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ORIGINAL ARTICLE

Asymmetrically hypointense veins on T2*w imaging and susceptibility-weighted imaging in ischemic stroke

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Abstract

AIM: To review the literature on the assessment of venous vessels to estimate the penumbra on T2*w imaging and susceptibility-weighted imaging (SWI).

METHODS: Literature that reported on the assessment of penumbra by T2*w imaging or SWI and used a validation method was included. PubMed and relevant stroke and magnetic resonance imaging (MRI) related conference abstracts were searched. Abstracts that had overlapping content with full text articles were excluded. The retrieved literature was scanned for further relevant references. Only clinical literature published in English was considered, patients with Moya-Moya syndrome were disregarded. Data is given as cumulative absolute and relative values, ranges are given where appropriate.

RESULTS: Forty-three publications including 1145 patients could be identified. T2*w imaging was used in 16 publications (627 patients), SWI in 26 publications (453 patients). Only one publication used both (65 patients). The cumulative presence of hypointense vessel sign was 54% (range 32%-100%) for T2* (668 patients) and 81% (range 34%-100%) for SWI (334 patients). There was rare mentioning of interrater agreement (6 publications, 210 patients) and reliability (1 publication, 20 patients) but the numbers reported ranged from good to excellent. In most publications (*n* = 22) perfusion MRI was used as a validation method (617 patients). More patients were scanned in the subacute than in the acute phase (596 patients *vs* 320 patients). Clinical outcome was reported in 13 publications (521 patients) but was not consistent.

CONCLUSION: The low presence of vessels signs on T2*w imaging makes SWI much more promising. More research is needed to obtain formal validation and quantification.

Key words: Acute ischemic stroke; Oxygen extraction fraction; Susceptibility-weighted imaging; T2*; Penumbra

Core tip: Thrombolytic therapy with intravenous tissue plasminogen activator is the only approved therapy for acute ischemic stroke. The detection of hypointense venous vessels with blood oxygenation level dependent (BOLD) imaging to assess the amount of penumbral tissue in acute ischemic stroke has emerged as a little noticed alternative imaging technique. In the present state the combined use of perfusion and BOLD imaging would provide further complementary information to help visualize and understand the role of the ischemic penumbra.

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INTRODUCTION

Assessment of penumbral tissue is a key concept to identify patients who may benefit from acute stroke therapy. One has to keep in mind that the penumbra cannot be regarded as a homogenous single entity but rather a gradient from ischemic core to normal tissue[1]. Therefore, whatever imaging method is used for penumbra detection, one or more arbitrary cut-off values need to be chosen to segment the brain image into normal tissue and ischemic core, with one or more penumbras in between. Despite oxygen-15 positron emission tomography (^{15}O-PET) being the gold standard to define the penumbra[2], its clinical use is very limited due to logistical and practical reasons. As a substitute, magnetic resonance imaging (MRI) with diffusion-weighted image (DWI)-perfusion-weighted image (PWI) mismatch is commonly used in the clinical work-up of stroke patients[3]. Although widely utilized, it has some methodological limitations. The DWI lesion does not seem to represent irreversibly damaged tissue[4], nor can PWI differentiate between penumbra and benign oligemia[5]. Recently, the use of blood oxygenation level dependent (BOLD) imaging as an alternative to DWI-PWI mismatch has stirred a lot of interest[6]. It is sensitive to an increased concentration of deoxyhemoglobin (DHb) and may therefore be an indirect marker of oxygen metabolism. There are two approaches to detect an increased oxygen extraction fraction (OEF) using BOLD: assessment of tissue and assessment of draining veins containing an increased fraction of DHb.

As the latter has been described by several authors, we will focus this review on the assessment of venous vessels to estimate the amount of penumbral tissue. We provide an overview on published data, take a glimpse at experimental studies and critically appraise the method's clinical value and suggest future research.

MATERIALS AND METHODS

Publications that reported on the assessment of the penumbra in ischemic stroke by hypointense vessels on T2*w imaging and/or SWI and performing at least one validation method were included. Search terms in PubMed were "T2*", "GRE", "SWI", "susceptibility weighted imaging", "leptomeningeal vessels/veins", "hypointense", "stroke". Full text articles and published abstracts from major stroke and MRI related conferences (*International Stroke Conference*, *European Stroke Conference*, *World Stroke Congress*, *World Congress of Neurology*, *ISMRM*, *ASNR*, *etc.*) were included in this review. Only literature published in English and dealing with human subjects was included, patients with Moya-Moya syndrome were disregarded. The reference section of retrieved publications was manually searched for further relevant literature. Abstracts with obviously overlapping content with full text articles that were probably first presented as an abstract and subsequently published as full text articles were excluded.

Statistical analysis

Data is presented as cumulative absolute and relative percentage values. Ranges are given where appropriate.

