THE ISCHEMIC PENUMBRA: STILL THE TARGET FOR STROKE THERAPIES?

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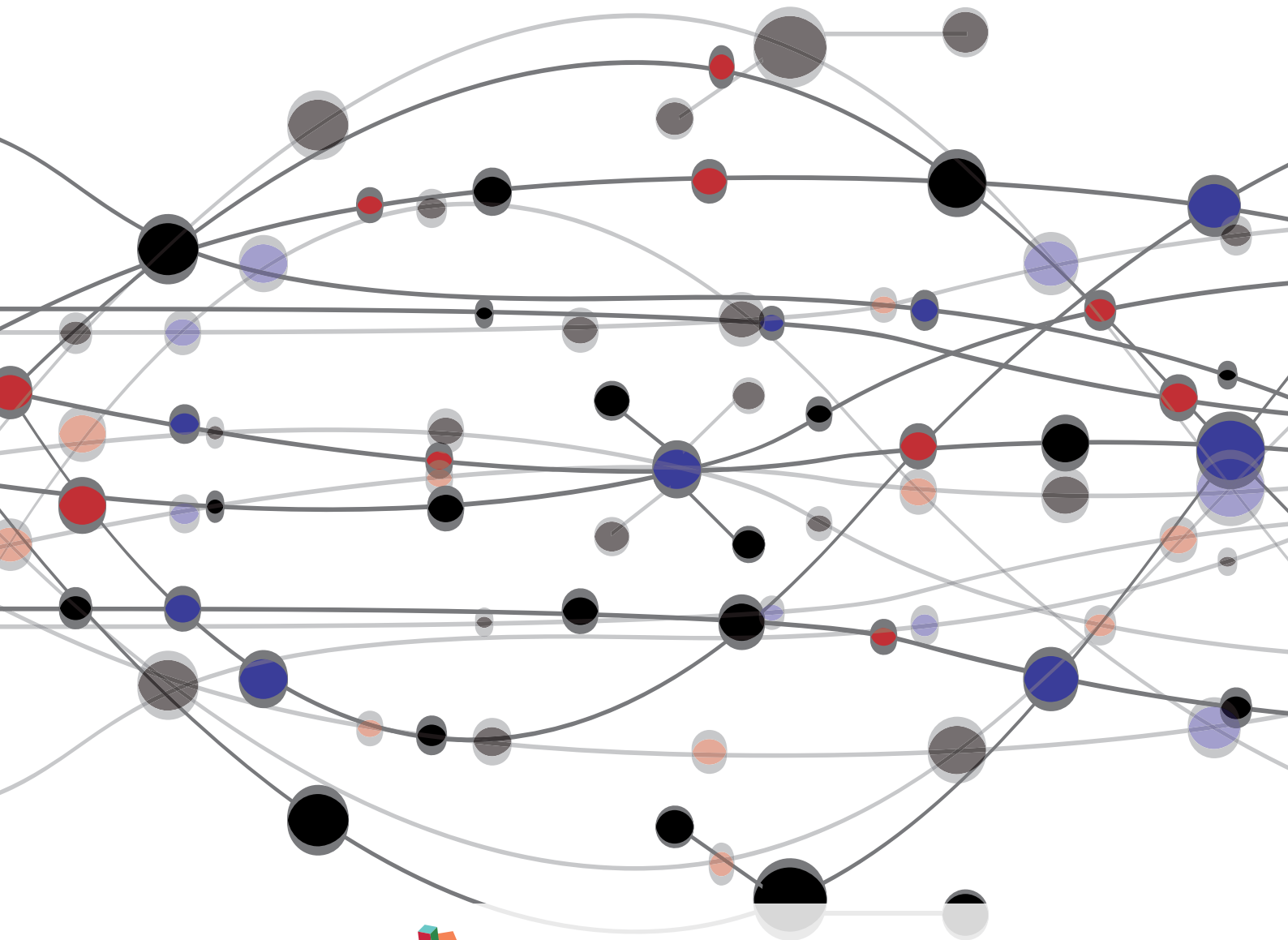

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THE ISCHEMIC PENUMBRA: STILL THE TARGET FOR STROKE THERAPIES?

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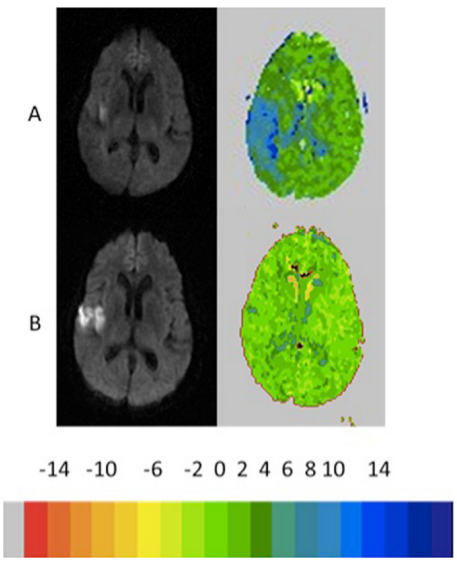

Ischemic penumbra represented by diffusion-perfusion mismatch at Day 1. Much of the area of hypoperfusion (which corresponded to dysfunctional, indicated by severity of the patient's neglect) progressed to infarct by Day 4.

Image taken from: Motta M, Ramadan A, Hillis AE, Gottesman RF and Leigh R (2015) Diffusion–perfusion mismatch: an opportunity for improvement in cortical function. Front. Neurol. 5:280. doi: 10.3389/fneur.2014.00280

The ischemic penumbra was initially defined by Symon, Lassen and colleagues in the 1970s as an area of brain tissue with inadequate blood flow to maintain electric activity of neurons but adequate blood flow to preserve the function of the ion channels. This area of tissue, receiving enough blood to survive but not enough to function, often surrounds or abuts the irreversibly damaged core in ischemic stroke. It was shown that if blood flow could be restored to this area of marginal perfusion, the tissue could survive and function again, and growth of the core could be prevented. Based on seminal PET studies, penumbra or "penumbral tissue" eventually took on a subtly different meaning - the area of brain that is destined to progress to infarct unless blood flow is restored within a particular time window. The penumbra thus became the target for all acute stroke interventions - to preserve viability of the tissue and restore function. New imaging techniques, including diffusion and perfusion MRI and CT perfusion, were developed to rapidly identify individuals with penumbra, who were thought to be the best candidates for aggressive interventions to restore blood flow, particularly beyond the licensed time-window for IV thrombolysis. However, most clinical trials have failed to establish the usefulness of identifying candidates for treatment in this way using pre-specified protocols and primary endpoints. These trials have used different and sometimes unvalidated thresholds of hypoperfusion as well as irreversible infarct and various definitions

of significant penumbra (or mismatch between irreversible infarct and hypoperfused, but salvageable tissue), and reanalysis of their data using more refined image processing showed post-hoc positivity. They have also evaluated outcome in a variety of ways, with few studies measuring the direct effect of restoring blood flow on the function of the penumbral tissue. Therefore, important remaining questions include how to define, characterize, and image the penumbra in acute stroke to achieve the greatest reliability and validity for what we want to measure, and whether this concept, so defined, provides an optimal target for stroke therapy using state-of-the-art trial design.

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EDITORIAL
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Editorial: The ischemic penumbra: still the target for stroke therapies?

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Keywords: acute ischemic stroke, penumbra, MRI perfusion, CT perfusion, tissue plasminogen activator

The ischemic penumbra refers to tissue at risk of infarction where perfusion is inadequate to support neuronal function, but just adequate to maintain cell viability (1). This dysfunctional, but salvageable tissue has been the target of all acute stroke therapies (2), and this concept underpinned the successful trials of intravenous thrombolysis using t-PA (3). Advanced imaging, including diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) MR and CT perfusion (CTp), was developed to rapidly identify stroke patients with still present penumbra, who were thought to be the best candidates for reperfusion therapies. However, early studies, using different methods for identifying penumbra, different measures of outcome, and different time-windows have not consistently confirmed the benefit of selecting treatment candidates on the basis of imaged penumbra. Therefore, some outstanding questions surround the optimal modality for imaging the penumbra, the most reliable thresholds in each modality, how long the penumbra can be maintained under what subject-specific circumstances, and the functional significance of persistent penumbra. These questions have taken on particular importance in light of the results of five recently completed randomized clinical trials showing benefit of endovascular treatment of stroke, when patients are carefully selected and treated on a timely basis. These trials include MR CLEAN (4), ESCAPE (5); EXTEND-IA (6), and two trials that have not been published, but the results of which have been presented at the International Stroke Conference [SWIFT PRIME (7) and REVASCAT[1]]. These trials have used different criteria to select patients for treatment, including different modalities of imaging (CT vs. MRI), but those that have shown the highest odds of favorable functional outcome have selected patients on the basis of having both a small core infarct, and either large volume of penumbral tissue ("tissue at risk") (6, 7) or the presence of moderate–good collateral circulation (5) that would support penumbral tissue in the face of proximal occlusion.

These recent studies, together with an earlier successful pilot trial of another thrombolytic agent that used MR-based selection of target penumbral patients (8) have shown the importance of selecting patients on the basis of the presence of penumbral tissue, but underscore the urgency of defining appropriate thresholds with imaging that can be obtained swiftly in order to maximize the efficiency of intervention. While the gold standard for both irreversibly ischemic core and penumbra has been defined by PET (2), PET cannot be obtained rapid enough to provide a practical guide for acute stroke treatment. Some centers are able to obtain rapid MRI, while most will rely likely on multiphase CT angiogram and/or CTp to guide intervention. It is critical that the stroke field adopts valid and reliable thresholds using any of these modalities to select candidates for intervention. Toward this goal, two MR vs. PET back-to-back studies have proposed validated MR-perfusion thresholds, based on small samples (9, 10). This Research Topic consists of a set of papers that addresses some of the controversies and intriguing questions that remain.

Kaesemann and colleagues (11) evaluated the impact of severe extracranial ICA stenosis on MRI measures of penumbra in patients with middle cerebral artery occlusion who were

[1] Davalos A, Jovin T. REVASCAT – clinicalTrials.gov, NCT01692379

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imaged within 4.5 h of onset. They evaluated core infarct volumes, mean transit time (MTT), T_{max}, cerebral blood volume (CBV), and cerebral blood flow (CBF) maps, as well as tissue at risk (T_{max} >6 – infarct volume). The presence of the additional extracranial stenosis did not affect measured infarct volume, MTT, T_{max}, or tissue at risk, but had a small influence on CBV. They hypothesized that extracranial stenosis may lead to ischemic preconditioning that results in improved collateral circulation and a consequent increase in CBV in the presence of acute stroke.

Wouters and co-workers (12) discuss proposed imaging criteria, including diffusion-FLAIR mismatch, for selecting patients who wake up with stroke and or have unknown onset. They point out that there are currently no data for selecting one set of criteria over another, but argue that identifying patients who have penumbral tissue with imaging should allow intravenous and/or endovascular treatment of many of these patients.

Leigh and colleagues (13) hypothesized that the conflicting conclusions from two large endovascular trials, MR RESCUE and DEFUSE 2, regarding the usefulness of MRI diffusion and perfusion imaging for selecting candidates for treatment were due to differences in definitions of core infarct and "tissue at risk." MRI scans from patients evaluated for endovascular therapy were processed using the methods published in the two trials. The volume of core infarct was consistently smaller when defined by MR RESCUE criteria than DEFUSE 2 criteria. The volume of tissue at risk was consistently larger when defined by the MR RESCUE criteria than DEFUSE 2 criteria. When these volumes were used to classify MRI scans, 9 out of 12 patients (75%) were classified as having salvageable tissue by MR RESCUE, while only 4 out of 12 patients (33%) were classified as having salvageable tissue by DEFUSE 2 criteria.

Marsh and co-workers (14) present two patients who underwent endovascular treatment with very different outcomes. They argue that robust collateral circulation supported a prolonged penumbra in the patient who showed minimal progression to infarct and outstanding functional outcome despite a delay in treatment.

Agarwal and colleagues (15) compared quantitative hemodynamic measures of CTp (volumes of penumbra defined by CBF, or PenCBF, and penumbra defined by MTT, or PenMTT), a visually defined CBF/CBV ASPECTS ratio, and a visually rated collateral circulation on CTA. They found that both PenCBF and PenMTT showed trends to decrease with increased time since onset. The CBF/CBV ASPECTS ratio, which was related to the PenCBF, significantly decreased with increased time since onset. In contrast, the rating of collateral response was not related to time since onset. These results raise some questions as to whether the presence of collaterals can be used as a surrogate for the presence of penumbral tissue in selecting candidates for intervention.

Campbell and colleagues (16) discuss challenges of imaging the penumbra and provide useful guidelines. They also discuss scenarios in which recanalization and reperfusion are discordant: both cases in which there is recanalization without reperfusion and reperfusion without recanalization (via enhanced retrograde collateral flow). Finally, they discuss infarct growth and the fact that there is sometimes persistent hypoperfusion that accounts for clinical deficits.

Motta et al. (17) investigated the clinical consequences of persistent hypoperfusion. They found that uninfarcted but hypoperfused tissue, with a threshold of 4–5.9 s delay on time-to-peak (TTP) maps on PWI occasionally persists for days and is associated with cognitive deficits such as aphasia or neglect. Furthermore, change in volume of hypoperfused tissue of 4–5.9 s delay and change in volume of ischemic tissue on DWI over the first few days were independently associated with change in cognitive function. Sebastian et al. (18) also show that persistent cortical hypoperfusion caused by arterial stenosis can cause aphasia or neglect (in cases of purely thalamic infarct), although some cases of aphasia after thalamic stroke are likely due to cortical dysfunction (diaschisis) in the absence of hypoperfusion caused by arterial stenosis.

Finally, Scalzo and colleagues (19) argue that there are likely to be detailed features of CT and MRI that are not currently tapped, which may provide useful information for guiding stroke intervention. Use of computer vision and machine learning to incorporate aspects of imaging data that we may not realize are relevant may yield data-driven approaches to clinical decision-support.

This Research Topic thus addresses important and timely concerns surrounding the issue of how the ischemic penumbra can best be rapidly identified on imaging in order to contribute to management of acute stroke.

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ORIGINAL RESEARCH ARTICLE
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Impact of severe extracranial ICA stenosis on MRI perfusion and diffusion parameters in acute ischemic stroke

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Purpose: The aim of this study was to investigate the impact of a coexisting internal carotid artery (ICA) stenosis on lesion volumes as well as diffusion and perfusion parameters in acute ischemic stroke resulting from middle cerebral artery (MCA) occlusion.

Material and methods: Magnetic resonance imaging data of 32 patients with MCA occlusion with or without additional ICA stenosis imaged within 4.5 h of symptom onset were analyzed. Both groups consisted of 16 patients. Acute diffusion lesions were semi-automatically segmented in apparent diffusion coefficient (ADC) MRI datasets. Perfusion maps of cerebral blood volume (CBV), cerebral blood flow, mean transit time and T_{max} were calculated using perfusion-weighted MRI datasets. Tissue-at-risk (TAR) volumes were generated by subtracting the ADC lesion from the hypoperfusion lesion defined by $T_{max} > 6$ s. Median ADC and perfusion parameter values were extracted separately for the diffusion lesion and TAR and used for statistical analysis.

Results: No significant differences were found between the groups regarding the diffusion lesion and TAR volumes. Statistical analysis of diffusion and perfusion parameters revealed CBV as the only parameter with a significant difference ($p = 0.009$) contributing a small effect ($\eta^2 = 0.11$) to the group comparison with higher CBV values for the patient group with a coexisting ICA stenosis, while no significant effects were found for the other diffusion and perfusion parameters analyzed.

Conclusion: The results of this study suggest that a coexisting ICA stenosis does not have a strong effect on tissue status or perfusion parameters in acute stroke patients except for a moderate elevation of CBV. This may reflect improved collateral circulation or ischemic preconditioning in patients with a pre-existing proximal stenosis balancing impaired perfusion from the stenosis.

Keywords: magnetic resonance imaging, brain ischemia, internal carotid artery stenosis, perfusion, diffusion

INTRODUCTION

Multi-parametric magnetic resonance imaging (MRI) is nowadays widely available and frequently used in most stroke centers (1). In particular, perfusion-weighted MR imaging (PWI) and diffusion-weighted MR imaging (DWI) have become important tools for today's diagnosis and treatment decision making in acute ischemic stroke patients.

Diffusion-weighted MR imaging is capable of displaying the water diffusion property of the cerebral tissue with high sensitivity (2). By this, DWI allows detecting acute ischemic stroke lesions within minutes after stroke symptom onset whereas brain regions displaying a strong diffusion restriction are assumed to represent the infarct core (3). PWI datasets on the other hand, enable the identification of cerebral tissue with reduced blood perfusion. It is typically assumed that the infarct core gradually expands into the hypoperfused tissue over time (4). The volumetric difference between the lesions defined in the PWI and DWI datasets is often used in the clinical and research setting as a surrogate for the ischemic penumbra or tissue-at-risk (TAR) (5–7). In general understanding, this TAR is the target for reperfusion therapy, e.g., using intravenous thrombolysis or thrombectomy, since it is assumed that the brain cells in this penumbra region are still salvageable in case of timely reperfusion.

The most common "phenotypic mechanisms" regarding the formation of an acute ischemic stroke are categorized by the TOAST (8) and CCS-classification system (9) into the four subtypes: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, and strokes with undetermined etiology, which includes combinations of all aforementioned subtypes. Pathophysiological considerations identify plausible differences between acute

strokes resulting from different etiologies regarding acute perfusion changes and collateral activation. Simplified, an acute embolic occlusion (cardioembolic stroke) is assumed to hit more or less healthy brain vasculature. In contrast to this, additional impairment of brain perfusion has to be considered in stroke resulting from large-artery atherosclerosis with pre-existing extracranial internal carotid artery (ICA) stenosis.

Thus, it may be hypothesized that an acute stroke patient with an artery occlusion and coexisting stenosis will suffer of a more serious hypoperfusion situation leading to a faster stroke evolution and worse outcome compared to a patient with the same artery occlusion but without a coexisting stenosis. On the other hand, it is widely accepted that the collateralization situation is a profound factor for the outcome severity after acute stroke (10, 11). Within this context, it may be hypothesized that a chronic carotid stenosis leads to a more profound development of the collateral circulation to compensate the long-lasting and constant perfusion impairment, which may be even beneficial to endure a hypoperfusion in case of an acute ischemic stroke. Another possible result of the perfusion deficit caused by a chronic carotid stenosis could be an ischemic preconditioning of the brain tissue leading to a protective effect as already described for cardial (12) and cerebral tissue (13).

The aim of this study was to study the impact of pre-existing high-grade ICA stenosis on tissue pathology in acute stroke. Within this context, we tested for differences in diffusion and perfusion parameters as well as volumes of infarct core and TAR of infarction between patients with occlusion of the proximal middle cerebral artery (MCA) with and without coexisting unilateral stenosis of the extracranial ICA.

MATERIALS AND METHODS

PATIENTS

In this retrospective cohort study, we examined MRI datasets of 32 patients admitted to our hospital with acute ischemic stroke due to occlusion of the MCA main stem alone (M1) or with coexisting ipsilateral stenosis of the ICA (M1 + ICA). Overall, 16 consecutive cases of M1 occlusion with coexisting ICA stenosis were included in this study, while 16 non-consecutive patients with M1 occlusion but without ICA stenosis were selected from our local database with a focus on achieving a balanced and age-matched group for comparison. The ICA stenosis was diagnosed by ultrasound imaging during the next 5 days after stroke symptom onset according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria (14) with a threshold >70%. A stenosis above this threshold is usually considered to represent a "high grade" and, thus, hemodynamically relevant ICA stenosis, which is also in accordance with consensus criteria established by expert panels of radiologists (15, 16). Patients with complete ICA stenosis (100%) were excluded from this study. After an initial exclusion of an intracerebral bleeding, PWI and DWI datasets were acquired among other MR image sequences within 4.5 h after symptom onset and prior to treatment in all patients.

The study was approved by the local ethics committee and informed consent was obtained from all subjects.

MR IMAGING

All MRI measurements were performed on a 1.5 T Avanto Scanner (Siemens, Erlangen, Germany).

Gradient-echo dynamic susceptibility contrast PWI datasets were acquired over a period of 90 s after application of contrast agent (approximately 15 ml of Bayer Magnevist, Bayer HealthCare, Leverkusen, Germany) with a TR = 2000 ms, TE = 45 ms, and flip angle = 90° and an image in-plane resolution of 0.94 mm^2. Each PWI dataset consisted of 24 slices of 5 mm thickness.

For DWI acquisition, a TR = 3500 ms, TE = 89 ms, flip angle = 90°, and diffusion weightings of 0 and 1000 s/mm^2 measured in three directions (in x, y, and z direction) were used. The image in-plane resolution and slice thickness of the DWI datasets were equal to the PWI datasets.

DATA ANALYSIS

In time-resolved 3D dynamic susceptibility contrast PWI datasets, the passage of contrast agent results in a reduction of signal values due to shortening of relaxation times. To enable a quantitative perfusion analysis, the single data points of each temporal signal curve $S(t)$ in the PWI datasets need to be converted to relative transverse relaxivity $\Delta R_2^*(t)$ changes using the following equation:

$$\Delta R_2^*(t) = -\frac{k}{\mathrm{TE}} \ln\left(\frac{S(t)}{S_0}\right) \quad (1)$$

where k denotes a proportionality constant, which was set to 1, TE the echo time, and S_0 the baseline MRI signal. Since $\Delta R_2^*(t)$ is only relative to the real contrast agent concentration, the correction formulas and values described in Ref. (17) were used for conversion of $\Delta R_2^*(t)$ to concentration time curves $C(t)$ in which the time-dependent contrast agent concentration is measured in millimoles:

$$\Delta R_2^*(t) = r_{\mathrm{tissue}} C(t), \quad (2)$$

where C is the contrast agent concentration and r_{tissue} the relaxation effect, which was set to 0.044 ms × mM^{-1} as appropriate for 1.5 T field strength. After conversion to concentration time curves, quantitative perfusion parameters were calculated for each voxel of the PWI dataset by solving the following equation:

$$C(t) = \mathrm{CBF} \cdot R(t) \otimes C_a(t), \quad (3)$$

where $C(t)$ denotes the tissue concentration curve, CBF the cerebral blood flow, $C_a(t)$ the arterial input function, $R(t)$ the residue function, and ⊗ the convolution operator. The arterial input function was interactively selected by an experienced observer as a single voxel next to the proximal segment of the MCA contralateral to the diffusion deficit with dynamic visualization of the concentration time curves. Afterward, the selected AIF for each patient was corrected using the corresponding correction formula and parameters for large vessels described in Ref. (17):

$$\Delta R_2^*(t) = rC(t) + qC(t)^2, \quad (4)$$

Here, $r = 7.6 \times 10^{-3}$ ms × mM^{-1} and $q = 574 \times 10^{-6}$ ms × mM^2 were used for correction of the AIFs obtained from the 1.5 T PWI datasets.

The block-circulant singular value decomposition as described by Wu et al. (18) together with a truncation threshold of 0.2 was

used to solve the Eq. (2). Apart from the CBF parameter, which results directly from the deconvolution in terms of the maximum value of the residual function, the cerebral blood volume (CBV) parameter was determined by calculating the area under the residue function, and the T_{max} parameter as the time point where the residue function reaches its maximum. Finally, the mean transit time (MTT) parameter was calculated according to the central volume theorem (19) dividing the CBV by the CBF parameter.

For segmentation of the acute diffusion restriction, the DWI dataset acquired with the two different *b*-values was used to calculate the corresponding apparent diffusion coefficient (ADC) parameter map using the Stejskal–Tanner equation (20). The DWI lesion was then segmented by interactively placing at least one seed point within the diffusion restriction, which was then used within a volume growing segmentation with a fixed upper ADC-threshold of 550×10^9 mm^2/s (21, 22).

For definition of the hypoperfused tissue, the PWI parameter maps were registered to the DWI sequences using a rigid registration technique with linear interpolation and maximization of the mutual information metric. After this, the segmented voxels of the diffusion restriction were used as seeds for a second volume growing segmentation based on the T_{max} maps. In accordance to recent stroke studies (23), a threshold of $T_{max} > 6$ s was used for the definition of hypoperfused tissue. The DWI lesion was then subtracted from the perfusion lesion to obtain two volumes-of-interests (VOIs), which do not overlap. These two VOIs (DWI lesion and TAR) were used for lesion volume quantification as well as extraction of the corresponding median values of ADC and four perfusion parameters (T_{max}, MTT, CBV, and CBF), which were used for statistical analysis (see **Figure 1**). Median instead of average values were used in this study due to the non-normal distribution of the physiological parameters.

All image processing steps were performed in this work using the in-house developed software tool AnToNIa (7).

STATISTICAL ANALYSIS

The distribution of each parameter was examined. In case of skew distributions, the median and interquartile range (IQR) are reported and in case of a normal distribution, the mean and corresponding standard deviation are reported.

Prior to performing statistical tests, the continuous values of the five perfusion and diffusion parameters were transformed to normal distributions using the Box–Cox technique (24), if required. Group comparisons were performed using Student's *t*-test for variables in interval scale with a normal distribution, Mann–Whitney *U*-test for variables in interval scale without normal distribution, and Fisher's-exact-test for variables in nominal scale.

A two-way MANOVA was used to compare the diffusion and perfusion parameters for region (DWI lesion vs. TAR) and group (M1 vs. M1 + ICA). All tests were performed two-sided. A *p*-value <0.05 was considered significant. Nominal *p*-values are reported without correction for multiplicity.

For the interpretation of effect sizes (25), a partial squared $\eta \geq 0.04$ was considered as a small, a partial squared $\eta \geq 0.25$ as a moderate, and a partial squared $\eta \geq 0.64$ as a large effect in accordance with the recommendations by Ferguson (26).

The statistical analysis was performed using IBM SPSS Statistics (Version 19.0, IBM, Armonk, NY, USA).

RESULTS

CLINICAL CHARACTERISTICS

Clinical characteristics of the patients included in this retrospective study are given in **Table 1**. Mean age was similar in both groups (68 years for the M1 group and 64 years in the M1 + ICA group). In contrast to this finding, there was an imbalance regarding the gender distribution with 81.3% female patients in the M1 group compared to only 18.8% female patients in the M1 + ICA group. Mean NIHSS-score at admission was 15 points in both groups. Time from symptom onset to MRI was also comparable for both groups.

INFARCT LESION VOLUMES AND PERFUSION PARAMETERS

Overall, large TAR volumes were found in both groups (see **Table 2**). Both the DWI lesion and the TAR volume were larger in the M1 group. However, this difference was not significant.

The results of the quantitative perfusion and diffusion analysis are given in **Table 3**. With respect to the different lesion

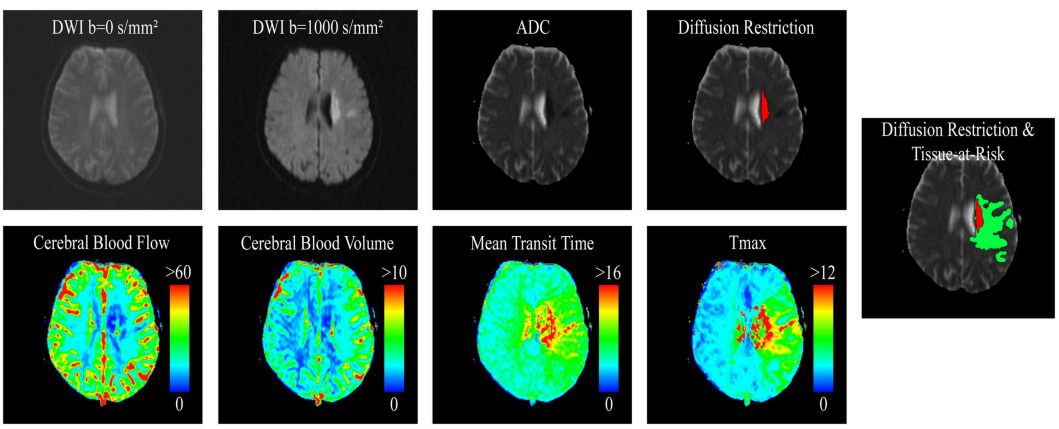

FIGURE 1 | Selected slice from a DWI dataset and corresponding apparent diffusion coefficient (ADC) parameter dataset used for definition of the diffusion restriction as well as corresponding perfusion parameter maps CBF (in milliliter per 100 gram per second), CBV (in milliliter per 100 gram), MTT (in seconds), and T_{max} (in seconds), also used for tissue-at-risk definition.

Table 1 | Patient's baseline data (mean ± SD).

	M1	M1 + ICA	*p*-Value
Gender			
Male	3 (18.8%)	13 (81.3%)	0.001
Female	13 (81.3%)	3 (18.8%)	0.001
Age (years)	68 (±12)	64 (±13)	0.328
NIHSS at admission	15 (±5)	15 (±6)	0.780
Time-to-MRI (minutes)	189 (±94)	137 (±65)	0.145

Table 2 | Median lesion volumes and interquartile range (Q1–Q3).

Region	M1	M1 + ICA	*p*-Value
DWI-lesion volume (ml)	9.7 (2.7–17.1)	4.8 (1.7–8.6)	0.381
Tissue-at-risk volume (ml)	69.0 (42.9–100.2)	52.2 (29.5–106.6)	0.724

Table 3 | Median VOI-based diffusion and perfusion parameters and interquartile range (Q1–Q3).

Parameter	M1	M1 + ICA
DWI lesion		
ADC (10^{-6} mm^2/s)	467.8 (453.3–531.6)	482.3 (445.2–525.4)
T_{max} (s)	14.1 (11.9–16.7)	15.1 (12.5–19.4)
CBF (ml/100 g/min)	10.9 (7.3–13.7)	14.0 (8.3–22.5)
CBV (ml/100 g)	2.1 (1.5–2.6)	2.7 (1.9–5.0)
MTT (s)	13.9 (11.5–14.8)	13.9 (11.7–16.4)
Tissue-at-risk		
ADC (10^{-6} mm^2/s)	824.1 (775.1–864.9)	839.8 (825.0–863.1)
T_{max} (s)	11.2 (9.7–12.9)	12.1 (10.4–14.2)
CBF (ml/100 g/min)	20.7 (15.6–24.0)	21.9 (15.5–27.3)
CBV (ml/100 g)	3.5 (3.2–4.4)	4.2 (3.1–5.9)
MTT (s)	11.7 (11.1–13.5)	13.9 (12.5–14.8)

compartments, lower median ADC, CBF, and CBV values were found in the DWI lesion compared to the TAR volume independent of the group, while prolonged median T_{max} values were found in the DWI lesion. Regarding the comparison of patients groups, the median ADC, CBF, CBV, and T_{max} values appeared elevated in both lesion compartments in the group with coexisting ICA stenosis. The overall highest relative difference between the groups was found for the CBV parameter regardless of the lesion component and CBF parameter within the DWI lesion.

