria of Rechtschaffen and Kales (1968) and short EEG arousal (>3 s) according to the American Sleep Disorders Association-ASDA-arousal definition (American Sleep Disorders Association ASDA, 1992; Bonnet et al., 2007). The respiratory parameters were defined according to the American Academy of Sleep Medicine (1999, 2014) Apnea-hypopnea index (number of apnea and hypopnea per hour of sleep, AHI) was calculated. The respiratory disturbance index also included flow limitation in the nasal cannula pressure transducer recording with a decrease of at least 20% of flow associated with an increase in respiratory effort indicated by a more negative peak end inspiration in the esophageal pressure (Pes) curve, which was diagnosed as resistive breaths (Guilleminault et al., 2001).

The diagnosis of mild SDB was based on the presence of habitual snoring, clinical symptoms and the following polysomnographic criteria: apnea index = 0 per hour of sleep (/h), hypopnea index (HI) < 1/h, RDI ≤ 10/h, and oxygen saturation > 92% (Whitney et al., 1998; Stepnowsky et al., 2004).

Briefly summarized, the following variables were tabulated based on these analyses: sleep onset latency defined as three consecutive epochs of stage 1, total sleep time (TST), sleep efficiency (TST/total recording time), time awake after sleep onset (WASO), N1, N2, N3, and REM sleep stages and their percentages based on TST, arousal index per hour of sleep, RDI, and AHI.

Heart rate variability (HRV) analysis

This analysis focused on HRV analysis. Each record was carefully manually reviewed to exclude visual artifacts and arrhythmias before further analysis.

Time domain analysis

A continuous ECG recording was extracted from the obtained and cleaned recording; each QRS complex was detected, and the normal-to-normal (RR) intervals determined. Five time-domain indexes were derived: the standard deviation of all Normal to Normal intervals (SDNN); the mean of the standard deviation of the 5-min NN intervals over the entire recording (SDNN index); the root mean square of the difference between successive NN intervals (RMS) and the proportion of adjacent normal NN intervals differing by >50 ms (pNN50).

Frequency domain analysis

Five consecutive minutes of stable ECG, artifact-free, from N2, Slow Wave Sleep (SWS) and REM sleep periods were recorded during the second sleep cycle for N1, N2, and N3 sleep stages and the fourth sleep cycle for REM sleep were selected. Spectral indexes for HRV were computed by Fast Fourier Transforms using 5-min Hanning windows. We chose the central 5-min period of the longest above-mentioned sleep stages. The power densities in the very low frequency (VLF, 0.0033–0.04 Hz), low frequency (LF, 0.04–0.15 Hz), and high frequency (HF, 0.15–0.4 Hz) components were calculated by integrating the power spectral density in the respective frequency bands. Normalized power spectra LF/HF were also calculated. Results were expressed in ms^2/Hz.

Statistical Analysis

Central tendency measures were expressed as mean and standard deviation. Two-way ANOVA for repeated measures followed by a Bonferroni *post-hoc* test was used to analyze the differences in HRV and sleep stages considering two main factors: (1) SDB children and controls (group), and (2) stage N2, N3, and REM sleep (sleep stage). The level of significance for the variance analyses was set at $p \leq 0.05$ using SPSS statistical package version 11.5. Correlations between HRV parameters and RDI were performed by means of a Spearman Correlation test.

RESULTS

General Results

All patients were chronic snorers. The children's parents reported hyperactivity, irritability, impulsivity, and/or depressed mood in 8 out of 10 patients, using a non-structured questionnaire with sleep questions (see **Table 1**). None of them fit the criteria for OSA based on polysomnography (AHI > 1). The mean RDI and sleep parameters are outlined in **Table 1**. Episodes of prolonged increased respiratory effort as seen in the esophageal pressure monitoring were observed in the SDB children's group, with a Pes nadir of (-20 ± 2 cm H_2O), but it was only considered as a respiratory event when followed by arousal. None of the control group members had abnormal sleep.

TABLE 1 | Demographic and PSG data[a].

Subjects data	Patients ($n = 10$)	Controls ($n = 10$)
Age	12 ± 5	13 ± 4
Tanner stage	>1	>1
Behavioral complaints	8/10	1/10
Chronic Snoring	10/10	0/10
AI/h	0/h	0/h
HI/h	0.8 ± 1.1/h	0/h
RDI/h	8.1 ± 1.3/h	0/h
SaO2 nadir %	96.1 ± 2.4	96.3 ± 3.4
CAP rate %	67.2 ± 9.1	48.3 ± 5.2
Sleep efficiency %	92.5 ± 3.5	91.4 ± 5.1
Sleep stages (minutes)		
N1	9.5 ± 4.2	11 ± 6.3
N2	254± 19.4	263 ± 24.3
N3	78 ± 8.2	92.2 ± 10.2
REM	96.9± 8.4	99.1 ± 9.2
Arousal index	7.6 ± 2.1	8.5 ± 1.7

[a] *All respiratory indexes were calculated per hour (/ h) of total sleep time. AI, apnea index; HI, hypopnea index; RDI, Respiratory Disturbance Index; CAP, cyclic alternating pattern. None of the variables were significantly significant. Data were presented as mean ± standard deviation.*

HRV Results

The time domain analysis showed significantly higher values of NN50 and pNN50 in the control children compared to those noted in snorers in all sleep stages. Looking at the frequency domain analysis, we found a significant decrease in total power for all sleep stages and an increase in LF/HF (a sympathetic index) for N2 sleep stage and REM sleep in the chronic snorer group. HRV results are outlined in **Table 2**.

Correlations Results

There were significant inverse correlations between the RDI and: NN50 for all sleep stages [stage 2: $r = -0.72$, $p = 0.01$; SWS: $r = -0.62$, $p = 0.01$; REM sleep: $r = -0.51$, $p = 0.01$]; pNN50 during sleep N2 sleep stage ($r = -0.51$, $p = 0.01$), and total power during SWS ($r = -0.44$, $p = 0.04$). The arousal index per hour was inversely correlated with NN50 during N2 sleep stage ($r = -0.59$, $p = 0.01$) and SWS ($r = -0.55$, $p = 0.01$).

DISCUSSION

We have shown previously that children without a clear decrease in oxygen saturation during sleep but with flow limitation and chronic snoring are symptomatic. Despite the absence of oxygen desaturation events, we found abnormalities in both sympathetic and parasympathetic components of the autonomic nervous system (ANS) for most sleep stages, as seen by the alteration in NN50, pNN50, Total Power, and LF/HF components of HRV. It is sometimes difficult to identify all the arousals that occur during sleep with visual scoring in children with mild SDB, but (Chervin et al., 2004), using a computerized algorithm and CAP scoring analysis, have shown that sleep disruption occurs during chronic snoring (Lopes and Guilleminault, 2006). Taken together, sleep EEG instability, chronic snoring, and increased respiratory effort impact on the ANS balance during sleep.

PNN50 and NN50 mostly reflect the parasympathetic component of the time domain HRV analysis (Bigger et al., 1989) while LF/HF reflects the sympathovagal balance to the heart estimated using the frequency domain HRV analysis. The parasympathetic component (HF) generally includes a wide range between 0.18 and 0.4 Hz. This rhythm is synchronous with the respiratory rate and mediated by the vagus nerve to the heart (Hirsch and Bishop, 1981). The total power includes the power in all frequency bands, and its reduction is generally interpreted as a reduction in HRV.

In adults and children with severe OSA and hypoxemia, an increase in sympathetic tone during sleep was found (O'Driscoll et al., 2011; Walter et al., 2018). We also observed a modest increase in sympathetic tone during N2 sleep stage and REM sleep, which did not correlate with RDI, in our population of chronic snorers, with no decrease in oxygen saturation. On the contrary, the only significant inverse correlation between RDI and ANS variables was with the parasympathetic tone and total ECG power. It has been shown that reduction in HRV in patients with heart failure and other medical conditions is associated with poor prognosis (Tsuji et al., 1996; Cohen and Benjamin, 2006).

Demonstration of abnormal regulation of the vagal tone in subjects with SDB and no repetitive decrease in oxygen saturation has already been reported in adults with Upper Airway Resistance Syndrome (Guilleminault et al., 2005), as well as the presence of low BP in children with a limited oxygen saturation decrease despite abnormal breathing during sleep (Guilleminault et al., 2004). Chronic snoring and flow limitation with a high CAP rate during sleep may abnormally change in the vagal tone as shown here. The measure of HRV was obtained in a unique situation in our study. The resting-baseline state prior to sleep could be a predictor of SDB as it enables comparation throughout the all sleep stages.

TABLE 2 | Two-Way ANOVA for repeated measures of HRV parameters for Snorer ($n = 10$) and Control groups ($n = 10$) according to sleep stage.

	Snorer group N2 stage	Control group N2 stage	Snorer group SWS	Control group SWS	Snorer group REM	Control group REM	$F_{(2,36)}$	$F_{(1,18)}$ group	p
RRi	783 ± 103	875 ± 142	785 ± 111	862 ± 159	778 ± 82	842.9 ± 118	Ns	ns	ns
SDNN	56.1 ± 23.9	88.8 ± 52.1	38.1 ± 23.7	78.8 ± 74.8	60.8 ± 29	94 ± 58.8	Ns	ns	ns
RMSSD	52.9 ± 29.4	97.1 ± 62.7	45 ± 32.5	103.6 ± 97.8	54.8 ± 45.6	89.7 ± 72.1	Ns	ns	ns
NN50	14 ± 13.1*	120 ± 75.4	17.3 ± 15.8*	115.6 ± 83.8	14.3 ± 15.1*	98.5 ± 63.1	Ns	19.4	0.0003
pNN50	24.3 ± 21*	46.8 ± 19.2	24.9 ± 23.7*	45.4 ± 24.2	20.1 ± 22.9*	35.8 ± 19.6	Ns	5.1	0.03
VLF	2436.3 ± 1235	3236 ± 4743	733.5 ± 349	1132 ± 822	3480 ± 3179	4988 ± 3777	Ns	ns	ns
LF	3181 ± 1770	3241 ± 1861	1668 ± 1157	1883 ± 944	3501 ± 1450	2455 ± 1160	Ns	ns	ns
HF	2622 ± 1247	3510 ± 1603	2903 ± 1739	3574 ± 1825	3501 ± 1450	2455 ± 1161	Ns	ns	ns
TP	5823 ± 4259*	9710 ± 6459	3715 ± 3074*	6899 ± 2591	7934 ± 5071*	10084 ± 5342	Ns	4	0.05
LF/HF	1.9 ± 1.3*	1.1 ± 0.7	0.7 ± 0.4#	0.6 ± 0.3#	2.8 ± 2.2*	1.1 ± 0.8	3.6	4.7	0.03, 0.04

*Data were presented as mean ± standard deviation. *Difference in HRV parameters in each sleep stage according to group factor; #Difference in HRV parameters, according to the interaction between two factors (sleep stages and groups). RRi, the interval between beat to beat (RR); SDNN, Standard deviation of NN intervals for period of interest; RMSSD, Root mean square of successive differences of NN intervals for period of interest; NN50, NN intervals > 50 ms different from previous (NN) for period of interest; pNN50, percentage of NN intervals > 50 ms different from previous (NN) for period of interest Root mean square of successive differences of NN intervals for period of interest; VLF, very low frequency; LF, low frequency; HF, high frequency; TP, total power; LF/HF, LF/HF average over 5-min periods or less that can purported to reflect sympathetic nervous system per parasympathetic nervous system balance.*

We found changes in the flexibility of cardiovascular fitness in our data, based on changes in the parasympathetic system followed by low HRV. There is a relationship between low HRV and the increase of depression and anxiety symptoms (Gorman and Sloan, 2000), and the sympathetic activation seen in anxiety disorders may represent a failure of inhibitory mechanisms as a result of the reduced parasympathetic modulation (Chalmers et al., 2014). Our results showed low HRV since childhood by chronic snoring, and it may be followed by an increased risk of cardiovascular morbidity. Moreover, the daily worry has been related with low HRV (Brosschot et al., 2007), and the measures of HRV may provide an important window into understanding stress and health (Thayer et al., 2012). The early changes in HRV from childhood into adulthood can be followed by influences in psychological and physiological self-regulation, according to a model of Neurovisceral Integration (Thayer and Lane, 2000; Thayer et al., 2009).

In 1999, Baharav et al. (1999) found a significant positive correlation between the autonomic balance, LF/HF (that estimates sympathetic tonus), and the RDI in OSA children compared to controls. However, the children described in that study had SaO2 decreases that were clearly below those seen in our group of chronic snorers where we noted a significant inverse correlation between RDI, the total ECG power, and parasympathetic tonus, suggesting predominant parasympathetic tonus impairment. We believe that one of the key differences is the degree of oxygen saturation decrease and probably also the difference in the type of abnormal breathing pattern noted with inspiration and the shortening of expiration during inspiratory snoring with a decrease in lung inflation via sympathetic activation reflex (St Croix et al., 1999). The major limitation of our study was the small size of the group we sampled using esophageal pressure monitoring. There is a need to apply new measures of sleep disruption, and HRV subtype measurement could be useful, particularly during the night because we monitor changes in sleep stages. The use of HRV is still unclear and the LF/HF ratio can be an inconclusive measurement (Billman, 2013). However, patients with insomnia may also exhibit a higher ratio of low-to-high frequency power (LF:HF-HRV), interpreted as an index of sympathovagal tone. Sleep-related changes in HRV are associated with other physiological changes (Israel et al., 2012). The evidence also suggests that HRV collected during a PSG can be useful in risk stratification models of several pathophysiological processes (Stein and Pu, 2012).

Finally, little is known about the consequences of impaired parasympathetic tonus during sleep. The most important finding in these results is the value of HRV measurement in mild sleep disordered breathing since not all sleep laboratories measure flow limitation or respiratory effort with esophageal pressure devices, thus underestimating the impact of mild sleep disordered-breathing, and describing it as habitual snoring without health consequences. The measurement of changes in HRV could be a useful tool in estimating the consequences of SDB in children and the dysregulation of the vagal tone may play a role in the reported syncope seen in late teenagers (Koenig et al., 2017) and early adult women with insomnia and UARS (Guilleminault et al., 1995; Poyares et al., 2002; Guilleminault and Davé, 2003).

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of name of guidelines, name of committee 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 ethics commitee.

AUTHOR CONTRIBUTIONS

All authors have worked with the data together. M-CL: Collected the data and conducted the full review. KS: Aided in the final interpretation of the data. LA-S: Generated data from PhD thesis and contributed to the English review. AR: Introduced the topics about HRV to the authors' department and was responsible for the data together with the first author. CG: Critical role in giving advice on interpreting the data.

REFERENCES

(1996). Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *Eur. Heart J.* 17, 354–381. doi: 10.1093/oxfordjournals.eurheartj.a014868

Ali, N. J., Pitson, D. J., and Stradling, J. R. (1993). Snoring, sleep disturbance, and behaviour in 4–5 year olds. *Arch. Dis. Child* 68, 360–366. doi: 10.1136/adc.68.3.360

American Academy of Sleep Medicine (2014). *International Classification of Sleep Disorders, 3rd Edn.* Darien, IL: American Academy of Sleep Medicine, 16.

American Academy of Sleep Medicine. (1999). Sleep-related breathing disorders in adults: for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 22, 667–689. doi: 10.1093/sleep/22.5.667

American Sleep Disorders Association ASDA (1992). EEG arousals: scoring rules and examples A preliminary report from Sleep Disorders Atlas Task Force of the American Sleep. Disorders Association. *Sleep* 15, 173–184.

Baharav, A., Kotagal, S., Rubin, B. K., Pratt, J., and Akselrod, S. (1999). Autonomic cardiovascular control in children with obstructive sleep apnea. *Clin. Auton. Res.* 9, 345–351. doi: 10.1007/BF02318382

Bigger, J. T. Jr, Albrecht, P., Steinman, R. C., Rolnitzky, L. M., Fleiss, J. L., and Cohen, R. J. (1989). Comparison of time- and frequency domain-based measures of cardiac parasympathetic activity in Holter recordings after myocardial infarction. *Am. J. Cardiol.* 64, 536–538. doi: 10.1016/0002-9149(89)90436-0

Billman, G. E. (2013). The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. *Front. Physiol.* 4:26. doi: 10.3389/fphys.2013.00026

Blunden, S., Lushington, K., Kennedy, D., Martin, J., and Dawson, D. (2000). Behavior and neurocognitive performance in children aged 5–10 years who snore compared to controls. *J. Clin. Exp. Neuropsychol.* 22, 554–568. doi: 10.1076/1380-3395(200010)22:5;1-9;FT554

Bonnet, M. H., Doghramji, K., Roehrs, T., Stepanski, E. J., Sheldon, S. H., Walters, A. S., et al. (2007). The scoring of arousal in sleep: reliability, validity, and alternatives. *J. Clin. Sleep Med.* 3, 133–145.

Brosschot, J. F., Van Dijk, E., and Thayer, J. F. (2007). Daily worry is related to low heart rate variability during waking andthe subsequent nocturnal sleep period. *Int. J. Psychophysiol.* 63, 39–47. doi: 10.1016/j.ijpsycho.2006.016

Chalmers, J. A., Quintana, D. S., Abbott, M. J., and Kemp, A. H. (2014). Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. *Front. Psychiatry*. 5:80. doi: 10.3389/fpsyt.2014.00080

Chervin, R. D., Burns, J. W., Subotic, N. S., Roussi, C., Thelen, B., and Ruzicka, D. L. (2004). Correlates of respiratory cycle-related EEG changes in children with sleep-disordered breathing. *Sleep* 27, 116–121. doi: 10.1093/sleep/27.1.116

Chervin, R. D., Hedger, K., Dillon, J. E., and Pituch, K. J. (2000). Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. *Sleep Med.* 1, 21–32. doi: 10.1016/S1389-9457(99)00009-X

Chervin, R. D., Ruzicka, D. L., Giordani, B. J., Weatherly, R. A., Dillon, J. E., Hodges, E. K., et al. (2006). Sleep-disordered breathing, behavior, and cognition in children before and after adenotonsillectomy. *Pediatrics* 117, e769–e778. doi: 10.1542/peds.2005-1837

Cohen, H., and Benjamin, J. (2006). Power spectrum analysis and cardiovascular morbidity in anxiety disorders. *Auton. Neurosci.* 128, 1–8. doi: 10.1016/j.autneu.2005.06.007

Gorman, J. M., and Sloan, R. P. (2000). Heart rate variability in depressive and anxiety disorders. *Am. Heart J.* 140, 77–83. doi: 10.1067/mhj.2000.109981

Gozal, D. (1998). Sleep-disordered breathing and school performance in children. *Pediatrics* 102, 616–620.

Guilleminault, C., and Davé, R. (2003). Upper airway resistance syndrome, insomnia, and functional somatic syndromes. *Chest* 123, 12–14. doi: 10.1378/chest.123.1.12

Guilleminault, C., Khramtsov, A., Stoohs, R. A., Kushida, C., Pelayo, R., Kreutzer, M. A., et al. (2004). Abnormal Blood Pressure in Pre-pubertal children with sleep disordered breathing. *Pediatr. Res.* 55, 76–84. doi: 10.1203/01.PDR.0000099791.39621.62

Guilleminault, C., Li, K., Khramtsov, A., Palombini, L., and Pelayo, R. (2004). Breathing patterns in prepubertal children with sleep-related breathing disorders. *Arch. Pediatr. Adolesc. Med.* 158, 153–161. doi: 10.1001/archpedi.158.2.153

Guilleminault, C., Poyares, D., Palombini, L., Koester, U., Pelin, Z., and Black, J. (2001). Variability of respiratory effort in relation to sleep stages in normal controls and upper airway resistance syndrome patients. *Sleep Med.* 2, 397–405. doi: 10.1016/S1389-9457(01)00111-3

Guilleminault, C., Poyares, D., Rosa, A., and Huang, Y. S. (2005). Heart rate variability, sympathetic and vagal balance and EEG arousals in upper airway resistance and mild obstructive sleep apnea syndromes. *Sleep Med.* 6, 451–457. doi: 10.1016/j.sleep.2005.03.014

Guilleminault, C., Stoohs, R., Kim, Y. D., Chervin, R., Black, J., and Clerk, A. (1995). Upper airway sleep disordered breathing in women. *Ann. Intern. Med.* 122, 493–501.

Guilleminault, C., Winkle, R., Korobkin, R., and Simmons, B. (1982). Children and nocturnal snoring: evaluation of the effects of sleep related respiratory resistive load and daytime functioning. *Eur. J. Pediatr.* 139, 165–171. doi: 10.1007/BF01377349

Halbower, A. C., Degaonkar, M., Barker, P. B., Earley, C. J., Marcus, C. L., Smith, P. L., et al. (2006). Childhood obstructive sleep apnea associates with neuropsychological deficits and neuronal brain injury. *PLoS Med.* 3:e301. doi: 10.1371/journal.pmed.0030301

Hirsch, J. A., and Bishop, B. (1981). Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate. *Am. J. Physiol.* 241, 620–629. doi: 10.1152/ajpheart.1981.241.4.H620

Horne, R. S. C., Shandler, G., Tamanyan, K., Weichard, A., Odoi, A., Biggs, S. N., et al. (2018). The impact of sleep disordered breathing on cardiovascular health in overweight children. *Sleep Med.* 41, 58–68. doi: 10.1016/j.sleep.2017.09.012

Israel, B., Buysse, D. J., Krafty, R. T., Begley, A., Miewald, J., and Martica Hall, M. (2012). Short-term stability of sleep and heart rate variability in good sleepers and patients with insomnia: for some measures, one night is enough. *Sleep* 35, 1285–1291. doi: 10.5665/sleep.2088

Jackman, A. R., Biggs, A. N., Walter, L. M., Embuldeniya, U. S., Davey, M. J., Nixon, G. M., et al. (2012). Sleep-disordered breathing in preschool children is associated with behavioral, but not cognitive, impairments. *Sleep Med.* 13, 621–631. doi: 10.1016/j.sleep.2012.01.013

Koenig, J., Rash JA Campbell, T. S., and Thayer JF Kaess, M. (2017). A meta-analysis on sex differences in resting-state vagal activity in children and adolescents. *Front. Physiol.* 8:582. doi: doi: 10.3389/fphys.2017.00582

Kwok, K. L., Yung, T. C., Ng, D. K., Chan, C. H., Lau, W. F., and Fu, Y. M. (2011). Heart rate variability in childhood obstructive sleep apnea. *Pediatr. Pulmonol.* 46, 205–210. doi: 10.1002/ppul.21268

Lopes, M. C., and Guilleminault, C. (2006). Chronic snoring and sleep in children: a demonstration of sleep disruption. *Pediatrics* 118, 741–746. doi: 10.1542/peds.2005-3046

Nisbet, L. C., Yiallourou, S. R., Walter, L. M., and Horne, R. S. (2014). Blood pressure regulation, autonomic control and sleep disordered breathing in children. *Sleep Med. Rev.* 18, 179–189. doi: 10.1016/j.smrv.2013.04.006

O'Brien, L. M., Mervis, C. B., Holbrook, C. R., Bruner, J. L., Carrie, J., Klaus, C. J., et al. (2004). Neurobehavioral implications of habitual snoring in children. *Pediatrics* 114, 44–49. doi: 10.1542/peds.114.1.44

O'Driscoll, D. M., Horne, R. S., Davey, M. J., Hope, S. A., Anderson, V., Trinder, J., et al. (2011). Increased sympathetic activity in children with obstructive sleep apnea: cardiovascular implications. *Sleep Med.* 12, 483–488. doi: 10.1016/j.sleep.2010.09.015

Poyares, D., Guilleminault, C., Rosa, A., Ohayon, M., and Koester, U. (2002). Arousal EEG spectral powerand pulse transit time in UARS and mild OSAS subjects. *Clin. Neurophysiol.* 113, 1598–1606. doi: 10.1016/S1388-2457(02)00214-6

Rechtschaffen, A., and Kales, A. A. (1968). *Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. Los Angeles Brain Information/Brain Research Institute. UCLA.

Somers, V. K., Dyken, M. E., Clay, M. P., and Abboud, F. M. (1995). Sympathetic neural mechanisms in obstructive sleep apnea. *J. Clin. Invest.* 96, 1897–1906. doi: 10.1172/JCI118235

Spruyt, K., and David Gozal, D. (2011). Pediatric sleep questionnaires as diagnostic or epidemiological tools: A review of currently available instruments. *Sleep Med. Rev.* 15:19e32. doi: 10.1016/j.smrv.2010.07.005

St Croix, C. M., Satoh, M., Morgan, B. J., JSkatrud, B., and Dempsey, J. A. (1999). Role of respiratory motor output in within-breath modulation of muscle sympathetic nerve activity in humans. *Circ. Res.* 85, 457–469.

Stein, P. K., and Pu, Y. (2012). Heart rate variability, sleep and sleep disorders. *Sleep Med. Rev.* 16, 47–66. doi: 10.1016/j.smrv.2011.02.005

Stepnowsky, C. J. Jr., Orr, W. C., and Davidson, T. M. (2004). Nightly variability of sleep-disordered breathing measured over 3 nights. *Otolaryngol. Head Neck. Surg.* 131, 837–843. doi: 10.1016/j.otohns.2004.07.011

Thayer, J. F., Fredrik, A., Fredrikson, M., Sollers, J. J., and Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neurosci. Biobehav. Rev.* 36, 747–756. doi: 10.1016/j.neubiorev.2011.11.009

Thayer, J. F., and Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *J. Affect. Disord.* 61, 201–216. doi: 10.1016/s0165-0327(00)00338-4

Thayer, J. F., Sollers, J. J., Labiner, D. M., Weinand, M., Herring, A. M., Lane, R. D., et al. (2009). Age related differences in prefrontal control of heart rate in humans: a pharmacological blockade study. *Int. J. Psychophysiol.* 72, 81–88. doi: 10.1016/j.ijpsycho.2008.04.007

Tsuji, H., Larson, M. G., Venditti, F. J. Jr, Manders, E. S., Evans, J. C., Feldman, C. L., et al. (1996). Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation* 94, 2850–2855. doi: 10.1161/01.CIR.94.11.2850

Urschitz, M. S., Guenther, A., Eggebrecht, E., Wolff, J., Urschitz-Duprat, P. M., Schlaud, M., et al. (2003). Snoring, intermittent hypoxia and academic performance in primary school children. *Am. J. Respir. Crit. Care Med.* 168, 464–468. doi: 10.1164/rccm.200212-1397OC

Walter, L. M., Nixon, G. M., Davey, M. J., Anderson, V., Walker, A. M., and Horne, R. S. (2013). Autonomic dysfunction in children with sleep disordered breathing. *Sleep Breath* 17, 605–613. doi: 10.1007/s11325-012-0727-x

Walter, L. M., Tamanyan, K., Nisbet, L. C., Davey, M. J., Nixon, G. M., and Horne, R. S. C. (2018). Obesity and anthropometric determinants of autonomic control in children with sleep-disordered breathing-which measurements matter? *Int. J. Obes.* 42, 1195–1201. doi: 10.1038/s41366-018-0130-1

Whitney, C. W., Gottlieb, D. J., Redline, S., Norman, R. G., Dodge, R. R., Shahar, E., et al. (1998). Reliability of scoring respiratory disturbance indices and sleep staging. *Sleep* 21, 749–757. doi: 10.1093/sleep/21.7.749

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Association Between Parkinson's Disease and Atrial Fibrillation: A Population-Based Study

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Introduction: Autonomic nervous system (ANS) dysfunction contributes to several non-motor symptoms of Parkinson's disease (PD). In addition, ANS plays a role in the genesis and maintenance of atrial fibrillation (AF). This study investigated the temporal association between PD and AF.

Methods: Data were obtained from the National Health Insurance Research Database of Taiwan. In total, 15,375 patients with newly diagnosed PD were matched with four controls each based on the propensity score. This study was bidirectional. A case-control study for the odds ratio (OR) of AF before PD and within 2 years of PD diagnosis was evaluated through conditional logistic regression. Furthermore, a cohort study on the subdistribution hazard ratio (SHR) for new-onset AF 2 years after PD diagnosis was evaluated using competing risk analysis.

Results: In the case-control study, PD was found to be significantly comorbid with AF (adjusted OR: 1.15, 95% confidence interval [CI]: 1.04–1.28). Subgroup analysis demonstrated that this association consistently presented in the absence of confounding factors of AF. In the cohort study, people with PD were found to have a lower risk of AF (adjusted SHR: 0.92, 95% CI: 0.86–0.98). However, a consistent association was not observed between the confounding factors of AF and PD during the subgroup analysis.

Conclusions: This study demonstrated that the premotor and early stages of PD were comorbid with AF, whereas the risk of AF was lower in the later stages. Thus, AF might be a premotor predictive biomarker and comorbidity of early PD.

Keywords: Parkinson's disease, atrial fibrillation, population-based study, autonomic nerve system, biomarker

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INTRODUCTION

Tremor, bradykinesia, rigidity, and postural instability are the cardinal motor symptoms of Parkinson's disease (PD). However, numerous non-motor symptoms (NMSs), such as depression, dementia, rapid eye movement sleep behavior disorder (RBD), and anosmia, are also comorbid with PD (1). The biological basis of NMSs are distinct from those of conventional motor symptoms. Motor symptoms result from the degeneration of dopaminergic neurons in the midbrain substantia nigra, whereas NMSs result from dysfunction of the serotonergic, cholinergic, and catecholaminergic systems (2). On the basis of these clinical and pathological findings, PD is presently recognized as a disease involving multiple systems and neurotransmitters (3).

Degeneration of the autonomic nervous system (ANS) contributes to certain NMSs of PD, the best-known of which is constipation. More than 60% of people with PD develop constipation because of poor intestinal peristalsis caused by a dysfunctional vagus nerve. Moreover, in most cases, constipation heralds the onset of motor symptoms (4). This sequential association has been supported by a postmortem study. Aggregated α-synuclein, the pathological marker of PD, was first identified in the mesenteric plexus in a preclinical study with PD models. The medullary vagal nucleus is the first area in the central nervous system (CNS) to accumulate α-synuclein, which echoes hypothesis regarding caudal–rostral spreading of the Lewy body (5). Today, constipation and other ANS-related NMSs are recognized as possible predictive biomarkers of PD (6).

Cardiac rhythm is regulated by ANS as well. Sympathetic and parasympathetic innervations originate from the paravertebral ganglia and vagal nerves, respectively. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and it is strongly associated with morbidity, mortality, and poor quality of life. AF stems from several etiologies, and rather than ischemic heart disease, heart failure, and hyperthyroidism, ANS plays a crucial role in AF, particularly for patients with no structural heart disease (7, 8).

Considering the role of the vagal nerve–related ANS system in PD and AF, PD may be comorbid with AF. Moreover, similar to other autonomic NMSs, AF may be a biomarker for the onset of PD motor symptoms. This study employed the National Health Insurance Research Database (NHIRD) of Taiwan to investigate whether AF is associated with newly diagnosed PD and evaluated the temporal relationship between both conditions.

METHODS

Institutional Review Board

This study was approved by the Joint Institutional Review Board of Taipei Medical University (TMU-JIRB No. 201701058).

Data Source and Study Design

This study was conducted using the NHIRD data files maintained by the Health and Welfare Data Science Center (HWDC). The NHIRD is a claims-based database managed by the National Health Insurance Administration of Taiwan; Taiwan's NHI provides coverage for 99% of its residents. The NHIRD files include inpatient, outpatient, and pharmaceutical claims and disease diagnoses coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). In addition, the enrollment files of beneficiaries and providers were also included. The data in this study were from 2000 to 2015. Additionally, we linked the collected data with the national death registry to obtain death records. The two data sets can be linked according to the regulations of the HWDC. Both case-control (diagnosed AF before and within a 2-year interval of the first PD diagnosis) and cohort (newly diagnosed AF 2 years after first PD diagnosis) studies were applied to examine the temporal relationship between PD and AF.

Participants

Newly diagnosed people with PD were defined as those who had at least two diagnostic claims (ICD-9-CM: 332.0) and prescription claims for dopaminergic agents between 2004 and 2011. The index date of PD was defined as the date of first PD diagnosis, hereafter referred to as the index PD. People who were aged < 45 years, had a history of stroke, or had received any antipsychotic drug before the index PD, were excluded to avoid the possibility of misclassification of secondary Parkinsonism. In addition, several predisposing factors may trigger AF directly (9). Therefore, we also excluded people with a history of rheumatic heart disease (ICD-9-CM: 390–398), other structural heart disease (ICD-9-CM: 420–425), thyroid disease (ICD-9-CM: 240–246), diseases of the adrenal gland (ICD-9-CM: 255), alcoholism (ICD-9-CM: 303), and AF onset within 6-month intervals of severe acute infection (ICD-9-CM: 995.9) and cardiothoracic/abdominal surgery (ICD-9 procedure codes of 30–39 and 42–75). The same exclusion criteria were used for the control participants.

Propensity Score Model

Matching aims to reduce potential selection bias in the observational studies. Propensity score matching (PSM) are widely utilized to diminish the confounding factors that inevitably occurs in studies investigating the effect of the exposures on the outcome. In PSM, matched are formed by virtue of sharing similar propensity score values. The weighted-value reveals the risk of the participant for the outcome of interest according to their underlying characteristics predispose them for that outcome irrespective of the exposure of interest (10).

In this study, the propensity score was measured on the basis of hypertension (HTN, ICD-9-CM: 401–405), diabetes mellitus (DM, ICD-9-CM: 250), hyperlipidemia (ICD-9-CM: 272), chronic heart failure (CHF, ICD-9-CM: 428), coronary artery disease (CAD, ICD-9-CM: 410–414), chronic lung disease (ICD-9-CM:415–417, 490–496, and 500–508), renal disease (ICD-9-CM: 580–589), and inflammatory dx (ICD-9-CM: 710, 714). The selection of these factors was based on the association with AF genesis (9). The effect of each factors on the AF was assessed by logistic regression (**Supplementary Table 1**). Controls without PD were assigned an index date of pseudo-PD diagnosis corresponding to the index date of PD diagnosis of their matched patients. Each person with PD was matched with four controls without PD based on age, sex, pseudo diagnostic year and the propensity score using a caliper of width equal to 0.2; consequently, the two cohorts had similar baseline characteristics but differed in PD diagnosis.

Study Outcome

Both the people with PD and controls were tracked or followed up for their risk of AF according to the study design. Patients with AF were defined as those who first had at least two diagnostic claims (ICD-9-CM: 427.31) and prescription claims for warfarin or oral anticoagulant agents without claims for venous thrombosis (ICD-9-CM: 453), pulmonary embolism (ICD-9-CM: 415, valvular replacement (ICD-9 procedure codes of 35), and antiphospholipid syndrome (ICD-9-CM: 286.53 and

286.59). AF, especially paroxysmal AF, is usually under-diagnosed with a certain latent period before diagnosis. Hence, in the case-control study, AF risk was measured within 2 years of PD or before the index date of PD/pseudo-PD diagnosis. In the cohort study, AF risk was measured 2 years after the index date of PD/pseudo-PD diagnosis. The selection process is presented in **Figure 1**.

Statistical Analysis

Baseline characteristics were analyzed using standardized mean difference (SMD). SMD > 0.1 indicated non-negligible differences between the two groups. The case-control study for the odds ratio (OR) of AF before PD and within the 2-year interval of PD diagnosis was evaluated using conditional logistic regression, and a cohort study for the subdistribution hazard ratio (SHR) of new-onset AF after PD diagnosis was evaluated using competing risk analysis. Because the participants were at a high risk of mortality, we applied competing risk model analyses to estimate the absolute relative AF risks. The follow-up period for each patient ranged from the index date of PD/pseudo-PD diagnosis to the date of AF diagnosis or death or the end of the observation period (December 31, 2015). All analyses were performed using SAS/STAT version 9.4 (SAS Institute Inc., Cary, NC, USA) and STATA 14 (Stata Corp LP, College Station, TX, USA). A $P < 0.05$ was considered significant.

RESULTS

Initially, the study included 15,434 newly diagnosed people with PD, among whom 59.2% were men. After the 1 to 4 PSM, 15,375 subjects remained in the study. After PSM, their mean age was 71.7 $\pm$ 9.9 years. The prevalence of previous or current comorbidity was 47.8, 20.7, and 2.5% for HTN, DM, and CHF, respectively (**Table 1**).

In the case-control study, compared with matched controls, newly diagnosed people with PD were significantly comorbid with AF (adjusted OR [aOR]: 1.15, 95% confidence interval [CI]: 1.04–1.28) (**Figure 2**). According to the subgroup analysis, elderly people (age $\geq$ 65 years) and women with PD were more likely to have AF. The remainder of the subgroup analysis focused on the effect of each confounding factor of AF on the association between PD and AF. People with PD were only comorbid with AF significantly in the absence of the following factors: HTN (aOR: 1.20, 95% CI: 1.00–1.42); DM (aOR: 1.21, 95% CI: 1.08–1.36); hyperlipidemia (aOR: 1.12, 95% CI: 1.00–1.26); CHF (aOR: 1.18, 95% CI: 1.06–1.36); CAD (aOR: 1.19, 95% CI: 1.06–1.35); chronic lung disease (aOR: 1.21, 95% CI: 1.07–1.36); renal disease (aOR: 1.18, 95% CI: 1.06–1.31); inflammatory disease (aOR: 1.15, 95% CI: 1.04–1.28); and statin prescription (aOR: 1.12, 95% CI: 1.01–1.26). These results indicated that the association between PD and AF was more notable when the confounding factors of AF were excluded.

In the cohort study, newly diagnosed people with PD had lower AF risk during the follow-up period (adjusted SHR: 0.92, 95% CI: 0.86–0.98) (**Figure 3**). In the subgroup analysis, elderly people and women with PD exhibited a similarly significant risk reduction. However, unlike in the case-control study, the remainder of the subgroup analysis did not reveal a consistent association between AF and the presence of confounding factors of AF. People with PD who had comorbid HTN, CAD, or chronic lung disease were at a greater risk of developing AF. Furthermore, people with PD without DM, CHF, renal disease, inflammatory disease, or statin prescription were more likely to develop AF.

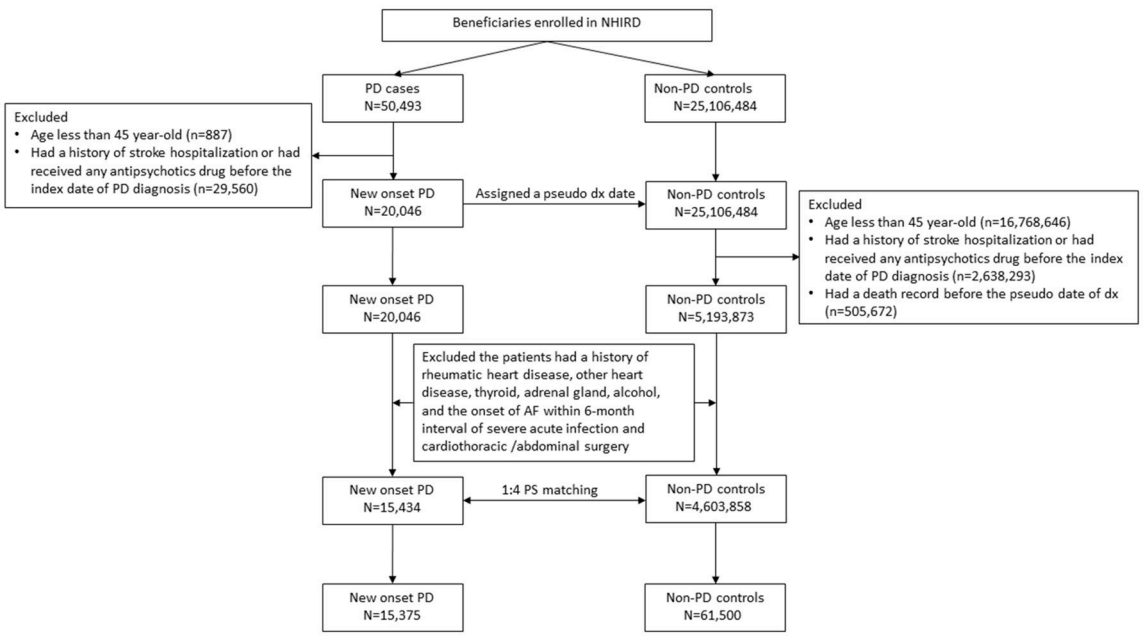

FIGURE 1 | Flowchart of patient selection flowchart. PD, Parkinson's disease and AF, atrial fibrillation. Propensity score, PS.

TABLE 1 | Basic characteristics of Parkinson's disease (PD) or Non-PD before and after Propensity Score Model (PSM).

	Before PSM					After PSM				
	PD		Non-PD			PD		Non-PD		
	N	(%)	*N*	(%)	SMD	*N*	(%)	*N*	(%)	SMD
Sample Size	15,434		4,603,858			15,375		61,500		
Male	9,144	(59.2)	2,553,140	(55.5)	0.077	9,113	(59.3)	36,452	(59.3)	<0.001
Age (y), Mean [SD]	71.7	[9.9]	57.4	[10.4]	1.412	71.7	[9.9]	71.7	[9.9]	<0.001
Age group										
45–64	3,444	(22.3)	3,545,590	(77.0)	1.307	3,443	(22.4)	13,773	(22.4)	<0.001
65	11,990	(77.7)	1,058,268	(23.0)	1.307	11,932	(77.6)	47,727	(77.6)	<0.001
Diagnostic year										
2004–2005	3,812	(24.7)	1,124,015	(24.4)	0.006	3,795	(24.7)	15,180	(24.7)	<0.001
2006–2007	3,955	(25.6)	1,178,943	(25.6)	0.002	3,943	(25.7)	15,772	(25.7)	<0.001
2008–2009	3,869	(25.0)	1,162,550	(25.2)	0.004	3,854	(25.0)	15,416	(25.0)	<0.001
2010–2011	3,798	(24.6)	1,138,350	(24.7)	0.001	3,783	(24.6)	15,112	(24.6)	<0.001
Comorbidity, yes										
HTN	7,398	(47.9)	927,199	(20.1)	0.614	7,355	(47.8)	29,713	(48.3)	0.010
DM	3,206	(20.8)	430,198	(9.3)	0.324	3,175	(20.7)	12,586	(20.5)	0.005
Hyperlipidemia	2,602	(16.9)	429,938	(9.3)	0.224	2,582	(16.8)	10,014	(16.3)	0.014
CHF	460	(3.0)	28,559	(0.6)	0.178	426	(2.8)	1,524	(2.5)	0.018
CAD	2,429	(15.7)	210,937	(4.6)	0.376	2,393	(15.6)	9,579	(15.6)	<0.001
CLD	2,316	(15.0)	241,166	(5.2)	0.328	2,283	(14.8)	9,089	(14.8)	0.002
Renal disease	660	(4.3)	58,419	(1.3)	0.184	644	(4.2)	2,362	(3.8)	0.018
Inflammatory dx	223	(1.4)	34,141	(0.7)	0.068	215	(1.4)	651	(1.1)	0.031
Statin prescription before index date	1,329	(8.6)	186,817	(4.1)	0.188	1,314	(8.5)	5,089	(8.3)	0.010

SMD (standardized mean difference) indicated the variable difference in means or proportions divided by standard error; imbalance defined as absolute value >0.1 dx, diagnosis; PD, Parkinson disease; HTN, hypertension; DM, diabetes mellitus; CHF, congestive heart failure; CAD, coronary heart disease; CLD, chronic lung disease.

DISCUSSION

This study demonstrated that people with PD were more likely to be comorbid with AF before and during the onset of motor symptoms. By contrast, people with PD were at a lower risk of AF in the later stages of PD. This discrepancy in the temporal relationship between the two diseases indicates that, similar to other ANS symptoms, AF may be an early NMS of PD.

ANS dysfunction is a common feature in the premotor and early stages of PD (11). For example, constipation occurs before the onset of motor symptoms of PD (4), and it is attributed to ANS degeneration. In addition, heart rate variability (HRV), another parameter of ANS function, is also affected before the onset of motor symptoms of PD. HRV has been found to decrease in people with RBD (12), and decreased HRV was associated with an increased PD risk in a community-based cohort (13). The association between ANS dysfunction and PD risk is supported by pathological findings. A postmortem study of people without Parkinsonism features found that 17% had α-synuclein pathology in the CNS. Among these people, the majority had alterations in the ANS, such as sacral parasympathetic nuclei, myenteric plexus of esophagus, sympathetic ganglia, and the vagus nerve (14). Anatomically, the vagus nerve is smaller in people with PD as measured through ultrasonography, which indicates potential degeneration and neuronal loss (15).

ANS plays an essential role in the genesis and maintenance of AF, and both the sympathetic and parasympathetic nerves regulate cardiac rhythm through the paravertebral sympathetic ganglia and vagal nerve, respectively (16). Unlike cardiac structural lesion–related AF, most idiopathic or lone AF (people with AF but without any other risk factor) is related to ANS dysfunction. For example, abnormal vagal tone, either elevated or suppressed, contributes to vagal AF. The Euro Heart Survey found that vagal AF accounted for 6% of people with paroxysmal AF (17). Vagal AF usually happens after eating or at night and without the adrenergic triggers. Moreover, athletes, especially endurance runners, were five times more likely to develop vagal AF in one cohort of a cross-country study (18). Because of the role of ANS in triggering AF, ganglionated plexi ablation can be used in the treatment of paroxysmal and persistent AF though autonomic denervation (19).

Using a nationwide population-based method, this study demonstrated the association between AF and newly diagnosed PD, finding that newly diagnosed people with PD were more likely to be comorbid with AF before and during the onset of motor symptoms. This association and temporal relationship support the hypothesis of caudal–rostral spreading of α-synuclein pathology, which indicates that the medullary vagal nucleus is the first region in the CNS to be involved in such pathology, followed by the onset of motor symptoms parallel

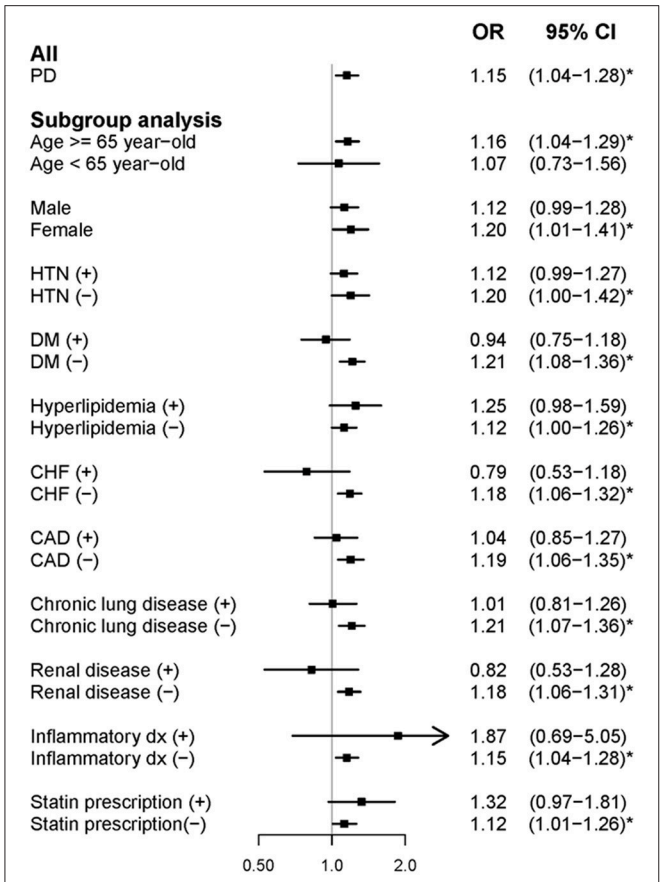

FIGURE 2 | Forest plot showing the adjusted odds ratio of atrial fibrillation among the study participants and subgroup analysis in the case-control study. aOR, adjusted odds ratio; PD, Parkinson's disease; HTN, hypertension; DM, diabetes mellitus; CHF, congestive heart failure; and CAD, coronary heart disease.

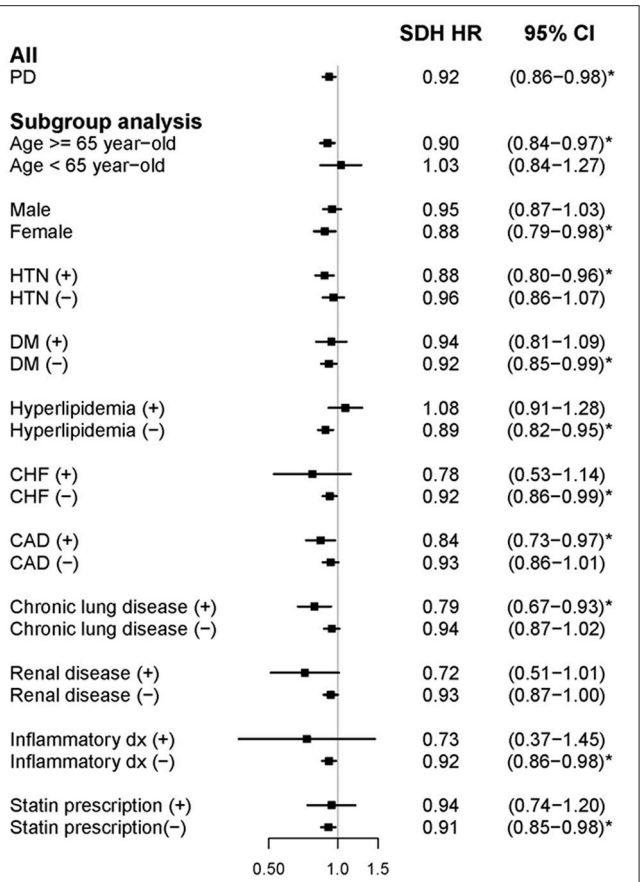

FIGURE 3 | Forest plot showing the adjusted subdistribution hazard ratio of atrial fibrillation among the participants and subgroup analysis in the cohort study. aSDH HR, adjusted subdistribution hazard ratio; PD, Parkinson's disease; HTN, hypertension; DM, diabetes mellitus; CHF, congestive heart failure; and CAD, coronary heart disease.

to α-synuclein accumulation in the midbrain. Conversely, they were at lower risk of AF during the follow-up period. After the diagnosis of PD, people tend to have a healthier lifestyle and regular medical check on the blood pressure, blood glucose, and lipid profile, which resulted in better general health condition than population and contribute to the reduction of the risk of AF. It was a limitation of NHIRD study that we could only match by the presence of disease claim without awareness of the severity of the disease. Meanwhile, in most of the occasion, AF is only detected when it became symptomatic, such as tachycardia or leading to stroke. People with PD, especially those with prominent tremor, may prescribe beta-blockers for controlling the tremor, which may mask the AF-induced tachycardia and under-diagnosed the AF.

A notable contribution of this study is identification of the temporal association between AF and PD. Although the prevalence of AF and PD is low, they remain major public health concerns. Moreover, as an ANS-related NMS of premotor PD, AF can serve as one of the predictive biomarkers of PD in the same manner as RBD, anosmia, and constipation, thereby improving the prediction accuracy of PD onset. For further future study to identify the association between AF with PD in the pre-motor stage, it is suggested that for people at high risk of PD (such as RBD or anosmia), the wearable applications should be considered to identify the AF or other kinds of cardiac arrhythmia in a longer-term, more comprehensive manner.

However, this study has several limitations. AF in some patients may be paroxysmal and asymptomatic, which results in delayed diagnosis. Thus, the temporal relationship between AF and PD may be biased. People with early motor symptoms of PD may visit clinics more frequently and receive more examinations, which increases the possibility of asymptomatic AF diagnosis. To eliminate this bias, this study adjusted the potential effect of the frequency of clinic visits when examining the association between AF and PD. In addition, many confounding factors occur in AF genesis, such as conventional vascular risk factors, structural heart disease, and systemic illnesses. This study did not investigate lone AF, which is the most ANS-related AF, because patients with lone AF are rare even in the NHRID database. Nevertheless, a subgroup analysis was performed that found that the association between PD and AF was significant in the absence of any one of them. Therefore, minimizing the confounding factors of AF may strengthen association

between the two diseases. Another limitation is that although PD diagnosis has been validated with satisfactory accuracy, there is a possibility of false classification of AF and PD in claims-based medical database research (20). Moreover, some lifestyle factors, such as smoking and coffee drinking or diseases without specific coding (e.g., RBD), which considerably affect PD risk, cannot be analyzed using a claims-based medical database (21). Although AF increases ischemic stroke risk, this study excluded patients with stroke history before PD diagnosis, which avoided possible bias from vascular parkinsonism. In our cohort, the mean age of PD diagnosis was 71.7 years, which was older than the typical onset age. However, a recent meta-analysis of the 17 epidemiological studies showed that the mean age of PD diagnosis was 71.6 years and the peak range of age was 70–79 years, which was similar to our cohort (22).

In conclusion, this study revealed that AF may be an NMS of PD, and people with PD were comorbid with AF before and during the onset of motor symptoms. Future studies may include AF as a premotor biomarker to develop a comprehensive PD prediction model.

AUTHOR CONTRIBUTIONS

Research project: **(A)** Conception: all. Organization: C-TH, LC, and L-NC. Execution: C-TH, LC, DW, and L-NC.

Statistical Analysis: **(A)** Design: C-TH, DW, and W-TC. **(B)** Execution: W-TC and L-NC. **(C)** Review and Critique: all.