RESULTS

Forty-three papers, conference abstracts and reports of cases (partially from review articles) with a total of 1145 patients were identified[7-49]. For details of the reviewed studies with relevant information, see Tables 1 and 2. Sixteen publications (627 patients) were identified using T2*w imaging (Table 1)[7-22]. SWI was used in 26 publications (453 patients, Table 2)[23-48]. In one publication both T2* and SWI was used (65 patients, Table 2)[49].

The cumulative presence of hypointense vessels was 54% (range 32%-100%) of 668 patients for T2* and 81% (range 34%-100%) of 334 patients for SWI. However, more single patient case reports were identified for SWI.

Inter-rater agreement was reported in six publications (210 patients)[7,14,15,17,19,21] and ranged from good (κ = 0.7)[14] to excellent (intraclass correlation = 0.99)[17]. The agreement between penumbra on T2*w imaging and dynamic susceptibility contrast (DSC)-MRI was quantified in one publication (20 patients)[17] and was 0.92 [time to peak and relative cerebral blood flow (CBF)] to 0.96 (mean transit time and relative cerebral blood volume).

In most publications perfusion MRI either utilizing DSC-MRI (n = 17441 patients)[7,10-12,16,17,20,23,25,28,31-34,37,40,43] or flow sensitive alternating inversion recovery (n = 4111 patients)[14,15,19,38] combined with DWI/apparent diffusion coefficient (ADC) was used for validation (perfusion method not stated in one publication, 65 patients[49]). In three publications one additional method was used [digital subtraction angiography (DSA)[16], iodine-123 iodoamphetamine single-photon emission computed tomography[20] or magnetic resonance angiography (MRA)[43]]. Conventional MRI (DWI/ADC, MRA, structural imaging) was used in 14 publications (315 patients)[8,9,21,24,26,27,29,30,35,36,44,46,47], in three publications[39,41,45] computed tomography or clinical data were used as additional methods. Clinical information and unspecified imaging was used in one publication (59 patients)[48]. One publication used clinical data alone (30 patients)[48]. DSA alone was used in one publication (22 patients)[13]. In one case series gold standard ^{15}O-PET was used for validation (number of patients not stated)[18].

Time of onset ranged from 3 h to 7 d with more publications reporting on the subacute (> 6 h, n = 15579 patients)[9,12,14,15,23,24,32,34,35,38,39,40,42,44,49] than the acute phase (≤ 6 h, n = 11337 patients)[7,10,11,13,16,17,19,21,22,25,47]. In one publication time from onset ranged from 3.5 to 8.5 h (49 patients)[41]. It was not provided in 16 publications (170 patients)[8,18,20,26-31,33,36,37,43,45,46,48].

Outcome was reported in 13 publications. In four publications (185 patients)[10,19,21,39] no correlation with clinical outcome was found. In four publications (107 patients)[11,13,16,22] a larger National Institute of Health Stroke Score improvement was observed, while in another four publications a worse outcome was found (210 patients)[7,35,41,48]. In one publication there was a better

Table 1 Publications using T2*w sequences

Ref.	*n*	Field strength	Occluded vessel	Time from onset	Validation method	Results
Hermier *et al*[7]	49	1.5 T	Anterior circulation	6 h	DWI; DSC-MRI	AVV obvious in 8/49, moderate in 15/49 patients, inter- and intra-observer reliability $r > 0.9$; Correlated with higher baseline NIHSS, larger DWI and PWI lesions, worse outcome, intracranial haemorrhage and more severe hemodynamic impairment
Liebeskind *et al*[8]	91	NS	MCA	NS	MRA; DWI	Hypointense vessels in or adjacent to the infarct in 40/91 patients
Liebeskind *et al*[9]	83	NS	MCA	Median 2 d	MRA	Unilateral hypointensity of the basal vein of Rosenthal was noted in 27/83 patients on the side of the occlusion
Hermier *et al*[10]	48	1.5 T	NS	6 h	DWI; DSC-MRI	AVLV present in 17/48 patients, within TTP lesion, not concordant with DWI lesion; No impact on clinical status and final stroke volume
Seo *et al*[11]	20	3 T	ICA, MCA	6 h	DSC-MRI; DWI	HVS present in 13/20 patients. Patients with asymmetrical HVS had better NIHSS improvement (8.1 ± 5.7 *vs* 2 ± 4.2)
Sohn *et al*[12]	86	NS	ICA, MCA	12 h	DSC-MRI; DWI	Present in 59/86 patients; HypoTCV associated with large perfusion defect, but low cholesterol and haemoglobin level may obscure its visibility
Ha *et al*[13]	22	3 T	MCA	6 h	DSA	Present in 7/22 patients. Patients with HLV showed larger baseline NIHSS (16.9 ± 3.4 *vs* 11.7 ± 5.3) and major improvement (≥ 8 points) was observed more often. It corresponded with delayed venous wash-out on DSA
Morita *et al*[14]	24	3 T	ICA, MCA	12 h	DWI; FAIR	CVS present in all patients, BS present in 23/24 patients, good interobserver agreement ($\kappa = 0.7$). Area defined by CVS/BS similar to hypoperfused area
Harada *et al*[15]	24	3 T	NS	12 h	FAIR; DWI	κ for cortical and deep vessel signs 0.84 and 0.72, respectively
Ha *et al*[16]	35	NS	MCA	6 h	DSC-MRI; DWI; DSA	HLV present in 12/35 patients. Patients with HLV had larger NIHSS improvement at 7 d (6.5 ± 4.6 d *vs* 0.5 ± 6.7 d) and bigger TTP-DWI mismatch. HLV corresponded with delayed venous wash-out
Kaya *et al*[17]	20	3 T	Large arteries	3 h	DWI; DSC-MRI	Present in all patients. Very good correlation of RMHV with final infarct ($r = 0.91$) and MTT/rCBV lesion ($r = 0.96$); very high interobserver correlation (ICC = 0.99)
Kinoshita *et al*[18]	NS (case series)	1.5 T	NS	NS	^{15}O-PET	Enhanced venous contrast (hypointensity and enlargement of veins), ipsilateral corresponding increased OEF
Harada *et al*[19]	33	3 T	ICA, MCA	3 h	FAIR; DWI	IschV present in 79% ($\kappa = 0.83$); Not correlated with worse outcome
Tada *et al*[20]	2	3 T	MCA (stenosis)	NS	DWI; DSC-MRI; ^{123}I-IMP SPECT	Area defined by ischemic signs was similar to area of hypoperfusion on MRI and SPECT
Rosso *et al*[21]	60	3 T	Anterior circulation	6 h	DWI; MRI	VTV present in 58.3% ($\kappa = 0.895$), correlated with larger infarcts and haemorrhage but not with baseline or follow-up NIHSS
Ryoo *et al*[22]	30	NS	ICA, MCA	6 h	Clinical	GRE vein present in 15/30 patients. Early neurological improvement (ΔNIHSS ≥ 8 or NIHSS ≤ 2 at 24 h) more frequently observed with GRE vein (8 patients *vs* 1 patients, $P = 0.014$)