MANOVA analysis revealed four parameters with a significant difference and notable effect size regarding the two lesion compartments (see **Table 4**). More precisely, the difference in ADC values between the DWI lesion and TAR showed a $\eta^2 = 0.90$ ($p = 0.001$), which denotes a large effect. However, since thresholding of the ADC parameter map was used for definition of the DWI lesion, this difference is not surprising. Furthermore, significant differences and small effect sizes between the two lesion compartments were also found for the T_{max} ($p = 0.003$, $\eta^2 = 0.14$), CBF ($p = 0.002$, $\eta^2 = 0.15$), and CBV ($p = 0.014$, $\eta^2 = 0.10$) perfusion parameters.

Table 4 | Diffusion and perfusion parameter effect sizes.

Parameter	Lesion compartment (DWI vs. TAR)	Group (M1 vs. M1 + ICA)
ADC	**$\eta^2 = 0.90$ ($p = 0.001$)**	$\eta^2 = 0.03$ ($p = 0.150$)
T_{max}	**$\eta^2 = 0.14$ ($p = 0.003$)**	$\eta^2 = 0.01$ ($p = 0.440$)
CBF	**$\eta^2 = 0.15$ ($p = 0.002$)**	$\eta^2 = 0.03$ ($p = 0.149$)
CBV	**$\eta^2 = 0.10$ ($p = 0.014$)**	**$\eta^2 = 0.11$ ($p = 0.009$)**
MTT	$\eta^2 = 0.02$ ($p = 0.305$)	$\eta^2 = 0.04$ ($p = 0.108$)

Bold font indicates $p < 0.05$.

Regarding the comparison of the two patient groups, a significant difference ($p = 0.009$) and a notable effect size of $\eta^2 = 0.11$ was only found for the CBV perfusion parameter. In other words, a pre-existing carotid stenosis explains 11% of the variance in CBV. Apart from this, all other parameters tested in this study did not reach significance in the MANOVA analysis.

DISCUSSION

In our comparison of diffusion and perfusion parameters, as well as lesion volumes in acute ischemic stroke, the CBV was the only perfusion parameter with a considerable difference between patients with and without coexisting high-grade stenosis of the ICA. More precisely, CBV was significantly higher in patients with a M1 + ICA stroke, which holds true for the DWI lesion as well as TAR. However, the effect of pre-existing ICA stenosis on CBV was rather small. All other diffusion and perfusion parameters tested in this study contributed no significant effect to the group comparison. To sum up, this finding relativizes speculations on the impact of large-artery atherosclerosis on brain perfusion in acute ischemic stroke.

In the setting of carotid stenosis in patients without stroke, Lythgoe et al. (27) studied MRI perfusion parameters (CBF, CBV, and MTT) in 16 patients with unilateral carotid stenosis and compared the findings with PET data. Overall, a mean CBF value of 43 ml/100 g/min, a mean CBV value of 3.8 ml/100 g, and a mean MTT value of 6.2 s was found for the analyzed group of patients with unilateral stenosis. In our study, we found considerably smaller CBF, longer MTT, and slightly smaller CBV values. These considerable differences are most likely an expression of the concomitant acute stroke. Lythgoe et al. concluded from the results of their study that the extent of the MTT prolongation corresponds best to the degree of the carotid stenosis, whereas the change in CBF and CBV could indicate hemodynamic alterations due to compensatory collateralization. In agreement with our findings, an average increase in CBV values was observed, while a CBF decrease was only found in few patients.

In a similar study by Kluytmans et al. (28), which focused on the comparison of MRI perfusion parameters between gray and white matter in 17 patients with symptomatic unilateral carotid stenosis without stroke and a control group, no significant alteration of the CBF values but a significant increase of CBV and MTT values was found in the stenosis group. Nighoghossian et al. (29) published a similar work including five patients with symptomatic unilateral carotid stenosis also without an acute stroke, in which prolonged MTT and higher CBV values compared to normal subjects were

found. This is similar to the slightly increased CBV in acute stroke patients with coexisting ICA stenosis as found in our study.

So far, there is only limited data regarding the diffusion and perfusion situation in case of an acute MCA occlusion and concurrent carotid stenosis. For example, Neumann-Haefelin et al. (30) conducted a study investigating MRI perfusion parameters [TTP, MTT, relative CBV (rCBV) and relative CBF (rCBF)] and TAR volume in 28 stroke patients before and after intravenous thrombolysis. The results of this study revealed significantly larger TAR volumes in the stenosis group while the resulting infarct lesions in the follow-up MRI datasets were significantly smaller compared to the group with MCA occlusion without stenosis. Regarding the MRI perfusion parameters, no significant differences were found for ADC, TTP, MTT, rCBV, and rCBV values in the DWI lesion or in the TAR volume. Significantly higher TTP and MTT and significantly lower rCBF were only found in the peripheral regions of the TAR for the subgroup with carotid stenosis. In contrast to our analysis, in which absolute CBF and CBV values were used, the relative CBF as a parameter adjusted to the contralateral unaffected hemisphere was calculated. Absolute perfusion values were used in this study since it was previously demonstrated that a stenosis may not only result in perfusion changes in the affected hemisphere but also in the contralateral hemisphere (31) such that a normalization with average perfusion values from the contralateral hemisphere may lead to erroneous results. On the contrary, it needs to be emphasized that absolute perfusion values as used in this work are dependent on the selected arterial input function to a higher degree than relative perfusion values. However, great care was taken in this study to select good and comparable arterial input functions such that the influence of this should be less important.

Another reason for the different results found in this study compared to the study by Neumann-Haefelin et al. may be the type of deconvolution technique used for perfusion parameter map calculation. More precisely, it has been shown that the block-circulant singular value decomposition, which was used in this work, is less sensitive to contrast agent arrival time differences between the arterial input function and tissue compared to the standard singular value decomposition (18) as used in the study by Neumann-Haefelin et al. (30). Within this context, it has been shown that the $T_{\max}$ (32) as well as the CBF parameter (18) are especially affected by the simple contrast agent delay when calculated using a standard singular value decomposition. Overall, the results of this study suggest that the impact of an additional ICA stenosis on typically used perfusion parameters is rather low, such that common thresholds used for perfusion-based stroke analysis and quantification may even be valid in case of a coexisting ICA stenosis.

Based on simple pathophysiological considerations, a pre-existing severe internal carotid stenosis may limit the capability to compensate an acute MCA occlusion event by reduced perfusion pressure onto the occluded artery and by reduced blood flow via collaterals supplied by the anterior cerebral artery. This should be measurable using MRI perfusion parameters in terms of a prolonged MTT and $T_{\max}$ as well as a decreased CBF and CBV. One might also expect larger stroke lesion volumes in patients with an additional carotid stenosis. However, the results of our study do not support this assumption since the CBV perfusion parameter was the only parameter for which a significant difference reaching only a small effect size was found in the group comparison, with slightly elevated values in the ICA + M1 group. Likewise, no significant differences were found regarding the volumes of the DWI lesion or TAR between the two groups.

One possible explanation for these findings may be that a carotid stenosis, which was developed over a long time, may lead to the development of cerebral collateralization as a compensatory mechanism, for which Lythgoe et al. found some evidence in their study in terms of elevated CBV values (27). Within this context, it was, for example, demonstrated by Kim et al. (11) that the status of the collateralization does not only affect the cerebral hemodynamics, but also the clinical outcome. Furthermore, Bang et al. (10) found that the presence of collateral flow improves the response toward intravenous thrombolysis. This implicates that collateralization plays an important clinical role in acute ischemic stroke.

The main finding of this study that the diffusion and perfusion differences between the two groups are rather subtle except for the CBV parameter may be an indication that the collateral situation is indeed improved in these patients. A recent study by Cortijo et al. (33) suggests that an increased CBV is the best perfusion marker for a good collateral situation. Thus, the fact that the CBV is the only parameter in this study for which a considerable alteration between the two groups was found further supports the theory of an improved collateral circulation in patients with a coexisting stenosis. The finding that no significant differences were found between the two groups regarding the DWI lesion as well as TAR volume may be also an indicator for an improved collateral circulation in patients with a coexisting stenosis. However, no systematically collected data on collateral activation were available for this retrospective study such that this point remains speculative.

Another potential reason for the elevated CBV values as well as the similar DWI and TAR volumes found in this study could be an ischemic preconditioning caused by the coexisting carotid stenosis. A study by Wegener et al. (13) investigated MRI datasets (DWI datasets) of 65 patients with a first-time occurrence of an ischemic territorial stroke with and without prodromal transient ischemic attacks (TIA). In brief, significantly smaller infarct lesions (as defined in ADC parameter maps) were found in patients who had a prodromal transient ischemic attack while the analyzed perfusion parameters (MTT, CBF, CBV) were similar in both groups. In our study, only a non-significant trend for smaller DWI-lesion volumes as well as increased CBV values was found in the stenosis group. This may result from the fact, that a previous TIA and pre-existing ICA stenosis do not have the same ischemic preconditioning effect, and it may be hypothesized that brain perfusion is more strongly compromised in a symptomatic TIA compared to an asymptomatic carotid stenosis. On the other hand, severe hypoperfusion originating from a stenosis affecting the same brain region as a subsequent stroke could induce ischemic preconditioning due to additional recruitment of local mechanisms like nitric oxide (34). Within this context, it was, for example, found in preclinical studies that an effective ischemic preconditioning can be achieved after temporal occlusion of the MCA in mice (35).

There are limitations to this study. First, the number of datasets used in this retrospective study is small and results need to be considered exploratory. Second, we were not able to analyze final infarct volumes as follow-up datasets were not available for all patients included in this study. Third, the precise stenosis degree was not available anymore for all patients but only the graded information, e.g., high grade >70% as used in this study as an inclusion criterion. Thus, it was not possible to correlate the perfusion, diffusion, and volumetric metrics to the precise stenosis degree, which would be an interesting subject for future studies. It should be also highlighted that patients with a complete stenosis (100%) were excluded from this study since it was hypothesized that the effect of a complete ICA occlusion on perfusion, diffusion, and lesion volumes may differ considerably from that of a high grade but non-complete stenosis. Thus, the inclusion of patients with a complete stenosis might lead to a more heterogeneous study group. However, this hypothesis should be tested in more detail in further studies. Finally, no differentiation of white and gray matter, which may be relevant for the CBF and CBV perfusion parameter, was performed since high-resolution T1-weighted MRI datasets were not available due to MR acquisition time limitations.

In summary, the results of our study suggest that extracranial ICA stenosis does not have a strong effect on brain perfusion in case of an acute ischemic stroke except for slightly elevated CBV values. This may indicate improved collateral circulation or ischemic preconditioning resulting from chronic hypoperfusion, which counteract the additional perfusion impairment in acute stroke patients with a coexisting stenosis.

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Wake-up stroke and stroke of unknown onset: a critical review

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Patients, who wake up with an ischemic stroke, account for a large number of the total stroke population, due to circadian morning predominance of stroke. Currently, this subset of patients is excluded from revascularization-therapy since no exact time of onset is known. A large group of these patients might be eligible for therapy. In this review, we assessed the current literature about the hypothesis that wake-up-strokes occur just prior on awakening and if this subgroup differs in characteristics compared to the overall stroke population. We looked at the safety and efficacy of thrombolysis and interventional techniques in the group of patients with unknown stroke-onset. We performed a meta-analysis of the diagnostic accuracy of the diffusion-FLAIR mismatch in identifying stroke within 3 and 4.5 h. The different imaging-selection criteria that can be used to treat these patients are discussed. Additional research on imaging findings associated with recent stroke and penumbral imaging will eventually lead to a shift from a rigid time-frame based therapy to a tissue-based individualized treatment approach.

Keywords: wake-up-stroke, unknown-onset stroke, thrombolysis, thrombectomy, circadian rhythm

INTRODUCTION

About one in six persons older than 45 will suffer from stroke in their remaining lifetime (1). The only Food and Drug Administration approved medical therapy for stroke is intravenous tissue plasminogen activator (alteplase or IV tPA), which should be administered preferably as quickly as possible within 4 h 30 min (2). Despite the efficacy of IV tPA, the narrow therapeutic window precludes wide scale use of the therapy mainly because a large majority of patients arrive too late in the hospital. Additionally, observational studies indicate that between 8 and 25% of patients come to the emergency room with an unknown time of symptom onset (3–7). This includes patients who were sleeping and woke up with stroke-symptoms or patients who are unable to state the time of symptom onset and in whom no witness is available. Theoretically, if patterns on cerebral imaging could serve as a substitute for the time since the stroke had occurred, then this subset of stroke patients would not be excluded from thrombolytic therapy. Another approach could be to rely on the presence of imaging characteristics indicative of large areas of viable tissue, regardless of the individual's time since symptom onset, and use this information to use thrombolysis or other treatment strategies.

A large randomized controlled trial is currently being conducted in Europe to test MRI-based thrombolysis in strokes of unknown onset (8). The approach is to select patients based on an imaging pattern that appears to substitute reasonably well for time since stroke onset, the so-called diffusion/FLAIR (DWI/FLAIR) mismatch.

Here, we review the literature on "strokes of unknown onset" or that occur on awakening. We moreover provide a detailed overview of treatment studies that have already been completed in wake-up-strokes.

MATERIALS AND METHODS

In this paper, we review the evidence supporting the hypothesis that strokes discovered on awakening are recent. We assess the current literature on the efficacy and safety of thrombolysis in wake-up-stroke patients and patients with unknown onset of stroke. Finally, we review the imaging techniques that are proposed to determine if a patient with unknown onset of stroke will benefit from thrombolytic therapy.

A single author searched for articles in the Pubmed and Embase bibliographic databases using the following search terms: "wake-up-stroke," "unknown-onset stroke," and both these terms with the additional term 'treatment,' "circadian variation and stroke," and "diffusion-flair mismatch." We restricted our search on articles between 1990 and May 2014. We reviewed articles in the reference lists of included articles. We restricted our search to articles published in English. The final reference list was generated on the basis of relevance to the topics covered in this review. We performed a meta-analysis of diagnostic studies that assessed the DWI/FLAIR mismatch pattern in relationship to time since onset in unselected patients with precisely known symptom onset. We excluded articles that only focused on posterior circulation stroke or in whom sensitivity and specificity could not be determined

from the provided information. Two of the authors (AW, VT) independently extracted the number of true positives, false positives, true negatives, and false negatives within the first 3 h and within the first 4.5 h after symptom onset of each of the included studies. Discrepancies between the two authors were resolved by consensus. Data analysis was conducted using the statistical program Stata (Version 12.0, StataCorp, College Station, TX, USA), and the user-written command-midas, a module for meta-analytical integration of diagnostic test accuracy studies (author Ben Dwamena, Division of Nuclear Medicine, Department of Radiology, University of Michigan Health System, Ann Arbor, USA).

RESULTS

CIRCADIAN VARIATION IN STROKE ONSET

Similar to acute myocardial infarction and sudden cardiac death, there is a diurnal variation in the onset of stroke, with a higher frequency of strokes occurring in the morning. The incidence of early-morning strokes rises with around 50% compared to the nightly incidence (9). This variation is seen regardless of the type of stroke (ischemic, hemorrhagic, and transient ischemic attacks) in some publications (10), but other studies suggest a tendency to a bimodal curve in hemorrhagic strokes, with a second peak in the afternoon (11).

The mechanisms underlying this diurnal variation in cerebrovascular events are not exactly known. Endogenous factors may play a role in this early-morning dominance in cardiovascular events. An increase in blood pressure, an increase in platelet aggregation, and a peak in prothrombotic factors are thought to be contributing factors (12–14). Blood pressure is typically lower during the night and increases upon awakening (12). This phenomenon is prone to individual variation with some people having an exaggerated response (15). This so-called "morning surge" in blood pressure, is an independent risk factor for stroke. It is speculated that the blood pressure leads to an increase in the likelihood of the rupture of a fragile atherosclerotic plaque. Timing the administration of anti-hypertensive medication in the evening has been proposed as strategy to circumvent the early-morning rise (16). A morning increase in platelet aggregation is mainly seen on arising and standing, and is probably due to an increase in catecholamine levels, platelet count, and hemo-concentration in the morning (14). An increase in the platelet adhesiveness in morning hours has been reported instead of increased platelet counts but this may be caused by different measurement-techniques (17). Furthermore, Kozinski et al. (18) examined the diurnal effect of clopidogrel on the inhibition of platelet aggregation. They found less inhibition in the morning hours. A small study ($n = 11$) showed an increase in Lp(a) and fibrinogen, during the morning hours (19). It is not well understood how these molecules contribute to acute cardiovascular events, apart from their effect on chronic atherosclerosis. A matutinal endothelial dysfunction has also been reported. Using high-resolution ultrasound of brachial artery flow-mediated dilatation, a blunting of endothelial function in the morning was found (20). Integrity of endothelial function is important for several homeostatic mechanisms that influence cardiovascular risk and in this way might contribute to acute cerebrovascular events. But again, no consistent results were found (21, 22).

Exogenous factors can play an additional role. The variation in circulatory factors can be a consequence of an early-morning response to arousal and physical activity in the awakening state (23). Data suggest a different response to exercise in the morning, with a blunting of the normal blood pressure lowering effects of exercise. Additionally, an association was found between the very common obstructive sleep apnoe syndrome (OSA) and the occurrence of wake-up-strokes (24). OSA is associated with intermittent hypoxemia and sympathetic overactivity, which increases the cardiovascular risk profile and possibly the prevalence of wake-up-strokes as well (**Figure 1**).

WAKE-UP-STROKE CHARACTERISTICS

The increase in stroke-occurrence in the morning has implications for possible treatment of patients with wake-up-stroke. If most of the strokes detected on awakening indeed occur in the early-morning hours just prior to awakening, the patients might be eligible for treatment. A recent epidemiologic study in the United States (7) found that 35.9% of wake-up-stroke patients would have been eligible for thrombolysis if arrival time were not a factor. To confirm or reject the hypothesis that wake-up-strokes occur early in the morning and have similar characteristics as strokes while awake, studies have been conducted to explore the possible differences between strokes detected on awakening and strokes while awake. Several studies report that the clinical and imaging characteristics do not differ between these groups (**Table 1**). One study (25) looked at the characteristics in terms of clinical impairment, NIHSS, age, gender, stroke subtype of patients with wake-up-stroke, and found no difference to a control-group with defined onset time. Functional outcome also was similar. Another study compared the clinical and imaging data of patients with known time of stroke-onset and those with wake-up-strokes, evaluated within 24 h after the moment, they were last seen normal (3). Both groups had similar perfusion (PWI) and DWI-lesion volumes on magnetic resonance imaging and a similarly high percentage of PWI/DWI mismatch, even in the subgroups of people within 3 h after detection. A CT-based imaging study (6) found no difference in percentage of CT perfusion CBF/CBV mismatch in 170 of the

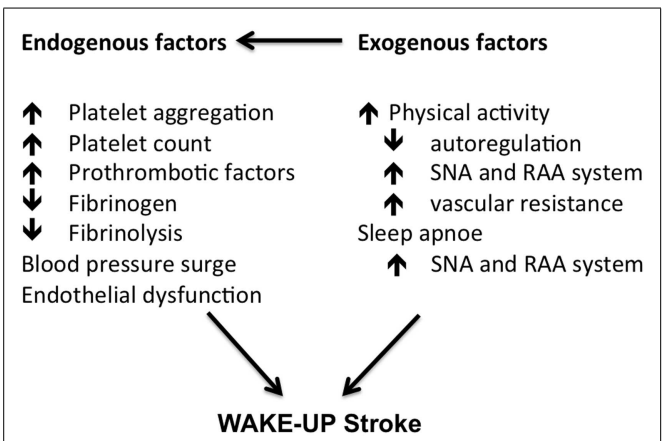

FIGURE 1 | Morning changes in cardiovascular factors contributing to a higher risk of stroke in the morning hours. Adapted from Ref. (23).

Table 1 | Clinical characteristic of patients with unknown-onset stroke.

Differences between patients with known and unknown stroke						
Authors	**Total number of patients (*n*)**	**Study set up and limitations**	**Wake-up (%) + unknown onset (%)**	**Clinical characteristics**	**Outcome**	**Imaging characteristics**
Koton et al. (25)	4408	Prospective, consecutive, hospital based	19	N.s.d. (age, gender, TOAST, NIHSS)	N.s.d.	Not specified
Fink et al. (3)	364	Prospective, consecutive, hospital based	27	N.s.d. (age, gender, TOAST, NIHSS)	Not specified	DWI/PWI mismatch ($p = 0.4$): n.s.d.
Silva et al. (6)	676	Prospective, hospital based ($n = 2$), consecutive. Not specified if reader was blinded, each center had own reader, time of detection was randomly chosen at 7.30 AM	20 + 18	N.s.d. (age, gender, TOAST, NIHSS); Unknown-onset patients were older ($p = 0.08$), more likely to be female ($p = 0.04$), and higher NIHSS ($p < 0.01$)	Not specified	CT perfusion CBF/CBV mismatch: n.s.d.
Serena et al. (27)	654	Retrospective, hospital based ($n = 6$), consecutive, three independent and blinded readers	24	Nsd. (age, gender, TOAST, NIHSS, aHT)	Not specified	Early signs of ischemia: n.s.d ($p = 0.35$)
Todo et al. (26)	81	Retrospective, consecutive, hospital based, only cardioemboligenic strokes, readers not specified	21 + 22	N.s.d (age, gender, TOAST, NIHSS)	Not specified	CT: more hypodens zones in unknown-onset group ($p > 0.001$)
Nadeau et al. (5)	2585	Prospective, consecutive, population based, informed consent, also inclusion of hemorrhagic strokes	13	More smokers ($p = 0.0016$), high blood pressure ($p = 0.0144$), and less tPa (2.1 vs. 13.5%)	Worse outcome: SIS seven points lower ($p = 0.0012$)	Not specified
Jimenez et al. (28)	813	Prospective, consecutive, hospital based	16	More obesity ($p = 0.058$), less tPa (0 vs. 3%)	Tendency to worse outcome ($p = 0.038$)	Not specified
Mackey et al. (7)	1854	Retrospective, hospital based ($n = 7$)	14.3	N.s.d. (age, gender, TOAST, NIHSS)	N.s.d.	Not specified

N.s.d = no significant difference, TOAST = trial of org 10172 in acute stroke treatment, aHT = arterial hypertension, SIS = stroke impact scale.

evaluated patients. Interestingly, patients with unknown time of onset occurring outside of awakening were also included, but this group had more neurological impairment and worse prognosis at discharge. Another study (26) found similar results with no differences in CT-findings between the known onset group and the wake-up group, but more hypodensities, indicative of later onset, were found in the unknown-onset group.

In contrast, some studies did report differences between wake-up strokes and strokes with defined onset. More severe neurological impairment and a non-significant trend toward worse functional outcome were observed in one study (28). Worse functional outcome, measured with the stroke impact scale (SIS-16) and a lower return to home after stroke was reported in a study that included hemorrhagic strokes. Worse outcomes were especially observed in subarachnoid hemorrhages occurring on awakening (5).

Although most studies report similar characteristics between strokes occurring at wake up and the strokes with a defined onset, these studies have limitations. Many studies were retrospective (7, 26, 27), single center (3, 25, 26, 28), and not population based (3, 6, 7, 25–28). Studies were heterogeneous in term of study population with some studies including hemorrhagic strokes (5). The inclusion and exclusion criteria varied across studies. Various imaging techniques were used and interpretation was not always blinded

Table 2 | Off-label treatment of patients with unknown-onset stroke.

Authors	Design	Number of patients with wake up or unknown-onset stroke control-group	Mean NIHSS	Mean age (years)	Door to needle time (min)	Type of stroke + time from symptom recognition till treatment	Imaging criteria	Treatment	sICH (%)	mRs 0–1 (%)	mRs 0–2 (%)
Iosif et al. (30)	Case-report	2	–	–	–	Wake-up	DWI/PWI and DWI/FLAIR mismatch	Intra-arterial tPa, thrombectomy			
Cho et al. (31)	Retrospective, observational three centers	32 223 (known onset)	14.5	67.5	154	Wake-up/unknown onset + 3–6 h	DWI/PWI –and DWI/FLAIR mismatch + DWI <1/2 ACM	IV tPa, IV tPa, and intra-arterial urokinase, intra-arterial urokinase	6.3	37.5	50
Adams et al. (32) AbESTT	Randomized clinical trial, >20 centers	22 (treatment) 21 (placebo) 758 (known onset)	10	68.6	?	Wake-up + <3 h	NCCT, CT < 1/2 ACM	Abciximab	13.6	10	32
Barreto et al. (4)	Retrospective, observational, 1 center	46 (treatment) 34 (no treatment) 174 (known onset)	16 (treatment) 10 (no treatment)	62.0	144	Wake-up + no further time specification	NCCT, CT > 1/3 ACM	IV tPa, IV tPa, and intra-arterial urokinase, intra-arterial urokinase	4.3	14	28
Breuer et al. (33)	Prospective, 1 center	10 (treatment) 35 (no treatment)	10.5 (treatment) 6 (no treatment)	68	80	Wake-up + <6 h	MRI visual PWI/DWI mismatch, no FLAIR hyperintensity, no DWI > 1/3 MCA	IV tPa (0.9 mg/kg)	0	31	60
Kim et al. (34)	Retrospective, 1 center	29 (treatment) 49 (no treatment)	13	66.9	?	Wake-up/unknown onset, <3 h	NCCT, CT < 1/3 ACM + Consecutive PWI before intra-arterial tPa	IV tPa, IV tPa, and intra-arterial urokinase, intra-arterial urokinase	10.3	37.6	44.8
Aoki et al. (35)	Prospective, 1 center	10	14	84	?	Wake-up/unknown onset, <3 h	DWI/FLAIR mismatch	IV tPa (0.6 mg/kg)	0	30	40
Ebinger et al. (36)	Observational substudy, 1 center	17 131 (known onset)	13	81	86	Wake-up/unknown onset + <24 h	MRI, DWI < 1/3 ACM	IV tPa (0.9 mg/kg)	0	29.4	41.2

(Continued)

Table 2 | Continued

Authors	Design	Number of patients with wake up or unknown-onset stroke control-group	Mean NIHSS	Mean age (years)	Door to needle time (min)	Type of stroke + time from symptom recognition till treatment	Imaging criteria	Treatment	sICH (%)	mRs 0–1 (%)	mRs 0–2 (%)
Kang et al. (37)	Prospective, 6 centers	83 (treatment) 156 (no treatment)	14	67.5	155	Wake-up/unknown onset + <6 h	DWI/PWI and DWI/FLAIR mismatch DWI < 1/3 ACM	IV tPa, IV tPa, and intra-arterial urokinase, intra-arterial urokinase	3.6	28.9	44.6
Michel et al. (38)	Single-center, prospective, randomized, double-blinded, placebo-controlled, phase II study	6 (treatment) 6 (no treatment)	16	59	122	Wake-up/unknown onset + <2 h	CT perfusion (MTT and CBV)	IV tPa (0.9 mg/kg)	0	?	4 (66.6)
Manawadu et al. (39)	Retrospective, case control, 1 center	68 326 (known onset)	12	74	73	Wake-up + >4.5 h, <12 h	NCCT, CT < 1/3 ACM	IV tPa (0.9 mg/kg)	2.9	16	37
Bai et al. (40)	Prispective, single center	48 138 (known onset)	11	61	?	Wake up + <12 h	MRI: DWI/FLAIR or T2 mismatch.	IV tPa	2	55	?
Natarajan et al. (41)	Retrospective, 1 center	30 (wake-up not specified)	13	72	210	Wake-up/known onset + 8–23 h	CT perfusion, >30% CBV CT <1/3 ACM	Intra-arterial thrombolysis, mechanical thrombectomy, balloon anioplasty, intra-arterial thrombolysis + mechanical thrombectomy, eptifibatide	33.3	?	20
Burkart et al. (42)	Retrospective, 1 center	40 (five unknown onset)	18	75.4	151	Wake-up/unknown onset/known onset + timing not further specified	Exclusion if MTT > 50% or NCCT > 1/3 ACM	Mechanical thrombectomy (sometimes with intra-arterial tPa or IV tPa)	10	?	50

(Continued)

Table 2 | Continued

Authors	Design	Number of patients with wake up or unknown-onset stroke control-group	Mean NIHSS	Mean age (years)	Door to needle time (min)	Type of stroke + time from symptom recognition till treatment	Imaging criteria	Treatment	sICH (%)	mRs 0–1 (%)	mRs 0–2 (%)
Stampfl et al (43)	Retrospective, observational, 1 center	19	17	73.7	–	Wake-up + timing not further specified	1. DWI/PWI > 50%, 2. CBV/TTP > 50%, + <1/3 MCA	Mechanical thrombectomy by stent-retriever-devices (sometimes with intra-arterial tPa pr IVtPa)	21.1	10	10
Jung et al. (44)	Prospective, 1 center	55 (wake-up) –, 22 (unknown onset) 782 (known onset)	15 (wake up) 18 (unknown onset)	61.9 (WUS), 63.5 (UOS)		Wake-up/unknown onset/known onset + <24 h	No stringent criteria, individual decision, PWI/DWI mismatch was assessed	Intra-arterial urokinase, mechanical thrombectomy, and intra-arterial urokinase, mechanical thrombectomy	3.7, 9.1	16.7, 23.8	37, 38.1

sICH = symptomatic intracranial hemorrhage, WUS = wake-up-stroke, UOS = unknown onset, NCCT = Non-contrast enhanced CT, mRs = modified ranking score, sICH = symptomatic intracranial hemorrhage. Barreto et al. (4): outcome-data were obtained at discharge, no long-term outcome available.

or performed by independent observers. Furthermore, publication bias cannot entirely be excluded, although this is unlikely since most of the studies are negative (i.e., showing no difference).

Further, prospective, population based, multicenter studies, using strictly defined inclusion criteria, employing standardized imaging with blind evaluation are therefore warranted.

MEDICAL AND INTERVENTIONAL THERAPY FOR PATIENTS WITH UNKNOWN TIME OF STROKE-ONSET: CURRENT EVIDENCE

We identified 12 studies in which wake-up-stroke-patients (WUS) were treated with intravenous tPA, either with or without intra-arterial therapy (**Table 2**). In 2006 (29) and 2008 (30) already, two case-reports were published about thrombolysis and mechanical reperfusion of patients with unknown stroke-onset. They suggested an imaging-based selection to define which patients would benefit from thrombolysis regardless of the time of stroke-onset.