Manuscript: **(A)** Writing of the first draft: C-TH, LC, and DW. **(B)** Review and Critique: all.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00022/full#supplementary-material

REFERENCES

1. Poewe W. Non-motor symptoms in Parkinson's disease. *Eur J Neurol.* (2008) 15(Suppl. 1): 14–20. doi: 10.1111/j.1468-1331.2008.02056.x
2. Ferrer I. Neuropathology and neurochemistry of nonmotor symptoms in Parkinson's disease. *Parkinsons Dis.* (2011) 2011:708404. doi: 10.4061/2011/708404
3. Titova N, Padmakumar C, Lewis SJG, Chaudhuri KR. Parkinson's: a syndrome rather than a disease? *J Neural Transmission* (2017) 124:907–14. doi: 10.1007/s00702-016-1667-6
4. Lin CH, Lin JW, Liu YC, Chang CH, Wu RM. Risk of Parkinson's disease following severe constipation: a nationwide population-based cohort study. *Parkinsonism Relat Disord.* (2014) 20:1371–5. doi: 10.1016/j.parkreldis.2014.09.026
5. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* (2003) 24:197–211. doi: 10.1016/S0197-4580(02)00065-9
6. Malek N, Lawton MA, Grosset KA, Bajaj N, Barker RA, Burn DJ, et al. Autonomic dysfunction in early Parkinson's disease: results from the United Kingdom tracking Parkinson's study. *Mov Disord Clin Pract.* (2016) 4:509–16. doi: 10.1002/mdc3.12454
7. Coumel P. Autonomic influences in atrial tachyarrhythmias. *J Cardiovasc Electrophysiol.* (1996) 7:999–1007. doi: 10.1111/j.1540-8167.1996.tb00474.x
8. Lombardi F, Malliani A, Pagani M, Cerutti S. Heart rate variability and its sympatho-vagal modulation. *Cardiovasc Res.* (1996) 32:208–16. doi: 10.1016/0008-6363(96)00116-2
9. Leonard I. Ganz D.S. Epidemiology of and risk factors for atrial fibrillation. In: Zimetbaum P, editor. *UpToDate.* Waltham, MA: UpToDate Inc. (2018).
10. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med.* (1998) 17:2265–81. doi: 10.1002/(SICI)1097-0258(19981015)17:19<2265::AID-SIM918>3.0.CO;2-B
11. Pont-Sunyer C, Hotter A, Gaig C, Seppi K, Compta Y, Katzenschlager R, et al. The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). *Mov Disord.* (2015) 30:229–37. doi: 10.1002/mds.26077
12. Valappil RA, Black JE, Broderick MJ, Carrillo O, Frenette E, Sullivan SS, et al. Exploring the electrocardiogram as a potential tool to screen for premotor Parkinson's disease. *Mov Disord.* (2010) 25:2296–303. doi: 10.1002/mds.23348
13. Alonso A, Huang X, Mosley TH, Heiss G, Chen, H. Heart rate variability and the risk of Parkinson's disease: the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Neurol.* (2015) 77:877–83. doi: 10.1002/ana.24393
14. Bloch A, Probst A, Bissig H, Adams H, Tolnay M. Alpha-synuclein pathology of the spinal and peripheral autonomic nervous system in neurologically unimpaired elderly subjects. *Neuropathol Appl Neurobiol.* (2006) 32:284–95. doi: 10.1111/j.1365-2990.2006.00727.x
15. Tsukita K, Taguchi T, Sakamaki-Tsukita H, Tanaka K, and T. Suenaga. The vagus nerve becomes smaller in patients with Parkinson's disease: a preliminary cross-sectional study using ultrasonography. *Parkinsonism Relat Disord.* (2018) 55:148–9. doi: 10.1016/j.parkreldis.2018.06.002
16. Yeh YH, Lemola K, and S. Nattel. Vagal atrial fibrillation. *Acta Cardiol Sin.* (2007) 23:1–12.
17. de Vos CB, Nieuwlaat R, Crijns HJ, Camm AJ, LeHeuzey JY, Kirchhof CJ, et al. Autonomic trigger patterns and anti-arrhythmic treatment of paroxysmal atrial fibrillation: data from the Euro Heart Survey. *Eur Heart J.* (2008) 29:632–9. doi: 10.1093/eurheartj/ehn025
18. Mont L, Sambola A, Brugada J, Vacca M, Marrugat J, Elosua R, et al. Long-lasting sport practice and lone atrial fibrillation. *Eur Heart J.* (2002) 23:477–82. doi: 10.1053/euhj.2001.2802
19. Katritsis GD, Katritsis DG. Cardiac autonomic denervation for ablation of atrial fibrillation. *Arrhythm Electrophysiol Rev.* (2014) 3:113–5. doi: 10.15420/aer.2014.3.2.113
20. Lee YC, Lin CH, Wu RM, Lin MS, Lin JW, Chang CH, Lai MS. Discontinuation of statin therapy associates with Parkinson disease: a population-based study. *Neurology* (2013) 81:410–6. doi: 10.1212/WNL.0b013e31829d873c
21. Kieburtz K, Wunderle KB. Parkinson's disease: evidence for environmental risk factors. *Mov Disord.* (2013) 28:8–13. doi: 10.1002/mds.25150
22. Macleod AD, Henery R, Nwajiugo PC, Scott NW, Caslake R, Counsell CE. Age-related selection bias in Parkinson's disease research: are we recruiting the right participants? *Parkinsonism Relat Disord.* (2018) 55:128–33. doi: 10.1016/j.parkreldis.2018.05.027

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REVIEW
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The Investigation of the Cardiovascular and Sudomotor Autonomic Nervous System—A Review

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The autonomic nervous system as operating system of the human organism permeats all organ systems with its pathways permeating that it is involved with virtually all diseases. Anatomically a central part, an afferent part and sympathetic and parasympathetic efferent system can be distinguished. Among the different functional subsystems of the autonomic nervous system, the cardiovascular autonomic nervous system is most frequently examined with easily recordable cardiovascular biosignals as heart rate and blood pressure. Although less widely established, sudomotor tests pose a useful supplement to cardiovascular autonomic assessment as impaired neurogenic sweating belongs to the earliest clinical signs of various autonomic neuropathies as well as neurodegenerative disorders and significantly reduces quality of life. Clinically at first, the autonomic nervous system is assessed with a detailed history of clinical autonomic function and a general clinical examination. As a lof of confounding factors can influence autonomic testing, subjects should be adequately prepared in a standardized way. Autonomic testing is usually performed in that way that the response of the autonomic nervous system to a well-defined challenge is recorded. As no single cardiovascular autonomic test is sufficiently reliable, it is recommended to use a combination of different approaches, an autonomic test battery including test to measure parasympathetic and sympathetic cardiovascular function (deep breathing test, Valsalva maneuver, tilt, or pressor test). More specialized tests include carotid sinus massage, assessment of baroreceptor reflex function, pharmacological tests or cardiac, and regional hemodynamic measurements. Techniques to measure functional integrity of sudomotor nerves include the quantitative sudomotor axon reflex sweat test, analysis of the sympathetic skin response as well as the thermoregulatory sweat test. In addition to these rather established techniques more recent developments have been introduced to reduce technical demands and interindividual variability such as the quantitative direct and indirect axon reflex testing or sudoscan. However, diagnostic accuracy of these tests remains to be determined. We reviewed the current literature on currently available autonomic cardiovascular and sudomotor tests with a focus on their physiological and technical mechanisms as well as their diagnostic value in the scientific and clinical setting.

Keywords: autonomic nervous system, laboratory evaluation of cardiovascular function, orthostatic tests, valsalva maneuver, heart rate variability, axon reflex, sympathetic, sudomotor function

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INTRODUCTION

Functional disorders in the autonomic or vegetative nervous system play an extremely important role in the suffering spectrum of many patients and in everyday medical practice (1). There is absolutely no disease or ailment that does not involve autonomic regulation or innervation disorders. The importance of the autonomic nervous system lies, among other things, in the fact that every organ of the human body is innervated and thus regulated by the autonomic nervous system (2, 3). Thus, the autonomic nervous system tries to restore "sympathy" (Galen) between the individual functional systems after a disturbance of the balance of the human body with the help of certain adjustment reactions. The cardiovascular system is most frequently examined in autonomic functional diagnostics (4). On the one hand, the measurement parameters of interest such as heart rate or blood pressure can be measured relatively easily and on the other hand prognostic statements can be made for patients e.g., after myocardial infarction or with diabetic neuropathy (5).

Anatomical Basics

Different areas of the brain are regarded as components of a complex central autonomic network that processes incoming information from the periphery (**autonomic afferences**) and generates a corresponding stimulus response to the peripheral target organs (**autonomic efference**) (6). Within this efferent system, two mostly opposing components are traditionally distinguished (2, 3):

- The sympathetic nervous system is the so-called "emergency system." After activation, it leads, among other things, to pupil dilation, acceleration of the heart rate, increase in heart power, and vascular resistance. After the sympathetic nerves have left the spinal cord in the thoracic and lumbar vertebrae, they still have to be switched over to the second sympathetic neuron either in prevertebral or paravertebral ganglia. If there is a disturbance prior to this ganglion switching, it is called preganglionic damage, otherwise it is called postganglionic damage. Acetylcholine is released as a transmitter at all preganglionic nerve endings and postganglionic at the sweat glands, while norepinephrine is released postganglionically at the effector organs with the exception of the sweat glands.
- The parasympathetic nervous system is simply understood as an opponent of the sympathetic system, i.e., as a "resting or recovery system" which, for example, plays a major role in controlling digestion. After activation, it leads, among other things, to pupil reduction, decrease in heart rate and activation of digestion. In the upper part it also supplies the eyes, tear and salivary glands, heart, lungs as well as the digestive tract after ganglion switching. The nerve fibers emerging from the coccyx are crucial in controlling the urinary tract and the lower digestive tract. The primary neurotransmitter of postganglionic parasympathetic neurons is acetylcholine.

Most organs of the body are innervated by efferent autonomic nerve fibers from both the sympathetic and parasympathetic nervous system. The cholinergic cardiac innervation delivers substantial supply to the ventricles in particular. Cholinergic/noradrenergic co-transmission is apparently a unique feature of the primate autonomic sympathetic nervous system (7). However, over the recent decades we learned that the autonomic nervous system does not operate only with acetylcholine and noradrenaline as classical transmitters (8), A growing number of different especially peptidergic signaling molecules (e.g., VIP, PACAP, CGRP, Substance P) have been described (9). This neuropeptide co-transmission in the autonomic nervous system increases the flexibility to synapses and circuits, including the surprising range of degrees of freedom.

Physiological Basics

In the regulation of the cardiovascular system, a sufficient blood supply to the tissue corresponding to the need must be ensured at all times as a decisive parameter. A sufficiently high blood pressure is essential for an adequate blood supply to the tissue. The autonomic nervous system with the **baroreceptor reflex** is decisively involved in its short-term regulation in particular (10, 11):

Special sensors in the area of the carotid sinus and the aortic arch can signal a drop in blood pressure via the cranial nerves IX and X to autonomic control centers in the brain, e.g., as a result of a change of position into the vertical body position (12). Certain circulatory centers in the brain stem, such as the nucleus tractus solitarii, process the signals and activate the sympathetic efference, which leads to an increased heart rate and inotropy, a mobilization of blood reserves from the venous system and an increase in systemic vascular resistance (13). At the same time, parasympathetic activity to the heart is reduced, which also contributes to an increase in heart rate.

The example of the baroreceptor reflex shows a basic principle of the autonomic nervous system, the **autonomic reflex arc** as a control loop (14, 15). Each of the various autonomic reflex arcs consists of an afferent, a central processing and an efferent component (16). The afferent signal mostly comes from specialized sensors such as the baroreceptor, which can detect changes in a biosignal and convert them into nerve impulses. The signal reaches the central nervous system via peripheral nerves or cranial nerves. After repeated neuronal switching, the afferent signal is further processed there in comparison with other signals and control information in higher regulation centers, whereby several specific central nervous processing centers usually exist for each reflex arc. From there, an efferent response is generated to the respective specific effector organs of the control loop, e.g., the smooth vascular muscles. The reaction of the effector organ helps to eliminate the disturbed state previously detected by the sensors with the help of a specific counter-regulatory mechanism.

The sudomotor autonomic system complements cardiovascular autonomic control in upholding a stable thermoregulation of the human body. The two major mechanisms involved in maintaining a constant body temperature of 37°C are dilation/constriction of cutaneous vessels and sweat production. The cerebral center of thermoregulation and sudomotor function is the hypothalamus which processes input from visceral and peripheral

thermoreceptors to determine sudomotor activity via two separate efferent pathways to regulate temperature control. These pathways are somatic motor fibers mediating an increase in body temperature by inducing muscle shivering as well as sympathetic fibers regulating blood vessel and sudomotor function, the latter resulting in a decrease of body temperature upon activation (17). Efferent sympathetic sudomotor pathways originate from the hypothalamus and travel via the pons and the lateral reticular medulla to the intermediolateral column. After leaving the spinal cord, the preganglionic cholinergic neurons of the intermediolateral column form synapses with postganglionic sympathetic cholinergic sudomotor neurons. Postganglionic control of cutaneous sweat glands is mediated by axons of these neurons which innervate the skin as unmyelinated C-fibers. Up to 3.5 liters of sweat can be produced per day depending on thermoregulatory demands. Autonomic control of sweat production is in large parts influenced by environmental factors, such as humidity, temperature and is additionally dependent of age and gender. Due to high complexity and susceptibility toward environmental factors as well as inter and intra subject variability of sweat gland density sudomotor function assessment comprises some of the technically most demanding tests of the autonomic nervous system.

Anamnesis of the Cardiovascular Autonomic Nervous System

Especially in patients with a suspected disorder of the cardiovascular autonomic nervous system, a good symptom as well as system-oriented anamnesis and a clinical examination must be carried out before a possible visit to the autonomic function laboratory (**Table 1**) (18). A good anamnesis and clinical examination are usually much more effective than a "blind" functional diagnosis in an autonomic functional laboratory.

Indication for Autonomic Testing

Cardiovascular and sudomotor autonomic testing are indicated for a number of disorders and conditions. Clinically autonomic testing is useful in defining the presence of autonomic dysfunction, to provide differential diagnostic information, or to quantify autonomic function regarding their natural history and response to treatment (19). Main clinical indications are:

- When generalized autonomic failure is suspected (20). Generalized autonomic failure can be due to multiple system atrophy (MSA), pure autonomic failure (PAF) or autonomic neuropathies (diabetic, amyloid, Sjogren's syndrome, subacute autoimmune). Getting the diagnosis of this disorder is important to evaluate the prognosis.
- To detect limited autonomic failure, which can masquerade under a number of guises as chronic idiopathic anhidrosis, syncope, orthostatic intolerance or distal small fiber neuropathy.
- To differentiate benign autonomic disorders that can mimic life-threatening disorders. For instance, benign neurocardiogenic syncope need to be evaluated to rule out generalized autonomic failure. Chronic idiopathic anhidrosis can only be diagnosed with normal sympathetic and parasympathetic function.
- To evaluate orthostatic intolerance (21). Orthostatic intolerance including orthostatic hypotension, syncope or postural orthostatic tachycardia syndrome (POTS) means development of symptoms of cerebral hypoperfusion or autonomic overaction on orthostatic challenge with resolution on recumbency. Cardiovascular autonomic testing can evaluate the presence and severity of this condition and can differentiate whether underlying autonomic failure is present.
- To differentiate multiple system atrophy (MSA) from typical Parkinson's disease which can be done nicely by combining cardiovascular and sudomotor testing (22).
- To monitor the clinical course of autonomic dysfunction over time. The twin attributes of autonomic testing, quantitation and non-invasiveness, render it ideally suited to monitor the time course of autonomic dysfunction.
- To evaluate the response to treatment of autonomic dysfunction. The autonomic problems may lessen in response to treatment. When treatment is initiated, the quantitative methods of autonomic testing are needed to evaluate if the patient is responding in an adequate way.

TABLE 1 | Selection of important symptoms in anamnesis and examination of the cardiovascular autonomic nervous system.

History of the cardiovascular system	
• Blood pressure:	Orthostatic hypotension or syncopes—severity, frequency, duration • Triggers: Orthostasis, food intake, heat, physical exertion, etc. • Accompanying symptoms: anxiety, nausea, vomiting, dizziness, tiredness, tachycardia, disturbed vision or hearing, headache/neck/back pain, etc. • Subjective countermeasures: e.g., sitting down, crouching down, lying down Elevated blood pressure when lying down
• Heart rate:	Tachycardia at rest, during exercise or orthostasis, cardiac arrhythmias: disturbed sinus arrhythmia, non-variable heart rate
• Vasomotion:	heat/cold intolerance, sensitivity to cold ("cold acra"), skin trophics, skin color

CARDIOVASCULAR AUTONOMIC FUNCTIONAL DIAGNOSTICS IN GENERAL

Functional diagnostics of the cardiovascular autonomic functional system is intended to help assess the functional integrity of certain autonomic reflex arcs in order to detect and localize disorders (23). To test such a reflex arc, the afferent pathway of the autonomic reflex arc must first be activated from the resting state of the human organism using a suitable stimulus such as an orthostatic test to examine the baroreceptor reflex. The test person should be in a relaxed state of rest, because otherwise the changes to be observed and evaluated cannot be understood as the effect of the disturbance stimulus used alone (24). Each test may therefore only be carried out after a sufficient rest period, also between the individual function tests. On the

other side, the respective disturbance stimulus used must always be standardized in order to be able to determine the existence of a normal or pathological reaction to the disturbance stimulus by comparison with the cardiovascular stimulus response of a normal collective in individual cases (25). In order to assess the autonomic efferent reflex response, the nerve activity in the efferent autonomic nerve can be measured directly by microneurography (26). An indirect evaluation by measuring functional parameters of the effector organs, such as heart rate or blood pressure, is much easier and is therefore more common (4, 16).

The quality of a functional test of the cardiovascular autonomic nervous system depends on whether a conclusion can be made after the examination regarding the existence, type, severity, localization, prognosis of a dysfunction and the therapeutic effectiveness on the individual patient. The ideal autonomic functional test should be easy and safe to perform, clearly understandable, non-invasive, reproducible, sensitive and specific as well as suitable for long-term studies (6, 27).

Even though most autonomic functional tests are relatively easy to perform, the interpretation of the test results is often difficult due to the complexity of the individual reflex arcs and the fact that many external and internal disturbances can influence the test results (8). For example, age, physical fitness, patient medication or even room temperature in the examination room are important influencing factors in autonomic functional diagnostics. This requires strict standardization of patient preparation, test procedures and evaluation using standard values and test algorithms created for all laboratories (28). Therefore, **Table 2** lists some recommendations for standardized patient preparation.

TABLE 2 | Advice on patient preparation in cardiovascular autonomic function diagnostics.

Important advice for patient preparation before autonomic testing
48 h before the examination the following should be discontinued
• Anticholinergics (e.g., antihistamines, antidepressants)
• Sympathomimetics (α- and β-agonists)
• Parasympathic mimetics
• Mineralocorticoids (e.g., 9-α-Fludrocortisone)
• Diuretics
24 h before the examination the following should be discontinued
• Sympathicolytics (α-antagonists, β-antagonists)
12 h before the examination the following should be discontinued
• Alcohol
• Analgesics
At the morning of the examination
• No wearing of confining clothing
• No corset
• No support stockings
3 h before the examination the following should be discontinued
• Nicotine
• coffee
• food

BIOSIGNALS USED IN CARDIOVASCULAR AUTONOMIC FUNCTION DIAGNOSTICS

The following biosignals are frequently used in cardiovascular autonomic function diagnostics:

- **Heart Rate:** Continuous ECG leads allow for a precise and current evaluation of the current heart rate. The heart rate, like blood pressure, is not a constant but a physiologically constantly changing biosignal. The investigation of this **heart rate variability (HRV)**, which is dependent on many factors (e.g., respiration), can provide information concerning the function of the cardiovascular autonomic nervous system (29). The days of manual evaluation of ECG strips are a thing of the past due to the automated and computer-aided algorithms available today. Although cardiac automaticity is intrinsically ensured by various pacemaker tissues, the autonomic nervous system regulates heart rate and rhythm in many ways. The variations of heart rate are modulated by a fine tuning of beat-to-beat control mechanisms by central (vasomotor and respiratory centers of the brain stem) and peripheral (oscillation of arterial blood pressure and respiration) oscillators (30). These oscillators generate rhythmic fluctuations of efferent nerve discharges which manifest themselves in short-term and long-term variations of the heart rate.
  An analysis of HRV allows for an evaluation of the status and function of the central oscillators, sympathetic and parasympathetic efference, humoral factors, and sinus node. The parasympathetic system mainly mediates reflective changes in heart rate to corresponding afferent signals of the arterial baroreceptors and the respiratory system, while the sympathetic system is mainly responsible for changes in heart rate to physical and mental stress. HRV is not clearly gender-dependent, but is clearly age-dependent (31). For more specific computer-aided HRV calculations, the ECG signal is sampled and digitized at a sampling frequency of 256 Hz (32). This is followed by an R-wave detection with subsequent RR interval calculation, whereby as many artifacts as possible are excluded by appropriate algorithms (27). Computer aided, the RR interval duration can be displayed over the interval number as a so-called tachogram.
  The raw data of the ECG recording must be statistically evaluated using appropriate methods due to the large amount of data. This can be done using the time domain analysis and the frequency domain analysis (33).
- The parameters of time domain analysis such as mean value, standard deviation or coefficient variation are relatively easy to calculate. Using mathematical statistical methods, essential and typical information can be filtered out of the measured signals and clearly displayed. Thus, the RR histogram shows the frequency of RR intervals at various lengths.
  In the frequency domain analysis, various spectral analytical methods allow conclusions to be drawn as to the variance distribution as a function of frequency and as to frequency-specific oscillations (33). Thus, not only the degree of variability described by the standard deviation can be

determined, but also the corresponding oscillation frequency. Spectral analysis converts series of sequential RR intervals into a sum of sinusoidal functions of varying amplitudes and frequencies (34). The various spectral components are assigned to the different parts of the autonomic nervous system: The high frequency *HF (0.15–0.5 Hz) component* is mainly caused by efferent vagal activity. The low frequency *LF (0.05–0.15 Hz) component*, in contrast to the HF component, does not permit such an unambiguous identification (35). Thus, one can see a quantitative marker of efferent sympathetic activity with significant influences from parasympathetic activity in the LF component. The low frequency components [*very low frequency VLF (0.05 Hz) and ultralow frequency ULF]* cannot yet be adequately assessed in their results. The relationship between the low frequency (LF) and the high frequency component (HF) of spectral response is called sympathovagal balance by some authors. However, it should be noted that a change in the low frequency component (LF) can be mediated both sympathetically and parasympathetically, as already mentioned above (35).

- **Blood Pressure:** A major function of the sympathetic nervous system is the regulation of vascular tone (activity of the smooth vascular muscles), which in turn determines blood pressure and thus blood flow through the blood vessels. Like the heart rate, blood pressure also shows considerable variability (36). Blood pressure can be measured intermittently or continuously (37). Non-invasive, continuous blood pressure measurement is the gold standard for autonomic functional diagnostics and not only allows for the detection of short-term or slight blood pressure changes. It also allows for the quantitative assessment of important circulatory functions such as the baroreceptor reflex or blood pressure variability (10).
- **Respiration:** Although respiration has a decisive influence on functions of the autonomic nervous system such as heart rate variability, it is often not recorded or its influence neglected in the context of autonomic functional diagnostics (31). Recording respiration is important, for instance, in assessing whether the patient has a physiological respiratory pattern. For example, important diagnostic information for hyperventilation or apnea syndrome can be obtained from recording respiratory data. Secondly, knowledge of respiratory rate and volume is important for assessing respiration-dependent and respiration-independent oscillations in heart rate, blood pressure and blood flow. For example, slow, deep breaths can amplify the low frequency oscillations of heart rate and blood pressure to such an extent that this can lead to the false conclusion that increased sympathetic activity is the cause of this effect (38).
- **Blood flow:** Because vascular tone is not accessible for direct measurement, blood flow is used as the typical measurement for assessing vascular tone and thus the sympathetic vasomotor system (39). A quantitative assessment of blood flow requires the use of special methods based either on the principle of measuring changes in tissue temperature *(thermometry)*, the principle of volume change by blood flow *(plethysmography)* or the principle of the Doppler effect *(laser Doppler and Doppler sonography)*. It could be used to diagnose endothelial dysfunction (40).

THE MOST IMPORTANT CARDIOVASCULAR AUTONOMIC FUNCTION TESTS

Deep Metronomic Breathing

Physiology

Physiologically, an increase in heart rate can be observed while inhaling and a decrease in heart rate while exhaling, which is mainly due to changing parasympathetic activity. The dependence of the heart rate on respiration is called respiratory sinus arrhythmia (RSA). During a metronomic respiration with six deep breaths per minute, maximum values of respiratory HRV are reached that can be compared to established norm values (28, 31). In addition to RSA, the predominant periodic fluctuations of the heart rate are the baroreceptor reflex heart rate change (so-called 10 s rhythm, and also known as the 3rd order blood pressure waves or described as Traube-Hering-Mayer waves) and the thermoregulatory heart rate change (41).

Implementation

In order to gain information about heart rate variability, the test person is instructed to breathe deeply and evenly so that the inhalation and exhalation phases each last 5 s. Avoid prolonging this test beyond 2 min because the hypocapnia that occurs will result in an increase in heart rate and reduced HRV.

Assessment

A simple assessment of HRV in metronomic respiration allows for the calculation of the strongly age-dependent quotient from the longest heart rate intervals during exhalation to the shortest intervals during inhalation **(I:E Ratio)** (42–45). For metronomic breathing at six breaths per minute, this age-dependent quotient should be >1.2. The E-I difference is the difference of the RR intervals during exhalation minus the RR intervals during inhalation during metronomic respiration. Physiological values are >15 beats per minute (bpm), threshold 11–14 bpm, pathological from 10 bpm.

Orthostatic Maneuver

Physiology

The simplest and most commonly used method for assessing cardiovascular feedback is to measure cardiovascular parameters (such as heart rate, blood pressure, noradrenaline concentration) during a change from horizontal to vertical body position (46). During the transition from lying to standing, a displacement of 400–600 ml of blood into the leg veins occurs as a result of hydrostatic pressure changes (47). This leads to a short-term reduction in the venous return flow to the heart, which in turn reduces the heart beat volume and thus the arterial blood pressure. Due to the very rapid onset of compensatory mechanisms, arterial blood pressure changes only slightly in healthy patients. However, in 10–15% of all people, orthostatic circulatory disorders are observed due to insufficiency of these compensatory mechanisms (48).

Implementation

Orthostatic test can be carried out actively (Schellong test) by the test person standing up independently, or passively (tilt table test) using a tilting table (optimum tilting angle of 60°) (49). Both methods differ from each other especially in terms of their initial cardiovascular reactions (16). The blood pressure should be recorded continuously or intermittently (every 2.5 min) over an interval of 5–10 min before and at least 10 min after the change in position, parallel to a continuous ECG. During the test, patients must avoid both hyperventilation and a Valsalva maneuver.

Assessment

The heart rate and blood pressure changes recorded during the test are evaluated:

- Heart rate changes within the first 30 s after getting up allow for an assessment of the cardiac parasympathetic system. The ratio of the longest RR interval at about 30 heartbeats to the shortest RR interval at about 15 heartbeats is defined as "30:15 ratio" or "Ewing ratio" and represents a reproducible age-dependent index of cardiovagal function (39). Modern devices no longer calculate the pure 30:15 ratio, but the quotient of the longest RR interval between 20 and 40th heartbeat and the shortest RR interval between 5 and 25th heartbeat. Physiologically, the 30:15 ratio has a value >1.04.
- In orthostatic diagnostics, a systolic or diastolic blood pressure drop of at least 20 or 10 mmHg within 3 min after active placement or erection on the tilt table indicates so-called **orthostatic hypotension** (50). If the orthostatic symptoms are so severe that the patient cannot stand for at least 3 min, the standing time until the occurrence of orthostatic-dependent symptoms is recorded.

For checking syncope or suspected **postural tachycardia syndrome (POTS)**, an extended tilt test with a tilting time of up to 90 min can be performed. The main symptom of POTS is an excessive orthostatic tachycardia, which is at least 30 BpM/min higher than the initial frequency or persistently above 120 BpM/min within 10 min of changing position (51, 52). In a **neurocardiogenic syncope**, a sudden drop in blood pressure usually occurs only after a prolonged period of inactivity, usually without compensatory tachycardia, but with a bradycardia as well as presyncopal or syncopal symptoms (53).

Other special forms of the tilt table test are the orthostatic test after food intake (*splanchnic vasodilatation*) and the orthostatic test after physical exertion (*muscular vasodilatation*) as well as the tilt table test with negative pressure application in the area of the lower body half (*lower body negative pressure test*) by means of a special pressure chamber (54).

Valsalva Maneuver

Physiology

The cardiovascular system's stimulus response to the Valsalva maneuver provides crucial information as to the integrity of the cardiovascular autonomic system e.g., the baroreceptor reflex. The hemodynamic response to a sudden, short-term increase in intrathoracic and abdominal pressure can be divided into four phases (55–57):

After a brief increase in blood pressure for 1–2 s (**Phase I**) due to mechanical compression of the aorta, arterial blood pressure decreases due to reduced cardiac preload and stroke volume (early **Phase II**). The decrease in systemic blood pressure is counteracted by an increase in heart rate and peripheral vasoconstriction, which causes arterial blood pressure to slowly rise back to a level at least equal to the previous blood pressure (late **Phase II**). After completion of the intrathoracic pressure increase, an excessive increase in diastolic and systolic blood pressure occurs after a brief mechanical drop in blood pressure (**Phase III**), because the venous reflux and thus the stroke volume suddenly increase, but the arterial vascular bed is constricted due to the still increased sympathetic activity (**Phase IV**). Due to the counter-regulatory activity of the baroreceptor reflex, the heart rate decreases.

Implementation

The patient generates the increase in intrathoracic and intraabdominal pressure of 40 mmHg for 10–20 s by exhaling through a special mouthpiece (e.g., a 5 or 10 ml syringe, the plunger rod of which has been removed and which is fitted with a small hole and connected to a blood pressure measuring device instead of a needle) (58). The deciding factor here is that the exhaling patient continuously generates a pressure between 20 and 40 mmHg with the epiglottis open (hence the hole in the syringe as a leak in the system). In order to be able to interpret the circulation reactions of the Valsalva maneuver more reliably, it is advisable to carry out the test three times. In general, the Valsalva maneuver can be considered both reproducible and sensitive. The position of the patient also plays an important role: the circulation effects are more pronounced in a seated position than when lying down. A conclusive test result depends to a large extent on the patient's cooperation.

Assessment

Continuous blood pressure recording is used to determine the changes in blood pressure caused by intrathoracic pressure changes, which allow the sympathetic activity and, if necessary, the severity of a functional disorder of the sympathetic cardiovascular system to be assessed (**Table 3**).

The heart rate changes during this maneuver are considered established sensitive and specific evaluation possibilities for the function of the parasympathetic functional system (25). The age-dependent Valsava ratio is calculated from the quotient of the longest RR interval (bradycardia) after the maneuver and the shortest RR interval (tachycardia) during or shortly after the end of the maneuver. Physiologically, a ratio is >1.21. The threshold range is between 1.11 and 1.20, pathological values are ≤ 1.10.

Pressor Functional Tests

Physiology

The pressor stimuli applied here all lead to a stimulation of the sympathetic afference independent of the baroreceptor afference (45, 59). All pressor tests lead to an increase in blood pressure and heart rate. In the isometric hand grip test and cold pressor test,

TABLE 3 | Physiological and pathological changes in arterial blood pressure during the various phases of the Valsalva maneuver.

Lesion	Phase I	Phase II (early)	Phase II (late)	Phase III	Phase IV
None	Stress dependent increase in blood pressure	Arterial pressure drop	Increase in arterial blood pressure	Short-term drop in blood pressure	Excessive rise in blood pressure
Parasympathetic	Normal	Reduced blood pressure drop	Normal	Normal	Normal
Sympathetic, slight	Normal	Slight increase in blood pressure drop	Reduced to missing blood pressure increase	Normal	Slight reduction of the increase in blood pressure
Sympathetic, moderate	Normal	Significant increase in blood pressure drop	Missing blood pressure increase	Normal	Significant reduction in blood pressure increase
Sympathetic, severe	Normal	Severe drop in blood pressure	Missing blood pressure increase	Normal	Missing blood pressure increase

peripheral receptors are activated in addition to an important cerebral activation. The effect of other stimuli, such as the mental arithmetic test, depends primarily on cerebral activation.

Implementation

The **isometric hand grip test** evaluates changes in heart rate and blood pressure over a 3 min compression of a hand dynamometer or a partially inflated blood pressure cuff to approximately one third of the maximum fist closure force (60). In the **cold pressor test**, the stimulus lies in the 2 min immersion of one hand in ice water (61). In the **mental arithmetic test**, the patient must solve a complex sequential arithmetic problem during a 2 min interval (62).

Assessment

In most cases, the pressor function tests provide valuable information as to the function of the efferent sympathetic system, whereby isometric hand grip and cold pressor tests are the most conclusive, given that the overall examination time required is quite short. The increase in heart rate and blood pressure are assessed in relation to the respective stimulus. It should be noted that many factors, such as muscle weakness, can influence test results independently of the autonomic nervous system.

Carotid Sinus Massage

Physiology

The carotid sinus massage examines the sensitivity of the baroreceptors of the carotid sinus and the parasympathetic efference. It should be used in syncope diagnosis if the patient's medical history suggests the suspicion of a hypersensitive carotid sinus. The maneuver leads physiologically to a moderate reduction in heart rate and possibly blood pressure as well.

Implementation

On a lying patient, the carotid sinus is observed with the head slightly bent backwards, palpated and a slight pressure is exerted for 20–30 s first on the right side and after a break of a few minutes also on the left side. If there is no cardiac response, the maneuver is repeated with increased massage pressure.

Assessment

Heart rate and blood pressure changes are assessed during sinus pressure application. While physiologically there is only a slight drop in heart rate and blood pressure, carotid sinus syndrome can cause asystole for more than 3 s and a significant drop in blood pressure (systolic blood pressure drop >50 mmHg) (19). Therefore, it may only be performed after strict diagnosis and Doppler sonographic examination of the cervical vessels as well as continuous ECG monitoring.

Baroreceptor Sensitivity

The exact evaluation of the baroreceptor reflex, the so-called baroreceptor sensitivity, is becoming increasingly important for the diagnosis and understanding of pathophysiological relationships in numerous neurological and cardiological diseases due to the decisive role of this reflex for cardiovascular regulation as described above. In addition to the pharmacological examination (so-called Oxford method) (37), in which the effects of drug-induced blood pressure changes on the heart rate are assessed, the examination is also available by means of "neck suction," i.e., a negative pressure stimulation of the neck region and thus of the baroreceptors, as well as the computer-assisted analysis of the relationships between spontaneous blood pressure and heart rate modulation. So trigonometric regressive spectral (TRS) analysis is a newly developed technique and solves several shortcomings of the traditional methods, mainly fast Fourier transform and autoregressive methods for spectral analysis (63). The analysis of a given electrocardiography recording (global data segment) is performed by multiple shifting local data segments, thus the software using TRS for spectral and baroreflex analysis is called multiple trigonometric regressive spectral analysis (MTRS) (27, 64).

Special Functional Tests of the Autonomic Cardiovascular System

Another test described in the literature is the squatting test, in which squatting leads to an increase in systemic arterial pressure followed by bradycardia (24). Active rising again leads to a drop in arterial blood pressure, followed by tachycardia. The significance of this test is controversial.

Pharmacological methods help to check the sensitivity of different receptors and the functional integrity of the autonomic nervous system (65). For example, the response of the circulatory system to the application of noradrenaline allows the sensitivity of alpha-adrenoceptors activated by noradrenaline to be assessed. A physiological increase of the heart rate after administration of atropine indicates an intact cardiac vagal control. Tyramine releases noradrenaline from the granules and cytosol of postganglionic sympathetic neurons, so that their lesion lacks

the characteristic increase in blood pressure and noradrenaline concentration after tyramine administration.

Pathological changes in metabolism and the function of neurotransmitters and hormones indicate the severity and localization of autonomic dysfunctions. The catecholamines—among them especially noradrenaline—are regarded as markers of sympathetic activity in plasma and urine, especially since there is a significant correlation between sympathetic nerve activity and noradrenaline concentration in plasma (66). During the orthostatic maneuver, blood samples can also be taken from patients before and after a change of position to determine neurotransmitters and hormones. However, it should be noted that the venous access is applied well before the start of the examination because the application of a venous access *per se* leads to significant changes in the hormone and neurotransmitter concentrations in the blood. In special cases, the determination of the hormones of the renin-angiotensin-aldosterone system or of vasopressin can also provide further information.

Sudomotor Assessment: Clinical Significance

Sudomotor dysfunction can lead to either increased or decreased sweating, both of which can have severe implications to the subject's wellbeing and quality of life. Sudomotor dysfunction can occur both in central disorders affecting centers of sudomotor control such as acute ischemic stroke, multiple sclerosis and neurodegenerative syndromes as well as autonomic peripheral neuropathies which selectively affect unmyelinated and small, lightly myelinated nerve fibers (67, 68). Autonomic peripheral neuropathy is most frequently caused by diabetes but can also result from various diseases such as acute and chronic infections, primary or hereditary amyloidosis, paraneoplastic disorders such as Lambert–Eaton syndrome as well as some neurotoxins (e.g., cisplatin, vacor) (67). Patients suffering from sudomotor function may report either increased sweating in higher environmental temperatures or heat intolerance due to anhidrosis. These symptoms can significantly limit quality of life, for example, when patients with hyperhidrosis avoid social embarrassment due to visibly increased sweating in high temperature environments. Therefore, care of patients with sudomotor dysfunction requires detailed anamnesis of habits and social life. Furthermore, dyshidrosis related changes to epidermal moisturization may lead to hyperkeratosis, rhagades, ulcers or impaired wound healing highlighting the value of thorough visual inspection in these patients (17). According the concept of neurogenic inflammation, the dense innervation network of sensory and autonomic fibers in peripheral organ tissues can mediate a rapid local and systemic neurogenic modulation of immunity (69). So peripheral neurons can play a significant role in immune dysfunction in autoimmune and allergic diseases.

Thermoregulatory Sweat Testing (TST)

The TST allows qualitative analysis of pre- and postganglionic sweating of the ventral body surface using quinizarin as color indicator to highlight sweating patters. Performing the TST requires a humidity controlled (35–40%) testing environment which needs to be preheated to 45–50°C where the testing subject is examined in a supine position on a testing table [1]. An indicator dye, which shows a pH change with a color change, is scattered on the complete ventral skin surface (omitting the eye, ears and perioral region) (17, 70). Environmental parameters may be adapted to achieve the optimal skin temperature of 38.5–39.5°C to produce sweating in a controlled and comparable fashion. Digital images of sweating patterns are then taken and the anhydrotic skin area is divided by the total skin area and multiplied with 100. Neurological disorders may show distinct sweat patterns that deviate from the physiological sweating pattern of the entire ventral body surface. If viewed in conjunction with techniques of postganglionic sudomotor function assessment, the TST can help discriminate preganglionic from postganglionic lesions (17, 19). Probably the most significant advantage of the technique in the clinical setting is its capability to define sweat patterns topographically which may lead the way for diagnosis of neurological disorders, such as neuropathies, ganglionopathies or generalized autonomic failure. The most important limitation of TST are its high technical demands. To date, fully equipped TST chambers are available only in a few specialized autonomic laboratories centers.

Quantitative Sudomotor Axon Reflex Sweat Test (QSART)

The QSART was first introduced in 1983 by Phillip Low and colleagues and has become the most established test of postganglionic sudomotor function (71). The technique assesses responses to pharmacological stimulation of the cutaneous axon reflex in sudomotor nerve fibers by iontophoresis of acetylcholine, a cholinergic neurotransmitter. Acetylcholine then binds to nicotinic and muscarinic receptors. Upon activation of these receptors local sweat production is evoked in the skin area where acetylcholine has been applied. This response is also referred to as the direct sweat response. The sweat response is however not restricted to direct sweating. In addition to the immediate sweat response an action potential is generated in the stimulated sudomotor nerve fibers, which is then antidromically conducted to an axon branch point to switch to adjacent sudomotor nerve fibers and the orthodromically travel to a neighboring population of sweat glands. There an indirect, axon reflex mediated sweat reaction is evoked in a skin area surrounding the area of acetylcholine iontophoresis (17, 71) (**Figure 1**). Quantitative evaluation of sweating in the indirect skin area is a surrogate marker of functional integrity of the sympathetic C fiber mediating the axon reflex. Local sweat output is determined as change of relative humidity over time with assessment of latency, magnitude and duration of the sudomotor response. The most commonly used skin testing sites are the forearm, proximal and distal leg and dorsum of the foot. In the clinical setting QSART should be performed if impairment of the postganglionic sudomotor nerve fibers is presumed. The most frequent observation in neurological disorders on QSART is an attenuation of sweat volume, e.g., in patients with length-dependent diabetic neuropathy (72). However, increased sweat responses to acetylcholine application may also be present in

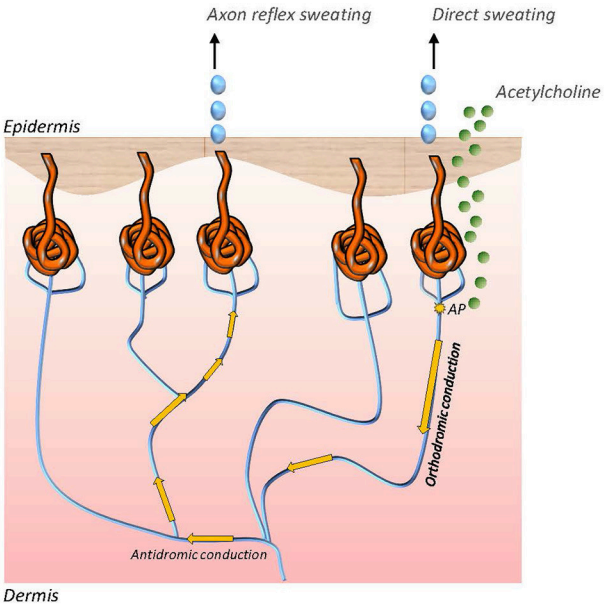

FIGURE 1 | Direct and axon reflex mediated sweating in sudomotor nerve fibers. While direct sweating occurs in the akin area of iontophoretic application of acetylcholine, indirect sweating is evoked by an axon reflex in adjacent sweat glands. The axon reflex response can be assessed to study functional integrity of the sympathetic C fiber which mediates the reflex.

small fiber neuropathy, particularly in early disease stages, due to supersensitivity of C fibers following denervation. QSART can be used in conjunction with TST to differentiate preganglionic from postganglionic damage in sudomotor nerve fiber. QSART has high diagnostic value as it shows low variability on repeated measures and between subjects, however it is limited by high technical demands and necessity of a stale testing environment with temperature and humidity control (17, 73).

Quantitative Direct and Indirect Test of Sudomotor Function (QDIRT)

The QDIRT was developed to assess postganglionic sudomotor function with temporal and spatial resolution of axon reflex mediated sweat responses in a technical setting which is less demanding than the QSART (74). The techniques utilizes repeated digital photography to capture axon reflex sweating upon iontophoresis of acetylcholine in a skin region pretreated with an indicator dye highlighting sweat droplet. Digital photographs are taken every 15 s over 7 min. The area of direct sweating is the skin region with direct contact to acetylcholine, whereas the area of axon reflex sweating is calculated as the total area of sweating minus the diameter of iontophoresis capsule (which is used to apply acetylcholine). Sweat droplets in the axon reflex region are analyzed for number, size and change in sweat area time. Although compared with QSART, QDIRT might decrease technical demands; the environmental prerequisites such as controlling for temperature humidity are still considerable limiting its clinical implication. More importantly QDIRT has been rarely used in research studies to date. Therefore, normative data to compare individual clinical diagnostic observations with are lacking. Multicentric prospective research of sudomotor (and pilomotor) function in patients with Parkinson's disease and healthy controls is currently under way (75).

Sympathetic Skin Response (SSR)

Assessment of sympathetic skin responses with continuous measurement of electrodermal activity following sympathetic stimulation is performed with a surface electromyography electrode placed on the patient's palm or sol and a reference electrode (76, 77). Sympathetic stimulation can be undertaken by electrical stimulation or deep inspiration. Environmental factors should be well controlled for with stable light conditions and room temperature between 22 and 24°C. In addition humidity should be controlled and kept stable. Data is expressed graph indicating changes of skin conductance level over time and is analyzed for latency and amplitude following sympathetic stimulation. SSR has been investigated extensively in research studies, e.g., in patients with spinal cord trauma or diabetic neuropathy. The technique has yielded high sensitivity for changes in electrodermal conductance following emotional responses. Therefore, it is frequently used in lie detector systems as well as in psychophysiological studies (78, 79). However, due age dependent decline in sympathetic responsiveness and high interindividual variability its use in individual patients is largely limited to conditions were complete absences of the response on one testing site can be compared with recordable responses on a separate testing site (**Figure 2**). Although extensive research has been undertaken to define sensitivity and specificity of SSR, the mechanisms mediating this somato-sympathetic reflex are poorly understood to date (77).

Sensitive Sweat Test (SST)

The Sensitive Sweat Test evaluates sweat secretion of each singular sweat gland and additionally captures quantity, location, and distribution of active sweat glands (77). Postganglionic sudomotor function is assessed upon iontophoresis of pilocarpine solution followed by staining of the stimulated skin region with povidone-iodine to highlight sweat droplets. A small video camera is placed on the skin are where iontophoresis is performed on.

Recording of the color change of the indicator dye due to pilocarpine induced sweating enables evaluation of sweat gland responsiveness with spatial and temporal resolution with the area of each color spot being proportional to sweat volume produced by the corresponding sweat gland and spread rate of each spot being proportional to sweat production over time. Pilocarpine is a direct cholinergic agonist, acting by activating tubular M3-receptors located on sweat glands. Axon-reflex responses are observed following pilocarpine application. The SSR therefore differs from QSART and QDIRT which primarily aim to evaluate neurogenic axon reflex mediated sweat responses. The technique is relatively fast to perform and requires a comparatively uncomplicated technical setting, highlighting its potential clinical use.

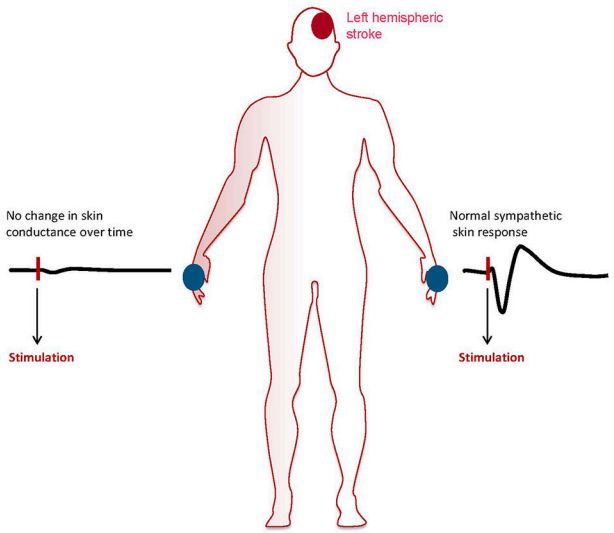

FIGURE 2 | Patient with left hemispheric acute ischemic stroke showing abolished sympathetic skin response on the right hand and normal responsitivity on the left hand. The graphs show skin conductance levels (micro Sievert) over time after sympathetic stimulation.

Spoon Test

The spoon test has been designed as non-quantitative bedside screening test of sudomotor dysfunction (80). It is based on the observation that smooth sliding of the convex side of a spoon is impeded by anhidrotic dry skin. The technique shows highest specificity and sensitivity for detection of anhidrosis when performed on the chest or forehead (80, 81). Although the techniques is extremely easy to perform it lacks any quantitative analysis of sudomotor function and its results depend on the investigator's subjective perception of the smoothness the spoon slides over the skin with. However, its sensitivity as a bedside screening tool exceeds that of other available screening tools such as visual inspection of the skin surface and might therefore be a valuable addition to standard physical examination in patients suspected of having a disease which potentially affects autonomic sudomotor function (81).

Sudoscan

Sudoscan is a recently developed technique which utilizes reverse iontophoresis and chronoamperometry to assess chloride ion concentration of the skin as a measure of sudomotor output. Applied electric current (incremental on the anode) induces a shift of chloride ions from the sweat glands to the external skin surface resulting in a current between the anode and a reference electrode which is proportional to the cutaneous chloride concentration. The technique is easy to perform and has been studied in patients with diabetic neuropathy (82–84). However, it remains to be determined whether sudoscan captures functional integrity of sweat glands, sudomotor nerve fibers or both to increase its diagnostic value in the diagnostic work up of patients with sudomotor dysfunction.

SUMMARY

In order to do justice to the variety of autonomic reflex systems in the autonomic functional laboratory, a combination of several different functional tests in the form of an autonomic test battery makes sense. No autonomic functional test alone is sufficiently valid. Functional tests to assess the parasympathetic nervous system (e.g., HRV in metronomic respiration) should be combined with functional tests to assess the sympathetic nervous system (e.g., blood pressure changes during orthostatic and Valsalva maneuvers).

In order to quantify the severity of an autonomic dysfunction, within a test battery such as the Ewing test battery (24) established for diabetic autonomic neuropathy, an evaluation system (0 points = physiological response, 1 = borderline response, 2 = pathological response) can be used to calculate an "autonomic test value" whose changes can be assessed, for example, in the course of a disease. Depending on the patient's symptoms or medical suspicion, more specific autonomic functional tests such as the carotid sinus massage presented here should also be carried out in special cases.

The practical implementation of autonomic functional diagnostics can be regarded as very safe. In essence, autonomic functional diagnostics can be performed without major patient stress and usually non-invasive. Nevertheless, due to possible heart rhythm disturbances, the ECG should be recorded continuously during the entire examination. In the case of an orthostatic test (change from the horizontal to the vertical body position), the subject should lie down immediately with the help of the examiner in the event of a drop in blood pressure or dizziness symptoms.

Due to the many interfering factors, autonomic functional diagnostics is relatively susceptible to external and internal influences, some of which can complicate the interpretation of test results. This makes standardized patient preparation and test execution all the more important in autonomic functional diagnostics. Due to the complexity of the autonomic nervous system, many phenomena have not yet been clarified, so that autonomic functional diagnostics is in a constant state of flux. For this reason, further training and cooperation between the various disciplines are crucial in the field of autonomic functional diagnostics.

Although less established and less widely used than cardiovascular autonomic testing, sudomotor assessment has been of increasing interest to both research studies and clinical diagnostic assessment. Improvement of precision and external validity as well as reduction of technical demands made this possible. Moreover, research has shown that neurogenic sweating is among the earliest clinical signs of a variety of autonomic neuropathies and neurodegenerative disorders highlighting diagnostic value of these techniques. However, further research is urgently needed to generate normative data sets beyond the well-studied QSART technique which shows high precision and low variability but is technically demanding. Normative data and detailed studies of sensitivity, specificity and external validity of newer techniques such as SST, QDIRT and Sudoscan are needed.

In summary, the established functional tests of the cardiovascular autonomic nervous system presented here are sufficiently standardized and well-proven. In most cases, they allow for an assessment of the cardiovascular autonomic nervous system by simple means. The daily application possibilities of these procedures in clinical routine should lead to the establishment of an autonomic functional laboratory in addition to the existing EEG, EMG, or ultrasound laboratories, which, in addition to routine diagnostics of autonomic functional disorders, can also offer a more specific diagnostics of cardiovascular autonomic functions. Although sudomotor testing using QSART and TST is also well studied, future technical improvement and research is needed to provide a set of sudomotor diagnostic techniques which yields a level of practicability and precision that is comparable to cardiovascular autonomic testing. Early and often profound affection of the sudomotor nervous system in prevalent neurological disorders such as synucleinopathies highlights the urgent need for well-designed studies in large cohorts with sudomotor dysfunction.

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TZ and TS: literature analysis and design of the study and writing the manuscript.