NS: Not stated; ICA: Internal carotid artery; MCA: Middle cerebral artery; DWI: Diffusion-weighted image; DSC-MRI: Dynamic susceptibility-contrast magnetic resonance imaging; MRA: Magnetic resonance angiography; AVV: Abnormal visibility of transcerebral veins; PWI: Perfusion-weighted image; AVLV: Abnormal visualization of leptomeningeal vessels; TTP: Time to peak; CVS: Cerebral vasospasm; BS: Brush sign; HVS: Hyperintense vessel sign; HLV: Hypointense leptomeningeal vessels; ^{15}O-PET: Oxygen-15 positron emission tomography; CT: Computed tomography; HypoTCV: Hypointense transcerebral or cortical veins; FAIR: Flow sensitive alternating inversion recovery; ^{123}I-IMP SPECT: Iodine-123 iodoamphetamine single-photon emission computed tomography; DSA: Digital subtraction angiography; NIHSS: National Institute of Health Stroke Score; RMHV: Region of multiple hypointense vessels; MTT: Mean transit time; rCBV: Relative cerebral blood volume; ICC: Intraclass correlation; OEF: Oxygen extraction fraction; VTV: Visibility of the transcerebral veins; GRE: Gradient-echo.

clinical outcome with normalized vessel appearance after successful recanalization (19 patients)[47].

The occluded vessel was located in the anterior circulation in 33 publications (864 patients)[7-9,11-14,16,19,21,22,24-40,44-47,49]. It was not stated in seven publications (250 patients)[10,15,18,23,41,42,48]. Other publications considered "large arteries" (20 patients)[17], the basilar artery (1 patient)[47], the posterior cerebral artery (1 patient)[46], TIA (9 patients)[43] and critical MCA stenosis (2 patients)[20].

Field strength was 1.5 T in 10 publications (180 patients)[7,10,18,23,25,26,31,37,40,46], 3 T in 11 publications (285 patients)[11,13-15,17,19-21,28,38,39] and not stated in 22 publications (662 patients)[8,9,12,16,22,24,27,29,30,32-36,41,42,43-45,48,49] while in one publication (19 patients)[47] both field strengths were used but not identified for individual patients.

For detailed differences between T2*w imaging and SWI see Table 3.