THROMBOLYSIS

Subsequent studies compared outcome after treatment of known- and unknown-onset ischemic stroke. One of the first was a retrospective study among three centers, which included 32 patients with unknown-onset stroke and 223 controls (31). There was no difference in the outcomes of the two groups. The limitations of this retrospective study include the small number of patients and the imbalance in treatment methods among the two groups with more use of intra-arterial thrombolysis in the unknown-onset group. Images were not analyzed uniformly and like in most of the current studies, only one reader was used to interpret the images. In the AbESTT-trial (32) abciximab, a GPIIbIIIb receptor blocker was tested in a randomized controlled trial as a potential treatment of acute ischemic stroke. A subgroup of WUS patients who presented within 3 h after symptom recognition was also included. Unfortunately inclusion of this subgroup was stopped early, because of an unacceptably high rate of symptomatic intracranial hemorrhages (SICH). In the end, it was shown that abciximab did not improve outcome overall. WUS patients in this study exhibited significantly more signs of early ischemia on CT compared to the non-wake-up group, suggesting that these patients did not have very early stroke and had less chance to respond to reperfusion-therapies. Barreto et al. (4) retrospectively compared the outcomes of wake-up patients who were treated with intravenous tPA, intra-arterial urokinase or a combination of both, and those who did not. Non-contrast CT was used to exclude a hypodensity larger than 1/3 of the middle cerebral artery territory. Multimodal neuroimaging was not a part of their study-protocol. Despite a greater clinical impairment, they found a higher rate of good outcomes in the treated patients, however, at the expense of an increased mortality. Additionally, a comparison was made between wake-up-strokes and patients with known onset time who received thrombolysis within 3 h of symptom onset. Having adjusted for baseline differences in NIHSS, outcomes were similar. This retrospective study is limited by its lack of clinical or imaging selection criteria, the various treatment modalities, a possible selection bias and the relatively small sample size. In a similar study, thrombolysis in wake-up patients was significantly associated with a favorable outcome at 3 months (odds ratio = 6.842) (34). When a large diffusion-deficit on MRI was found, tPA-administration was

Table 3 | Characteristics of the proposed imaging-modalities.

	Advantages	Disadvantages
CT perfusion	• Widely available at ER • Fast • Low cost • Easy patient monitoring • Helps to identify patients who would benefit from therapy and those with high hemorrhagic risk	• Additional radiation dose • IV contrast • Difficult to detect small infarcts • Protocols and guidelines for quantitative thresholds vary • Different post-processing programs • AIF (arterial input function) and VOF (venous input function) difficult to localize • False positive results: Decreased blood flow due to vascular stenosis, extensive white matter disease, seizure and vasospasm • False negative results: partial volume effect around blood vessels
MRI perfusion	• High sensitivity and high predictive value for ischemia • Increasing evidence that ADC can reliable predict ischemic core • PWI/DWI mismatch for selection of patients who would benefit from therapy and those with high hemorrhagic risk (malignant profile)	• Duration of scan • Limited availability • Use of a contrast agent • Limitations: pacemakers, claustrophobia • Monitoring of patients is more difficult • Protocols and guidelines for quantitative thresholds vary • Different post-processing programs
DWI/FLAIR mismatch	• Imaging marker for timing of stroke-onset based on pathophysiologic tissue changes in the evolution of acute stroke • Qualitative assessment → no need for long postprocessing • Validation in large PRE-FLAIR study	• Relative high interrater- and intrarater-variability • Sensitivity is quite low → stroke-patients within time-interval to benefit from tPA can be missed

stopped. This happened in 5 out of the 22 cases at various time points after tPA infusion started. This increased the heterogeneity in the study population and highlights the need for uniform pre-treatment imaging selection criteria. A small study ($n = 10$), without a control-group, showed a safe selection of patients based on DWI/FLAIR mismatch with no SICH occurring (35). However, the sample size was obviously small and a lower than currently accepted dose of tPA (0.6 mg/kg) was used. Also the time from last seen well till treatment was on average 5.6 h, which is lower than in most other studies. A similar observational study reported no SICH and no difference in outcome in 17 similarly selected patients (36). The study of Kang et al. (37) had multiple advantages over the previous ones. A large group of patients with unknown-onset time of stroke ($n = 83$) were included and they used well-defined clinical and imaging selection criteria. Only WUS-patients were treated who both had a DWI/PWI and a DWI/FLAIR mismatch. After adjusting for age, sex, and baseline NIHSS score, reperfusion therapy significantly increased the incidence of good clinical outcomes in unclear-onset stroke patients compared to a matched-cohort of untreated patients (odds ratio, 2.25). However, although the clinical inclusion criteria were similar, the control patients did not undergo the same stringent imaging selection criterion, which biases the findings of this study. Other limitations were the participation of two centers with no previous experience in MRI-based thrombolysis studies. Only 1 of the 10 patients treated in these centers, did have a good outcome. Although they used two MRI-based selection criteria, no pre-trial training was foreseen. Organization of a training course in advance could have increased the reproducibility of the image protocols.

MECHANICAL THROMBECTOMY

Four studies [(41–44); **Table 2**] examined the possible benefit of mechanical thrombectomy, all based on perfusion (CT or MRI) scans and clinical criteria to include patients. One study (43) included 19 patients with wake-up-strokes. They used stent-retriever-devices for mechanical thrombectomy. Compared to other studies with known onset stroke, a larger number of SICH were found and patients had less favorable outcome after 3 months. Another study (44) found no significant difference in outcome between known and unknown-onset stroke patients. However, selection of patients was based on individual decision making and various treatment techniques were used over the years.

SUMMARY

From these pilot-studies, we conclude that many patients with wake-up or unknown-onset stroke might be helped by revascularization-therapy with relative safety. There is more experience with intravenous treatment than with endovascular therapies. Limitations in using clinical databases are the possible bias in selection of patients, completeness of data, and retrospective determination of outcome. Moreover, publication bias cannot be excluded, as there are no small studies published, which show

unfavorable results. Only two studies (32, 38) testing thrombolysis or thrombectomy were randomized. One was the AbESTT-trial (32), discussed previously and the other one was a small pilot-study with only 12 patients included (38). The imaging selection criteria used to select patients for treatment were not uniform, since most centers used individual decision making to treat this subset of patients. A large clinical randomized trial is therefore needed to confirm these preliminary results.

PROPOSED IMAGING SELECTION METHODS

Unknown time of onset is clearly a major reason not to receive thrombolysis (45). In the studies with off-label treatment of unknown-onset stroke patients, different imaging selection criteria have been used [**Table 2**; (46)]. These include visual or semi-quantitative analysis of the FLAIR-DWI mismatch, PWI-DWI mismatch, or CT perfusion based approaches (**Table 3**; **Figure 2**).

DWI-FLAIR MISMATCH

Several groups used the presence of a DWI/FLAIR mismatch to guide thrombolysis in patients with unknown-onset stroke (33, 35, 37, 40). The idea behind the FLAIR-DWI mismatch analysis principle is based on the pathophysiology of acute cerebral ischemia. Diffusion-weighted imaging is most sensitive to a restriction of the Brownian motion of extracellular water caused by cytotoxic edema. This phenomenon is already present within minutes after the event. FLAIR-images are sensitive for the detection of vasogenic edema, a phenomenon, which starts gradually in the hours after the initial event. This edema is thought to reflect loss of the integrity of the blood brain barrier.

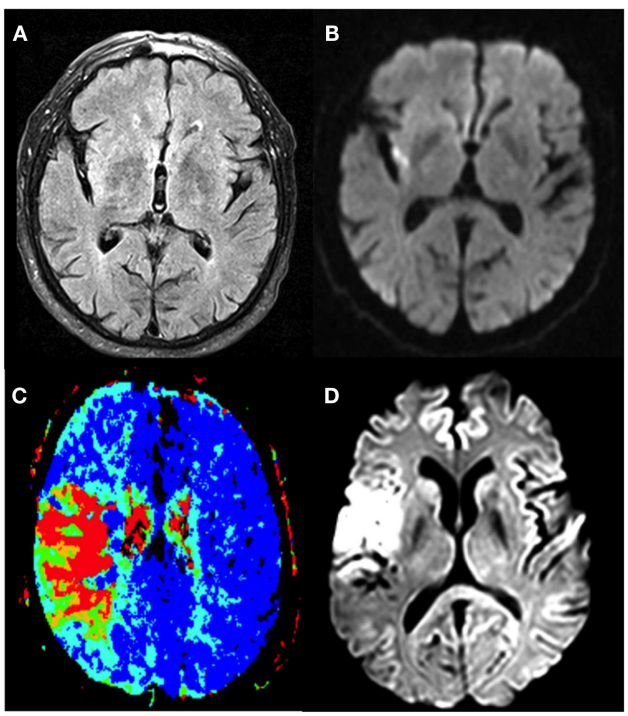

FIGURE 2 | The different imaging techniques used to select stroke-patients who would benefit from therapy. Patient 1 exhibits no FLAIR-lesion **(A)** and a clear DWI-lesion **(B)**, the so-called DWI-FLAIR mismatch pattern. Patient 2 has a PWI/DWI mismatch on imaging, with **(C)** representing the lesion on Tmax, and **(D)** the corresponding diffusion lesion.

A large multicenter observational study showed that the pattern of an acute ischemic lesion seen with DWI but not with FLAIR-imaging, decreases with longer time between onset of symptoms and MRI scanning (47). DWI/FLAIR mismatch had a sensitivity of 62%, a specificity of 78%, and a positive likelihood ratio of 3.6, for the detection of stroke patients within 4.5 h of stroke onset. In that study, a visual analysis was used that required complete absence of even subtle FLAIR lesions. In a later substudy (48), a more liberal visual rating system was used, in which subtle FLAIR lesions were still considered as DWI/FLAIR mismatch. This improved the sensitivity (0.86), but decreased the specificity (0.48) of this pattern to detect lesions within 4.5 h. The positive likelihood ratio for the liberal rating system was 2.6. The disadvantage of the liberal rating system is an increase in the interrater-variability for "subtle" FLAIR lesions. **Figure 3** shows a meta-analysis of reported diagnostic studies that assessed the DWI/FLAIR mismatch pattern in relationship to time since onset in patients with precisely known symptom onset. The overall sensitivity of the DWI/FLAIR mismatch for detecting stroke within 3 h is 74% and within 4.5 h is 62%, with a specificity of 82% at both time points. The diagnostic accuracy is quite heterogeneous and may reflect differences in inclusion criteria, definitions of FLAIR/DWI mismatch, acquisition techniques, proportions of small, and infratentorial lesions between the studies.

Semi-quantitative analysis of the FLAIR signal intensities has been proposed in order to avoid interpretation issues (53). However, this is controversial and in the PRE-FLAIR study an improvement over quantitative analysis of FLAIR signal was not better than visual analysis (48, 54). It has been shown that a significant amount of wake-up-stroke patients has such a DWI/FLAIR mismatch pattern (55). There are limitations though of the sole use of DWI/FLAIR mismatch to select patients for therapy. First there is no certainty about which technique (liberal or strict) has to be used to visually assess the presence of a DWI/FLAIR mismatch. Second, because of the low sensitivity, a large amount of possible eligible patients will be excluded from therapy. The interpretation of the mismatch pattern also depends on the type of stroke. With every 10 ml increase in diffusion volume, the odds to find a flair positive lesion increases with 7% (47). For patients with an infratentorial stroke, the DWI/FLAIR mismatch pattern seems to be less robust in identifying patients with early onset (56). The risk of bleeding in patients with a DWI/FLAIR mismatch is still uncertain. One recent study suggests a higher risk of bleeding with early FLAIR-hyperintensity (57), while another study found no association (58). Flair-positivity might be associated with a worse outcome after 3 months, but this finding still needs to be confirmed (59). Other imaging parameters have to be found to make a more optimal selection of patients who would benefit from therapy.

CT PERFUSION

Another approach is to select patients based on the presence of imaging markers of tissue at risk or other imaging characteristics. CT combined with perfusion CT is a widely available

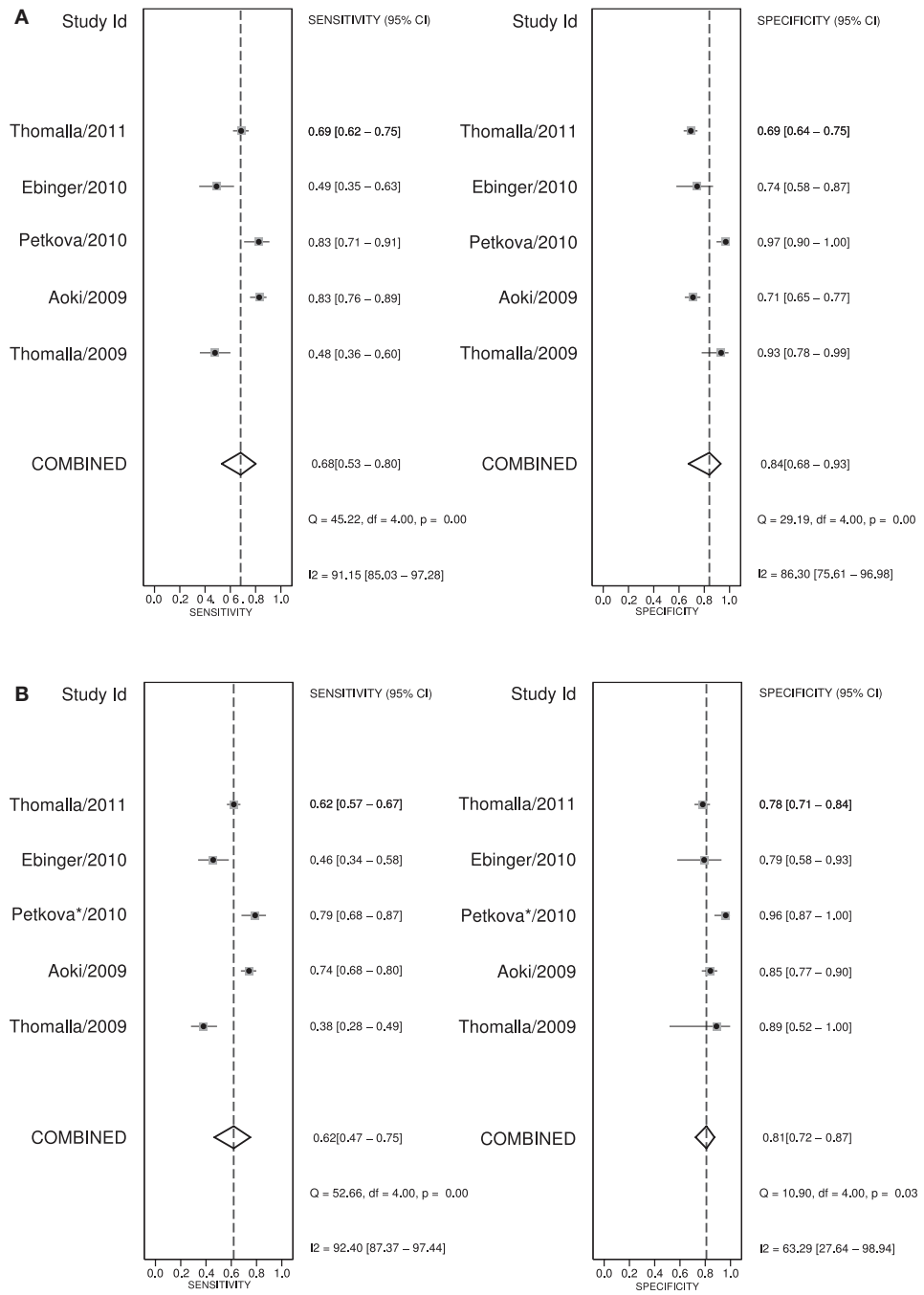

FIGURE 3 | Meta-analysis (47, 49–52) of the "strict" DWI/FLAIR mismatch pattern predicting stroke onset before 3 and 4 h. (A) shows the sensitivity and specificity for predicting stroke-onset before 3 h and **(B)** shows these values for stroke-onset before 4.5 h. *To predict stroke onset before 4.5 h the "liberal" method of DWI/FLAIR mismatch was used in the study of Petkova et al. (49).

technique that may help decide if patients with unknown-onset stroke, are eligible for off-label use of thrombolysis (29, 38, 41). Different hemodynamic parameters like cerebral blood volume (CBV), cerebral blood flow (CBF), delay time (Tmax), and mean transit time (MTT) have been proposed to identify areas of critical hypoperfusion. The ischemic core is variously defined as a region with markedly reduced CBV or CBF combined with prolonged MTT or Tmax. However, a real consensus on which parameter and threshold best represents critical hypoperfusion and core has not emerged yet. Different definitions with different thresholds have been proposed to define the tissue at risk. Wintermark et al. (60) did a ROC analysis and proposed an optimal threshold of 2 ml/100 g for CBV to define the ischemic core and 145% of MTT to define the tissue at risk of infarction. More recent evidence

suggests that relative CBF might be better to define infarct core then CBV (61, 62). The more recent literature suggests a threshold of CT-Tmax of >6 s to define the tissue at risk (63). Despite that no real consensus exists about the thresholds that should be used, the speed and wide availability make perfusion CT an interesting alternative compared to other perfusion-modalities.

PWI/DWI MISMATCH

Perfusion and diffusion based MR imaging techniques have been advocated as an imaging selection method in wake-up strokes (**Figure 2**). The disadvantage of the latter technique is the longer imaging time required and the limited availability of MRI compared to CT. Dynamic susceptibility contrast enhanced MRI is the most widely used technique. Arterial spin labeling is a newer method and has no need for contrast, but requires, in general, longer imaging times. MRI does have the advantage of a reliable prediction of the ischemic core with ADC-maps (64). However, the possible reversibility of the diffusion lesion, questions the paradigm that diffusion lesions represent the ischemic core. Analysis of the EPITHET-data showed that true DWI-lesion reversal is uncommon and if present would rarely alter treatment decision making (65). As with CT, difficulties arise in determining the optimal thresholds to differentiate ischemic core from salvageable brain tissue (66). Also the selection of the most optimal parameter or combination of parameters is still a matter of debate (67). An ADC-threshold of 600×10^{-6} mm^2/s seems a fairly robust parameter in predicting ischemic core tissue (64). The mismatch between an area that has a Tmax > 6 s and is below this ADC-threshold is currently considered in several clinical trials as an operational definition of the tissue at risk. A substudy of DEFUSE 2 (68) supported this hypothesis by showing that in patients with a strong reperfusion, there is a high correlation between baseline DWI-volume and final infarct and in patients with minimal or no reperfusion, there is a high correlation between the baseline PWI-volume and final infarct. To determine the tissue at risk the PWI-DWI mismatch is useful, with 120% most commonly used to define a mismatch, although more stringent criteria have been advocated, with studies now advocating a perfusion-diffusion ratio that is larger than 180%, dependent on the parameter that is used to define the perfusion abnormality. MRI can also detect the so-called " malignant" profile. The DEFUSE-data (69) showed that patients with a baseline DWI-lesion bigger than 100 ml and/or a PWI lesion of 100 ml or more with 8 s or longer of Tmax delay, suffered more intracranial hemorrhages after early reperfusion. The major drawback in the clinical use of MRI perfusion is that the extent of perfusion abnormalities varies among perfusion parameters, software packages, and various algorithms and that upon today no consensus is reached. Other techniques to define tissue at risk, like FDG-PET or SPECT, are less easily used in clinical practice. Two large trials to treat wake-up patients are currently ongoing, one based on DWI/FLAIR mismatch (WAKE-UP) (8) and one based on penumbral imaging (EXTEND) (70).

CONCLUSION

Wake-up-stroke and stroke with unknown time of onset are frequent. These patients are at present excluded from thrombolytic therapy. Evidence suggests that these strokes occur closely on awakening and most observational studies did not find differences in terms of clinical features or outcome after therapy, suggesting that at least a subset of these patients could benefit of thrombolysis or endovascular treatment. Selection of eligible patients is preferably done using neuro-imaging, but the optimal imaging selection strategy for treating these patients has not yet been defined. The proposed selection modalities have not been properly evaluated in randomized trials, therefore, inclusion in these trials is primordial. In case randomization is not possible, advocating treatment on the basis of the presence of a DWI/FLAIR mismatch or PWI/DWI mismatch can generally not be recommended. In this scenario, treatment must remain an individualized decision. Ongoing randomized controlled trials testing these strategies are the WAKE-UP trial (8) and the EXTEND-trial (70). Identifying a safe and efficacious selection strategy will not only benefit patients with WUS, but also allow moving away from a rigid time window based approach for all patients.

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A comparison of two methods for MRI classification of at-risk tissue and core infarction

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Objective: To compare how at-risk tissue and core infarction were defined in two major trials that tested the use of MRI in selecting acute stroke patients for endovascular recanalization therapy.

Methods: MRIs from 12 patients evaluated for possible endovascular therapy were processed using the methods published from two major trials, MR RESCUE and DEFUSE 2. Specifically, volumes of at-risk tissue and core infarction were generated from each patient's MRI. MRIs were then classified as whether or not they met criteria for salvageable tissue: "penumbral pattern" for MR RESCUE and/or "target profile" for DEFUSE 2 as defined by each trial.

Results: Volumes of at-risk tissue measured by the two definitions were correlated ($p = 0.017$) while the volumes of core infarct were not ($p = 0.059$). The volume of at-risk tissue was consistently larger when defined by the penumbral pattern than the target profile while the volume of core infarct was consistently larger when defined by the target profile than the penumbral pattern. When these volumes were used to classify the MRI scans, 9 out of 12 patients (75%) were classified as having a penumbral pattern, while only 4 out of 12 patients (33%) were classified as having a target profile. Of the 9 patients classified as penumbral pattern, 5 (55%) were classified differently by the target profile.

Interpretation: Our analysis found that the MR RESCUE trial defined salvageable tissue in a way that made it more likely for patients be labeled as favorable for treatment. For the cohort of patients examined in this study, had they been enrolled in both trials, most of the patients identified as having salvageable tissue by the MR RESCUE trial would not have been considered to have salvageable tissue in the DEFUSE 2 trial. Caution should be taken in concluding that MRI selection for endovascular therapy is not effective as imaging selection criteria were substantially different between the two trials.

Keywords: MR RESCUE, DEFUSE 2, MRI, penumbra, DWI, PWI, at-risk tissue, core infarction

BACKGROUND

In the stroke literature, the term "penumbra" was originally introduced to describe brain tissue that is electrically dysfunctional due to inadequate blood flow (1). The term was subsequently adopted by the MRI literature to reflect "at-risk" tissue estimated by diffusion–perfusion mismatch (DPMM). It is theorized that tissue that does not have restricted water movement on diffusion weighted imaging (DWI) but does have disrupted blood delivery on perfusion weighted imaging (PWI) represents salvageable brain tissue that will not evolve to complete cerebral infarction if blood flow is restored (2). The assumption is that penumbral tissue defined in this manner can be used to select patients for endovascular recanalization therapies that aim to restore blood flow (3). The mismatch hypothesis was recently tested in two large multicenter NIH-funded clinical trials, DEFUSE 2 (4) and MR RESCUE (5).

In both trials, tissue represented by MRI voxels was classified as at-risk or not at-risk based on diffusion and perfusion values. The DEFUSE 2 trial used the DPMM to define a "target profile" based on thresholds whereas the MR RESCUE trial used the DPMM to identify a "penumbral pattern" based on an equation. The two trials also differed in their conclusion with regard to the validity of the DPMM in identifying patient for endovascular therapy. DEFUSE 2 found that the DPMM could be used to identify patients who would have a good outcome with endovascular therapy. The DEFUSE 2 trial, however, did not investigate what would happen if patients with favorable MRI profiles were treated with medical therapy alone. MR RESCUE did not find that the DPMM could identify patients that would benefit from endovascular therapy. MR RESCUE did have a control group and thus was able to determine what would happen when patients who were thought to have at-risk tissue on MRI received medical therapy alone. One of the conclusions of the MR RESCUE trial was that a penumbral pattern on MRI conferred a better outcome but that endovascular therapy, even in the setting of a penumbral pattern, was of no additional benefit.

There are several potential reasons why these two trials led to opposite conclusions. Enrollment biases and differences in recanalization rates likely contributed. (6) However, the ability of these trials to identify a potential benefit of endovascular therapy, hinges on an accurate and unbiased estimate of at-risk tissue and core infarction. If the MRI measures used were inaccurate, then the entire premise upon which they are based falls apart. The dissimilar results of these two trials could be accounted for if the measures used were correct in one case and incorrect in the other. The negative results of the MR RESCUE could be explained if the definition overestimated at-risk tissue and under-estimated core infarction. The purpose of this study was to look at how the definition of at-risk tissue and core infarction differed between these two trials such that their results can be appropriately interpreted.

MATERIALS AND METHODS

Twelve patients who presented to our institution with acute ischemic stroke were retrospectively identified under an IRB approved protocol as having had an acute MRI scan with DWI and PWI for possible endovascular therapy. DWI and PWI were co-registered with an AIR linear transform using Diffeomap software (mristudio.org). Apparent diffusion coefficient (ADC) maps were calculated from B0 and B1000 source images using Matlab software (mathworks.com). Time-to-maximum (T_{max}) maps were generated from the PWI source images after deconvolution of the arterial input function using a circular single value decomposition in Olea Sphere software (olea-medical.com). All subsequent processing to calculate the target profile and the penumbral pattern were done in Matlab.

For each MRI scan, a region of interest (ROI) was defined in the affected MCA territory as having a T_{max} value $\geq$2 s or an ADC value $\leq$700 $\mu m^2/s$. ROIs were manually reviewed and edited to remove areas, which were artifactual such as the ventricular system. Then every voxel in the ROI was classified as being at-risk, core infarct, or neither for each of the definitions in the two studies. For the target profile (DEFUSE 2), at-risk was defined by voxels with ADC $\geq$ 600 $\mu m^2/s$ and $T_{max} > 6$ s and core infarct was defined as ADC $< 600\ \mu m^2/s$. Classification was based on absolute volumes and was not influenced by registration. For the penumbral pattern (MR RESCUE), at-risk tissue was defined by having a $T_{max} > 2$ s and by not being classified as core infarct. Core infarct in the penumbral pattern was defined by the equation $0.0044*ADC - 0.125*T_{max} - 0.902 \geq 0$. This definition of the penumbral pattern was used in the MR RESCUE trial until 2010 according to the published protocol (enrollment ran from 2004 to 2011).

Using these definitions, the volume of at-risk tissue and the volume of core infarct were calculated for each MRI. Using these volumes, a mismatch ratio, defined as the volume of at-risk tissue divided by the volume of core infarct, was generated for each definition. A percent core, defined as the proportion of the at-risk tissue which is core infarct, was generated for each. Additionally, the volume of tissue characterized by very low or absent blood flow (no-flow) was calculated for use in the classification of the target profile. This no-flow lesion was defined as tissue with $T_{max} > 10$ s.

An MRI was classified as having a penumbral pattern if it demonstrated a core infarct of $\leq$90 mL and a percent core of $\leq$70%. An MRI was classified as having a target profile if it demonstrated a core infarct $<$70 mL, a no-flow lesion $<$100 mL, and a mismatch ratio of $\geq$1.8.

The volumes of at-risk and core infarct tissue were compared between the two definitions using a paired t-test. Statistical analysis was done with the Stata software package (stata.com).

RESULTS

Of the 12 patients included in the analysis, 4 where female and their mean age was 68. Four of the patients had a known time of onset and had a mean time to MRI of 163 min. The remaining eight patients were wake-up strokes and had a mean time from wake-up to MRI of 193 min. All patients had a right middle cerebral artery (MCA) occlusion except for two, who had a left MCA occlusion, and one, who had a left posterior cerebral artery occlusion. **Table 1** shows the salvageable tissue classifications of the 12 MRI scans, as

Table 1 | At-risk tissue volumes, core infarct volumes, salvage classifications, percent cores, and mismatch ratios for each patient MRI scan in the study are displayed.

MRI scan	At-risk volume (mL)		Core infarct volume (mL)		Classification		Percent core (%)		Mismatch ratio	
	Penumbral pattern	Target profile	Penumbral pattern	Target profile	Penumbral pattern?	Target profile?	Penumbral pattern	Target profile	Penumbral pattern	Target profile
1	75	58	5	6	Yes	Yes	7	10	13.8	9.7
2	7	3	1	3	Yes	No	20	120	5.0	0.8
3	25	12	9	17	Yes	No	37	150	2.7	0.7
4	121	40	7	24	Yes	No	6	59	16.5	1.7
5	58	23	8	14	Yes	No	14	62	7.2	1.6
6	46	33	48	84	No	No	103	255	1.0	0.4
7	61	62	47	41	No	No	77	66	1.3	1.5
8	33	10	2	3	Yes	Yes	7	27	14.9	3.7
9	160	93	35	36	Yes	Yes	22	38	4.6	2.6
10	47	31	7	28	Yes	No	15	90	6.7	1.1
11	25	21	19	20	No	No	75	92	1.3	1.1
12	103	47	13	14	Yes	Yes	13	31	7.8	3.3

well as at-risk volumes, core infarct volumes, percent cores, and mismatch ratios. Nine out of 12 patients (75%) where classified as having a penumbral pattern (MR RESCUE), while only 4 out of 12 patients (33%) were classified as having a target mismatch (DEFUSE 2). Of the nine patients classified as having salvageable tissue by the MR RESCUE trial, 5 (55%) would have been classified differently by the DEFUSE 2 trial.

Although the at-risk volumes of the two definitions were correlated ($p = 0.017$), the penumbral pattern volume (mean ± SD = 63 ± 45 mL) was almost always larger than the target profile volume (mean ± SD = 36 ± 26 mL). The core infarct volumes on the other hand did not reach significance ($p = 0.059$). The target profile core infarct volumes (mean ± SD = 24 ± 22 mL) were almost always larger than the penumbral pattern core infarct volumes (mean ± SD = 17 ± 17 mL). Because of the way that the MR RESCUE defines at-risk tissue and core infarct, an increase in one is linked to a decrease in the other. There is no such a dependency between the two measures for the DEFUSE 2 definition. **Figure 1** demonstrates that the MR RESCUE had larger volumes of at-risk tissue and smaller volumes of core infarct, while the DEFUSE 2 identified volumes that fell in between.

We assessed if the differences in both at-risk and core infarct volume between the two trials are a result of a bias being introduced by one of the definitions, which would be captured by an offset. The at-risk volumes and core infarct volumes for each patient as defined by the two trials are plotted next to each other and connected by a line in **Figure 2**. **Figure 2** demonstrates that the rank order is different between the two definitions as the lines frequently cross. **Figure 3** is a box plot of the absolute difference in volumes between the definitions demonstrating that the

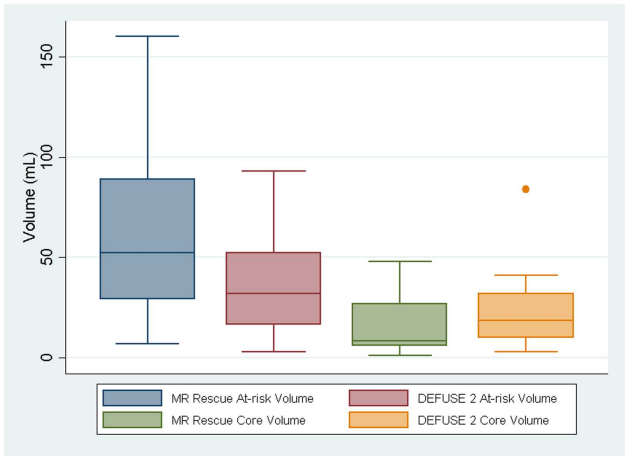

FIGURE 1 | The volumes of at-risk tissue and core infarct are displayed as a box plot for each trial.