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REFERENCES

1. Goldstein DS, Robertson D, Esler M, Straus SE, Eisenhofer G. Dysautonomias: clinical disorders of the autonomic nervous system. *Ann Intern Med*. (2002) 137:753–63. doi: 10.7326/0003-4819-137-9-200211050-00011
2. Wehrwein EA, Orer HS, Barman SM. Overview of the Anatomy, physiology, and pharmacology of the autonomic nervous system. *Compr Physiol*. (2016) 6:1239–78. doi: 10.1002/cphy.c150037
3. Karemaker JM. An introduction into autonomic nervous function. *Physiol Measure*. (2017) 38:R89–118. doi: 10.1088/1361-6579/aa6782
4. Ziemssen T, Reichmann H. Cardiovascular autonomic dysfunction in Parkinson's disease. *J Neurol Sci*. (2010) 289:74–80. doi: 10.1016/j.jns.2009.08.031
5. Bauer A. Identifying high-risk post-infarction patients by autonomic testing - Below the tip of the iceberg. *Int J Cardiol*. (2017) 237:19–21. doi: 10.1016/j.ijcard.2017.03.087
6. Beissner F, Meissner K, Bär K-J, Napadow V. The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. *J Neurosci*. (2013) 33:10503–11. doi: 10.1523/JNEUROSCI.1103-13.2013
7. Weihe E, Schütz B, Hartschuh W, Anlauf M, Schäfer MK, Eiden LE. Coexpression of cholinergic and noradrenergic phenotypes in human and nonhuman autonomic nervous system. *J Comp Neurol*. (2005) 492:370–9. doi: 10.1002/cne.20745
8. Nusbaum MP, Blitz DM, Marder E. Functional consequences of neuropeptide and small-molecule co-transmission. *Nat Rev Neurosci*. (2017) 18:389–403. doi: 10.1038/nrn.2017.56
9. Benarroch EE. Neuropeptides in the sympathetic system - presence, plasticity, modulation, and implications. *Ann Neurol*. (1994) 36:6–13. doi: 10.1002/ana.410360105
10. La Rovere MT, Pinna GD, Raczak G. Baroreflex sensitivity: measurement and clinical implications. *Ann Noninvasive Electrocardiol*. (2008) 13:191–207. doi: 10.1111/j.1542-474X.2008.00219.x
11. Malliani A, Montano N. Gold standard in assessing baroreceptive function. *Hypertension* (2004) 43:e24. doi: 10.1161/01.HYP.0000120966.82562.90
12. Vanoli E, Adamson PB. Baroreflex sensitivity: methods, mechanisms, and prognostic value. *PACE* (1994) 17:434–45. doi: 10.1111/j.1540-8159.1994.tb01410.x
13. Benarroch EE. The arterial baroreflex: functional organization and involvement in neurologic disease. *Neurology* (2008) 71:1733–8. doi: 10.1212/01.wnl.0000335246.93495.92
14. Kawada T, Sugimachi M. Open-loop static and dynamic characteristics of the arterial baroreflex system in rabbits and rats. *J Physiol Sci*. (2016) 66:15–41. doi: 10.1007/s12576-015-0412-5
15. Li K, Reichmann H, Ziemssen T. Recognition and treatment of autonomic disturbances in Parkinson's disease. *Expert Rev Neurother*. (2015) 15:1189–203. doi: 10.1586/14737175.2015.1095093
16. Ziemssen T, Reichmann H. Cardiovascular autonomic testing in extrapyramidal disorders. *J Neurol Sci*. (2011) 310:129–32. doi: 10.1016/j.jns.2011.07.032
17. Buchmann SJ, Penzlin AI, Illigens BM-W. Assessment of sudomotor function. *Clin Auton Res*. (2018) 19:79. doi: 10.1007/s10286-018-0530-2
18. Reimann M, Schmidt C, Herting B, Prieur S, Junghanns S, Schweitzer K, et al. Comprehensive autonomic assessment does not differentiate between Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. *J Neural Trans*. (2010) 117:69–76. doi: 10.1007/s00702-009-0313-y
19. Low PA, Tomalia VA, Park KJ. Autonomic function tests: some clinical applications. *J Clin Neurol*. (2013) 9:1–8. doi: 10.3988/jcn.2013.9.1.1
20. Rana AQ, Ahmed US, Chaudry ZM, Vasan S. Parkinson's disease: a review of non-motor symptoms. *Expert Rev Neurother*. (2015) 15:549–62. doi: 10.1586/14737175.2015.1038244
21. 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*. (2016) 264:1567–82. doi: 10.1007/s00415-016-8375-x
22. Pavy-LeTraon A, Brefel-Courbon C, Dupouy J, Ory-Magne F, Rascol O, Sénard J-M. Combined cardiovascular and sweating autonomic testing to differentiate multiple system atrophy from Parkinson's disease. *Neurophysiol Clin*. (2018) 48:103–10. doi: 10.1016/j.neucli.2017.11.003
23. Ziemssen T, Reichmann H. Treatment of dysautonomia in extrapyramidal disorders. *Ther Adv Neurol Disord*. (2010) 3:53–67. doi: 10.1177/1756285609348902
24. Weimer LH. Autonomic testing: common techniques and clinical applications. *Neurologist* (2010) 16:215–22. doi: 10.1097/NRL.0b013e3181cf86ab
25. Hilz MJ, Dütsch M. Quantitative studies of autonomic function. *Muscle Nerve* (2006) 33:6–20. doi: 10.1002/mus.20365
26. Querido JS, Wehrwein EA, Hart EC, Charkoudian N, Henderson WR, Sheel AW. Baroreflex control of muscle sympathetic nerve activity as a mechanism for persistent sympathoexcitation following acute hypoxia in humans. *AJP Regul Integr Compar Physiol*. (2011) 301:R1779–85. doi: 10.1152/ajpregu.00182.2011
27. Viehweg J, Reimann M, Gasch J, Rüdiger H, Ziemssen T. Comparison of baroreflex sensitivity estimated from ECG R-R and inter-systolic intervals obtained by finger plethysmography and radial tonometry. *J Neural Transm*. (2016) 123:481–90. doi: 10.1007/s00702-016-1535-4
28. Ravits JM. AAEM minimonograph #48: autonomic nervous system testing. *Muscle Nerve* (1997) 20:919–937.
29. Billman GE. Heart rate variability - a historical perspective. *Front Physiol*. (2011) 2:86. doi: 10.3389/fphys.2011.00086

30. Palma JA, Benarroch EE. Neural control of the heart: recent concepts and clinical correlations. *Neurology* (2014) 83:261–71. doi: 10.1212/WNL.0000000000000605
31. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. *Front Public Health* (2017) 5:46–17. doi: 10.3389/fpubh.2017.00258
32. Ziemssen T, Gasch J, Ruediger H. Influence of ECG sampling frequency on spectral analysis of RR intervals and baroreflex sensitivity using the EUROBAVAR data set. *J Clin Monit Comput.* (2008) 22:159–168. doi: 10.1007/s10877-008-9117-0
33. ChuDuc H, NguyenPhan K, NguyenViet D. A review of heart rate variability and its applications. *APCBEE Procedia* (2013) 7:80–5. doi: 10.1016/j.apcbee.2013.08.016
34. Seely AJE, Macklem PT. Complex systems and the technology of variability analysis. *Crit Care* (2004) 8:R367–84. doi: 10.1186/cc2948
35. Sassi R, Cerutti S, Lombardi F, Malik M, Huikuri HV, Peng C-K, et al. Advances in heart rate variability signal analysis: joint position statement by the e-Cardiology ESC Working Group and the European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society. *Europace* (2015) 17:1341–53. doi: 10.1093/europace/euv015
36. Saul JP. Respiration and blood pressure variability: mechanical and autonomic influences. *Fundam Clin Pharmacol.* (1998) 12 (Suppl. 1):17s—22s.
37. Gasch J, Reimann M, Reichmann H, Rüdiger H, Ziemssen T. Determination of baroreflex sensitivity during the modified Oxford maneuver by trigonometric regressive spectral analysis. *PLoS ONE* (2011) 6:e18061. doi: 10.1371/journal.pone.0018061
38. Tzeng Y, Sin P, Lucas S, Ainslie P. Respiratory modulation of cardio-vagal baroreflex sensitivity. *J Appl Physiol* (2009) 107:718–24. doi: 10.1152/japplphysiol.00548.2009
39. Ewing DJ, Campbell IW, Clarke BF. Heart-rate response to standing as a test for automatic neuropathy. *Br Med J.* (1978) 1:1700. doi: 10.1136/bmj.1.6128.1700-c
40. Reimann M, Weiss N, Ziemssen T. Different responses of the retinal and cutaneous microcirculation to transient dysmetabolic conditions. *Atheroscler Suppl.* (2015) 18:1–7. doi: 10.1016/j.atherosclerosissup.2015.02.001
41. Friedrich C, Rüdiger H, Schmidt C, Herting B, Prieur S, Junghanns S, et al. Baroreflex sensitivity and power spectral analysis during autonomic testing in different extrapyramidal syndromes. *Mov Disord.* (2010) 25:315–24. doi: 10.1002/mds.22844
42. Zaza A, Lombardi F. Autonomic indexes based on the analysis of heart rate variability: a view from the sinus node. *Cardiovasc Res.* (2001) 50:434–2. doi: 10.1016/S0008-6363(01)00240-1
43. Schmidt C, Herting B, Prieur S, Junghanns S, Schweitzer K, Globas C, et al. Autonomic dysfunction in different subtypes of multiple system atrophy. *Mov Disord.* (2008) 23:1766–72. doi: 10.1002/mds.22187
44. Schmidt C, Herting B, Prieur S, Junghanns S, Schweitzer K, Reichmann H, et al. Autonomic dysfunction in patients with progressive supranuclear palsy. *Mov Disord.* (2008) 23:2083–9. doi: 10.1002/mds.22289
45. Li K, Lindauer C, Haase R, Rüdiger H, Reichmann H, Reuner U, et al. Autonomic Dysfunction in Wilson's disease: a comprehensive evaluation during a 3-year follow up. *Front Physiol.* (2017) 8:778. doi: 10.3389/fphys.2017.00778
46. James MA, Potter JF. Orthostatic blood pressure changes and arterial baroreflex sensitivity in elderly subjects. *Age Ageing* (1999) 28:522–30. doi: 10.1093/ageing/28.6.522
47. Florian JP, Simmons EE, Chon KH, Faes L, Shykoff BE. Cardiovascular and autonomic responses to physiological stressors before and after six hours of water immersion. *J Appl Physiol.* (2013) 115:1275–89. doi: 10.1152/japplphysiol.00466.2013
48. Perlmuter LC, Sarda G, Casavant V, Mosnaim AD. A review of the etiology, associated comorbidities, and treatment of orthostatic hypotension. *Am J Ther.* (2013) 20:279–91. doi: 10.1097/MJT.0b013e31828bfb7f
49. Aydin AE, Soysal P, Isik AT. Which is preferable for orthostatic hypotension diagnosis in older adults: active standing test or head-up tilt table test? *CIA* (2017) 12:207–12. doi: 10.2147/CIA.S129868
50. 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. *Clin Auton Res.* (2011) 21:69–72. doi: 10.1007/s10286-011-0119-5
51. Low PA, Sandroni P, Joyner M, Shen W-K. Postural tachycardia syndrome (POTS). *J Cardiovasc Electrophysiol.* (2009) 20:352–8. doi: 10.1111/j.1540-8167.2008.01407.x
52. Fedorowski A. Postural orthostatic tachycardia syndrome: clinical presentation, aetiology, and management. *J Intern Med.* (2018) doi: 10.1111/joim.12852. [Epub ahead of print].
53. Rosanio S, Schwarz ER, Ware DL, Vitarelli A. Syncope in adults: systematic review and proposal of a diagnostic and therapeutic algorithm. *Int J Cardiol.* (2011) 162:149–57. doi: 10.1016/j.ijcard.2011.11.021
54. Brown CM, Dütsch M, Hecht MJ, Neundörfer B, Hilz MJ. Assessment of cerebrovascular and cardiovascular responses to lower body negative pressure as a test of cerebral autoregulation. *J Neurol Sci.* (2003) 208:71–8. doi: 10.1016/S0022-510X(02)00438-0
55. Schmidt C, Herting B, Prieur S, Junghanns S, Schweitzer K, Globas C, et al. Valsalva manoeuvre in patients with different Parkinsonian disorders. *J Neural Trans* (2009) 116:875–80. . doi: 10.1007/s00702-009-0239-4
56. Hilz MJ, Liu M, Koehn J, Wang R, Ammon F, Flanagan SR, et al. Valsalva maneuver unveils central baroreflex dysfunction with altered blood pressure control in persons with a history of mild traumatic brain injury. *BMC Neurol.* (2016) 16:1–12. doi: 10.1186/s12883-016-0584-5
57. Looga R. The Valsalva manoeuvre–cardiovascular effects and performance technique: a critical review. *Respir Physiol Neurobiol.* (2005) 147:39–49. doi: 10.1016/j.resp.2005.01.003
58. Goldstein DS, Cheshire WP. Beat-to-beat blood pressure and heart rate responses to the Valsalva maneuver. *Clin Auton Res.* (2017) 27:361–7. doi: 10.1007/s10286-017-0474-y
59. Hilz MJ, Axelrod FB, Braeske K, Stemper B. Cold pressor test demonstrates residual sympathetic cardiovascular activation in familial dysautonomia. *J Neurol Sci.* (2002) 196:81–9. doi: 10.1016/S0022-510X(02)00029-1
60. Bond V, Curry BH, Adams RG, Pemminati S, Gorantla VR, Millis RM. Cardiovascular responses to an isometric handgrip exercise in females with prehypertension. *N Am J Med Sci.* (2016) 8:243–9. doi: 10.4103/1947-2714.185032
61. Silverthorn DU, Michael J. Cold stress and the cold pressor test. *Adv Physiol Educ.* (2013) 37:93–6. doi: 10.1152/advan.00002.2013
62. Mestanik M, Mestanikova A, Visnovcova Z, Calkovska A, Tonhajzerova I. Cardiovascular sympathetic arousal in response to different mental stressors. *Physiol Res.* (2015) 64 (Suppl. 5):S585–94.
63. Ziemssen T, Reimann M, Gasch J, Rüdiger H. Trigonometric regressive spectral analysis: an innovative tool for evaluating the autonomic nervous system. *J Neural Transm.* (2013) 120 (Suppl. 1):27–33. doi: 10.1007/s00702-013-1054-5
64. Li K, Rüdiger H, Haase R, Ziemssen T. An innovative technique to assess spontaneous baroreflex sensitivity with short data segments: multiple trigonometric regressive spectral analysis. *Front Physiol.* (2018) 9:1033–8. doi: 10.3389/fphys.2018.00010
65. Kimber J, Mathias CJ, Lees AJ, Bleasdale-Barr K, Chang HS, Churchyard A, et al. Physiological, pharmacological and neurohormonal assessment of autonomic function in progressive supranuclear palsy. *Brain* (2000) 123 (Pt 7):1422–30. doi: 10.1093/brain/123.7.1422
66. Strahler J, Fischer S, Nater UM, Ehlert U, Gaab J. Norepinephrine and epinephrine responses to physiological and pharmacological stimulation in chronic fatigue syndrome. *Biol Psychol.* (2013) 94:160–6. doi: 10.1016/j.biopsycho.2013.06.002
67. Freeman R. Autonomic peripheral neuropathy. *Lancet* (2005) 365:1259–70. doi: 10.1016/S0140-6736(05)74815-7
68. Siepmann T, Illigens BMW, Reichmann H, Ziemssen T. [Axon-reflex based nerve fiber function assessment in the detection of autonomic neuropathy]. *Nervenarzt* (2014) 85:1309–14. doi: 10.1007/s00115-014-4120-9
69. Chiu IM, Hehn von CA, Woolf CJ. Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. *Nat Neurosci.* (2012) 15:1063–7. doi: 10.1038/nn.3144
70. Illigens BMW, Gibbons CH. Sweat testing to evaluate autonomic function. *Clin Auton Res.* (2009) 19:79–87. doi: 10.1007/s10286-008-0506-8

71. Low PA, Caskey PE, Tuck RR, Fealey RD, Dyck PJ. Quantitative sudomotor axon reflex test in normal and neuropathic subjects. *Ann Neurol.* (1983) 14:573–80. doi: 10.1002/ana.410140513
72. Vinik AI, Névoret M-L, Casellini C. The new age of sudomotor function testing: a sensitive and specific biomarker for diagnosis, estimation of severity, monitoring progression, and regression in response to intervention. *Front Endocrinol.* (2015) 6:94. doi: 10.3389/fendo.2015.00094
73. Evaluation of sudomotor function. Evaluation of sudomotor function. *Clin Neurophysiol.* (2004) 115:1506–13. doi: 10.1016/j.clinph.2004.01.023
74. Gibbons CH, Illigens BMW, Centi J, Freeman R. QDIRT - Quantitative direct and indirect test of sudomotor function. *Neurology* (2008) 70:2299–304. doi: 10.1212/01.wnl.0000314646.49565.c0
75. Siepmann T, Pintér A, Buchmann SJ, Stibal L, Arndt M, Kubasch AS, et al. Cutaneous autonomic pilomotor testing to unveil the role of neuropathy progression in early parkinson's Disease (CAPTURE PD): protocol for a multicenter study. *Front Neurol.* (2017) 8:212. doi: 10.3389/fneur.2017.00212
76. Vetrugno R, Liguori R, Cortelli P, Montagna P. Sympathetic skin response. *Clin Auton Res.* (2003) 13:256–70. doi: 10.1007/s10286-003-0107-5
77. Novak P. Electrochemical skin conductance: a systematic review. *Clin Auton Res.* (2017) 15:193–13. doi: 10.1007/s10286-017-0467-x
78. Emad R, Zafarghasempour M, Roshanzamir S. Sympathetic skin response in incomplete spinal cord injury with urinary incontinence. *Ann Indian Acad Neurol.* (2013) 16:234–8. doi: 10.4103/0972-2327.112479
79. Meijer EH, Smulders FTY, Johnston JE, Merckelbach HLGJ. Combining skin conductance and forced choice in the detection of concealed information. *Psychophysiology* (2007) 44:814–22. doi: 10.1111/j.1469-8986.2007.00543.x
80. Tsementzis SA. The spoon test - a simple bedside test for assessing sudomotor autonomic failure. *J Neurol Neurosurg Psychiatr.* (1985) 48:378–80. doi: 10.1136/jnnp.48.4.378
81. Russell C. The spoon test: a valid and reliable bedside test to assess sudomotor function. *Clin Auton Res.* (2017) 27:91–5. doi: 10.1007/s10286-017-0401-2
82. Selvarajah D, Cash T, Davies J, Sankar A, Rao G, Grieg M, et al. SUDOSCAN: A Simple, Rapid, and Objective Method with Potential for Screening for Diabetic Peripheral Neuropathy. *PLoS ONE* (2015) 10:e0138224. doi: 10.1371/journal.pone.0138224
83. Loavenbruck AJ, Hodges JS, Provitera V, Nolano M, Wendelshafer-Crabb G, Kennedy WR. A device to measure secretion of individual sweat glands for diagnosis of peripheral neuropathy. *J Peripher Nerv Syst.* (2017) 22:139–48. doi: 10.1111/jns.12212
84. Krieger S-M, Reimann M, Haase R, Henkel E, Hanefeld M, Ziemssen T. Sudomotor testing of diabetes polyneuropathy. *Front Neurol.* (2018) 9:803. doi: 10.3389/fneur.2018.00803

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Cardiac 123I-MIBG Scintigraphy in Neurodegenerative Parkinson Syndromes: Performance and Pitfalls in Clinical Practice

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Purpose: Cardiac [^{123}I]metaiodobenzylguanidine scintigraphy (123I-MIBG), reflecting postganglionic cardiac autonomic denervation, is proposed for early detection of Parkinson's disease (PD; reduced tracer uptake) and separation from Multiple System Atrophy (MSA; preserved tracer uptake). However, several recent studies report on frequent unexpected 123I-MIBG results in PD and MSA. We sought to determine, whether 123I-MIBG is feasible to discriminate PD from MSA in unselected geriatric patients in clinical practice.

Materials and Methods: We screened consecutive patients, that underwent 123I-MIBG for diagnostic reasons. Delayed 123I-MIBG uptake (heart/mediastinum ratio; H/M ratio) was verified by clinical diagnosis of PD, MSA, and ET based on a two-stage clinical assessment: comprehensive baseline (including autonomic testing and additional neuroimaging) and confirmatory clinical follow-up.

Results: 28 patients with clinical diagnosis of PD ($N = 11$), MSA ($N = 9$), and Essential Tremor (ET, $N = 8$) were identified. In one third (9/28) nuclear medical diagnosis deviated from clinically suspected syndrome. Visual interpretation of 123I-MIBG identified two cases (MSA and ET) with indeed normal 123I-MIBG uptake. Detailed review of clinical phenotypes provided only in two cases (PD and ET) an adequate explanation (correction of initial diagnosis and confounding drug history) for unexpected 123I-MIBG. In conclusion, 123I-MIBG did not match initial clinical phenotype in 27% PD, 44% MSA, and 25% ET patients.

Conclusion: 123I-MIBG scintigraphy is a known specific and valuable technique in scientific approaches and well-defined and highly selected samples. However, predictability of 123I-MIBG based nuclear medical diagnosis for individual cases and thus, feasibility in routine clinical practice is limited. Our clinical series emphasize clinical verification of 123I-MIBG results on an individual basis in clinical routine.

Keywords: Parkinson's disease, Lewy body disorders, multiple system atrophy, MIBG scintigraphy, autonomic function

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INTRODUCTION

Parkinson's Disease (PD) and Multiple System Atrophy (MSA) are pathophysiological distinct disorders, that share a common clinical phenomenology. When compared to PD, MSA is characterized by a more rapid deterioration and limited clinical response to levodopa substitution. Despite the use of clinical consensus criteria (1, 2) discrimination of MSA and PD, especially at early stages, is challenging as neuropathological confirmed case series indicate (3).

Cardiac 123I-metaiodobenzylguanidine (123I-MIBG) scintigraphy is used to discriminate PD and MSA by means of cardiac postganglionic autonomic involvement (4–6). Cardiac uptake of the synthetic norepinephrine analog (123I-MIBG) depends on integrity of postganglionic sympathetic neurons. Since α-synuclein dependent neurodegeneration in PD affects both pre- and postganglionic autonomic neurons, cardiac 123I-MIBG uptake is impaired, whereas in MSA, with predominately preganglionic autonomic failure, cardiac 123I-MIBG uptake is thought to be preserved. Braune et al. (6) reported on 100% sensitivity and specificity of cardiac 123I-MIBG scintigraphy in differentiating PD and MSA, respectively. Recent clinical studies confirmed the high sensitivity and report on specificity more than 77% (7, 8). As such, 123I-MIBG scintigraphy is recommended (level A) by the European Federation of Neurological Societies and the Movement Disorder Society task force (9) for the differential diagnosis of Parkinson syndromes.

However, there is an increasing number of reports on impaired cardiac autonomic innervation in non-idiopathic Parkinson such as MSA. In a longitudinal study, Nagayama et al. (10) report consistently on a high sensitivity (87.7%) of cardiac 123I-MIBG scintigraphy in PD, but 179 of 269 patients (66.5%) with non-Lewy body pathology showed a diminished cardiac 123I-MIBG uptake as well, resulting in a low specificity of 37.4%. In recent studies up to 30% of MSA patients present with reduced cardiac 123I-MIBG uptake (10–12) and in one study (13) H/M ratio was diminished in even 7 out of 9 MSA patients.

These unexpected 123I-MIBG results in MSA can be attributed in part to known confounders of 123I-MIBG uptake such as myocardial lesions, cardiomyopathy, chronic heart failure or peripheral neuropathy, and concomitant medication (14). In MSA, a transsynaptic neurodegeneration causing secondary postganglionic neuronal decline is further postulated (11).

In contrast to prospective trials of highly selected samples, we report on our experience of 123I-MIBG performance in a non-selected clinical sample of patients suffering various neurodegenerative Parkinson's syndromes. We therefore verified the nuclear medical based classification of MSA, ET, and PD by combining the diagnostic value of additional neuroimaging [e.g., 123I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane single photon emission computed tomography (123I-FP-CIT SPECT)], levodopa responsiveness, autonomic function tests and a two-stage clinical assessment covering a mean follow-up of 3 years. In this clinical series we sought to highlight potential pitfalls of cardiac 123I-MIBG imaging in routine clinical use and to discuss overestimated clinical implications.

PATIENTS AND METHODS

Patients

Consecutive patients, that underwent 123I-MIBG scintigraphy for differential diagnosis of a Parkinson syndrome within a 24-month recruitment period at our University Medical Center, were approached to participate in this clinical series. The study was approved by the Institutional Review Board of Charité—University Medicine Berlin, Germany and all patients gave written informed consent before participation.

Clinical Assessment

Nuclear medical diagnosis derived from the results of cardiac 123I-MIBG scintigraphy (PD: reduced 123I-MIBG uptake, MSA: preserved 123I-MIBG uptake, Essential Tremor (ET): preserved 123I-MIBG uptake). Clinical diagnosis derived from (1) a comprehensive clinical assessment based on consensus diagnostic criteria (1, 2) and appropriate scales of clinical severity [PD: UPDRS (15), MSA: UMSARS (16)], (2) standardized test of levodopa responsiveness (UPDRS motor part before and 30 min after oral administration of 200 mg levodopa/50 mg benserazide), (3) autonomic reflex screen (ARS), and (4) results of supporting imaging including transcranial mesencephalic sonography, structural MRI, dopamine transporter SPECT (123I-FP-CIT SPECT), and dopamine receptor SPECT (123I-IBZM SPECT). Clinical diagnosis was further verified by a long-term follow-up were initial diagnostic classification was re-evaluated based on progression of motor and non-motor symptoms, sustained levodopa responsiveness, and survival period. If subjects were unable to present for clinical follow-up, general practitioner or family members were contacted.

Cardiac 123I-MIBG Scintigraphy

Cardiac scintigraphy was performed according to standard operation procedures of the Department of Nuclear Medicine, Charité—University Medicine Berlin (17). Thyroid was blocked by sodium perchlorate and drugs known to affect 123I-MIBG binding, such as α-blockers, reserpine derivates, and sympathomimetics, were stopped for least 24 h. 185 MBq 123I-MIBG (AdreView Iobenguane (123I) Injection, GE Healthcare, Braunschweig, Germany) was intravenously applied. Tracer uptake was detected by double-head gamma camera equipped with a low energy high resolution (LEHR) collimator (Millenium VG5 Hawkeye with VPC-45K collimator; GE Medical Systems-EU, Buc, France or Symbia TruePoint SPECT-CT; Siemens, Erlangen, Germany). For imaging a 15% window was focused on 159 keV. Planar anterior images were obtained 4 h (delayed) post-injection (to assess only the active neuronal tracer uptake) and analyzed using Brain Registration and Analysis Software Suites (BRASS) (Hermes Medical Solutions; Stockholm, Sweden). Regions of interest (ROI [counts/voxel]) were placed manually on planar anterior images rectangular in the upper mediastinum and circular covering the left ventricle of the heart. Delayed heart to mediastinum ratio (H/M ratio) was calculated as ROI heart/ROI mediastinum with a site-specific cut-off value of 1.7. Semi-quantitative BRASS analysis was supplemented by secondary visual interpretation. Internal

TABLE 1 | Patient characteristics—epidemiologic distribution, clinical data, and neuroimaging results.

		Controls	MSA	PD	*p*-value
DEMOGRAPHIC DATA					
N		8	9	11	
Age	[Years]	64.8 ± 10.5	61.1 ± 10.8	69.6 ± 8.3	0.302[a]
Gender	[f: m]	3: 5	3: 6	4: 7	
BMI	[kg/m^2]	25.7 ± 4.1	23.0 ± 3.2	25.3 ± 4.7	0.373[a]
Disease duration	[Years]	n.a.	5.2 ± 2.6	5.5 ± 4.3	0.867[c]
$UxxRS_{off}$	[Points]	n.a.	34.3 ± 6.1	24.3 ± 8.9	
Follow-up	[Months]	41.2 ± 18.8	37.3 ± 23.3	29.1 ± 20.8	
AUTONOMIC FUNCTION TESTS					
$CASS_{cardiovagal}$	[Points]	0.1 ± 0.4	0.8 ± 1.3	0.6 ± 1.0	0.579[a]
$CASS_{adrenergic}$	[Points]	0.7 ± 0.5	2.4 ± 1.2[d]	1.0 ± 0.0[e]	0.001[a]
ΔSBP	[mmHg]	7.1 ± 13.7	−37.4 ± 28.5[d]	−1.6 ± 14.4[e]	0.001[a]
ASP	[Points]	29.5 ± 26.3	49.0 ± 23.7	21.9 ± 14.8	0.033[b]
NEUROIMAGING					
H/M $ratio_{delayed}$	n.a.	2.2 ± 0.5	1.7 ± 0.3[f]	1.5 ± 0.5[d]	<0.01[b,d]
$SR_{contralateralputamen}$	n.a.	2.3 ± 0.3	0.7 ± 0.6[g]	0.7 ± 0.4[d]	<0.001[a,e]

BMI, Body Mass Index; $UxxRS_{off}$ for PD: UPDRS, Motor Impairment Score part III (off medication); $UxxRS_{off}$ for MSA: UMSARS, Motor Impairment Score part II (off medication); CASS, adrenergic/cardiovagal subscore of Composite Autonomic Scoring Scale; ΔSBP, Change of systolic blood pressure during head-up tilt; ASP, Autonomic Symptome Profile; H/M $ratio_{delayed}$, heart/mediastinum ratio (4 h post-injection); $SR_{contralateralputamen}$, specific binding ratio (contralateral to the clinically more affected side), n.a., not available. p-value < 0.05 was considered to be significant. [a]Kruskal-Wallis Test; [b]One-way analysis of variance; [c]Unpaired, two-tailed t-test. post hoc analysis between groups (Dunn's Multiple Comparison Test and Tukey's Multiple Comparison Test, respectively): [d]$p < 0.01$ vs. ET; [e]$p < 0.05$ vs. MSA; [f]$p < 0.05$ vs. ET; [g]$p < 0.001$ vs. ET.

control was performed by evaluation of control tissue (salivary gland) and SPECT images.

Autonomic Reflex Screen (ARS)

Cardiovagal and adrenergic function was assessed as heart rate response to deep breathing and blood pressure response to Valsalva maneuver and passive head-up tilt, respectively (17) and scored on the objective Composite Autonomic Scoring Scale (CASS, cardiovagal, and adrenergic subscores without sudomotor function) (18).

Statistics

Group data are expressed as mean (standard deviation; SD). Statistical significance was considered at a p-value < 0.05 (Prism 5.02 for Windows, GraphPad Software, Inc., CA, USA).

RESULTS

Within a 24-month period, we identified 28 patients (10 female, 18 male; mean age 65.5 ± 10.1 years) who underwent cardiac 123I-MIBG scintigraphy. Clinical indication for nuclear imaging were suspected Parkinson's disease (PD, $N = 11$), MSA ($N = 9$), and ET ($N = 8$) (see **Table 1**). Mean cardiac 123I-MIBG H/M ratio (cut-off value 1.7) of both, PD and MSA, were significantly decreased compared to patients without an underlying neurodegenerative disorder (ET 2.2 ± 0.5; MSA 1.7 ± 0.3; $p < 0.05$; PD 1.5 ± 0.5; $p < 0.01$). In this small sample however, no significance could be revealed between PD and MSA patients.

Nuclear medical diagnosis deviated from clinically suspected syndrome in 9 of the 28 cases: cardiac 123I-MIBG binding was preserved in 3 PD but reduced in 4 MSA and 2 ET patients. To exclude the potential confounding effect of different reporting physicians, all 123I-MIBG scintigraphy images were re-evaluated by an experienced physician blinded for the suspected clinical diagnosis. Increased mediastinal background activity led to an adjustment of nuclear medical diagnosis in two cases with indeed normal myocardial uptake but "pathological" H/M ratio (ET H/M ratio of 1.58; MSA H/M ratio of 1.65).

The clinical phenotype, long-term follow-up, and results of additional imaging studies are discussed for the remaining 7 cases with unexpected cardiac 123I-MIBG scintigraphy results (see **Table 2**; detailed case description is provided as **Supplementary Materials**).

Case 1: 59–62 Years, Possible MSA-P

Clinical Phenotype

Five years of symmetric bradykinesia and rigidity with postural instability and shuffling gait; startle myoclonus and pyramidal tract signs (hyperreflexia) within left upper extremity; *non-motor*: severe palilalia and dysphagia, urge incontinence, obstipation, erectile dysfunction, sialorrhea, and mild neurogenic orthostatic hypotension; UMSARS = 38 pts.

Imaging

cardiac 123I-MIBG scintigraphy: H/M ratio 1.27.

123I-FP-CIT SPECT: visually asymmetric (right) reduced putaminal tracer uptake.

Discussion

Clinical follow up (rapid progression, early death) strengthened the initial diagnosis of MSA-P. Medical history and clinical

TABLE 2 | Summary of pitfalls in cases with an unexpected 123I-MIBG scintigraphy result.

Unexpected 123I-MIBG results			
Pitfall		**Case**	**Reference**
FALSE POSITIVE H/M RATIO			
Autonomic Neuropathy/ Ganglionopathy	Ganglionopathy	No. 3	(4)
	Diabetes mellitus	No. 4	(19)
	Post-polio syndrome	No. 2	(20)
Medication	Amiodarone	No. 4	(14)
Cardiac rhythm disease	Sick-sinus-syndrome	No. 4	(21)
FALSE NEGATIVE H/M RATIO			
Medication	Calcium channel blocker	No. 6	(14)
	Amiodarone (long-term administration)	No. 4	(14)
Incorrect diagnosis	Progressive Supranuclear Palsy (PSP)	No. 5	
Erroneous position of mediastinal ROI	Abnormal anatomy (post-operative/hereditary)	No. 7	

H/M ratio, heart/mediastinum ratio; ROI, region of interest.

exam did not reveal clinically significant neuropathy nor concomitant medication sufficiently explaining reduced cardiac 123I-MIBG uptake.

Case 2: 63–66 Years, Possible MSA-C

Clinical Phenotype

Five years of right sided Parkinsonism (bradykinesia, rigidity), cerebellar, and pyramidal tract signs; *non-motor*: apraxia, dysphagia, obstipation, erectile dysfunction, sialorrhea, and mild neurogenic orthostatic hypotension; UMSARS = 33 pts.

Imaging

cardiac 123I-MIBG scintigraphy: H/M ratio 1.14.

123I-FP-CIT SPECT: visually symmetric reduced tracer uptake (putamen, striatum, nucleus caudatus).

Discussion

Clinical diagnosis in this case is less robust as current consensus diagnostic criteria consider dementia as a non-supporting feature of MSA. However, MODIMSA study (22) showed evidence that frontal-executive dysfunction and cognitive impairment is indeed associated with MSA. Spinocerebellar atrophy (SCA) causes progressive ataxia, Parkinsonism and pyramidal tract signs but patients' familiar history was unremarkable and genetic screen for SCA 1,2,3, and 6 was negative. Patient had a history of poliomyelitis during childhood and thus might have developed post-polio syndrome. However, lower motoneuron disability in our patient did not progress clinically nor does electromyography showed signs of active denervation (6-year follow-up). Autonomic neuropathy has been reported in a case of post-polio syndrome (20). However, cerebellar symptoms as well as dementia cannot be explained by the diagnosis of post-polio syndrome.

Case 3: 59–62 Years, Probable MSA-P

Clinical Phenotype

Two years of symmetric Parkinsonism (bradykinesia, rigidity, and postural instability), shuffling gait, postural instability, wheeled walker, impaired fine motor skills; *non-motor*: urinary retention requiring catheterization, obstipation, cold-hand sign, and severe neurogenic orthostatic dysregulation; UMSARS = 26 pts.

Imaging

cardiac 123I-MIBG scintigraphy: H/M ratio 1.45.

123I-FP-CIT SPECT: asymmetric (right) reduced tracer uptake (putamen, striatum, nucleus caudatus).

Discussion

Reduction of deep tendon reflexes (ankle) led initially to the suspicion of axonal motor neuropathy. However, protopathic sensibility and bathyesthesia were unremarkable, studies of compound nerve conduction velocity, somatosensible potentials as well as sympathetic skin response (upper extremities) were within normal limits. Thus, reduced cardiac 123I-MIBG binding might be related to clinically insignificant ganglionopathy.

Case 4: 73–76 Years, Essential Tremor

Clinical Phenotype

3.5 year history of action and postural tremor (right > left), no bradykinesia or rigidity; *non-motor*: none (including autonomic history).

Imaging

cardiac 123I-MIBG scintigraphy: H/M ratio 1.49.

123I-FP-CIT SPECT: normal.

Discussion

Patient has a history of type II diabetes that led to distal symmetric neuropathy (hypopallesthesia, absent ankle deep tendon reflex) and sick-sinus syndrome. Reduction of cardiac 123I-MIBG binding has been described in both, sick-sinus-syndrome (21) and diabetic neuropathy (19). However, the effect of amiodarone is discussed controversially. On the one hand amiodarone is postulated to reduce 123I-MIBG uptake directly and on the other hand, through an improved sympathetic tone due to long-term administration, supposed to increase 123I-MIBG uptake and block partially 123I-MIBG washout (14). Due to long half-life amiodarone might not completely washed out prior to 123I-MIBG scintigraphy.

Case 5: 53–56 Years, Parkinson's Disease

Clinical Phenotype

Two years of mild asymmetric Parkinsonism (bradykinesia, rigidity, disturbed fine motor skills), dysarthria, hypomimia; *non-motor*: hypersomnia, depressive mood; UPDRS = 18 pts.

Imaging

cardiac 123I-MIBG scintigraphy: H/M ratio 2.08.

123I-FP-CIT SPECT: asymmetric (left) reduced tracer uptake (striatum, putamen).

Discussion

Patients major complain was dysarthria (palilalia) that was unresponsive to levodopa. Subsequently, the treating neurologist recommended bilateral subthalamic nucleus stimulation that was ineffective for dysarthria and all other Parkinson symptoms. During the 8-year follow-up, patients' motor symptoms progressed and he developed supranuclear gaze palsy and severe postural instability. The patient did not develop autonomic failure and no frontal-executive dysfunction. Eventually, the diagnosis of Progressive Supranuclear Palsy (PSP—Parkinson phenotype, PSP rating scale = 24 pts., PSP staging system = 3) was established and deep brain stimulation was discontinued. In this case, cardiac 123I-MIBG scintigraphy correctly pointed toward non-idiopathic Parkinson's disease. Clinical phenotype (Parkinsonism), preserved levodopa response, and absence of gaze palsy prevented early recognition of PSP.

Case 6: 64–67 Years, Parkinson's Disease

Clinical Phenotype

Two years history of asymmetric bradykinesia, rigidity and predominant resting tremor; *non-motor*: none, ARS without cardiovagal or adrenergic failure; UPDRS = 24 pts.

Imaging

cardiac 123I-MIBG scintigraphy: H/M ratio 2.11.

123I-FP-CIT SPECT: bilateral reduced tracer uptake (putamen, striatum, nucleus caudatus).

Discussion

No definite confounder of cardiac MIBG binding could be identified in this case. Patient's pharmacotherapy was limited to calcium channel blocker and rasagiline. Even though, calcium channel blockers might increase slightly H/M ratio, the extent of increased H/M ratio is not reasonable (14). Moreover, there is no evidence for rasagiline altering 123I-MIBG uptake. There were no clinical signs or symptoms if concomitant neuropathy and no history of unstable angina pectoris characteristics.

Case 7: 80–83 Years, Parkinson's Disease

Clinical Phenotype

Four years of asymmetric (left) severe bradykinesia and rigidity, resting and postural tremor, postural imbalance, camptocormia; *non-motor*: none, no evidence of cardiovagal or adrenergic failure in ARS, no orthostatic hypotension; UPDRS = 29 pts.

Imaging

cardiac 123I-MIBG SPECT: H/M ratio 2.23, corrected to 2.16.

123I-FP-CIT SPECT: asymmetric (left) reduced tracer uptake (putamen, striatum, nucleus caudatus).

Discussion

Patient had a history of celiac disease and intestinal resection. Revision of the 123I-MIBG scintigraphy data revealed an erroneous position of the mediastinal ROI covering relocated stomach. Despite that correction, 123I-MIBG H/M ratio still lay within normal limits (2.16).

DISCUSSION

Myocardial 123I-MIBG uptake reflects the density and integrity of postganglionic sympathetic nerve endings. Due to the differential involvement of postganglionic sympathetic fibers in PD but not MSA, reduction of cardiac 123I-MIBG uptake is used to discriminate both disorders (6). While several studies (23, 24) propose an association of reduced 123I-MIBG H/M ratio in PD with longer disease duration, occurrence of non-motor symptoms and autonomic impairment, others (25, 26) could not confirm this relationship.

In our clinical series, indication for cardiac 123I-MIBG examination based on either atypical clinical course or symptom presentation. As such, our sample represent a highly selected but in clinical practice common group of patients, as nuclear medical exams are usually not ordered in clinical obvious cases. Among these patients, nuclear medical diagnostic classification based on cardiac 123I-MIBG scintigraphy differed from the clinically suspected syndrome in one third of cases. Furthermore, group wise comparison of cardiac 123I-MIBG H/M ratio failed in this small and selected sample to separate MSA from PD. This is unexpected considering the high sensitivity and specificity of cardiac 123I-MIBG scintigraphy to differentiate PD from other neurodegenerative disorders [pooled specificity range from 77 (8) to 91% (7)].

The discrepancy between nuclear medical and clinical diagnosis is explained in part by known confounders of 123I-MIBG scintigraphy. 123I-MIBG binding is reduced in areas with impaired sympathetic innervation such as fibrous tissue (e.g., myocardial infarction). However, none of our patients showed focal defects in myocardial 123I-MIBG uptake nor had a history of unstable angina pectoris characteristics. One PD patient (case 7) suffered from mild coronary heart disease without effect on H/M ratio. 123I-MIBG uptake is reduced when other compounds (14) compete for norepinephrine transporter binding at the presynaptic membrane of postganglionic sympathetic neurons. Moreover, besides this direct alteration of 123I-MIBG uptake, amiodarone is discussed to slightly increase 123I-MIBG uptake through improvement of sympathetic tone (case 4) (14). Cardiac autonomic neuropathy or ganglionopathy can cause cardiac sympathetic denervation and thus low 123I-MIBG binding (19). Despite being clinically unremarkable, ganglionopathy might underlie H/M ratio reduction in case 3. For a summary of the possible pitfalls in interpreting 123I-MIBG results, based on our clinical series, see **Table 2**.

More recent studies however, confirm our observation and report patients with unexpected results of cardiac 123I-MIBG scintigraphy, not sufficiently explained by concomitant medication or pathology. Nagayama et al. (11) reported on H/M ratio below the cut-off in 30 out of 96 cardiac 123I-MIBG examinations performed in 52 MSA patients. Neuropathological studies further indicate myocardial sympathetic involvement in MSA, leading probably to a decreased 123I-MIBG uptake. Orimo et al. revealed reduced TH-immunoreactivity in cardiac tissue and sympathetic ganglia of 6/15 MSA patients (27). Moreover, Sone et al. observed phosphorylated α-synuclein deposits as neuronal cytoplasmic inclusions in sympathetic

ganglia of 11/26 MSA patients, that could be partially classified as Lewy bodies (hematoxylin-eosin staining) (28). Cardiac sympathetic denervation in MSA is unlikely the result of secondary postganglionic sympathetic degeneration as H/M ratio shows no temporal trend in repeated 123I-MIBG scans and H/M ratio does not correlate with clinical severity (11). Cook et al. (29) reported almost abolished norepinephrine content in myocardial tissue in an autopsied MSA patient with α-synuclein deposits limited to glia cells but not in neurons or sympathetic ganglia. Thus, minor cardiac sympathetic denervation does occur in MSA. In difference to PD, cardiac sympathetic degeneration in MSA is limited to TH-immunoreactive sympathetic nerve fibers (27) and an association with Lewy body pathology is still diversely discussed (28, 29).

With respect to PD, Orimo et al. (30) reported a pooled sensitivity of the delayed H/M ratio of 89.7% to detect Lewy body pathology. However, 123I-MIBG scintigraphy quantifies cardiac sympathetic denervation that is associated with Parkinsonism but not the underlying Lewy body pathology. It is noteworthy that in non-neurodegenerative Parkinsonism (associated with Parkin, DJ-1, PINK1, and LRRK2 mutations) cardiac sympathetic impairment is far more heterogeneous and 123I-MIBG scintigraphy remains unremarkably in over 50% of cases (23). Involvement of cardiac sympathetic fibers has been reported in early and premotor stages of PD (incidental Lewy body disease), even before neuronal cell loss and Lewy body pathology could be detected within the dorsal vagal nucleus and the nigrostriatal dopaminergic system (5). This may account for the reduced cardiac 123I-MIBG uptake in early stages of PD as reported by Umemura et al. (26). In the same study, however, 28 mostly early stage PD patients (15%) had H/M ratios above the cut-off [1.85 (26)]. In another prospective trial of 70 PD patients with 2 or more 123I-MIBG exams, mean H/M ratio was reduced at baseline and declined significantly over a 3-year follow-up (23). Nevertheless, 28/70 individuals had only mildly reduced or normal 123I-MIBG H/M ratios at baseline. Finally, Kim et al. (24) raise the question whether a "normal heart" phenotype of PD exists. In their study of 160 cases with *de-novo* PD, 44 had normal cardiac 123I-MIBG uptake.

In contrast to well-defined and highly selected samples in prospective trials, we report in our clinical series on the performance of cardiac 123I-MIBG in a clinical setting. As such, indication for nuclear imaging was based solely on individual clinical necessity, which in turn causes a selection bias toward non-typical symptom presentation and early disease stages whereas cases with instant clinical diagnosis are neglected. Among Parkinson patients however, age-dependent metabolic and vascular conditions are common. We deliberately did not exclude patients with concomitant conditions (other than history of unstable angina pectoris characteristics pointing to a probable myocardial infarction) that potentially involve the CNS or affect autonomic testing to assess feasibility of cardiac 123I-MIBG imaging under actual clinical conditions. As neuropathological confirmation is not available, final diagnostic classification relies on combined clinical criteria (comprehensive clinical exam, levodopa responsiveness, and clinical follow-up) of limited specificity as well.

In summary, cardiac 123I-MIBG scintigraphy is a highly specific and valuable tool to discriminate Parkinson syndromes and to access postganglionic autonomic (cardiac) impairment. 123I-MIBG analysis delivers important insights in pathophysiological processes and plays a significant role in scientific approaches and in specific clinical diagnostics in the broad spectrum of movement disorders and other diseases and syndromes. Group wise comparisons of delayed H/M ratio proved repeatedly to be sensitive and specific in detection and differentiation of PD from other neurodegenerative disorders. As in other imaging diagnostics, frequent pitfalls and restrictions have to be recognized and considered in the interpretation of these findings. We need to emphasize that 123I-MIBG scintigraphy is usually applied in geriatric patients, an age group where comorbidities and these pitfalls occur frequently. Thus, predictability for individual cases and feasibility in routine clinical practice are diminished. The confounding effects of concomitant medications, a progressive decline of 123I-MIBG uptake [∼3%/year (23)] and a growing understanding of the complex and overlapping pattern of neurodegeneration in Parkinson syndromes, still requires clinical verification of the 123I-MIBG scintigraphy results on an individual basis. In the routine clinical practice, interpretation and drawing consequences from 123I-MIBG scintigraphy results have to be done carefully and should be in the hands of very experienced physicians and movement disorder specialists, respectively.

DATA AVAILABILITY

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

AL and CS contributed conception and design of the study. LZ organized the database and performed the statistical analysis. CS wrote the first draft of the manuscript. AL, LZ, and CS wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00152/full#supplementary-material

REFERENCES

1. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, Wood NW, Colosimo C, Durr A, Fowler CJ, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* (2008) 71:670–676. doi: 10.1212/01.wnl.0000324625.00404.15
2. Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. *Neurology* (1992) 57:S34–8.
3. Joutsa J, Gardberg M, Roytta M, Kaasinen V. Diagnostic accuracy of parkinsonism syndromes by general neurologists. *Park Relat Disord.* (2014) 20:840–4. doi: 10.1016/j.parkreldis.2014.04.019
4. Rascol O, Schelosky L. 123I-metaiodobenzylguanidine scintigraphy in Parkinson's disease and related disorders. *Mov Disord.* (2009) 24(Suppl. 2):S732–41. doi: 10.1002/mds.22499
5. Orimo S, Takahashi A, Uchihara T, Mori F, Kakita A, Wakabayashi K, et al. Degeneration of cardiac sympathetic nerve begins in the early disease process of Parkinson's disease. *Brain Pathol.* (2007) 17:24–30. doi: 10.1111/j.1750-3639.2006.00032.x
6. Braune S, Reinhardt M, Schnitzer R, Riedel A, Lucking CH. Cardiac uptake of [123I]MIBG separates Parkinson's disease from multiple system atrophy. *Neurology* (1999) 53:1020–5.
7. King AE, Mintz J, Royall DR. Meta-analysis of 123I-MIBG cardiac scintigraphy for the diagnosis of Lewy body-related disorders. *Mov Disord.* (2011) 26:1218–24. doi: 10.1002/mds.23659
8. Treglia G, Stefanelli A, Cason E, Cocciolillo F, Di Giuda D, Giordano A. Diagnostic performance of iodine-123-metaiodobenzylguanidine scintigraphy in differential diagnosis between Parkinson's disease and multiple-system atrophy: a systematic review and a meta-analysis. *Clin Neurol Neurosurg.* (2011) 113:823–9. doi: 10.1016/j.clineuro.2011.09.004
9. Berardelli A, Wenning GK, Antonini A, Berg D, Bloem BR, Bonifati V, et al. EFNS/MDS-ES/ENS [corrected] recommendations for the diagnosis of Parkinson's disease. *Eur J Neurol.* (2013) 20:16–34. doi: 10.1111/ene.12022
10. Nagayama H, Hamamoto M, Ueda M, Nagashima J, Katayama Y. Reliability of MIBG myocardial scintigraphy in the diagnosis of Parkinson's disease. *J Neurol Neurosurg Psychiatry* (2005) 76:249–51. doi: 10.1136/jnnp.2004.037028
11. Nagayama H, Ueda M, Yamazaki M, Nishiyama Y, Hamamoto M, Katayama Y. Abnormal cardiac [(123)I]-meta-iodobenzylguanidine uptake in multiple system atrophy. *Mov Disord.* (2010) 25:1744–7. doi: 10.1002/mds.23338
12. Kollensperger M, Seppi K, Liener C, Boesch S, Heute D, Mair KJ, et al. Diffusion weighted imaging best discriminates PD from MSA-P: a comparison with tilt table testing and heart MIBG scintigraphy. *Mov Disord.* (2007) 22:1771–6. doi: 10.1002/mds.21614
13. Frohlich I, Pilloy W, Vaillant M, Diederich NJ. Myocardial MIBG scintigraphy: a useful clinical tool? : A retrospective study in 50 parkinsonian patients. *Neurol Sci.* (2010) 31:403–6. doi: 10.1007/s10072-010-0218-4
14. Jacobson AF, Travin MI. Impact of medications on mIBG uptake, with specific attention to the heart: comprehensive review of the literature. *J Nucl Cardiol.* (2015) 22:980–93. doi: 10.1007/s12350-015-0170-z
15. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord.* (2008) 23:2129–70. doi: 10.1002/mds.22340
16. Wenning GK, Tison F, Seppi K, Sampaio C, Diem A, Yekhlef F, et al. Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). *Mov Disord.* (2004) 19:1391–402. doi: 10.1002/mds.20255
17. Zange L, Noack C, Hahn K, Stenzel W, Lipp A. Phosphorylated alpha-synuclein in skin nerve fibres differentiates Parkinson's disease from multiple system atrophy. *Brain* (2015) 138:2310–21. doi: 10.1093/brain/awv138
18. Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. *Mayo Clin Proc.* (1993) 68:748–52. doi: 10.1016/S0025-6196(12)60631-4
19. Paolillo S, Rengo G, Pagano G, Pellegrino T, Savarese G, Femminella GD, et al. Impact of diabetes on cardiac sympathetic innervation in patients with heart failure: a 123I meta-iodobenzylguanidine (123I MIBG) scintigraphic study. *Diabetes Care* (2013) 36:2395–401. doi: 10.2337/dc12-2147
20. Borg K, Sachs C, Kaijser L. Autonomic cardiovascular responses in antecedent poliomyelitis. *Acta Neurol Scand.* (1988) 77:402–8. doi: 10.1111/j.1600-0404.1988.tb05926.x
21. Matsumura K, Nakase E, Saito T, Kikkawa N, Haiyama T. Assessment of myocardial perfusion and cardiac sympathetic nerve dysfunction in patients with sick sinus syndrome–evaluation of coronary hemodynamics and 201TlCl/123I-MIBG myocardial SPECT. *Kaku Igaku* (1994) 31:1321–8.
22. Stankovic I, Krismer F, Jesic A, Antonini A, Benke T, Brown RG, et al. Cognitive impairment in multiple system atrophy: a position statement by the Neuropsychology Task Force of the MDS Multiple System Atrophy (MODIMSA) study group. *Mov Disord.* (2014) 29:857–67. doi: 10.1002/mds.25880
23. Tsujikawa K, Hasegawa Y, Yokoi S, Yasui K, Nanbu I, Yanagi T, et al. Chronological changes of 123I-MIBG myocardial scintigraphy and clinical features of Parkinson's disease. *J Neurol Neurosurg Psychiatry* (2015) 86:945–51. doi: 10.1136/jnnp-2015-310327
24. Kim JS, Park HE, Park IS, Oh YS, Ryu DW, Song IU, et al. Normal "heart" in Parkinson's disease: is this a distinct clinical phenotype? *Eur J Neurol.* (2017) 24:349–56. doi: 10.1111/ene.13206
25. Matsui H, Nishinaka K, Oda M, Komatsu K, Kubori T, Udaka F. Does cardiac metaiodobenzylguanidine (MIBG) uptake in Parkinson's disease correlate with major autonomic symptoms? *Park Relat Disord.* (2006) 12:284–8. doi: 10.1016/j.parkreldis.2005.12.008
26. Umemura A, Oeda T, Hayashi R, Tomita S, Kohsaka M, Yamamoto K, et al. Diagnostic accuracy of apparent diffusion coefficient and 123I-metaiodobenzylguanidine for differentiation of multiple system atrophy and Parkinson's disease. *PLoS ONE* (2013) 8:e61066. doi: 10.1371/journal.pone.0061066
27. Orimo S, Kanazawa T, Nakamura A, Uchihara T, Mori F, Kakita A, et al. Degeneration of cardiac sympathetic nerve can occur in multiple system atrophy. *Acta Neuropathol.* (2007) 113:81–6. doi: 10.1007/s00401-006-0160-y
28. Sone M, Yoshida M, Hashizume Y, Hishikawa N, Sobue G. Alpha-Synuclein-immunoreactive structure formation is enhanced in sympathetic ganglia of patients with multiple system atrophy. *Acta Neuropathol.* (2005) 110:19–26. doi: 10.1007/s00401-005-1013-9
29. Cook GA, Sullivan P, Holmes C, Goldstein DS. Cardiac sympathetic denervation without Lewy bodies in a case of multiple system atrophy. *Park Relat Disord.* (2014) 20:926–8. doi: 10.1016/j.parkreldis.2014.04.003
30. Orimo S, Suzuki M, Inaba A, Mizusawa H. 123I-MIBG myocardial scintigraphy for differentiating Parkinson's disease from other neurodegenerative parkinsonism: a systematic review and meta-analysis. *Park Relat Disord.* (2012) 18:494–500. doi: 10.1016/j.parkreldis.2012.01.009

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REVIEW
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Autonomic Dysfunction in α-Synucleinopathies

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The α-synucleinopathies are a group of neurodegenerative diseases characterized by abnormal accumulation of insoluble α-synuclein in neurons and glial cells, comprising Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). Although varying in prevalence, symptom patterns, and severity among disorders, all α-synucleinopathies have in common autonomic nervous system dysfunctions, which reduce quality of life. Frequent symptoms among α-synucleinopathies include constipation, urinary and sexual dysfunction, and cardiovascular autonomic symptoms such as orthostatic hypotension, supine hypertension, and reduced heart rate variability. Symptoms due to autonomic dysfunction can appear before motor symptom onset, particularly in MSA and PD, hence, detection and quantitative analysis of these symptoms can enable early diagnosis and initiation of treatment, as well as identification of at-risk populations. While patients with PD, DLB, and MSA show both central and peripheral nervous system involvement of α-synuclein pathology, pure autonomic failure (PAF) is a condition characterized by generalized dysregulation of the autonomic nervous system with neuronal cytoplasmic α-synuclein inclusions in the peripheral autonomic small nerve fibers. Patients with PAF often present with orthostatic hypotension, reduced heart rate variability, anhydrosis, erectile dysfunction, and constipation, without motor or cognitive impairment. These patients also have an increased risk of developing an α-synucleinopathy with central involvement, such as PD, DLB, or MSA in later life, possibly indicating a pathophysiological disease continuum. Pathophysiological aspects, as well as developments in diagnosing and treating dysautonomic symptoms in patients with α-synucleinopathies are discussed in this review.

Keywords: autonomic dysfunction, α-synucleinopathies, Parkinson disease, dementia with Lewy bodies, multiple system atrophy, pure autonomic failure, dysautonomia

INTRODUCTION

The α-synucleinopathies are neurodegenerative diseases characterized by the abnormal accumulation of α-synuclein aggregates in neurons and glial cells. These include, in order of prevalence: Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), as well as various rare neuroaxonal dystrophies (1). A highly related condition, pure autonomic failure (PAF), features generalized dysregulation of the autonomic nervous system, with neuronal cytoplasmic α-synuclein inclusions in the peripheral autonomic small nerve fibers, and is regarded as a high-risk condition to develop PD, DLB, or MSA (2, 3).

Dysautonomic symptoms are frequently found in the various α-synucleinopathies, and can occur in any stage of the disease, even in their prodromal states. Autonomic dysfunction includes symptoms such as orthostatic hypotension (OH), reduced heart rate variability, supine hypertension, constipation, fecal incontinence, urinary, and sexual dysfunction. These symptoms are originated by the damage to distinct components of the central and peripheral autonomic nervous system (4–7).

Deposits of α-synuclein accumulate first in peripheral nerves, including those in the skin and enteric mucosa, advancing toward the brain through the vagal and olfactory nerves and progressing through the encephalon, in a determined pattern according to the particular disease phenotype (1, 8–10). This pathological progression can explain the early apparition of non-motor symptoms, among them, autonomic nervous system dysfunction (11, 12).

Dysautonomic manifestations of the specific α-synucleinopathies are caused by the involvement of various components of the autonomous nervous system. In PD, cardiovascular autonomic dysfunction is related to a loss of peripheral noradrenergic innervation, while constipation most likely reflects direct involvement of the enteric nervous system neurons. In MSA, dysautonomic symptoms are mostly related to degeneration of preganglionic autonomic neurons of the brainstem and spinal cord (13).

Recently, the identification of α-synuclein deposits in skin biopsies has opened a window to better understand autonomic denervation, as well as providing a sensitive and specific biomarker for early diagnosis of the α-synucleinopathies, with a strong correlation between α-synuclein load in cutaneous small fibers and measures of cardiovascular autonomic function, and skin pilomotor and sudomotor responses (10, 14–17).

PREVALENCE AND IMPACT OF AUTONOMIC DYSFUNCTION IN α-SYNUCLEINOPATHIES

PD is the second most-common neurodegenerative disease, affecting 2–3% of the population above 65 years of age (18). The prevalence of autonomic dysfunction in PD ranges between 50 and 70% (19–21). The most common dysautonomic symptoms in PD are constipation, urinary dysfunction, and OH (20). Dysautonomic symptoms have been proposed as part of the criteria for prodromal PD, together with REM sleep behavior disorder, molecular neuroimaging biomarkers, sub-threshold parkinsonism, hyposmia, depression, and anxiety (12, 22). In PD, dysautonomic syndromes have a heterogeneous presentation, and their progression is not predictable, however, their presence is associated with a deterioration in autonomy and quality of life, regardless of the duration of the disease, cognitive decline, or the severity of motor symptoms (5, 23).

DLB is the second most frequent neurodegenerative dementia, affecting up to 0.7% of the population above 60 years of age, and causing up to 24% of the total cases of dementia worldwide (24). Dysautonomic symptoms are a part of the supportive clinical features for the diagnostic criteria of this disease, and their estimated prevalence is 62% (21, 25, 26). In DLB, autonomic dysfunction can be a prodromal feature (11): in a case series of 90 patients with DLB, more than half displayed dysautonomic symptoms (particularly OH) prior to the onset of cognitive impairment (27).

MSA is an infrequent cause of dementia, with an incidence of 3 per 100,000 person-years in people above 50 years of age (28). Dysautonomia is a core clinical criteria for this condition, which subdivides into two phenotypes, depending on the predominance of motor symptoms (cerebellar or parkinsonian), additional to autonomic dysfunction (29). Autonomic dysfunction can precede the onset of motor symptoms of MSA in up to 50% of patients (30). Urinary dysfunction and OH are the most frequent dysautonomic symptoms of MSA, with an earlier onset of urinary symptoms, particularly in the cerebellar phenotype (30, 31). In MSA, severe dysautonomia and the early combination of dysautonomic and motor symptoms are poor prognostic factors, regardless of the phenotype (32).