A number of terms have been used to describe the finding of hypointense venous vessels on T2*w or SWI images: Abnormal visualisation of leptomeningeal vessel, abnormal visualisation of transcerebral veins, cortical vessel sign, veins on gradient echo, hypointense leptomeningeal vessels, hypointense vessels, hypointense vessel sign, hypointense transcerebral or cortical veins, ischemic vessel signs, increased vessel contrast, multiple hypointense vessels and visibility of transcerebral veins have been used almost synonymously. A "region of multiple hypointense vessels" describes the area that is bordered and thus

Table 2 Publications using susceptibility-weighted imaging and combining T2*w imaging and susceptibility-weighted imaging

Ref.	*n*	Field strength	Occluded vessel	Time from onset	Validation method	Results
Ida[23]	62	1.5 T	NS	24 h	DSC-MRI; DWI	IVC were noted in 77.4%, agreement with perfusion defect in all patients
Tong *et al*[24]	1	NS	MCA	3 d	ADC	Prominent asymmetric medullary veins exceeding the area of the DWI lesion
Mittal *et al*[25]	1	1.5 T	MCA	2 h	DWI; DSC-MRI	Prominently hypointense cortical veins exceeding the area of the DWI lesion, similar to PWI lesion
Santhosh *et al*[26]	1	1.5 T	MCA	NS	DWI	Prominent veins exceeding the area of the DWI lesion
Tsui *et al*[27]	1	NS	MCA	NS	DWI	Prominent hypointense veins exceeding the area of the DWI lesion
Christoforidis *et al*[28]	6	3 T	MCA	NS	DSC-MRI; DWI	MHV were noted within the MTT lesion while they absent within the DWI lesion
Hingwala *et al*[29]	1	NS	MCA	NS	DWI	Prominent veins exceeding the area of the DWI lesion
Huisman *et al*[30]	1	NS	MCA	NS	ADC/DWI	Prominent intramedullary veins exceeding the area of the DWI lesion
Mittal *et al*[31]	2	1.5 T	MCA	NS	ADC/DWI; DSC-MRI	Prominent hypointense veins exceeding the area of the DWI lesion, similar to PWI lesion
Yen *et al*[32]	1	NS	MCA	4 d	DWI; DSC-MRI	Prominent venous hypointensities exceeding the area of the DWI lesion, similar to PWI lesion
Kesavadas *et al*[33]	2	NS	MCA	NS	DSC-MRI; ADC/DWI	Prominent veins exceeding the area of the DWI lesion, similar to PWI lesion
Park *et al*[34]	82	NS	ICA, MCA	3 d	DSC-MRI; DWI	MHV visible in 73/82 patients, excellent agreement with TTP maps
Lin *et al*[35]	53	NS	ICA, MCA	12 h	Traditional MRI	Hypointense transmedullary veins predisposed to worse outcome (OR = 2.2)
Meoded *et al*[36]	2	NS	MCA, ACA	NS	Conventional MRI; DWI	Prominent intramedullary veins were noted within the DWI lesion. In one case prominent sulcal veins matched the area of infarct growth.
Gasparotti *et al*[37]	1	1.5 T	ICA	NS	DWI; DSC-MRI	SWI lesion exceeded DWI lesion and matched MTT lesion
Yamashita *et al*[38]	30	3 T	MCA	7 d	DWI; FAIR	Increased venous contrast in 22/30 patients, area similar to hypoperfused tissue
Huang *et al*[39]	44	3 T	MCA	2 d	DWI; MRA; CT	Prominent veins present in 15/44 patients; Not correlated with haemorrhage or outcome
Kao *et al*[40]	15	1.5 T	MCA	18 h	DWI; DSC-MRI	MTT-DWI and SWI-DWI mismatch similar to predict infarct growth
Tsai *et al*[41]	49	NS	NS	3.5-8.5 h	MRI; Clinical	Presence of hypointense veins in all patients with worse outcome and haemorrhagic complications
Meoded *et al*[42]	8	NS	NS	72 h	DWI	DWI > SWI mismatch found in 1/15 affected regions
Park *et al*[43]	9	NS	TIA	NS	DWI; DSC-MRI; MRA	4/9 patients with DWI negative TIA showed asymmetric hypointense vessels, in accordance with perfusion deficit and stenosed/occluded vessel
Fujioka *et al*[44]	1	NS	ICA	10 h	MRI	SWI lesion exceeding DWI lesion matured into infarction
Verschuuren *et al*[45]	1	NS	MCA, ACA	NS	ADC; CT	SWI lesion exceeding ADC lesion matured into infarction on CT
Meoded *et al*[46]	1	1.5 T	MCA, PCA	NS	T2; ADC	SWI lesion matches ADC lesion; Mismatch also noted, indicating critical perfusion
Baik *et al*[47]	19	1.5 T and 3 T	ICA, MCA, BA	Median 2.5 h	DWI	Prominent veins present in affected territory which disappeared after recanalization (10/10 patients); After recanalization within DWI lesion: Equally prominent in 10/19 patients, small DWI lesions, good clinical outcome (7 d NIHSS median 3.5, 90 d mRS median 0) indicating normalisation; Less prominent in 5/19 patients, large DWI lesions, poor clinical outcome (7 d NIHSS median 13, 90 d mRS median 4) indicating futile reperfusion; Mixed in 4/19 patients, medium DWI lesions, relatively poor outcome (7d NIHSS median 13, 90 d mRS median 2)
Tsai[48]	59	NS	NS	NS	Imaging; Clinical	34 patients improved or stable (clinical, imaging), 25 worse; SWI correlated with poor prognosis
Sohn *et al*[1][49]	65	NS	Anterior circulation	12 h	Perfusion MRI	Asymmetrical HVS in 98% (SWI) and 74% (T2*w)