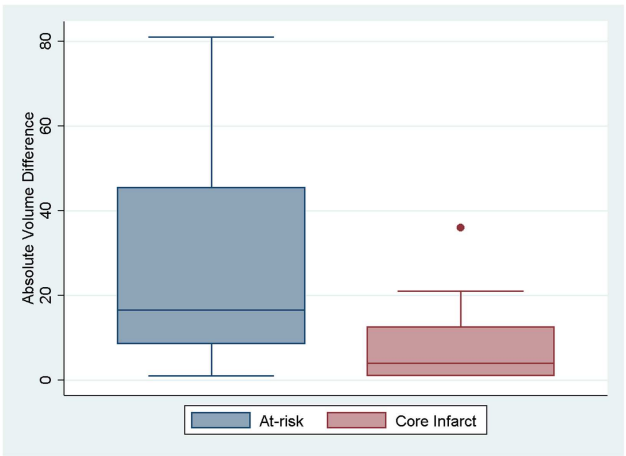

FIGURE 3 | Box plots showing the absolute difference between the two definitions for at-risk tissue and core infarct are displayed.

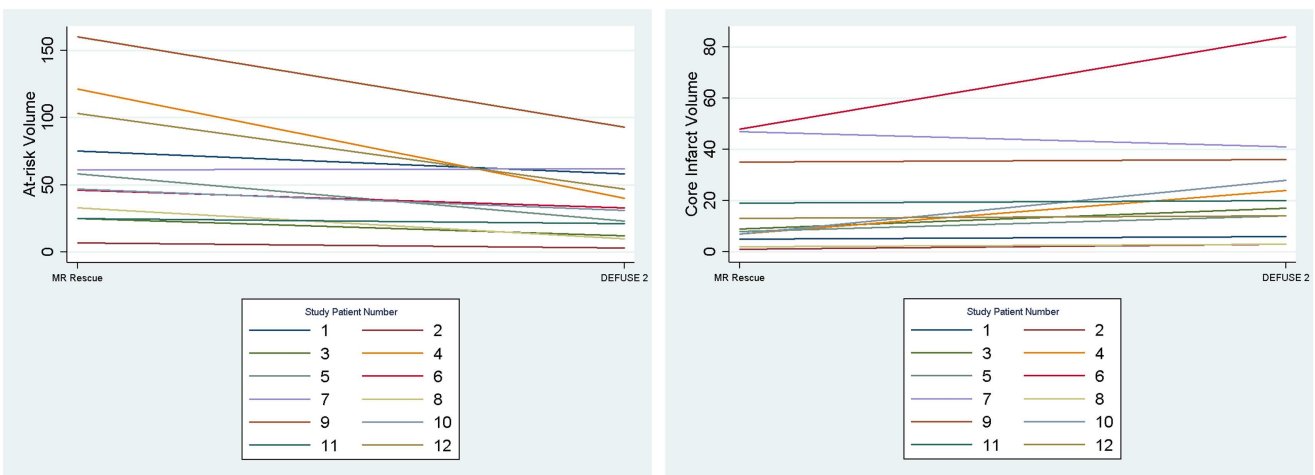

FIGURE 2 | The volumes of at-risk tissue and core infarct are plotted for each patient with lines connecting the values calculated by the two methods (MR RESCUE and DEFUSE 2). This demonstrates that the rank order of volumes assigned by the definitions is different.

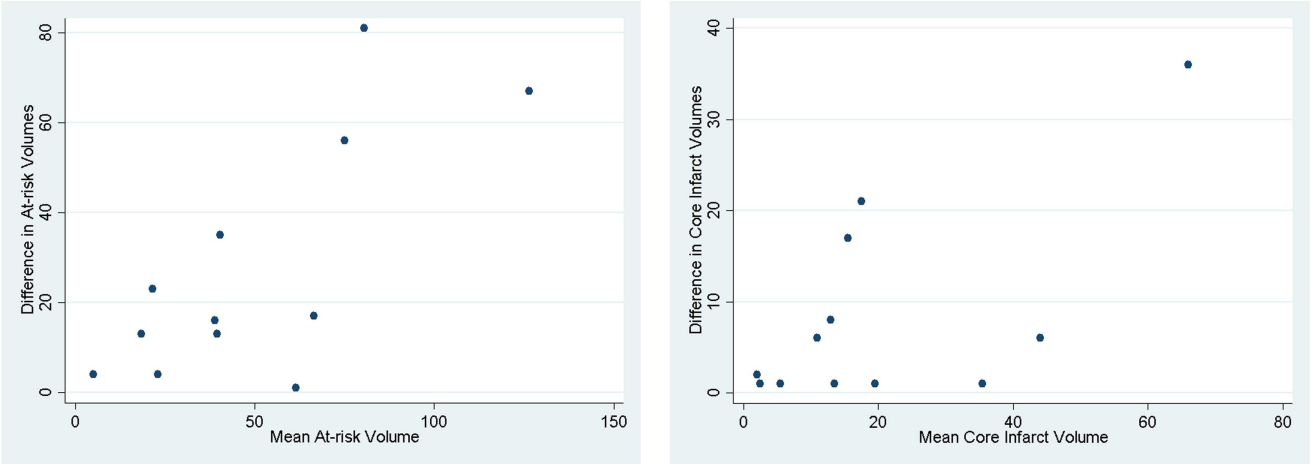

FIGURE 4 | Bland–Altman plots demonstrating how the two methods designed to measure the same parameter have different results. The mean of the two methods is plotted against the difference in the two methods.

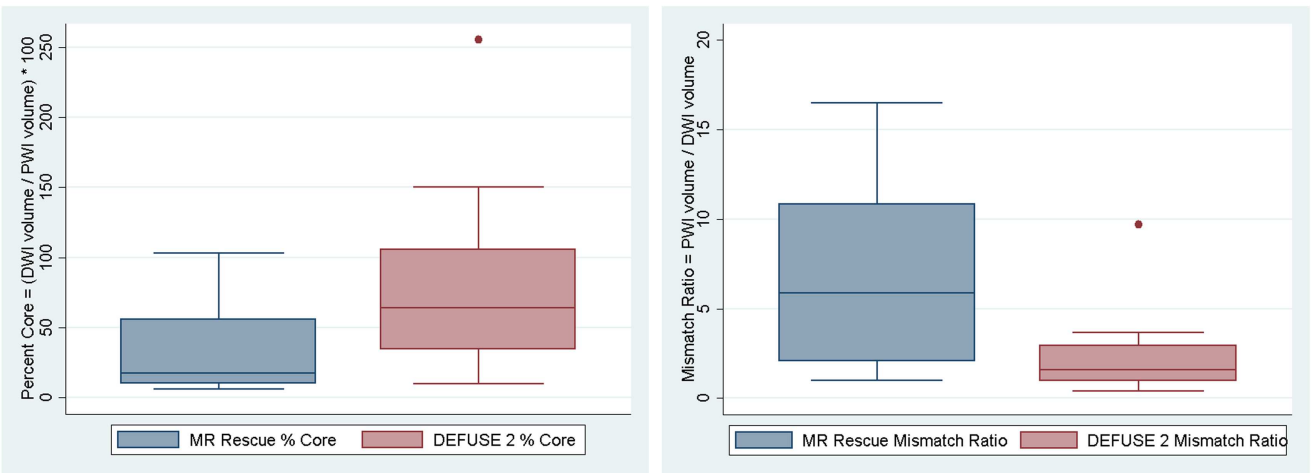

FIGURE 5 | The percent core and mismatch ratios for each trial are displayed as a box plot.

differences between the two definitions are themselves variable. **Figure 4** shows Bland–Altman plots comparing the mean volume measured by the two methods with the difference in volume measured by the two methods. This type of analysis is used for judging two methods designed to measure the same parameter. In this case, it demonstrates that for at-risk tissue, and to a lesser extent core infarct, the two methods rarely agree and the difference is more pronounced at higher volume measurements. For at-risk volumes, the scatter points fall mostly above the diagonal while for core infarct volumes the scatter points fall mostly below the diagonal, which demonstrates that the two definitions affect the at-risk and core infarct volumes in opposite directions. This difference in the salvageable tissue estimation for the two trials is further amplified when percent core and mismatch ratios are calculated. The mean percent core, which can be thought of as the percent of the perfusion deficit that has infarcted, for the penumbral pattern, was $33 \pm 33\%$, while for the target profile it was $83 \pm 67\%$. The mean mismatch ratio for the target profile was 2.3 ± 2.5, while for the penumbral pattern it was $6.9 \pm 5.5\%$ (**Figure 5**).

DISCUSSION

The role of endovascular therapy in the management of acute stroke remains controversial. Anecdotal experience tells us that endovascular therapy can be effective in some cases. Three recent randomized clinical trials of endovascular recanalization therapy have failed to demonstrate a benefit (5, 7, 8) Without a positive clinical trial, it seems unlikely that endovascular therapy will remain a treatment option. One of these trials, MR RESCUE, may appear to some as an example of why MRI-based patient selection should not be part of future clinical trials. However, if the MR RESCUE definition of penumbra is flawed, then we may wrongly discard a tool that could help identify a subset of patients for

whom endovascular therapy may indeed be effective. Thus it is very important that the calculations used to identify salvageable tissue are carefully scrutinized.

In this study, the salvageable tissue profiles for the MR RESCUE and DEFUSE 2 trials were compared and contrasted in 12 new patients evaluated at our center. The penumbral pattern (MR RESCUE) consistently identified larger volumes of tissue at risk (therefore possibly over-estimating the potential benefit from recanalization) compared to the target profile (DEFUSE 2). Additionally, the penumbral pattern consistently identified a smaller core ischemic volume than the target profile. The importance of the volume of the ischemic core is gaining appreciation in the literature. (9–11) Unlike the core defined by the penumbral pattern, the core defined by the target profile has been tested in other populations. (12) Not only does the penumbral pattern consistently identify a smaller ischemic core, but the volume threshold for the core, above which a patient is unlikely to respond to therapy, was higher for MR RESCUE (90 vs 70 mL for DEFUSE 2). The differences in the definition of the ischemic core could also have played a part in different outcomes between the trials.

MR RESCUE, therefore, had a higher probability of defining any give patient's tissue as salvageable compared to DEFUSE 2. Specifically, the penumbral pattern of the MR RESCUE trial likely included larger core volumes, no-flow lesions, smaller mismatches, and smaller penumbras. This could explain the lack of association between endovascular therapy and good outcome in this trial.

There are several limitations to this study. This was a small sample of patients which may not be representative of the patients enrolled in the trials discussed. Specifically, patients with unknown time of onset were not included in either trial. This analysis demonstrates how one small population would be differently classified by the two methods, but is not powered such that it can be generalized to the specific patients enrolled in the two trials. Additionally, the two MRI analysis methods were replicated manually and may not fully represent the automated way MRIs were processed in each trial.

Although the analysis presented here does not tell us how specific patients enrolled in the two trials would have been differently classified by the two methods, it does indicate that the results of the MR RESCUE trial should not be considered conclusive evidence against a role of MRI in the selection of patients for endovascular therapy. The DEFUSE 2 trial will need to be repeated but with the addition of a control group who have a salvageable MRI pattern but do not receive endovascular therapy. MR RESCUE trial provides the equipoise needed to conduct such a trial.

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Collaterals: an important determinant of prolonged ischemic penumbra versus rapid cerebral infarction?

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Intravenous tissue plasminogen activator is the mainstay for the treatment of acute ischemic stroke in patients presenting within 4.5 h of symptom onset. Studies have demonstrated that treating patients early leads to improved long-term outcomes. MR imaging currently allows quantification of the ischemic penumbra in order to better identify individuals most likely to benefit from intervention, irrespective of "time last seen normal." Its increasing use in clinical practice has demonstrated individual differences in rate of infarction. One explanation for this variability is a difference in collateral blood flow. We report two cases that highlight the individual variability of infarction rate, and discuss potential underlying mechanisms that may influence treatment decisions and outcomes.

Keywords: penumbra, ischemic stroke, collaterals, intra-arterial thrombolysis, recovery

INTRODUCTION

Intravenous tissue plasminogen activator (IV tPA) is approved by the FDA for the treatment of acute ischemic stroke for patients presenting within 3 h of symptom onset. Additional benefit has been shown within the 4.5 h window (1, 2). Subsequent studies have demonstrated improved outcomes for patients treated early, indicating that time is an important factor in determining the success of thrombolysis (3). This is most likely because vessel occlusion results in a poorly perfused ischemic core those infarcts rapidly, with a larger area of marginally perfused tissue, or penumbra (4). Neurons within the hypoperfused area are unable to maintain a resting potential, resulting in clinical dysfunction, but are not yet irreversibly damaged (5). The time that is required for the ischemic core to expand to match the penumbra is variable from patient to patient. One study showed that 91% of patients had a favorable diffusion (core) to perfusion (penumbra) mismatch on neuroimaging within 3 h from "last seen normal" falling to 72% by 3–6 h post-symptom onset (6, 7). Importantly, a small group of patients continued to display a favorable mismatch up to 24 h from symptom onset. We present two cases that demonstrate this individual variability of infarct progression.

CASE PRESENTATION

CASE 1

WS is a 70-year-old man with a history of hypertension, hyperlipidemia, and diabetes, who presented with aphasia and a right hemiparesis. He was last seen normal by his wife at 9 p.m. the evening prior to admission. When she came to bed at 2 a.m. she noted that he could not move his right side or communicate, and called EMS. He arrived in the Emergency Department at 2:34 a.m. His blood pressure was 121/60 mmHg. Serum glucose was 126. He was noted to be in atrial fibrillation. His troponin was elevated at 7.12 with mild ST segment changes. His NIH stroke scale was 12, with points given for disorientation, gaze preference, dysarthria, aphasia, and hemiparesis. He was outside of the window for treatment with IV tPA. Work-up was initiated. He vomited during CT angiogram, requiring intubation for airway protection. Coffee ground emesis was also noted. Cerebral perfusion was maximized with fluids and positioning and he was admitted to the Neurocritical Care Unit for further monitoring. Permissive hypertension was allowed as per our institution's policy regarding treatment of acute stroke; however, his systolic blood pressures remained around 120 mmHg. He did not exhibit evidence of perfusion dependence on examination so hypertensive therapy was not pursued. Due to medical instability, an MRI of the brain was not performed until the following morning. Neuroimaging revealed a large perfusion deficit encompassing much of the left middle cerebral artery (MCA) territory, matching his clinical deficits, with no clear diffusion abnormality (**Figures 1A,B**). He remained symptomatic, and the decision was made to proceed with intra-arterial intervention given the lack of infarcted tissue. Over 16 h after being last seen normal, successful recanalization was achieved using the penumbra clot retrieval device. Angiography demonstrated robust collateral flow through the pial vessels (**Figure 2A**). Follow-up MR imaging showed only a small area of diffusion restriction. His aphasia and hemiparesis markedly improved after recanalization, and 4 days later he walked out of the hospital with no rehabilitation needs.

CASE 2

LD is an 86-year-old woman with a history of hypertension, hyperlipidemia, and recurrent breast cancer, who presented with right

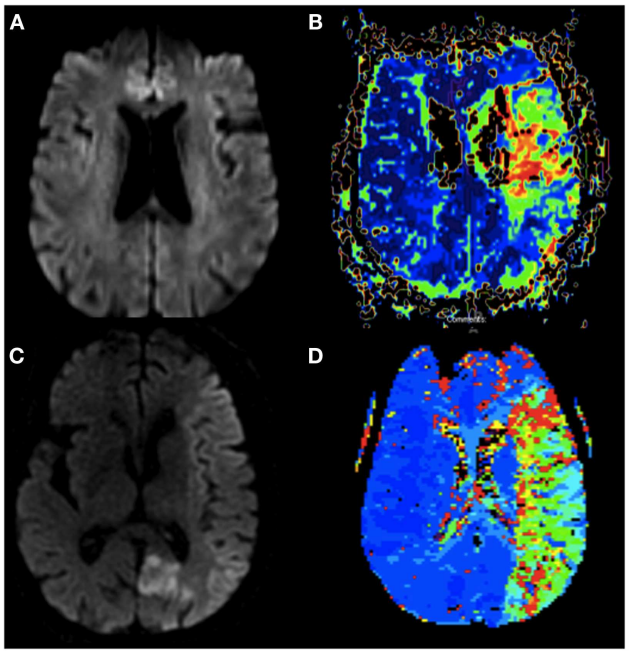

FIGURE 1 | (A) Diffusion weighted imaging of Case 1 without evidence of infarction 16 h after onset of symptoms. **(B)** Perfusion weighted imaging (TTP) of Case 1 showing patchy hypoperfusion of the left MCA. **(C)** Diffusion weighted imaging of Case 2 <60 min from stroke onset with early changes throughout the entire left MCA territory and her prior subacute left PCA infarct. **(D)** Perfusion weighted imaging (TTP) of Case 2 showing hypoperfusion of the entire left MCA.

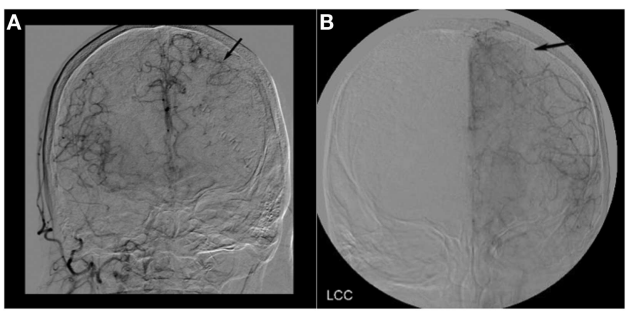

FIGURE 2 | (A) Cerebral angiogram of Case 1 showing robust collateral flow through the pial vessels in the late arterial phase (black arrow). **(B)** Cerebral angiogram of Case 2 showing a lack of collateral flow through the pial vessels in the late arterial phase (black arrow).

sided weakness and vision loss. She was last seen normal the night prior to admission and was therefore not an IV tPA candidate. An MRI of the brain showed diffusion restriction within the left posterior cerebral artery territory. A CT angiogram showed mild atherosclerotic changes. She was awaiting a transthoracic echocardiogram prior to discharge and recovering well until hospital day 3. At 9:40 a.m. she walked to the bathroom unassisted, but was found 3 min later by the neurology team to be aphasic, with left gaze deviation, and a dense right hemiparesis. Her NIH stroke scale was 19. A head CT showed no intracranial hemorrhage, but a hyperdense left MCA sign. Acute ischemia was suspected. Given her recent PCA stroke she was again not a candidate for IV tPA. A hyperacute MRI was completed <60 min after the onset of symptoms to determine if she was a candidate for intra-arterial intervention. Despite the short time between symptom onset and imaging, a significant area of new restricted diffusion involving mainly the cortex was noted within the left hemisphere, along with a larger perfusion deficit and cut off of the M1 branch of the left MCA (**Figures 1C,D**). Given the acute onset of symptoms and presence of a diffusion/perfusion mismatch, the decision was made to proceed with intervention. Angiography demonstrated a lack of collaterals without significant flow through the pial vessels (**Figure 2B**). Unfortunately, despite complete recanalization within 4 h of symptom onset, a large portion of the MCA territory was infarcted on follow-up imaging. She remained aphasic and densely hemiparetic through to discharge to a rehabilitation facility.

DISCUSSION

MRI and CT perfusion allow real-time quantification of infarcted versus hypoperfused tissue; however, the trials looking at the use of MR imaging to predict who will benefit from late recanalization have been mixed (8–12). Therefore, time from symptom onset continues to be the standard indicator of which patients will benefit most from recanalization. Here, we describe two cases that illustrate the individual variability in the time course of infarction between patients presenting with large vessel occlusion. In Case 1, time of recanalization was prolonged from stroke onset, yet irreversible damage was minimal. Additional cases have been reported in the literature, with viable tissue being documented up to 17 h from stroke onset (13–15). In Case 2, after only 60 min, a significant portion of the vascular territory had already undergone infarction. In both cases, response to treatment paralleled imaging characteristics, but did not parallel the outcomes predicted by time alone.

The increased availability of MRI and advent of perfusion imaging techniques provide an opportunity to identify patients with a "favorable ischemic profile" independent of time from stroke onset (12). This favorable profile appears more common in the hyperacute setting, but as illustrated above, prolonged mismatches may occur. Conversely, unfavorable mismatches can also occur after only a short period of vessel occlusion (16). Correctly identifying both groups may help to tailor therapy beyond current guidelines. Studies looking for the favorable profile have, to date, yielded mixed results (8–12). It is likely that we simply have yet to consistently identify the right subgroup who will benefit, and/or have failed to account for an additional critical unmeasured variable. One reason that studies like MR RESCUE (8) have been disappointing may be because perfusion weighted imaging likely does not adequately take into account collateral blood flow, and that slowed flow is not the same as absent flow. In MR RESCUE, the information obtained was "presence of a mismatch," but at no point was comment made regarding presence of favorable collateral blood flow on angiogram, which we believe would have been useful information in deciding whether to move forward with recanalization. Though these studies have

failed to give rise to definitive criteria that reliably predict good long-term outcome, they have confirmed the presence of a select group who continue to have significant diffusion/perfusion mismatches far outside the accepted 4.5 h window (12). While it is statistically more likely for a favorable mismatch to occur early, failing to account for these individuals would result in a missed opportunity for intervention given their prolonged therapeutic window (6, 17).

In an elegant set of experiments, Jones et al. showed that with a reduction of cerebral blood flow (CBF) in an animal occlusion model, the amount of reduced flow predicted irreversible infarction. They found that reduction of local CBF in the range of 23 cc/100 gm/min resulted in reversible paralysis without infarction once blood flow was reinstated. Of interest, reduction of local CBF further to 10–12 cc/100 gm/min for 2–3 h resulted in irreversible infarction (18). In humans with acute stroke, the specific factors that determine rate of infarction and the local CBF remain unclear; however, the primary contributor is likely the presence versus absence of viable collaterals. Collateral flow through the pial vessels was clearly evident on the angiogram in our "late infarcter" (Case 1), but poorly visualized in our "early infarcter" (Case 2) (19). Prior studies looking at both digital subtraction angiography (DSA) and CT angiography in predicting outcomes of thrombolysis have shown similar results, confirming that those with better long-term outcomes typically exhibit more robust flow through the collaterals (20, 21).

If rate of infarction is dependent on the presence of viable collaterals, it is important to consider factors that may influence collateral flow. Collaterals may be seen in response to acute vascular occlusion, or as the result of chronic stenosis of a single vessel (i.e., Moyamoya syndrome). Patients who are younger and those with a lower atherosclerotic burden may have the ability to muster better acute collateral flow (22). When relatively healthy pial vessels are successfully recruited following an MCA occlusion, the resulting infarct often spares much of the cortex, rather than involving the entire vascular territory (23, 24). Similarly, vascular stenosis of a single large artery stimulates chronic collateralization within the vascular bed, making the specific territory more resistant to ischemia should the vessel occlude.

In addition to collateral blood flow, when there is a chronic low-flow state or vascular stenosis, ischemic preconditioning may occur. This phenomenon was first described in the cardiac literature and has been well demonstrated in MCA occlusion models (25). In humans, it has been observed that patients undergoing balloon occlusion, and those with prior transient ischemic attacks, have smaller strokes when the same vascular distribution is subsequently compromised (26, 27). It seems that brain exposed to chronic ischemia (i.e., large vessel stenosis) is better able to tolerate future ischemic events due to physiologic and molecular changes within the affected neurons (25).

Our cases, in the context of these prior studies, support the concept that the combination of robust collateral blood flow (either acutely or chronically) and some degree of existing ischemic preconditioning, in conjunction with other factors such as the metabolic demand of the at risk tissue (with gray matter areas being most at risk) and systolic blood pressure affecting overall cerebral perfusion, results in patients who are "late infarcters" (28). In Case 1, following clot retrieval it was apparent that WS had some degree of pre-existing MCA stenosis. This likely led to chronic collateralization, as evidenced by robust flow through his pial vessels. Unfortunately, the presence of favorable collaterals and prior ischemic preconditioning are not variables that can be easily determined on current MR imaging. Accordingly, they may be the critical variables missing from the prior "late thrombolysis" studies.

For the population as a whole, time remains the single most important variable used to predict who will benefit from thrombolysis. However, with advances in neuroimaging, a surrogate marker that allows better individualization of treatment would be ideal. Though expansion of the ischemic core likely occurs over a fairly predictable time course, we have shown two cases that illustrate significant variability. A better understanding of the role of collateral blood flow and ischemic preconditioning may allow us to better identify those individuals who may be "late infarcters," or even develop strategies to slow infarction rate.

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Is CT-based perfusion and collateral imaging sensitive to time since stroke onset?

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Purpose: CT-based perfusion and collateral imaging is increasingly used in the assessment of patients with acute stroke. Time of stroke onset is a critical factor in determining eligibility for and benefit from thrombolysis. Animal studies predict that the volume of ischemic penumbra decreases with time. Here, we evaluate if CT is able to detect a relationship between perfusion or collateral status, as assessed by CT, and time since stroke onset.

Materials and methods: We studied 53 consecutive patients with proximal vessel occlusions, mean (SD) age of 71.3 (14.9) years, at a mean (SD) of 125.2 (55.3) minutes from onset, using whole-brain CT perfusion (CTp) imaging. Penumbra was defined using voxel-based thresholds for cerebral blood flow (CBF) and mean transit time (MTT); core was defined by cerebral blood volume (CBV). Normalized penumbra fraction was calculated as Penumbra volume/(Penumbra volume + Core volume) for both CBF and MTT (Pen_{CBF} and Pen_{MTT}, respectively). Collaterals were assessed on CT angiography (CTA). CTp ASPECTS score was applied visually, lower scores indicating larger lesions. ASPECTS ratios were calculated corresponding to penumbra fractions.

Results: Both Pen_{CBF} and Pen_{MTT} showed decremental trends with increasing time since onset (Kendall's tau-$b = -0.196$, $p = 0.055$, and -0.187, $p = 0.068$, respectively). The CBF/CBV ASPECTS ratio, which showed a relationship to Pen_{CBF} (Kendall's tau-$b = 0.190$, $p = 0.070$), decreased with increasing time since onset (Kendall's tau-$b = -0.265$, $p = 0.006$). Collateral response did not relate to time (Kendall's tau-$b = -0.039$, $p = 0.724$).

Conclusion: Even within 4.5 h since stroke onset, a decremental relationship between penumbra and time, but not between collateral status and time, may be detected using perfusion CT imaging. The trends that we demonstrate merit evaluation in larger datasets to confirm our results, which may have potential wider applications, e.g., in the setting of strokes of unknown onset time.

Keywords: CT perfusion, collaterals, stroke, time, onset

INTRODUCTION

CT-based perfusion and collateral imaging is increasingly used in the assessment of patients with acute stroke (1–6). Thus, CT perfusion (CTp) is used to identify core and penumbra by mapping cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) (1, 7). CBF (2) and MTT (2, 8, 9) thresholds have been used to identify penumbral tissue, while CBV (9) has been used for mapping the infarct core. While there have been a number of studies demonstrating that CTp may be used to identify these tissue compartments, there is some disagreement in the literature about its utility in routine clinical practice to guide early treatment decisions (10). However, its wider availability, shorter scanning times, and lower costs (11) make it potentially more attractive as a clinical tool than MRI which is an expensive and time intensive resource, and may not be available 24 hours a day at many institutions for the assessment of acute stroke.

Time of stroke onset is a critical factor in determining eligibility for and benefit from thrombolysis (12). From a pathophysiological perspective, ischemic penumbra is the therapeutic target for acute stroke therapies (1, 13, 14). An important concept relating to the penumbra remains that, unless salvaged, it gets recruited to the ischemic core with time (15). While PET remains the gold standard for penumbral imaging (14, 15), MRI, and CT-based methods have been applied in clinical cohorts to study penumbral tissue and relationship with clinical outcomes (16, 17). Pre-clinical studies and few human imaging based studies report a falling frequency of target mismatch as a surrogate for penumbral tissue with increasing time from ictus (18). We hypothesized that within the therapeutic window for thrombolysis, a decremental relationship

of penumbra with time since stroke onset could be applied using perfusion CT imaging in a clinical population. The further aim of establishing such a relationship would be in the setting where time of stroke onset is unknown, and physiological imaging may have a role (1, 19). Physiological imaging also has potential for extending the time window for early treatments beyond 4.5 h, and some successful studies including patients up to 6 h have already emerged (20, 21).

We studied a cohort of patients with whole head CTp imaging within the currently licensed window for thrombolysis, namely 4.5 h. We examined voxel-based quantitative tissue fractions against time since onset. CTp thresholds have been shown to be robust in that, they are not time dependent within this window and potentially up to 15 h from ictus (22); and can thus be reliably applied in this early time window. Given the hemodynamic changes after an acute vascular occlusion, i.e., falling CBF and subsequently CBV (15), these two parameters alongside MTT were applied to quantitatively describe the penumbra. To further explore a clinically translatable index, visually assessed ASPECTS score for CTp maps, as previously described in the literature (23, 24), was examined against quantitative fractions and further, against time since onset.

We aimed to show that CTp is a reasonable imaging modality to capture these expected tissue changes, given the current uncertainties regarding its utility, as outlined above. Relationship of penumbra and time has been studied previously in physiological imaging studies (16, 18) and we aimed to demonstrate that CTp imaging may be applied in a clinical population to confirm these expected relationships. In addition, given the potential role of collateral status in maintaining the penumbra (25–27), collateral circulation was also examined against time. This is an important area of current research and such a relationship has not, to our knowledge, been previously assessed.

MATERIALS AND METHODS

APPROVALS

We recruited patients from the Cambridge Acute Stroke Database. Ethical approval was granted by the South East Research Ethics Committee and the National Information Governance Board (NIGB, UK). Patients or next of kin provided written informed consent. When consent was unavailable, approval was in place for retrieval of clinical and imaging data.

PATIENT RECRUITMENT

A cohort of consecutive anterior circulation stroke patients ($n = 53$) with proximal arterial occlusions, i.e., the intracranial internal carotid artery (ICA) or proximal middle cerebral artery (MCA) (M1), confirmed on CTA, was recruited between December 2009 and February 2013. We selected proximal occlusions to avoid including patients where recanalization had already occurred; thus, penumbral tissue could be reliably studied. All patients had presented within 4.5 h of clearly known onset of symptoms, were being assessed for thrombolysis and underwent CTp as part of the acute stroke imaging protocol at our institution. All patients had presented with their first clinical stroke and had a clear defect on CTp. Lacunar strokes were excluded because penumbral tissue characterization is unclear in these cases (28). Baseline clinical data were recorded prospectively.