A syndrome that deserves special attention in the study of α-synucleinopathies is pure autonomic failure (PAF). PAF is defined by the presence of chronic OH, without clinical signs of central neurodegeneration (2, 33). Patients with PAF can also display supine hypertension, constipation, urinary symptoms and thermic dysregulation (7). In a 4-year follow-up study of 100 patients with PAF, 34% progressed to an α-synucleinopathies. The risk of conversion was seven times higher in subjects that, in addition to dysautonomic symptoms, presented a REM sleep behavior disorder. Patients that progressed to PD or DLB had a higher prevalence of hyposmia, worse response to the head-up tilt test, and a longer disease course; while those that converted to MSA had a younger onset dysautonomia and a higher prevalence of urinary and bowel dysfunction. The subjects that did not convert to any of these diseases had significantly lower levels of blood epinephrine (6). α-synuclein has also been found in skin biopsies and postganglionic sympathetic neurons of PAF patients, reflecting a common pathological precursor between PAF and other α-synucleinopathies (13, 34). An autonomic-only presentation of MSA can be indistinguishable from PAF, specially in the early stages (35).

SPECIFIC DYSAUTONOMIC SYMPTOMS IN α-SYNUCLEINOPATHIES

OH is the main clinical feature of cardiovascular autonomic dysfunction, and it is defined as sustained drop in systolic

pressure of at least 20 mm Hg and/or a sustained diastolic drop of at least 10 mm Hg within the first 3 min after standing up (36, 37). This time cut-off might not be sensitive for α-synucleinopathies, in which the presentation is most commonly that of delayed OH, therefore, measuring blood pressure for at least 10 min has been recommended (36). Delayed OH has been documented as a risk factor for α-synucleinopathies, and frequently progresses to OH with a high associated mortality (38). Noradrenergic cardiac and extracardiac denervation, as well as the lack of arterial baroreflexes in α-synucleinopathies are causal factors of this symptom (39, 40). The loss of baroreceptor sensitivity has been documented through spectral analysis of heart rate (R-R interval) and systolic arterial pressure variability in PAF (41) and PD (42), even before the onset of OH (43, 44). A functional association between OH and cognitive decline in α-synucleinopathies has been documented, given that OH aggravates neural damage because of cerebral hypoperfusion (36, 45, 46). OH affects 30–60% of PD patients, and has been linked to an elevated frequency of falls, detriment of physical activity, and use of health care services, even if OH is asymptomatic (23, 29, 47, 48). The frequency of OH varies according to the stage of the disease, from 14% in early-stage PD patients to 52% in later cases or older individuals (49–51). Around 68% of patients with DLB display OH, and about 17% suffer associated syncope (26, 36, 52). OH affects around 43% of patients with MSA from early stages of the disease, and of these, 50% also display post-prandial hypotension, as well as nocturnal and supine hypertension (30, 53, 54). This condition is more frequent and more severe in the cerebellar phenotype of MSA when compared to the parkinsonian subtype (55).

Constipation is defined as a frequency of less than three bowel movements in 1 week (56). Between 54 and 90% of PD patients suffer from constipation, and out of these, 48% report the onset of constipation up to 10 years prior to the onset of motor symptoms (20, 57, 58). Constipation is more frequent in patients with a rigid-bradykinetic phenotype and is related to the presence of neuropsychiatric symptoms, such as anxiety, depression, and insomnia (57). Constipation may start even before in MSA than in PD (59). In patients with DLB, a frequency of 30% has been documented (60).

In patients with α-synucleinopathies, the gastrointestinal function is disturbed at all levels. Dysphagia in PD and DLB tends to be mild, and appears in later stages of the disease, while in MSA it can be early and severe. Aspiration pneumonia is a common cause of death in α-synucleinopathies, and higher gastrointestinal symptoms (attributable to esophageal dysmotility and gastroparesis) diminish the quality of life of these patients (58, 61).

Urinary dysfunction is present in up to 71% of PD patients, mostly with nocturia and altered urinary frequency (62). In a Japanese study that included 32 patients with DLB, a 90% prevalence of urinary dysfunction was found, with a predominance of nocturia, followed by urinary incontinence and detrusor hyperactivity (63). Up to 96% of MSA patients display urinary symptoms, which tend to be more severe than in PD, and 60% start before the onset of motor symptoms (with a mean of 4 years before diagnosis), mostly with post-residual volume alterations (53, 62, 64).

Erectile dysfunction is defined as the incapacity to achieve or maintain a penile erection long enough to allow a sexual relation (65). In a 7-year follow-up study of 3,153 patients with erectile dysfunction, a 1.52-times higher risk of PD was found, with an even higher risk if cardiovascular risk factors, such as diabetes or hypertension, was concurrent (66). Erectile dysfunction is present in up to 97% of men diagnosed with MSA, and it is the initial symptom in 48% of male patients, preceding motor symptoms for as long as a decade (30, 59, 64). Female sexual dysfunction has been less studied in α-synucleinopathies, but a higher prevalence of this disorder has been found in female PD patients than in age-matched controls, and it is related to older age and a higher severity of depressive symptoms (67).

CLINICAL ASSESSMENT OF AUTONOMIC DYSFUNCTION IN α-SYNUCLEINOPATHIES

Clinical tests designed to measure the end-organ responses to the autonomic nervous systems can be used to quantitatively analyze autonomic dysfunction, playing an important role in the clinical assessment of α-synucleinopathies.

Tests of cardiovagal function include heart rate variability with deep breathing, postural changes (such as the head-up tilt test), or the Valsalva maneuver, in which the patient forcefully exhales into a sphygmomanometer with an open glottis at a pressure of 40 mmHg for 15 s. Sympathetic adrenergic function can be assessed by measuring blood pressure response to postural change, Valsalva maneuver or isometric exercise, as well as by the cold pressor test, in which the subject is instructed to immerse his or her hand in ice water for 1 min (68). The decrease of heart rate and blood pressure variability can be accurately demonstrated through power spectrum techniques, which provide a quantitative assessment of said variability (41, 43, 69, 70). Ambulatory blood pressure monitoring can also provide sensitive markers of autonomous nervous system failure, such as post-prandial hypotension and nocturnal/supine hypertension (71, 72).

Clinical assessments of sudomotor function include thermoregulatory sweat testing, quantitative sudomotor axon reflex testing, silicone impression, the sympathetic skin response, the acetylcholine sweat-spot test, and quantitative direct and indirect axon reflex testing, as well as electromyographic skin potentials (73, 74). Cutaneous autonomic pilomotor testing, in which iontophoresis of phenylephrine induces a local neurogenic pilomotor erection ("goose bumps") as a measure of functional integrity of autonomic skin nerve fibers, is an approach to capture the progression of autonomic nerve dysfunction and α-synuclein deposition (75).

Differential diagnosis of the parkinsonian subtype of MSA and PD or other parkinsonian syndromes is mostly based on the evaluation of autonomic dysfunction (9, 30). Clinical autonomic cardiovascular tests can distinguish MSA and PD with a sensitivity of 91% and a specificity of 92%. (123)-I-myocardial

metaiodobenzyguanidine (MIBG) scintigraphy can distinguish these entities with a sensitivity of 90% and specificity of 82% (7, 30). Cardiovagal baroreflex is also sensitive for the differentiation between MSA and PD, being disproportionally affected in MSA (76). Added sweating and thermoregulation tests have also been found to improve differential diagnostic reliability (77, 78).

MOLECULAR AND CELLULAR ASPECTS OF AUTONOMIC DYSFUNCTION IN α-SYNUCLEINOPATHIES

Mutations in the gene encoding for α-synuclein, SNCA, as well as in some of the genes collectively referred to as PARK (including the LRRK2 and VPS35 genes), have been associated with variants of autosomal dominant PD, and others such as PARK2, PINK1, and PARK7 to autosomal recessive PD. Although the mechanism has not been completely clarified, it is known that mutated proteins have different roles in autophagy and the degradation of nerve cells. Familial cases of DLB have been associated with mutations in the PARK, SNCA, SNCB, and LRRK2 genes. In the rare familial cases of MSA, there is a reported association to SNCA and COQ2 genes. Autonomic dysfunction has been associated with six SNCA mutations in different groups, including subjects with PAF prior to the onset of motor symptoms (79, 80).

TABLE 1 | Pharmacological and non-pharmacological strategies for dysautonomic symptoms in α-synucleinopathies.

Dysautonomic symptom	Pharmacological strategy	Non-pharmacological strategy
Orthostatic hypotension	• Expansion of intravascular volume with fludrocortisone (58) • Increase of peripheral vascular resistance with midodrine, droxidopa or norepinephrine transporter inhibitors, such as atomoxetine, yohimbine, ergotamine, and caffeine (58, 83) • Potentiation of peripheral cholinergic neurotransmission (84) • Domperidone in non-cardiac patients (85)	• Discontinue antihypertensive and other medications that can cause orthostatic hypotension (84) • Physical contermaneuvers (e.g., standing with legs crossed, squatting, active tensing of leg muscles, breathing-related maneuvers to increase inspiratory resistance, and avoiding getting up too quickly or standing motionless) (58, 86) • Use of compression stockings (58) • Increase the consumption of water and drinks with caffeine during meals (58, 86) • Eat small, frequent meals (86) • Physical activity such as water exercise, recumbent bicycling, or rowing (86) • Avoid alcohol consumption (86) • Avoid situations that increase core body temperature such as prolonged hot showers (86) • Plantar mechanical stimulation is a promising approach for the regulation of heart rate variability in PD (42, 69)
Supine hypertension	• Antihypertensives: captoptil, nevibolol, clonidine, hydralazine, losartan (58) • Clonidine, nitroglycerin patches, and short-acting nifedipine (83, 84)	• At night, tilt the bed to achieve an angle of 30 or 45 degrees (58) • The application of abdominal local heat could be of benefit (58)
Constipation	• Bulk laxatives, like psyllium or methylcellulose (58) • Osmotic laxatives (polyethylene glycol, magnesium, lactuslose) (58)	• Probiotics, high fiber diets, olive oil • Adequate hydration (58) • Physical activity (87)
Dysphagia and excessive salivation	• Botulinum toxin in the distal esophagus could improve dysphagia (58) • Vocal fold augmentation, including injection laryngoplasty (88) • In patients with sialorrhea, treatment with glycopyrrolate and the local application of anticholinergics, as drops of sublingual atropine or ipatropium spray (58)	• Reduce the volume of food (58) • Eat slowly (58) • Eat foods with a more liquid consistency (58) • Speech and swallowing therapy (61, 89)
Gastroparesis	• Dopamine blockers like metoclopramide, itopride (58) • Motilin receptor agonists such as erythromycin (58) • Serotonergic agonists like cisapride (58)	• Low fat diet (58) • Small but frequent meals (58)
Urinary dysfunction	• B3-adrenergic agonists like mirabregon (58) • Antimuscarinic agents such as oxybutynin, atripine, scopolamine (58) • Alpha-adrenergic blockers like tamsolusin (58)	• Biofeedback (58) • Deep brain stimulation of the subthalamic nulcei (90)
Erectile dysfunction	• Phosphodiesterase type 5 (PDE-5) inhibitors, with caution because of potentially severe hypotension (58) • Intraurethral prostaglandin suppositories (58)	• Psychotherapy, sex counseling seeking "pleasure oriented" activity instead of "goal-oriented" intercourse (91) • Vacuum pump devices (58) • Surgical placement of penis prosthesis (58)
Female sexual dysfunction	• Hormonal replacement therapy (58)	• Psychotherapy, sex counseling seeking "pleasure oriented" activity instead of "goal-oriented" intercourse (58, 91) • Vaginal lubrication (58)

The families carrying PD with a chromosomal triplication of SNCA present OH with evidence of sympathetic cardiac denervation and frequent associated falls up to 3 years before the onset of the disease. However, there are triplications of SNCA without documented autonomic dysfunctions. This phenotypic heterogeneity could be explained by the variability in the genomic size of SNCA triplications, meaning that different genes could be involved. In addition to OH, other dysautonomic symptoms, such as urinary incontinence and severe constipation of early onset, are more frequent in triplications of SNCA compared to duplications. A sympathetic cardiac denervation has also been found in heterozygous carriers with biallelic mutations of PARK2, causal of the most common autosomal recessive form of PD. Other mutations in the LRRK gene are also associated with different autonomic profiles in PD, with symptoms such as constipation, neurogenic bladder, and erectile dysfunction (79).

The central autonomic network and preganglionic sympathetic and parasympathetic neurons are variably affected in the different α-synucleinopathies. In PD and DLB, the dorsal motor nucleus of the vagus nerve, and in MSA the ventrolateral medulla, hypothalamus and preganglionic neurons are key structures affected that explain the origin of autonomic dysfunction (13). PAF involves generalized loss of sympathoadrenomedullary cells, as reflected by plasma levels of catechols and metanephrines, in contrast to MSA and PD, where adrenomedullary cells seem to remain intact, but organ-selective sympathetic denervation occurs (81). Furthermore, α-synuclein-containing glial cytoplasmic inclusions have been found in the Oluf's nucleus of MSA-affected individuals, which might account for early urinary, defecatory and sexual symptoms (64).

In brain tissue, an abnormal accumulation of α-synuclein has been found in the left posterior part of the insula of patients with PD, correlated with the presence of OH. The inclusions of α-synuclein in the hypothalamus of patients with PD may be linked to hypothalamic dysfunction, resulting from lesions in the thermoregulatory centers of the preoptic area, causing hypothermia, episodes of sweating, or hypohidrosis. In MSA, the neurons of the paraventricular nucleus project to the intermediolateral cell column, and their dysfunction can contribute to the lack of control of sympathetic function, causing OH. Both MSA and DLB show a loss of tyrosine hydroxylase in neurons of the periaqueductal gray matter, which is related to autonomic cardiovascular and urinary dysfunction (13). With respect to constipation and gastrointestinal symptoms presented by patients, α-synuclein inclusions have been detected in colon biopsies up to 8 years before the onset of motor symptoms of PD and, although the studies are not consistent, it is believed that the presence of extracellular α-synuclein is associated with acute and chronic inflammatory conditions of the intestine (82).

TREATMENT OF AUTONOMIC DYSFUNCTION IN α-SYNUCLEINOPATHIES

Dysautonomic symptoms are among the most debilitating in α-synucleinopathies, but, when recognized, they can be treated using both pharmacological and non-pharmacological strategies, including the suspension of potentially causing or aggravating medications, and patient education. **Table 1** shows the therapeutic strategies for this group of symptoms.

CONCLUSIONS

Dysautonomic symptoms frequently occuring in α-synucleinopathies comprise cardiovascular, gastrointestinal, urogenital and thermoregulatory disturbances. These symptoms reduce quality of life and worsen prognosis. The understanding of their pathophysiology, as well as the detection of α-synuclein deposition and autonomic dysfunction in the premotor stages of α-synucleinopathies may be key for identifying novel treatment targets and improving clinical outcomes. While causative treatment is not yet available, improvement of quality of life can be achieved by personalized symptomatic treatment regimens, which includes both and pharmacological and non-pharmacological strategies.

AUTHOR CONTRIBUTIONS

JM-V: oversight of teamwork, literature search and review of articles, writing of abstract and parts 2, 3, and 4; JF-V: literature search and review of articles, writing of parts 1, 2, and 4; EB-V: review of articles, writing of parts 5 and 6; AS-O and B-MI: proofreading, expert advice on theoretical and clinical aspects; TS: proofreading, expert advice on theoretical and clinical aspects, identification of additional relevant papers.

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REFERENCES

1. McCann H, Stevens CH, Cartwright H, Halliday GM. α-Synucleinopathy phenotypes. *Park Relat Disord*. (2014) 20(Suppl.1):S62–7. doi: 10.1016/S1353-8020(13)70017-8
2. Coon EA, Low PA. Pure autonomic failure without alpha-synuclein pathology: an evolving understanding of a heterogeneous disease. *Clin Auton Res.* (2017) 27:67–8. doi: 10.1007/s10286-017-0410-1
3. Kaufmann H, Goldstein DS. Editorial: pure autonomic failure: a restricted lewy body synucleinopathy or early parkinson disease? *Neurology*. (2010) 74:536–7. doi: 10.1212/WNL.0b013e3181d26982
4. Palma J-A. Autonomic dysfunction in Parkinson's disease and other synucleinopathies: introduction to the series. *Mov Disord*. (2018) 33:347–8. doi: 10.1002/mds.27347
5. Leclair-Visonneau L, Magy L, Volteau C, Clairembault T, Le Dily S, Préterre C, et al. Heterogeneous pattern of autonomic dysfunction in Parkinson's disease. *J Neurol*. (2018) 265:933–41. doi: 10.1007/s00415-018-8789-8

6. Kaufmann H, Norcliffe-Kaufmann L, Palma J, Biaggioni I, Low PA, Singer W, et al. Natural history of pure autonomic failure: a United States prospective cohort. *Ann Neurol*. (2017) 81:287–97. doi: 10.1002/ana.24877
7. Merola A, Espay AJ, Zibetti M, Romagnolo A, Rosso M. Pure autonomic failure versus prodromal dysautonomia in Parkinson' s disease : insights from the bedside. *Mov Disord*. (2016) 4:141–44. doi: 10.1002/mdc3.12360
8. Braak H, Tredici K Del, Rüb U, de Vos RAI, Jansen Steur ENH, Braak E. Staging of brain pathology related to sporadic Parkinson' s disease staging of brain pathology related to sporadic Parkinson' s disease. *Neurobiol Aging*. (2003) 4580:197–211. doi: 10.1016/S0197-4580(02)00065-9
9. Levin J, Kurz A, Arzberger T, Giese A, Höglinger GU. The differential diagnosis and treatment of atypical Parkinsonism. *Dtsch Arztebl Int*. (2016) 113:61–9. doi: 10.3238/arztebl.2016.0061
10. Doppler K, Ebert S, Üçeyler N, Trenkwalder C, Ebentheuer J, Volkmann J, et al. Cutaneous neuropathy in Parkinson's disease: a window into brain pathology. *Acta Neuropathol*. (2014) 128:99–109. doi: 10.1007/s00401-014-1284-0
11. Fujishiro H, Nakamura S, Sato K, Iseki E. Prodromal dementia with Lewy bodies. *Geriatr Gerontol Int*. (2015) 15:817–26. doi: 10.1111/ggi.12466
12. Mahlknecht P, Gasperi A, Djamshidian A, Kiechl S, Stockner H, Willeit P, et al. Performance of the Movement Disorders Society criteria for prodromal Parkinson's disease: a population-based 10-year study. *Mov Disord*. (2018) 33:405–13. doi: 10.1002/mds.27281
13. Coon EA, Cutsforth-Gregory JK, Benarroch EE. Neuropathology of autonomic dysfunction in synucleinopathies. *Mov Disord*. (2018) 33:349–58. doi: 10.1002/mds.27186
14. Siepmann T, Penzlin AI, Illigens BMW, Reichmann H. Should skin biopsies be performed in patients suspected of having Parkinson's disease? *Parkinsons Dis*. (2017) 2017:6064974. doi: 10.1155/2017/6064974
15. Siepmann T, Illigens BMW, Barlinn K. Alpha-synuclein in cutaneous small nerve fibers. *Neuropsychiatr Dis Treat*. (2016) 12:2731–5. doi: 10.2147/NDT.S117423
16. Donadio V, Incensi A, Rizzo G, Capellari S, Pantieri R, Stanzani Maserati M, et al. A new potential biomarker for dementia with Lewy bodies. *Neurology*. (2017) 89:318–26. doi: 10.1212/WNL.0000000000004146
17. Gibbons CH, Garcia J, Wang N, Shih LC, Freeman R. The diagnostic discrimination of cutaneous α-synuclein deposition in Parkinson disease. *Neurology*. (2016) 87:505–12. doi: 10.1212/WNL.0000000000002919
18. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. *Nat Rev Dis Prim*. (2017) 3:17013. doi: 10.1038/nrdp.2017.13
19. Merola A, Romagnolo A, Comi C, Rosso M, Artusi CA, Zibetti M, et al. Prevalence and burden of dysautonomia in advanced Parkinson's disease. *Mov Disord*. (2017) 32:796–7. doi: 10.1002/mds.26970
20. Martinez-Martin P, Chaudhuri KR, Rojo-Abuin JM, Rodriguez-Blazquez C, Alvarez-Sanchez M, Arakaki T, et al. Assessing the non-motor symptoms of Parkinson's disease: MDS-UPDRS and NMS scale. *Eur J Neurol*. (2015) 22:37–43. doi: 10.1111/ene.12165
21. Walter BL. Cardiovascular autonomic dysfunction in patients with movement disorders. *Cleve Clin J Med*. (2008) 75:S54.
22. Rutten S, Ghielen I, Vriend C, Hoogendoorn AW, Berendse HW, Leentjens AFG, et al. Anxiety in Parkinson's disease: symptom dimensions and overlap with depression and autonomic failure. *Parkinsonism Relat Disord*. (2015) 21:189–93. doi: 10.1016/j.parkreldis.2014.11.019
23. Merola A, Romagnolo A, Rosso M, Suri R, Berndt Z, Maule S, et al. Autonomic dysfunction in Parkinson's disease: a prospective cohort study. *Mov Disord*. (2018) 33:391–7. doi: 10.1002/mds.27268
24. Hogan DB, Fiest KM, Roberts JI, Maxwell CJ, Dykeman J, Pringsheim T, et al. The prevalence and incidence of dementia with Lewy bodies: a systematic review. *Can J Neurol Sci*. (2016) 43:S83–95. doi: 10.1017/cjn.2016.2
25. Mckeith IG, Sci M, Boeve BF, Dickson DW, Halliday G, Taylor J-P, et al. Diagnosis and management of dementia with Lewy bodies Fourth consensus report of the DLB Consortium. *Neurology*. (2017) 89:88–100. doi: 10.1212/WNL.0000000000004058
26. Horimoto Y, Matsumoto M, Akatsu H, Ikari H, Kojima K, Yamamoto T, et al. Autonomic dysfunctions in dementia with Lewy bodies. *J Neurol*. (2003) 250:530–3. doi: 10.1007/s00415-003-1029-9
27. Fujishiro H, Iseki E, Nakamura S, Kasanuki K, Chiba Y, Ota K, et al. Dementia with Lewy bodies: early diagnostic challenges. *Psychogeriatrics*. (2013) 13:128–38. doi: 10.1111/psyg.12005
28. Krismer F, Wenning GK. Multiple system atrophy: insights into a rare and debilitating movement disorder. *Nat Rev Neurol*. (2017) 13:232–43. doi: 10.1038/nrneurol.2017.26
29. Laurens B, Vergnet S, Lopez MC, Foubert-Samier A, Tison F, Fernagut PO, et al. Multiple system atrophy - state of the art. *Curr Neurol Neurosci Rep*. (2017) 17:5. doi: 10.1007/s11910-017-0751-0
30. Bhatia KP, Stamelou M. Nonmotor features in atypical Parkinsonism. 1st ed. *Int Rev Neurobiol*. (2017) 1285–301. doi: 10.1016/bs.irn.2017.06.001
31. Zheng J, Yang X, Chen Y, Zhao Q, Tian S, Huang H, et al. Onset of bladder and motor symptoms in multiple system atrophy: differences according to phenotype. *Clin Auton Res*. (2017) 27:103–6. doi: 10.1007/s10286-017-0405-y
32. Glasmacher SA, Leigh PN, Saha RA. Predictors of survival in progressive supranuclear palsy and multiple system atrophy: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. (2017) 88:402–11. doi: 10.1136/jnnp-2016-314956
33. Isonaka R, Holmes C, Cook GA, Sullivan P, Sharabi Y, Goldstein DS. Pure autonomic failure without synucleinopathy. *Clin Auton Res*. (2017) 27:97–101. doi: 10.1007/s10286-017-0404-z
34. Shishido T, Ikemura M, Obi T, Yamazaki K, Terada T, Sugiura A, et al. Alpha-synuclein accumulation in skin nerve fibers revealed by skin biopsy in pure autonomic failure. *Neurology*. (2010) 74:608–10. doi: 10.1212/WNL.0b013e3181cff6d5
35. Palma J-A, Norcliffe-Kaufmann L, Kaufmann H. Diagnosis of multiple system atrophy. *Auton Neurosci*. (2018) 211:15–25. doi: 10.1016/j.autneu.2017.10.007
36. Joseph A, Wanono R, Flamant M, Vidal-Petiot E. Orthostatic hypotension: a review. *Nephrol Ther*. (2017) 13:S55–67. doi: 10.1016/j.nephro.2017.01.003
37. Scorza FA, Fiorini AC, Scorza CA, Finsterer J. Cardiac abnormalities in Parkinson's disease and Parkinsonism. *J Clin Neurosci*. (2018) 53:1–5. doi: 10.1016/j.jocn.2018.04.031
38. Gibbons CH, Freeman R. Clinical implications of delayed orthostatic hypotension. *Neurology*. (2015) 85:1362–7. doi: 10.1212/WNL.0000000000002030
39. Norcliffe-Kaufmann L, Kaufmann H, Palma J-A, Shibao CA, Biaggioni I, Peltier AC, et al. Orthostatic heart rate changes in patients with autonomic failure caused by neurodegenerative synucleinopathies. *Ann Neurol*. (2018) 83:522–31. doi: 10.1002/ana.25170
40. Jain S, Goldstein DS. Cardiovascular dysautonomia in Parkinson disease: from pathophysiology to pathogenesis. *Neurobiol Dis*. (2012) 46:572–80. doi: 10.1016/j.nbd.2011.10.025
41. Furlan R, Piazza S, Bevilacqua M, Turiel M, Norbiato G, Lombardi F, et al. Pure autonomic failure: complex abnormalities in the neural mechanisms regulating the cardiovascular system. *J Auton Nerv Syst*. (1995) 51:223–35. doi: 10.1016/0165-1838(94)00135-7
42. Barbic F, Galli M, Dalla Vecchia L, Canesi M, Cimolin V, Porta A, et al. The effects of mechanical stimulation of the feet on gait and cardiovascular autonomic control in Parkinson's disease. *Am J Physiol Circ Physiol*. (2014) 116:495–503. doi: 10.1152/japplphysiol.01160.2013
43. Barbic F, Perego F, Canesi M, Gianni M, Biagiotti S, Costantino G, et al. Early abnormalities of vascular and cardiac autonomic control in Parkinson's disease without orthostatic hypotension. *Hypertension*. (2007) 49:120–6. doi: 10.1161/01.HYP.0000250939.71343.7c
44. Strano S, Fanciulli A, Rizzo M, Marinelli P, Palange P, Tiple D, et al. Cardiovascular dysfunction in untreated Parkinson's disease: a multi-modality assessment. *J Neurol Sci*. (2016) 370:251–5. doi: 10.1016/j.jns.2016.09.036
45. Udow SJ, Robertson AD, Macintosh BJ, Espay AJ, Rowe JB, Lang AE, et al. "Under pressure": is there a link between orthostatic hypotension and cognitive impairment in α-synucleinopathies? *J Neurol Neurosurg Psychiatry*. (2016) 87:1311–21. doi: 10.1136/jnnp-2016-314123
46. Centi J, Freeman R, Gibbons CH, Neargarder S, Canova AO, Cronin-Golomb A. Effects of orthostatic hypotension on cognition in Parkinson disease. *Neurology*. (2017) 88:17–24. doi: 10.1212/WNL.0000000000003452
47. Merola A, Romagnolo A, Rosso M, Lopez-Castellanos JR, Wissel BD, Larkin S, et al. Orthostatic hypotension in Parkinson's disease: does it matter if asymptomatic? *Parkinsonism Relat Disord*. (2016) 33:65–71. doi: 10.1016/j.parkreldis.2016.09.013

48. Mol A, Reijnierse EM, Hoang PTSB, van Wezel RJA, Meskers CGM, Maier AB. Orthostatic hypotension and physical functioning in older adults: a systematic review and meta-analysis. *Ageing Res Rev*. (2018) 48:122–44. doi: 10.1016/j.arr.2018.10.007
49. Bonuccelli U, Lucetti C, Del Dotto P, Ceravolo R, Gambaccini G, Bernardini S, et al. Orthostatic hypotension in *de novo* Parkinson disease. *Arch Neurol.* (2003) 60:1400–4. doi: 10.1001/archneur.60.10.1400
50. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord Off J Mov Disord Soc.* (2009) 24:1641–9. doi: 10.1002/mds.22643
51. Matinolli M, Korpelainen JT, Korpelainen R, Sotaniemi KA, Myllylä VV. Orthostatic hypotension, balance and falls in Parkinson's disease. *Mov Disord Off J Mov Disord Soc.* (2009) 24:745–51. doi: 10.1002/mds.22457
52. Bengtsson-Lindberg ME, Larsson VS, Minthon LB, Wattmo CAS, Londos EY. Evaluation of systolic and diastolic hypotension in dementia with Lewy bodies and Alzheimer's disease. *Heal Aging Clin Care Elder*. (2013) 5:33–9. doi: 10.4137/HACCE.S12670
53. Sakakibara R, Hattori T, Uchiyama T, Kita K, Asahina M, Suzuki A, et al. Urinary dysfunction and orthostatic hypotension in multiple system atrophy: which is the more common and earlier manifestation? *J Neurol Neurosurg Psychiatry*. (2000) 68:65–9. doi: 10.1136/jnnp.68.1.65
54. Fanciulli A, Göbel G, Ndayisaba JP, Granata R, Duerr S, Strano S, et al. Supine hypertension in Parkinson's disease and multiple system atrophy. *Clin Auton Res*. (2016) 26:97–105. doi: 10.1007/s10286-015-0336-4
55. Wenning GK, Granata R, Krismer F, Dürr S, Seppi K, Poewe W, et al. Orthostatic hypotension is differentially associated with the cerebellar versus the parkinsonian variant of multiple system atrophy: a comparative study. *Cerebellum*. (2012) 11:223–6. doi: 10.1007/s12311-011-0299-5
56. Andy UU, Vaughan CP, Burgio KL, Alli FM, Goode PS, Markland AD. Shared risk factors for constipation, fecal incontinence, and combined symptoms in older US adults. *J Am Geriatr Soc*. (2016) 64:e183–8. doi: 10.1111/jgs.14521
57. Gan J, Wan Y, Shi J, Zhou M, Lou Z, Liu Z. A survey of subjective constipation in Parkinson's disease patients in shanghai and literature review. *BMC Neurol.* (2018) 18:1–9. doi: 10.1186/s12883-018-1034-3
58. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. *Mov Disord*. (2018) 33:372–90. doi: 10.1002/mds.27344
59. Savica R, Bradley BF, Mielke MM. When do a-Synucleinopathies start? An epidemiological timeline a review. *JAMA Neurol*. (2018) 75:503–9. doi: 10.1001/jamaneurol.2017.4243
60. Stubendorff K, Aarsland D, Minthon L, Londos E. The impact of autonomic dysfunction on survival in patients with dementia with lewy bodies and Parkinson's disease with dementia. *PLoS ONE*. (2012) 7:e45451. doi: 10.1371/journal.pone.0045451
61. Suttrup I, Warnecke T. Dysphagia in Parkinson's disease. *Dysphagia*. (2016) 31:24–32. doi: 10.1007/s00455-015-9671-9
62. Sakakibara R, Tateno F, Yamamoto T, Uchiyama T, Yamanishi T. Urological dysfunction in synucleinopathies: epidemiology, pathophysiology and management. *Clin Auton Res.* (2018) 28:83–101. doi: 10.1007/s10286-017-0480-0
63. Tateno F, Sakakibara R, Ogata T, Kishi M, Tsuyusaki Y, Takahashi O, et al. Lower urinary tract function in dementia with Lewy bodies (DLB). *Mov Disord*. (2015) 30:411–5. doi: 10.1002/mds.25985
64. McKay JH, Cheshire WP. First symptoms in multiple system atrophy. *Clin Auton Res*. (2018) 28:215–21. doi: 10.1007/s10286-017-0500-0
65. Shamloul R, Ghanem H. Erectile dysfunction. *Lancet*. (2013) 381:153–65. doi: 10.1016/S0140-6736(12)60520-0
66. Yang Y, Liu H, Lin T, Kuo Y, Hsieh T. Relationship between erectile dysfunction, comorbidity, and Parkinson's disease: evidence from a population-based longitudinal study. *J Clin Neurol*. (2017) 13:250. doi: 10.3988/jcn.2017.13.3.250
67. Varanda S, Ribeiro da Silva J, Costa AS, Amorim de Carvalho C, Alves JN, Rodrigues M, et al. Sexual dysfunction in women with Parkinson's disease. *Mov Disord*. (2016) 31:1685–93. doi: 10.1002/mds.26739
68. Freeman R, Chapleau MW. Testing the autonomic nervous system. In: Said G, Krarup C, editors. *Handbook of Clinical Neurology*, 3rd ed. Elsevier BV (2013). p. 115–36. doi: 10.1016/B978-0-444-52902-2.00007-2
69. Bassani T, Bari V, Marchi A, Tassin S, Dalla Vecchia L, Canesi M, et al. Model-free causality analysis of cardiovascular variability detects the amelioration of autonomic control in Parkinson's disease patients undergoing mechanical stimulation. *Physiol Meas*. (2014) 35:1397. doi: 10.1088/0967-3334/35/7/1397
70. Malliani A, Lombardi F, Pagani M. Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. *Br Heart J*. (1994) 71:1. doi: 10.1136/hrt.71.1.1
71. Luciano GL, Brennan MJ, Rothberg MB. Post-prandial hypotension. *Am J Med*. (2010) 123:281-e1. doi: 10.1016/j.amjmed.2009.06.026
72. Umehara T, Matsuno H, Toyoda C, Oka H. Clinical characteristics of supine hypertension in *de novo* Parkinson disease. *Clin Auton Res*. (2016) 26:15–21. doi: 10.1007/s10286-015-0324-8
73. Illigens BMW, Gibbons CH. Sweat testing to evaluate autonomic function. *Clin Auton Res*. (2009) 19:79–87. doi: 10.1007/s10286-008-0506-8
74. Buchmann SJ, Penzlin AI, Kubasch ML, Illigens BMW, Siepmann T. Assessment of sudomotor function. *Clin Auton Res*. (2018) 29:41–53. doi: 10.1007/s10286-018-0530-2
75. Siepmann T, Pintér A, Buchmann SJ, Stibal L, Arndt M, Kubasch AS, et al. Cutaneous autonomic pilomotor testing to unveil the role of neuropathy progression in early Parkinson's disease (CAPTURE PD): protocol for a multicenter study. *Front Neurol*. (2017) 8:1–9. doi: 10.3389/fneur.2017.00212
76. Roy S, Jaryal AK, Srivastava AK, Deepak KK. Cardiovagal baroreflex sensitivity in Parkinson's disease and multiple-system atrophy. *J Clin Neurol*. (2016) 12:218–23. doi: 10.3988/jcn.2016.12.2.218
77. Pavy-LeTraon A, Brefel-Courbon C, Dupouy J, Ory-Magne F, Rascol O, Senard JM. Combined cardiovascular and sweating autonomic testing to differentiate multiple system atrophy from Parkinson's disease. *Neurophysiol Clin*. (2018) 48:103–10. doi: 10.1016/j.neucli.2017.11.003
78. Augustis S, Saferis V, Jost WH. Autonomic disturbances including impaired hand thermoregulation in multiple system atrophy and Parkinson's disease. *J Neural Transm.* (2017) 124:965–72. doi: 10.1007/s00702-016-1665-8
79. Chelban V, Vichayanrat E, Schottlaende L, Iodice V, Houlden H. Autonomic dysfunction in genetic forms of synucleinopathies. *Mov Disord*. (2018) 33:359–71. doi: 10.1002/mds.27343
80. da Silva CP, de Abreu GM, Cabello Acero PH, Campos M, Pereira JS, Sarah SR, et al. Clinical profiles associated with LRRK2 and GBA mutations in Brazilians with Parkinson's disease. *J Neurol Sci*. (2017) 381:160–4. doi: 10.1016/j.jns.2017.08.3249
81. Goldstein DS, Holmes C, Sharabi Y, Brentzel S, Eisenhofer G. Plasma levels of catechols and metanephrines in neurogenic orthostatic hypotension. *Neurology*. (2003) 60:1327–32. doi: 10.1212/01.WNL.0000058766.46428.F3
82. Sharma A, Kurek J, Morgan JC, Wakade C, Rao SSC. Constipation in Parkinson's disease: a nuisance or nuanced answer to the pathophysiological puzzle? *Curr Gastroenterol Rep*. (2018) 20:1–9. doi: 10.1007/s11894-018-0609-x
83. Shibao CA, Kaufmann H. Pharmacotherapy of cardiovascular autonomic dysfunction in Parkinson disease. *CNS Drugs*. (2017) 31:975–89. doi: 10.1007/s40263-017-0473-5
84. 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
85. Bacchi S, Chim I, Kramer P, Postuma RB. Domperidone for hypotension in Parkinson's disease: a systematic review. *J Parkinsons Dis*. (2017) 7:603–17. doi: 10.3233/JPD-171209
86. Arnold AC, Raj SR. Orthostatic hypotension: a practical approach to investigation and management. *Can J Cardiol*. (2017) 33:1725–8. doi: 10.1016/j.cjca.2017.05.007
87. Amara AW, Memon AA. Effects of exercise on non-motor symptoms in Parkinson's disease. *Clin Ther*. (2018) 40:8–15. doi: 10.1016/j.clinthera.2017.11.004
88. Howell RJ, Webster H, Kissela E, Gustin R, Kaval F, Klaben B, et al. Dysphagia in Parkinson's disease improves with vocal augmentation. *Dysphagia*. (2019). doi: 10.1007/s00455-019-09982-z. [Epub ahead of print].

89. Speyer R, Baijens L, Heijnen M, Zwijnenberg I. Effects of therapy in oropharyngeal dysphagia by speech and language therapists: a systematic review. *Dysphagia*. (2010) 25:40–65. doi: 10.1007/s00455-009-9239-7
90. Dafsari HS, Silverdale M, Strack M, Rizos A, Ashkan K, Mahlstedt P, et al. Nonmotor symptoms evolution during 24 months of bilateral subthalamic stimulation in Parkinson's disease. *Mov Disord*. (2018) 33:421–30. doi: 10.1002/mds.27283
91. Bronner G. Sexual problems in Parkinson's disease: the multidimensional nature of the problem and of the intervention. *J Neurol Sci*. (2011) 310:139–43. doi: 10.1016/j.jns.2011.05.050

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Spectral Analysis of Heart Rate Variability: Time Window Matters

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Spectral analysis of heart rate variability (HRV) is a valuable tool for the assessment of cardiovascular autonomic function. Fast Fourier transform and autoregressive based spectral analysis are two most commonly used approaches for HRV analysis, while new techniques such as trigonometric regressive spectral (TRS) and wavelet transform have been developed. Short-term (on ECG of several minutes) and long-term (typically on ECG of 1–24 h) HRV analyses have different advantages and disadvantages. This article reviews the characteristics of spectral HRV studies using different lengths of time windows. Short-term HRV analysis is a convenient method for the estimation of autonomic status, and can track dynamic changes of cardiac autonomic function within minutes. Long-term HRV analysis is a stable tool for assessing autonomic function, describe the autonomic function change over hours or even longer time spans, and can reliably predict prognosis. The choice of appropriate time window is essential for research of autonomic function using spectral HRV analysis.

Keywords: trigonometric regressive spectral analysis, fast fourier tranform (FFT), heart rate variability, multiple trigonometric regressive spectral analysis, long-term, short-term

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INTRODUCTION

Heart rate variability (HRV) is the physiological phenomenon of variation in heart beats. Even in resting states, spontaneous fluctuations of the intervals between two successive heart beats occur. Spectral analysis of HRV is a non-invasive and easy-to-perform tool for evaluating cardiac autonomic activity (1). Two critical frequency domain parameters obtained from spectral analysis are widely used: low frequency (LF) power (0.04–0.15 Hz) represents both sympathetic and vagal influences; high frequency (HF) power (0.15–0.40 Hz) reflects the modulation of vagal tone. In addition, LF/HF ratio indicates the balance between sympathetic and vagal tones (2). HRV analysis has been widely used in numerous cohorts, and plays an important role in describing the patients' autonomic dysfunctions, tracking the natural fluctuations of autonomic function, evaluating the autonomic changes following various interventions, and predicting prognosis.

PREPROCESSING OF THE ECG DATA

Before spectral analysis for HRV, there are a series of preprocessing steps. The preprocessing procedures include sampling and digitizing, artifact identification, RR data editing, RR interval rejection, NN data sequence; for some methods (e.g., fast Fourier transform) interpolation and sampling of the tachogram are needed (2). It is noticeable that these preprocessing steps could influence the HRV analysis results.

Firstly, the device should have a sufficient sampling rate. A low sampling rate (<200 Hz) can affect the identification of QRS complex, and lead to inaccurate RR intervals, then leads to distorted HRV analysis (2, 3). It is recommended that the sampling rate should not be lower than 250 Hz (3).

Before spectral analysis, we need to carefully inspect the ECG to identify potential artifacts, ectopic beats, and arrhythmic events. Since HRV analysis is based on the sinus rhythm, if left untreated, these artifacts and non-sinus events would introduce errors (4). For short-term HRV analysis, if possible, recordings that are free of artifacts, ectopic beats, and arrhythmia should be chosen. If the selected data include technical artifacts, such as missed beats (caused by failure to detect the R peak) and electrical noise, we can edit the data by a proper interpolation based on the neighboring RR intervals (4). In contrast, the methods editing ectopic beats are uncertain. There are various approaches to mitigate the influence of ectopic beats, including deletions of the ectopic beats and numerous interpolation methods (5). Overall, simply deleting the ectopic beats is not recommended because it loses ECG information and obtains distorted LF and HF power (5, 6). The choice of interpolation methods depends on the type of ectopic beat, quality of data, and the study population. For a ventricular premature beat, the period between the normal beats before and after the premature beat is approximately twice the mean RRI, and an intermediate insertion between the two neighboring normal beats is acceptable (4, 7). However, a supraventricular ectopic beat can reset the sinoatrial node activity, and more complicated interpolation approaches might be appropriate (7). In this occasion, commonly used interpolation methods include interpolation of degree zero, interpolation of degree one, cubic spline interpolation, integral pulse frequency modulation model, etc. Until now, how to choose the best technique still needs further investigation, and head-to-head comparisons are warranted (5–7).

For fast Fourier transform, to satisfy the requirement of equal distance, interpolation is needed, and we would discuss this issue in the following section. Sometimes, automatic filters are employed; it might theoretically improve the statistical reliability of the data. But we should observe its impact to the spectral components, because this operation may incur errors (2, 4).

COMMONLY USED SPECTRAL HRV ANALYSIS METHODS

Most commonly, power spectral analysis of HRV is analyzed through fast Fourier transform and autoregressive models, by commercial devices or non-commercial software (8). In most cases, both methods obtain comparable results, but we need to notice their differences.

The algorithm of fast Fourier transform is relatively simple and has low computational cost. However, fast Fourier transform based spectral analysis is subjected to the problem of non-equal distance of RR intervals and a requirement of stationary data segments. In addition, the length of data segments influences the basic oscillation and the frequency resolution of fast Fourier transform analysis (2, 9). Therefore, fast Fourier transform based HRV analysis needs artificial interpolation to satisfy the demand on equal distance, but the interpolation would introduce biases. Typically, it works on a stable ECG segment of at least 5 min, this restriction on length sometimes limits its application (such as in dynamic processes) (2, 9).

The autoregressive method is also a popular tool for spectral analysis of HRV, it does not need interpolation, and the length of data required for analysis is shorter than fast Fourier transform. However, one of the disadvantages of the autoregressive method is its complexity, the choice of models and model order varies across different studies and this parameter substantially affects the results (2). Furthermore, several studies showed that the autoregressive method was not able to detect frequency domain parameters and generated null values in a substantial proportion of patients with diabetes or hypertension (10, 11).

There have been several autoregressive models in ECG signal processing. Burg's algorithm, the least square approach and Yule-Walker method are commonly used (12–14). Each method has its advantages and disadvantages. Both Yule-Walker method and Burg algorithm suffer from the problems of spectral line splitting and the bias in the positioning of spectral peaks (12, 14). However, Burg's algorithm has a better resolution and a higher spectral fidelity for short data records than Yule-Walker method, and Burg's algorithm has no implied windowing which distorts spectrum in Yule-Walker method (14, 15). The least square approach has improvements in the issues of spectral line splitting and the bias in the positioning of spectral peaks, but is less stable than Burg's algorithm (12, 13, 15). Generally, they obtain similar results in most situations (13, 16), but Burg's algorithm is a more stable approach and is preferable among the three methods (13, 15).

If the model order is too high, the model is more susceptible to the interference of noise and might slit peaks. If the model order is too low, the spectral peaks are smoothed considerably, their positions might be altered and some peaks might be missed; moreover, the analysis may even obtain null results (4, 17). There are many methods for the guidance of choosing the most appropriate order, such as Akaike information criteria, Akaike's final prediction error, final prediction error, Rissanen's minimum description length, etc. Akaike information criteria is the most widely used method (2, 4, 17).

Trigonometric regressive spectral (TRS) analysis is a newly developed and advanced analytical and statistical technique, it describes the rhythms of R–R intervals with trigonometric regression functions (18). In contrast to the fast Fourier transform, TRS does not need interpolation on non-equidistant heart beats, and provides a pure physiological spectrum using trigonometric regression. TRS searches one frequency at a time; therefore, the length of the data segment can be as short as 20–30 s (9, 18, 19). This feature makes TRS suitable for describing dynamic processes. TRS works in a shifting approach. Each analysis (TRS) spectrum is only performed within a local data segment (20–30 s); analyses of local data segments are repeated

in successive segments shifted by one, two, or more beats within the whole global data segment (multiple TRS analysis, so called MTRS) (18, 19). Since the traditionally used global data segment is 1–2 min, we call this approach short-term MTRS. We have successively applied short-term MTRS analysis in healthy subjects and patients with various disorders (including diabetes and hypertension); it has been used for describing the resting cardiovascular autonomic function of specific populations and depicting the dynamic response of HRV to various stimulations, including Valsalva maneuver, metronomic deep breathing, head-up tilt test, cold pressor test, mental stress, and short-acting vasoactive medications (20–27). Overall, TRS is an outstanding technique for spectral analyses in autonomic function research in comparison to fast Fourier transform and the autoregressive method. We summarize the character of the three solutions for spectral analysis of HRV in **Table 1**.

In addition, Lomb periodogram is another option for spectral analysis of HRV without the need of interpolation on RRIs. Lomb periodogram determines the power spectrum at any given frequency by fitting the sine wave using a least squares method. It outperformed fast Fourier transform and autoregressive method in several studies (32, 33). However, the non-random components of HRV and the 1/f noise in the spectra negatively influence the performance of Lomb periodogram (34). A recent study indicated that a smoothing procedure for Lomb periodogram may improve its capability in spectral analysis (35). Overall, Lomb periodogram is an relatively infrequently used method for spectral analysis, further methodological improvements and applications in clinical research are warranted (35, 36).

Furthermore, it is noteworthy that commonly used spectral analyses of HRV employ second order statistics, which is suitable for Gaussian distribution and linear systems (37, 38). However, the human cardiovascular system is not a linear system, and may not accord with Gaussian distribution. Theoretically, bispectral analysis has been developed to solve this problem (37, 38). Although studies using bispectral analysis for HRV assessment is still rare, it is a promising tool in HRV analysis. Since this article focuses on spectral analysis, further discussion of this method is out of the scope of this article.

TABLE 1 | Summary of main spectral analysis methods.

Methods	First publication on spectral analysis of HRV in human	Requirements for applications	Advantages	Disadvantages	Commonly used length in short-term spectral analysis
FFT	• Sayers (28) • Hyndman et al. (29)	• Stationary ECG data • Sufficient length of data, • Equidistance between RRIs	• Simplicity of the algorithm, • High processing speed, • Good reproducibility • Widely available in commercial devices and research toolboxes	• Require interpolation, • Not appropriate for non-stationary data, • Need to work on an adequate length of data (usually 5 min), • Spectral components influenced by data length,	2–5 min; 5 min is preferred
Autoregressive models	• Pagani et al. (30, 31)	• Stationary ECG data	• Smoother spectral components, • Easy post-processing of the spectrum, • Lower requirements on the length of data than FFT, • Also widely available in commercial devices and research toolboxes	• Not appropriate for non-stationary data, • Complexity in choosing the suitable models, thus lack comparability between studies.	200–512 RRIs
MTRS	• Rudiger et al. (18)	• Only general requirements for HRV analysis such as free of ectopic beats and arrhythmia	• Can work on relatively short data segments (20–30 s), • Can be applied in non-stationary conditions, • Do not need interpolation and capture real physiological oscillations	• Relatively less widely available	1–5 min; 1.5–2 min is most frequently chosen

ECG, electrocardiography; FFT, fast Fourier transform; HRV, heart rate variability; MTRS, multiple trigonometric regressive spectral analysis; RRI, RR interval.

THE ISSUE OF TIME WINDOW IN SPECTRAL HRV ANALYSIS

The time window of ECG analyzed is a key issue in the spectral analysis of HRV (39, 40). Most of the studies using spectral analysis of HRV via fast Fourier transform or autoregressive method work on ECG segments of 2–5 min, and previous applications of MTRS are on ECG segments of 1–2 min. Recently, various techniques for time-frequency analysis in non-stationary conditions have been developed, which mainly include short time Fourier transform, time variant autoregressive modeling, wavelet transform, and Wigner-Ville transform (41, 42). These techniques can obtain instant power spectral profiles of HRV during highly dynamic processes. Spectral analysis of HRV using longer time windows (usually from 1–24 h) has been reported, mainly using fast Fourier transform or autoregressive method. Long-term spectral analysis of HRV has been used in determining the autonomic function, assessing its changes, and predicting prognosis. Shorter and longer time windows have their own advantages and disadvantages according to the particular application scenarios. In the following sections, we will discuss the characteristics of short-term and long-term HRV analysis. In addition, we will also introduce our newly developed long-term MTRS analysis.

LONG-TERM SPECTRAL HRV ANALYSIS BASED ON SHORT-TERM SPECTRAL HRV ANALYSIS

Fast Fourier transform and autoregressive based HRV analyses conventionally work on ECG recordings of 2–5 min (2, 3, 8). As mentioned earlier, short-term MTRS analysis mainly works on 1–2 min (2, 3). The short-term HRV analysis is often the basis for longer time windows. The most common strategy for long-term HRV analysis is to divide the target time window (e.g., 1 or 24 h) into consecutive 1–5 min epochs, and averaging the individual values of HRV parameters of all these epochs to obtain the mean value of the target time window (2, 39, 40). MTRS has been traditionally used in short-term HRV analysis, but recently we have developed a newer version of MTRS, which also used the averaging strategy. For a target ECG segment of 30 min to 24 h, this target ECG segment is firstly divided into consecutive 1–2 min global data segments. The spectral profiles of these consecutive 1–2 min global data segments are obtained through the shifting local data segments of 20–30 s as described before. Then the results of all the 1–2 min global data segments are averaged to obtain the mean values of the spectral parameters of the whole target time window. **Figure 1** illustrates the strategy by showing how a given 30 min ECG recording is divided into 15 2-min global data segments. Each 2-min global segment was analyzed as our traditional short-term MTRS analysis, and then the results of all these 2-min global data segments are averaged to obtain the mean value of the whole targeted 30-min segment. This strategy can be applied even in longer time windows including 24 h. **Figure 2A** shows the LF and HF values of the 30 2-min global segments within an hour in a patient with multiple sclerosis, these 2-min values will be averaged to obtain the targeted 1-h results. **Figure 2B** shows an application of this long-term MTRS analysis in a patient with multiple sclerosis, who had taken 0.5 mg fingolimod. This figure shows the mean 1 h LF and HF powers of the 6 h after fingolimod intake. This dividing and averaging process is a common strategy for long-term spectral analysis of HRV, and the underlying algorithm can be fast Fourier transform, autoregressive method, or MTRS, etc. (43, 44).

Another strategy is to view the target time window as a whole data segment, and perform spectral analysis on this data segment en bloc (e.g., 1 or 24 h). For LF and HF, these two strategies obtained similar results over the 24 h time window (43).

THE ADVANTAGES AND DISADVANTAGES OF SHORT AND LONG TIME WINDOWS

The cardiovascular system is a spatially and temporally complex system. It is built from a dynamic web of interconnected feedback loops. Heart rate, blood pressure, and HRV parameters keep fluctuating constantly, both in the resting state and under various internal and external stimulations (9, 45, 46). We can estimate HRV parameters in the resting state, during standing and daily activities, in different stages of sleep, and their responses to medications. Choosing the most appropriate time window for HRV analysis can optimize its application. **Table 2** summarizes the advantages and disadvantages of short- and long-term spectral analysis of HRV.

The advantages of short-term HRV analysis are as follows.

1. It is easy to perform; only several minutes' recording is enough.
2. It is convenient to control the confounding factors such as body position, physical activity, respiration, environmental factors like temperature.
3. It needs least time for data processing compared to long-term analysis.
4. Can describe dynamic HRV change within a short period.

Its main disadvantage is that the short-term HRV analysis might not be stable owing to the constant fluctuation of HRV parameters. Furthermore, short-term spectral analysis cannot estimate long RRI fluctuations, such as the ultra-low frequency component (ULF) (2, 39).

Time-frequency analysis can be viewed as a special case of short-term spectral analysis; it is able to closely track the instant changes of the spectral profiles of HRV. This is a fast developing area attracting active research. Short time Fourier transform and time variant autoregressive modeling are based on fast Fourier transform and autoregressive modeling; their time resolutions are not satisfactory (42). Wigner-Ville transform based time frequency-analysis has better temporal and frequency resolutions by independent controls of time and frequency filtering (47). However, its main limitation is the interference of cross-terms, which influences the accuracy. Various techniques seek to address this issue. Among them,

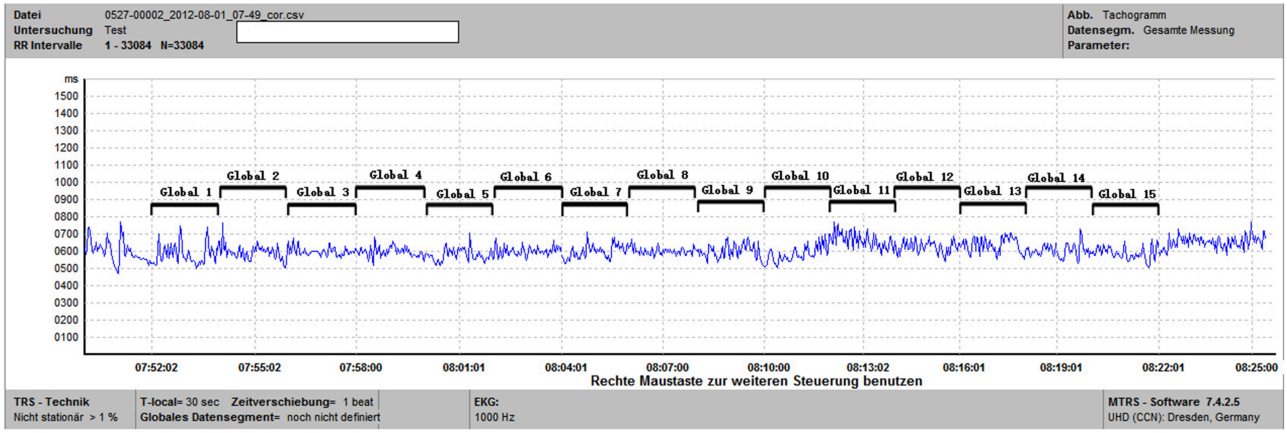

FIGURE 1 | This is a tachogram from the MTRS software. For the specified time window of 30 min (from 07:52 to 08:22), we calculated the frequency domain parameters of 15 2-min global data segments (Global 1 to Global 15) and then computed the average of these 15 segments.

smoothing in the time and frequency directions significantly suppresses the cross-terms, and smoothed pseudo Wigner–Ville distribution (SPWVD) have excellent performance in comparison with short time Fourier transform and time variant autoregressive modeling methods in comparative studies (42, 48). Wavelet transform also provides a good time resolution and the time-frequency resolution can be optimized by setting an appropriate wavelet filter. In contrast to short time Fourier transform, which has fixed windows for time and frequency, time resolution of wavelet transform depends on the frequency of interest and can obtain more precise spectral components (49). The limitations of wavelet analysis are: (1) the obtained frequency bands are not exactly the same as the recommendations of the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology. (2) The performance is unsatisfactory when more than one spectral component is present (49, 50). In several comparative studies, wavelet transform outperformed short time Fourier transform and time variant autoregressive modeling (42, 51, 52). Although mainly used in time-frequency analysis, wavelet transform has also been used in short-term spectral analysis, and was consistent with the output of fast Fourier transform (53). Other relatively less used time-frequency analyses include Gabor transform, modified B distribution, etc. Gabor transform can implement a signal adaptive analysis which eliminate the influence of noise and improves the accuracy (54, 55). Modified B distribution can achieve high time-frequency resolutions and suppress cross-terms (48). Time-frequency analysis is a fast developing field; further researches are needed to establish well-accepted techniques.