[1]Publication combining T2*w imaging and susceptibility-weighted imaging. NS: Not stated; ICA: Internal carotid artery; MCA: Middle cerebral artery; ACA: Anterior cerebral artery; ADC: Apparent diffusion coefficient; BA: Basilar artery; FAIR: Flow sensitive alternating inversion recovery; MRA: Magnetic resonance angiography; CT: Computed tomography; PCA: Posterior cerebral artery; IVC: Increased vessel contrast; TIA: Transient ischemic attack; DWI: Diffusion-weighted image; PWI: Perfusion-weighted image; MTT: Mean transit time; DSC-MRI: Dynamic susceptibility-contrast magnetic resonance imaging; NIHSS: National Institute of Health Stroke Score; mRS: Modified ranking scal; SWI: Susceptibility-weighted imaging; HVS: Hypointense vessel sign; MHV: Multiple hypointense vessels.

defined by hypointense vessels. The "brush sign" was described as a hypointense area along the course of subependymal and medullary veins in deep white matter.

DISCUSSION

Fundamentals of the penumbra and the BOLD-signal

The occlusion of a brain-supplying artery causes a disruption in the supply of oxygen through decreased CBF. The threshold of 20 mL per 100 g/min is considered the threshold for penumbra but this value is likely to be time dependent[50]. The cerebral metabolism rate of oxygen ($CMRO_2$) in viable, *i.e.*, penumbral tissue is still at a near normal level (approximately 3.5 mL per 100 g/min) which causes the OEF to rise from its normal range to its theoretical maximum of 100%[51]. As can be

Table 3 Comparison of publications using T2*w imaging and susceptibility-weighted imaging *n* (%)

	T2*w imaging publications (patients)	SWI publications (patients)
Number of publications	17 (692)[1]	27 (518)[1]
Presence of vessel signs	54%	81%
	16 (668)	21 (334)
Interrater agreement	κ = 0.7 to > 0.9 and ICC = 0.99	-
	6 (210)	
Reliability assessment	r = 0.92-0.96	-
	1 (20)	
Occluded vessel		
Anterior circulation	12 (598)[1]	22 (331)[1]
Large arteries	1 (20)	-
Critical MCA stenosis	1 (2)	-
TIA	-	1 (9)
BA	-	1 (1)[2]
NS	3 (72)[3]	4 (178)
Time from onset		
≤ 6 h	9 (317)	2 (18)[4]
> 6 h	5 (282)	12 (364)[1]
3.5-8.5 h	-	1 (49)
NS	3 (93)[3]	13 (87)
Outcome		
Worse outcome	1 (49)	3 (161)
Better NIHSS improvement	4 (107)	-
Better outcome with normalisation	-	1 (19)
No correlation	3 (141)	1 (44)
Validation method		
DSC-MRI	7 (260)	10 (181)
FAIR	3 (81)	1 (30)
Conventional MRI	3 (234)	11 (242)
^{15}O-PET	1 (NS)	-
DSA	1 (22)	-
Field strength		
1.5 T	3 (97)	7 (83)
3 T	8 (205)	3 (80)
NS	6 (390)[1,3]	17 (355)[1,5]

[1]Including one publication using T2*w imaging and susceptibility-weighted imaging (SWI) (Sohn *et al*[49]), thus the total number of studies and patients differs from the one stated in the main text; [2]Including one patient with occluded BA (Baik *et al*[47]); [3]Number of subjects not stated (Kinoshita *et al*[18]); [4]Including 17 patients ≤ 6 h and 2 patients > 6 h (Baik *et al*[47]); [5]Including those who used 1.5 T and 3 T (Baik *et al*[47]). NS: Not stated; ICA: Internal carotid artery; MCA: Middle cerebral artery; BA: Basilar artery; TIA: Transient ischemic attack; DSC-MRI: dynamic susceptibility-contrast magnetic resonance imaging; FAIR: Flow sensitive alternating inversion recovery; ^{15}O-PET: Oxygen-15 positron emission tomography; DSA: Digital subtraction angiography; NIHSS: National Institute of Health Stroke Score.

seen in Equation 1 it is described as the ratio of $CMRO_2$ and CBF multiplied with the oxygen content of blood (CaO_2).

$$OEF = CMRO_2/(CBF \times CaO_2).$$

While the increased OEF can keep $CMRO_2$ stable over some time it causes the concentration of DHb to increase as the oxygen is transferred from oxyhemoglobin (OHb) to tissue and DHb is generated (Figures 1 and 2). However, as the BOLD signal is a composite of CBF, $CMRO_2$ and cerebral blood volume (CBV) related signal changes their individual contributions can be difficult to establish. Dilatation of veins could thus in theory lead to an increased CBV (pooling of DHb) without concommitant change in overall flow or $CMRO_2$ but may be detected by perfusion MRI. The phenomenon of darkening veins was already observed in early experimental stroke studies and was related to an increase in DHb[52].