WHOLE-BRAIN CT PERFUSION IMAGING ACQUISITION AND ANALYSIS

Plain CT and CTp were acquired in succession using Siemens® Somatom Definition Flash Scanner. Perfusion images were acquired after a 4 s delay following an injection of 50 ml of Niopam-300 with a PSI injector at a rate of 5 ml/s and a saline chaser bolus, via a 16–18 gage intravenous cannula. *Z*-axis coverage was 70–100 mm, with acquisition parameters of 80 kV and 240–250 mA, rotation time of 0.28–1 s, and reconstructed slice thickness of 10 mm with 4–6 mm overlap.

Raw perfusion data were analyzed on a Siemens® workstation using Syngo® VPCT *Neuro* software. Brain parenchyma was isolated by skull bone contour findings; CSF and calcifications were removed by automatic thresholding. The arterial input function (AIF) and venous outflow function were semi-automatically selected from the anterior cerebral artery (ACA) and superior sagittal sinus respectively. In two cases, the MCA was used to derive AIF. Major vessels were removed by applying relative thresholding to the maximal voxel enhancement. Adaptive spatial filtering was performed that did not smooth over edges and vessel borders. Subsequently, quantitative maps of relative CBF, CBV, and MTT were obtained using a deconvolution algorithm.

Quantitative maps were transferred to a Windows® PC and segmented using voxel-based thresholds to define at-risk tissue or "penumbra" and irreversibly damaged tissue or "core" (3). This was performed using in-house software (3, 17) in Matlab® (R2007b, The MathWorks Inc.) run using SPM8 (Wellcome Trust Centre for Imaging Neuroscience, London, UK).

PENUMBRA FRACTION DEFINITIONS

Penumbra was defined using a previously validated, voxel-based quantitative threshold based for CBF [volume of tissue where each voxel had a CBF ratio of affected to unaffected hemisphere (A/U) $\leq$0.50 outside the core] based on large clinical series (2). For further substantiation, we also applied a threshold based on MTT (9, 29, 30) (volume of tissue where each voxel had an MTT ratio of A/U $\geq$1.45 outside the core). Ischemic core was defined using a CBV threshold [volume of tissue where each voxel had a CBV ratio of A/U $\leq$0.65 (9, 31)].

Normalized penumbra fractions, i.e., Pen_{CBF} and Pen_{MTT} were subsequently calculated as Penumbra volume/(Penumbra volume + Core volume).

COLLATERAL SCORES

Collateral scores were independently assessed, without access to clinical information, by a senior neuroradiologist (DJS) with over 10 years of experience in evaluating CTp and CT angiography.

The collateral score used in this study is based on description of angiographic appearance of collateral vessels (32) and applied to CTA maximum intensity projections previously (3, 33–35). We used reconstructed 20 mm axial CTA maximum intensity projections (MIP's) and assigned collateral scores as follows:

0 = Absent collaterals
1 = Collaterals filling $\leq$50% of the occluded arterial territory
2 = Collaterals filling >50% but <100% of the occluded arterial territory
3 = Collaterals filling 100% of the arterial territory.

ASPECTS SCORING

Two assessors (Tomasz Matys and Smriti Agarwal) independently scored the unthresholded perfusion maps (**Figures 1A–C**) for each subject. Briefly, ASPECTS score was assigned on a scale of 0–10 for each of the three perfusion maps, a lower score indicating a more extensive perfusion deficit within the stroke lesion. The unaffected hemisphere was used as a reference. While evaluating the maps, raters did not have access to clinical information except for side of the lesion. Individual parameters for each subject were scored on a different calendar day to avoid systematic bias. ASPECTS score for each parameter was averaged from the two readings and this value was used for final analysis.

We evaluated CBF/CBV ASPECTS ratio and MTT/CBV ASPECTS ratio against corresponding penumbra fractions, i.e., Pen_{CBF} and Pen_{MTT}, respectively. Where we found a relationship between the two, the corresponding ASPECTS ratio was evaluated against time since onset.

STATISTICAL ANALYSIS

All analyses were performed using IBM SPSS, version 19 for Macintosh and Microsoft Excel 2011. Mean (SD) and median (IQR) values are reported here for baseline clinical characteristics.

For the ASPECTS scoring, interobserver agreement was measured using Kappa statistic (36, 37) and further measure of internal consistency was applied using Cronbach's alpha (38).

To test our hypothesis, we performed non-parametric correlations using Kendall's tau-*b* for penumbra fraction, ASPECTS ratios and collateral score against time since stroke onset.

Two sided *p*-values were obtained and considered significant if <0.05.

RESULTS

BASELINE CLINICAL FEATURES

Fifty-three patients were included in this study. Demographic and pertinent clinical data are described in **Table 1**. Imaging was performed at a mean (SD) time of 125.2 (55.3) minutes from stroke onset. Forty-six patients (86.8%) received intravenous thrombolytic therapy with alteplase. Median (IQR) stroke severity score on the NIHSS (39) was 15 (6). Small vessel disease did not appear in the TOAST classification given that lacunar strokes were excluded. Majority of patients (50.9%) had a cardioembolic etiology for their stroke. About 58.5% of patients had hypertension as a comorbidity and 56.6% had atrial fibrillation.

PENUMBRA FRACTIONS AND COLLATERAL SCORES AGAINST TIME SINCE ONSET

Correlations between penumbra fractions and collateral scores with time since onset are shown in **Table 2**. Penumbra fraction derived using a CBF threshold, i.e., Pen_{CBF} correlated showing a statistical trend, although non-significantly, with time since stroke onset (Kendall's tau-$b = -0.196$, $p = 0.055$). Penumbra fraction derived using an MTT threshold, i.e., Pen_{MTT} showed a similar trend (Kendall's tau-$b = -0.187$, $p = 0.068$).

Collateral score did not correlate with time since stroke onset (Kendall's tau-$b = -0.039$, p value $= 0.724$).

ASPECTS SCORE RATIO AND TIME SINCE ONSET

There was significant inter observer agreement based on Fleiss kappa values (36, 37) for ASPECTS scoring and these were 0.581 for CBV ($p < 0.0001$), 0.421 for CBF ($p = 0.003$), and 0.542 for MTT ($p < 0.0001$). As an additional measure of internal consistency, intraclass correlation coefficients were noted in terms of Cronbach's alpha (38) and these values were 0.739 for CBV, 0.598 for CBF, and 0.713 for MTT indicating that the measurements were reliable and consistent between the two raters.

CBF/CBV ASPECTS ratio showed a positive statistical trend for a relationship with Pen_{CBF} (Kendall's tau-$b = 0.190$, p value $= 0.070$); MTT/CBV ASPECTS did not show a relationship with Pen_{MTT} (Kendall's tau-$b = -0.094$, p value $= 0.368$). CBF/CBV ASPECTS ratio was thus, used as a surrogate for the quantitative penumbra fraction, so simple visual assessment of perfusion maps could be examined against time since onset.

There was a significant inverse relationship between ASPECTS CBF/CBV against time since stroke onset (Kendall's tau-$b = -0.265$, p value $= 0.006$) as shown in **Table 2**.

Figure 2 shows the relationship between Pen_{CBF} ratio and time, and between CBF/CBV ASPECTS ratio and time.

DISCUSSION

Our quantitative analysis, using CBF and MTT thresholds derived from published literature, showed a trend for a relationship of penumbra fraction with time, in the expected negative direction. Toward an application in the wider clinical setting, we also investigated visual assessment of perfusion abnormalities, applying the previously validated ASPECTS approach (23, 40) to CTp. Interobserver agreement and internal consistency measures for the two raters were in keeping with published literature (24). At variance with the quantitative analysis, the visual analysis using the CBF/CBV ASPECTS ratio showed a statistically significant decremental relationship over time. Larger studies are warranted to confirm these visual assessment-based findings and explore clinical applicability in detail.

MRI-based timing of stroke lesions has been previously investigated in detail, with DWI-FLAIR mismatch being a predictor of stroke onset within 4.5 h (36), leading on to an ongoing clinical trial (41). While MRI-based methods have been more widely studied (36), perfusion CT-based evaluations are limited (42, 43). Given the ease of access, shorter scanning times, lower cost, and less susceptibility to movement artefacts (11, 44), CTp has potential clinical utility and has been successfully compared to MRI-based methods in acute stroke (45).

One potential issue with using quantitative thresholds to identify the penumbra and core using CTp that could account for our marginal findings, is the lack of formal validation so far, resulting in various groups using different data processing and perfusion variables and thresholds (10, 46). Generally, penumbral imaging holds potential promise to clinical translation, although a number of early trials of treatments using these methods have been negative (47). There are a number of limitations of these studies including methodological variability and lack of evaluation in an early time window due to previous evidence being based on plain CT imaging. More recently, two positive trials used CTp and quantitative perfusion thresholds to select optimal candidates to evaluate new thrombolytic agents (20) and endovascular intervention (21), may lead to changes in practice in due course.

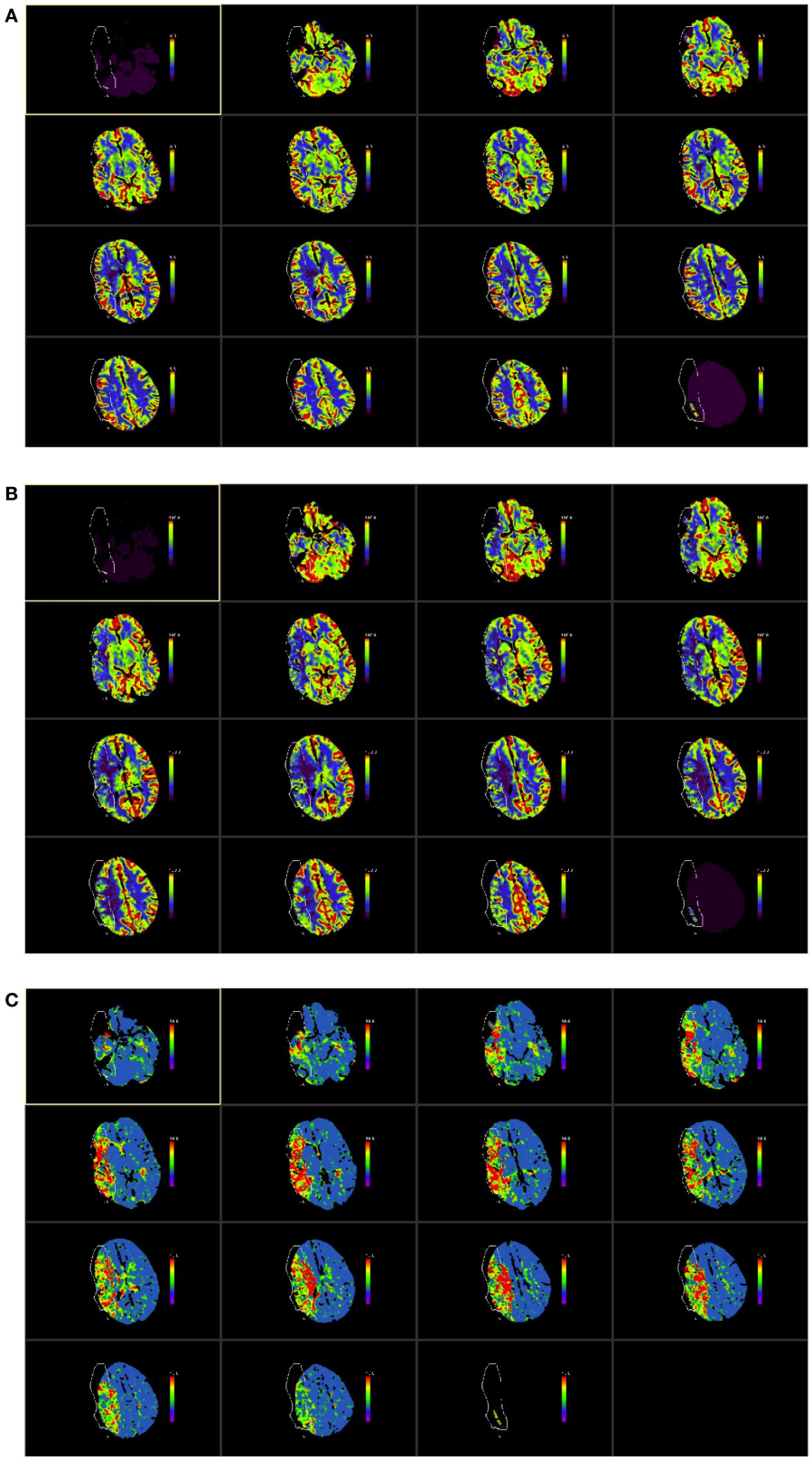

FIGURE 1 | ASPECTS score was applied CT perfusion maps.

(*Continued*)

FIGURE 1 | Continued
The ASPECTS template divides each hemisphere into 10 vascular regions covering the MCA territory, which include 6 middle cerebral artery cortical regions (M1–M6), caudate nucleus, lentiform nucleus, internal capsule, and insular cortex (23, 24). The CTP maps used were those for cerebral blood volume [CBV **(A)**], cerebral blood flow [CBF **(B)**], and mean transit time [MTT **(C)**] as shown in the illustrative figures below. The images were color scaled, as follows, for each of the parameters consistently across all study subjects: CBV scaled at 0–6 ml/100 ml, CBF color scaled at 0–100 ml/100 ml/s and MTT scaled at 0–10 s. The example in this figure shows a proximal right MCA stroke (outlined in figure). The unaffected hemisphere was used as a reference and each ASPECTS region was compared with the corresponding region on the unaffected hemisphere to assign a score. Each map was scored visually on each of the 10 regions of the ASPECTS template with a score of 0 if the affected side showed a comparative abnormality and a score of 1 if no relative abnormality was seen; thus a total ASPECTS score could vary from 0 to 10 for each of the perfusion maps, with 0 denoting an abnormality across all ten regions and 10 indicating no abnormality in the affected hemisphere. Each rater scored the scans individually and average of the two was subsequently used for the study analysis. In this example, average ASPECTS score was 7 for CBV, 3 for CBF and 2 for MTT.

Table 1 | Baseline characteristics ($n = 53$).

Mean age in years (SD)	71.3 (14.9)
Sex (M:F)	24:29
Median NIHSS (IQR)	15 (6)
Mean time to imaging in minutes (SD)	125.2 (55.3)
Mean systolic blood pressure (SD)	152.3 (22.2)
Mean diastolic blood pressure (SD)	82.4 (15.7)
Mean blood glucose (SD)	7.6 (1.6)
Mean CRP (SD)	15.3 (29.1)
Mean hematocrit (SD)	0.40 (0.04)
Mean full blood count (SD)	9.5 (3.9)
Mean platelet count (SD)	225.4 (61.7)
Mean body temperature (SD)	36.4 (0.7)
Hypertension *n* (%)	31 (58.5)
History of smoking *n* (%)	24 (45.3)
Current smoking *n* (%)	7 (13.2)
Diabetes mellitus *n* (%)	4 (7.5)
Atrial fibrillation *n* (%)	30 (56.6)
Premorbid antiplatelet therapy *n* (%)	17 (32.1)
Premorbid statin therapy *n* (%)	18 (33.9)
Premorbid antihypertensive therapy *n* (%)	30 (56.6)
Thrombolysis administration *n* (%)	46 (86.8)
Mean premorbid modified Rankin score (SD)	0.4 (0.8)
Mean modified Rankin score at 3 months (SD)	2.4 (2.1)
TOAST classification *n* (%)	
Large vessel disease	5 (9.4)
Cardioembolic	27 (50.9)
Other	21 (39.6)

Table 2 | Correlations of penumbra fractions and collateral score with time since stroke onset.

Parameter	Kendall's tau-*b*	*p* value
CBF derived penumbra fraction (Pen_{CBF}) vs. time since stroke onset	−0.196	0.055
MTT derived penumbra fraction (Pen_{MTT}) vs. time since stroke onset	−0.187	0.068
CBF/CBV ASPECTS ratio vs. time since stroke onset	−0.265	0.006
Collateral score vs. time since stroke onset	−0.039	0.724

Our data show that collateral response does not change over time in the early window we studied. One explanation is that collateral response may be intrinsically variable in individuals with proximal occlusions and thus, either present or not (48). It is in turn feasible that the collateral status affects the relationship between the penumbra ratio and time, complicating the across-subject relationship. For instance, one would expect that if there are good collaterals, the ratio would remain higher for a longer period, until the penumbral tissue has exhausted its energy reserve and proceeds to infarction (13, 14). Thus, the difference in collaterals between individuals may explain why time only trended toward association with penumbra ratio, as the rate of conversion to an ischemic core is dependent on not only time, but also the presence or absence of efficient collaterals in any given individual. Our small sample size precludes a meaningful multivariate analysis to answer these questions. Future studies with larger patient populations are thus needed.

Thus far published CT-based characterization of "wake up/strokes of unclear onset" have not been able to identify any specific features compared to those events where the time of onset is known (33, 35, 49, 50), with the exception of one study that found higher frequency of hypodensity on non-contrast CT in the "wake up/unclear onset" group (33). Heterogeneity in time since onset may be one reason. There is some evidence in clinical studies that stroke on awakening may develop shortly prior to presentation unlike unwitnessed stroke due to other reasons (33, 51) and thus, at least in a subset of patients where time of symptom onset is not known, CTp parameters that we describe may have role. However, we acknowledge that the lack of patients beyond the 4.5-h window is a clear limitation of our study with respect to wake up/unknown time of onset strokes. Larger studies with patients beyond this time window may help confirm the trends we demonstrate in our quantitative data and ASPECTS derived metrics. We studied patients in the time window for current thrombolysis license (52) due to the observational nature of our study. However, given the current clinical evidence-based guidelines or thrombolysis in stroke cover the first 4.5 h post ictus, our study may also have utility in this very clinical setting.

Another confound of our study, which may explain why we were unable to detect statistically significant relationships in our quantitative data, is the small sample size. Larger datasets of patients in longer time windows are needed to confirm the trends that we demonstrate, both, with respect to the quantitative findings and the visual assessment-based findings. We also recognize that the visual assessment approach could be improved further, particularly for CBF, while future studies will need to assess optimal

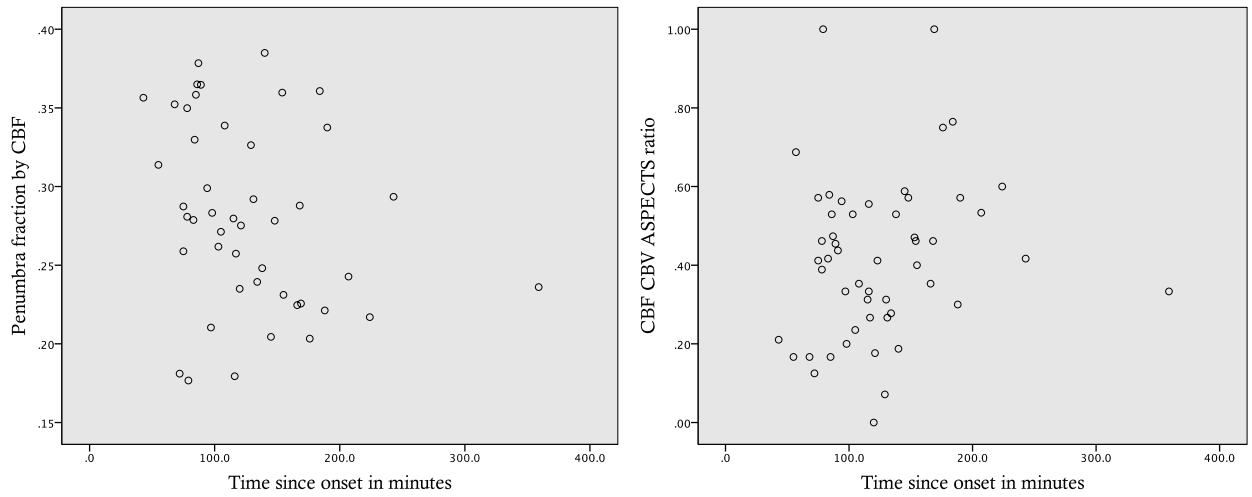

FIGURE 2 | Perfusion parameters and time since stroke onset. Scatter plots for penumbra fraction defined by a CBF threshold (Pen_{CBF}) and CBF/CBV ASPECTS ratios against time since stroke onset.

thresholds when applying the quantitative method, which may provide more reliable clinically applicable indices.

CONCLUSION

In this pilot study of patients with proximal arterial occlusions, we find some evidence towards a relationship between CTp and time since onset within the currently licensed thrombolysis window, which if confirmed in larger studies with broader inclusion times, could have implications in the clinical setting of strokes of unknown onset time.

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Vessel occlusion, penumbra, and reperfusion – translating theory to practice

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The management of ischemic stroke is at a critical juncture. Administration of intravenous tPA is currently restricted to within 4.5 h from stroke onset with several trials in longer time windows proving neutral (1, 2). Revascularization success with tPA in major vessel occlusion is widely recognized as suboptimal (3). Alternative thrombolytic agents with theoretical efficacy advantages such as tenecteplase and desmoteplase are yet to show benefit in phase 3 trials. The promise of endovascular therapy has also yet to translate into positive randomized trials (4–6), although a new generation of devices is currently being studied. While it is possible that these therapeutic approaches are simply ineffective, the heterogeneity of stroke pathophysiology is likely to be contributing to the neutral results we often observe.

Imaging selection has been proposed as a means of reducing heterogeneity by identifying patients with the potential to benefit from revascularization and therefore enhancing the probability of success in trials of new therapies. However, whether it is sufficient to demonstrate an occluded artery as the target or to also require evidence of salvageable downstream tissue has been debated. The recent announcement of neutral results in DIAS 3 (7), a trial that compared desmoteplase versus placebo 3–9 h after stroke onset in patients with vessel occlusion, without reference to downstream tissue status other than what was visible on non-contrast CT, will no doubt further stimulate this discussion. It is, therefore, salient to consider the current methods to identify salvageable ischemic penumbra and the potential value of commonly used surrogates for clinical outcome, chiefly reperfusion, recanalization, and infarct growth.

IDENTIFYING SALVAGEABLE TISSUE

There are some stroke patients who do not have an identifiable vessel occlusion. It is well recognized that such patients generally have an excellent natural history and will not benefit from revascularization therapy. This has led to one body of opinion that identifying vessel occlusion is the key criterion for treatment selection (8). It is true that the majority of patients with a vessel occlusion have some non-functioning but potentially salvageable ischemic penumbra downstream, at least early after stroke onset. However, patients with a large ischemic core at admission imaging not only have very little chance of benefit from treatment, they may well have worse outcome after "successful" revascularization due to hemorrhage and malignant edema and so actively detract from any positive treatment effect (9, 10). Unfortunately, in trials, there is also a risk of such patients being over-represented due to perceived lack of equipoise in those with more favorable imaging profiles or financial incentives to recruit.

There are several potential methods to rapidly identify salvageable tissue in clinical practice. In the absence of recanalization, collateral blood flow is the determinant of penumbral survival. Collaterals can be imaged using non-invasive CT or MR angiography (11, 12). Traditional static CT or MR angiography is limited in its ability to assess collateral flow as it is delayed (whereas CTA is timed to normal peak arterial flow) and relatively low flow (which reduces detection by time of flight MRA) leading to potential underestimation of collateral quality. However, dynamic acquisitions are now available for both CT and MR, including reformatted perfusion imaging protocols, and can fully characterize collateral flow (11, 13). These angiographic methods are typically scored using simple visual scales.

Perfusion imaging with CT or MR also provides a dynamic assessment of collateral flow with high temporal resolution and post-processing to represent delay and flow in a more quantitative manner. The perfusion maps require thresholding in order to separate potentially at risk "penumbra" from non-threatened "benign oligemia" as the visual extent of the abnormality overestimates tissue at risk (14, 15). For MR and CT, T_{max} (time to maximum) >6 s has been supported by several studies (16–19). When CT perfusion is used, a separate threshold to distinguish irreversibly injured "ischemic core" versus penumbra is required with cerebral blood flow being more accurate than cerebral blood volume for this purpose (20–22). The larger the "mismatch" between small core and large penumbra, the more likely it is that the patient will respond favorably to revascularization. Whichever method is chosen, better collateral flow scores and mismatch volumes are strongly and consistently associated with improved outcome after reperfusion. With the advent of fully

automated perfusion processing software (23, 24), the argument that perfusion imaging is too complex, time consuming, or challenging to implement and standardize across multiple centers has become obsolete. Indeed, the objective reproducibility of "mismatch," in contrast to visual scoring of collaterals, is a major advantage. The neutral DIAS 3 results with suggestion of benefit in the "per protocol" population (7) indicate that even accurately determining if there is a vessel occlusion poses challenges in a multicenter trial. Presumably, attempts to score collaterals, a much more subjective process, will require significant site education and training if such approaches are to be successful.

The alternative to directly visualizing collateral flow is to identify patients with large ischemic core, which is a direct result of poor collateral flow. Large ischemic core at admission imaging is a reliable indicator of poor outcome (25), although the location of the core also requires consideration. Diffusion MRI is the most accurate method of assessing core in current clinical practice (26). Major reversibility of diffusion lesions with currently available treatments appears uncommon, even in early time windows (27, 28). Thresholded cerebral blood flow or cerebral blood volume can generally provide similar information using CT perfusion imaging (20, 21, 29, 30).

It is important to remember that collateral flow in ischemic stroke is a dynamic process. The fluctuations in clinical severity that clinicians observe may result from fluctuation in collateral flow and, therefore, the snapshot provided by imaging may not reflect the collateral status that has been present over the entire period since stroke onset. This can lead to classification errors in both directions. An improvement in collateral flow can elevate CBF and CBV above the threshold for "core" and may cause temporary post-reperfusion reversal of the diffusion lesion leading to underestimation of core volume (27). A patient imaged just after a deterioration in collateral flow may appear to have a large core based on CBV or CBF and may even have a diffusion lesion but rapid recovery in collaterals could reverse this situation. However, it is important to realize that such cases are exceptions rather than the norm and do not negate the value of advanced imaging. Correlation with the clinical features can prevent misinterpretation in some cases.

REPERFUSION VERSUS RECANALIZATION

The question of the most appropriate revascularization endpoint has been often debated (31). Early endovascular trials were criticized for assessing recanalization of the target vessel without consideration of downstream reperfusion. Clearly, opening the M1 segment of the middle cerebral artery without also establishing flow in M2 vessels is of little clinical value. This, however, reflects a flaw in the measurement scales rather than the concept of recanalization.

A significant advance has been the development of consensus around assessment of angiographic reperfusion that focuses on re-establishment of downstream perfusion with the "modified Treatment In Cerebral Ischemia" (mTICI) (32) score. There has been increasing recognition that a score of 2a (<50% reperfusion of the affected territory), which was included as a "successful" endovascular outcome in earlier studies does not lead to acceptable rates of good outcome. Even mTICI 2b (>50% reperfusion of affected territory) has significantly worse outcomes than mTICI 3 (complete reperfusion), emphasizing the importance of obtaining as close to full reperfusion as possible (4, 17).

In general, recanalization of the major vessels does translate to tissue reperfusion. There are, however, scenarios where recanalization and reperfusion are incongruent, which are worthy of consideration. Recanalization can occur without reperfusion. As mentioned above, many descriptions of this in the literature relate to overly simplistic recanalization scales that focus too narrowly on one segment of the vascular tree without regard for the adjacent segments. However, in animal models, reperfusion at a capillary level often fails despite macrovascular recanalization – termed the "no-reflow" phenomenon. This does not reconcile particularly well with clinical experience where complete removal of thrombus generally leads to normalization of the perfusion imaging appearance (or in some cases hyperperfusion, **Figure 1B**), even in regions that have been irreversibly injured ("non-nutritional reperfusion"). It is possible that clinical perfusion imaging is reflecting flow in larger vessels and showing arteriolar shunting, and is too insensitive to demonstrate occlusion at the capillary level. At any rate, this phenomenon would be restricted to areas we currently regard as irreversibly injured core. To our knowledge, there has not been a description of "no-reflow" in areas thought to be penumbral prior to revascularization. Whether therapeutic strategies to prevent capillary sludging and no-reflow could transform the prognosis for regions we currently regard unsalvageable is an interesting speculation, but seems a rather distant possibility.

Tissue perfusion can also improve without recanalization due to recruitment of collateral blood flow, which can occur in some patients over time. It is visualized as a reduction in perfusion delay and improved blood flow (**Figure 1A**). This form of improved perfusion may be associated with clinical improvement. However, as long as the vascular occlusion remains, the patient has an ongoing risk of collateral "failure" and clinical deterioration. The mechanisms of deterioration in collateral flow are not well understood but presumably clot migration and hemodynamic fluctuations may contribute. Indeed, the observed association of general anesthesia with worse outcome after endovascular therapy (33) may relate to periprocedural hypotension impairing collateral flow. Clearly enhancing or stabilizing this retrograde collateral perfusion is a potential therapeutic strategy and has formed the basis of several attempts to improve collateral flow, although none have translated to clinical practice at this stage. Given the ongoing risk of deterioration in collateral flow, conventional anterograde reperfusion should remain the primary treatment strategy for most patients.