Long-term HRV analysis can collect ECG information from 1 h to an entire day. It is more stable than short-term analysis. Directly analyzing the entire long-term target time window can estimate longer fluctuations including the ULF power (2, 39). However, long-term recordings are more expensive and time-consuming; long-term recordings obtain more noise and dealing with the noise is challenging. In addition, environmental factors (temperature, humidity, etc.) and daily activities during recording vary within and between subjects.

To some extent, the comparison between short-term and 24-h long-term HRV analysis is similar as the comparison between office blood pressure and 24 h ambulatory blood pressure monitoring. Because the blood pressure also fluctuates constantly, office blood pressure has substantial randomness, while ambulatory blood pressure monitoring incorporates recordings during resting, activity, and sleeping of a whole day and is more stable than office blood pressure (56, 57).

THE APPLICATION OF SPECTRAL HRV ANALYSIS IN DIFFERENT OCCASIONS

It is noteworthy that age and gender can influence frequency domain HRV parameters. Generally, females have higher total power and HF power, and lower LF power and LF/HF ratio than males (40, 58–60). Some studies reported that this gender difference gradually disappear after the age of 40–50 (58, 59). With increasing age, total power and absolute values of LF and HF power decrease, while this trend is not significant for normalized values of LF and HF (22, 58–61). LF/HF ratio gradually increases until about 50 years, then decrease afterwards (60, 61). We should keep the effect of age and sex in mind in the application of spectral analysis of HRV.

Evaluate Autonomic Function in a Specific Population

Short-term HRV analysis is frequently used in assessing the cardiovascular autonomic function of a specific population. Many diseases lead to a decreased HF power and/or an increased LF power, including patients with myocardial infarction (62), hypertension (63), cardiac syndrome X (64, 65), neurodegenerative diseases including Parkinson's disease,

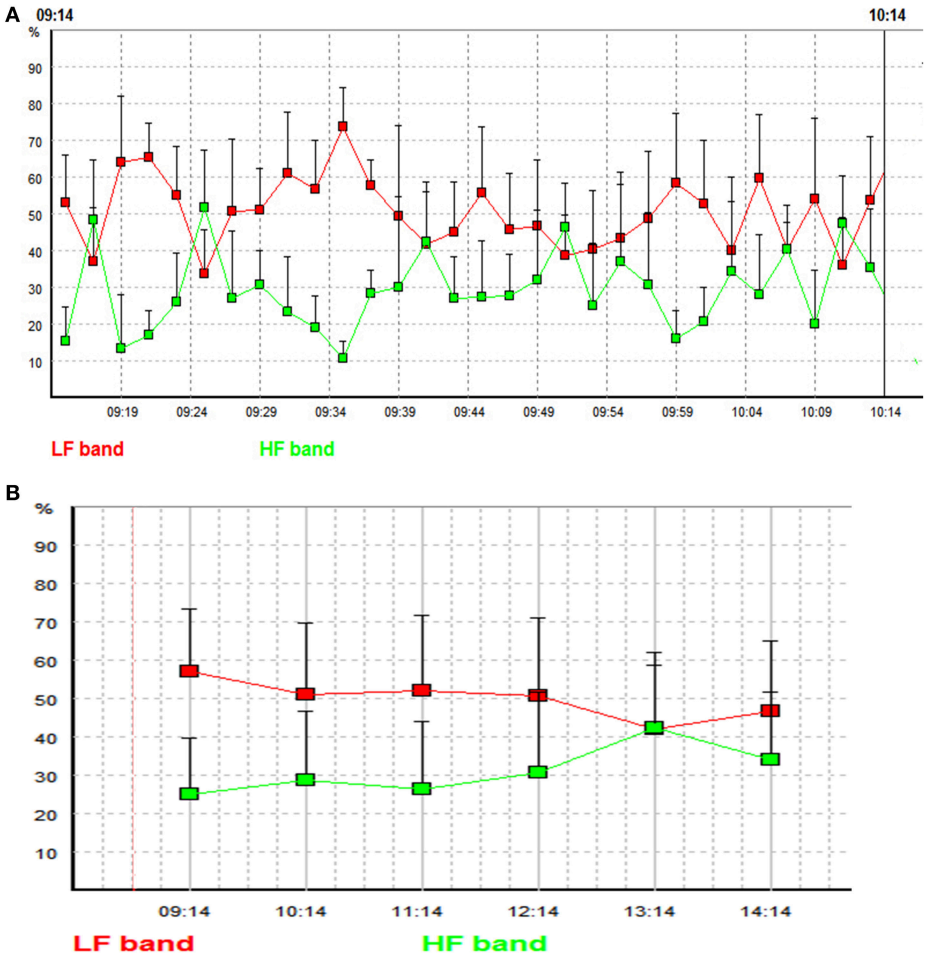

FIGURE 2 | (A) LF and HF powers of the 30 2-min global segments within an hour (from 9:14 to 10:14 in the morning) in a patient with multiple sclerosis. Each square indicates the LF or the HF power of an individual 2-min global segment. Red line represents low frequency band, and green line represents high frequency band. The x-axis represents time and the y axis represents the relative LF and HF powers (the proportions (in percent) of LF and HF powers in the total power). **(B)** Mean LF and HF powers of the 6 h after fingolimod intake in a patient with multiple sclerosis. Each square indicates the mean value of LF or HF power of a targeted 1 h time window. Red line represents low frequency band, and green line represents high frequency band. The x-axis represents time and the y axis represents the relative LF and HF powers [the proportions (in percent) of LF and HF powers in the total power].

multiple system atrophy, and progressive supranuclear palsy (26, 66), affective disorders (67), and septic shock (68).

Long-term HRV analysis for this purpose is often performed on holter recordings, the researchers can select the daytime/awakening and the nighttime/sleep periods for analysis, or use the entire 24 h recording. In patients with panic disorder, the decrease of total power and ULF power is more pronounced during sleep than the whole day averaged values (69). In addition, HRV analysis of the recordings during sleep has shown that the patients with panic disorder had higher LF power than the controls, but the LF power during daytime or of the whole 20 h were similar in panic disorder patients and the controls (69). Haapaniemi et al. found that all the spectral components of HRV were lower in the patients with Parkinson's disease (70). Endurance-trained men have an increased HF power compared to untrained men over the 24 h (71).

Although in general, HRV analyses based on different lengths of time windows are closely correlated (72, 73), the results from different time windows are sometimes inconsistent. In the study by Yeragani et al. HRV analysis of the sleeping hours showed a higher relative LF power in the patients with panic disorder, which was not found for the awakening hours or the entire 24 h recordings (69). A study using short-term HRV analysis revealed an increased LF power in panic disorder during awakening time (67).

Considering the constant fluctuations of cardiovascular autonomic function, long-term HRV parameters may be more stable for describing the autonomic function in a specific population. If feasible, long-term ECG recordings of several hours to 24 h should be preferred over short-term ECG recordings for the assessment of autonomic state of a specific population.

TABLE 2 | Advantages and disadvantages of short- and long-term spectral analysis of HRV.

	Advantages	Disadvantages
Short-term	• Easy to perform • Convenient to control the confounding factors • Needs less time for data processing • Can describe dynamic HRV change within a short period	• Not stable owing to the constant fluctuation of heart beat intervals • Cannot analyze ULF power
Long-term	• A stable tool for HRV analysis • Can analyze ULF power	• More expensive and time consuming • Include more noise • Influenced by activities and environmental factors

HRV, heart rate variability; ULF, ultra-low frequency component.

Description of Changes of Cardiac Autonomic Function

Both short and long time windows have been applied in evaluating changes across hours or months. In addition, short-term HRV analysis is able to track dynamic changes within a short time period such as several minutes.

Short-term HRV analysis has been widely used in tracking changes. It can measure real-time cardiac autonomic alterations during interventions. Thayer et al. computed 3.5–5 min ECG recordings during baseline, relaxation, and worry states. They found that worry was associated with decreased HF power (74). With short-term MTRS, Friedrich et al. assessed HRV changes from the resting state to deep breathing, orthostasis, and Valsalva maneuver in healthy controls, patients with Parkinson's disease, multiple system atrophy, or progressive supranuclear palsy, and found the different responses in the autonomic examinations of these distinct diseases (21). Short-term HRV analysis has also been used to measure changes over hours, such as circadian rhythm, changes during an acute disease course, and response after a medication. For this application, data segments of several minutes were selected from each hour, and then the HRV variables of the selected data segments were calculated as the representative results of the corresponding hours. This approach has been used to measure the circadian rhythm of HRV parameters in healthy subjects and shift workers, as well as the abnormalities of the HRV circadian rhythm in patients with hypertension (75–77). In addition to circadian changes, short-term HRV analysis has been used to delineate the cardiac autonomic function changes within several hours after taking a medication or other interventions, including levodopa, fingolimod, alcohol, and coronary angioplasty (78–81). Comparing resting short-term HRV parameters at baseline with those parameters several weeks, months, or even years later, it could reflect the changes of cardiac autonomic function across a long period. We have conducted a study which followed up patients with Wilson's disease for 3 years. We applied short-term MTRS analysis on ECG and blood pressure recordings during rest, deep breathing, orthostasis, and handgrip test. The short-term MTRS analysis on various examinations showed that cardiovascular autonomic function in Wilson's disease was generally stable across 3 years, though there were mild changes in a few parameters (79).

The remarkable ability to track instant changes of HRV makes time-frequency analysis a rapidly expanding field of research. Especially SPWVD and wavelet transform have an excellent temporal resolution, and have been used in delineating transient changes of HRV. In a study by Jasson et al., SPWVD continuously followed the changes of LF and HF during an orthostatic tilt test (52). In a recent study, SPWVD can be used to detect drowsiness by analyzing the HRV of three driving databases (82). Toledo et al. used wavelet transform to detect the instant change of autonomic tone during thrombolysis in myocardial infarction patients, at least one of the HRV parameters presented remarkable changes during the reperfusion process, and the infarct locations were related to the pattern of HRV parameter changes (83).

Long-term HRV analysis is commonly used in the studies of the circadian rhythm of cardiac autonomic function. In this type of studies, hourly HRV parameters (either averaging consecutive short segments within each hour or directly analyzing the whole hour en bloc) were usually calculated on selected hours of a 24 h holter recording. In addition, some studies computed the averaged daytime and nighttime averaged HRV parameters. In healthy subjects, LF power and LF/HF ratio have higher values during the daytime and lower values during the nighttime, while HF power has lower values during the daytime and higher values during the nighttime (84, 85). On the contrary, this circadian rhythm disappears in patients with acute myocardial infarction or ischemic stroke (84, 86). In addition to circadian rhythm, long-term HRV analysis can be used to measure the change of cardiac autonomic function caused by various interventions. Recently, we have applied our long-term MTRS HRV analysis in the investigation of the effects of fingolimod first dose on cardiovascular autonomic function. We calculated hourly HRV parameters using the long-term MTRS tool which employed an averaging approach as mentioned before. That study has revealed that the LF power decreased and HF power increased in the several hours after initial fingolimod administration, and these changes were consistent with heart rate alteration (40). Long-term HRV analysis integrating heart rate information of a whole day is a stable tool for the evaluation of the changes of cardiac autonomic function across long time spans. Initiating fingolimod treatment induces a transient alteration in cardiac autonomic function; its chronic effect has been disclosed by long-term HRV analysis. Simula et al. followed up the multiple sclerosis patients treated with fingolimod for 3 months. The long-term HRV analysis showed decreased absolute values of LF and HF

powers compared with baseline, while the LF/HF ratio remained unchanged (58).

Generally, for changes across a long time, these HRV analyses based on different time windows yield similar results, such as two studies of HRV changes induced by fingolimod across several months in patients with multiple sclerosis, one of the studies used a 10 min finger arterial blood pressure recording and the other study used 24 h Holter recording (87, 88). However, we need to consider the effects of time window length. Although both short-term and long-term HRV analysis using the TRS algorithm showed that fingolimod increased HF in patients with multiple sclerosis, only long-term MTRS analysis showed that the changes of LF and HF were consistent with other related HRV parameters. This comparison indicates that long-term HRV analysis is more stable and can acquire consistent results among related variables (40, 79). Again, longer time windows obtain more stable results than short time windows. Thus, for tracking changes of cardiovascular autonomic function across minutes, only short-term HRV analysis can be used, while long-term HRV analysis should be preferred for depicting changes across hours to even longer time span if feasible.

Predict the Patients' Outcomes

Initially, only long-term HRV parameters were used for the prediction of prognosis in patients with cardiovascular diseases (89). Then gradually, a variety of time windows have been applied in predicting the outcome in diverse diseases.

Short-term HRV analysis has been used in predicting outcomes both in the short-run and the long-run. Pontet et al. have identified LF calculated from a 10 min ECG as a good predictor of multiple organ dysfunction syndrome in the next few days in septic patients (90). In another study on sepsis patients, normalized HF power and standard deviation of the NN interval (SDNN) were valuable predictors of in-hospital mortality (91). For outcome prediction in the long-run, reduced short-term LF power during controlled respiration is a strong predictor of sudden death in the patients with chronic heart failure (92), and multiple time and frequency domain parameters obtained from a 2-min ECG recordings could predict end-stage renal disease and chronic kidney disease related hospitalization in the participants of the Atherosclerosis Risk in Communities (ARIC) study (93).

Because of its stability, long-term HRV analysis has been widely applied in the prediction of outcomes. Tsuji et al. analyzed the 2 h of ambulatory ECG recordings of the subjects of the Framingham Heart Study. After a 4-year follow-up, SDNN, and all the frequency domain parameters were associated with mortality, especially LF was the strongest predictor in a multivariate model (94). Long-term HRV analysis of 24 h ECG recordings performed in the acute, subacute, and chronic stages of myocardial infarction can predict mortality (44, 95, 96). Twenty-four-hour long-term HRV analysis has also been used to predict prognosis in patients with other cardiovascular diseases such as sudden cardiac death and idiopathic dilated cardiomyopathy (97, 98).

In addition to traditional frequency domain parameters, power law relationship of HRV is a derivative approach of long-term spectral HRV analysis. It describes the distribution of the spectral characteristics of RRI oscillations, and is computed by regressing the log (power) on the log (frequency) of HRV between frequencies 10^{-2} and 10^{-4} (99–101). The slope of the regression line is the most commonly used power law parameter for risk stratification (101, 102). The slope of the power law relation outperformed traditional long-term frequency domain HRV parameters in patients with acute myocardial infarction and elderly people (101, 102). Its performance in other populations warrants further investigation.

Comparing the predicting performance of different time windows is a critical issue, and previous studies have produced inconsistent results. Lü et al. demonstrated that SDNN of a 5-min ECG recording could predict the mortality of patients with myocardial infarction, but was inferior to long-term HRV indices (103). In contrast, Bigger et al. compared the power spectral measures of HRV calculated from short ECG recording segments (2, 5, 10, and 15 min) with those from 24 h long-term recordings, and concluded that both short and long-term HRV analyses were excellent predictors of mortality in patients with myocardial infarction (104). Malik et al. showed that HRV analysis of 24 h predicted prognosis better than HRV analysis based on arbitrary selected 1 h ECG segments in patients with myocardial infarction (105), while Voss et al. found that HRV analysis calculated from stationary daytime and nighttime 30 min ECG recordings provided at least a comparable prognosis prediction as 24 h long-term analysis (106).

Although these results seem incompatible, we need to note their methodological differences. Lü only used time domain parameters and other studies used frequency domain with or without time domain parameters. Voss et al. selected the most stationary daytime and nighttime 30 min ECG recordings, while some other studies chose the segments arbitrarily. We can refer to the researches on the abilities of office blood pressure and ambulatory blood pressure monitoring to predict prognosis. Ambulatory blood pressure monitoring predicts cardiovascular outcomes better than office blood pressure (57, 107). Similarly, long-term HRV analysis should be preferred for prediction of prognosis if applicable.

SUMMARY

In medical research, HRV analysis has been used to describe the autonomic function of specific populations, track the change of autonomic function across various time spans, and predict the patients' outcome. Short-term HRV analysis is easy to perform, with the prominent advantage that it can track dynamic changes of cardiac autonomic function within minutes. Recently developed time-frequency analysis further enhances the ability of HRV analysis to track active changes of cardiovascular autonomic function. The most predominant advantage of long-term HRV analysis is its stability, it is a stable tool for assessing the autonomic function, describe the chronic autonomic function changes over hours or even longer

time spans, and can reliably predict prognosis in patients with cardiovascular diseases.

AUTHOR CONTRIBUTIONS

TZ, KL, and HR were involved in the conception and design of this article. KL performed the literature search and drafted the manuscript. TZ and HR critically revised the manuscript.

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REFERENCES

1. Ziemssen T, Siepmann T. The investigation of the cardiovascular and sudomotor autonomic nervous system - a review. *Front Neurol.* (2019) 10:53. doi: 10.3389/fneur.2019.00053
2. Camm AJ, Malik M, Bigger JT, Breithardt G, Cerutti S, Cohen RJ, et al. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur Heart J.* (1996) 17:354–81. doi: 10.1093/oxfordjournals.eurheartj.a014868
3. Ziemssen T, Gasch J, Ruediger H. Influence of ECG sampling frequency on spectral analysis of RR intervals and baroreflex sensitivity using the EUROBAVAR data set. *J Clin Monit Comput.* (2008) 22:159–68. doi: 10.1007/s10877-008-9117-0
4. Kuusela T. Methodological aspects of heart rate variability analysis. In: Kamath MV, Watanabe M, Upton A, editors. *Heart Rate Variability (HRV) Signal Analysis: Clinical Applications*. Boca Raton, FL: CRC Press (2013). p. 9–42. doi: 10.1201/b12756-4
5. Peltola MA. Role of editing of R-R intervals in the analysis of heart rate variability. *Front Physiol.* (2012) 3:148. doi: 10.3389/fphys.2012.00148
6. Salo MA, Huikuri HV, Seppanen T. Ectopic beats in heart rate variability analysis: effects of editing on time and frequency domain measures. *Ann Noninvasive Electrocardiol.* (2001) 6:5–17. doi: 10.1111/j.1542-474X.2001.tb00080.x
7. Mateo J, Laguna P. Analysis of heart rate variability in the presence of ectopic beats using the heart timing signal. *IEEE Trans Biomed Eng.* (2003) 50:334–43. doi: 10.1109/TBME.2003.808831
8. Singh B, Bharti N. Software tools for heart rate variability analysis. *Int J Recent Sci Res.* (2015) 6:3501–6.
9. Ziemssen T, Reimann M, Gasch J, Rudiger H. Trigonometric regressive spectral analysis: an innovative tool for evaluating the autonomic nervous system. *J Neural Trans.* (2013) 120(Suppl. 1):S27–33. doi: 10.1007/s00702-013-1054-5
10. Chemla D, Young J, Badilini F, Maison-Blanche P, Affres H, Lecarpentier Y, et al. Comparison of fast Fourier transform and autoregressive spectral analysis for the study of heart rate variability in diabetic patients. *Int J Cardiol.* (2005) 104:307–13. doi: 10.1016/j.ijcard.2004.12.018
11. Silva GJ, Ushizima MR, Lessa PS, Cardoso L, Drager LF, Atala MM, et al. Critical analysis of autoregressive and fast Fourier transform markers of cardiovascular variability in rats and humans. *Braz J Med Biol Res.* (2009) 42:386–96. doi: 10.1590/S0100-879X2009000400012
12. Marple L. A new autoregressive spectrum analysis algorithm. *IEEE Transac Acoust Speech Signal Process.* (1980) 28:441–54. doi: 10.1109/TASSP.1980.1163429
13. Vuksanovic B, Alhamdi M. AR-based method for ECG classification and patient recognition. *Int J Biometr Bioinform.* (2013) 7:74.
14. Kay SM, Marple SL. Spectrum analysis—a modern perspective. *Proc IEEE.* (1981) 69:1380–419. doi: 10.1109/PROC.1981.12184
15. De Hoon M, Van der Hagen T, Schoonewelle H, Van Dam H. Why Yule-Walker should not be used for autoregressive modelling. *Ann Nucl Energy.* (1996) 23:1219–28. doi: 10.1016/0306-4549(95)00126-3
16. Stavrinou ML, Sakellaropoulos GC, Trachani E, Sirrou V, Polychronopoulos P, Nikiforidis G, et al. Methodological issues in the spectral analysis of the heart rate variability: application in patients with epilepsy. *Biomed Signal Process Control.* (2014) 13:1–7. doi: 10.1016/j.bspc.2014.03.002
17. Dantas EM, Sant'Anna ML, Andreao RV, Goncalves CP, Morra EA, Baldo MP, et al. Spectral analysis of heart rate variability with the autoregressive method: what model order to choose? *Comput Biol Med.* (2012) 42:164–70. doi: 10.1016/j.compbiomed.2011.11.004
18. Rudiger H, Klinghammer L, Scheuch K. The trigonometric regressive spectral analysis–a method for mapping of beat-to-beat recorded cardiovascular parameters on to frequency domain in comparison with Fourier transformation. *Comput Methods Programs Biomed.* (1999) 58:1–15. doi: 10.1016/S0169-2607(98)00070-4
19. Li K, Rudiger H, Haase R, Ziemssen T. An innovative technique to assess spontaneous baroreflex sensitivity with short data segments: multiple trigonometric regressive spectral analysis. *Front Physiol.* (2018) 9:10. doi: 10.3389/fphys.2018.00010
20. Ruediger H, Seibt R, Scheuch K, Krause M, Alam S. Sympathetic and parasympathetic activation in heart rate variability in male hypertensive patients under mental stress. *J Hum Hypertens.* (2004) 18:307–15. doi: 10.1038/sj.jhh.1001671
21. Friedrich C, Rudiger H, Schmidt C, Herting B, Prieur S, Junghanns S, et al. Baroreflex sensitivity and power spectral analysis during autonomic testing in different extrapyramidal syndromes. *Mov Disord.* (2010) 25:315–24. doi: 10.1002/mds.22844
22. Reimann M, Friedrich C, Gasch J, Reichmann H, Rudiger H, Ziemssen T. Trigonometric regressive spectral analysis reliably maps dynamic changes in baroreflex sensitivity and autonomic tone: the effect of gender and age. *PLoS ONE.* (2010) 5:e12187. doi: 10.1371/journal.pone.0012187
23. Gasch J, Reimann M, Reichmann H, Rudiger H, Ziemssen T. Determination of baroreflex sensitivity during the modified Oxford maneuver by trigonometric regressive spectral analysis. *PLoS ONE.* (2011) 6:e18061. doi: 10.1371/journal.pone.0018061
24. Reimann M, Hamer M, Schlaich M, Malan NT, Rudiger H, Ziemssen T, et al. Autonomic responses to stress in Black versus Caucasian Africans: the SABPA study. *Psychophysiology.* (2012) 49:454–61. doi: 10.1111/j.1469-8986.2011.01328.x
25. Reimann M, Hamer M, Schlaich MP, Malan NT, Ruediger H, Ziemssen T, et al. Greater cardiovascular reactivity to a cold stimulus is due to higher cold pain perception in black Africans: the sympathetic activity and ambulatory blood pressure in africans (SABPA) study. *J Hyperten.* (2012) 30:2416–24. doi: 10.1097/HJH.0b013e328358faf7
26. Friedrich C, Rudiger H, Schmidt C, Herting B, Prieur S, Junghanns S, et al. Baroreflex sensitivity and power spectral analysis in different extrapyramidal syndromes. *J Neural Transm.* (2008) 115:1527–36. doi: 10.1007/s00702-008-0127-3
27. Krause M, Rudiger H, Bald M, Nake A, Paditz E. Autonomic blood pressure control in children and adolescents with type 1 diabetes mellitus. *Pediatr Diabetes.* (2009) 10:255–63. doi: 10.1111/j.1399-5448.2008.00447.x
28. Sayers BM. Analysis of heart rate variability. *Ergonomics.* (1973) 16:17–32. doi: 10.1080/00140137308924479
29. Hyndman BW, Gregory JR. Spectral analysis of sinus arrhythmia during mental loading. *Ergonomics.* (1975) 18:255–70. doi: 10.1080/00140137508931460
30. Pagani M, Lombardi F, Guzzetti S, Sandrone G, Rimoldi O, Malfatto G, et al. Power spectral density of heart rate variability as an index of sympatho-vagal interaction in normal and hypertensive subjects. *J Hyperten Suppl.* (1984) 2:S383–5.
31. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circul Res.* (1986) 59:178–93. doi: 10.1161/01.RES.59.2.178

32. Moody GB, editor. Spectral analysis of heart rate without resampling. In: *Proceedings of Computers in Cardiology Conference*, London: IEEE (1993).
33. Laguna P, Moody GB, Mark RG. Power spectral density of unevenly sampled data by least-square analysis: performance and application to heart rate signals. *IEEE Trans Biomed Eng.* (1998) 45:698–715. doi: 10.1109/10.678605
34. Castiglioni P, Di Rienzo M, editors. On the evaluation of heart rate spectra: the lomb periodogram. In: *Computers in Cardiology,* Indianapolis, IN: IEEE (1996).
35. Estévez M, Machado C, Leisman G, Estévez-Hernández T, Arias-Morales A, Machado A, et al. Spectral analysis of heart rate variability. *Int J Disabil Hum Dev.* (2016) 15:5–17. doi: 10.1515/ijdhd-2014-0025
36. Fonseca D, Netto AA, Ferreira R, de Sá AM, editors. Lomb-scargle periodogram applied to heart rate variability study. In: *2013 ISSNIP Biosignals and Biorobotics Conference: Biosignals and Robotics for Better and Safer Living (BRC)*, Rio de Janerio: IEEE (2013).
37. Chua KC, Chandran V, Acharya UR, Lim CM. Cardiac state diagnosis using higher order spectra of heart rate variability. *J Med Eng Tech.* (2008) 32:145–55. doi: 10.1080/03091900601050862
38. Saliu S, Birand A, Kudaiberdieva G, editors. Bispectral analysis of heart rate variability signal. In: *2002 11th European Signal Processing Conference*, Toulouse: IEEE (2002).
39. Kleiger RE, Stein PK, Bigger JT Jr. Heart rate variability: measurement and clinical utility. *Ann Noninvas Electrocardiol.* (2005) 10:88–101. doi: 10.1111/j.1542-474X.2005.10101.x
40. Li K, Konofalska U, Akgun K, Reimann M, Rudiger H, Haase R, et al. Modulation of cardiac autonomic function by fingolimod initiation and predictors for fingolimod induced bradycardia in patients with multiple sclerosis. *Front Neurosci.* (2017) 11:540. doi: 10.3389/fnins.2017.00540
41. Pichot V, Gaspoz JM, Molliex S, Antoniadis A, Busso T, Roche F, et al. Wavelet transform to quantify heart rate variability and to assess its instantaneous changes. *J Appl Physiol.* (1999) 86:1081–91. doi: 10.1152/jappl.1999.86.3.1081
42. Pola S, Macerata A, Emdin M, Marchesi C. Estimation of the power spectral density in nonstationary cardiovascular time series: assessing the role of the time-frequency representations (TFR). *IEEE Trans Biomed Eng.* (1996) 43:46–59. doi: 10.1109/10.477700
43. Rottman JN, Steinman RC, Albrecht P, Bigger JT Jr., Rolnitzky LM, Fleiss JL. Efficient estimation of the heart period power spectrum suitable for physiologic or pharmacologic studies. *Am J Cardiol.* (1990) 66:1522–4. doi: 10.1016/0002-9149(90)90551-B
44. Carpeggiani C, L'Abbate A, Landi P, Michelassi C, Raciti M, Macerata A, et al. Early assessment of heart rate variability is predictive of in-hospital death and major complications after acute myocardial infarction. *Int J Cardiol.* (2004) 96:361–8. doi: 10.1016/j.ijcard.2003.07.023
45. Dietrich A, Rosmalen JG, Althaus M, van Roon AM, Mulder LJ, Minderaa RB, et al. Reproducibility of heart rate variability and baroreflex sensitivity measurements in children. *Biol Psychol.* (2010) 85:71–8. doi: 10.1016/j.biopsycho.2010.05.005
46. Parati G. Blood pressure variability: its measurement and significance in hypertension. *J Hypertens Suppl.* (2005) 23:S19–25. doi: 10.1097/01.hjh.0000165624.79933.d3
47. Novak P, Novak V. Time/frequency mapping of the heart rate, blood pressure and respiratory signals. *Med Biol Eng Comput.* (1993) 31:103–10. doi: 10.1007/BF02446667
48. Aimie-Salleh N, Malarvili M, Phillip AC. Quantitative comparison of time frequency distribution for heart rate variability using performance measure. *J Wireless Netw Commun.* (2015) 5:1–5. doi: 10.5923/c.jwnc.201501.01
49. Mainardi LT. On the quantification of heart rate variability spectral parameters using time-frequency and time-varying methods. *Philos Transac Seri A.* (2009) 367:255–75. doi: 10.1098/rsta.2008.0188
50. Mainardi LT, Bianchi AM, Cerutti S. Time-frequency and time-varying analysis for assessing the dynamic responses of cardiovascular control. *Crit Rev Biomed Eng.* (2002) 30:175–217. doi: 10.1615/CritRevBiomedEng.v30.i123.80
51. Carvalho J, Rocha A, Junqueira L, Neto JS, Santos I, Nascimento F, editors. A tool for time-frequency analysis of heart rate variability. In: *Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, Cancun. (2003). p. 2574–77.
52. Carvalho J, Rocha A, Junqueira L, Neto JS, Santos I, Nascimento F. A tool for time-frequency analysis of heart rate variability. In Conference proceedings. *Annu Int Conf IEEE Eng Med Biol Soc.* (2003). 2574–77.
53. Verlinde D, Beckers F, Ramaekers D, Aubert AE. Wavelet decomposition analysis of heart rate variability in aerobic athletes. *Auton Neurosci.* (2001) 90:138–41. doi: 10.1016/S1566-0702(01)00284-3
54. Yeh HM, Chang YC, Lin C, Yeh CH, Lee CN, Shyu MK, et al. A new method to derive fetal heart rate from maternal abdominal electrocardiogram: monitoring fetal heart rate during cesarean section. *PLoS ONE.* (2015) 10:e0117509. doi: 10.1371/journal.pone.0117509
55. Schiecke K, Wacker M, Benninger F, Feucht M, Leistritz L, Witte H. Advantages of signal-adaptive approaches for the nonlinear, time-variant analysis of heart rate variability of children with temporal lobe epilepsy. In: *Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, Chicago, IL. (2014). p. 6377–80.
56. O'Brien E, Parati G, Stergiou G, Asmar R, Beilin L, Bilo G, et al. European society of hypertension position paper on ambulatory blood pressure monitoring. *J Hyperten.* (2013) 31:1731–68. doi: 10.1097/HJH.0b013e328363e964
57. Whelton PK, Carey RM, Aronow WS, Casey DE Jr., Collins KJ, Dennison Himmelfarb C, et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines. *Hypertension.* (2017) 71:1269–324. doi: 10.22141/2307-1257.7.1.2018.122220
58. Voss A, Schroeder R, Heitmann A, Peters A, Perz S. Short-term heart rate variability–influence of gender and age in healthy subjects. *PLoS ONE.* (2015) 10:e0118308. doi: 10.1371/journal.pone.0118308
59. Ramaekers D, Ector H, Aubert AE, Rubens A, Van de Werf F. Heart rate variability and heart rate in healthy volunteers. Is the female autonomic nervous system cardioprotective? *Eur Heart J.* (1998) 19:1334–41. doi: 10.1053/euhj.1998.1084
60. Antelmi I, de Paula RS, Shinzato AR, Peres CA, Mansur AJ, Grupi CJ. Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. *Am J Cardiol.* (2004) 93:381–5. doi: 10.1016/j.amjcard.2003.09.065
61. Zhang J. Effect of age and sex on heart rate variability in healthy subjects. *J Manipulat Physiol Ther.* (2007) 30:374–9. doi: 10.1016/j.jmpt.2007.04.001
62. Lombardi F, Sandrone G, Spinnler MT, Torzillo D, Lavezzaro GC, Brusca A, et al. Heart rate variability in the early hours of an acute myocardial infarction. *Am J Cardiol.* (1996) 77:1037–44. doi: 10.1016/S0002-9149(96)00127-0
63. Piccirillo G MM, Fimognari FL, Marigliano V. Heart rate variability in hypertensive subjects. *Int J Cardiol.* (1996) 53:291–8. doi: 10.1016/0167-5273(95)02538-3
64. Adamopoulos S, Rosano GM, Ponikowski P, Cerquetani E, Piepoli M, Panagiota F, et al. Impaired baroreflex sensitivity and sympathovagal balance in syndrome X. *Am J Cardiol.* (1998) 82:862–8. doi: 10.1016/S0002-9149(98)00493-7
65. Gulli G, Cemin R, Pancera P, Menegatti G, Vassanelli C, Cevese A. Evidence of parasympathetic impairment in some patients with cardiac syndrome X. *Cardiovasc Res.* (2001) 52:208–16. doi: 10.1016/S0008-6363(01)00369-8
66. Maetzler W, Karam M, Berger MF, Heger T, Maetzler C, Ruediger H, et al. Time- and frequency-domain parameters of heart rate variability and sympathetic skin response in Parkinson's disease. *J Neural Transm.* (2015) 122:419–25. doi: 10.1007/s00702-014-1276-1
67. Rechlin T, Weis M, Spitzer A, Kaschka WP. Are affective disorders associated with alterations of heart rate variability? *J Affect Disord.* (1994) 32:271–5. doi: 10.1016/0165-0327(94)90091-4

68. Annane D, Trabold F, Sharshar T, Jarrin I, Blanc AS, Raphael JC, et al. Inappropriate sympathetic activation at onset of septic shock: a spectral analysis approach. *Am J Respir Crit Care Med.* (1999) 160:458–65. doi: 10.1164/ajrccm.160.2.9810073
69. Yeragani VK, Sobolewski E, Igel G, Johnson C, Jampala VC, Kay J, et al. Decreased heart-period variability in patients with panic disorder: a study of Holter ECG records. *Psychiatry Res.* (1998) 78:89–99. doi: 10.1016/S0165-1781(97)00136-4
70. Haapaniemi TH, Pursiainen V, Korpelainen JT, Huikuri HV, Sotaniemi KA, Myllyla VV. Ambulatory ECG and analysis of heart rate variability in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* (2001) 70:305–10. doi: 10.1136/jnnp.70.3.305
71. Goldsmith RL, Bigger JT Jr., Steinman RC, Fleiss JL. Comparison of 24-hour parasympathetic activity in endurance-trained and untrained young men. *J Am College Cardiol.* (1992) 20:552–8. doi: 10.1016/0735-1097(92)90007-A
72. Fei L, Statters DJ, Anderson MH, Malik M, Camm AJ. Relationship between short- and long-term measurements of heart rate variability in patients at risk of sudden cardiac death. *Pacing Clin Electrophysiol.* (1994) 17(11 Pt 2):2194–200. doi: 10.1111/j.1540-8159.1994.tb03825.x
73. Costa O, Lago P, Rocha AP, Carvalho MJ, Freitas A, Freitas J, et al. Heart rate variability in 24-hour Holter recordings. Comparative study between short- and long-term time- and frequency-domain analyses. *J Electrocardiol.* (1994) 27:251–4. doi: 10.1016/S0022-0736(94)80009-X
74. Thayer JF, Friedman BH, Borkovec TD. Autonomic characteristics of generalized anxiety disorder and worry. *Biol Psychiatry.* (1996) 39:255–66. doi: 10.1016/0006-3223(95)00136-0
75. Nakagawa M, Iwao T, Ishida S, Yonemochi H, Fujino T, Saikawa T, et al. Circadian rhythm of the signal averaged electrocardiogram and its relation to heart rate variability in healthy subjects. *Heart.* (1998) 79:493–6. doi: 10.1136/hrt.79.5.493
76. Freitas J, Lago P, Puig J, Carvalho MJ, Costa O, de Freitas AF. Circadian heart rate variability rhythm in shift workers. *J Electrocardiol.* (1997) 30:39–44. doi: 10.1016/S0022-0736(97)80033-7
77. Chakko S, Mulingtapang RF, Huikuri HV, Kessler KM, Materson BJ, Myerburg RJ. Alterations in heart rate variability and its circadian rhythm in hypertensive patients with left ventricular hypertrophy free of coronary artery disease. *Am Heart J.* (1993) 126:1364–72. doi: 10.1016/0002-8703(93)90535-H
78. Sriranjini SJ, Ganesan M, Datta K, Pal PK, Sathyaprabha TN. Effect of a single dose of standard levodopa on cardiac autonomic function in Parkinson's disease. *Neurol India.* (2011) 59:659–63. doi: 10.4103/0028-3886.86536
79. Hilz MJ, Wang R, de Rojas Leal C, Liu M, Canavese F, Roy S, et al. Fingolimod initiation in multiple sclerosis patients is associated with potential beneficial cardiovascular autonomic effects. *Ther Adv Neurol Disord.* (2017) 10:191–209. doi: 10.1177/1756285616682936
80. Koskinen P, Virolainen J, Kupari M. Acute alcohol intake decreases short-term heart rate variability in healthy subjects. *Clin Sci.* (1994) 87:225–30. doi: 10.1042/cs0870225
81. Bonnemeier H, Hartmann F, Wiegand UK, Irmer C, Kurz T, Tolg R, et al. Heart rate variability in patients with acute myocardial infarction undergoing primary coronary angioplasty. *Am J Cardiol.* (2000) 85:815–20. doi: 10.1016/S0002-9149(99)00873-5
82. Vicente J, Laguna P, Bartra A, Bailon R. Drowsiness detection using heart rate variability. *Med Biol Eng Comput.* (2016) 54:927–37. doi: 10.1007/s11517-015-1448-7
83. Toledo E, Gurevitz O, Hod H, Eldar M, Akselrod S. Wavelet analysis of instantaneous heart rate: a study of autonomic control during thrombolysis. *Am J Physiol Regul Integr Comp Physiol.* (2003) 284:R1079–91. doi: 10.1152/ajpregu.00287.2002
84. Huikuri HV, Niemela MJ, Ojala S, Rantala A, Ikaheimo MJ, Airaksinen KE. Circadian rhythms of frequency domain measures of heart rate variability in healthy subjects and patients with coronary artery disease. Effects of arousal and upright posture. *Circulation.* (1994) 90:121–6. doi: 10.1161/01.CIR.90.1.121
85. Bilan A, Witczak A, Palusinski R, Myslinski W, Hanzlik J. Circadian rhythm of spectral indices of heart rate variability in healthy subjects. *J Electrocardiol.* (2005) 38:239–43. doi: 10.1016/j.jelectrocard.2005.01.012
86. Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllyla VV. Circadian rhythm of heart rate variability is reversibly abolished in ischemic stroke. *Stroke.* (1997) 28:2150–4. doi: 10.1161/01.STR.28.11.2150
87. Simula S, Laitinen T, Laitinen TM, Tarkiainen T, Hartikainen P, Hartikainen JE. Effect of fingolimod on cardiac autonomic regulation in patients with multiple sclerosis. *Mult Scler.* (2016) 22:1080–5. doi: 10.1177/1352458515604384
88. Racca V, Rovaris M, Vaini E, Cavarretta R, Ferratini M, Toccafondi A, et al. 6-Month effects of fingolimod on indexes of cardiovascular autonomic control in multiple sclerosis. *J Am College Cardiol.* (2016) 68:2027–9. doi: 10.1016/j.jacc.2016.08.032
89. Kleiger RE, Miller JP, Bigger JT Jr., Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol.* (1987) 59:256–62. doi: 10.1016/0002-9149(87)90795-8
90. Pontet J, Contreras P, Curbelo A, Medina J, Noveri S, Bentancourt S, et al. Heart rate variability as early marker of multiple organ dysfunction syndrome in septic patients. *J Crit Care.* (2003) 18:156–63. doi: 10.1016/j.jcrc.2003.08.005
91. Chen WL, Chen JH, Huang CC, Kuo CD, Huang CI, Lee LS. Heart rate variability measures as predictors of in-hospital mortality in ED patients with sepsis. *Am J Emerg Med.* (2008) 26:395–401. doi: 10.1016/j.ajem.2007.06.016
92. La Rovere MT, Pinna GD, Maestri R, Mortara A, Capomolla S, Febo O, et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation.* (2003) 107:565–70. doi: 10.1161/01.CIR.0000047275.25795.17
93. Brotman DJ, Bash LD, Qayyum R, Crews D, Whitsel EA, Astor BC, et al. Heart rate variability predicts ESRD and CKD-related hospitalization. *J Am Soc Nephrol.* (2010) 21:1560–70. doi: 10.1681/ASN.2009111112
94. Tsuji H, Venditti FJ Jr., Manders ES, Evans JC, Larson MG, Feldman CL, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. *Circulation.* (1994) 90:878–83. doi: 10.1161/01.CIR.90.2.878
95. Bigger JT Jr., Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation.* (1992) 85:164–71. doi: 10.1161/01.CIR.85.1.164
96. Bigger JT Jr, Fleiss JL, Rolnitzky LM, Steinman RC. Frequency domain measures of heart period variability to assess risk late after myocardial infarction. *J Am College Cardiol.* (1993) 21:729–36. doi: 10.1016/0735-1097(93)90106-B
97. Myers GA, Martin GJ, Magid NM, Barnett PS, Schaad JW, Weiss JS, et al. Power spectral analysis of heart rate variability in sudden cardiac death: comparison to other methods. *IEEE Trans Biomed Eng.* (1986) 33:1149–56. doi: 10.1109/TBME.1986.325694
98. Fauchier L, Babuty D, Cosnay P, Fauchier JP. Prognostic value of heart rate variability for sudden death and major arrhythmic events in patients with idiopathic dilated cardiomyopathy. *J Am College Cardiol.* (1999) 33:1203–7. doi: 10.1016/S0735-1097(99)00021-2
99. Kobayashi M, Musha T. 1/f fluctuation of heartbeat period. *IEEE Trans Biomed Eng.* (1982) 29:456–7. doi: 10.1109/TBME.1982.324972
100. Saul JP, Albrecht P, Berger RD, Cohen RJ. Analysis of long term heart rate variability: methods, 1/f scaling and implications. *Comput Cardiol.* (1988) 14:419–22.
101. Bigger JT Jr., Steinman RC, Rolnitzky LM, Fleiss JL, Albrecht P, Cohen RJ. Power law behavior of RR-interval variability in healthy middle-aged persons, patients with recent acute myocardial infarction, and patients with heart transplants. *Circulation.* (1996) 93:2142–51. doi: 10.1161/01.CIR.93.12.2142
102. Huikuri HV, Makikallio TH, Airaksinen KE, Seppanen T, Puukka P, Raiha IJ, et al. Power-law relationship of heart rate variability as a predictor of mortality in the elderly. *Circulation.* (1998) 97:2031–6. doi: 10.1161/01.CIR.97.20.2031

103. Fei L, Copie X, Malik M, Camm AJ. Short- and long-term assessment of heart rate variability for risk stratification after acute myocardial infarction. *Am J Cardiol.* (1996) 77:681–4. doi: 10.1016/S0002-9149(97)89199-0
104. Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. *Circulation.* (1993) 88:927–34. doi: 10.1161/01.CIR.88.3.927
105. Malik M, Camm AJ. Significance of long term components of heart rate variability for the further prognosis after acute myocardial infarction. *Cardiovasc Res.* (1990) 24:793–803. doi: 10.1093/cvr/24.10.793
106. Voss A, Schroeder R, Vallverdu M, Schulz S, Cygankiewicz I, Vazquez R, et al. Short-term vs. long-term heart rate variability in ischemic cardiomyopathy risk stratification. *Front Physiol.* (2013) 4:364. doi: 10.3389/fphys.2013.00364
107. Siu AL. Force USPST. Screening for high blood pressure in adults: U.S. Preventive services task force recommendation statement. *Ann Intern Med.* (2015) 163:778–86. doi: 10.7326/M15-2223

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MINI REVIEW
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Heart Rate Variability and Cognitive Function: A Systematic Review

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Background: Autonomic dysfunctions may precede the development of cognitive impairment, but the connection between these dimensions is unclear. This systematic review aims to analyze the relationship between heart rate variability (HRV) and cognitive functions.

Methods: The review process was conducted according to the PRISMA-Statement. Restrictions were made, selecting the studies in English and published in peer-review journals, including at least one cognitive measure and presenting the measurement of HRV. Studies that included participants with medical conditions, dementia, psychiatric disorders, strokes, and traumatic brain injury were excluded. Twenty studies were selected, with a total of 19,431 participants. The results were divided into different cognitive domains determined *a priori*: global cognitive functioning, attention, processing speed, executive functions, memory, language and visuospatial skills.

Results: Both increased sympathetic activity and decreased parasympathetic activity seem to be associated with a worse performance in the cognitive domains considered, in the absence of dementia and severe cardiovascular diseases or other medical and psychiatric diseases.

Conclusion: The results highlight the influence of the autonomic nervous system (ANS) in cognitive functioning. However, the marked interest facing toward a specific domain, i.e., the executive functions, and the relatively small number of the studies on this topic do not allow understanding better this relationship. Despite these limits, HRV could be considered a promising early biomarker of cognitive impairment in populations without dementia or stroke. This index should be evaluated within a preventative perspective to minimize the risk of developing cognitive impairment.

Keywords: heart rate variability, global cognitive functioning, attention, executive functions, language, processing speed, memory, visuospatial skills

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INTRODUCTION

Rationale

Cognitive functions are mental abilities that allow the correct interpretation and management of environmental information. These skills are distributed along a continuum that involves optimal cognitive functioning at one extreme and dementia at the other (Petersen, 2004). Proper cognitive functioning is essential to perform both the simplest tasks of everyday life and the most complex

activities. Many factors can contribute to the physiological decline of cognitive functions in general, or of a specific domain, linked to the aging process (DeCarli, 2003; Murman, 2015).

Sometimes, the cognitive changes associated with aging became clinically significant and severe enough to compromise social and daily life functioning. The challenge of modern science, given the current sociodemographic conditions (i.e., population aging), is precisely to understand the reasons for this pathological decline, as well as to try to identify the early markers of cognitive impairment.

Cognitive functioning worsens under conditions of autonomic (Thayer and Lane, 2009; Thayer et al., 2010) and cardiovascular (O'donnell et al., 2012) dysfunctions. Within this perspective, a promising physiological correlate of cognitive functioning is heart rate variability (HRV) that is considered an index of autonomic control of the heart. HRV reflects the oscillations in the interval (ms) between consecutive heartbeats (R-R intervals) that result mainly from the dynamic interaction between the parasympathetic and the sympathetic inputs to the heart through the sinoatrial node (Malik, 1996; Thayer and Lane, 2000; Reyes del Paso et al., 2013).

Heart rate variability analysis can be conducted in the time domain, frequency domain, and by using non-linear analyses. In the time-domain, it is possible to calculate: (a) the standard deviation of all R–R intervals (SDNN) that reveals the components responsible for variability in the recording period (Malik, 1996); and (b) the root mean square of successive standard deviation (RMSSD) and the percentage of consecutive regular sinus RR intervals over 50 ms (pNN50) that should reflect vagal tone (Thayer and Lane, 2000; Kleiger et al., 2005; Shaffer et al., 2014; Laborde et al., 2017).

In the frequency domain, the oscillatory components are usually differentiated into different spectral profiles (Malik, 1996; Berntson et al., 1997; Reyes del Paso et al., 2013). Ultra-low frequencies (ULF; <0.0033 Hz) can only be evaluated using 24-h recordings, and reflect circadian oscillations, body temperature, metabolism, and activity of the renin-angiotensin system (Laborde et al., 2017). Very-low frequencies (VLF; 0.0033–0.04 Hz) represent long-term regulation mechanisms, thermoregulation, and hormonal mechanisms (Malik, 1996; Laborde et al., 2017). The low frequencies (LF; 0.04–0.15 Hz) reflect a mix between the sympathetic and vagal influences and are considered a marker of cardiac outflow influenced by both sympathetic and parasympathetic branches of the autonomic nervous system (ANS) (Malik, 1996; Laborde et al., 2017). Initially, it was assumed that only sympathetic outflow contributes to the LF-HRV. However, this view is not without controversial opinions. In particular, some authors suggest that LF-HRV primarily reflects parasympathetic influence (Reyes del Paso et al., 2013), and it is potentially affected by other cardiac mechanisms such as baroreflex sensitivity (e.g., Goldstein et al., 2011). High frequencies (HF; 0.15–0.40 Hz) reflect vagal tone (Malik, 1996; Laborde et al., 2017) and can be taken as an index of cardiac parasympathetic tone (Reyes del Paso et al., 2013). Finally, the LF/HF-HRV ratio has long been considered as an index of sympathovagal balance. However, this viewpoint has been strongly criticized (e.g., Billman et al., 2015), because the physiological bases are not clear (Laborde et al., 2017). For these reasons, this index, although widely used, would have a low predictive value (Laborde et al., 2017).

The cardiac vagal tone has frequently been linked to cognitive and emotional control (e.g., Porges, 1995; Hansen et al., 2003; Duschek et al., 2009). Within the HRV spectrum, the high-frequency band corresponds to parasympathetic cardiac activity. Parasympathetic influences are essential for the successful adaptation of the individual to changing environmental demands (Porges, 1995; Thayer and Lane, 2000, 2009; Reyes Del Paso et al., 2009). A reduction in vagal control (i.e., decreased HF-HRV) could indicate a lack of ability to respond flexibly to changing demands, reducing the range of possible options and thus limiting the individuals' ability to generate appropriate responses and inhibit inappropriate ones.

According to the Neurovisceral Integration Model, there is an association between cardiac vagal tone and the functioning of attentional and emotional self-regulatory systems (Thayer and Lane, 2000, 2009). The neurovisceral integration hypothesis has suggested that the brain areas involved in self-regulation are also involved in cardiac autonomic activity through the vagus nerve (Ellis and Thayer, 2010; Thayer et al., 2012). These areas include the anterior, insular, and orbitofrontal cortices; amygdala; periaqueductal gray matter; ventral striatum; and autonomic motor nuclei of the brainstem (Thayer et al., 2012).

Further studies have confirmed the existence of an association between higher resting HRV and active inhibitory prefrontal-subcortical circuits (Thayer and Lane, 2000, 2009; Sakaki et al., 2016). In particular, higher resting-state HRV appears to be related to increased activity in executive brain regions (Thayer et al., 2012), while lower resting HRV seems to be related to hypoactive prefrontal regulation (Thayer and Sternberg, 2006; Park and Thayer, 2014). Consequently, a vagal control of the heart appear to be associated with the effective functioning of self-regulatory neural circuits, which permit the organism to respond quickly and flexibly to environmental demands (Thayer and Lane, 2000, 2009; Thayer and Friedman, 2004; Thayer et al., 2009; Thayer et al., 2012).

This hypothesis was formulated for the first-time considering emotion regulation and dysregulation (Thayer and Lane, 2000). According to this view, affective regulation requires selective attention to emotionally relevant stimuli and the inhibition of attention to irrelevant stimuli. Therefore, from a neurovisceral perspective, attentional and emotional regulations run together in the process of self-regulation and goal-directed behaviors. This extension of the neurovisceral hypothesis to other cognitive domains can allow improving the understanding of the relationship between the ANS and cognitive functioning.

Aims

The general aims of this systematic review of the literature are: (a) to analyze the relationship between autonomic regulation and cognitive processes in the absence of affective dimensions and pathological aspects; (b) according to the hypothesis of the neurovisceral integration model, to understand the relationship between executive functioning and HRV; (c) to investigate

the relationships between HRV and other cognitive domains (i.e., processing speed, attention, memory, language, visuospatial skills), to highlight whether HRV can be considered an index of general cognitive functioning; (d) to evaluate whether HRV can be considered as a predictor of cognitive performance.

METHODS

The review process was conducted according to the PRISMA-Statement (Liberati et al., 2009; Moher et al., 2009).

Research Strategies

A systematic analysis of the international literature was carried out by selecting articles published in peer-review journals, using PubMed, PsycINFO, PsycARTICLES, and MEDLINE databases. The last research was conducted on June 10, 2018. Restrictions were made, limiting the study to academic publications in which the full text was published in English, and the study included human populations without age, gender, or ethnicity restrictions. The search strategy used the following syntax: "(cognit* or neuropsych*) and (HRV or heart rate variability or vagal tone or vagal activity)."

Eligibility Criteria

From the list of potential articles produced by systematic research, we selected the studies that included one or more cognitive measures and the measurement of HRV. Studies that included participants with medical conditions, which could potentially influence this relationship and those that included participants with a diagnosis of dementia, psychiatric disorders, strokes, and traumatic brain injury were excluded.

The first exclusion of non-inherent studies was made by analyzing titles and abstracts of the articles. Subsequently, the reading of the full text allowed further selection. Two researchers made the selection independently; inconsistent decisions between them were resolved by consulting a supervisor.

Data Collection

According to the PICOS approach (Liberati et al., 2009), the following information has been extracted from each selected study: (1) author(s) and year of publication (2) characteristics of participants (including age, years of education, gender); (3) type of HRV measures (including measurement in the time or frequency domain); (4) cognitive domain analyzed (global, executive functions, processing speed, language, memory, attention, visuospatial skills); (5) nature and direction of the identified relationship. These data are summarized in **Table 1**. Only HRV resting measurements have been considered because the heterogeneity of cognitive tasks could influence recovery measures hindering finest comparisons between the variables.

The neuropsychological tests used in the selected studies were associated, as defined by the authors, with some cognitive *a priori* domains (global functioning, attention, executive functions, memory, visuospatial skills, language, and processing speed). Performance in the various domains was analyzed, considering a single test or a composite score based on the measures of multiple neuropsychological tests (see **Table 2**).

RESULTS

Selection of the Studies

The flowchart shows the number of studies identified from the databases and examined by the authors, the number of articles, assessed for eligibility, and included in the review; the reasons for possible exclusions are also reported (**Figure 1**). The final analysis included 20 studies.

Results of the Selected Studies

Demographic Data

The 20 studies that met the inclusion criteria were conducted from 2001 to 2018 and involved 19,431 people. Participants were aged between 18.4 (Gillie et al., 2014) and 76.0 years (Zeki Al Hazzouri et al., 2014). The percentage of men in the studies ranged from 0 (Kim et al., 2006) to 72% (Britton et al., 2008). Three studies did not report information about the participants' gender (Hansen et al., 2003, 2004; Shah et al., 2011). Only one study presented a gender comparison (Frewen et al., 2013). Almost all of the researchers carried out a cross-sectional analysis, and only one study performed a longitudinal evaluation (Britton et al., 2008).