Red blood cells carry haemoglobin which is present as OHb and DHb. Other cellular components of blood (leucocytes, platelets) do not contribute to oxygenation related signal changes. OHb has four outer electrons one of which is shared between the chelated hem iron and oxygen which makes OHb diamagnetic. In DHb, the four unpaired outer electrons are in a high-spin state which gives it paramagnetic properties[53].

This makes DHb an endogenous contrast agent which can be noninvasively imaged with appropriate MRI techniques. DHb induces local magnetic field inhomogeneity in vessels and surrounding tissue and causes faster transverse relaxation decay. T2*w images pick up that process which is translated into reduced T2* signal[54]. In addition to faster transverse relaxation decay, a phase dispersion is induced. This is exploited by SWI which combines both the magnitude and the phase information and thus further enhances differences in susceptibility than T2*w imaging alone. For an in-depth explanation of the SWI technique and further clinical examples please refer to the extensive reviews by Sehgal *et al*[55], Haacke *et al*[56] and Tong *et al*[24].

Quantitative susceptibility mapping (QSM) is a development of SWI which utilizes the phase data. It requires further postprocessing to obtain quantitative information on local susceptibility[57,58]. QSM may in the future be able to quantify oxygen saturation and thus provide fully quantitative and completely non-invasive information on oxygen metabolism.

The above stated pathophysiological considerations suggest that veins that appear hypointense and more pronounced in diameter may be used to assess oxygenation and in the face of acute ischemic stroke also may detect metabolically active tissue.

Intermethod and interrater reliability

The depiction of hypointense veins can provide an approximation of the spatial extent of compromised oxygen metabolism. Although it has been qualitatively assessed, quantitative data is scarce. The published data however suggest that an estimation of the affected area is possible and reasonably reliable. The method does not deliver quantitative information and is only an indirect indicator of OEF. The main disadvantage is the fact that the exact relationship between discernible hypointensity within the vessels and increased OEF is unknown. Recently, SWI has been indirectly validated against arterial spin labelling[59] and has also been validated against ^{15}O-PET in patients with chronic cerebrovascular disease[60]. However, formal validation is still missing and thus only subjective though reproducible[7,14,15,17,19,21] rater-dependent assessment is available.

T2 vs SWI*

There is only one publication directly comparing SWI

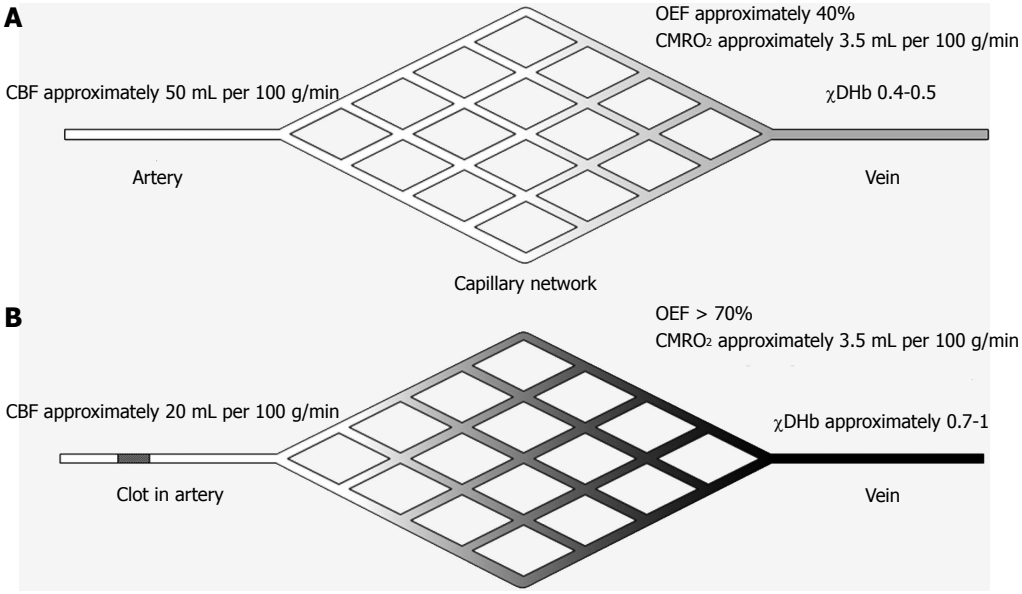

Figure 1 Schematic drawing of brain supplying artery, capillary network and draining vein and the sequence of events leading to an increased visibility of draining veins on T2*w imaging and susceptibility-weighted imaging during acute ischemic stroke. A: In the normal brain cerebral blood flow (CBF) is approximately 40 mL per 100 g/min to sustain normal brain function. Oxygen extraction fraction (OEF) and cerebral metabolism rate of oxygen ($CMRO_2$) are in the range of approximately 40%-50% and 3.5 mL per 100 g/min respectively. The fraction of deoxyhemoglobin (χDHb) provides the normal appearing venous vessels on T2*w and susceptibility-weighted imaging; B: When the blood supply is interrupted CBF drops to approximately 20 mL per 100 g/min (penumbral threshold) or < 10 mL per 100 g/min (ischemic threshold). In penumbral tissue $CMRO_2$ can be kept stable by an increase of OEF to > 70%. In effect, χDHb rises to its maximum (assuming optimal arterial oxygenation) and draining veins may appear more pronounced and hypointense.