INFARCT GROWTH

The original definition of ischemic penumbra was of hypoperfused and electrically non-functional tissue that could regain function with rapid reperfusion (34, 35). This was subsequently operationalized as a tissue that was at risk of infarction in the absence of reperfusion – a somewhat different construct. Infarct growth

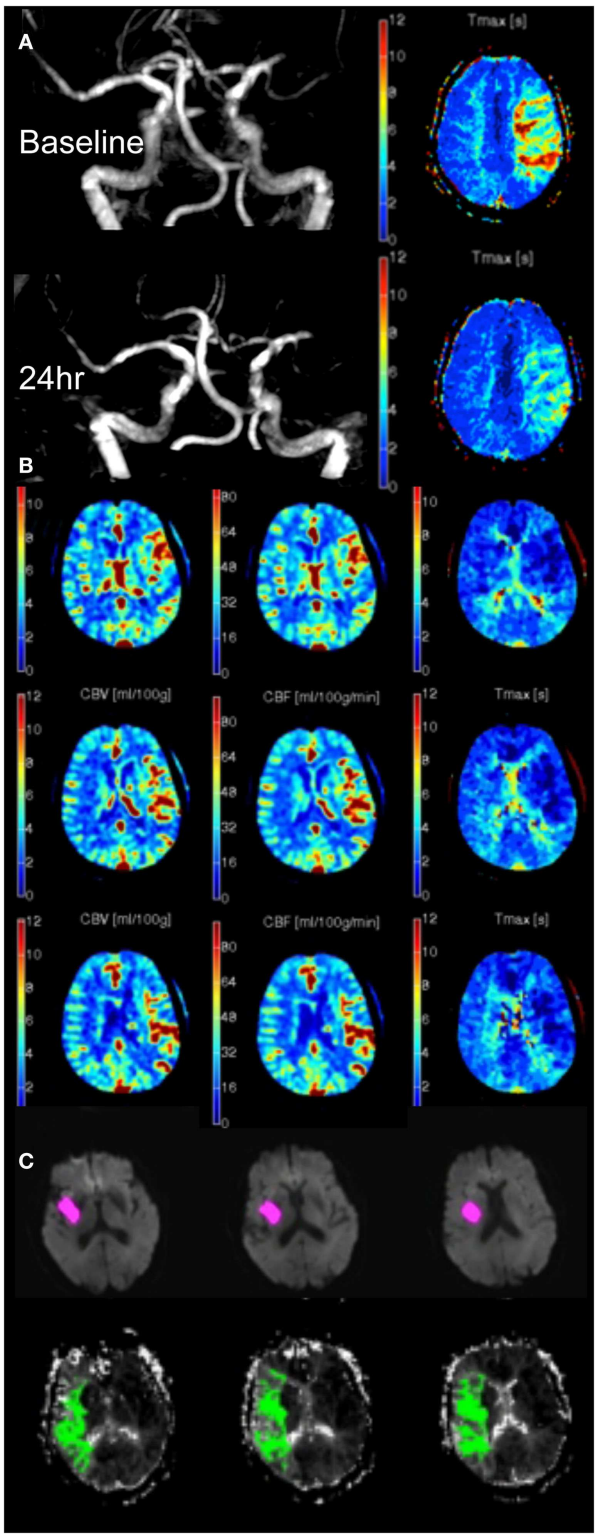

FIGURE 1 | (A) MRA and T_{max} in a patient with left MCA occlusion at 5 and 24 h. Despite persistent occlusion, the volume of $T_{max} > 6$ s has reduced from 56 to 0 mL due to improved collateral supply. **(B)** Post-reperfusion hyperperfusion indicated by increased CBV (left), CBF (middle), and reduced T_{max} (right) in a patient with recent reperfusion of left MCA occlusion. **(C)** MRI diffusion (pink) and perfusion ($T_{max} > 6$ s, green) imaging 24 h post-stroke onset showing persistent hypoperfused tissue, which was contributing to the patient's clinical deficit but had not developed diffusion restriction.

in the absence of reperfusion is associated with worse clinical outcome and infarct growth has, therefore, been used as a surrogate outcome in trials. There are important practical considerations in the measurement of infarct growth. The aim is to measure true territorial expansion in the infarct. However, initial edema and subsequent atrophy confound this and mean that there is no perfect time to assess "growth." In addition, progressive loss to follow-up at later time points can introduce bias as those who die and are, therefore, unevaluable are more likely to have had infarct growth. There is also uncertainty about the duration of true infarct growth, although data suggest that this is generally complete within 24 h after stroke onset (36). Assessment at 24 h is, therefore, attractive as it minimizes loss to follow-up, precedes much of the edema that peaks at 3–5 days, and can be used to assess reperfusion, recanalization, and hemorrhagic transformation.

It is important to recognize that infarct growth is not universal in the absence of reperfusion. Early follow-up imaging frequently shows regions of persistent hypoperfusion that have not developed diffusion restriction but appear to still be contributing to the observed clinical deficit (**Figure 1C**). The clinical significance and prognosis of persistent hypoperfusion is not well understood but it raises the possibility that infarct growth may not fully encapsulate the clinical impact of reperfusion.

FUTURE DIRECTIONS AND ONGOING TRIALS

There are a number of key lessons from recent trials. It seems clear that the use of non-contrast CT and clinical selection criteria will not deliver progress in extending the therapeutic time window or providing an evidence base for endovascular therapy. There are good theoretical reasons and suggestive evidence from existing neutral trials that assessing collaterals or core in addition to vessel occlusion may be beneficial and the technical requirements to achieve this are no longer an inconvenience.

Imaging selection has been hampered by a proliferation of approaches with limited standardization. The principles of identifying a target vessel occlusion and good collateral flow are well established.

However, the optimal practical implementation of these concepts remains uncertain, and clinical practice will no doubt gravitate to the approaches that lead to success in clinical trials. Undoubtedly, the field of acute stroke therapy faces challenges but there is tremendous potential to transform clinical outcomes with new therapies, guided by imaging. It is an exciting time to be practicing stroke medicine.

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Diffusion–perfusion mismatch: an opportunity for improvement in cortical function

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Objective: There has been controversy over whether diffusion–perfusion mismatch provides a biomarker for the ischemic penumbra. In the context of clinical stroke trials, regions of the diffusion–perfusion mismatch that do not progress to infarct in the absence of reperfusion are considered to represent "benign oligemia." However, at least in some cases (particularly large vessel stenosis), some of this hypoperfused tissue may remain dysfunctional for a prolonged period without progressing to infarct and may recover function if eventually reperfused. We hypothesized that patients with persistent diffusion–perfusion mismatch using a hypoperfusion threshold of 4–5.9 s delay on time-to-peak (TTP) maps at least sometimes have persistent cognitive deficits relative to those who show some reperfusion of this hypoperfused tissue.

Methods: We tested this hypothesis in 38 patients with acute ischemic stroke who had simple cognitive tests (naming or line cancelation) and MRI with diffusion and perfusion imaging within 24 h of onset and again within 10 days, most of whom had large vessel stenosis or occlusion.

Results: A persistent perfusion deficit of 4–5.9 s delay in TTP on follow up MRI was associated with a persistent cognitive deficit at that time point ($p < 0.001$). When we evaluated only patients who did not have infarct growth ($n = 14$), persistent hypoperfusion (persistent mismatch) was associated with a lack of cognitive improvement compared with those who had reperfused. The initial volume of hypoperfusion did not correlate with the later infarct volume (progression to infarct), but change in volume of hypoperfusion correlated with change in cognitive performance ($p = 0.0001$). Moreover, multivariable regression showed that the change in volume of hypoperfused tissue of 4–5.9 s delay ($p = 0.002$), and change in volume of ischemic tissue on diffusion weighted imaging ($p = 0.02$) were independently associated with change in cognitive function.

Conclusion: Our results provide additional evidence that non-infarcted tissue with a TTP delay of 4–5.9 s may be associated with persistent deficits, even if it does not always result in imminent progression to infarct. This tissue may represent the occasional opportunity to intervene to improve function even days after onset of symptoms.

Keywords: diffusion–perfusion mismatch, acute ischemic stroke, penumbra, NIHSS, functional outcome

INTRODUCTION

At the onset of an ischemic stroke, an occluded blood vessel results in diminished blood flow to a region of brain tissue, resulting in cerebral ischemia. Ischemic tissue becomes electrically dysfunctional and can progress to infarction. The term ischemic penumbra was coined by Astrup and colleagues in the 1970s to characterize a state of brain tissue in which "neurons remain structurally intact but functionally inactive" and in which a regional increase in cerebral blood flow can restore this activity (1). From experiments in baboons, they reported dual thresholds for ischemia; the threshold for cell death (signaled by the release of K+) was markedly lower than the threshold for complete electrical failure of neurons. In its original use, the "penumbra" differentiated the outer rim, or "half shadow" of tissue, which had reached the threshold for electrical failure, from the inner core of infarction, which had reached the threshold for sustained energy failure resulting in ion pump failure (2). Thus, acute occlusion of a large cerebral artery typically results in region of diminished blood flow in which the central core experiences the most severe ischemia and can rapidly progress to infarct. Surrounding the core there may be a region of hypoperfusion that is ischemic but not infarcted; this area is commonly referred to as the ischemic penumbra. The penumbra is electrically dysfunctional tissue that, when reperfused, will regain function.

With the introduction of positron emission tomography (PET) imaging, regional cerebral blood flow could be measured in

humans, and the thresholds for ischemia and dysfunction were further defined. The concept of ischemic penumbra was elaborated by Muir and colleagues (3) to include the following criteria: "(a) hypoperfusion <20 mL/100 g/min; (b) abnormal neuronal function documented by a correlation with acute clinical deficit; (c) physiological and/or biochemical characteristics consistent with cellular dysfunction but not death; (d) uncertain fate; and (e) salvage of this tissue is correlated with better clinical recovery" (p. 761). Surrounding the layer of ischemic penumbra (reduced cerebral blood flow to <20 mL/100 g/min) exhibiting impaired neural function but preserved tissue integrity, it was recognized there was often a third zone of reduced blood flow. This zone was defined as tissue with relatively small reductions in blood flow of 20–50 mL/100 g/min. It was assumed this tissue would maintain function for a protracted time and would be unlikely to proceed to infarction, and was thus labeled "benign oligemia."

With the advent of multimodal MRI, a different biomarker for the penumbra was proposed (3, 4). Diffusion weighted imaging (DWI), which measures the movement of water in brain tissue, was used to delineate ischemic tissue that had sustained energy failure and thus exhibited diffusion restriction. Perfusion weighted imaging (PWI), which uses a bolus tracking dynamic scan to measure the delivery of blood to the brain, was used to delineate the region of ischemia. Thus, the difference between the DWI lesion and the PWI lesion was postulated to be a biomarker for the ischemic penumbra. This biomarker has held up when compared to biomarkers of penumbra obtained from PET imaging (5–7).

As the field of acute stroke treatment was emerging, it was postulated that the diffusion–perfusion mismatch would guide treatment and predict response to therapy. In order to use this biomarker in such a manner it had to be adapted into a predictive model. Initially, it was hypothesized that in the absence of acute vessel recanalization, the infarcted core would grow into the ischemic penumbra and the opportunity for clinical recovery would be lost. This hypothesis has been the driving force behind most MRI-guided acute stroke research.

In the context of the MRI-guided therapies, the term "penumbra" has now come to be understood as "tissue at risk." A number of authors have pointed out that the diffusion–perfusion mismatch includes both hypoperfused tissue that will imminently infarct ("tissue at risk") and hypoperfused tissue that will survive despite hypoperfusion ("benign oligemia") (8). In the context of MRI-guided therapies, benign oligemia is thought to be irrelevant, and it is excluded from the lesion targeted for reperfusion therapy.

It has been shown that MRI based thresholds of hypoperfusion are capable of separating benign oligemia from tissue that is at-risk of imminent infarction. The threshold for distinguishing benign oligemia from tissue at risk has varied across studies and changed over time; however, the most frequently used threshold in the current literature is a time-to-maximum of 6 s (9). However, there might be tissue in between tissue at risk for imminent progression to infarct and benign oligemia – tissue that will remain dysfunctional if blood flow remains compromised and will regain function if blood flow is restored. A number of case reports of improvement in function after reperfusion by carotid endarterectomy, carotid stenting, or blood pressure elevation even days after stroke onset indicate the existence of this tissue that exists in a state of limbo between adequate blood flow for function and immediate risk of infarction (10–12). It is not entirely clear how this dysfunctional tissue survives over days with "misery perfusion"; it may do so by collateral blood flow or intermittent blood flow from the main arterial supply. Nevertheless, MRI might be able to define the thresholds of this hypoperfused, dysfunctional tissue. Data from the case reports of reversible function days after stroke indicate that a delay in time-to-peak (TTP) arrival of contrast of 4–5.9 s might represent tissue that is dysfunctional but not always at immediate risk of progression to infarction (particularly in cases of large vessel stenosis). This segment of penumbral tissue is important to define, as it may represent an opportunity to improve at least cortical function in special cases long after the typical window for reperfusion therapies.

A study using PET as the gold standard found that a TTP threshold of 4.2 s (or Tmax threshold of 5.2 s) corresponds to penumbra as operationally defined above (see definition by Muir and colleagues), and indicated that the TTP threshold might be a more stable (3, 5). Another study found that non-deconvolved TTP outperformed Tmax in distinguishing oligemia from tissue at risk (13), and using local arterial input functions did not improve the predictive performance of the algorithms over conventional methods. Other studies have shown that reperfusion of penumbral tissue identified on MRI results in not only tissue salvage but also improved outcomes (14). However, the clinical relevance of a persistent hypoperfusion in the range of TTP of 4–5.9 s delay has not been adequately addressed.

As noted, a few studies have shown that individuals with persistent hypoperfused tissue of 4–5.9 s delay in TTP have shown improved function with reperfusion (10–12). Thus, these studies illustrate that the diffusion–perfusion mismatch defined by MRI can reveal penumbra as originally described by Astrup and colleagues in primates – marginally perfused, dysfunctional tissue that can regain function if reperfused (3). These results mirror results of other studies showing improvement in function with reperfusion of penumbra defined by PET or CT perfusion (15–19). What these previous studies did not do, however, was show that persistent diffusion–perfusion mismatch, defined by hypoperfusion thresholds of 4–5.9 s delay in TTP, was associated with persistent dysfunction. Tissue within this range of TTP is often considered to be within the "benign oligemia" range, because it does not always progress to infarct. Persistent hypoperfused tissue of 4–5.9 s delay in TTP beyond the infarct that is associated with persistent deficits, in the absence of infarct growth, would provide evidence that hypoperfused tissue of 4–5.9 s delay in TTP may not be so benign.

Here, we address the question, "Is benign oligemia really benign?" We hypothesized that patients with a persistent diffusion–perfusion mismatch defined using upper and lower hypoperfusion thresholds of TTP 4–5.9 s delay have persistent dysfunctional tissue and poorer performance on cognitive tests when compared with patients who have reperfused, whether or not there is growth of the infarct. We studied this hypothesis by evaluating changes in volumes of infarct and hypoperfusion in a cohort of patients who underwent serial imaging and cognitive testing over several days during hospitalization for an acute ischemic stroke. Most of these patients had large vessel stenosis or occlusion, which

carries the greatest risk for persistence of a diffusion–perfusion mismatch.

MATERIALS AND METHODS

Subjects were identified from a database of acute ischemic stroke patients who had been recruited from the inpatient stroke service under an IRB approved protocol to undergo serial cognitive and MRI testing, utilizing the following criteria: (1) clinical diagnosis of unilateral anterior circulation stroke, (2) cognitive testing and MRI scan performed within 24 h at two time points within 10 days, and (3) adequate quality DWI and PWI images for volumetric analysis at both time points. Patients had a variety of acute stroke interventions, often attempts to restore perfusion, including induced blood pressure elevation, carotid stenting, urgent endarterectomy, and intraarterial thrombolysis, at the discretion of the primary clinical team.

Cognitive testing consisted of a picture naming task for left hemisphere strokes and a line cancelation test for right hemisphere strokes both of which were scored as a percent error. The line cancelation test usually requires <2 min to administer. The picture naming test usually requires <10 min to administer. These tests are described in previous papers (14). For both, 10% error rate represents >3 SD from mean for normal controls (14).

Volumes of ischemia on DWI were calculated by manual delineation of a region of interest (ROI) that was bright on DWI and dark on apparent diffusion coefficient (ADC) maps. Volumes of hypoperfusion on PWI were calculated by manually segmenting thresholded TTP maps. We calculated volumes of tissue with delay in TTP of 4–5.9 and ≥6 s delay relative to normal tissue (the homologous voxels in the contralateral hemisphere). Perfusion source images were exported as a DICOM time series using OsiriX software. Then, TTP maps were generated and analyzed by ImageJ software[1] by a technician blinded to cognitive test scores. TTP maps were calculated in seconds beyond normal using the homologous region in the unaffected hemisphere as a reference. TTP maps were used instead of Tmax maps as they have been shown to be as effective in detecting perfusion abnormalities and are simple and reproducible (5). We chose two separate thresholds to determine the volume of tissue with 4–5.9 s delay in TTP (tissue we hypothesized to be potentially viable, but dysfunctional), and tissue with ≥6 s delay in TTP (tissue more likely to be at immediately risk to progress to infarct).

Lack of reperfusion was defined as a <10% reduction in the PWI lesion volume. Infarct growth was defined as a >10% increase in DWI lesion volume. We chose these small thresholds of volume change in order to evaluate the effects of failure to reperfuse, in the absence of infarct growth (i.e., the persistence of diffusion–perfusion mismatch, using thresholds of hypoperfusion of TTP delay 4–5.9 or ≥6 s). Some treatment studies define "reperfusion" as >50% (or greater) reduction in PWI volume (14, 20). However, in our study we did not want patients with partial reperfusion, who may also have partial improvement, to contaminate the effect of sustained diffusion–perfusion mismatch, which is the target population for this study. Therefore, relatively strict definitions for lack of reperfusion and infarct growth were used.

[1]http://imagej.nih.gov/

We first tested the hypothesis that patients who showed no reperfusion of tissue with 4–5.9 s delay in TTP would show less change in cognitive score than patients who showed reperfusion, irrespective of infarct growth, using a *t*-test in the Stata 13.1 software package[2] to compare the two groups. Patients were separated into two groups based on whether or not they experienced infarct growth, defined as an increase of 10% in the DWI lesion volume from the first time point to the second time point. These two groups were each further divided based on whether there was reperfusion – defined as a 10% reduction in volume of hypoperfusion on PWI from the first to the second time point (**Figure 1**). Patients with neither reperfusion nor infarct growth were considered to be the best example of persistent diffusion–perfusion mismatch with PWI threshold of 4–5.9 s delay in TTP. Changes in cognitive scores were compared between the two subgroups (reperfusion vs. persistent hypoperfusion) with *t*-tests.

We also evaluated the Pearson correlation between baseline volume of hypoperfusion (using 4–5.9 s delay in TTP) and (1) final infarct volume measured by volume of ischemia on the second DWI, and (2) persistent hypoperfusion measured by volume of hypoperfusion measured on the second PWI. We also evaluated the Pearson correlation between change in cognitive score and change in volume of hypoperfusion using 4–5.9 s delay in TTP, to test the hypothesis that change in hypoperfusion reflects change in cortical function. However, it is not assumed that there is a direct relationship between the cognitive test score and the change in volume since location of reperfusion likely also plays a significant role. Finally, to determine if the change in volume of hypoperfused tissue contributed to cognitive change independently of change in infarct volume, we carried out a multivariable linear regression analysis, with cognitive change as the dependent variable, and changes in volumes of ischemia on DWI and hypoperfusion on

[2]http://www.stata.com/

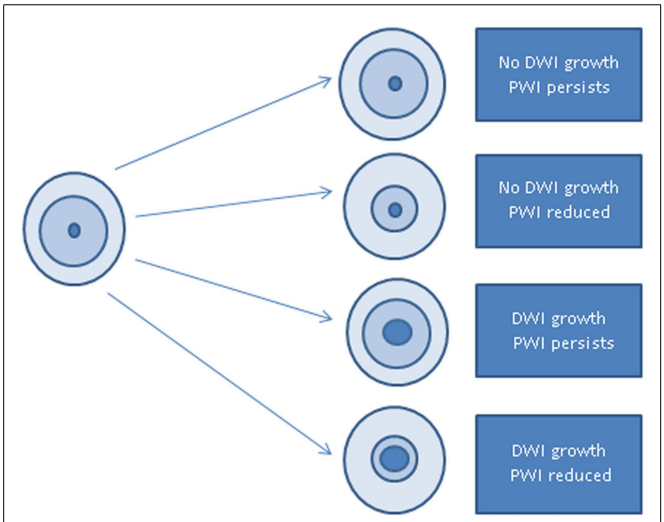

FIGURE 1 | Schematic of study design: outer circle represents brain; middle circle represents volume of hypoperfusion on PWI; inner circle represents volume of ischemia on DWI.

Table 1 | Etiology and treatment of patients included.

	Angioplasty/ embolectomy/ stent/intraarterial tPA/CEA	Blood pressure augmentation with medications[a]	Blood pressure augmentation permissive hypertension +/− intravenous fluids	Anti-platelets + statin only	Anti-coagulation
Intracranial stenoisis/occlusion ($n=21$)	1	14	6		
Extracranial ICA stenosis ($n=2$)	2				
Acute ICA occlusion or dissection ($n=2$)					2
Watershed post CABG ($n=1$)				1	
Cardioembolic ($n=6$)					6
Hypercoagulable state (cancer) ($n=2$)			1		1
Uncertain etiology (OCP, PFO) ($n=2$)				2	
Small vessel disease ($n=2$)				2	

[a]*pressors, midodrine, and/or fludrocortisone.*

ICA, internal carotid stenosis; CABG, coronary artery bypass graft; OCP, oral contraceptive pills; PFO, patent foramen ovale.

PWI (with thresholds of 4–5.9 and ≥6 s delay) as the independent variables.

RESULTS

Of the 38 patients identified from the database who met the inclusion criteria, 45% were women; mean age was 61 years. There were 29 patients with a left hemisphere stroke and 9 with a right hemisphere stroke. **Table 1** summarizes their etiology and recorded treatment based on retrospective review of their medical records. The mean volume of ischemia on initial DWI was 20.0 cc (range 0–140.4 cc); mean volume of hypoperfusion on initial PWI was 26.8 cc (range 0–111.8 cc) using a threshold of 4–5.9 s TTP, and mean 25.3 (0–116.5 cc) using a threshold of ≥6 s TTP. Mean baseline National Institutes of Health Stroke Scale Score was 6.5 (range 0–24). The mean baseline error rate on the naming test was 57.9% errors (range 0–100% errors). Mean baseline error rate on the cancelation (neglect) test was 43.2% (0–99% errors).

We first evaluated the change in cognitive test error rate for those who failed to reperfuse (had a persistent diffusion–perfusion mismatch; $n=15$) compared to those who reperfused ($n=23$) in the entire group of patients (irrespective of infarct growth). Using a 10% reduction in perfusion abnormality with a threshold of 4–5.9 s delay on TTP maps, there was a significant difference in the change in error rates on cognitive testing between those who failed to reperfuse (mean 3% *increase* in error rate) vs. those who did reperfuse [mean 40% *decrease* in error rate, $t(36)=4.1$, $p=0.0001$]. Using a 10% reduction in perfusion abnormality with a threshold of 6 s delay on TTP maps, there was also a significant difference in the change of error rates on cognitive testing, with an increase in errors for those without reperfusion compared to a decrease in error rates for those who did reperfuse [mean 14 vs. −34; $t(36)=3.99$; $p=0.0003$].

Of the 14 patients without infarct growth, the diffusion–perfusion mismatch persisted in 8 (57%) patients who had a mean separation between MRI scans of 3.9 days. Comparing patients with persistent diffusion–perfusion mismatch with those who had reperfused revealed significantly less change in cognitive impairment in those with persistent functional diffusion–perfusion mismatch [−5 vs. −40%; $t(12)=2.4$; $p=0.02$]. Examples of patients in each group are shown in **Figures 2–5**. **Figure 6** shows a boxplot of the change in error rates for patients in each of the four groups based on PWI and DWI change. When evaluating the difference between change in cognitive score between those with persistent diffusion–perfusion mismatch when based on a TTP threshold of 6 s instead of 4–5.9 s, the relationship between persistent cognitive deficit and persistent diffusion–perfusion mismatch was not significant but showed the same trend [−2 vs. −34%; $t(12)=1.9$; $p=0.075$].

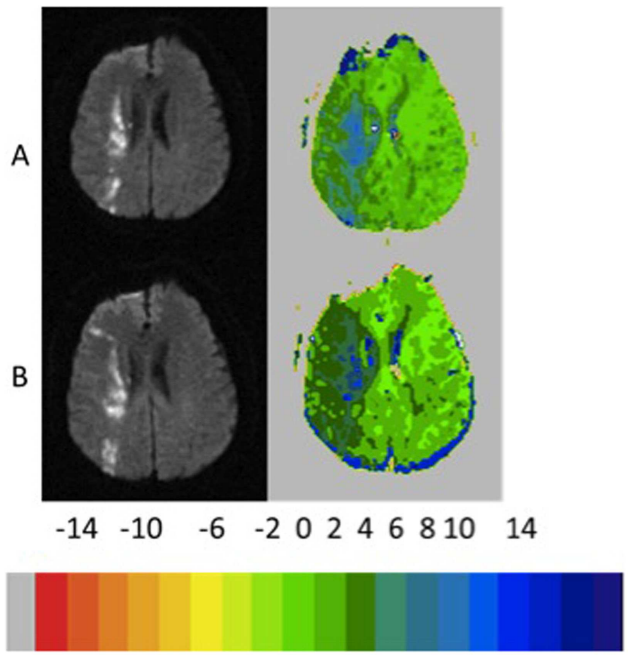

FIGURE 2 | Example of patient who showed growth of infarct of >10% with <10% reperfusion and persistent severe left neglect on line cancelation task (85 and 71% errors, 3 days later). The color key shows the relative delay in TTP (each color corresponds to 2 s delay in TTP arrival of contrast).

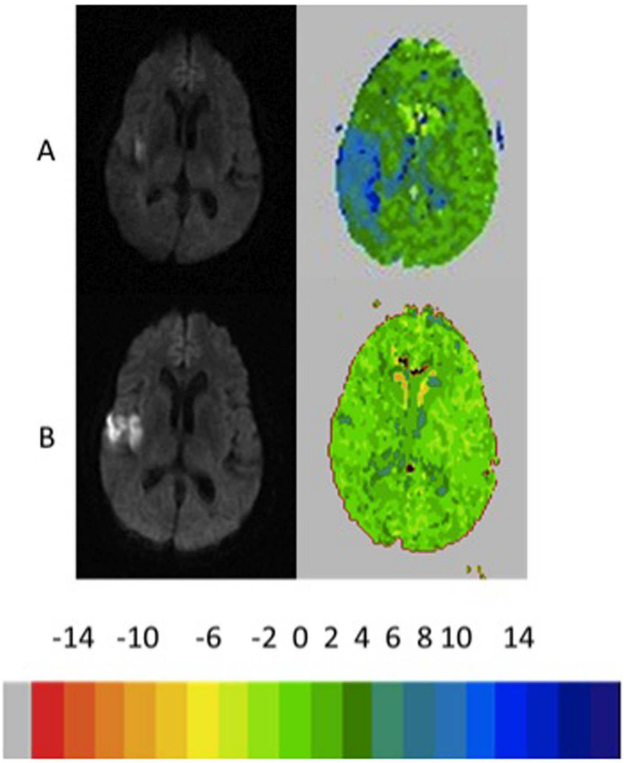

FIGURE 3 | Example of patient who showed growth of infarct >10% with reperfusion >10% reperfusion with recovery from left neglect on the line cancelation task (99–0% errors, 4 days later). The color key shows the relative delay in TTP (each color corresponds to 2 s delay in TTP arrival of contrast).

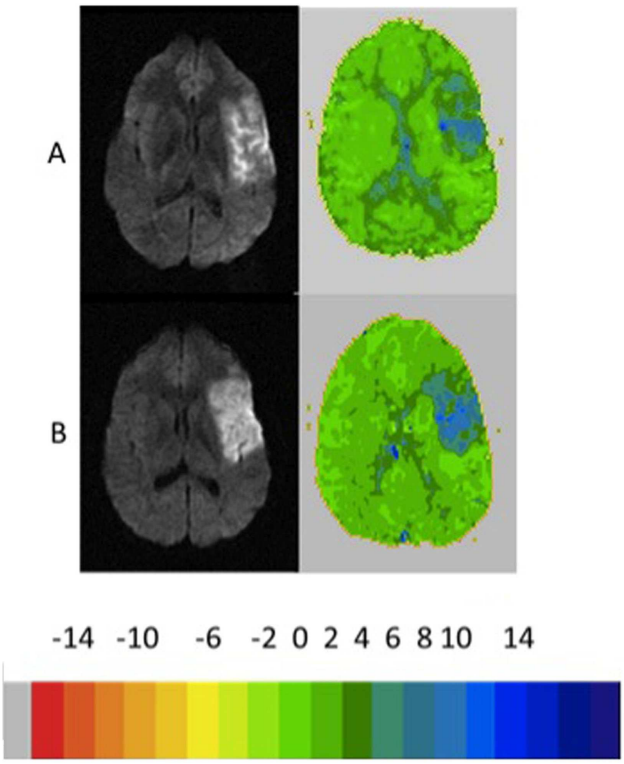

FIGURE 4 | Example of patient who showed no growth infarct (<10%) with <10 reperfusion and persistent severe naming impairment (100 and 100% errors, 4 days later). The color key shows the relative delay in TTP (each color corresponds to 2 s delay in TTP arrival of contrast).

Infarct growth was present in 24 (63%) patients. Even among these patients, many had persistent diffusion–perfusion mismatch (see **Figures 3** and **6**). Those who failed to reperfuse showed an increase in error rate, while those who reperfused showed a decrease in error rate; the difference was significant, both using a threshold of 4–5.9 s delay in TTP [8 vs. −39%; $t(22) = 3.3$; $p = 0.002$] and using a threshold of 6 s delay in TTP [26 vs. −34%; $t(12) = 3.6$; $p = 0.002$].

There was a *reduction* in DWI lesion volume in eight patients; seven of these patients also showed a >10% reduction in volume of hypoperfusion with 4–5.9 s delay, and associated reduction in errors on cognitive testing. One patient who showed a decrease in DWI lesion showed an *increase* in volume of hypoperfusion on PWI, and an *increase* in error rate on cognitive testing.

For the patients in this study, the initial volume of hypoperfusion with 4–5.9 s TTP delay did not correlate with the final infarct size ($r = 0.051$; $p = 0.76$). However, the initial volume of hypoperfusion did correlate with the final volume of hypoperfusion ($r = 0.53$; $p = 0.0006$). Moreover, the change in volume of hypoperfusion with 4–5.9 s delay in TTP correlated with the change in cognitive score ($r = 0.58$; $p = 0.0001$) (**Figure 7**). We merged the scores for naming error rate (left hemisphere stroke) and neglect error rate (right hemisphere stroke) for this analysis, which seemed reasonable, as the scores were comparable in capturing variability: the mean change in naming error rate was −22.8 (±SD 39.3). The mean change in neglect error rate was −22.6 (±SD 30.8).

Finally, to determine if change in volume of hypoperfusion was associated with change in cognitive function independently of change in volume of ischemia on DWI, we carried out a multivariable regression analysis. We found that both change in volume of hypoperfusion with TTP delay of 4–5.9 s ($\beta = 0.542$; $p = 0.002$) and change in volume of ischemia on DWI ($\beta = -0.314$; $p = 0.023$) independently contributed to change in error rate on cognitive testing (in opposite directions). Together, these two variables accounted for 43% of the variance in change in cognitive score ($r^2 = 0.43$; $p = 0.0001$). Change in volume of hypoperfusion with ≥6 s delay in TTP was not independently associated with change in cognitive score.