Many studies (Hansen et al., 2003, 2004; Kim et al., 2006; Britton et al., 2008; Frewen et al., 2013; Zeki Al Hazzouri et al., 2014; Mahinrad et al., 2016; Ottaviani et al., 2018) carried out statistical analysis controlling some confounding variables, such as demographics (age, gender, years of education, ethnicity), clinical (body mass index; blood pressure; heart rate; cardiovascular diseases, cholesterol, diabetes), and behavioral (smoking, exercise, alcohol consumption) variables.

HRV Measurement

Except for one study (Mahinrad et al., 2016), HRV measurement was conducted by a continuous ECG recording, which lasted at least 5 min, as recommended by the guidelines of the European society of cardiology and the North American society (Malik, 1996).

Heart rate variability was evaluated considering time-domain analyses (Hansen et al., 2003; Zeki Al Hazzouri et al., 2014, 2017), frequency-domain analyses (Melis and Van Boxtel, 2001; Hansen et al., 2004; Duschek et al., 2009; Drucaroff et al., 2011; Kimhy et al., 2013; Gillie et al., 2014; Mann et al., 2015; Mahinrad et al., 2016; Williams et al., 2016; Colzato and Steenbergen, 2017; Colzato et al., 2018), or both (Kim et al., 2006; Britton et al., 2008; Drucaroff et al., 2011; Solernó et al., 2012; Frewen et al., 2013; Colzato et al., 2018; Ottaviani et al., 2018).

The HF-HRV analysis was the most frequently reported (Melis and Van Boxtel, 2001; Hansen et al., 2003, 2004; Kim et al., 2006; Britton et al., 2008; Drucaroff et al., 2011; Shah et al., 2011; Solernó et al., 2012; Kimhy et al., 2013; Gillie et al., 2014;

TABLE 1 | Participants' characteristics, cognitive domains analyzed, HRV measurements, and links to cognitive performances in the selected studies.

Study	Participants				Cognitive Domain								
	Group	N	Age M (SD)[a]	Sex (% men)[a]	GC	ME	EF	LG	AT	PS	VS	Domain HRV	Relation between HRV and cognitive performances
Melis and Van Boxtel, 2001		52	22.0 (3.0)	48	✓							HF; MF*	Positive
Hansen et al., 2003		53	23.0				✓		✓			HF	Positive
Hansen et al., 2004		37	19.1				✓		✓			HF	Positive
Kim et al., 2006		311	65–85	0	✓							RMSSD; HF	Positive
Britton et al., 2008		5375	58.0 (6.0)	72	x	x	x	x	✓			SDNN; LF; HF.	No Relation
Duschek et al., 2009		60	24.5 (3.7)	47								MF*	Positive
Drucaroff et al., 2011		18	47.7 (15.7)	27.8			✓					SDNN; LF; HF	Positive
Shah et al., 2011		416	55.0 (2.9)		✓							HF	Positive
Solernó et al., 2012		19	21.5 (0.5)	47	✓						✓	RMSSD; SDNN; HF.	Positive
Frewen et al., 2013	Male Female	2145 2618	61.8 (8.3) 61.5 (8.39	100 0	✓	✓	x	✓	x		✓	SDNN; LF; LF/HF	Positive
Kimhy et al., 2013		817	57.11 (11.15)	44.2			✓					HF	Positive
Gillie et al., 2014		75	18.4	36.4		✓[b]						HF; LF	Positive
Zeki Al Hazzouri et al., 2014		869	76.0 (6.0)	41	✓			✓				SDNN; RMSSD	Positive
Mann et al., 2015		533	54.9 (10.7)	46.3			✓					HF	Positive
Williams et al., 2016		104	19.25 (1.43)	54					✓			HF	Positive
Mahinrad et al., 2016		3583	75.0 (3.0)	47	✓	x	✓			✓		HF	Positive
Colzato and Steenbergen, 2017	High HRV Low HRV	44 44	21.3 (0.3) 21.1 (0.3	43.2 43.2			✓	.				HF	Positive
Zeki Al Hazzouri et al., 2017		2118	45.0 (4.0)	42		x	✓					SDNN; RMSSD	Positive
Colzato et al., 2018		90	22.1 (2.5)	33.3			✓					RMSSD; HF	Positive
Ottaviani et al., 2018		50	24.2 (4.0)	38			✓					RMSSD; HF	Positive

*M, mean; SD, standard deviation;, domain assessed but not resulted impairment in this study;, domain assessed and resulted impairment in this study; GC, global cognition; ME, memory; LG, language; AT, attention; EF, executive functioning; PS, information processing speed; VS, visuospatial skills; HF, high-frequency band; RMSSD, root mean square of successive RR interval differences; SDNN, standard deviation of NN intervals; LF, low-frequency band; LF/HF, ratio of LF-to-HF power; [a]not reported in all studies; [b]ability to suppress unwanted memory; *MF, mid frequency band (0.06–0.14 Hz).*

TABLE 2 | Neuropsychological tests used for the evaluation of the cognitive domains in the included studies.

Cognitive domain	Task	Study
Global cognition	Inductive reasoning tasks	Melis and Van Boxtel, 2001
	Mini-Mental State Examination (MMSE)	Kim et al., 2006; Mahinrad et al., 2016
	Modified Mini-Mental State Examination (3MSE)	Zeki Al Hazzouri et al., 2014
	Alice-Heim 4-I (AH4-I)	Britton et al., 2008
	Bennett–Seashore–Wesman Differential Aptitude Test	Solernó et al., 2012
	Montreal Cognitive Assessment (MoCA)	Frewen et al., 2013
Memory	Computerized Working Memory Test	Hansen et al., 2003, 2004
	20-word free recall test of short-term verbal memory	Britton et al., 2008
	Montreal Cognitive Assessment (MoCA) Subtest	Frewen et al., 2013
	Unwanted memory Test	Gillie et al., 2014
	Composite Score	Shah et al., 2011[a]
	Rey Auditory-Verbal Learning Test	Zeki Al Hazzouri et al., 2017
	Picture-Word Learning Test	Mahinrad et al., 2016
	Spanish and English verbal learning test (SEVLT)	Zeki Al Hazzouri et al., 2014
Language	Montreal Cognitive Assessment (MoCA) subtest	Frewen et al., 2013
	Mill Hill Vocabulary Test	Britton et al., 2008
Attention	Modified Flanker Task	Williams et al., 2016
	Montreal Cognitive Assessment (MoCA) Subtest	Frewen et al., 2013
	Test d2	Duschek et al., 2009
	California Computerized Assessment Package (CALCAP)	Hansen et al., 2003, 2004
Executive function	Montreal Cognitive Assessment (MoCA) Subtest	Frewen et al., 2013
	California Computerized Assessment Package (CALCAP)	Hansen et al., 2003, 2004
	Verbal fluency	Britton et al., 2008
	Computerized working memory task	Hansen et al., 2003, 2004
	Composite Score	Kimhy et al., 2013[b]; Mann et al., 2015[c]
	Stop-change paradigm	Colzato and Steenbergen, 2017
	Rule Shift Cards and the Hayling Sentence Completion Test	Ottaviani et al., 2018
	Iowa Gambling Task and Game of Dice Task	Drucaroff et al., 2011
Processing speed	Task-switching paradigm	Colzato et al., 2018
	Stroop Task	Mahinrad et al., 2016; Zeki Al Hazzouri et al., 2017
	Letter-Digit Coding	Mahinrad et al., 2016
Visuospatial abilities	Bennett–Seashore–Wesman Differential Aptitude Test	Solernó et al., 2012
	Montreal Cognitive Assessment (MoCA) Subtest	Frewen et al., 2013

[a]Verbal Selective Reminding Test (SRT) and the visual SRT; [b]Digits Backward task, Red/Green task (a variant of the classic Go/No Go) and Category Fluency; [c]Brief Test of Adult Cognition (BTAC) and Stop and Go Switch Task (SGST).

Mann et al., 2015; Mahinrad et al., 2016; Williams et al., 2016; Colzato and Steenbergen, 2017; Colzato et al., 2018; Ottaviani et al., 2018). The LF/HF HRV ratio (Frewen et al., 2013), the LF-HRV band (Britton et al., 2008; Drucaroff et al., 2011; Frewen et al., 2013; Gillie et al., 2014), the mid-frequency (MF) HRV band (Melis and Van Boxtel, 2001; Duschek et al., 2009), the standard deviation of mean RR interval (SDNN) (Britton et al., 2008; Drucaroff et al., 2011; Solernó et al., 2012; Frewen et al., 2013; Zeki Al Hazzouri et al., 2014, 2017) and the square root of the mean squared differences of successive RR intervals (RMSSD) (Kim et al., 2006; Solernó et al., 2012; Zeki Al Hazzouri et al., 2014, 2017; Colzato et al., 2018; Ottaviani et al., 2018) were also evaluated.

Cognitive Domain

All the cognitive domains were examined; global cognitive functioning (eight studies), memory (eight studies), language (two studies), attention (five studies), executive functions (thirteen studies), visuospatial skills (two studies), and processing speed (one study) (for references, see **Table 1**).

HRV and Global Cognition (*n* = 8)

An association between HRV and global cognitive performance was reported. Only Britton et al. (2008) fail to find this relationship. Specifically, a low HRV was related to poorer performance (Melis and Van Boxtel, 2001; Kim et al., 2006; Solernó et al., 2012; Frewen et al., 2013; Zeki Al Hazzouri et al., 2014; Mahinrad et al., 2016) also after the adjustment of data for demographic, clinical and behavioral confounding variables (Kim et al., 2006; Frewen et al., 2013; Zeki Al Hazzouri et al., 2014; Mahinrad et al., 2016).

One study emphasized the role of the respiration rate (Melis and Van Boxtel, 2001), highlighting that poor reasoners

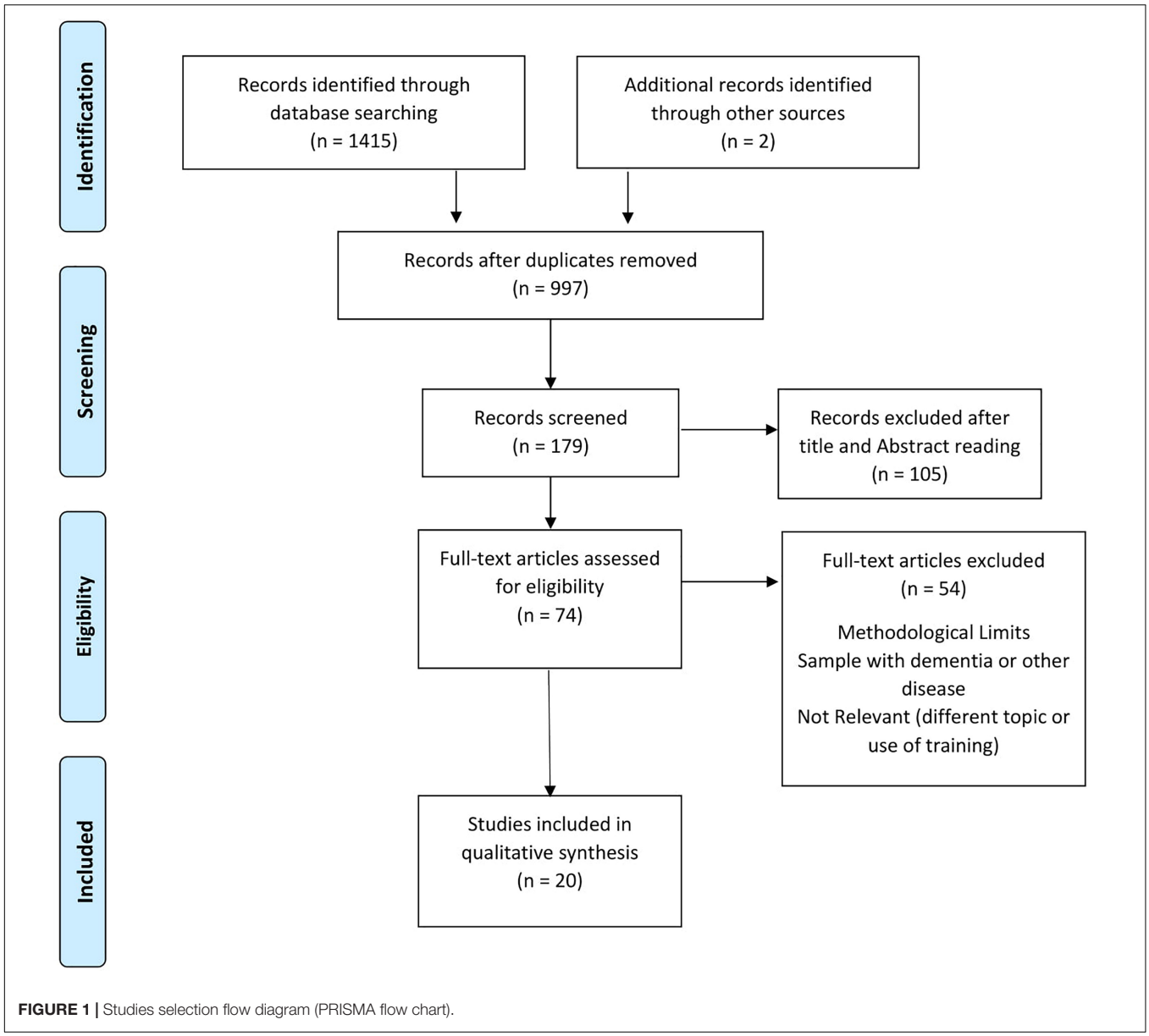

FIGURE 1 | Studies selection flow diagram (PRISMA flow chart).

had higher levels of sympathetic activity and respiratory rate than good reasoners.

HRV and Memory (*n* = 8)

Three studies (Shah et al., 2011; Frewen et al., 2013; Gillie et al., 2014; Zeki Al Hazzouri et al., 2014) found a relationship between HRV and memory functionality, also after controlling demographic and clinical variables (Shah et al., 2011; Frewen et al., 2013).

People with higher HRV levels demonstrate a better ability to control over memory and a better ability to suppress unwanted memories (Gillie et al., 2014). Lower HRV is independently associated with a worse performance both in short and long-term verbal memory (Shah et al., 2011; Frewen et al., 2013).

However, some studies did not find a relationship between verbal (Britton et al., 2008; Mahinrad et al., 2016; Zeki Al Hazzouri et al., 2017) or visuospatial memory (Shah et al., 2011) and HRV.

HRV and Language (*n* = 2)

Frewen et al. (2013) reported that reduced HRV is associated with lower linguistic performance, also after the adjustment of data for demographic, clinical and behavioral confounding variables. Conversely, Britton et al. (2008) did not find any relationship between HRV and linguistic performance.

HRV and Attention (*n* = 5)

Four studies (Hansen et al., 2003, 2004; Duschek et al., 2009; Williams et al., 2016) found that individual differences in

resting HRV predicted attentional performance. Lower HRV was associated with worse performance, also after the adjustment of the data for confounding variables (Duschek et al., 2009; Williams et al., 2016). However, these results were not confirmed by Frewen et al. (2013), who did not find any relationship between HRV and attention.

HRV and Executive Functions (*n* = 13)

The executive domain was the most investigated. The studies demonstrated an association between lower HRV and poor executive performance; however, two studies (Britton et al., 2008; Frewen et al., 2013) did not confirm these findings.

Lower HRV predicted poorer performance on tasks involving executive functioning independently from demographic, clinical and behavioral confounding variables.

HRV and Visuospatial Skills (*n* = 2)

Considering visuospatial abilities, only Frewen et al. (2013) observed a relationship with HRV. Lower HRV was associated with poor visuospatial performance, also after the adjustment of the data for demographic, clinical and behavioral confounding variables.

HRV and Processing Speed (*n* = 1)

The only study (Mahinrad et al., 2016) that investigated processing speed showed that people with lower HRV had worse performance and experienced a higher decline in processing speed, independently from demographic and clinical characteristics.

DISCUSSION

Summary of Evidence

The role of ANS on emotional regulation is well-known, whereas its links with cognitive functions are less well defined. Some studies concerning the general arousal (Lindsley, 1951), the attentional orienting (Sokolov, 1990), the alerting (Turpin and Siddle, 1978), and the regulation of actions (Jennings and van der Molen, 2005) have reported specific autonomic changes that were concurrent with cognitive functioning.

The first studies that have tried to identify a specific relationship between vagal tone and cognitive functions have highlighted changes in HRV depending on the type or complexity of the task (Lacey and Lacey, 1958; Richards and Casey, 1991). Based on these findings, some theories have been developed to explain the relationship between HRV and cognitive functioning. Among these, there is the Polyvagal Theory of Porges (1992), which highlights the importance of the vagus nerve for cognitive functions and in particular for the attentional processes. More recently, Thayer et al. (2009) developed the Neurovisceral Integration Model, which hypothesized a cortical integration between the executive, autonomic, and emotional functionality. The ANS is controlled by cortical circuits located in the prefrontal cortex, the anterior cingulate gyrus, the orbitofrontal cortex, and the amygdala, which are also crucial for cognitive and emotional processes (Critchley, 2009; Parasuraman and Jiang, 2012). The authors hypothesized that a sympathetic hyperactivation, with consequent prefrontal hypoactivation, would facilitate the disinhibition of the amygdala, i.e., an adaptive response; the amygdala would promote a decrease in HRV and an increase in heart rate (Thayer and Lane, 2009). This hypervigilant reaction would be related to reduced cognitive flexibility and vice versa; under parasympathetic activity conditions, the lack of prefrontal hypoactivation would be expressed through an increase in HRV with improved cognitive functions (Thayer and Lane, 2009).

One of the aims of this review was to analyze the neurovisceral integration hypothesis considering the performance that involved executive components in the absence of affective dimensions and pathological aspects.

A close examination of the selected studies confirms the relationships between resting HF-HRV and cognitive functioning, supporting the neurovisceral hypothesis in the absence of affective dimensions. The early results of Hansen et al. (2003) suggested a connection between resting HF-HRV, processing speed, and the accuracy of responses to monitoring tasks, with a stronger association when working memory was required; participants with high HF-HRV performed better than participants with low HF-HRV. The same set of tests was administered in a subsequent study (Hansen et al., 2004), and the results were replicated. These results were also confirmed during a condition of a threat of shock (Hansen et al., 2009).

Subsequently, numerous studies have analyzed the association between executive functions and HRV, considering both time and frequency domains, and in some cases with a large sample (Kimhy et al., 2013; Mahinrad et al., 2016; Zeki Al Hazzouri et al., 2017). A relationship with HRV was confirmed considering different executive functions (Hansen et al., 2004; Mann et al., 2015; Mahinrad et al., 2016; Colzato and Steenbergen, 2017). Moreover, participants with high resting-state HRV (indexed by RMSSD), as compared to participants with low resting-state HRV, demonstrated better action cascading (Colzato and Steenbergen, 2017), underlining that high resting HRV is associated with the optimal functioning of the prefrontal-subcortical inhibitory circuits that sustain flexible and adaptive responses to environmental demands (Colzato and Steenbergen, 2017).

Another aim of this review was to analyze the relationship between HRV and different cognitive domains. Many studies have found that reduced HRV in both time domain (RMSSD, SDNN) and frequency domain (HF, LF, LF/HF) were associated with weaker cognitive performance in both global cognition and specific cognitive domains.

Interestingly, the various HRV indices appear related to cognitive domains differently.

Lower LF-HRV, which is influenced by both sympathetic and parasympathetic branches of ANS, was linked to worse cognitive performance, in particular considering memory, language and global cognitive scores (Solernó et al., 2012; Frewen et al., 2013). Melis and Van Boxtel (2001) reported that high MF (Mid-Frequency band: 0.06–0.14 Hz), regulated by both the sympathetic and parasympathetic branches of the ANS, was associated with better performance in spatial tasks and to poorer

verbal reasoning ability, while high HF-HRV was associated with better verbal reasoning ability. On the other hand, lower HF-HRV, which reflects vagal modulation, appears to be associated with weaker performance in global cognitive functions, such as those measured by the Mini-Mental State Examination (Kim et al., 2006), verbal reasoning abilities (Solernó et al., 2012), inhibition of memory responses (Gillie et al., 2014), or executive functions (Hansen et al., 2004; Mann et al., 2015; Mahinrad et al., 2016; Colzato and Steenbergen, 2017). These results can be due to the lateralisation of autonomic functions (Melis and Van Boxtel, 2001). In particular, sympathetic activation is related to visual and motor cortices, while parasympathetic activation is linked to the activity of prefrontal areas.

Moreover, some studies (Kim et al., 2006; Collins et al., 2012) reported a link between low HF-HRV and the risk of developing cognitive impairment. According to this hypothesis, low LF-HRV has been associated with white matter lesions in patients with Mild Cognitive Impairments (Zulli et al., 2005; Galluzzi et al., 2009) and Alzheimer's Disease (Murakami et al., 2002; Zulli et al., 2005; de Vilhena Toledo and Junqueira, 2008). These results linked to others that identified a change in the LF/HF ratio based on the type and difficulty of the task (Luft et al., 2009; Mukherjee et al., 2011), reinforce the idea that the various parameters of HRV are associated with different cognitive functions.

The results under the umbrella of the memory domain are particularly fascinating. Although a general relationship between HRV and verbal memory was found, visual memory seems not to be associated with HRV. This finding can be explained by considering that many brain regions involved in visual functions, including parietal, temporal, and occipital lobes, all lie outside of the central autonomic network (Desimone, 1996; Pessoa et al., 2002). Therefore, HRV may correlate with verbal, but not visual, memory performance because verbal memory more specifically involves the central autonomic network.

In general, it is evident that executive functions, as well as global cognitive functioning, are the most investigated dimensions about HRV. The other cognitive domains (attention, processing speed, visuospatial skills, memory, and language) were the object of investigations that appear to be characterized by many methodological limits from both a quantitative and a qualitative point of view. A critical aspect of the studies measuring HRV is given by the numerous confounding variables. The results are particularly relevant when confounding variables are controlled; in some cases, the relationship became stronger, while in others, the adjustment for the confounding variables modifies the terms of the relationship. This pattern of results appears to indicate that other variables mediate the relationship between HRV and cognitive functions. HRV changes according to many factors, such as gender (Sztajzel et al., 2008), BMI (Koenig et al., 2014), anxiety (Chalmers et al., 2014), stress (Dishman et al., 2000), heart rate (Gąsior et al., 2016), and smoking habits (Levin et al., 1992; Karakaya et al., 2007), and so became important controlling these variables. Consequently, the analyses of their specific influence in mediating HRV effects on cognitive functioning are compelling. It is interesting to note that, in contrast to the other domains, the executive domain was significantly associated with HRV, above and beyond significant confounding variables (i.e., cardiovascular risk, age, and gender). This association is not surprising and reinforces the idea that HRV is strongly associated with the neuronal activity of the prefrontal cortex, which in turn regulates the executive functions (Thayer et al., 2009).

In contrast to results of other studies, Britton et al. (2008) did not show any correlation between HRV parameters and cognitive functioning, even if they considered a large cohort of people with characteristics similar to those of other studies. These inconsistent results could be due to the high variability of the data, which is attributable to some methodological procedures; for example, the participants were selected in different phases of one longitudinal study and this procedure can have implied effects due to both the survival and the selection of the sample. Another explanation could be the high percentage of males present in the sample (72%). Several studies show that men, compared to women, had a higher RR interval, a higher LF-HRV, and a lower HF-HRV (Koenig and Thayer, 2016). Finally, the tests used in this study (Whitehall II cognitive test battery) did not assess executive functions in detail.

Another aim of this study was to evaluate the predictive value of HRV for cognitive performance. The analyzed studies found that a higher HRV, both in time and frequency domains, were associated with finest cognitive performance, even after adjustment for the confounding variables commonly associated with HRV (i.e., age, gender, years of education, body mass index, blood pressure, cardiovascular diseases). Therefore, even if caution must be employed in defining the HRV as a predictor of performance in several cognitive domains, the results obtained from this review seem promising in that sense. However, more longitudinal studies and further research on poorly considered cognitive domains are needed to allow reliable inferences in this regard.

Limitations

This systematic review of the literature aimed to carry out an analysis of the scientific studies concerning the link between the activity of the autonomic system and cognitive functioning.

Although we have tried to control the research methodology as much as possible, this study presents some limitations that could undermine the generalizability of the results. One weakness is given by the heterogeneity of the population and measures; this heterogeneity does not allow performing a quantitative analysis (i.e., meta-analysis) that would have given greater force to the conclusions.

Another limitation could be indirectly linked to the publication bias. The choice to include only academic articles published in peer-review journals may have limited the selection of only those studies that have obtained results in line with the literature. As a consequence, the results may overestimate this relationship. Moreover, the choice to select only studies published in English could have led to the elimination of studies conducted on other populations and written in different languages, further limiting the generalizability of the results. Moreover, the marked interest in a specific domain, i.e., the executive functions, and

the relatively small number of studies in this topic does not allow to a conclusion concerning the involvement of the other cognitive domains. Finally, another limitation is represented by the overwhelming presence of cross-sectional studies that do not enable to few causal inferences on the relationship between HRV and cognitive functioning to be made.

Future Perspectives

To overcome these limitations, in future psychophysiological studies it will be useful to utilize the emerging guidelines for reporting HRV parameters (e.g., Laborde et al., 2017), which can improve the quality of data, allow to more transparent reporting, and lead to more analysable data in quantitative analysis (e.g., meta-analysis).

Further research should aim to increase the studies on the relationship between HRV and some cognitive domains, such as attention, language, processing speed, and visuospatial skills., that are disregarded by the studies until now. Likely these cognitive domains have been neglected because they are never associated with an early cognitive impairment.

Of particular note is the attentional domain because it has been evaluated with tests that do not allow a complete assessment of this multidimensional construct.

Other essential aspects to consider in future studies are the vagal reactivity and the recovery processes that have been linked to cognitive performance (Capuana et al., 2014). Vagal reactivity represents the change between baseline and a specific event, like completing a task, and it is essential recording it to evaluate the individual's adaptability to the situation (Laborde et al., 2018). Recovery is usually seen as a process of restoration; it refers to the change between the event and a time point after the event when the vagal activity has to be similar to the baseline. Comparable to vagal reactivity, vagal recovery plays a crucial role in the adaptability of the organism (Laborde et al., 2018). These two aspects are poorly analyzed with cognitive functioning. However, according to the vagal tank theory (Laborde et al., 2018), considering the vagal activity and the vagal recovery during different cognitive tasks could be interesting. This type of study could allow us understanding better how cardiac vagal control influences several key self-regulatory aspects of behavior and also evaluating whether the differences between baseline, task execution, and recovery are related to cognitive impairment.

CONCLUSION

In this review, we focused on the analysis of the autonomic baseline that allows us to make inferences about the predictive value of autonomic homeostasis on cognitive impairment. Despite providing very relevant information, this analysis does not adequately enable the understanding of the mechanisms involved. Some studies that have analyzed HRV changes during the performance of cognitive tasks have shown that autonomic functionality varies according to the complexity and type of the task (Luft et al., 2009; Mukherjee et al., 2011).

Although this review has highlighted how some cognitive domains are more heavily investigated than others, in general, higher resting HRV is related to better performance in cognitive tasks. In contrast, lower resting HRV is associated with a lack of prefrontal control of the subcortical activity, which results in poor functioning of self-regulatory systems (Thayer and Lane, 2000; Thayer et al., 2009). In summary, a higher HF-HRV has been linked to better cognitive performance, and a lower HF-HRV has been associated with cognitive impairment.

In conclusion, this review highlights that the autonomous nervous system and the neurocognitive systems operate in close interaction. The results suggest that autonomic markers (LF, HF, LF/HF, SDNN) can be considered as early biomarkers for the measurement of cognitive impairment in populations without dementia or stroke. An initial analysis of these biomarkers could allow the implementation of preventative measures of autonomic control to prevent the worsening of cognitive decline.

AUTHOR CONTRIBUTIONS

MC and GF were responsible for the conception of the review, the literature research, and writing the manuscript. FF supervised the selection of the studies and contributed to the revision of the manuscript. All authors revised, read, and approved the submitted version.

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REFERENCES

Berntson, G. G., Bigger, J. T., Eckberg, D. L., Grossman, P., Kaufmann, P. G., Malik, M., et al. (1997). Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology* 34, 623–648. doi: 10.1111/j.1469-8986.1997.tb02140.x

Billman, G. E., Huikuri, H. V., Sacha, J., and Trimmel, K. (2015). An introduction to heart rate variability: methodological considerations and clinical applications. *Front. Physiol.* 6:55. doi: 10.3389/fphys.2015.00055

Britton, A., Singh-Manoux, A., Hnatkova, K., Malik, M., Marmot, M. G., and Shipley, M. (2008). The association between heart rate variability and cognitive impairment in middle-aged men and women. *The Whitehall II cohort study. Neuroepidemiology* 31, 115–121. doi: 10.1159/000148257

Capuana, L. J., Dywan, J., Tays, W. J., Elmers, J. L., Witherspoon, R., and Segalowitz, S. J. (2014). Factors influencing the role of cardiac autonomic regulation in the service of cognitive control. *Biol. Psychol.* 102, 88–97. doi: 10.1016/j.biopsycho.2014.07.015

Chalmers, J. A., Quintana, D. S., Abbott, M. J., and Kemp, A. H. (2014). Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. *Front. Psychiatry* 5:80. doi: 10.3389/fpsyt.2014.00080

Collins, O., Dillon, S., Finucane, C., Lawlor, B., and Kenny, R. A. (2012). Parasympathetic autonomic dysfunction is common in mild cognitive impairment. *Neurobiol. Aging* 33, 2324–2333. doi: 10.1016/j.neurobiolaging.2011.11.017

Colzato, L. S., Jongkees, B. J., Wit, M., Molen, M. J. W., and Steenbergen, L. (2018). Variable heart rate and a flexible mind: higher resting-state heart rate variability

predicts better task-switching. *Cogn. Affect. Behav. Neurosci.*. 18, 730–738. doi: 10.3758/s13415-018-0600-x

Colzato, L. S., and Steenbergen, L. (2017). High vagally mediated resting-state heart rate variability is associated with superior action cascading. *Neuropsychologia* 106, 1–6. doi: 10.1016/j.neuropsychologia.2017.08.030

Critchley, H. D. (2009). Psychophysiology of neural, cognitive and affective integration: fMRI and autonomic indicants. *Int. J. Psychophysiol.* 73, 88–94. doi: 10.1016/j.ijpsycho.2009.01.012

de Vilhena Toledo, M. A., and Junqueira, L. F. Jr. (2008). Cardiac sympathovagal modulation evaluated by short-term heart interval variability is subtly impaired in Alzheimer's disease. *Geriatr. Gerontol. Int.* 8, 109–118. doi: 10.1111/j.1447-0594.2008.00456.x

DeCarli, C. (2003). Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. *Lancet Neurol.* 2, 15–21. doi: 10.1016/S1474-4422(03)00262-X

Desimone, R. (1996). Neural mechanisms for visual memory and their role in attention. *Proc. Natl. Acad. Sci.* 93, 13494–13499. doi: 10.1073/pnas.93.24.13494

Dishman, R. K., Nakamura, Y., Garcia, M. E., Thompson, R. W., Dunn, A. L., and Blair, S. N. (2000). Heart rate variability, trait anxiety, and perceived stress among physically fit men and women. *Int. J. Psychophysiol.* 37, 121–133. doi: 10.1016/S0167-8760(00)00085-4

Drucaroff, L. J., Kievit, R., Guinjoan, S. M., Gerschcovich, E. R., Cerquetti, D., Leiguarda, R., et al. (2011). Higher autonomic activation predicts better performance in iowa gambling task. *Cogn. Behav. Neurol.* 24, 93–98. doi: 10.1097/WNN.0b013e3182239308

Duschek, S., Muckenthaler, M., Werner, N., and del Paso, G. A. R. (2009). Relationships between features of autonomic cardiovascular control and cognitive performance. *Biol. Psychol.* 81, 110–117. doi: 10.1016/j.biopsycho.2009.03.003

Ellis, R. J., and Thayer, J. F. (2010). Music and autonomic nervous system (dys) function. *Music Percept.* 27, 317–326. doi: 10.1525/mp.2010.27.4.317

Frewen, J., Finucane, C., Savva, G. M., Boyle, G., Coen, R. F., and Kenny, R. A. (2013). Cognitive function is associated with impaired heart rate variability in ageing adults: the Irish longitudinal study on ageing wave one results. *Clin. Auton. Res.* 23, 313–323. doi: 10.1007/s10286-013-0214-x

Galluzzi, S., Nicosia, F., Geroldi, C., Alicandri, A., Bonetti, M., Romanelli, G., et al. (2009). Cardiac autonomic dysfunction is associated with white matter lesions in patients with mild cognitive impairment. *J. Gerontol. Ser. A: Biol. Sci. Med. Sci.* 64, 1312–1315. doi: 10.1093/gerona/glp105

Gąsior, J. S., Sacha, J., Jeleń, P. J., Zieliński, J., and Przybylski, J. (2016). Heart rate and respiratory rate influence on heart rate variability repeatability: effects of the correction for the prevailing heart rate. *Front. Physiol.* 7:356. doi: 10.3389/fphys.2016.00356

Gillie, B. L., Vasey, M. W., and Thayer, J. F. (2014). Heart rate variability predicts control over memory retrieval. *Psychol. Sci.* 25, 458–465. doi: 10.1177/0956797613508789

Goldstein, D. S., Bentho, O., Park, M. Y., and Sharabi, Y. (2011). Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. *Exp. Physiol.* 96, 1255–1261. doi: 10.1113/expphysiol.2010.056259

Hansen, A. L., Johnsen, B. H., Sollers, J. J. III, Stenvik, K., and Thayer, J. F. (2004). Heart rate variability and its relation to prefrontal cognitive function: the effects of training and detraining. *Eur. J. Appl. Physiol.* 93, 263–272. doi: 10.1007/s00421-004-1208-0

Hansen, A. L., Johnsen, B. H., and Thayer, J. F. (2003). Vagal influence on working memory and attention. *Int. J. Psychophysiol.* 48, 263–274. doi: 10.1016/S0167-8760(03)00073-4

Hansen, A. L., Johnsen, B. H., and Thayer, J. F. (2009). Relationship between heart rate variability and cognitive function during threat of shock. *Anxiety Stress Coping* 22, 77–89. doi: 10.1080/10615800802272251

Jennings, J. R., and van der Molen, M. W. (2005). Preparation for speeded action as a psychophysiological concept. *Psychol. Bull.* 131, 434–459. doi: 10.1037/0033-2909.131.3.434

Karakaya, O., Barutcu, I., Kaya, D., Esen, A. M., Saglam, M., Melek, M., et al. (2007). Acute effect of cigarette smoking on heart rate variability. *Angiology* 58, 620–624. doi: 10.1177/0003319706294555

Kim, D. H., Lipsitz, L. A., Ferrucci, L., Varadhan, R., Guralnik, J. M., Carlson, M. C., et al. (2006). Association between reduced heart rate variability and cognitive impairment in older disabled women in the community: women's health and aging study I. *J. Am. Geriatr. Soc.* 54, 1751–1757. doi: 10.1111/j.1532-5415.2006.00940.x

Kimhy, D., Crowley, O. V., McKinley, P. S., Burg, M. M., Lachman, M. E., Tun, P. A., et al. (2013). The association of cardiac vagal control and executive functioning–findings from the MIDUS study. *J. Psychiatr. Res.* 47, 628–635. doi: 10.1016/j.jpsychires.2013.01.018

Kleiger, R. E., Stein, P. K., and Bigger, J. T. Jr. (2005). Heart rate variability: measurement and clinical utility. *Ann. Noninvasive Electrocardiol.* 10, 88–101. doi: 10.1111/j.1542-474X.2005.10101.x

Koenig, J., Jarczok, M. N., Warth, M., Ellis, R. J., Bach, C., Hillecke, T. K., et al. (2014). Body mass index is related to autonomic nervous system activity as measured by heart rate variability—a replication using short term measurements. *J. Nutr. Health Aging* 18, 300–302. doi: 10.1007/s12603-014-0022-6

Koenig, J., and Thayer, J. F. (2016). Sex differences in healthy human heart rate variability: a meta-analysis. *Neurosci. Biobehav. Rev.* 64, 288–310. doi: 10.1016/j.neubiorev.2016.03.007

Laborde, S., Mosley, E., and Mertgen, A. (2018). Vagal tank theory: the three rs of cardiac vagal control functioning–resting, reactivity, and recovery. *Front. Neurosci.* 12:458.

Laborde, S., Mosley, E., and Thayer, J. F. (2017). Heart rate variability and cardiac vagal tone in psychophysiological research–recommendations for experiment planning, data analysis, and data reporting. *Front. Psychol.* 8:213. doi: 10.3389/fpsyg.2017.00213

Lacey, J. I., and Lacey, B. C. (1958). Verification and extension of the principle of autonomic response-stereotypy. *Am. J. Psychol.* 71, 50–73.

Levin, F. R., Levin, H. R., and Nagoshi, C. (1992). Autonomic functioning and cigarette smoking: heart rate spectral analysis. *Biol. Psychiatry* 31, 639–643. doi: 10.1016/0006-3223(92)90254-W

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P., et al. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 6:e1000100. doi: 10.1371/journal.pmed.1000100

Lindsley, D. B. (1951). "Emotion," in *Handbook of Experimental Psychology*, ed. S. S. Stevens (Oxford: Wiley), 473–516.

Luft, C. D. B., Takase, E., and Darby, D. (2009). Heart rate variability and cognitive function: effects of physical effort. *Biol. Psychol.* 82, 186–191. doi: 10.1016/j.biopsycho.2009.07.007

Mahinrad, S., Jukema, J. W., van Heemst, D., Macfarlane, P. W., Clark, E. N., de Craen, A. J. M., et al. (2016). 10-Second heart rate variability and cognitive function in old age. *Neurology* 86, 1120–1127. doi: 10.1212/WNL.0000000000002499

Malik, M. (1996). Heart rate variability: standards of measurement, physiological interpretation, and clinical use: task force of the European society of cardiology and the north American society for pacing and electrophysiology. *Ann. Noninvasive Electrocardiol.* 1, 151–181. doi: 10.1111/j.1542-474x.1996.tb00275.x

Mann, S. L., Selby, E. A., Bates, M. E., and Contrada, R. J. (2015). Integrating affective and cognitive correlates of heart rate variability: a structural equation modeling approach. *Int. J. Psychophysiol.* 98, 76–86. doi: 10.1016/j.ijpsycho.2015.07.003

Melis, C., and Van Boxtel, A. (2001). Differences in autonomic physiological responses between good and poor inductive reasoners. *Biol. Psychol.* 58, 121–146. doi: 10.1016/S0301-0511(01)00112-0

Moher, D., Liberati, A., Tetzlaff, J., and Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann. Intern. Med.* 151, 264–269. doi: 10.7326/0003-4819-151-4-200908180-00135

Mukherjee, S., Yadav, R., Yung, I., Zajdel, D. P., and Oken, B. S. (2011). Sensitivity to mental effort and test–retest reliability of heart rate variability measures in healthy seniors. *Clin. Neurophysiol.* 122, 2059–2066. doi: 10.1016/j.clinph.2011.02.032

Murakami, S., Yamanaka, T., Kubo, Y., Wada, T., Yano, S., Nishimura, Y., et al. (2002). Heart rate variability analysis and neurobehavioral function in community-dwelling older people aged 75 or older. *Nihon Ronen Igakkai Zasshi.* 39, 520–526. doi: 10.3143/geriatrics.39.520

Murman, D. L. (2015). The impact of age on cognition. *Semin. Hear.* 36, 111–121. doi: 10.1055/s-0035-1555115

O'donnell, M., Teo, K., Gao, P., Anderson, C., Sleight, P., Dans, A., et al. (2012). Cognitive impairment and risk of cardiovascular events and mortality. *Eur. Heart J.* 33, 1777–1786. doi: 10.1093/eurheartj/ehs053

Ottaviani, C., Zingaretti, P., Petta, A. M., Antonucci, G., Thayer, J. F., and Spitoni, G. F. (2018). Resting heart rate variability predicts inhibitory control above and beyond impulsivity. *J. Psychophysiol.* doi: 10.1027/0269-8803/a000222

Parasuraman, R., and Jiang, Y. (2012). Individual differences in cognition, affect, and performance: behavioral, neuroimaging, and molecular genetic approaches. *Neuroimage* 59, 70–82. doi: 10.1016/j.neuroimage.2011.04.040

Park, G., and Thayer, J. F. (2014). From the heart to the mind: cardiac vagal tone modulates top-down and bottom-up visual perception and attention to emotional stimuli. *Front. Psychol.* 5:278. doi: 10.3389/fpsyg.2014.00278

Pessoa, L., McKenna, M., Gutierrez, E., and Ungerleider, L. G. (2002). Neural processing of emotional faces requires attention. *Proc. Natl. Acad. Sci.* 99, 11458–11463. doi: 10.1073/pnas.172403899

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *J. Intern. Med.* 256, 183–194. doi: 10.1111/j.1365-2796.2004.01388.x

Porges, S. W. (1992). Vagal tone: a physiologic marker of stress vulnerability. *Pediatrics* 90, 498–504.

Porges, S. W. (1995). Cardiac vagal tone: a physiological index of stress. *Neurosci. Biobehav. Rev.* 19, 225–233. doi: 10.1016/0149-7634(94)00066-A

Reyes Del Paso, G. A., González, M. I., Hernández, J. A., Duschek, S., and Gutierrez, N. (2009). Tonic blood pressure modulates the relationship between baroreceptor cardiac reflex sensitivity and cognitive performance. *Psychophysiology* 46, 932–938. doi: 10.1111/j.1469-8986.2009.00832.x

Reyes del Paso, G. A., Langewitz, W., Mulder, L. J., Van Roon, A., and Duschek, S. (2013). The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: a review with emphasis on a reanalysis of previous studies. *Psychophysiology* 50, 477–487. doi: 10.1111/psyp.12027

Richards, J. E., and Casey, B. J. (1991). Heart rate variability during attention phases in young infants. *Psychophysiology* 28, 43–53. doi: 10.1111/j.1469-8986.1991.tb03385.x

Sakaki, M., Yoo, H. J., Nga, L., Lee, T. H., Thayer, J. F., and Mather, M. (2016). Heart rate variability is associated with amygdala functional connectivity with MPFC across younger and older adults. *Neuroimage* 139, 44–52. doi: 10.1016/j.neuroimage.2016.05.076

Shaffer, F., McCraty, R., and Zerr, C. L. (2014). A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. *Front. Psychol.* 5:1040. doi: 10.3389/fpsyg.2014.01040

Shah, A. J., Su, S., Veledar, E., Bremner, J. D., Goldstein, F. C., Lampert, R., et al. (2011). Is heart rate variability related to memory performance in middle-aged men? *Psychosomatic Med.* 73, 475–482. doi: 10.1097/PSY.0b013e3182227d6a

Sokolov, E. N. (1990). The orienting response, and future directions of its development. *Pavlovian J. Biol. Sci.* 25, 142–150.

Solernó, J. I., Pérez Chada, D., Guinjoan, S. M., Pérez Lloret, S., Hedderwick, A., Vidal, M. F., et al. (2012). Cardiac autonomic activity predicts dominance in verbal over spatial reasoning tasks: results from a preliminary study. *Auton. Neurosci. Basic Clin.* 167, 78–80. doi: 10.1016/j.autneu.2011.10.008

Sztajzel, J., Jung, M., and Bayes de Luna, A. (2008). Reproducibility and gender-related differences of heart rate variability during all-day activity in young men and women. *Ann. Noninvasive Electrocardiol.* 13, 270–277. doi: 10.1111/j.1542-474X.2008.00231.x

Thayer, J. F., Åhs, F., Fredrikson, M., Sollers, J. J. III, and Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neurosci. Biobehav. Rev.* 36, 747–756. doi: 10.1016/j.neubiorev.2011.11.009

Thayer, J. F., and Friedman, B. H. (2004). "A neurovisceral integration model of health disparities in aging," in *Critical Perspectives on Racial and Ethnic Differences in Health in Late Life*, eds N. B. Anderson, R. A. Bulatao, and B. Cohen (Washington, DC: National Academies Press), 567–603.

Thayer, J. F., Hansen, A. L., Saus-Rose, E., and Johnsen, B. H. (2009). Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. *Ann. Behav. Med.* 37, 141–153. doi: 10.1007/s12160-009-9101-z

Thayer, J. F., and Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *J. Affect. Disord.* 61, 201–216. doi: 10.1016/S0165-0327(00)00338-4

Thayer, J. F., and Lane, R. D. (2009). Claude Bernard and the heart–brain connection: further elaboration of a model of neurovisceral integration. *Neurosci. Biobehav. Rev.* 33, 81–88. doi: 10.1016/j.neubiorev.2008.08.004

Thayer, J. F., and Sternberg, E. (2006). Beyond heart rate variability: vagal regulation of allostatic systems. *Ann. N. Y. Acad. Sci.* 1088, 361–372. doi: 10.1196/annals.1366.014

Thayer, J. F., Yamamoto, S. S., and Brosschot, J. F. (2010). The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int. J. Cardiol.* 141, 122–131. doi: 10.1016/j.ijcard.2009.09.543

Turpin, G., and Siddle, D. A. (1978). Cardiac and forearm plethysmographic responses to high intensity auditory stimulation. *Biol. Psychol.* 6, 267–281. doi: 10.1016/0301-0511(78)90029-7

Williams, D. P., Thayer, J. F., and Koenig, J. (2016). Resting cardiac vagal tone predicts intraindividual reaction time variability during an attention task in a sample of young and healthy adults. *Psychophysiology* 53, 1843–1851. doi: 10.1111/psyp.12739

Zeki Al Hazzouri, A., Elfassy, T., Carnethon, M. R., Lloyd-Jones, D. M., and Yaffe, K. (2017). Heart rate variability and cognitive function in middle-age adults: the coronary artery risk development in young adults. *Am. J. Hypertens.* 31, 27–34. doi: 10.1093/ajh/hpx125

Zeki Al Hazzouri, A., Haan, M. N., Deng, Y., Neuhaus, J., and Yaffe, K. (2014). Reduced heart rate variability is associated with worse cognitive performance in elderly Mexican Americans. *Hypertension* 63, 181–187. doi: 10.1161/HYPERTENSIONAHA.113.01888

Zulli, R., Nicosia, F., Borroni, B., Agosti, C., Prometti, P., Donati, P., et al. (2005). QT dispersion and heart rate variability abnormalities in Alzheimer's disease and in mild cognitive impairment. *J. Am. Geriatr. Soc.* 53, 2135–2139. doi: 10.1111/j.1532-5415.2005.00508.x

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Autonomic Dysfunction in Preeclampsia: A Systematic Review

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Background: Preeclampsia (PE) is a major obstetric complication that leads to severe maternal and fetal morbidity. Early detection of preeclampsia can reduce the severity of complications and improve clinical outcomes. It is believed that the autonomic nervous system (ANS) is involved in the pathogenesis of PE. We aimed to review the current literature on the prevalence and nature of ANS dysfunction in women with PE and the possible prognostic value of ANS testing in the early detection of PE.

Methods: Literature search was performed using Medline (1966–2018), EMBase (1947–2018), Google Scholar (1970–2018), BIOSIS (1926–2018), Web of science (1900–2018); CINAHL (1937–2018); Cochrane Library, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Methodology Register (1999–2018). Additionally, the reference lists of articles included were screened.

Results: A total of 26 studies were included in the present review presenting data of 1,854 pregnant women. Among these women, 453 were diagnosed with PE, 93.6% (424/453) of which displayed autonomic dysfunction. ANS function was assessed by cardiovascular reflex tests ($n = 9$), heart rate variability ($n = 11$), cardiac baroreflex gain ($n = 5$), muscle sympathetic nerve activity (MSNA) ($n = 3$), and biomarkers of sympathetic activity ($n = 4$). Overall, 21 studies (80.8%) reported at least one of the following abnormalities in ANS function in women diagnosed with PE compared to healthy pregnant control women: reduced parasympathetic activity ($n = 16/21$, 76%), increased sympathetic activity ($n = 12/20$, 60%), or reduced baroreflex gain ($n = 4/5$, 80%). Some of these studies indicated that pressor and orthostatic stress test may be useful in early pregnancy to help estimate the risk of developing PE. However, autonomic function tests seem not to be able to differentiate between mild and severe PE.

Conclusions: Current evidence suggests that autonomic dysfunction is highly prevalent in pre-eclamptic women. Among autonomic functions, cardiovascular reflexes appear

to be predominantly affected, seen as reduced cardiac parasympathetic activity and elevated cardiac sympathetic activity. The diagnostic value of autonomic testing in the prediction and monitoring of autonomic failure in pre-eclamptic women remains to be determined.

Keywords: preeclampsia, autonomic nervous system modulation, sympathetic activity, parasympathetic activity, heart rate variability, baroreflex sensitivity, muscle sympathetic nerve activity

INTRODUCTION

Rationale

Preeclampsia (PE) is a complex gestational disorder, with a worldwide prevalence of 5–8% (1). Diagnostic criteria for PE have been changing over the years. A new onset hypertension (>140/90 mmHg) after 20 weeks of pregnancy in women who were normally normotensive was recently revised and updated by the American Collage of Obstetricians and Gynecologists (ACOG) to include other complications in case of absence of proteinuria (2).

PE is a major cause of maternal mortality and is regarded as a risk factor for cardiovascular mortality. PE increases the risk of premature death, ischemic and cardiovascular diseases, type 2 diabetes mellitus and hypothyroidism in mothers (3). The complications of PE extend also to the offspring with an increased risk of cardiovascular and metabolic disorders later in life (4). The exact etiology of PE remains elusive, but several theories were proposed. A noteworthy hypothesis postulated that preeclampsia originates from placental dysfunction (5). It seems likely that prohypertensive factors are released into the circulation as a response to diminished adaptive capability of the vasculature in the uteroplacental unit, placental ischemia, and reperfusion (6, 7).

The autonomic nervous system (ANS) has a prominent role in the cardiovascular system adaptation to pregnancy (8). Normal pregnancy is associated with a decrease of parasympathetic and increase of sympathetic activity at rest and upon cardiovascular reflexes stimulation which returnes to baseline after delivery. These changes maintain optimal uteroplacental blood flow (9, 10).

Most studies evaluating the autonomic nervous activity in preeclampsia showed contradicting results. This may be attributed to the fact that some of these studies were cross-sectional or, if longitudinal, compared data in pregnancy with post-partum values, only a few studies were performed before the onset of disease and none were performed before pregnancy. Moreover, most non-invasive methods show large inter-individual variability (11, 12).

Testing the Autonomic Nervous System

ANS function can be assessed by different tests and techniques. Earlier techniques were limited to some extent by being invasive which limited their routine use, which dictates the development of new, non-invasive techniques with less risk to the mother and fetus allowing incorporation into the routine clinical care in pregnancy.

The most common tests evaluate the cardiovascular reflexes in response to certain maneuvers. Examples are orthostatic stress test, deep breathing test, cold pressor test, Valsalva maneuver, head-up tilt test, isometric hand grip test, and mental stress test. These tests are non-invasive, allowing for bedside evaluation of sympathetic and parasympathetic function by experienced practioners (13).

Heart rate variability (HRV) is a widely used non-invasive clinical tool that provides a valuable measure of parasympathetic function through 24 h monitoring using a Holter device (14). The derived HRV indices are determined in two domains, time domain and frequency domain. The majority of HRV parameters indicate parasympathetic influences (15), while only low frequency (LF) power is influenced by the sympathetic nervous system (16).

Another approach to evaluate the autonomic nervous system activity is to measure the sensitivity of baroreceptors embedded in the carotid sinus and aortic arch walls. Baroreceptor reflex serves as "buffering" mechanism to control sudden fluctuations in blood pressure.

Baroreflex assessment involves simultaneous measurement of heart rate (HR) and blood pressure (BP). Spontaneous fluctuations in BP can be used or BP changes can be provoked by (i) non-invasive procedures (e.g., Valsalva maneuver, lower body negative pressure, or neck suction technique) or (ii) pharmacological agents (e.g., phenylephrine infusion) (12). Both methods rely on the detection of sequences and the regression slope of RR-interval and systolic blood pressure (RRI-SBP) plots yield the baroreflex gain (BRG). Beyond sequence technique, spectral analysis can also be used to evaluate spontaneous corresponding BP-HR changes (**Table 1**).

Another tool that provides an estimate of sympathetic activity is measuring plasma and urinary catecholamines in addition to other blood markers e.g., neuropeptide Y (17). All biomarkers of sympathetic activity share the limitation of being affected by numerous confounding factors that can make interpretation difficult (18).

A recent technique to evaluate sympathetic activity is microneurography during which the sympathetic outflow to the muscle or skin is recorded (19). Muscle sympathetic nerve activity (MSNA) describes well the cardiac sympathetic activity and can be used both for measuring baseline sympathetic activity and response to various stimuli. Its invasiveness and technically challenging nature represent the principal limitations of this method (18).

Objectives

The objective of this systematic review is to search the existing literature related to the ANS functions in pregnant women diagnosed with preeclampsia, identify the most frequently reported variables and approach their pathophysiological

TABLE 1 | Definition of ANS assessment parameters included in the review.