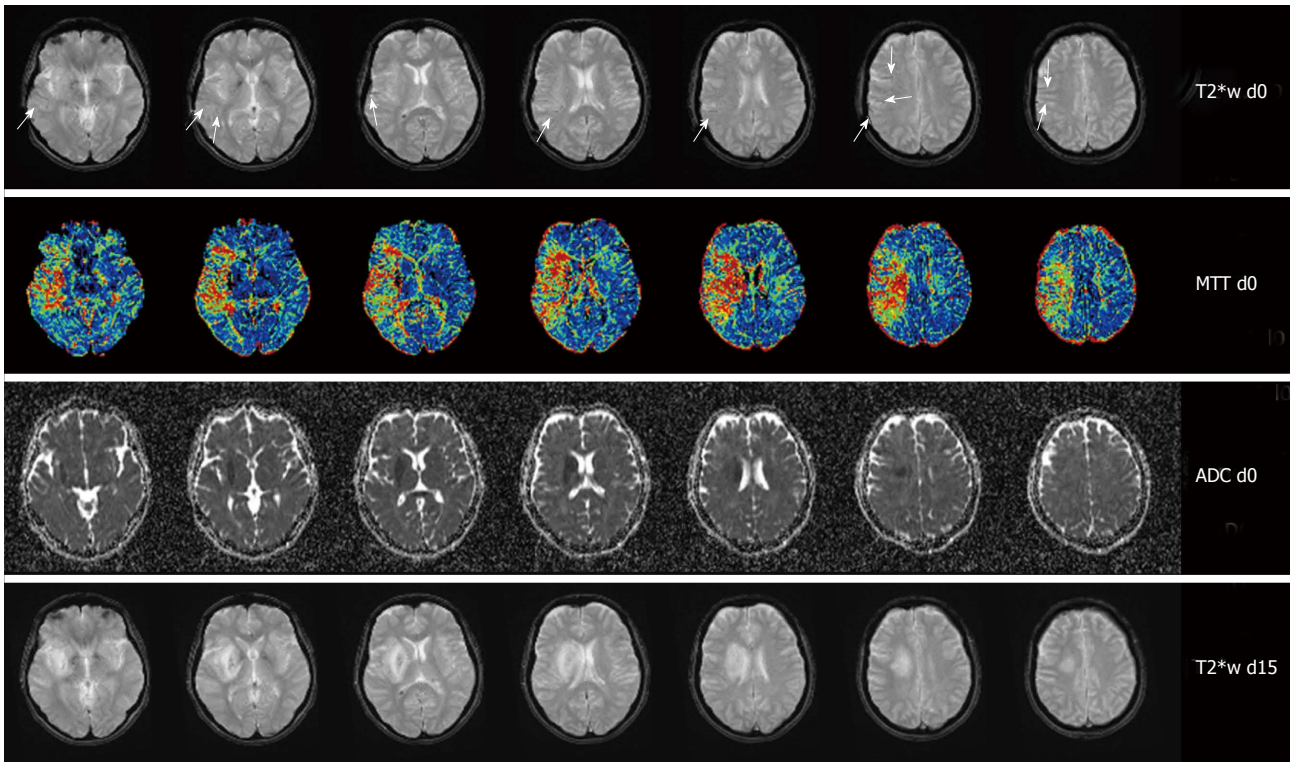

Figure 2 Image montage of magnetic resonance imaging findings in a 46-year-old woman with a right middle cerebral artery occlusion 321 min after symptom onset and an National Institute of Health Stroke Score of 11 on admission. Note the subtle asymmetrically prominent veins (arrows) on T2*w imaging (first row) within the mean transit time (MTT) lesion (second row) but outside the apparent diffusion coefficient (ADC) lesion (third row) on the day of admission (d0). On follow-up imaging 15 d later (d15) vessel appearance has normalized (fourth row).

and T2*w imaging in the same set of patients[49]. As expected, the sensitivity of T2*w imaging compared to SWI was significant (74% *vs* 98%). Accordingly, the pooled presence of vessel signs on T2* compared to

SWI in the reviewed publications was considerably lower (54% *vs* 81%). The low presence of vessel signs in T2*w images is worrying and make SWI a much more suitable candidate sequence.