DISCUSSION

Restoration of blood flow is the goal of all acute ischemic stroke treatments. Preventing infarct and tissue death is a logical target for acute intervention. Previous studies have shown that imaging (PET or MRI) can identify this tissue at risk. However, focusing only on tissue at risk for imminent progression to infarct carries the potential risk of ignoring subacute brain ischemia that might persist beyond the initial event. In this study, we demonstrated that the diffusion–perfusion mismatch with hypoperfusion thresholds

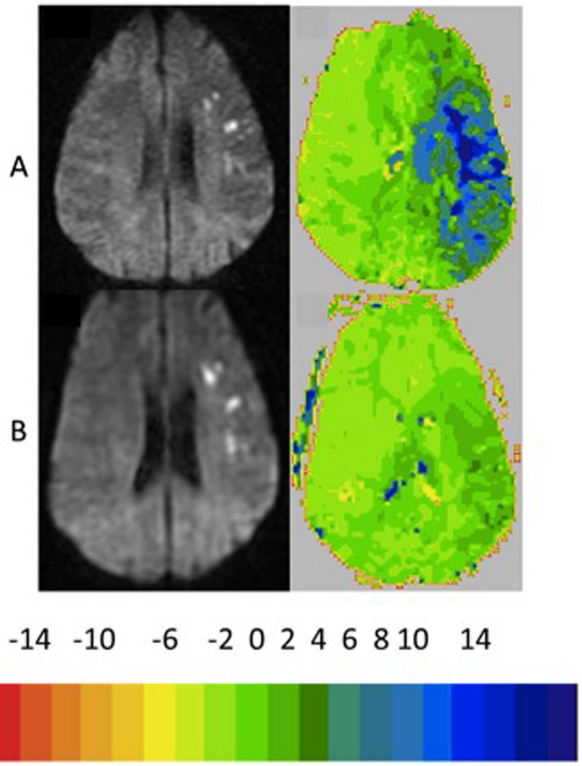

FIGURE 5 | Example of patient who showed no growth infarct (<10%) with >10 reperfusion with improvement in naming performance to normal performance (23 and 10% errors, 4 days later). The color key shows the relative delay in TTP (each color corresponds to 2 s delay in TTP arrival of contrast).

of 4–5.9 s delay in TTP can sometimes persist for days and seems to result in persistent cognitive deficits. Those who failed to reperfuse this tissue failed to improve in cognition; while those who reperfused did improve ($p < 0.001$).

In our study, "benign oligemia" defined as tissue with 4–5.9 s delay in TTP was not always benign. Rather, at least some of this tissue seemed to represent "misery perfusion" described by Baron in 1981, which can show functional recovery if reperfused (15). The persistence of perfusion deficits in this range was associated with persistent cognitive deficits when compared with those who reperfused. We confirmed that the initial volume of hypoperfusion with TTP 4–5.9 s delay in TTP did not predict final infarct volume, but did correlate with final volume of hypoperfusion. Furthermore, change in volume of TTP delay correlated with change in cortical dysfunction (measured by change in cognitive score). These results are also consistent with the proposal that tissue with this degree of hypoperfusion (4–5.9 s delay) measured with PWI represents reversibly dysfunctional tissue, even if it is not *always* at imminent risk for progression to infarct. On the other hand, tissue with TTP delay of ≥6 s TTP delay was not associated with change in cognitive function, independently of change in volume of ischemia of DWI and change in volume of hypoperfusion with 4–5.9 s delay. Tissue with ≥6 s TTP delay likely includes much more tissue that is not reversible days after stroke.

There were several limitations to this study. This is a retrospective analysis of prospectively collected data collected over a few years. The MRI scan parameters were not standardized and varied considerably with regard to pulse sequences and magnet strength. The scans at the two time points were not registered, as no high-resolution anatomical scan was obtained with these clinical scans. We were also not able to register the DWI to the PWI on voxel-by-voxel basis; therefore, hypoperfusion defined as 4–5.9 s delay in TTP may have also included some core infarct. However, it is unlikely that the hypoperfused tissue defined with these dual thresholds included much core infarct, because reperfusion of the tissue with 4–5.9 s TTP delay (reduction in that volume) was associated with improvement in cognitive function, independently of change in infarct volume. Cognitive testing may be cumbersome when time is of essence in treatment of acute stroke. However, the simple cognitive tests we used here take <10 min to administer. We also note that these patients were not typical stroke patients. They had a second MRI scan that included PWI 2–10 days after the first. This second scan was generally obtained because persistent hypoperfusion was suspected or to evaluate the effectiveness of intervention to improve perfusion or collateral blood flow (such as temporary induced blood pressure elevation). Thus, there was a relatively small percentage of lacunar strokes, and a relatively large percentage of large vessel stenosis, as the etiology of stroke.

We do not wish to claim that the rate of persistent diffusion–perfusion mismatch observed in this study is representative for an acute stroke population. Rather, our goal was to demonstrate that diffusion–perfusion mismatch with a hypoperfusion threshold of 4–5.9 s delay in TTP can sometimes persist, and appears to represent dysfunctional tissue that can recover function if blood flow is restored. As noted, is not clear how this tissue sometimes survives days after onset – perhaps by misery perfusion from the main arterial supply, or from collateral circulation, either of which may fluctuate with any variable that changes the mean arterial pressure or intracranial pressure (body position, respiratory rate, temperature, and so on). A relatively small number of patients with persistent hypoperfusion of 4–5.9 s delay in TTP showed some infarct growth, indicating that the area of hypoperfusion included some "tissue-at-risk" as well as "benign oligemia."

Future studies should address some of the limitations of this study, by evaluating both the fate and the clinical consequences of voxels that that are initially non-infarcted (using a specific ADC threshold) but hypoperfused (using various TTP ranges, e.g., 2–3, 3–4, 4–5 s). This analysis should be done on a large, unselected series of acute ischemic stroke patients, using serial imaging registered to high resolution anatomical images, so that DWI and PWI can be registered to each other at each time point and across time points.

Despite its limitations our study indicates that symptomatic, reversible perfusion deficits can be identified by diffusion–perfusion mismatch using a hypoperfusion threshold of 4–5.9 s TTP delay and can occasionally persist for days without progressing to infarction. Thus, the diffusion–perfusion mismatch defined in this way may be clinically useful for identifying patients who might still benefit from reperfusion (e.g., urgent carotid endarterectomy, stenting, efforts to increase collateral blood flow). Failure to restore blood flow to tissue with a TTP delay of 4–5.9 s

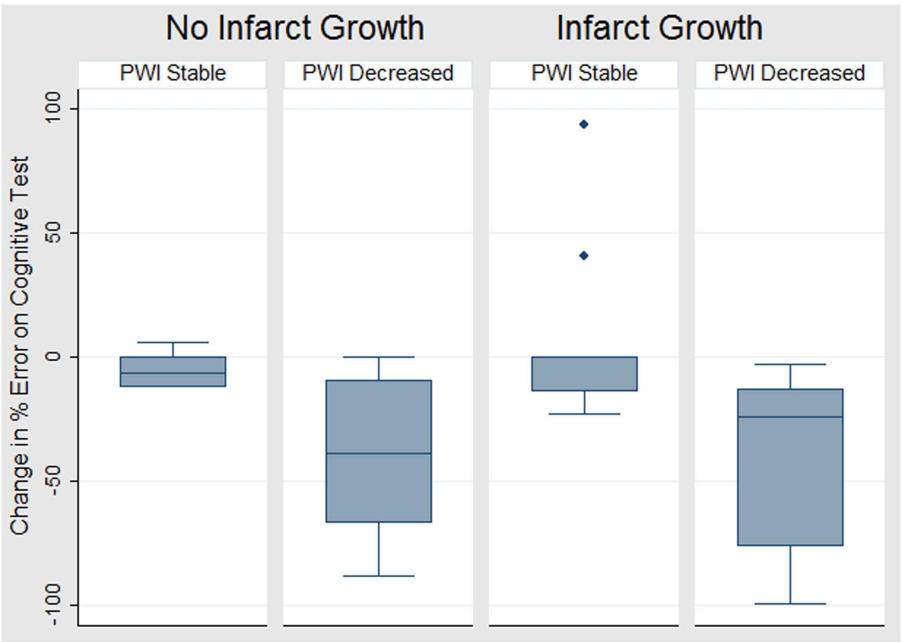

FIGURE 6 | Boxplot of the change in cognitive score (i.e., change in error rate – negative values indicate improved cognition) for each of four groups defined by change on DWI and PWI.

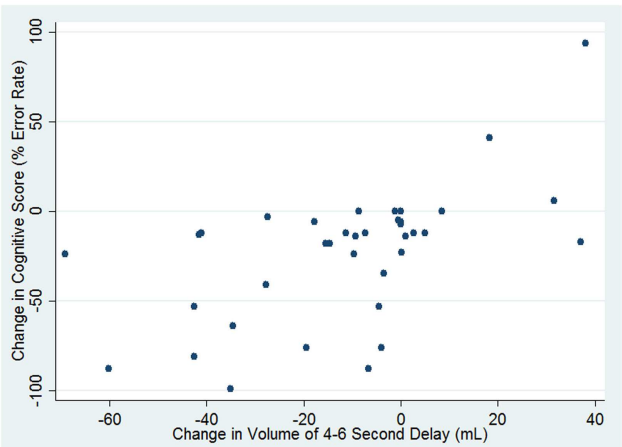

FIGURE 7 | Correlation between change in cognitive score and change in volume of hypoperfusion (defined as TTP delay of 4–5.9 s).

seems to result in persistent deficits in some cases even if it does not result in imminent progression to infarct. These results do not detract from the usefulness of the diffusion–perfusion mismatch model (or other models of the penumbra) for identifying tissue at risk and patients who require acute intervention, but provide yet another way this imaging might be useful in clinical care.

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Aphasia or neglect after thalamic stroke: the various ways they may be related to cortical hypoperfusion

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Although aphasia and hemispatial neglect are classically labeled as cortical deficits, language deficits or hemispatial neglect following lesions to subcortical regions have been reported in many studies. However, whether or not aphasia and hemispatial neglect can be caused by subcortical lesions alone has been a matter of controversy. It has been previously shown that most cases of aphasia or hemispatial neglect due to acute non-thalamic subcortical infarcts can be accounted for by concurrent cortical hypoperfusion due to arterial stenosis or occlusion, reversible by restoring blood flow to the cortex. In this study, we evaluated whether aphasia or neglect occur after acute thalamic infarct without cortical hypoperfusion due to arterial stenosis or occlusion. Twenty patients with isolated acute thalamic infarcts (10 right and 10 left) underwent MRI scanning and detailed cognitive testing. Results revealed that 5/10 patients with left thalamic infarcts had aphasia and only 1 had cortical hypoperfusion, whereas 2/10 patients with right thalamic infarcts had hemispatial neglect and both had cortical hypoperfusion. These findings indicate that aphasia was observed in some cases of isolated left thalamic infarcts without cortical hypoerfusion due to arterial stenosis or occlusion (measured with time-to-peak delays), but neglect occurred after isolated right thalamic infarcts only when there was cortical hypoperfusion due to arterial stenosis or occlusion. Therefore, neglect after acute right thalamic infarct should trigger evaluation for cortical hypoperfusion that might improve with restoration of blood flow. Further investigation in a larger group of patients and with other imaging modalities is warranted to confirm these findings.

Keywords: acute thalamic stroke, aphasia, neglect, cortical hypoperfusion, diaschisis

INTRODUCTION

The role of subcortical structures in cognitive processing remains somewhat elusive. Over the last decades, the advent of functional imaging has led to a better understanding of the role of subcortical structures in cognitive processing. The thalamus has been of particular interest to researchers given that it projects to all areas of the neocortex including those areas in the frontal, temporal, and parietal regions that are commonly associated with language and cognition. Many functional imaging studies of language reveal thalamic participation in a variety of tasks and processes (1–10).

A recent study reviewed the role of the thalamus in 50 functional imaging studies of language tasks (11). The author found that thalamic activation was most commonly associated with generation tasks and naming; and the thalamic activation was seen bilaterally, left greater than right, along with activation in frontal and temporal cortical regions. Left parietal activation was seen in few studies. The peaks of activation loci were seen in all thalamic nuclei, with a bias toward left-sided and midline activation. The results of this literature review suggest that the thalamus may play a role in processes that involve the manipulation of lexical information, and that thalamic activation may be modulated by the difficulty of task demands. Similar results are reported in the clinical literature. Aphasia after left thalamic damage has also reported in numerous studies (4, 12–22). Further, language and cognitive deficits caused by stereotactic surgery (e.g., thalamotomy) or electric stimulation of the thalamus provided additional information about the role of specific thalamic nuclei in language and cognitive processes underlying language tasks (23–26).

In contrast to the large corpus of evidence that suggests involvement of the thalamus in language functions, the role of the thalamus in visuo-spatial processing, attention, and perception appears more obscure (27–34). A recent meta-analysis review explored the cognitive, affective, and behavioral disturbances following vascular thalamic lesions (35). The authors reviewed a study corpus of 465 patients with vascular thalamic lesions published in the literature since 1980 and found that 42 out of 465 (9%) cases had isolated thalamic lesions. Most of the cases reported pertained to language deficits after left thalamic lesion. Of patients with isolated thalamic lesions who were tested, 38.5% were impaired in spatial attention, 43.8% were impaired in comprehension, and 72.2% were impaired in naming. This review clearly highlights the importance of thalamus in higher-order behavioral functions;

however, the mechanism that accounts for aphasia and neglect after thalamic lesion is still debated.

Several hypotheses have been advanced to explain the role of the thalamus in higher-order behavior (36). Nadeau and Crosson described five potential mechanisms associated with lesions of the thalamus: (1) direct impact of the thalamic lesion indicating that the thalamus is a crucial component of the cerebral network underlying neurocognitive processing; (2) diaschisis, or functional depression of regional neuronal metabolism and cerebral blood flow in anatomically connected cortical regions following dysfunction of the lesioned thalamus; (3) occlusion or stenosis of large cerebral vessels independently causing a thalamic stroke and hypoperfusion of the cortex; (4) cortical infarcts not detected by imaging; or (5) impaired "release" of language segments formulated by cortical regions into output. A sixth potential mechanism is indicated by animal studies showing alterations in cortical excitability in areas distant to the infarct that may be mediated by NMDA-dependent processes, spreading depression, or inflammation (37), rather than only anatomical disconnection. Diminished neuronal activity in an area remote to the infarct is the broadest meaning of "diaschisis." Although the original concept proposed by Von Monakow (38) required an anatomical disconnection, the concept has developed recently to include a number of different forms of diaschisis, only some of which involve structural disconnection [see in Ref. (39) for review].

Baron and colleagues provided early evidence that deficits seen after thalamic lesion are secondary to cortical dysfunction due to diaschisis (40). They reported that, in patients with thalamic lesions, the magnitude of cognitive impairment was positively correlated with the degree of ipsilateral cortical hypometabolism demonstrated by PET [see also in Ref. (22)]. In previous studies, Baron and colleagues (41) also demonstrated that suppressed synaptic activity associated with reduction in metabolic demand in areas of diaschisis results in a reduction in cerebral blood flow. This spared neurovascular coupling in diaschisis was demonstrated by evaluating cerebral blood flow in regions of reduced glucose and oxygen metabolism. Since then, many others have demonstrated aphasia or neglect after thalamic lesions associated with cortical dysfunction attributable to diaschisis (35). In these cases, cortical dysfunction is demonstrated by measuring cortical metabolism or regional cerebral blood flow. Another study demonstrated a strong association between lesions in the right superior longitudinal fasciculus (SLF II) and left spatial neglect in a group study, and showed that right thalamic stroke was associated with chronic left neglect *only* when SLF II was damaged (42). This study provided evidence for the importance of thalamocortical connections (particularly to frontoparietal cortex) in the pathogenesis of chronic neglect.

However, some cases of aphasia or hemispatial neglect due to acute subcortical infarcts the associated cortical hypoperfusion cannot be attributed to diaschisis. Rather, the concurrent cortical hypoperfusion has been attributed to vascular stenosis or occlusion and seems to be responsible for the aphasia or neglect accounted in these cases (43, 44). In the one study, subcortical infarctions with aphasia and neglect were consistently associated with cortical hypoperfusion (in the middle cerebral artery territory), and reversal of the cortical hypoperfusion by restoring blood flow was associated with immediate resolution of their cortical deficits. Because reperfusion of the cortex, with the persistence of the subcortical infarct, would not have altered diaschisis or other potential mechanisms, the aphasia that resolved must have been due to hypofused, dysfunctional tissue that recovered function with reperfusion (44). Tissue that is receiving enough blood to survive but not enough to function, and recovers function by restoring blood flow, is the original meaning of "penumbra" (45). Penumbra has more recently come to mean tissue that will progress to infarct if blood flow is not restored [see in Ref. (46), this issue]. Therefore, at least some cases of aphasia due to subcortical infarcts are due to "penumbra" as originally defined – what we will refer to as "hypoperfusion due to arterial stenosis or occlusion").

The cortical hypoperfusion associated with subcortical aphasia and neglect in the study by Hillis and colleagues (44) did not reflect diaschisis, for two reasons. First, cortical hypoperfusion was measured with dynamic contrast perfusion-weighted imaging (PWI) time-to-peak (TTP) maps, using a threshold of >2.5 s delay (although all had areas of cortical hypoperfusion with >4 s delay as well). While hypoperfusion due to diaschisis can occasionally be visualized (e.g., in cases of crossed cerebellar diaschisis due to large hemispheric strokes), the average delay in areas of diaschisis is 2 s or less, and does not correlate with measures of diaschisis obtained with PET (47, 48). Secondly, as noted, both the deficits and the hypoperfusion were reversed immediately with restored blood flow to the cortex (via stenting, urgent endarterectomy, or blood pressure elevation). Reperfusion did not alter the infarct; nor would it have altered diaschisis caused by the infarct.

It seems clear that thalamic lesions can cause aphasia or neglect by diaschisis. It is less clear how often aphasia or neglect after thalamic stroke is due cortical hypoperfusion caused by cortical stenosis or occlusion. The cases of reperfusion in the Hillis et al. study (44) described above included no thalamic lesions, so that study did not shed light on whether thalamic aphasia or neglect signals the presence of cortical hypoperfusion requiring restoration of blood flow. One reason that an answer to this question would be clinically useful is that it could be helpful in guiding acute intervention. For example, if the cognitive sequelae are frequently caused by cortical hypoperfusion due to stenosis or occlusion (the original meaning of penumbra), then acute intervention should focus on identifying marginally perfused tissue and restoring blood flow to improve function.

We hypothesized that some cases of thalamic infarction cause aphasia or neglect (directly or due to diaschisis) and other cases of thalamic infarction are associated with cortical hypoperfusion due to large vessel stenosis or occlusion that causes the aphasia or neglect. In the latter cases, cortical hypoperfusion can be due to a single plaque in the posterior cerebral artery (PCA) that both causes the infarct (by occluding a small branch to the thalamus) *and* causes cortical hypoperfusion of the larger PCA cortical territory. It is both scientifically and clinically important to determine if both of these mechanisms lead to thalamic aphasia or neglect. From a cognitive neuroscience standpoint, it is important to determine the role of the thalamus in language and spatial processing. From a clinical standpoint, it is important to determine whether aphasia or neglect in cases of thalamic stroke indicate the presence of hypoperfused tissue due to arterial stenosis or occlusion,

such that function might be restored by reperfusion. Often perfusion imaging is not available, so that neurologists depend on the concept of a "diffusion-clinical mismatch" to guide urgent clinical decisions (49). That is, if a small stroke on diffusion-weighted imaging (DWI) cannot account for the clinical deficit, the patient is assumed to have marginally perfused tissue that accounts for the deficits, and would benefit from reperfusion. It is not clear whether or not a thalamic stroke on DWI, with aphasia or neglect represents a "diffusion-clinical mismatch." In the current study, we determined the extent to which aphasia and hemispatial neglect with infarcts restricted to the thalamus could be accounted for by concurrent cortical hypoperfusion by studying patients with acute stroke with DWI and PWI TTP maps (to show cortical hypoperfusion due to arterial stenosis or occlusion) and detailed cognitive testing. We did not attempt to distinguish whether deficits in the absence of cortical hypoperfusion due to arterial stenosis or occlusion were due to the lesion itself or due to diaschisis.

MATERIALS AND METHODS

PARTICIPANTS

A series of 20 participants with a first acute ischemic stroke, limited to the thalamus were recruited from the Johns Hopkins Hospital, Baltimore for this study. All participants were admitted and received MRI within 24 h of symptom onset. Additional exclusion criteria were as follows: (i) contraindication for MRI (e.g., implanted ferrous metal, claustrophobia); (ii) allergy to Gadolinium; (iii) hemorrhage on initial CT or MRI; (iv) impaired arousal or agitation requiring ongoing sedation; and (v) history of global intellectual deterioration (e.g., dementia); (vi) uncorrected visual acuity or hearing acuity. All participants gave informed consent (if they demonstrated intact comprehension), or their closest relative or legal representative consented (if they had impaired comprehension) to the study according to the Human Subjects Protocol. The study was approved by the Johns Hopkins University Institution Review Board.

A subset of 10 participants had isolated left thalamic infarct (infarct limited to the thalamus); (6 men and 4 women) and 10 participants had isolated right thalamic lesions (8 men and 2 women). The age of the participants ranged from 32 to 57 years, with a mean of 45.3 years (SD = 8.8) for those with isolated left thalamic lesions and from 35 to 68 years, with a mean of 52.3 years (SD = 9.8) for those with isolated right thalamic lesions. We were unable to determine which thalamic nuclei were affected due to the low spatial resolution of the DWI scans relative to thalamic nuclei. Therefore, the patients were grouped according to which thalamic artery was involved: tuberothalamic (polar); paramedian (thalamoperforator); inferior lateral (thalamogeniculate); and posterior choroidal (32, 50). MRI scans and testing was obtained after any acute treatment; two patients received IV tPA.

IMAGING PROTOCOL

MRI scans were obtained within 24 h from admission to the hospital. Participants had T2, fluid attenuation inversion recovery (FLAIR; to evaluate for old lesions), susceptibility weighted images (to evaluate for hemorrhage), PWI (to evaluate for areas of hypoperfusion), DWI (to evaluate for acute ischemia), MR angiography (to evaluate for stenosis, occlusion, aneurysm). DWI and PWI scans were 5 mm in thickness and provided whole-brain coverage. The total scan time lasted for approximately 30 min.

To measure the volume of infarct for each patient, a threshold of >30% intensity increase from the unaffected area in the DWI was applied, and a neurologist (KO), blinded to the behavioral data, manually modified the boundary of the thresholded area to remove false-positive and false-negative areas on RoiEditor[1] (51). Ten randomly selected images were used to test intra and inter-operator reproducibility of this method. The intraclass correlation coefficient (ICC) was used to evaluate consistency of infarct volumes. Intra- and inter-observer reliability were excellent; the ICC was 0.98 for both within and across observers.

Areas of hypoperfusion in PWI were determined with TTP maps, using ImageJ[2]. TTP maps and DWI were co-registered with T2, which have better spatial resolution. The presence or absence of cortical hypoperfusion was identified by a trained technologist and neurologist blinded to the results of language testing. Regions of hypoperfusion were delineated by analysis of 20 color TTP maps. Hypoperfusion was defined as >4 s mean delay in TTP arrival of contrast across voxels in the region of interest (ROI) relative to the homologous region in the non-ischemic hemisphere. This threshold was selected because it corresponds to dysfunctional tissue defined in our previous studies and defined by PET (52, 53). For both left and right hemisphere stroke patients, we examined the entire cortex within the territory of the middle cerebral artery and PCA, as aphasia and neglect have been reported in association with lesions in each territory. The area of apparent hypoperfusion was segmented and served as the ROI. A mirror image of that ROI was drawn on the opposite hemisphere in the homologs region to compare the mean TTP. White matter hyperintensities were rated using the Cardiovascular Health Study (CHS) rating scale (ranging from 0 to 9, with 9 being "most extensive"). 0 was considered "none"; scores of 1–3 were considered "mild"; 3–6 "moderate," and 7–9 "severe."

TEST BATTERY

All participants received testing within 48 h from admission to the hospital. Cognitive testing was completed after MRI scans. Participants with left thalamic stroke were administered a set of lexical tasks with stimuli matched for length (all stimuli), as well as for frequency and word class (for words). The tasks included (a) oral naming of black and white pictures [(54); $n = 17$]; (b) oral naming of objects with tactile input ($n = 17$); (c) oral reading of words ($n = 34$) and pseudowords ($n = 25$); and (d) auditory word comprehension using word/picture verification tasks (with 17 items, each presented once with the correct match, once with a semantically related foil, and once with a phonologically related foil). Please see in Ref. (44) for details.

Patients with right hemisphere stroke were given a battery of bedside tests to evaluate for hemispatial neglect at various levels of spatial representation. The tasks included the following:

(a) Perceptual tasks in which 30 circles and 30 circles with gaps are presented. Ten circles have a gap on the left side; 10 have a

[1] http://www.MRIstudio.org

[2] http://rsb.info.nih.gov.proxy1.library.jhu.edu/ij

gap on the right; and 10 have no gap. The participant is asked to circle all the complete circles and draw an *X* over circles with a gap (55). Two forms of the task were presented: once with large circles, one with small circles.

(b) Perceptual motor tasks, including: line bisection, clock drawing, and copying the "Ogden scene" (a house, a fence and two trees).

(c) Oral reading and oral spelling of lists of frequency-matched and length-matched words and pseudowords. Only errors restricted to the contralesional (left) half of the word (e.g., sand read or spelled as "hand" or "and") were scored as neglect errors.

(d) Motor extinction test, in which patients without hemiplegia were asked to click a golf counter with each hand, as quickly as possible for 1 min. The clicking rate was tested in three conditions: (i) each hand independently; (ii) the two hands simultaneously, with the hands at the subject's sides; and (iii) the two hands simultaneously, with arms crossed across the chest (to distinguish impaired clicking with the left relative to the right hand versus impaired clicking on the left versus the right side of the midsagittal plane of the body (28).

Norms were obtained for the language and neglect battery by administering each battery to 46 volunteer control subjects who were awaiting surgical repair of unruptured intracerebral aneurysms or awaiting cardiac bypass surgery. Mean scores for each subtest ranged from 98.0% (SD = 3.1) correct in oral reading to 100% (SD = 0) correct in tactile naming. Abnormal performance was defined as 89% correct or lower; normal performance was defined as 90% correct or higher. This cut-off was selected because 89% was 3 SD below the mean on the subtest with the lowest mean. No control subject scored below 90% correct on any subtest of the battery. Participants were considered to have aphasia or neglect if they scored below 90% correct on any one or more of the subtests.

DATA ANALYSES

Volume of infarct and hypoperfusion was measured as described above, without knowledge of language or neglect scores. The association between aphasia or hemispatial neglect and cortical hypoperfusion due to arterial stenosis or occlusion was evaluated by chi-square tests. Correlations between aphasia or neglect scores and volume of thalamic lesion and volume of hypoperfusion were evaluated by Spearman's rank correlation.

RESULTS

Patient characteristics are given in **Tables 1** and **2**.

APHASIA AND LEFT THALAMIC LESION

Of the10 patients with isolated left thalamic lesions, 5 had aphasia (see **Table 1** for language scores). Four of the five aphasic patients had normal cortical perfusion. All patients with aphasia had fluent speech. Three had isolated naming deficits with normal comprehension/repetition; all of these had normal cortical perfusion (**Figure 1**, top). Another two patients had both naming impairment and auditory comprehension impairment, and one of these patients had cortical hypoperfusion due to arterial stenosis (**Figure 1**, bottom). Cortical hypoperfusion was seen in the MCA and/or PCA territory (e.g., inferior temporal cortex) in areas reported to be important for language, in all cases with aphasia.

Table 1 | Demographic information for left thalamic infarct patients.

ID	Age/ sex	Education (years)	Lesion volume (cm^3)	Hypoperfusion volume (cm^3)	Naming % error	Auditory comprehension % error
PATIENTS WITH APHASIA						
1	57/M	12	4.256	2.6	12[a]	47[a]
2	37/M	12	4.091	–	35[a]	0
3	50/F	12	2.668	–	20[a]	41[a]
4	38/M	16	0.420	–	46[a]	5
5	39/F	12	0.879	–	46[a]	0
PATIENTS WITHOUT APHASIA						
6	32/M	12	1.243	–	0	6
7	51/F	12	0.738	–	3	10
8	41/M	12	0.382	3.71	6	0
9	55/F	12	0.409	–	0	0
10	53/M	16	0.822	–	0	0

[a] *Evidence of aphasia.*

Table 2 | Demographic information for right thalamic infarct patients.

ID	Age/ sex	Education (years)	Lesion volume (cm^3)	Hypoperfusion volume (cm^3)	Copy scene % error	Line bisection % error
PATIENTS WITH NEGLECT						
11	68/M	5	0.418	2.07	78[a]	12[a]
12	61/M	12	0.827	6.27	15[a]	4
PATIENTS WITHOUT NEGLECT						
13	35/M	12	0.699	–	0	1.87
14	53/M	12	0.347	–	0	0.4
15	46/F	11	0.215	–	0	2.6
16	43/F	12	0.791	–	0	3.4
17	50/M	10	1.036	–	0	3.82
18	59/M	11	0.600	–	3	2.5
19	48/M	12	1.169	–	3	1.9
20	60/M	7	0.703	–	3	3.6

[a] *Evidence of neglect.*

Five patients with left thalamic lesions did not have aphasia; and four of these patients had normal cortical perfusion. One patient with no language deficit had cortical hypoperfusion. The hypoperfusion was in the left parietal cortex. Other associated neurological deficits in patients with left thalamic lesions included right-sided weakness, numbness, and dysarthria.

There was no association between the presence of left cortical hypoperfusion and either naming impairment ($X^2 = 0.0$, $p = 1$) or auditory comprehension impairment ($X^2 = 1.4$, $p = 0.24$). Further, there was no significant correlation between volume of thalamic infarct and severity of the naming impairment ($\rho = -0.098$;

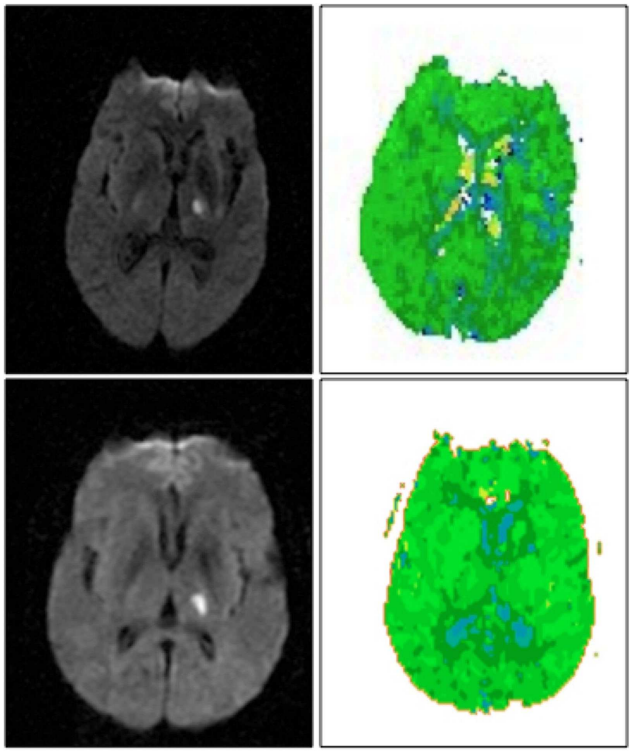

FIGURE 1 | Left thalamic infarct with cortical hypoperfusion associated with cortical hypoperfusion (top) and without cortical hypoperfusion (bottom). DWI scans are shown on the left, PWI scans are shown on the right. Scans are in radiological convention (left hemisphere on right). Blue areas are hypoperfused.