Parameter	Definition	Abnormality
Tools and techniques for ANS assessment		
1-TESTS OF AUTONOMIC CARDIOVASCULAR REFLEXES		
A) Orthostatic stress test		
Heart rate response to orthostasis	Heart rate response to standing up unaided following a period of lying quietly on a couch. The normal response is an immediate increase in heart rate (around the 15th beat) after standing up followed by a nadir in heart rate (around the 30th beat). The 30:15 ration (of the longest RR interval around the 30th beat to the shortest RR interval around the 15th beat) forms part of the Ewing battery of cardiovascular tests.	30:15 ratio $\leq$ 1, of baroreceptor origin, indicates the parasympathetic function
Systolic blood pressure response to orthostasis	Systolic blood pressure response to standing up unaided following a period of lying quietly on a couch. The postural drop in systolic blood pressure forms part of the Ewing's battery of cardiovascular tests	A decrease in systolic blood pressure $\geq$20 mmHg indicates sympathetic dysfunction
B) Deep breathing test		
Heart rate variation to deep breathing	Heart rate variation to deep breathing at a rate of 6 breaths per min. The differences between the average of the largest accelerations during inspiration and the largest decelerations during exhalation are calculated. It forms part of the Ewing's battery of cardiovascular tests	HR difference $\leq$10 characterizes the parasympathetic activity
C) Cold pressor test		
Blood pressure response to cold pressor test	Blood pressure response to immersion of hand in a container of cold water for 1–3 min. The diastolic blood pressure response is normally $\geq$ 15 mmHg.	Diminished responses indicate sympathetic dysfunction and increased responses indicate exaggerated sympathoexcitation
2- ANALYSIS OF HEART RATE VARIABILITY (HRV)		
RMSSD	The square root of the mean squared differences of successive normal inter-beat (NN) intervals. Time domain estimate of short-term variation of HRV	Reduced values indicate parasympathetic dysfunction
NN50	The number of differences in consecutive NN intervals that are longer than 50 ms. Time domain measure.	Reduced values indicate parasympathetic dysfunction
pNN50%	NN50 as a percentage of the total number of NN intervals. Time domain measure	Reduced values indicate parasympathetic dysfunction
SDNN	The standard deviation of all NN intervals. An estimate of overall HRV. Time domain measure	Reduced values indicate parasympathetic dysfunction
SDANN	The standard deviation of the average NN intervals calculated over successive l 5-min segments of the entire recording. Time domain estimate of long-term variation in HRV	Reduced values indicate parasympathetic dysfunction
SDSD	The standard deviation of differences between adjacent NN intervals. Time domain measure	Reduced values indicate parasympathetic dysfunction
HF power	High-frequency (0.15–0.4 Hz) power of RR interval. Frequency domain measure	Reduced levels indicate reduced parasympathetic activity
SD 1	The standard deviation of the Poincare plot (non-linear technique). Short-term HRV parameter	Reduced levels indicate reduced heart rate variability
Respiratory sinus arrhythmia	Rhythmical fluctuations in heart rate periods during inspiration (acceleration) and expiration (deceleration)	Reduced respiratory sinus arrhythmia represents reduced parasympathetic activity
LF power	Low-frequency power of RR interval in the range 0.04–0.15 Hz. Frequency domain measure indicating mainly sympathetic activity (also parasympathetic component). to a smaller extent	Increased levels indicate heightened sympathetic activity
LF/HF ratio	The ratio of low-frequency/high-frequency power of RR intervals. Frequency domain measure of sympatho-parasympathetic balance	Increased levels indicate predominantly heightened sympathetic activity
3-MICRONEUROGRAPHY		
Muscle sympathetic nerve activity	Intra-neural recordings of muscle sympathetic nerve activity (MSNA) using tungsten microelectrodes inserted percutaneously into a peripheral nerve (typically peroneal nerve) allow direct measurement of vasoconstrictor sympathetic outflow	Increased levels indicate sympathetic over-activity
4- BIOMARKERS OF SYMPATHETIC ACTIVITY		
a) Catecholamines	Catecholamines such as epinephrine, norepinephrine, and their metabolites detected in the plasma or urine (24-h collection) may represent sympathetic activity. Confounding factors include medications, diurnal variations, and concomitant diseases	Increased levels may indicate sympathetic over-activity

(Continued)

TABLE 1 | Continued

Parameter	Definition	Abnormality
b) Plasma neuropeptide Y	Peripheral marker peptide released with norepinephrine following sympathetic activation	Increased levels may indicate sympathetic over-activity
5- BAROREFLEX SENSITIVITY TESTING TECHNIQUES		
a) Sequence technique		
Regression slope of SBP—RR interval slopes	Blood pressure and RR interval are recorded simultaneously at rest. sequences of 3 or more consecutive beats characterized by a progressive increase or decrease in BP, which results in lengthening or shortening of the RR interval (consecutively) are identified	The reduced slope indicates impaired cardiac cardiac baroreflex gain
b) Oxford technique		
Regression slope of SBP and RR interval or heart rate	Phenylephrine (alpha-1 agonist) causes an increase in blood pressure, which results in a baroreflex-mediated slowing of the heart rate	The reduced slope indicates impaired cardiac baroreflex sensitivity
c) Spectral analysis		
a-index	Spectral analysis of the R-R interval and arterial sytolic blood pressure Computes the gain in the relationship between SAP and RR interval during spontaneous oscillations. The gain in the mid frequency band (0.07–0.14 Hz) between these two signals represents baroreflex gain	Reduced value indicates impaired cardiac baroreflex gain

significance. The greater aim is to contribute to forming a basis for the identification of the most useful tools to detect and monitor autonomic dysfunction in pre-eclamptic women.

METHODS

Study Design

The present systematic review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (20). Inclusion criteria were observational studies including pregnant women currently diagnosed with preeclampsia or at increased risk of PE compared to a healthy pregnant control group. Animal studies, studies having no control arm and case report studies were excluded.

Participants, Interventions, Comparators

Studies in pregnant women diagnosed with preeclampsia of any ethnicity or pregnant women at increased risk of PE due to having a history of PE in a preceding pregnancy were eligible for inclusion.

We excluded studies in women with eclampsia, pre-existing medical disorders like diabetes mellitus, metabolic syndrome, cardiac diseases, renal disease, thyrotoxycosis and chronic hypertension disease, fetal and maternal complications, renal disease, HELLP (hemolysis, elevated liver function, and low platelets) syndrome, diabetes mellitus, hepatic disease, infections, and autoimmune diseases.

Study interventions included techniques used to assess ANS function including such as clinical cardiovascular reflex tests, measurement of plasma and urine level of sympathetic activity biomarkers, heart rate variability testing, baroreflex sensitivity, and microneurography. Comparator group constitutes normotensive pregnant women. Criteria for inclusion were healthy, normotensive women with appropriately grown fetuses, normal blood pressure throughout pregnancy (BP $<$ 140/90 mm Hg), gave birth to healthy children, uncomplicated pregnancy, matched at gestational age to the PE group. Pregnant women having histories of hypertension, diabetes, cardiovascular or renal disease before pregnancy; taking antihypertensive medication or any medications other than iron supplementation were excluded.

Systematic Review Protocol

Literature search was performed by using Medline (1966–2018), Web of science (1900–2018); CINAHL (1937–2018), EMBase (1947–2018); Google Scholar (1970–2018), BIOSIS (1926–2018); the Cochrane Library, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Methodology Register (1999–2018). Additionally, the reference lists of the selected studies were also screened. No restrictions on language or date were applied during the literature research. The date of the last search was set on 1 August 2018. The search strategy included the search term "preeclampsia" in combination with each of the following terms; "autonomic," "sympathetic," "parasympathetic," "vagal," "heart rate variability," "baroreflex," "catecholamine," "epinephrine," "norepinephrine," "adrenaline," "noradrenaline," "Valsalva," "hand grip," "cold pressor," "orthostasis," and "baroreceptor gain" and is schematically presented in the PRISMA flowchart (**Figure 1**).

Two authors (Yousif D and Bellos I) independently screened all articles for eligibility, potential disagreements were resolved by the consensus among all authors.

Data Sources, Studies Selection, and Data Extraction

The studies were selected in three consecutive steps. First, the titles and abstracts of all electronic articles were screened to assess their eligibility according to the inclusion criteria. Second, the selected articles were retrieved as full texts. In the third stage, all observational studies that evaluated autonomic functionality in women with preeclampsia and healthy normotensive pregnant women were included. Animal studies, case reports, review articles as well as conference abstracts were excluded. Two

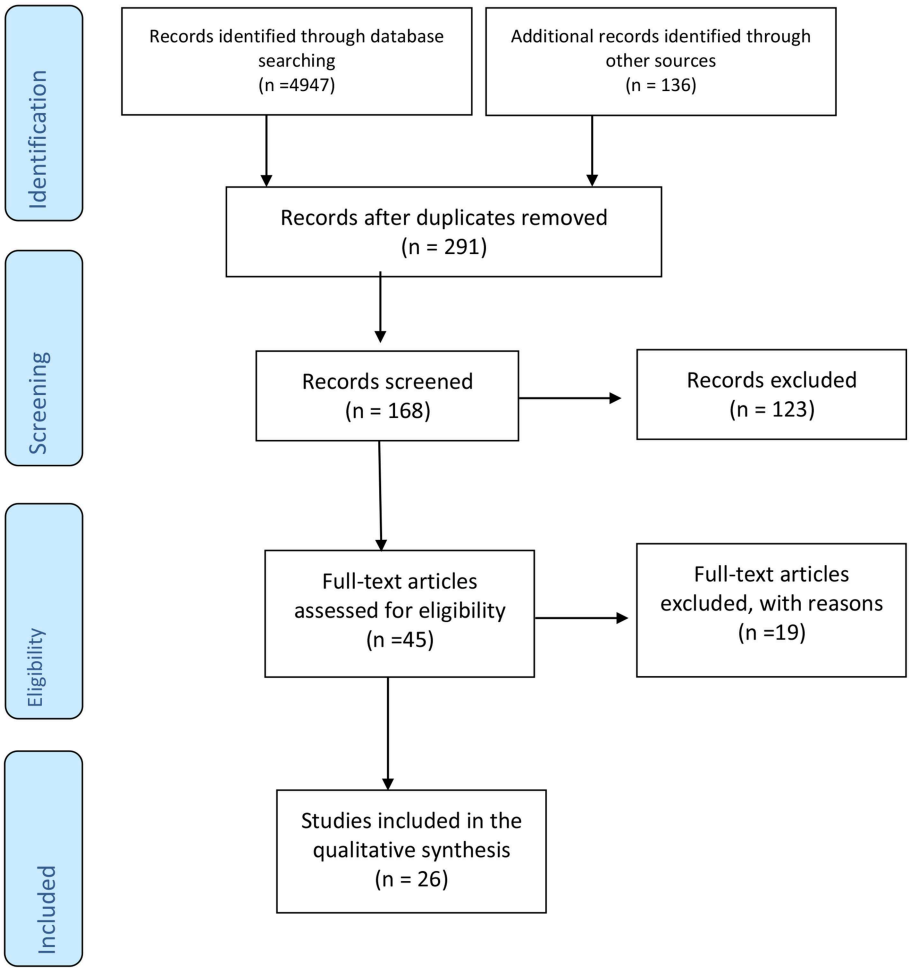

FIGURE 1 | PRISMA diagram showing systematic search process, which started with 4,947 articles identified through searching Medline, EMBase, BIOSIS, Web of Science, CINAHL, and the entire Cochrane Library in addition to 136 articles retrieved from the references list of the selected studies. Duplicate articles were excluded. From 168 articles screened, 123 articles were excluded because they didn't meet the inclusion criteria (animal studies, letter to the editor, case reports). The number of full articles assessed for eligibility was 45, of which 19 articles were found not- eligible due to lacking a PE group, lacking a healthy control group or including non pregnant women with history of PE. Finally, 26 studies were found eligible for inclusion in our review.

reviewers "Yousif D and Bellos I" independently extracted data from the appropriate trials using a pre-designed standard form. The retrieved data comprised: author names, year of publication, study design, exclusion criteria, number of patients, maternal age, gestational age, parity, gravidity, type of autonomic function assessment, catecholamine plasma concentration (adrenaline, noradrenaline, dopamine), neuropeptide Y level, time and frequency indices for heart rate variability, heart rate, and blood pressure variability in response to cardiovascular reflex tests (30:15 ratio, Valsalva ratio), MSNA and baroreceptor sensitivity index.

Data Analysis

Findings from the eligible studies were aggregated to produce a qualitative summary structured around the study design, sample size, type and outcome of intervention and population characteristics.

RESULTS

Study Selection and Characteristics

Out of 45 eligible full-text articles, 26 observational studies were finally included in the present review, 22 were cross-sectional studies and 4 were longitudinal studies.

Nineteen studies were excluded after reading the full text based on various reasons: 13 studies included other types of pregnancy-induced hypertension but not preeclampsia. Two studies did not include a control arm of normotensive healthy pregnant women. Four studies included women who were formerly diagnosed with preeclampsia but not pregnant during the study.

One thousand eight hundred fifty-four was the total number of women included. Among them, 453 subjects were diagnosed with PE, 1,104 subjects were healthy pregnant controls, 150 subjects were included as a normotensive non-pregnant group,

and 147 subjects represented other hypertensive pregnancy disorders (chronic hypertensive pregnancy, pregnancy-induced hypertension PIH, and gestational hypertension) in 8 studies.

The methodological characteristics (study design, exclusion criteria, examined test, gestational age, maternal age) and NOS (new castle ottawa scale) scores are described in **Table 2**.

The definition of Preeclampsia was inconsistent between studies. In 10 studies, PE was defined according to the International Society for the Study of Hypertension in Pregnancy which was "evidence of elevated blood pressure (evidence of antihypertensive drug treatment and/or evidence of systolic blood pressure 140 mmHg and/or diastolic blood pressure 90 mmHg during pregnancy on two or more occasions) and detection of proteinuria defined as 0.3 g/day or greater in a 24-h specimen or 0.3 g/l (1. dipstick) or greater in a random urine determination" (47).

In three studies, PE was defined according to the recommendations of National High Blood Pressure Education Program Working as "proteinuria > 300 mg per 24 h, no history of hypertension, cardiovascular, or renal disease, and blood pressure values exceeding 140/90 mmHg after the 20th week of gestation, confirmed by two consecutive readings, with blood pressure reverting to normal within 2 months after delivery" (48).

In three other studies, PE was defined according to the clinical criteria established by The American College of Obstetricians and Gynecologist as the "occurrence of hypertension defined as systolic blood presseure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg after 20 weeks of gestation in woman who is normotensive before, and proteinuria defined as presence of 300 mg or more of protein in 24 h urine sample or > 2+ on dipstick" (49).

Diagnostic criteria for PE was not reported in two studies (24, 46).

Three studies have included severe PE patients diagnosed according to different criteria. In one study, severe PE was defined according to a diastolic blood pressure of more than 110 mmHg (27). While in another study, severe PE was defined as "when two or more of the following findings evolved after 24 weeks of gestation, systolic blood pressure of at least 160 mmHg or diastolic blood pressure at least 110 mmHg on two or more occasions, separated at least a day and measured while the patient was on bed-rest, proteinuria of at least 5 g/24 h and subjective symptoms of headache, dizziness, visual disturbances reported by the mother" (38).

A third study diagnosed severe PE as having "blood pressure higher than 160 mmHg systolic and 110 mmHg diastolic or (and) thrombocytopenia, serum creatinine more than 1.1 mg/L, elevated blood concentration of liver transaminases to twice normal concentration, pulmonary edema, cerebral, or visual disturbances" (26).

Exclusion criteria for PE patients in 58% of the studies were a history of chronic hypertension, diabetes mellitus, any cardiac/renal disease, liver/thyroid disease, and current antihypertensive treatment. Multiple pregnancies were exclusion criteria in 23% of studies. Other exclusion criteria in 19 % of the studies were: pregnancy loss (delivery before 28 weeks), intrauterine growth retardation, HELLP syndrome, age < 16 years, premature rupture of membranes, Hirschsprung's disease, diabetic neuropathy, a recent history of diarrhea and vomiting and hematocrit < 32%.

It is important to note that in 88.5% of the studies, the maternal age was comparable between the PE group and the healthy pregnant control group and in 77% of the studies, the PE group was matched for gestational age with a healthy pregnant control group. The outcomes of each study included in the review are presented in **Table 3**.

Synthesized Findings

Each study was classified according to the type of autonomic test performed and the normality of the PE group response in comparison to the control group into either normal or abnormal.

A total of 33 autonomic tests was performed in the included studies. Most of the studies (78%) used one ANS assessment test, 19% of the studies used two assessment tests (30, 31, 38, 42, 43), and one study used three types of tests (25).

Table 4 summarizes the number and the outcome for each ANS test.

Heart rate variability was analyzed in 11 studies, either alone in six studies or in combination with one or two tests in five studies. Both time and frequency domains were computed in seven studies (25–27, 30, 36, 42, 43), while in one study only time domain parameters were shown (29). Three studies reported only frequency domain indices (28, 34, 35).

HRV tests showed significant ANS dysfunction presented as elevated sympathetic activity and suppressed parasympathetic activity in eight studies, while three studies showed no significant difference between the PE group and the control group (28, 36, 43).

One prospective cohort study evaluated the predictive value of spectral analysis of heart rate and blood pressure for hypertensive diseases of pregnancy at 28 weeks of pregnancy. Although useful for pregnancy-induced hypertension; it was not able to detect women who developed PE afterward in pregnancy (28).

Two studies had further categorized PE patients into mild and severe based on diastolic blood pressure of <110, or >110 mmHg, respectively, the results of which were contradicting. One study did not show any significant difference comparing time and frequency domain measurements between mild and severe PE (27). On the other hand, a study by Lakhno (26) showed that mean sympathovagal balance (LF/HF) increased gradually in association with the progredient severity of PE even when subjects were on antihypertensive medications.

Additionally, they investigated correlations between the maternal and fetal time domain and noticed a loss of fetal-maternal hemodynamic coupling in case of severe PE vs. a positive weak correlation in case of mild PE (26).

Orthostatic stress test, cold pressor test, and deep breathing test represented the cardiovascular reflex test procedures performed in nine studies.

Orthostatic stress test was performed in six studies, the results showed consistently sympathetic dominance and parasympathetic withdrawal in PE patients compared to the normotensive control group (25, 30–32, 37, 38, 50).

TABLE 2 | Characteristics of studies included in the review.

References	Study design	Exclusion criteria	Examined test	Maternal age (years)		Gestational age (weeks)		NOS score
				PE	Control	PE	Control	
BIOMARKERS								
Egerman et al. (21)	Case-control	Chronic hypertension	Serum neuropeptide Y	23.7 ± 1.0	22.1 ± 1.1	35.7 ± 1.4	36.9 ± 1.0	9
Manyonda et al. (22)	Case-control	Multigravidity	Cord blood noradrenaline	28.5 (21–34)	28.4 (19–39)	31.6 (28–37)	36 (28–42.7)*	8
Øian et al. (23)	Case-control	History of hypertension, chronic kidney disease	Arterial/venous epinephrine, norepinephrine, dopamine	28 ± 2	27 ± 1	32.5 ± 1.3	33.5 ± 1.3	8
Beilin et al. (24)	Prospective	NR	Plasma renin activity, angiotensin II, norepinephrine, epinephrine	NR		NR		7
CARDIOVASCULAR REFLEX TESTS								
Chaswal et al. (25)	Case-control	NR	Heart rate variability, deep breathing test, orthostatic stress test	26.88 ± 3.52	26.35 ± 2.53	NR		8
Lakhno (26)	Case-control	Multiple pregnancies, eclampsia, history of hypertension diabetes mellitus, any cardiac/renal disease, thyrotoxicosis	24-h Holter heart rate variability	25.6 ± 6.8	26.5 ± 4.1	36.8 ± 2.2	37.1 ± 3.6	8
Musa et al. (27)	Case-control	History of hypertension, diabetes mellitus, renal disease, liver/thyroid disease	Heart rate variability	30.6 ± 6	30 ± 6.2	33.8 ± 4.3	32.9 ± 4	8
Flood et al. (28)	Prospective	Pregnancy loss/delivery before 28 weeks	Heart rate variability	27.9 ± 6.3	26.4 ± 5.1	28		6
Yokuşoglu et al. (29)	Case-control	Multiple pregnancies, intrauterine growth restriction, HELLP syndrome	24-h Holter heart rate variability	29 ± 4	27 ± 4	33 ± 3	39 ± 6*	9
Swansburg et al. (30)	Case-control	Age < 16 years, multiple pregnancies, premature rupture of membranes, Hirschsprung's disease	Heart rate variability, orthostatic stress test, fetal heart rate, spontaneous Baroreflex sensitivity	28.3 ± 6.6	29.9 ± 4.7	37 ± 2.6	35.8 ± 2	7
Rang et al. (31)	Prospective	Intrauterine growth restriction without hypertension	Orthostatic stress test, paced breathing test	28.6 ± 2.3	29.9 ± 4	Pre-pregnancy, 6, 8, 12, 16, 20, 32, 12 postpartum		8
Miyake et al. (32)	Case-control	Mild preeclampsia	Orthostatic stress test	29.9 ± 3.4	29.9 ± 4.3	34.6 ± 3.6	36.1 ± 2.2	7

(Continued)

TABLE 2 | Continued

References	Study design	Exclusion criteria	Examined test	Maternal age (years)		Gestational age (weeks)		NOS score
				PE	Control	PE	Control	
Woisetschläger et al. (33)	Prospective	History of hypertension, current antihypertensive treatment, fever, diabetes mellitus	Cold pressor test	28 ± 6	27 ± 5	17.3 ± 1.8	18.5 ± 2.2	9
Yang et al. (34)	Case-control	Diabetic neuropathy, any cardiac disease, any drug intake	Heart rate variability	30 ± 1	28 ± 1	35 ± 1	34 ± 1	8
Lewinsky and Riskin-Mashiah (35)	Case-control	Diabetes mellitus, any drug intake except iron supplementation	Heart rate variability, supine pressor test	24 ± 5	25 ± 4	35 ± 4	33 ± 3	6
Eneroth and Storck (36)	Case-control	History of hypertension, diabetes mellitus, renal disease, any drug intake	Heart rate variability	NR		33.4 ± 1.6	33.0 ± 2	8
Ahmad et al. (37)	Cross-sectional	Recent history of diarrhea and vomiting, hematocrit <32%	Orthostatic stress test	24.8 ± 2	*1st trimester:* 26.4 ± 3.16 *2nd trimester:* 29 ± 2.3 *3rd trimester:* 28. ± 2.4	32 ± 1.9	*1st trimester:* 9.8 ± 3.16 *2nd trimester:* 20.7 ± 1.68 *3rd trimester:* 33.5 ± 2.35	8
Airaksinen et al. (38)	Case-control	Any cardiovascular or renal disease, diabetes mellitus	Deep breathing test, orthostatic stress	28 (17–37)	28 (23–38)	35 (32–39)	34 (32–38)	7
MUSCLE SYMPATHETIC NERVE ACTIVITY								
Fischer et al. (39)	Prospective	History of hypertension, cardiac/renal disease	Muscle sympathetic nerve activity, forearm blood flow, blood pressure after forearm occlusion	31.7 ± 3.9		22 ± 4, 33 ± 5,and 26 ± 6 postpartum		8
Greenwood et al. (40)	Case-control	Secondary hypertension, diabetes mellitus, malignancy, neurologic dysfunction	Muscle sympathetic nerve activity	27.5 ± 1.5	28 ± 1.2	35 ± 1.1	35 ± 0.6	8
Schobel et al. (41)	Case-control	History of hypertension, cardiac/renal disease	Muscle sympathetic nerve activity	26 ± 1	26 ± 1	33 ± 1	32 ± 1	7
BAROREFLEX SENSITIVITY								
Weber et al. (42)	Case-control	Diabetes mellitus, cardiac/renal disease, multiple pregnancy	Heart rate variability, baroreflex sensitivity	30.3 ± 6.3	31.9 ± 5.0	33 ± 3	33 ± 3	9
Faber et al. (43)	Cross-sectional	NR	Heart rate and blood pressure variability, baroreflex sensitivity	27 (22–31)	28 (24–31)	32 (30–36)	35 (32–37)	8

(Continued)

TABLE 2 | Continued

References	Study design	Exclusion criteria	Examined test	Maternal age (years)		Gestational age (weeks)		NOS score
				PE	Control	PE	Control	
Silver et al. (44)	Case-control	History of hypertension, diabetes mellitus, multiple pregnancy, vasoactive medication, or intravenous hydration	Vagal baroreflex gain	25.4 ± 4.5	25.2 ± 4.7	34.1 ± 2.9	34.0 ± 3.5	9
Molino et al. (45)	Case-control	History of hypertension, cardiac/renal disease	Baroreflex gain, interbeat interval	32 (29–33)	31 (30–34)	35.0 (32.0–36.0)	32.5 (28.5–36.5)	7
Seligman (46)	Case-control	NR	Baroreflex sensitivity-phenylephrine or angiotensin II infusion			NR		3

*The table shows the study design, the exclusion criteria, the examined ANS test, maternal age (years), gestational age (weeks), and the risk of bias scores by Newcastle Ottawa score (NOS) for each study. Data that was not reported in the studies were denoted NR. *:statistically significant difference between the two groups.*

One prospective study aimed to evaluate the value of blood pressure response to orthostatic challenge for early prediction of women who develop preeclampsia in the second half of pregnancy. Responses to orthostatic stress were recorded at 8-time points, before pregnancy, at first, second, and third trimester and 15 weeks after delivery. Results showed that, for women who developed PE later in pregnancy, significantly higher blood pressure drop to orthostatic stress before pregnancy, during the first, and the second trimester when compared to women with uncomplicated pregnancy. This results support the hypothesis that sympathetic hyperactivity develops early in pregnancy before the clinical presentation of PE and may play a role in the (31).

Cold pressor test was performed in one prospective cohort study, as one of the cardiovascular reflex test procedure, early in pregnancy between 16 and 20 gestational weeks (33). Results showed a significant increase in sympathetic activity in subjects who developed PE later in pregnancy in comparison to subjects with uncomplicated pregnancy which may suggest its value as an early detection tool for the risk of PE. This can be explained by an increased vasoconstrictive response to a physiological stimulus in women with preeclampsia as a sign of increased vascular reactivity before clinical manifestation of the disease.

Deep breathing test was performed in three studies, all showed reduced parasympathetic activity in the PE group (25, 38, 51).

It is worth mentioning that the results of the studies that showed abnormal ANS function in PE patients were consistent regarding the pattern of the ANS dysfunction, which was inhibition of the parasympathetic tone and/or increased sympathetic activity, except for one study which reported that PE patients exhibited a significant increase in the time domain parameters of heart rate variability and baroreflex sensitivity compared to the control group (42). This controversy could be explained by subject selection. Weber et al had further classified patients in the PE group according to the onset of diagnosis into early-onset preeclampsia (PE diagnosed at $< 34+0$ weeks of gestation) and late-onset preeclampsia (PE diagnosed at $\geq 34+0$ weeks of gestation). Amelioration of autonomic function was observed only in patients with late-onset PE.

Biomarkers of sympathetic activity were used to assess ANS in four studies. Results from these studies were controversial. In one of them, neuropeptide Y plasma level was determined and no significant difference was found between the PE group and healthy control group (21). Three studies measured catecholamine (adrenaline, noradrenaline) blood levels. Two studies reported significantly increased catecholamine levels in the PE group when compared to the healthy control group (22, 23).

Kjeldsen et al. further compared arterial and venous catecholamine levels. His results showed that both arterial and venous levels of adrenaline and dopamine were significantly elevated where only arterial but not venous noradrenaline levels were significantly increased in the PE group (23). A small study showed no significant difference in the biomarkers of ANS activity in the PE group in comparison to the healthy pregnant control group (24). Beilin et al. evaluated the diurnal pattern of catecholamine (adrenaline and noradrenaline) and pressor hormones (renin and angiotensin 2) in normal and hypertensive pregnancies. Results of this study showed that levels from the 2 pressor hormones fell progressively in all groups and were lower in PE group, the diurnal pattern of noradrenaline with lower levels at midnight was not observed in PE while plasma adrenaline level showed no significant difference between PE and healthy control group.

TABLE 3 | List of autonomic measures for studies included in the review.

References	*n* (PE/control)	Autonomic measure		
			PE	Control
BIOMARKERS				
Egerman et al. (21)	12/12	NPY (ng/mL)	33.3 ± 3.6	32.2 ± 3.5
Manyonda et al. (22)	12/26	Venous NE (ng/ml)	1.93 (0.20)*	1.15 (0.12)
		Venous EPI (ng/ml)	0.25 (0.035)*	0.23 (0.033)
		Cord NE venous plasma (ng/ml)	1.94 (0.26)*	1.16 (0.09)
		Cord NE arterial (ng/ml)	2.95 (0.97)*	1.8 (0.18)
Øian et al. (23)	13/13	Arterial EPI (ng/ml)	125 (24)*	43 (5)
		Arterial EPI (ng/ml)	337 (39)*	243 (19)
		Arterial dopamine (ng/ml)	214 (77)*	32 (6)
		venous NE (ng/ml)	67 (10)*	37 (6)
		venous NE (ng/ml)	299 (38)	256 (24)
		venous dopamine (ng/ml)	73 (11)*	41 (7)
Beilin et al. (24)	8/10	Plasma renin activity (ng/ml/h)	2.22*	7.55 (10)
		Plasma angiotensin 2	28.36*	57.9
		Free plasma EPI	0.028*	0.024
		Free plasma NE	0.308	0.229
CARDIOVASCULAR REFLEX TESTS				
Chaswal et al. (25)	40/40	30:15 (OS)	1.13 (0.11)	1.22 (0.11)*
		HR (DB) (bpm)	13.48 (6.12)	22.6 (8.18)*
		SDNN, ms	26.17 (2.7)	34.98 (1.1)*
		RMSSD, ms	18.04 (2.33)	34.68 (2.62)*
		LF, ms^2	125.56 (19.36)	192.9 (19.7)*
		LF/HF	2.9 (2.4)*	1.7 (1.5)
		HF, ms^2	132.28 (37.8)	447.24 (63)*
Lakhno (26)	76/30	SDNN, ms	92.99 (10)*	111.8 (14.1)
		RMSSD, ms	19.5 (5.5)*	41.6 (8.5)
		LF, ms^2	271 (51.6)*	349.5 ± 42.6
		HF, ms^2	90.85 (17.5)*	375.4 ± 56.1
		LF/HF	3.35 (0.85)*	0.9 ± 0.3
Musa et al. (27)	60/60	LF Norm, ms^2	49.80 (16.25)*	44.55 (19.15)
		Ln LF/HF	0.04 (0.68)*	−0.28 (0.91)
		HF norm, ms^2	45.08 (15.29)*	55.87 (19.56)
		Ln LF	4.01 (1.58)*	3.49 (1.23)
Flood et al. (28)	27/332	HF-HRV, geometric mean	363 (197, 668)	358 (314, 408)
		LF-BPV (SBP), geometric mean (95% CI)	8.9 (7.0, 11.3)	9.7 (9.1, 10.3)
		LF-BPV (DBP), geometric mean (95% CI)	4.3 (3.5, 5.3)	4.1 (3.9, 4.4)
Yokuşoglu et al. (29)	34/29	SDNN, ms	109 ± 52*	130 ± 56
		SDANN, ms	80 ± 33*	108 ± 37
		HRV-triangular index	27 ± 9*	32 ± 10
Swansburg et al. (30)	9/18	PNS(HF/TP)	0.22 (0.15)*	0.11 (0.14)
		SNS(HF/LF) lying to standing	1.6–4.5*	1.9–2.8
Rang et al. (31)	8/30	Phase difference in the supine position LF	8 week = 77 (18)*	64 (15)
			12 week =77 (22)*	61 (19)
			20 week = 79 (37)*	63 (30)
		OS- Delta MAP-, mmhg	16 week = 26 (18–33)*	15 (10–17)
			20 week = 30 (24–37)*	12 (10–20)
Miyake et al. (32)	17/138	TPR (%) postural change	45 (4)*	18 (10)
		SBP (%) postural change	−7.5 (0.8)*	−5 (0.5)

(Continued)

TABLE 3 | Continued

References	*n* (PE/control)	Autonomic measure		
			PE	**Control**
		HF (%) postural change	−50 (19)*	48 (20)
		LF/HF (%) postural change	390 (210)*	80 (20)
Woisetschläger et al. (33)	10/113	CP-SBP, mmHg	14.2 (5.5)*	8.5 (7.2)
		CP-DBP, mmHg	7.3 (4.9)*	3.9 (4.7)
Yang et al. (34)	17/17	Ln (LF/HF)	1 (1.3)*	0.3 (0.5)
		LF% (nu)	60 (65)*	55 (60)
		Ln HF, ms^2	3.57 (0.4)	5.79 (0.22)*
Lewinsky and Riskin-Mashiah (35)	15/25	VLF, s^2/Hz	288 (214)/556 (322)*	281 (225)/278 (194)
		HF, s^2/Hz	78 (79)/78 (78)	52 (52)/49(59)
		TP, s^2/Hz	544 (322)/878 (397)*	472 (341)/475 (291)
Eneroth and Storck (36)	15/15	Average R-R interval (24h), ms	770 ± 133*	690 ± 50
		LF power (24 h), ms	925 ± 362	839 ± 288
		HF power (24 h)	597 ± 742	655 ± 337
		Average R-R interval, ms (daytime)	736 ± 132*	642 ± 47
		Average R-R interval, ms (night time)	824 ± 159	789 ± 77
Ahmad et al. (37)	• 16/78 • 1st trimester = 25 • 2nd trimester = 25 • 3rd trimester = 28	Rate of HR change (bpm)	0.83 (0.16)*	1st = 0.94 (0.13) 2nd = 0.9 (0.14) 3rd = 0.72 (0.13)*
		Lying BP, mmHg	135/90 ± 13/6	3rd:105/64 ± 15/11
		Standing BP, mmHg	146/100 ± 17/14	111/70 ± 12/6
		Delta HR, bpm	12 (3)*	3rd = 16 (3)
Airaksinen et al. (38)	14/11	OS-30:15 ratio	1.15 (0.17)*	1.39 (0.14)
		DB-HR, bpm	12 (4)*	18 (6)
		SBP standing up, mmHg	−11 (32)	4 (12)
Fischer et al. (39)	6/16	MSNA (burst/min)	M1: 21 (9)*, M2: 29 (14)* vs. postpartum M3: 9 (5)	
		Gestational MSNA, burst/min	M1: 21 (5), M2: 27 (6), M3: 7 (4)	M1: 21 (11), M2: 30 (16), M3: 9 (6)
Greenwood et al. (40)	11/11	s-MSNA (impulses/100 beats)	PE = 62 (10.8)*	39 (7.7), PIH: 128 (23.4)*
		MSNA (bursts/100 beats)	PE = 51 (7.1)	28 (2.3)*, PIH:62 (3.8)*
Schobel et al. (41)	9/8	SNA, bursts per min	33 (3)*	10 (1)
		MSNA, burst/min	6 PE –During preg: 36 (4)* vs. after delivery: 13 (2)*	
Weber et al. (42)	24/72 Early onset: 10/30 Late onset: 14/42	SDNN, ms	46.5 ± 17.4* late 33.2 ± 10.7 early 41.0 ± 16.1 all	37.1 ± 12.2 late 35.2 ± 9.9 early 36.5 ± 11.2 all
		RMSSD, ms	33.3 ± 18.9* late 17.7 ± 9.5 early 26.8 ± 17.3*all	21.0 ± 8.9 late 19.9 ± 10.3 early 20.5 ± 9.4 all

(Continued)

TABLE 3 | Continued

References	*n* (PE/control)	Autonomic measure		
			PE	Control
		HF, ms^2	5.58 ± 0.98 *late	4.87 ± 0.93 late
			4.44 ± 1.18 early	4.81 ± 0.96 early
			5.11 ± 1.19 all	4.84 ± 0.94 all
		BRS, ms/mmHg	13.6 ± 7.0* late	10.4 ± 3.8 late
			9.1 ± 4.4 early	10.3 ± 4.9 early
			11.7 ± 6.4 all	10.4 ± 4.2 all
Faber et al. (43)	44/80	BPV: SDNN, ms	9 (8–10)*	8 (7–9)
		BPV: RMSSD, ms	2.5 (2.1–2.8)*	3.1 (2.8–3.6)
		brady_2.5-5, NU	16 (8–25)*	11 (6–18)
		tachy_slope, ms/mmHg	6.9 (5.7–9.6)	6.4 (4.9–9.3)
		HRV: SDNN, ms	43 (29–51)	44 (31–53)
		HRV: RMSSD, ms	18 (12–28)	16 (10–24)
		HRV: LF, ms^2	0.15 (0.10–0.20)	0.16 (0.07–0.25)
Silver et al. (44)	20/20	Baroreflex gain: VM- (ms/mmHg)	6.6 ± 2.5*	10.1 ± 3.2
		DB-BP (ms/mm Hg)	10.0 ± 5.9	14.1 ± 6.9
		Spontaneous HRV (ms/mmHg)	7.2 ± 2.6*	10.8 ± 4.1
Molino et al. (45)	9/8	BRG index (a-index) ms/mmHg	At rest: 5.60 (5.25–6.90)*	At rest: 7.98 (6.71–9.93)*
			Standing: 4.07 (3.70–6.92)	Standing: 5.70 (5.24–7.18)
		IBI variability		
		LF (NU)	At rest: 0.62 (0.47–0.69)	At rest: 0.48 (0.35–0.76)
		HF (NU)	Standing: 0.56 (0.48–0.66)	Standing: 0.62 (0.47–0.76)
Seligman (46)		BRS, ms/mmHg	3.6*	10.3 (19–9)

Data extracted include author name, the sample size for PE group and healthy pregnant control group and the results of ANS assessments performed in each study.
*Values denoted by *represent statistical significance. 30:15, ratio of the longest inter-beat (RR) interval around the 30th beat to the shortest RR interval around the 15th beat; BP, blood pressure; BPV, blood pressure variability; brady_2.5-5, Number of brady cardiac baroreflex fluctuations with a slope <50 ms/mmHg; BRG, baroreflex gain (ms/mmHg); BRS, baroreceptor sensitivity; CP, cold pressor test; DB, deep breathing test; DBP, diastolic blood pressure; EPI, epinephrine; HF, high-frequency power in the range 0.15–0.40 Hz; HR, heart rate; HRV, heart rate variability; HRV-triangular index, integral of the density of the RR interval histogram divided by its height; IBI, interbeat interval; LF, low-frequency power in the range 0.04–0.15 Hz; LF/HF ratio, low frequency to high-frequency ratio; MAP, mean arterial pressure; MSNA, Muscle sympathetic nerve activity; NE, norepinephrine; NN, inter-beat interval; NPY, neuropeptide Y; NU, normalized units; OS, orthostatic stress test; PNS (HF/TP), parasympathetic indicator; RMSSD, square root of the mean of the sum of the squares of difference between adjacent NN intervals; RR interval, the time between two R-peak of ECG heart-beat waveform; SBP, systolic blood pressure; SDANN, standard deviation of the averages of NN intervals in all 5-min segments of the entire recording; SDNN, standard deviation of all NN intervals; SNA, sympathetic nerve activity; SNS, sympathetic indicator; tachy_slope, slope of the regression line between all tachycardiac baroreflex fluctuations; TPR, total peripheral resistance; TP, total power; VLF, very low frequency; VM, Valsalva's maneuver.*:statistically significant difference.*

MSNA was measured in three studies, two of which showed sympathetic hyperactivity in PE compared to healthy pregnant controls (40, 52). A small prospective longitudinal study evaluated whether MSNA can predict women who develop PE later in pregnancy. In this study MSNA was recorded at three-time points (twice during pregnancy and one time postpartum) in healthy pregnant women at increased risk of developing PE (39). Results from Fischer et al showed significant increased MSNA during normal pregnancy compared to postpartum values but did not show a significant difference between MSNA values in women who developed PE later in pregnancy and women who had a normal pregnancy. This showed that MSNA has no value in predicting the risk of PE in high-risk patients.

Cardiac baroreflex gain was assessed in five studies. Three studies showed that PE women exhibit significant reduction in baroreflex gain (44–46).

Techniques used for determination of BRG were variable. Silver et al. and Molino et al. used cross-spectral analysis of parallel spontaneous heart rate and blood pressure changes to measure BRG. BRG was computed as alpha index, i.e., "the square root of the ratio of the powers of interbeat interval in the low-frequency range to corresponding spectral components of systolic blood pressure" (44, 45).

Seligman used an invasive technique, which is using intravenous phenylephrine or angiotensin to induce bradycardia. The sensitivity of baroreflex was calculated in milliseconds of cardiac slowing per millimeter rise in systolic pressure (46).

Results from one large cross-sectional study comparing heart rate variability, blood pressure variability and baroreflex gain across different pregnancy-induced hypertensive disorders (chronic hypertension and pregnancy-induced hypertension)

TABLE 4 | Summary of the outcome of autonomic assessment.

Autonomic test	Abnormal response	Normal (no significant difference between PE and control)	Number of tests
Heart rate variability	8	3	11
Orthostatic stress	6	0	6
Deep breathing	3	0	3
Cold pressor	1	0	1
Baroreceptor reflex gain	4	1	5
Biomarkers of sympathetic activity	2	2	4
Muscle sympathetic nerve activity	2	1	3
Total number of tests	26	7	33

The table shows types and number of ANS tests performed within 26 studies included in the review; Heart rate variability HRV = 11, Orthostatic stress = 6, deep breathing test = 3, cold pressor test = 1, Baroreflex sensitivity = 5, Biomarkers of sympathetic activity' = 4, Muscle sympathetic nerve activity = 3. A total number of tests performed was 33.
The number of studies with abnormal results for each test type is described, HRV tests showed (72%), abnormal response cardiovascular reflex testing (orthostatic stress, deep breathing, and cold pressor test) results showed a 100%abnormal response. Baroreflex sensitivity showed an 80% abnormal response, Biomarkers of sympathetic activity showed 50 % abnormal response and muscle sympathetic nerve activity showed 66% abnormal; response. The overall response from all tests performed showed 78.8% abnormal ANS response with cardiovascular reflex testing providing the most consistent results.

showed that although a significant elevation in blood pressure variability was seen in the PE group, this increase did not lead to elevated spontaneous baroreflex (43). In this study, the sequence method was used to estimate BRG. This method is based on identifying consecutive cardiac beats in which an increase in systolic blood pressure is accompanied by an increase in heart rate, or in which a decrease in systolic blood pressure is accompanied by a decrease in heart rate. The regression line between the systolic blood pressure and heart rate produces an estimate of BRG. Similarly, the sequence technique was used by Weber et al. however, results obtained were contradicting. Baroreflex gain was significantly increased only in women with late-onset PE compared to healthy pregnant controls (42).

Overall, 80.8% of the studies included in our review reported at least one of the following abnormalities in ANS function: parasympathetic withdrawal, sympathetic hyperactivity or reduced baroreflex sensitivity. ANS dysfunction was prevalent in 93.6% of the patients diagnosed with PE.

Risk of Bias

The methodological quality of the included observational studies was tested using the Newcastle-Ottawa Scale (NOS) (53) which examines the risk of bias in observational studies by evaluating the selection of study groups, comparability of groups and ascertainment of either the exposure or outcome of interest. NOS consists of 8 items with 3 subscales, the total maximum score of these 3 subsets is 9. The outcomes of the quality assessment using the Newcastle–Ottawa Scale are presented in **Table 2**. A standard criterion for what constitutes a high-quality study has not yet been universally established. We considered a study that scored ≥7 a high-quality study. The mean value for the included studies is 7.6.

DISCUSSION

Summary of Main Findings

Role of Dysautonomia in Preeclampsia

The major finding of our systematic review is that autonomic dysfunction seems to be a frequent sign in women with pre-eclamptic pregnancy which manifests as elevated sympathetic tone, reduced parasympathetic tone, and reduced baroreflex gain. These changes lead to a pattern of neural dysfunction which is dominated by impairment of cardiovascular autonomic function. The role of preeclampsia in the development of cardiovascular disturbances has been discussed to a rapidly growing extent. Women with a history of preeclampsia have a 2-fold higher risk of cardiovascular and cerebrovascular disease (54). Autonomic cardiovascular failure might contribute to this risk. An alternative (or complementary) explanation may be impairment of structural and functional integrity of the vasculature induced at the time of pre-eclamptic pregnancy as well as a higher cardiovascular risk burden in later life in women who had preeclampsia (55). These mechanisms appear to cause cumulative organ damage in pre-eclamptic women progressing even beyond the time of pregnancy. It was recently shown that previously pre-eclamptic women have greater cerebral structural changes than women who have normotensive pregnancies (56). This damage was most pronounced in the temporal lobe and increased with time, consistent with continued cumulative damage post pregnancy. Whether autonomic dysfunction contributes to brain changes beyond pregnancy remains uncertain. It is however interesting that brain changes in pre-eclamptic women appear to target the temporal lobe which harbors the insular center of autonomic cardiovascular control. It remains speculative if changes seen on autonomic function tests correlate with these structural changes.

Most research investigating the pathophysiology of preeclampsia showed less attention toward a possible role of the ANS.

Studies in healthy pregnancy compared to non-pregnant women showed that pregnancy itself, even when uncomplicated by preeclampsia, is characterized by an increase in sympathetic tone and a decrease in respiratory sinus arrhythmia together with. significantly elevated heart rate supports the existence of an underlying increase in sympathetic cardiac activity (35).

Studies in women diagnosed with PE indicate that, pre-eclamptic women showed higher cardiac output and heart rate which is regarded as a sign of increased sympathetic activity in addition to exaggerated peripheral vascular resistance and higher blood pressure which can be mediated, in part, by a substantial increase in sympathetic vasoconstrictor activity (52).

The role of sympathetic nervous activity SNA in the pathophysiology of PE has been extensively studied. A possible mechanism could be that early elevations in SNA encourage placental ischemia/reperfusion events and hypoxia-induced release of pro-hypertensive factors into the maternal circulation (8). It is also possible that placental ischemic factors reduce the

vasoconstriction-buffering mechanisms in the blood vessel wall supporting the development of hypertension (57, 58).

However, the consistency of observations on cardiovascular autonomic dysfunction in pre-eclamptic women among studies included in our review indicates a potential pathophysiological role of dysautonomia in the course of PE which seems to exceed what can be explained by cumulative cardiovascular risk factors alone.

Furthermore, the relationship between fetal and maternal autonomic balance appears to play a role in the development of cardiovascular complications during or after pre-eclamptic pregnancy. Interestingly, the patterns of autonomic dysfunction seem to differ between pre-eclamptic women and their offspring. While maternal sympathetic overactivity modulates HRV by suppressing parasympathetic tone both in mild and severe cases of PE, fetal cardiac dysautonomia appears to be dominated by an increase in a sympathetic tone which leads to the suppression of fetal biophysical activity and the development of fetal distress in cases of severe PE (26).

Another approach to improve our understanding of autonomic dysfunction in pre-eclamptic women is to study the neuroendocrine axis. Normal pregnancy is associated with dramatic changes in hemodynamics and is accompanied by changing levels of various pressor hormones and vasoactive metabolites (59). In studies of pregnant women, biochemical biomarkers of sympathetic activity showed conflicting results which may be due to the fact that their levels are influenced by various factors such as activity of the neural efferent, release of the synaptic transmitter, reuptake mechanisms and regional blood flow (60), in addition to the fact that pregnancy itself affects the production and clearance of catecholamines (61). However, it is well-established that disturbed placentation and placental functioning in early pregnancy leads to inadequate spiral artery remodeling and thereby to chronic placental ischemia (62). Reactive oxygen species and cytokines released from the ischemic placenta as well as acute phase proteins trigger systemic oxidative stress and inflammatory response which then provokes the release of antiangiogenic factors. These factors inhibit angiogenesis and vasodilatation which result in endothelial dysfunction and increase arterial stiffness (63–67). Increased sympathetic activity was found in normotensive pregnant women, and it was even greater in women with gestational hypertension and preeclampsia at term (68). Since both endothelial function and arterial stiffness are in parts subject to autonomic neural control (predominantly sympathetic), it seems plausible that autonomic and antiangiogenic pathways are interlinked in the pathogenesis of preeclampsia and its cardiovascular complications in later life (69).

Predictive Role of Autonomic Function Testing

Studies of microneurography showed that MSNA levels are elevated in normotensive pregnancy compared to non-pregnant controls with significantly increased levels in PE patients but have no value in predicting PE in high-risk women (39). These findings are consistent with a study, which proved increased MSNA levels and impaired cardiac baroreceptor gain in patients with hypertensive pregnancy disorders (PIH and PE) and that MSNA levels returned to normal level after delivery (70). However, a long term follows up study showed that in previously pre-eclamptic women with treated hypertension sympathetic outflow is increased compared to normotensive control women despite similar ambulatory blood pressure values. Remarkably, this observation was made 40 years after the pre-eclamptic pregnancy indicating that long sympathetic changes in those women who have preeclampsia and continue to have hypertension post pregnancy (71). Although signs and symptoms of preeclampsia become apparent late in pregnancy, there is some evidence, that the observed increased sympathetic activity, may already be present before the clinical presentation of preeclampsia (72, 73).

Different methods were used for the clinical assessment of autonomic cardiovascular control in women diagnosed with PE. Non-invasive assessment of autonomic cardiovascular control was evaluated as a predictive tool to early identify women at increased risk of developing PE. They have the advantage of bearing minimal risk for the mother and the fetus and can be repeated during pregnancy. However, their results are limited by the fact that autonomic regulation of blood pressure can be disturbed at several levels between the hypothalamus and the periphery (59).

Overall, studies evaluating autonomic tests as a predictive tool showed inconsistent results That may be due to methodological factors and study design. Most studies are cross-sectional with a few numbers of longitudinal studies conducted before or early in pregnancy. Also, the performance of the different cardiovascular tests is not uniform and standardized besides the difference in blood pressure measurement methods (50). Recent studies have shown promising results using other tools such as circulating small non-coding RNA as a predictive tool for PE in the first trimester (74).

Limitations

The present review is limited by the case-control design of the majority of the studies, while results from the prospective trials showed controversial results regarding the predictive value of different ANS testing for early detection of PE. A further limitation is the methodological heterogeneity present between studies, regarding the different definitions of preeclampsia, the nature of included PE population (late onset PE, early onset PE, severe and mild PE).

CONCLUSIONS

Autonomic dysfunction is highly prevalent in pre-eclamptic women and might contribute to their increased cardiovascular and cerebrovascular risk. Tests of cardiovascular autonomic function such as orthostatic stress and cold pressor tests might be helpful to identify subjects at risk and monitor disease progression.

Biomarkers of sympathetic activity do not seem to be reliable tools to assess the sympathetic function in preeclampsia. MSNA is elevated in normal pregnancy which is further augmented in PE and also shows long term changes in those women who

have had preeclampsia and continue to have hypertension after delivery. However, the technique seems to have low value in predicting the risk of PE in high-risk patients.

Dysautonomia in PE may be alleviated by an easy-to-learn technique, the heart rate variability biofeedback. It has been shown to improve both autonomic functioning and perinatal anxiety and depression (75, 76).

It is noteworthy that at this stage autonomic function testing is not able to differentiate between mild and severe PE. However, severe but not mild PE is accompanied by loss of the maternal-fetal hemodynamic coupling as seen with maternal and fetal RSA in women diagnosed with PE.

Further studies are needed to demonstrate the predictive value of ANS testing and their applicability as an ambulatory test alone or in combination with other biomarkers to predict the risk of PE early in pregnancy. Selection of recruited PE patients according to the onset and severity of disease might help further elucidate the underlying pathophysiology.

DATA AVAILABILITY

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

AUTHOR'S NOTE

This work is part of a Masters thesis of the Master's Program in Clinical Research, Center for Clinical Research and Management Education, Division of Health Care Sciences, Dresden international University, Dresden, Germany.

AUTHOR CONTRIBUTIONS

DY drafted the first version of the manuscript. APe, MH, BI, APi, and TS have made substantial contributions by reviewing the manuscript for intellectual content, language and design. IB, DY, and TS have made substantial contributions to drafting the figures and tables displayed in this article. TS is the corresponding author.