SWI has long been hampered by long acquisition times of about 10 min, making it unsuitable for acute stroke studies due to extreme susceptibility to movement artefacts. This is corroborated by the fact that only three publications using SWI in the acute clinical setting could be identified[25,41,47]. By the time of writing this article however, scanning time has been reduced to about 3 min for whole brain coverage, facilitating its usage in clinical protocols. More publications and patients were included using T2*w imaging. This is not completely surprising as T2*w imaging is already incorporated in MRI stroke protocols used in many institutions. However, their purpose is currently the detection of haemorrhage[61] and screening for blooming artefacts caused by thrombus in large vessel occlusion[62]. Attractively, both T2* and SWI combine information on haemorrhage that would preclude thrombolytic treatment, with information on penumbral tissue. Additionally, there is no need for the application of contrast agent in the light of potential albeit small risks of anaphylactic reactions and nephrogenic systemic fibrosis.

Clinical outcome

The findings regarding clinical outcome are heterogeneous. The reviewed publications either indicate larger improvement measured on the National Institute of Health Stroke Scale or worse outcomes. However, this finding is not necessarily a contradiction. Larger volumes of penumbral tissue may result in worse outcome if tissue at risk is not rescued by adequate therapy. The difference is thus likely an effect of successful therapy and not the volume of penumbral tissue itself.

Preclinical basic research

As stated before, there is not one penumbra but a 4-dimensional gradient from necrosis to healthy tissue[1]. Depending on the occluded vessel, duration of ischemia, the tissue-specific vulnerability of certain areas of the brain, dynamics of reperfusion damage, *etc.*, various necrotic and apoptotic pathways are activated. Recently, more modes of cell death have been identified[63]. Putative neuroprotective or neuroregenerative drugs will only work in a small window of this 4-dimensional space. Therefore, the need for MRI sequences that specifically visualize certain aspects of infarction and good segmentation algorithms are needed, so the effects of the drugs can be assessed correctly and not be masked by other processes that take place during infarction. Very little preclinical basic research[64] has been done so far on the imaging method presented in this review.

In conclusion, the detection of hypointense venous vessels with BOLD imaging to assess the amount of penumbral tissue in acute ischemic stroke has emerged as a little noticed alternative imaging technique. Although the data seems very encouraging and indirect validation has provided very convincing results, validation with gold standard PET or at least with complementary perfusion MRI in the acute phase is still missing. Further studies especially on SWI should be conducted since the data already available seem to merit further evaluation of this technique. A reliability assessment should be conducted and, in particular the possibilities of SWI in the acute clinical setting should be evaluated. It could prove useful in the non-acute setting or when no other imaging is available or when functional assessment of stenosis or occlusion is needed[65]. However, in the present state the combined use of perfusion and BOLD imaging would provide further complementary information to help visualize and understand the role of the ischemic penumbra.

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COMMENTS

Background

Thrombolytic therapy with intravenous recombinant tissue plasminogen activator (rt-PA) is the only approved therapy for acute ischemic stroke. The target tissue for rt-PA therapy is the ischemic penumbra: electrically silent but viable and salvagable tissue. If no penumbra is present a given patient will only be subjected to the risks of rt-PA treatment. Thus, an accurate estimation of penumbral tissue to assess the risks and benefits of thrombolytic therapy is paramount.

Research frontiers

In recent years magnetic resonance imaging (MRI) using the diffusion- and perfusion-weighted imaging mismatch concept was widely used to map the ischemic penumbra. It defines the penumbra as the difference between tissue that is terminally infarcted on diffusion weighted imaging and tissue that is undersupplied on perfusion MRI: the so-called mismatch. However, this concept proved to be an oversimplification. That is why an imaging protocol that provides insight into oxygen metabolism is needed.

Innovations and breakthroughs

Recently, blood oxygenation level dependent (BOLD) imaging has become a candidate sequence to map the ischemic penumbra. In short, it visualizes an increased deoxyhemoglobin (DHb) concentration. An increased DHb concentration is the signature of tissue that displays an elevated oxygen extraction fraction (OEF), a hallmark of the penumbra. Two approaches are generally used: Direct assessment of penumbral tissue, definition of penumbral tissue by draining veins. In this article the assessment of draining veins is reviewed.

Applications

Asymmetrically hypointense draining veins on T2*w and even more on SWI could serve as a surrogate marker for penumbral tissue. However, further validation and quantification is needed.

Terminology

Penumbra: Tissue that has become undersupplied and electrically silent by an acute ischemic stroke. However, this tissue is still viable and can be salvaged by therapy; OEF: The percentage of oxygen extracted from the bloodstream by brain tissue. In normal tissue about 40%, elevated in penumbral tissue up to 100%; susceptibility weighted imaging: MRI sequence that combines the signal from T2*w imaging with phase information and thus enhances the contrast. BOLD imaging: Group of imaging methods that utilize the susceptibility difference between paramagnetic DHb and diamagnetic oxyhemoglobin. Any given change in oxygenation status will alter the signal.

Peer review

This work represents a nice overview of what has been done in the field so far and points out that consistent reporting is necessary. However, it also points out that this is an important observation and should be more carefully studied as it could have a significant impact on the diagnosis and treatment of patients.

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