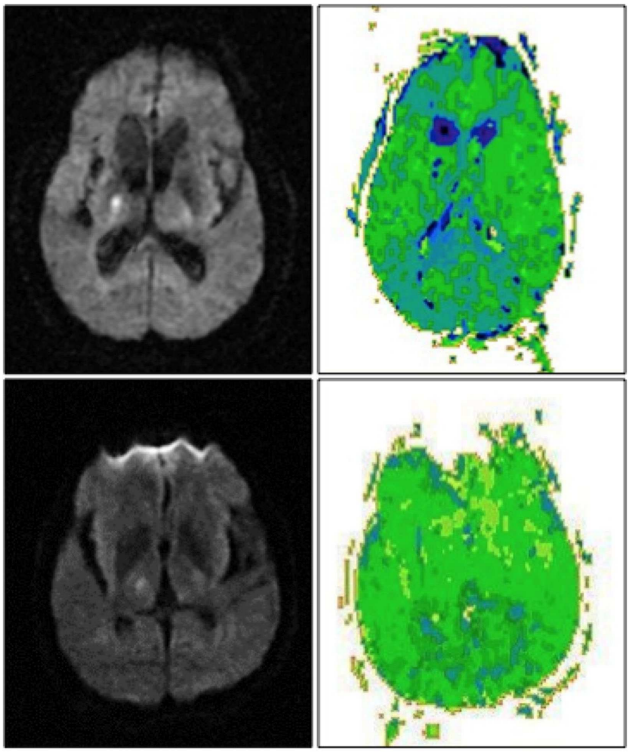

FIGURE 2 | Right thalamic infarct with cortical hypoperfusion and associated neglect (top) and without cortical hypoperfusion and no associated neglect (bottom). DWI scans are shown on the left, PWI scans are shown on the right. Scans are in radiological convention (right hemisphere on left). Blue/darker green areas are hypoperfused.

$p = 0.79$) or severity of comprehension impairment ($\rho = -0.084$; $p = 0.82$).

HEMISPATIAL NEGLECT AND RIGHT THALAMIC LESION

Of the10 patients with exclusively right thalamic lesions, two had left hemispatial neglect. Both the patients had cortical hypoperfusion (**Figure 2**, top). The area of hypoperfusion included inferior temporal/fusiform cortex, which has been associated with hemispatial neglect (56). Eight patients without hemispatial neglect showed no cortical hypoperfusion (**Figure 2**, bottom) ($X^2 = 10$; $p = 0.001$). Other associated neurological deficits in patients with right thalamic lesions included left-sided weakness, numbness, and dysarthria.

Severity of neglect measured by deviation to the right on line bisection task correlated with volume of cortical hypoperfusion ($\rho = 0.67$; $p = 0.02$), but did not correlate with volume of thalamic lesion ($\rho = -0.26$; $p = 0.65$).

LESION LOCATION

As is the case for most thalamic strokes (50), the majority of lesions were in the distribution of the inferior lateral (thalamogeniculate) artery, which arises from the PCA (**Tables 3** and **4**). There were too few patients with white matter intensities (three with left thalamic lesions, one with right thalamic lesion, mostly mild) to determine any association with neglect or aphasia (**Tables 3** and **4**).

DISCUSSION

The goal of the present study was to evaluate whether acute thalamic aphasia or neglect can be caused by cortical hypoperfusion due to large vessel stenosis or occlusion. We also wished to determine the frequency of this mechanism relative to that of a direct thalamic cause or diaschisis (presumably via disruption of subcortical–cortical circuits). We were not able to evaluate diaschisis in this study, using TTP to study perfusion (47). Our study indicates that cortical hypoperfusion due to large vessel stenosis or occlusion cannot adequately explain language deficits in patients with acute left thalamic stroke. On the other hand, cortical hypoperfusion due to arterial stenosis may account for, or at least contribute substantially to, hemispatial neglect in acute right thalamic stroke.

Our results from patients with left thalamic lesions are consistent with the findings of several studies showing that the language deficits that frequently follow isolated thalamic strokes may be caused by dysfunction of the thalamic-cortical system via diaschisis (36, 40, 57). This proposal assumes that the loss of input from the thalamus directly causes the cortical dysfunction, which secondarily results in mild diffuse hypoperfusion detectable by SPECT or PET because of spared neurovascular coupling (19). For example, in the Radanovic study of five patients with left thalamic stroke, there was a correspondence between cortical hypoperfusion and

Table 3 | Lesion characteristics for patients with left thalamic stroke.

ID	Large vessel stenosis/occlusion	Arterial territory of infarct	White matter changes	Lesion volume (mm^3)	Hypoperfusion volume (cm^3)	Naming % error	Auditory comprehension % error
PATIENTS WITH APHASIA							
1	Left PCA occlusion	Inferior lateral (thalamogeniculate)	Mild	4.256	2.6	12[a]	47[a]
2	No stenosis	Inferior lateral (thalamogeniculate)	None	4.091	–	35[a]	0
3	No stenosis	Tuberothalamic (polar)	None	2.668	–	20[a]	41[a]
4	No stenosis	Posterior choroidal	Mild	0.420	–	46[a]	5
5	No stenosis	Inferior lateral (thalamogeniculate)	None	0.879	–	46[a]	0
PATIENTS WITHOUT APHASIA							
6	Left MCA and PCA stenosis	Inferior lateral (thalamogeniculate)	None	1.243	–	0	6
7	No stenosis	Inferior lateral (thalamogeniculate)	Mild	0.738	–	3	10
8	Midbasilar and left PCA stenosis	Inferior lateral (thalamogeniculate)	None	0.382	3.71	6	0
9	No stenosis	Inferior lateral (thalamogeniculate)	None	0.409	–	0	0
10	No stenosis	Posterior choroidal	None	0.822	–	0	0

[a] *Evidence of aphasia.*

Table 4 | Lesion characteristics for patients with right thalamic stroke.

ID	Large vessel stenosis/occlusion	Arterial territory of infarct	White matter changes	Lesion volume (cm^3)	Hypoperfusion volume (cm^3)	Copy scene % error	Line bisection % error
PATIENTS WITH NEGLECT							
11	Severe right PCA stenosis	Inferior lateral (thalamogeniculate)	None	0.418	2.07	78[a]	12*
12	Severe right PCA stenosis; right M1 stenosis	Inferior lateral (thalamogeniculate)	None	0.827	6.27	15[a]	4
PATIENTS WITHOUT NEGLECT							
13	Left vertebral artery dissection	Posterior choroidal	None	0.699	–	0	1.87
14	No stenosis	Inferior lateral (thalamogeniculate)	None	0.347	–	0	0.4
15	No stenosis	Posterior choroidal	None	0.215	–	0	2.6
16	No stenosis	Posterior choroidal	Mild	0.791	–	0	3.4
17	Congenitally absent right vertebral artery	Inferior lateral (thalamogeniculate)	None	1.036	–	0	3.82
18	Mild (30–40%) left ICA stenosis	Inferior lateral (thalamogeniculate)	None	0.600	–	3	2.5
19	Mild right PCA and left MCA stenosis	Posterior choroidal	None	1.169	–	3	1.9
20	No stenosis	Posterior choroidal	None	0.703	–	3	3.6

[a] *Evidence of neglect.*

the naming impairments (present in three of five patients) and comprehension impairments (present in four of five patients), suggesting that the thalamus's participation in language is made through its influence on the cortex.

The proposed account of diaschisis does not fully explain the results in patients with right thalamic lesions. Only 2 out of the 10 patients had hemispatial neglect, and both the patients had cortical hypoperfusion as seen on PWI TTP maps (>4 s delay). This degree of delay is not a reflection of decreased metabolic demand, but caused by large vessel stenosis or occlusion (confirmed by MRA in these cases). Furthermore, the severity of neglect correlated with volume of hypoperfusion, not volume of infarct. Because we had only 10 patients, we cannot conclude that hemispatial neglect occurs *only* when there is cortical hypoperfusion caused by arterial stenosis. In fact, other studies indicate that at least chronic neglect occurs only when there is disruption of thalamocortical white matter tracts (42). However, cortical hypoperfusion due to arterial stenosis or occlusion (that is independent of the thalamic infarct) does seem to have a significant role in the development of marked hemispatial neglect in acute stroke. The thalamic lesions in patients with neglect mainly involved the inferior lateral (thalamogeniculate) territory, which supplies the ventroposerior medial (VPM) and ventroposterior lateral (VPL) nuclei, and only a small portion of the ventrolateral nucleus (32). As VPM and VPL are not known to have a role in attention, neglect can in these case can be explained by cortical hypoperfusion due to plaque in the right PCA (which also occluded the inferior lateral artery as it branched off the PCA, which caused the thalamic infarct).

The relatively young age of our stroke participants may also have influenced the results. The mean age of the participants with right thalamic stroke in this study was 52.3 years. Gottesman et al. (58) found that among patients with acute right hemispheric

stroke, neglect occurs at higher frequency and at increasing severity in older patients (above 65 years). This age effect is independent of the size of the stroke and the severity of other presenting clinical symptoms. Similarly, Ringman et al. (59) found that older patients experience neglect at higher rates than younger patients. Thus, our participants had a lower risk of hemispatial neglect due to relatively young age. Perhaps, only those relatively young stroke patients with large vessel stenosis and severe cortical hypoperfusion had neglect; while older patients with thalamic lesions without severe cortical hypoperfusion (but only cortical diaschisis) would have neglect. Likewise, increased burden of white matter disease is associated with increased severity of neglect (60); but only one patient with right thalamic stroke had mild white matter disease, perhaps because of the young age of our population.

Is it plausible that both hypoperfusion due to arterial stenosis and diaschisis co-exist in some cases. Reperfusion of the cortex is one way to disentangle these mechanisms. Restoring blood flow to the cortex eliminates hypoperfusion caused by arterial stenosis, but would not affect diaschisis (because the thalamic lesion is still present). Future studies of thalamic stroke before and after intervention to restore blood flow to hypoperfused cortex would be useful.

In summary, the present study indicates that some cases of neglect after thalamic stroke are at least partially due to cortical hypoperfusion caused by arterial (PCA) stenosis or occlusion. Therefore, hemispatial neglect in the presence of an infarct restricted to the thalamus should raise the suspicion for presence of marginally perfused tissue that might recover function if reperfused, and perhaps the need for perfusion or vessel imaging and intervention. In contrast, we were not able to identify such a mechanism in thalamic aphasia. Rather, our results provide additional evidence that the left thalamus has a direct role in language processing (at least) by activating cortical areas involving specific tasks. The small size of our patient group demands further studies to support these findings. Multimodality imaging, including vessel imaging, diffusion tensor imaging, functional imaging studies, and measurement of rCBF would further clarify the roles of various potential mechanisms [including distinct types of diaschisis; (39)] of underlying thalamic aphasia and neglect.

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Data science of stroke imaging and enlightenment of the penumbra

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Imaging protocols of acute ischemic stroke continue to hold significant uncertainties regarding patient selection for reperfusion therapy with thrombolysis and mechanical thrombectomy. Given that patient inclusion criteria can easily introduce biases that may be unaccounted for, the reproducibility and reliability of the patient screening method is of utmost importance in clinical trial design. The optimal imaging screening protocol for selection in targeted populations remains uncertain. Acute neuroimaging provides a snapshot in time of the brain parenchyma and vasculature. By identifying the at-risk but still viable penumbral tissue, imaging can help estimate the potential benefit of a reperfusion therapy in these patients. This paper provides a perspective about the assessment of the penumbral tissue in the context of acute stroke and reviews several neuroimaging models that have recently been developed to assess the penumbra in a more reliable fashion. The complexity and variability of imaging features and techniques used in stroke will ultimately require advanced data driven software tools to provide quantitative measures of risk/benefit of recanalization therapy and help aid in making the most favorable clinical decisions.

Keywords: acute stroke, cerebral ischemia, neurology, neuroimaging, MRI imaging, CT imaging

INTRODUCTION

Stroke is a leading cause of death and a major cause of long-term disabilities across the globe. In the United States, 795,000 people are affected by strokes each year resulting in about $74 billion of total annual costs (1). Encouraging results of recent clinical trials [such as EXTEND-IA (2), ESCAPE (3), SWIFT-PRIME (4), and MR CLEAN (5)] have demonstrated the promise of endovascular therapies, yet we are far from a cure for stroke and much work remains to further increase the potential recovery in targeted populations. Neurovascular disorders are now recognized as a prominent public health issue worldwide due to aging populations and the socioeconomic burden of stroke. Improved utilization of stroke imaging to derive maximal knowledge from embedded data and associated underlying features may be leveraged to tailor therapeutic decisions and optimize outcomes after acute stroke.

In the best-case scenario, the treatment of acute ischemic stroke can lead to a full recovery. This generally happens when revascularization occurs early enough. If revascularization is not achieved or if it occurs too late, chances of recovery decrease and severe complications associated with devastating neurological effects become more likely. Revascularization, or rapidly reopening occluded arteries, is therefore the main interventional strategy in acute ischemic stroke. The purpose of such therapy is to restore perfusion in the ischemic tissue. As of today, the only FDA-approved therapy for reopening vessels in acute ischemic stroke remains intravenous tissue plasminogen activator (tPA) (6). Endovascular interventions such as intra-arterial thrombolysis and mechanical thrombectomy have both demonstrated potential for improved outcomes after stroke. The possible benefits of these therapies have to be carefully balanced with the concomitant risks, including hemorrhagic transformation (7) and other complications (8). The most common way to estimate the potential benefit is by measuring the extent of the salvageable ischemic tissue, previously described as the penumbra.

This paper provides a perspective on the penumbra by identifying a few challenges that render the characterization and definitions uneasy and by discussing the lessons that we have learned so far and toward where they could lead in the future of stroke care. After describing the current clinical practice (see Current Clinical Practice) and pathophysiology (see Pathophysiology of Cerebral Ischemia), we review imaging based definition of the penumbra. We then describe the heterogeneity of acute stroke in terms of imaging patterns (see Imaging Definitions of Penumbra). Finally, we discuss in Section "MRI and CT Definitions," how advanced methods such as computer vision and machine could help to bring a new dimension to the understanding and definition of salvageable tissue.

CURRENT CLINICAL PRACTICE

Cerebral ischemia is a dynamic process that spans from hyperacute presentation to acute, subacute, and chronic phases. Minimizing the time elapsed from stroke onset to treatment has been a priority target of current clinical practice (9) as acting early and decisively becomes integral to improving patient outcomes.

While the safety time window for IV-tPA administration is 3 h in all and 4.5 h in a subset of patients, exact time of stroke onset is usually unknown and the onset of symptoms is used as an indirect marker of stroke. Last known well time is widely used as the standard to designate stroke onset. It is, however, an approximate variable for two main reasons. First, about 15% of all strokes occur during sleep and therefore the time of onset for those patients is

only approximate. Second, the last known well time, or the start of the detectable symptoms may not correspond to the exact time of the true stroke onset. Time is a relative notion in stroke as it has been shown that the dynamics of lesion growth and the rate of cell death in the ischemic territory vary drastically from patient to patient. Several studies (10) have shown that some patients could benefit from thrombolysis and recanalization procedures after the 4.5 h window. However, variability of response and increased risk associated with late therapies leads to heterogeneous results related to successful recovery.

Facing this uncertainty, the selection of patients who may benefit from reperfusion therapy is one of the most critical tasks in acute stroke care. Evidence suggests that time alone is not sufficient to optimally select patients and that neuroimaging can play an influential role in refining treatment decisions. Imaging, such as multimodal CT, MRI, and angiography, have been increasingly used and reflect a snapshot of the state of the brain tissue at a point in time. The most important task of imaging has been to rule out intracranial hemorrhage for determination of tPA eligibility. Visual examination of non-contrast CT or GRE offer high accuracy in detecting any sign of hemorrhage (11). Beyond exclusion for safety reasons, neuroimaging is used to determine eligibility for endovascular treatments and quantification of possible benefits. This is done through identifying at-risk, but viable and ischemic tissue. The penumbra is seen as the target tissue for revascularization therapies as it is thought of as viable but tissue at risk of becoming irreversibly infarcted. When reperfusion or collateral circulation is established, these areas may recover. Without reperfusion, such brain cells in the penumbra will die, and the lesion will expand. In addition to the assessment of the penumbra, the collateral status of the involved cerebrovascular territory, which represents the quality of the blood flow diversion in the presence of arterial occlusion, is also recognized as a predictor of poor outcome. Although multimodal CT or MRI can be used to characterize acute strokes, guide treatment decisions, and evaluate recovery, the image acquisition, processing, and interpretation are complex and time-consuming and may lead to unnecessary delays in care. There is an overt need to accelerate imaging protocols and extract imaging markers to guide clinical decisions in acute stroke.

PENUMBRA IN PERSPECTIVE

PATHOPHYSIOLOGY OF CEREBRAL ISCHEMIA

The ischemic penumbra is described as the cerebral parenchyma adjacent to the area of dense ischemic infarction. Early on, multiple animal models were used to examine the limits of cerebral blood flow (CBF) volumes at which cerebral ischemia has functional implications on neuronal networks (12–16). Astrup et al. (17) described the ischemic core and penumbra as a ring of parenchyma surrounding an area of dense ischemia at the center. They further described the ischemia as existing in a range between a threshold of electrical failure as in the penumbra contrasted with a threshold of energy and ion pump failure that exists in the ischemic core. The greatest value hence in defining the ischemic penumbra is perhaps the potential that exists for its salvage by timely restoration of blood flow prior to reaching the threshold for neuronal cell death. The ischemic cascade in itself involves both apoptotic and necrotic cell death mechanisms (18). Patterns of cerebral arterial and venous blood flow have been characterized as consistent with autoregulation, oligemia, ischemia, or irreversible injury by using positron emission tomography (PET) and obtaining objective information with regards to CBF, CBV, metabolic rate of oxygen, and oxygen extraction (19). However, the use of PET imaging in acute stroke remains limited due to impracticability.

IMAGING DEFINITIONS OF PENUMBRA

Neuroimaging plays a major role at several stages during the clinical management of patients treated for acute ischemic stroke. It is used to confirm diagnosis of stroke with respect to symptomatic presentation and clinical examination, to determine blood flow pathology by locating the stenosed or occluded vessel, to direct treatment decisions by identifying ischemic tissue or presence of hemorrhage, to guide endovascular procedures, and to assess treatment response and neurological recovery of the patient. In this section, we review imaging definitions of the penumbra that are used to estimate the benefits of an endovascular procedure and balance them with the risk of complications.

MRI and CT definitions

The availability of MRI in clinical practice permits estimation of the infarct core and the extent of penumbral tissue. The infarct core is detected as the volume of abnormal diffusion-weighted image (DWI). The volumetric difference, or mismatch, observed between the DWI and perfusion-weighted image (PWI) abnormalities is considered as a reliable indicator of salvageable tissue at risk (20–22). TTP or $T_{\max}$ parameters, extracted from PWI images, are thresholded to obtain a volume of hypoperfused but viable tissue. While a meaningful volume of penumbral tissue supports the decision for reperfusion therapy, there is no consensus in the computation of mismatch [it is usually in the range $T_{\max} > (2, 10)$ s] or on the exact definition of what significant mismatch constitutes (23, 24). In a systematic study of the patients enrolled in the DEFUSE study (25), it was found that a mismatch ratio of 38% provided the highest accuracy for identifying patients in whom reperfusion was associated with a favorable response (for a $T_{\max}$ threshold of 2 s).

Although MR perfusion studies accurately detect early signs of ischemia, it is contraindicated for some patients (e.g., with metallic foreign body or claustrophobia), not available in many institutions, and may not be utilized in a timely fashion. CT perfusion (CTP), on the other hand, is usually associated with lower cost, greater availability, and faster imaging. It has been established as an attractive alternative imaging method in many stroke care facilities. Although MR perfusion is more sensitive to early ischemic changes, the parameter maps extracted with CTP and MR perfusion are closely correlated. CTP can delineate infarct core and penumbral tissue using CBF and CBV thresholds of 34% (in comparison to a region defined in the healthy hemisphere) and 2.5 mL/100 g, respectively (26). These thresholds allow for automatic computation of infarct core and penumbral maps comparable to the ones obtained from MR perfusion (27). With the extraction of more advanced feature maps from perfusion studies (as described in the subsequent paragraphs), it is anticipated that some features extracted from MRI may not be equivalent with CTP. Such competitivity might be beneficial to bring further

imaging advances in the long run. The importance of continued focus on developing these imaging modalities and in streamlining protocols lies in the potential for preventing further neurological deterioration in patients presenting with acute ischemic stroke.

Alternative quantitative methods

Beyond the DWI/PWI mismatch and CTP models, other imaging modalities and quantitative models have been studied to estimate the extent of viable tissue at risk. These models are typically built by analyzing voxel intensity at onset with respect to the observed tissue fate, as measured in FLAIR images several days after intervention. Wu et al. (28) evaluated a generalized linear model (GLM) based on DWI and PWI in 14 patients. Rose et al. (29) used Gaussian models trained on multiple parameters to predict tissue outcome in 19 patients. Other studies were performed based on logistic regression (30) and ISODATA (31) applied to apparent diffusion coefficient (ADC) and CBF. The main advantage of these methods is that they do not rely on specific thresholds to make predictions and can handle noisy observations better. Most recently, Kidwell et al. (32) described a voxel-based multimodal CT and MRI models aimed to effectively define penumbral patterns.

Regional models. Infarct growth rate or the evolving ischemic core is quite variable, likely driven by collateral status, and may spatially vary over time due to regional hemodynamic compromise. Even in some cases of successful revascularization, the ischemic core may still expand into nearby or adjacent brain tissue. Consequently, a healthy voxel surrounded by injured tissue at early stages is more likely to become irreversibly damaged even though it may not meet the criterion to be labeled as tissue at risk. Unlike previously mentioned quantitative models that consider each voxel independently, research efforts (33) have shown that the regional distribution of intensities surrounding a voxel at early stages may capture characteristics about the dynamic of lesion growth and be predictive of tissue outcome (**Figure 1**). These studies have integrated regional information by exploiting spatial correlation between voxels (34), prior map of spatial frequency-of-infarct (35), and neural networks (36). Such emerging approaches offer potential refinement of single voxel-based models of penumbra.

Gradient: a glimpse at spatiotemporal changes. Finding the optimal threshold of a single parameter that generalizes across a diversified patient population is not trivial and beyond current methods. Instead, recent studies (37) have indicated that the local gradient (i.e., relative spatial change) of a parameter may be a complementary predictor. Gradient images can be computed reliably using a series of image filtering operations. CBV-gradient maps were retrospectively studied on 42 acute MCAO cases with serial MRI (37). CBV is an essential measure of perfusion in acute ischemic stroke that is biphasic in nature; it exhibits peripheral hyperemia (increase) and central collapse (decrease) near the ischemic core. When used to detect ultimate infarction, CBV often underestimates final volume. CBV gradients, on the other hand, represent the propensity for hemodynamic failure to distinguish benign hyperemia from penumbra surrounding the ischemic core. As seen in **Figure 2**, CBV gradient maps are able to demonstrate a concentric region of abnormality around the ischemic core. CBV gradient maps are able to accurately classify voxel outcome defined as infarction on day 5 fluid attenuation inversion recovery sequences, correctly predicting voxel-based hemodynamic failure. Although CBV gradient is not observed on uniformly low distributions of CBV, it can depict zones around the ischemic core that are vulnerable to hemodynamic failure and infarct evolution; thus refining further the estimation of the penumbra.

Perfusion angiography. MRI-based estimates of penumbra are only feasible in the acute phase and the follow-up of treatment. If the patient is deemed eligible for endovascular thrombectomy, a significant time lapse may occur from MRI; thus leading to possible infarct growth and inaccurate penumbra volume estimates due to time inconsistencies. Estimation of viable tissue through routine biplane angiograms is currently being investigated in research settings and may become available during thrombectomy in the near future. Dedicated processing software, such as perfAngio®, can

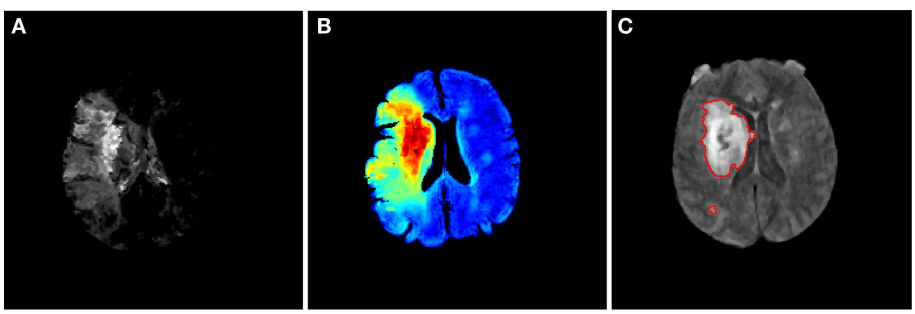

FIGURE 1 | Illustration of map of tissue outcome (B) predicted from Tmax (A) using a regional computational model. Red areas in **(A)** depict tissue likely to be infarcted (despite intervention), while green areas represent tissue at risk and can be thought of as penumbral tissue. The groundtruth in terms of Flair (at day 4) is shown in **(C)**.

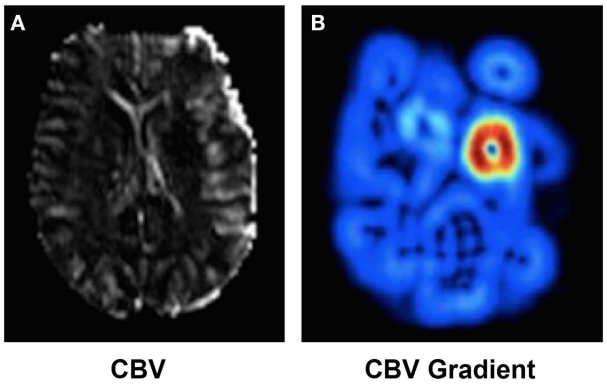

FIGURE 2 | CBV (A) and CBV (B) gradient map computed in presence of a MCA occlusion. High CBV gradient (shown in red in **(B)**) indicates areas at risk of collateral failure.

process the angiogram within seconds to extract perfusion parameters. It stems from video densitometry theory that relates blood flow to the observed image intensity. Parameters such as CBF, CBV, MTT, and TTP can be displayed in color-mapped images. While animal studies (38) have demonstrated that absolute flow could be estimated precisely from DSA, it has several practical limitations in the acute stroke setting. Challenges arise in such approaches as the diameter of the vessels and exact parameters of the x-ray imaging system are typically unknown. While raw DSA data are generally used to visualize flow at the macrovascular level (large blood vessels), flow parameters extracted with DSA perfusion provide insights about the microvascular circulation as recently demonstrated in a recent animal study (39).

Although these alternative models of the penumbra may provide more accurate raw prediction of tissue outcome in presence of reperfusion, they have yet to be effectively translated into clinical decision support tools.

HETEROGENEITY OF ISCHEMIC STROKE AND POTENTIAL OF STROKE IMAGING

Generalization in stroke care is challenged by the wide variability of symptoms presentation and outcomes observed across patients. Identifying population subgroups that may share similar outcomes after stroke may be identified by specific patterns in stroke imaging. Importantly, such data-driven approaches using the examples of imaging techniques highlighted above may ultimately permit tailored therapies for the individual stroke patient. Even with revascularization of various stroke patients presenting with proximal middle cerebral artery occlusion, the heterogeneity of collateral status and patterns of ischemic injury may limit our ability to predict subsequent outcomes. Unfortunately, routine clinical parameters and even basic imaging variables used in clinical practice cannot reliably portend expected outcomes. For instance, age and stroke severity remain highly influential variables in determining stroke outcomes across a population, yet such variables may be less informative for predicting the outcome of an individual patient.

Distinct lesion patterns are known to occur depending on the severity, location, and evolution of a stroke. Significant research efforts have been devoted to study if specific lesions patterns would help prediction of early prognosis of three different time points after ischemic stroke: unstable hospital course, recurrence of stroke, and poor neurological outcome at 3 month follow-up. Bang et al. (40) classified DWI lesions into six groups: territorial, other cortical, small superficial, internal border zone, small deep, and other deep infarcts. The study focused on 426 patients with acute cerebral infarcts within the middle cerebral artery territory and any recurrent strokes and prognosis at 3 month follow-up were recorded. DWI lesion pattern was a stronger and more consistent predictor of outcome than DWI lesion volume. Such results indicate that the DWI lesion pattern may help in recognition of likely differences in the early prognostic endpoints after ischemic stroke, and DWI analysis may guide targeted interventions to prevent negative outcomes.

COMPUTER VISION AND MACHINE LEARNING FOR CLINICAL DECISION SUPPORT

Patient selection and clinical decisions in acute stroke are often guided by review of noisy raw images or use of complex imaging features that requires a high level of expertise and experience. For example, although collateral grade is an important predictor of outcome, it is not trivial to assess and as a result, very few neurologists routinely grade collateral status. To circumvent such issues in the complexity of stroke imaging and their visual interpretation in real time, the solution has been so far to simplify, and perhaps over-simplify, the amount of information used so that it can become readily amenable to make a decision. One can easily argue that inclusion criteria in current clinical trials have so far followed the same logic with specific cut-off mismatch volume values, etc. With the availability of big data analytics, modern computer vision techniques and machine learning algorithms are revolutionizing many aspects of daily life. Several domains (such as finance and weather forecasting) where fast and accurate decisions have to be made based on a very complex amount of information have already started to integrate machine learning in their decision-making process. The real purpose of these technologies is not to replace the clinician, but rather to provide a translation of the data into a more meaningful representation. While computer vision methods can be developed to extract subtle visual features from complex images, machine learning algorithms can be designed to combine a very large amount of complex information into a more easily interpretable "benefit" or "risk" score, with associated confidence value. The application of such methods in stroke imaging may lead to automated, objective quantification of images and would avoid issues of operator or reader dependence.

CONCLUSION

Stroke imaging techniques provide extensive data on the pathophysiology of acute ischemic stroke, including the therapeutic target of the penumbra. Clinical decision-making and selection strategies for therapeutic interventions, formulated from estimates of risk–benefit associated with penumbral extent, may be enhanced with extraction of detailed features currently untapped

in routine clinical practice. Data science of routine multimodal CT or MRI studies may yield clinically relevant knowledge to improve patient outcomes in the future. Such recently developed techniques will be further bolstered in coming years as increasingly larger imaging datasets may be shared from around the world. Ultimately, practical automated computer vision and machine learning approaches may provide critical information in real time, immediately prior to and even during therapeutic interventions.

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