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REFERENCES

1. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol*. (2009) 33:130–7. doi: 10.1053/j.semperi.2009.02.010
2. ACOG practice bulletin No. 202 summary. (2019). *Obstet Gynecol.* 133:211-4. doi: 10.1097/aog.0000000000003019
3. Tranquilli AL, Landi B, Giannubilo SR, Sibai BM. Preeclampsia: no longer solely a pregnancy disease. *Pregnancy Hypertens*. (2012) 2:350–7. doi: 10.1016/j.preghy.2012.05.006
4. O'Tierney-Ginn PF, Lash GE. Beyond pregnancy: modulation of trophoblast invasion and its consequences for fetal growth and long-term children's health. *J Reproduct Immunol*. (2014) 104–105:37–42. doi: 10.1016/j.jri.2014.04.002
5. Townsend R, O'Brien P, Khalil A. Current best practice in the management of hypertensive disorders in pregnancy. *Integrat Blood Pressure Control*. (2016) 9:79–94. doi: 10.2147/IBPC.S77344
6. Benyo DF, Miles TM, Conrad KP. Hypoxia stimulates cytokine production by villous explants from the human placenta. *J Clin Endocrinol Metabol.* (1997) 82:1582–8. doi: 10.1210/jc.82.5.1582
7. Veerbeek JH, Brouwers L, Koster MP, Koenen SV, van Vliet EO, Nikkels PG, et al. Spiral artery remodeling and maternal cardiovascular risk. *J Hypertens*. (2016) 34:1570–7. doi: 10.1097/HJH.0000000000000964
8. Karumanchi SA, Granger JP. Preeclampsia and pregnancy-related hypertensive disorders. *Hypertension*. (2016) 67:238–42. doi: 10.1161/HYPERTENSIONAHA.115.05024
9. Heiskanen N, Saarelainen H, Valtonen P, Lyyra-Laitinen T, Laitinen T, Vanninen E, et al. Blood pressure and heart rate variability analysis of orthostatic challenge in normal human pregnancies. *Clin Physiol Funct Imag*. (2008) 28:384–90. doi: 10.1111/j.1475-097X.2008.00818.x
10. Ekholm EM, Piha SJ, Erkkola RU, Antila KJ. Autonomic cardiovascular reflexes in pregnancy. a longitudinal study. *Clin Autonom Res*. (1994) 4:161–65. doi: 10.1007/BF01826181
11. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int J Cardiol*. (2010) 141:122–31. doi: 10.1016/j.ijcard.2009.09.543
12. Robbe HW, Mulder LJ, Rüddel H, Langewitz WA, Veldman JB, Mulder G. Assessment of baroreceptor reflex sensitivity by means of spectral analysis. *Hypertension.* (1987) 10:538–43. doi: 10.1161/01.HYP.10.5.538
13. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care.* (1985) 8:491–8. doi: 10.2337/diacare.8.5.491
14. Camm AJM, Malik JT, Bigger G, Breithardt S, Cerutti RJ, Cohen P, et al. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task force of the European society of cardiology and the north American society of pacing and electrophysiology. *Circulation*. (1996) 93:1043–65. doi: 10.1161/01.CIR.93.5.1043
15. Kingwell BA, Thompson JM, Kaye DM, McPherson GA, Jennings GL, Esler MD. Heart rate spectral analysis, cardiac norepinephrine spillover, and muscle sympathetic nerve activity during human sympathetic nervous activation and failure. *Circulation*. (1994) 90:234–40. doi: 10.1161/01.CIR.90.1.234
16. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. *Front Public Health*. (2017) 5:258. doi: 10.3389/fpubh.2017.00258
17. Morris MJ, Russell AE, Kapoor V, Cain MD, Elliott JM, West MJ, et al. Increases in plasma neuropeptide y concentrations during sympathetic activation in man. *J Auton Nerv Syst*. (1986) 17:143–9. doi: 10.1016/0165-1838(86)90089-5
18. Freeman R. Assessment of cardiovascular autonomic function. *Clin Neurophysiol*. (2006) 117:716–30. doi: 10.1016/j.clinph.2005.09.027
19. Grassi G, Esler M. How to assess sympathetic activity in humans. *J Hypertens*. (1999) 17:719–34. doi: 10.1097/00004872-199917060-00001
20. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses : the PRISMA statement. *Int J Surg.* (2010) 8:336–41. doi: 10.1016/j.ijsu.2010.02.007
21. Egerman RS, Andersen RN, Manejwala FM, Baha M. Neuropeptide Y and nitrite levels in preeclamptic and normotensive gravid women. *Am J Obstet Gynecol.* (1999) 181:921–23. doi: 10.1016/S0002-9378(99)70326-1
22. Manyonda IT, Obstetrician C, Slater C. A role for noradrenaline in pre-eclampsia : towards a unifying hypothesis for the pathophysiology. *Br J Obstet Gynaecol*. (1998) 105:641–48. doi: 10.1111/j.1471-0528.1998.tb10179.x

23. Øian P, Kjeldsen SE, Eide I, Maltau JM. Increased arterial catecholamines in pre-eclampsia. *Acta Obstet Gynecol Scand*. (1986) 65:613–7. doi: 10.3109/00016348609158398
24. Beilin LJ, Deacon J, Michael CA, Vandongen R, Lalor CM, Barden AE, et al. Diurnal rhythms of blood pressure, plasma renin activity, angiotensin ii and catecholamines in normotensive and hypertensive pregnancies. *Clin Exp Hypertens*. (1983) 2:271–93. doi: 10.3109/10641958309006086
25. Chaswal M, Kapoor R, Batra A, Verma S, Yadav BS. Heart rate variability and cardiovascular reflex tests for assessment of autonomic functions in preeclampsia. *Int J Hypertens*. (2018) 2018:8163824. doi: 10.1155/2018/8163824
26. Lakhno I. Autonomic imbalance captures maternal and fetal circulatory response to pre-eclampsia. *Clini Hypertens*. (2017) 23:5. doi: 10.1186/s40885-016-0061-x
27. Musa SM, Adam I, Lutfi MF. Heart rate variability and autonomic modulations in preeclampsia. *PLoS ONE*. (2016) 11:152704. doi: 10.1371/journal.pone.0152704
28. Flood P, McKinley P, Monk C, Muntner P, Colantonio LD, Goetzl L, et al. Beat-to-beat heart rate and blood pressure variability and hypertensive disease in pregnancy. *Am J Perinatol*. (2015) 32:1050–8. doi: 10.1055/s-0035-1548542
29. Yokuşoglu M, Dede M, Uzun M, Baysan O, Köz C, Cemal Yenen M, et al. Cardiac autonomic balance is impaired in preeclampsia. *Turkiye Klinikleri J Med Sci*. (2009) 29:605–10.
30. Swansburg ML, Brown CA, Hains SM, Smith GN, Kisilevsky BS. Maternal cardiac autonomic function and fetal heart rate in preeclamptic compared to normotensive pregnancies. *Can J Cardiovasc Nurs*. (2005) 15:42–52.
31. Rang S, Wolf H, van Montfrans GA, Karemaker JM. Serial assessment of cardiovascular control shows early signs of developing pre-eclampsia. *J Hypertens*. (2004) 22:369–76. doi: 10.1097/00004872-200402000-00022
32. Miyake Y, Ohnishi M, Fujii TK, Yamamoto T, Yoneda C, Takahashi S, et al. The effects of postural changes of Baroreflex gain in normal and hypertensive pregnancies. *Clin Exp Hypertens*. (2002) 24:23–31. doi: 10.1081/CEH-100108712
33. Woisetschläger C, Waldenhofer U, Bur A, Herkner H, Kiss H, Binder M, et al. Increased blood pressure response to the cold pressor test in pregnant women developing pre-eclampsia. *J Hypertens*. (2000) 18:399–403. doi: 10.1097/00004872-200018040-00007
34. Yang CC, Chao TC, Kuo TB, Yin CS, Chen HI. Preeclamptic pregnancy is associated with increased sympathetic and decreased parasympathetic control of HR. *Am J Physiol Heart Circ Physiol*. (2000) 278:1269–73. doi: 10.1152/ajpheart.2000.278.4.H1269
35. Lewinsky RM, Riskin-Mashiah S. Autonomic imbalance in preeclampsia: evidence for increased sympathetic tone in response to the supine-pressor test. *Obstetrics Gynecol*. (1998) 91:935–9. doi: 10.1097/00006250-199806000-00011
36. Eneroth E, Storck N. Preeclampsia and maternal heart rate variability. *Gynecol Obstetric Invest*. (1998) 45:170–3. doi: 10.1159/000009949
37. Ahmad HR, Akhtar S, Khan MA, Khan KS, Qureshi AA, Romana H, et al. Dynamic and steady state response of heart rate to orthostatic stress in normotensive and hypertensive pregnant women. *Eur J Obstet Gynecol Reprod Biol*. (1996) 66:31–7.
38. Airaksinen KE, Kirkinen P, Takkunen JT. Autonomic nervous dysfunction in severe pre-eclampsia. *Eur J Obstetr Gynecol Reproduct Biol*. (1985) 19:269–76. doi: 10.1016/0028-2243(85)90040-1
39. Fischer T, Schobel HP, Frank H, Andreae M, Schneider KT, Heusser K. Pregnancy-induced sympathetic overactivity: a precursor of preeclampsia. *Euro J Clin Invest*. (2004) 34:443–8. doi: 10.1111/j.1365-2362.2004.01350.x
40. Greenwood JP, Scott EM, Walker JJ, Stoker JB, Mary DA. The magnitude of sympathetic hyperactivity in pregnancy-induced hypertension and preeclampsia. *Am J Hypertens*. (2003) 16:194–99. doi: 10.1016/S0895-7061(02)03256-9
41. Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia—a state of sympathetic overactivity. *New Engl J Med*. (1996) 335:1480–5. doi: 10.1056/NEJM199611143352002
42. Weber TM, Lackner HK, Roessler A, Papousek I, Kolovetsiou-Kreiner, V. Lucovnik M, et al. Heart rate variability and baroreceptor reflex sensitivity in early- versus late-onset preeclampsia. *PLoS ONE*. (2017) 12:e0186521. doi: 10.1371/journal.pone.0186521
43. Faber R, Baumert M, Stepan H, Wessel N, Voss A, Walther T. Baroreflex sensitivity, heart rate, and blood pressure variability in hypertensive pregnancy disorders. *J Human Hypertens*. (2004) 18:707–12. doi: 10.1038/sj.jhh.1001730
44. Silver HM, Tahvanainen KUO, Kuusela TA, Eckberg DL. Comparison of vagal baroreflex function in nonpregnant women and in women with normal pregnancy, preeclampsia, or gestational hypertension. *Am J Obstet Gynecol*. (2001) 184:1189–95. doi: 10.1067/mob.2001.112871
45. Molino P, Veglio F, Genova GC, Melchio R, Benedetto C, Chiarolini L, et al. Baroreflex control of heart rate is impaired in pre-eclampsia. *J Human Hypertens*. (1999) 13:179–83. doi: 10.1038/sj.jhh.1000789
46. Seligman SA. Baroreceptor reflex function in pre-eclampsia. *J Obstetr Gynaecol Br Commonwealth*. (1971) 78:413–16. doi: 10.1111/j.1471-0528.1971.tb00294.x
47. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. *Am J Obstet Gynecol*. (1988) 158:892–8. doi: 10.1016/0002-9378(88)90090-7
48. Report of the national high blood pressure education program working group on high blood pressure in pregnancy. *Am J Obstet Gynecol*. (2000) 183:S1–22. doi: 10.1067/mob.2000.107928
49. Roberts JM, August PA, Bakris G, Barton JR, Bernstein IM, Druzin M, et al. (2013). Hypertension in pregnancy. *Obstetr Gynecol*. 122:1122–31. doi: 10.1097/01.AOG.0000437382.03963.88
50. Rang S, Wolf H, Montfrans GA, Karemaker JM. Non–invasive assessment of autonomic cardiovascular control in normal human pregnancy and pregnancy- associated hypertensive disorders. *J Hypertens*. (2002) 20:2111–9. doi: 10.1097/00004872-200211000-00002
51. Voss A, Baumert M, Baier V, Stepan H, Walther T, Faber R. Autonomic cardiovascular control in pregnancies with abnormal uterine perfusion. *Am J Hypertens*. (2006) 19:306–12. doi: 10.1016/j.amjhyper.2005.08.008
52. Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia—a state of sympathetic overactivity. *Obstet Gynecol Survey*. (1997) 52:211–2. doi: 10.1097/00006254-199704000-00002
53. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. (2004). *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analysis*. Available online at: http://ci.nii.ac.jp/naid/10020590649/en/. (accessed February 26, 2018).
54. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. (2008). Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J*. 156:918–30. doi: 10.1016/j.ahj.2008.06.042
55. Lazdam M, Davis EF, Lewandowski AJ, Worton SA, Kenworthy Y, Kelly B, et al. Prevention of vascular dysfunction after preeclampsia: a potential long-term outcome measure and an emerging goal for treatment. *J Pregnancy*. (2012) 2012:704146. doi: 10.1155/2012/704146
56. Siepmann T, Boardman H, Bilderbeck A, Griffanti L, Kenworthy Y, Zwager C, et al. Long-term cerebral white and gray matter changes after preeclampsia. *Neurology*. (2017) 88:1256–64. doi: 10.1212/WNL.0000000000003765
57. Spradley FT. Sympathetic nervous system control of vascular function and blood pressure during pregnancy and preeclampsia. *J Hypertens*. (2018) 37:476–87. doi: 10.1097/HJH.0000000000001901
58. Rangaswami J, Naranjo M, McCullough PA. Preeclampsia as a form of type 5 cardiorenal syndrome: an underrecognized entity in women's cardiovascular health. *Cardiorenal Med*. (2018) 8:160–72. doi: 10.1159/000487646
59. Fu Q, Levine BD. Autonomic circulatory control during pregnancy in humans. *Semin Reprod Med*. (2009) 27:330–7. doi: 10.1055/s-0029-1225261
60. Ruprai R, Ghuge S. A comparative study of autonomic function tests (sympathetic and parasympathetic) in three trimesters of pregnancy. *Int J Med Sci Public Health*. (2017) 6:139–42. doi: 10.5455/ijmsph.2017.08072016574
61. Zhou SS, Zhou YM, Li D, Chen NN. Preeclampsia and future cardiovascular risk: a point of view from the clearance of plasma vasoactive amines. *Hypertens Pregnancy*. (2016) 35:1–14. doi: 10.3109/10641955.2015.1115062
62. Redman CW, and Sargent IL. Placental stress and pre-eclampsia: a revised view. *Placenta*. (2009) 30:38–42. doi: 10.1016/j.placenta.2008.11.021
63. Rodie VA, Freeman DJ, Sattar N, Greer IA. Pre-eclampsia and cardiovascular disease: metabolic syndrome of pregnancy? *Atherosclerosis*. (2004) 175:189–202. doi: 10.1016/j.atherosclerosis.2004.01.038
64. Poston L. Endothelial dysfunction in pre-eclampsia. *Pharmacol Rep* . (2006) 58:69–74.

65. Levine RJ, Lam C, Qian C, Yu KF, Maynard SE, Sachs BP, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *N Engl J Med*. (2006) 355:992–1005. doi: 10.1056/NEJMoa 055352
66. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med*. (2004) 350:672–83. doi: 10.1056/NEJMoa031884
67. Ahmad S, Ahmed A. Elevated placental soluble vascular endothelial growth factor receptor-1 inhibits angiogenesis in preeclampsia. *Circulat Res*. (2004) 95:884–91. doi: 10.1161/01.RES.0000147365.86159.f5
68. Jarvis SS, Shibata S, Bivens TB, Okada Y, Casey BM, Levine BD, et al. Sympathetic activation during early pregnancy in humans. *J Physiol*. (2012) 590:3535–43. doi: 10.1113/jphysiol.2012.228262
69. Wang A, Rana S, Karumanchi SA. Preeclampsia: the role of angiogenic factors in its pathogenesis. *Physiology*. (2009) 24:147–58. doi: 10.1152/physiol.00043.2008
70. Greenwood JP, Scott EM, Stoker JB, Walker JJ, Mary DA. Sympathetic neural mechanisms in normal and hypertensive pregnancy in humans. *Circulation*. (2001) 104:2200–4. doi: 10.1161/hc4301.098253
71. Collén AC, Manhem K, Sverrisdóttir YB. Sympathetic nerve activity in women 40 years after a hypertensive pregnancy. *J Hypertens*. (2012) 30:1203–10. doi: 10.1097/HJH.0b013e3283531ed2
72. Bosio PM, McKenna PJ, Conroy R, O'Herlihy C. Maternal central hemodynamics in hypertensive disorders of pregnancy. *Obstet Gynecol*. (1999) 94:978–84. doi: 10.1016/S0029-7844(99)00430-5
73. Andreas M, Kuessel L, Kastl SP, Wirth S, Gruber K, Rhomberg F, et al. Bioimpedance cardiography in pregnancy: a longitudinal cohort study on hemodynamic pattern and outcome. *BMC Pregnancy Child*. (2016) 16:128. doi: 10.1186/s12884-016-0918-8
74. Yoffe L, Gilam A, Yaron O, Polsky A, Farberov L, Syngelaki A, et al. Early detection of preeclampsia using circulating small non-coding RNA. *Sci Rep*. (2018) 8:3401. doi: 10.1038/s41598-018-21604-6
75. Beckham AJ, Greene TB, Meltzer-Brody S. A pilot study of heart rate variability biofeedback therapy in the treatment of perinatal depression on a specialized perinatal psychiatry inpatient unit. *Arch Womens Mental Health*. (2013) 16:59–65. doi: 10.1007/s00737-012-0318-7
76. Pinter A, Szatmari S, Horvath T, Penzlin AI, Barlinn K, Siepmann M, et al. Cardiac dysautonomia in depression – heart rate variability biofeedback as a potential add-on therapy. *Neuropsychiatr Dis Treat*. (2019) 15:1287–310. doi: 10.2147/NDT.S200360

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Takotsubo Cardiomyopathy—Acute Cardiac Dysfunction Associated With Neurological and Psychiatric Disorders

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Takotsubo cardiomyopathy (TTC) is an acute and reversible cardiac wall motion abnormality of the left myocardium. Although many studies focused on etiology, diagnostic and treatment of TTC, precise clinical guidelines on TTC are not available. Research revealed emotional and physical triggering factors of TTC and emphasized the association of TTC with psychiatric and particularly acute neurological disorders. Similar clinical presentation of acute coronary syndrome (ACS) and TTC patients, makes an anamnestic screening for TTC risk factors necessary. In psychiatric anamnesis affective disorders and chronic anxiety disorders are presumably for TTC. Subarachnoid hemorrhages and status epilepticus are typical acute neurological associated with a higher risk for TTC. Moreover, magnetic resonance imaging (MRI) studies reveled brain alterations of the limbic system and reduced connectivity of central autonomic nervous system structures. Diagnosis of TTC is made by elevation of cardiac enzymes, electrocardiogram (ECG) and visualization of myocardial wall motion. Major differential diagnoses like acute coronary syndrome and myocarditis are hereby in synopsis with anamnesis with respect of possible emotional and physical triggering factors of TTC ruled out. In most cases the TTC typical wall motion abnormalities resolve in weeks and therapy is only necessary in hemodynamic instable patients and if rare complications, like cardiac wall ruptures occur. Recently, the two-parted International expert consensus document on Takotsubo syndrome was published, providing a detailed characterization of TTC and allows clinicians to understand this cardiac dysfunction with a multidisciplinary view.

Keywords: Takotsubo (stress) cardiomyopathy, autonomic (vegetative) nervous system, psychiatric disorders, neurological disorders, affective disorders

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INTRODUCTION

Takotsubo cardiomyopathy (TTC), also known as left ventricular apical ballooning syndrome (LVBS), transient apical ballooning, stress cardiomyopathy, or broken heart syndrome, is an acute and reversible wall motion abnormality classically of the left ventricular myocardium and was firstly described by Sato et al. (1) and Ghadri et al. (2). The Japanese term "Takotsubo" means "octopus pot" and describes the characteristic left ventricular end-systolic apical ballooning phenomenon, which can be visualized in transthoracic echocardiogram (TTE) or coronary angiography with left ventriculography. The classical morphological pattern of TTC is an apical akinesia with basal

hyperkinesia of the left ventricular myocardium (3). However, there have been further wall motion abnormalities in TTC described, such as basal, midventricular, and lateral akinesia of the left ventricular myocardium and also involvement of the right ventricular myocardium as part of a biventricular involvement or isolated right ventricular wall motion abnormality (3). Typically, TTC patients present with clinical symptoms suggestive for an acute coronary syndrome (ACS), such as chest pain, dyspnea, syncope, and nausea with sudden onset after an emotional or physical stressor (4). From an epidemiological point of view patients diagnosed with TTC are typically postmenopausal female patients with a mean age of 66.8 years (5, 6). However, the epidemiology of TTC was shown to be more complex according to various retrospective studies. Biomarkers used in diagnosis of TTC are the cardiac enzymes troponin, creatine kinase, and N-terminal prohormone of brain natriuretic peptide (NT-proBNP), which are classically elevated, but show lower peak values than in patients with ACS. Although, ECG changes in TTC patients are not specific, most commonly ST-elevations in leads II, III, aVF, aVR, and V5 to V6 are seen (7). Additionally, repolarization abnormalities (T-wave inversions) are commonly seen in ECGs of TTC patients, as well as QTc-prolongations. Recently, the International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria) as part of an international expert consensus document have been published and support differentiation of TTC patients with no ST-elevation in ECG and ACS patients (8). The clinical challenge in emergency rooms is to rule out an ACS as most important differential diagnosis of TTC. Moreover, acute infectious myocarditis or pericarditis are relevant differential diagnoses of TTC. Complications of TTC include ventricular arrhythmias, acute heart failure with cardiogenic shock as a result of primary pump failure or left ventricular outlet tract obstruction, whereas rare complications are cardiac wall ruptures or formation of left ventricular thrombus (2, 9). Generally, the wall-motion abnormalities normalize within hours to weeks in TTC patients (9). We reviewed the current available literature to outline the pathophysiological mechanisms of TTC, focusing on linking TTC to psychiatric, and neurological disorders. Moreover, we briefly describe the diagnostical workflow in emergency rooms of patients with suggested TTC. We conclude our review with a concise overview about therapeutic strategies of TTC.

EPIDEMIOLOGY OF TAKOTSUBO CARDIOMYOPATHY

The incidence and prevalence of TTC are reported to be increasing, certainly due to a more sensitive clinical screening of patients in e.g., chest pain units for TTC. Deshmukh et al. studied the occurrence of TTC from the Nationwide Inpatient Sample database of US hospitalizations based on the International Classification of Diseases (ICD) in 2008 and demonstrated that 0.02% of all patients hospitalized in the US were diagnosed with TTC (10). Two percent of patients with clinical suspected ACS were diagnosed with TTC (7). Interestingly, data derived from the International Takotsubo Registry revealed patients characteristics with TTC in the United States and Europe and showed that of 1,750 studied patients diagnosed with TTC 89.8% were postmenopausal women with a mean age of 66.8 years (5, 6). Importantly, higher in-hospital mortality rates of male TTC patients compared to female TTC patients have been observed retrospectively (11, 12). However, Patel et al. found in their analysis no significant sex difference in respect of overall mortality rates of TTC patients aged $\geq$50 years (11). Remarkably, a significant higher prevalence of neurologic or psychiatric disorder rates among TTC patients compared to ACS patients has been reported (5). Additionally, male TTC patients $\geq$50 years showed physical triggers prior to the onset of TTC more often, whereas female TTC patients $\geq$50 years seem to suffer from premorbid psychiatric disorders more frequently (11). Notably, female patients showed higher recurrence rates of TTC compared to male TTC patients (11). Singh et al. detected an annual rate of TTC recurrence of 1.5% (13). Moreover, one retrospective analysis revealed a TTC recurrence of 6.1% during a follow up period of 6 years (14). Effectiveness of pharmacologic therapy in order to prevent reoccurrence of TTC is under current investigation. Tendentially, prescription of ACE-inhibitors is reported to be inversely correlated to recurrence of TTC in retrospective analysis (15). Furthermore, β2-adrenergic agonist agents intake was found to be associated with higher TTC prevalence (16).

PATHOPHYSIOLOGICAL MECHANISMS OF TAKOTSUBO CARDIOMYOPATHY

The underlying pathophysiological mechanism of TTC is not completely understood until today. Over the last decades numerous animal experiments and clinical studies have been conducted to elucidate the pathophysiology of TTC, outlining TTC as a multifactorial acute, and reversible cardiac disorder. Nevertheless, it is unquestioned that emotional and physical stress are frequent triggers of TTC (17). Initially, Sato et al. explained the pathophysiology of TTC with simultaneous spasms of coronary arteries (1, 18). The theory of simultaneous coronary vasospasm as underlying mechanism of TTC was disproved, as endomyocardial biopsies taken from TTC patients showed histopathological patterns of myocardial abnormalities, which are not characteristic for infarcted, stunned or hibernating myocardium (7). Furthermore, coronary microvascular dysfunction as etiology of TTC has been studied, but data are still not distinct up to now (7, 9).

However, an association of increased sympathetic activity resulting in systemic blood catecholamine excess, and TTC has been demonstrated in numerous studies (2). Some authors discuss increased blood catecholamine levels rather as a triggering factor than an underlying pathophysiological mechanism of TTC. Interestingly, to date only one study showed extremely high plasma concentrations of catecholamines, whereas other studies showed nearly normal catecholamine blood levels in TTC patients (9). Research has drawn attention to the role of β2-adrenoceptors, as high epinephrine blood levels induce a β2-adrenoceptor coupling change from membranous

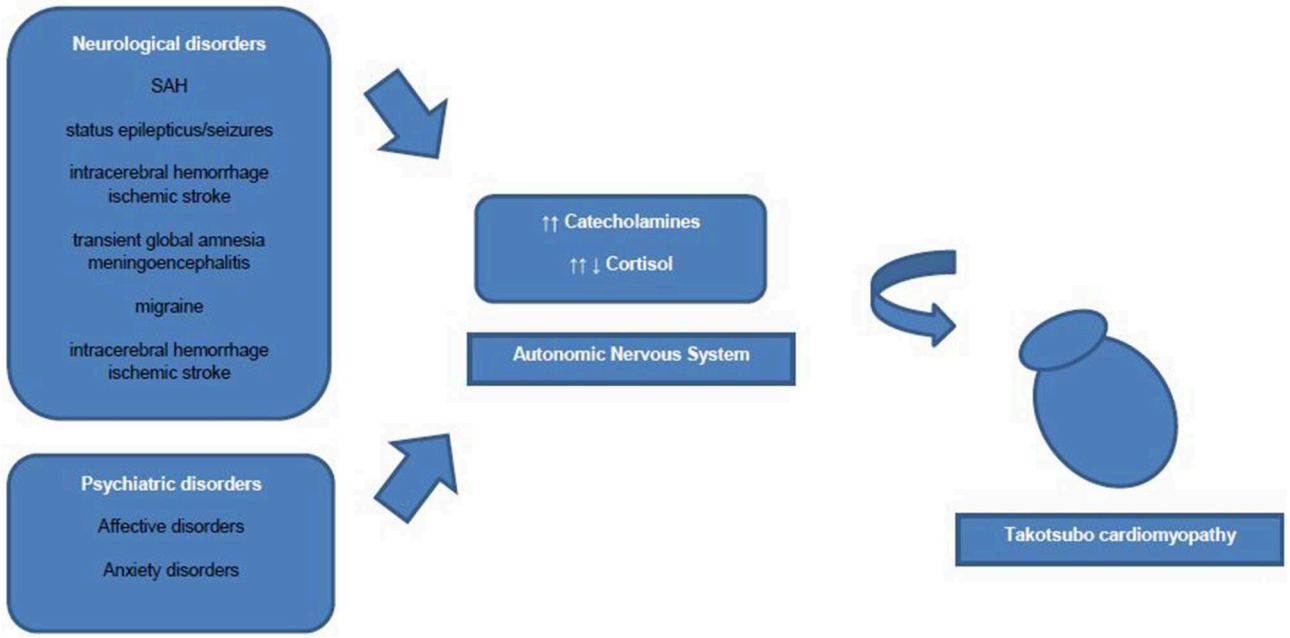

FIGURE 1 | Linking neurological and psychiatric disorders to Takotsubo cardiomyopathy.

Gs proteins to Gi proteins with a consecutive negative inotropic effect (19). Therefore, the reversible nature of ventricular ballooning after normalization of catecholamine blood levels could be explained by these compensatory biochemical processes. Additionally, regional differences in myocardial expression of β2-adrenergic receptor density have been shown, which mediate the cellular effects of the increased catecholamine blood concentrations and explain the regional left ventricular myocardial stunning (2). Besides circulating blood catecholamines, secreted from the adrenal medulla, ventricular sympathetic nerve fiber terminals release norepinephrine and a hyperactivation of these cardiac sympathetic nerve terminals with increased synaptic norepinephrine levels and consecutive activation of post-synaptic α_1-, β_1-, and β_2–receptors as leading pathomechanism is discussed currently. However, sympathetic nerve fiber density is higher in basal myocardium as in ventricular myocardium and therefore blood circulating epinephrine seems to have a greater influence on apical ventricular myocardium then norepinephrine released from the sympathetic nerve terminals in apical myocardium (19) (**Figure 1**).

Recent research on the pathogenesis of TTC demonstrated an association of inflammatory myocardial processes in TTC patients, linking catecholamine stress-induced TTC to inflammatory responses of the myocardium in experimental animal studies. Wilson et al. characterized the myocardial inflammatory response in TTC based on animal experimental studies with catecholamine induced TTC, showing a predominant myocardial M1 macrophages infiltration in TTC without a switch of M1 macrophages (proinflammatory tissue destructive) to M2 macrophages (anti-inflammatory tissue reparative/profibrotic) (20). Importantly, Wilson et al. found in their study a positive correlation of increasing EF with the percentage of M2 macrophages (20). However, it remains to be elucidated, whether inflammatory myocardial processes are occurring prior TTC or are results of TTC in further animal-based experimental and clinical studies, in order to develop specific therapeutic strategies. Not only local myocardial inflammatory processes have been described, but also persistent systemic peripheral inflammatory response in TTC patients has been studied, making potential long term pharmacological anti-inflammatory treatment of TTC considerable. Systemic peripheral inflammation denoted in elevated serum levels of interleukin-6, chemokine ligand 1, $CD14^{++}CD16^{-}$ monocytes, and non-classical $CD14^{+}CD16^{++}$ monocytes have been described in clinical studies (21). Whereas, serum levels of intermediate $CD14^{++}CD16^{+}$ monocytes and non-classical $CD14^{+}CD16^{++}$ monocytes were reduced (21). Scally et al. reported persistent peripheral systemic inflammation processes in TTC patients in follow-up measurements of pro-inflammatory cytokines, whereby serum concretions of interleukin 6 and interleukin 8 remained elevated (21). In clinical settings inflammatory processes in context of TTC can be visualized as myocardial edema in cardiac magnetic resonance imaging (MRI) more favorable in T2 weighted imaging of the myocardium (21, 22).

Recent studies focus on cardiac ion channel activity modulated by inflammatory cytokines and the resulting change of cardiac action potential duration, which should be mentioned as an association of inflammation and TTC has been previously described. It has been postulated, that both circulating cytokines directly affect ion channels of cardiomyocytes and indirectly increase the risk for the occurrence of cardiac electrophysiological disturbance through increased sympathetic

output from central and peripheral autonomic nervous system nerve fibers (23). These changes in cardiac action potentials are mainly pictured through QTc prolongation in ECG and has been proven to be associated with high blood levels of acute phase proteins (23). An increase of QT interval is therefore called an acquired cardiac channelopathy. The suggested pathophysiological mechanisms are both changes in expression and function of potassium and calcium channels (23). It has been demonstrated, that IL-1β and IL-6 enhance cardiac calcium channels (23). Contrary, potassium channels have been reported to be reduced expressed via activation of TNFα pathways (23). Interestingly, so far no studies demonstrated a change of expression or function of cardiac sodium channels via cytokines (23). Moreover, an inflammatory reflex has been described in patients with QT prolongation. The underlying cardiac changes are mediated through a cytokine mediated central activation of sympathetic nerve fibers. As a consequence of this activation cytokine production and activation of β2-adrenergic receptors expressed in circulating lymphocytes and monocytes is decreased (23). The sympathetic nerve fiber activation results in cardiac activation of calcium and potassium channels leading to increased duration of cardiac action potential (23). Increased calcium ion influx and decreased potassium efflux from cardiomyocytes results in an increase of cardiac action potential and therefore a prolongation of the QT interval (24). Additionally, studies have shown an strong association of high c-reactive protein blood levels and QT interval prolongation (24). Not only acute phase proteins have been demonstrated to modulate cardiac ion channel function, but also antibodies, e.g., anti-Sjögren's-syndrome-related antigen A have been found to influence potassium channels of ventricular cardiomyocytes resulting in QT prolongation (25).

Numerous studies suggested the existence of genetic predisposition for TTC. Genetic polymorphisms for cardiac α1-, β1-, and β2-adrenergic receptors, GRK5, and estrogen receptors have been described (3). However, the genetic associates need to be evaluated in larger TTC cohorts in the future.

TAKOTSUBO CARDIOMYOPATHY AND NEUROLOGICAL DISORDERS

Multiple clinical cases of emerging TTC after acute disorders of the central nervous system published. Over the last decades remarkable interactions of the brain and heart derived from clinical complications of patients with neurological disorders followed or accompanied by newly cardiac disorders have been described. Hence, the term brain-heart-syndrome was introduced compromising cardiac damage following brain disorders (26). **Table 1** summarizes the key studies of the association of TTC and neurological and psychiatric disorders.

Common acute neurological disorders associated with the occurrence of TTC are ischemic strokes, subarachnoid hemorrhages and seizures (2). Whereas, subarachnoid hemorrhages were found to be strongly associated with TTC in various studies. In a recently published cross-sectional study the strongest associations between acute neurological diseases with following TTC have been found for subarachnoid hemorrhages, status epilepticus and less commonly for seizures (27). Interestingly, Morris et al reported a negative association of traumatic brain injury and TTC (27). Further neurological disorders associated with TTC are transient global amnesia, meningoencephalitis, migraine headache, intracerebral hemorrhage and ischemic stroke (27). In one study patients with aneurysmal subarachnoid hemorrhage induced TTC showed a high association with inter alia (i.a.) following cerebral vasospasm, pulmonary edema and longer duration of intubation (28). Hence, acute neurological disorders are counted to be an important physical trigger of TTC and every patient with symptoms suggestive for ACS should be worked up carefully regarding possible TTC. Over the last decades research focused on the hypothalamic-pituitary-adrenal axis (HPA-axis) as major neuroendocrine system regulating the release of i.a. cortisol from the adrenal gland, shifting the metabolism to higher stress levels (26). Higher serum cortisol levels have been correlated with stroke severity and insular damage (26). Additionally, the sympathetic activity levels are increased in patients with ischemic stroke due to activation of the HPA axis, resulting in i.a. significant increases of catecholamine blood levels. Those lead to higher risks of occurrence of arrhythmias and myocardial damage with resulting inflammatory responses of the affected myocardial area (26, 29). Local myocardial necrosis can lead to advanced inflammatory processes with antigen-dependent autoimmunity and exaggerated immune-mediated tissue damage, which needs to be further investigated in TTC patients (29). Furthermore, animal studies have shown an increase of plasma catecholamine levels after ischemic stroke, which is directly proportional to the incidence of myocardial damage followed by cardiac damage (26). Especially, ischaemic or hemorrhage stroke of the insular cortex are reported to have major influence on cardiac function (26). Interestingly, the right hemisphere seems to control the sympathetic activity, whereas the left hemisphere regulates parasympathetic activity (26). For example infarctions of the left hemisphere of the brain are associated with arrhythmias, a decreased cardiac wall motion and an increased risk of adverse cardiac outcome (26).

Moreover, anatomical brain alterations have been described in TTC patients. A MRI study performed with a TTC cohort derived from the International Takotsubo Registry visualized reduced gray-matter volume of structures in the brain areas of the limbic system, such as the amygdala, insula, cingulate cortex and hippocampus in patients with TTC (30). However, it remains to be elucidated, whether these anatomic abnormalities are pathophysiological factors contributing to the pathogenesis of TTC or the consequence of TTC (30). Furthermore, cerebral MRI imaging of TTC patients has shown a reduced connectivity of both the brain regions of the limbic system and the autonomic nervous system (30).

TAKOTSUBO CARDIOMYOPATHY AND PSYCHIATRIC DISORDERS

In general, prevalence rates of psychiatric and neurological disorders are reported to be high in patients with TTC (2, 5). Also, TTC patients have been found to have higher rates

TABLE 1 | Key studies on association between Takotsubo cardiomyopathy with neurological and psychiatric disorders.

Study	Study type	Number of patients	Associated neurological psychiatric disorder
Morris et al. (27)	Cross-sectional retrospective analysis	National inpatient sample TTC with acute neurological disorder = 155,105 TTC without acute neurological disorder = 149,273	Association of TTC with following acute neurological disorders: SAH (OR 11.7; 95% CI 10.2–13.4), status epilepticus (OR 4.9; 95% CI 3.7–6.3), seizures (OR 1.3; 95% CI 1.1–1.5), transient global amnesia (OR 2.3; 95% CI 1.5–3.6), meningoencephalitis (OR 2.1; 95% CI 1.7–2.5), migraine (OR 1.7; 95% CI 1.5–1.8), intracerebral hemorrhage (OR 1.3; 95% CI 1.1–1.5), and ischemic stroke (OR 1.2; 95% CI 1.1–1.3. Traumatic brain injury is negative associated with TTC (OR 0.7; 95% CI 0.6–0.9)
Lee et al. (28)	Cross-sectional retrospective analysis	Mayo Clinic neurological intensive care unit SAH-induced TTC = 8 No controls	Association of TTC with aneurysmal SAH with following cerebral vasospasm ($n = 6$) and pulmonary edema ($n = 5$)
Templin et al. (5)	Cross-sectional retrospective analysis	International Takotsubo registry TTC = 455 ACS = 455	55.8% of TTC patients had history or an acute episode of neurologic or psychiatric disorder, whereas only 25.7% ACS patients had neurological psychiatric disorder ($P < 0.001$)

ACS, acute coronary syndrome; SAH, subarachnoid hemorrhage; TTC, Takotsubo cardiomyopathy.

of psychiatric and neurological disorders compared to ACS patients (2). Common predisposing triggering factors of TTC are life events associated with emotional (e.g., panic or anxiety, surprise birthday parties) and physical (e.g., acute respiratory failure or central nervous system conditions) stress (5, 31). More recent data have shown, that emotional triggers are not as common as physical triggers in TTC patients (5). More specific, existing physical triggers of TTC were found to be independent predictors for in-hospital complications (5). Noteworthy, female TTC patients reported more anamnestic emotional triggers prior the occurrence of TTC than male TTC patients, who showed physical triggers prior to the onset of TTC more often (5). Smeijers et al. demonstrated in a small retrospective analysis TTC patients exhibit significant higher levels of depressive symptoms in well-established Patient Health Questionnaire compared to healthy controls (32). Additionally, data derived from the International Takotsubo Registry revealed that 42.3% of studied TTC patients were diagnosed with a psychiatric disorder, whereby 50.0% of these TTC patients had an affective disorder (5). El-Sayed et al. demonstrated within a large retrospective demographic analysis comparing TTC patients with orthopedic and myocardial infarction patients that TTC patients had higher risk for substance abuse (drug and alcohol abuse) (33). Additionally, the intake of medication to treat affective disorders such as selective norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, or benzodiazepines was reported to be more prevalent in TTC patients than in healthy controls (2, 5). Moreover, TTC patients are reported to not have significantly higher general anxiety levels than healthy controls, but higher levels of illness-related anxiety levels (32). Another study showed a high prevalence of diagnosed chronic anxiety disorder prior to the occurrence of TTC (34). Additionally, preadmission anxiety has been found in a case control study to be associated with the occurrence of TTC (35). Remarkably, Summers et al. suggested chronic psychological stress as a risk factor and acute stress as a triggering factor of TTC (34). Psychoneuroendocrinological seen patients with anxiety disorders or depression show increased sympathetic responses to emotional and physical stressors (36). The emotional stress triggering activation of the autonomic nervous system is mediated via two neurohumoral axes: the sympathetic-adrenal-medulla axis with catecholamine release in the adrenal medulla (immediate activation after stressor) and the HPA axis (activation via chronic stressors) with consecutive cortisol release from the adrenal cortex (36). Notably, also low cortisol blood levels have been reported in patients with chronic stress as compensatory mechanism to avoid hypercortisolism (36). Thus, the inhibitory effects of catecholamine release through high cortisol blood levels disappear and which can result in myocardial stunning (36). However, in order to further elucidate the neuroendocrinological mechanisms in TTC, future studies with larger patient cohorts under controlled study surroundings are necessary.

Further, type-D-personality is a controversial debated risk factor of TTC (2). Interestingly, one study revealed pre-existing psychiatric illness is related with an increased risk of TTC, but not an increased 30 day or long-term mortality (37).

DIAGNOSTIC OF TAKOTSUBO CARDIOMYOPATHY

The most important clinical tool in diagnosing TTC appears to be an accurate anamnesis of emotional and physical events prior to the onset of the patient's symptoms, if possible. Additionally, assessment of the patient's medical history, particularly of preexisting psychiatric and neurological diseases, is fundamental in the diagnostical workflow of TTC. As clinical presentation of ACS and TTC patients is similar, firstly blood levels of cardiac enzymes are obtained. Commonly, troponin as marker of cardiomyocytes necrosis is elevated, whereas the creatine kinase is usually only slightly elevated in TTC patients (8). High troponin values were shown to be a predictor of a worse in-hospital outcome, because of e.g., the occurrence of malign arrhythmias (8). However, there are patients where troponin

is either slightly or not elevated, which led to the term of disproportionately troponin elevation if compared to the seen wall motion abnormalities in TTC patients (6). In general, peak values of troponin blood levels are lower than in patients with ACS (8). An important clinical marker of TTC is elevation of N-terminal prohormone of brain natriuretic peptide (NT-proBNP), which has been shown to be associated directly with the degree of increased blood concentration of catecholamines as a marker of sympathetic overreaction and the severity of left ventricular dysfunction with associated systemic complications, such as pulmonary edema (38). ECG is routinely performed mainly to rule out acute coronary syndrome and myocarditis as differential diagnosis of TTC. Moreover, >95% of TTC patients show ECG abnormalities during the acute phase (3).

ELECTROCARDIOGRAM

The electrocardiogram (ECG) can be either completely unremarkable or shows ST-segment elevations or ST-segment depression in leads II, III, aVF, aVR, and V5 to V6 (2). Further, T wave inversions suggestive for cardiac repolarization abnormalities can occur in ECGs of TTC patients (39). Prolongation of QT-Intervals (>500 ms) indicate a higher risk for the occurrence of malign and potential life-threatening arrhythmias, such as torsades de pointes and ventricular fibrillation (3, 40). Consequently, close monitoring of ECG and haemodynamic parameters is recommended in TTC patients. Interestingly, recent clinical studies focused on QT prolongation and inflammatory processes in TTC patients. Song et al. have found significant higher levels of c-reactive protein in TTC patients presenting with QT prolongation in a retrospective analysis (40). Perazzolo et al. correlated the pathophysiological ECG changes in TTC patients with myocardial changes in T2-weighted signal cardiac MRI (41). In this study a correlation of apicobasal gradient of myocardial edema and dynamic T wave inversions and QT prolongation, indicating a dispersion of repolarization between apical and basal myocardial regions have been described (41). Elevated catecholamine blood concentrations are postulated as mutual pathophysiological element in TTC and SAH patients. Over the last decades various studies revealed a possible link between local cardiac sympathetic disruptions and reversible T-wave changes in ECG and is together seen with QTc-prolongation (42).

To differentiate TTC patients with ST-Elevations in ECG from ACS patients and also patients with non ST-Elevations, which are hemodynamically unstable and suspected TTC (typical wall motion abnormalities in TTE) patients need to undergo urgent coronary angiography to exclude relevant stenosis of the coronary arteries (8). In 2018 the InterTAK Diagnostic Score as part of the International expert consensus document on Takotsubo syndrome was published and suggested to be utilized in patients with no ST-elevations in ECG, but high probability of TTC (2). By use of the InterTAK Diagnostic Score patients with symptoms suggestive for an ACS and TTC patients with no ST-elevations in the ECG are distinguished (**Table 2**) (8). The InterTAK Diagnostic Score is positive, if ≥70 points are achieved. In these patients TTE is the recommended as next diagnostical step. Patients achieving ≤70 points are recommended to undergo coronary angiography with left ventriculography. Hemodynamically stable patients, with visualized TTC typical wall motion abnormalities and positive InterTAK Diagnostic Score are recommended to receive a coronary computed tomography angiography to visualize coronary status (8).

Prior the publication of the InterTAK Diagnostic Score of TTC the modified Mayo Clinic Criteria of TTC were commonly used to diagnose TTC in clinical routine (**Table 3**) (43). Another diagnostical definition was released by the European Society of Cardiology extending the modified Mayo Clinic Criteria of TTC (**Table 4**) (3).

THERAPEUTIC STRATEGIES OF TAKOTSUBO CARDIOMYOPATHY

The International expert consensus document on Takotsubo syndrome provides the most important strategies in treatment of TTC. Hence the clinical presentation of TTC patients is similar to ACS patients, prehospital treatment of TTC is identical to patients with ACS. It is recommended in TTC patients presenting in cardiogenic shock to avoid catecholamine treatment, as their use have shown higher mortality rates in TTC patients, which seems to be consistent with the assumed underlying pathophysiological mechanisms of TTC (8, 44). In the presence of left ventricular outflow tract obstruction after-load reducing medication is contraindicated. TTC Patients with

TABLE 2 | International Takotsubo diagnostic criteria score (InterTAK diagnostic score).

25 points	Female sex
24 points	Emotional stress
13 points	Physical stress
12 points	No ST-segment depression
11 points	Psychiatric disorders
9 points	Neurological disorders
6 points	QTc-Interval prolongation

TTC, Takotsubo cardiomyopathy.
Modified from Ghandri et al. (8).

TABLE 3 | Modified Mayo Clinic diagnostical criteria of Takotsubo cardiomyopathy.

1. Transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and frequently, but not always, a stressful trigger.
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
3. New ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
4. Absence of pheochromocytoma and myocarditis.

ECG, Electrocardiogram.
Modified from Akashi et al. (43).

TABLE 4 | Diagnostic criteria for Takotsubo cardiomyopathy of the European Society of Cardiology.

1. Transient regional wall motion abnormalities of LV or RV myocardium which are frequently, but not always, preceded by a stressful trigger (emotional or physical).
2. The regional wall motion abnormalities usually extend beyond a single epicardial vascular distribution, and often result in circumferential dysfunction of the ventricular segments involved.
3. The absence of culprit atherosclerotic coronary artery disease including acute plaque rupture, thrombus formation, and coronary dissection or other pathological conditions to explain the pattern of temporary LV dysfunction observed (e.g., hypertrophic cardiomyopathy, viral myocarditis).
4. New and reversible ECG abnormalities (ST-segment elevation, ST depression, LBBB, T-wave inversion, and/or QTc prolongation) during the acute phase (3 months).
5. Significantly elevated serum natriuretic peptide (BNP or NT-proBNP) during the acute phase.
6. Positive but relatively small elevation in cardiac troponin measured with a conventional assay (i.e., disparity between the troponin level and the amount of dysfunctional myocardium present).
7. Recovery of ventricular systolic function on cardiac imaging at follow-up (3–6 months).

BNP, B-type natriuretic peptide; ECG, Electrocardiogram; LBBB, Left Bundle Branch Block; LV, left ventricular; NT-proBNP, NT-proB-type Natriuretic Peptide; RV, right ventricular.
Modified from Lyon et al. (3).

primary pump failure may need mechanical left ventricular assist devices or an establishment of venoarterial-extracorporeal membrane oxygenation. Also, in cases of mild TTC close monitoring of patients in an intensive care unit setting is necessary to detect and treat possible arrhythmias adequately. Long term medication with beta-blockers after discharge from hospital, if not contraindicated, should be evaluated. However, randomized studies with large patients cohorts focusing on long-term treatment of TTC are needed.

CONCLUSION

In conclusion, TTC is an acute and reversible cardiac disease, which is associated with acute dysfunction of the central and autonomic nervous system. However, detailed molecular mechanisms need to be further elucidated, as the role of circulating and synaptic catecholamines as part of the autonomic nervous system are in their precise pathophysiological role unclear. Beside psychiatric disorders neurological disorders, especially acute neurological disorders have been shown to be associated with the occurrence of TTC. Cardiac enzymes are elevated in most TTC cases. Ultimately, every patient with suspected TTC needs visualization of myocardial wall motion in either TTE and/or coronary catheterization with left ventriculography depending on patient's hemodynamic stability. Non-specific ECG changes in TTC patients are reported, however the initial ECG can show either ST-segment elevations or ST-segment depressions, as well as negative T-waves and QTc-Interval prolongation in the initial ECG Acute treatment of TTC depends on patient's vitals and the occurrence of possible complications, like left ventricular outflow tract obstruction or wall ruptures. In most cases close monitoring for cardiac arrhythmia and symptomatic therapy is sufficient. In order to understand TTC in more detail and to develop specific cardiac diagnostical tools and therapeutic strategies both molecular and clinical research need to be performed in future. However, the recently published International expert consensus document on Takotsubo syndrome allows an extensive clinical characterization of TTC and should be used in daily clinical routine to provide excellent patient care.

AUTHOR CONTRIBUTIONS

SB conceptualized and drafted the manuscript. DL made substantial intellectual and editing contributions to the manuscript. CS reviewed the manuscript for style and language.

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REFERENCES

1. Satoh H, Tateishi H, Ushida T, Kodama K, Haze K, Hon M. *Takotsubo-Type Cardiomyopathy Due to Multivessel Spasm Clinical Aspects of Myocardial Injury: From Ischaemia to Heart Failure (in Japanese)*. Tokyo: Kagakuhyoironsya Co. (1990). p. 56–64.
2. Ghadri J-R, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International expert consensus document on Takotsubo syndrome (part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Euro Heart J.* (2018) 39:2032–46. doi: 10.1093/eurheartj/ehy076
3. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, et al. Current state of knowledge on Takotsubo syndrome: a position statement from the taskforce on Takotsubo syndrome of the heart failure association of the european society of cardiology. *Eur J Heart Fail.* (2016) 18:8–27. doi: 10.1002/ejhf.424
4. Khalid S, Khalid A, Maroo P. Risk factors and management of Takotsubo cardiomyopathy. *Cureus.* (2018) 10:e2626. doi: 10.7759/cureus.2626
5. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of Takotsubo (Stress) cardiomyopathy. *N Engl J Med.* (2015) 373:929–38. doi: 10.1056/NEJMoa1406761
6. Yalta K, Yilmaztepe M, Zorkun C. Left ventricular dysfunction in the setting of Takotsubo cardiomyopathy: a review of clinical patterns and practical implications. *Cardiac Fail Rev.* (2018) 4:14–20. doi: 10.15420/cfr.2018:24:2
7. Akashi YJ, Nef HM, Lyon AR. Epidemiology and pathophysiology of Takotsubo syndrome. *Nat Rev Cardiol.* (2015) 12:387–97. doi: 10.1038/nrcardio.2015.39
8. Ghadri J-R, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International expert consensus document on Takotsubo syndrome (part II): diagnostic workup, outcome, and management. *Euro. Heart J.* (2018) 39:2047–62. doi: 10.1093/eurheartj/ehy077
9. Y-Hassan S, Tornvall P. Epidemiology, pathogenesis, and management of Takotsubo syndrome. *Clin Auton Res.* (2018) 28:53–65. doi: 10.1007/s10286-017-0465-z

10. Deshmukh A, Kumar G, Pant S, Rihal C, Murugiah K, Mehta JL. Prevalence of Takotsubo cardiomyopathy in the United States. *Am Heart J.* (2012) 164:66–71.e61. doi: 10.1016/j.ahj.2012.03.020
11. Patel SM, Chokka RG, Prasad K, Prasad A. Distinctive clinical characteristics according to age and gender in apical ballooning syndrome (Takotsubo/stress cardiomyopathy): an analysis focusing on men and young women. *J Cardiac Fail.* (2013) 19:306–10. doi: 10.1016/j.cardfail.2013.03.007
12. Konstantinos G, El-Battrawy I, Schramm K, Uzair A, Hoffmann U, Martin B, et al. Comparison and outcome analysis of patients with Takotsubo cardiomyopathy triggered by emotional stress or physical stress. *Front Psychol.* (2017) 8:527. doi: 10.3389/fpsyg.2017.00527
13. Singh K, Carson K, Usmani Z, Sawhney G, Shah R, Horowitz J. Systematic review and meta-analysis of incidence and correlates of recurrence of Takotsubo cardiomyopathy. *Int J Cardiol.* (2014) 174:696–701. doi: 10.1016/j.ijcard.2014.04.221
14. El-Battrawy I, Ansari U, Behnes M, Hillenbrand D, Schramm K, Haghi D, et al. Clinical and echocardiographic analysis of patients suffering from recurrent Takotsubo cardiomyopathy. *J Geriatr Cardiol.* (2016) 13:888–93. doi: 10.11909/j.issn.1671-5411.2016.11.002
15. Brunetti ND, Santoro F, De Gennaro L, Correale M, Gaglione A, Di Biase M. Drug treatment rates with beta-blockers and ACE-inhibitors/angiotensin receptor blockers and recurrences in Takotsubo cardiomyopathy: a meta-regression analysis. *Int J Cardiol.* (2016) 214:340–2. doi: 10.1016/j.ijcard.2016.03.196
16. Tornvall P, Collste O, Ehrenborg E, Jarnbert-Petterson H. A case-control study of risk markers and mortality in Takotsubo stress cardiomyopathy. *J Am Coll Cardiol.* (2016) 67:1931–6. doi: 10.1016/j.jacc.2016.02.029
17. Roshanzamir S, Showkathali R. Takotsubo cardiomyopathy a short review. *Curr Cardiol Rev.* (2013) 9:191–6. doi: 10.2174/1573403X113090 30003
18. Kurisu S, Sato H, Kawagoe T, Ishihara M, Shimatani Y, Nishioka K, et al. Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. *Am Heart J.* (2002) 143:448–55. doi: 10.1067/mhj.2002.120403
19. Lyon AR, Rees PSC, Prasad S, Poole-Wilson PA, Harding SE. Stress (Takotsubo) cardiomyopathy—a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nat Clinic Pract Cardiovasc Med.* (2008) 5:22. doi: 10.1038/ncpcardio1066
20. Wilson HM, Cheyne L, Brown PAJ, Kerr K, Hannah A, Srinivasan J, et al. Characterization of the myocardial inflammatory response in acute stress-induced (Takotsubo) cardiomyopathy. *JACC Basic Transl Sci.* (2018) 3:766–78. doi: 10.1016/j.jacbts.2018.08.006
21. Scally C, Abbas H, Ahearn T, Srinivasan J, Mezincescu A, Rudd A, et al. Myocardial and systemic inflammation in acute stress-induced (Takotsubo) cardiomyopathy. Circulation. (2018) 139:1581–92. doi: 10.1161/CIRCULATIONAHA.118.037975
22. Kohan AA, Levy Yeyati E, De Stefano L, Dragonetti L, Pietrani M, Perez de Arenaza D, et al. Usefulness of MRI in Takotsubo cardiomyopathy: a review of the literature. Cardiovasc Diagn Ther. (2014) 4:138–46. doi: 10.3978/j.issn.2223-3652.2013.10.03
23. Lazzerini PE, Capecchi PL, Laghi-Pasini F. Long QT syndrome: an emerging role for inflammation and immunity. *Front Cardiovasc Med.* (2015) 2:26. doi: 10.3389/fcvm.2015.00026
24. Lazzerini PE, Capecchi PL, El-Sherif N, Laghi-Pasini F, Boutjdir M. Emerging arrhythmic risk of autoimmune and inflammatory cardiac channelopathies. *J Am Heart Assoc.* (2018) 7:e010595. doi: 10.1161/JAHA.118.0 10595
25. Lazzerini PE, Laghi-Pasini F, Boutjdir M, Capecchi PL. Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies. *Nat Rev Immunol.* (2019) 19:63–4. doi: 10.1038/s41577-018-0098-z
26. 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
27. Morris NA, Chatterjee A, Adejumo OL, Chen M, Merkler AE, Murthy SB, et al. The risk of Takotsubo cardiomyopathy in acute neurological disease. *Neurocrit Care.* (2018) 30:171–6. doi: 10.1007/s12028-018-0591-z
28. Lee VH, Connolly HM, Fulgham JR, Manno EM, Brown RD Jr, Wijdicks EF. Tako-tsubo cardiomyopathy in aneurysmal subarachnoid hemorrhage: an underappreciated ventricular dysfunction. *J Neurosurg.* (2006) 105:264–70. doi: 10.3171/jns.2006.105.2.264
29. Sattler S, Couch LS, Harding SE. Takotsubo syndrome: latest addition to the expanding family of immune-mediated diseases?. *JACC Basic Trans Sci.* (2018) 3:779–81. doi: 10.1016/j.jacbts.2018.11.003
30. Hiestand T, Hanggi J, Klein C, Topka MS, Jaguszewski M, Ghadri JR, et al. Takotsubo syndrome associated with structural brain alterations of the limbic system. *J Am Coll Cardiol.* (2018) 71:809–11. doi: 10.1016/j.jacc.2017.12.022
31. Redfors B, Shao Y, Omerovic E. Stress-induced cardiomyopathy (Takotsubo)–broken heart and mind? *Vascu Health Risk Manage.* (2013) 9:149–54. doi: 10.2147/VHRM.S40163
32. Smeijers L, Szabó BM, Kop WJ. Psychological distress and personality factors in Takotsubo cardiomyopathy. *Neth Heart J.* (2016) 24:530–7. doi: 10.1007/s12471-016-0861-3
33. El-Sayed AM, Brinjikji W, Salka S. Demographic and co-morbid predictors of stress (Takotsubo) cardiomyopathy. *Am J Cardiol.* (2012) 110:1368–72. doi: 10.1016/j.amjcard.2012.06.041
34. Summers MR, Lennon RJ, Prasad A. Pre-morbid psychiatric and cardiovascular diseases in apical ballooning syndrome (tako-tsubo/stress-induced cardiomyopathy): potential pre-disposing factors? *J Am Coll Cardiol.* (2010) 55:700–1. doi: 10.1016/j.jacc.2009.10.031
35. Salmoirago-Blotcher E, Rosman L, Wittstein IS, Dunsiger S, Swales HH, Aurigemma GP, et al. Psychiatric history, post-discharge distress, and personality characteristics among incident female cases of Takotsubo cardiomyopathy: a case-control study. *Heart Lung.* (2016) 45:503–9. doi: 10.1016/j.hrtlng.2016.07.008
36. Kastaun S, Gerriets T, Tschernatsch M, Yeniguen M, Juenemann M. Psychosocial and psychoneuroendocrinal aspects of Takotsubo syndrome. *Nat Rev Cardiol.* (2016) 13:688. doi: 10.1038/nrcardio. 2016.108
37. Nayeri A, Rafla-Yuan E, Farber-Eger E, Blair M, Ziaeian B, Cadeiras M, et al. Pre-existing psychiatric illness is associated with increased risk of recurrent Takotsubo cardiomyopathy. *Psychosomatics.* (2017) 58:527–32. doi: 10.1016/j.psym.2017.04.008
38. Nguyen TH, Neil CJ, Sverdlov AL, Mahadavan G, Chirkov YY, Kucia AM, et al. N-terminal pro-brain natriuretic protein levels in Takotsubo cardiomyopathy. *Am J Cardiol.* (2011) 108:1316–21. doi: 10.1016/j.amjcard.2011.06.047
39. Gupta S, Gupta MM. Takotsubo syndrome. *Indian Heart J.* (2018) 70:165–74. doi: 10.1016/j.ihj.2017.09.005
40. Song BG, Chung SM, Kim SH, Kim HJ, Kang GH, Park YH, et al. The QT prolongation and clinical features in patients with Takotsubo cardiomyopathy: experiences of two tertiary cardiovascular centers. *Anadolu Kardiyol Derg.* (2014) 14:162–9. doi: 10.5152/akd.2013.4745
41. Perazzolo Marra M, Zorzi A, Corbetti F, De Lazzari M, Migliore F, Tona F, et al. Apicobasal gradient of left ventricular myocardial edema underlies transient T-wave inversion and QT interval prolongation (Wellens' ECG pattern) in Tako-Tsubo cardiomyopathy. *Heart Rhythm.* (2013) 10:70–7. doi: 10.1016/j.hrthm.2012.09.004
42. Y-Hassan, S. The pathogenesis of reversible T-wave inversions or large upright peaked T-waves: sympathetic T-waves. *Int J Cardiol.* (2015) 191:237–43. doi: 10.1016/j.ijcard.2015.04.233
43. Akashi YJ, Goldstein DS, Barbaro G, Ueyama T. Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. *Circulation.* (2008) 118:2754–62. doi: 10.1161/CIRCULATIONAHA.108.767012
44. Templin C, Ghadri JR, Napp LC. Takotsubo (Stress) cardiomyopathy. *N Engl J Med.* (2015) 373:2689–91. doi: 10.1056/NEJMc15 12595

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