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Pronostic factors on MRI in patients with acute ischemic stroke

Yu Xie

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par Yu XIE

Facteurs Pronostiques en IRM chez les Patients Présentant un Accident Vasculaire Cérébral Ischémique Aigu

Soutenance le 05 Novembre 2018

Membres du jury :

Rapporteurs :	Pr Jean-Marc OLIVOT	Université Toulouse III-Paul Sabatier, Toulouse
	Pr Valérie WOLFF	Université de Strasbourg, Strasbourg
Examineurs :	Dr Gabriela HOSSU	Université de Lorraine, Nancy, co-directrice de thèse
	Pr Serge BRACARD	Université de Lorraine, Nancy, directeur de thèse
	Pr Jean-Marc CONSTANS	Université de Picardie Jules Verne, Amiens
	Pr Sébastien RICHARD	Université de Lorraine, Nancy
Invitée :	Pr Catherine OPPENHEIM	Université Paris Descartes, Paris

Laboratoire d'Imagerie Adaptative Diagnostique et Interventionnelle – INSERM U1254
Bâtiment Recherche, CHRU de Nancy Brabois, Rue du Morvan,
54511 VANDOEUVRE-LES-NANCY

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List of Abbreviations

ADC	Apparent Diffusion Coefficient
AIF	Arterial Input Function
ASPECTS	Alberta Stroke Program Early CT Score
AUC	Area Under the Curve
AVC	Accident Vasculaire Cérébral
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CI	Confidence Interval
CSF	CerebroSpinal Fluid
CT	Computed Tomography
DWI	Diffusion weighted imaging
DSC	Débit Sanguin Cérébral
EPI	Echo-Planar Imaging
FDA	Food and Drug Administration
FLAIR	FLuid-Attenuated Inversion Recovery
ICA	Internal Carotid Artery
IVT	Intravenous thrombolysis
IVTMT	Intravenous thrombolysis and mechanical thrombectomy
MCA	Middle Cerebral Artery
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
mTICI	modified Thrombolysis in Cerebral Infarction
MTT	Mean Transit Time
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
PET	Positron Emission Tomography
PWI	Perfusion weighted imaging
RCT	Randomized Clinical Trials
ROC	Receiving Operating Characteristic
rtPA	recombinant tissue Plasminogen Activator
sICH	symptomatic IntraCranial Hemorrhage

SVM	Support Vector Machine
T2WI	T2-Weighted Image
THRACE	THRombectomie des Artères CERébrales
Tmax	Time to maximum
TOF	Time-Of-Fight
TOAST	Trial of Org 10172 in Acute Stroke Treatment
TTM	Temps de Transit Moyen
TTP	Time To Peak
VLP	Volume Lésionnel Prétraitement
VSC	Volume Sanguin Cérébral

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General introduction

Stroke is a major cause of death and disability worldwide. Of all stroke patients, about 87% are ischemic (1). The challenge for ischemic stroke treatment is to restore blood supply in the early stage and to salvage the ischemic “penumbra”, i.e. brain tissue at the risk of infarction but not infarcted yet (2). To date, the two Food and Drug Administration (FDA) approved treatments are intravenous thrombolysis by recombinant tissue plasminogen activator (rtPA) and mechanical thrombectomy (3). It is crucial to select appropriate patients for therapy based on an assessment of treatment benefit and risk. Stroke imaging plays an important role in diagnosing and guiding treatment strategies in the acute phase. The main goals are to rule out intracranial hemorrhage, define the ischemic penumbra and visualize the vessel status. Magnetic resonance imaging (MRI) is one of the most efficient stroke imaging modalities.

The overall aim of this thesis is to investigate the prognostic value of MRI in acute ischemic stroke evaluation for clinical outcome. We will focus on two essential sequences in ischemic stroke assessment: diffusion weighted imaging (DWI) and perfusion weighted imaging (PWI) (4). We first studied the prediction of the brain tissue viability after ischemic stroke by using pretreatment DWI and PWI parameters. Then the predictive role of pretreatment DWI in terms of lesional volume for clinical outcome was investigated. In the end, ischemic lesion location distribution measured on pretreatment DWI was analyzed to provide more accurate prediction for functional outcome.

The thesis will be presented in an article-based form organized in the following order:

In **Chapter 1**, we will provide an overall background and the state of art of our work. We first present the anatomy and vasculature of the brain, the epidemiology, the pathophysiology, the treatment and the assessment scale of ischemic stroke. This part is followed by a brief introduction of the basic concept of MRI and the common sequences clinically used in ischemic stroke assessment: DWI, PWI, fluid-attenuated inversion recovery (FLAIR), T2*-weighted imaging and magnetic resonance angiography. The concept and application of PWI-DWI mismatch will be explained afterwards. In the end, we will introduce the THRACE (THRombectomy des Artères CERébrales) study of which this thesis work is a part.

In **Chapter 2**, the role of different DWI and PWI derived parameters in the evaluation of brain tissue viability is investigated. We analyzed 36 patients selected from THRACE study who underwent both baseline DWI and PWI and day-7 images. Our results suggested that apparent diffusion coefficient and relative cerebral blood flow were potential candidates for

predicting tissue viability in acute ischemic stroke, in both initial abnormal diffusion areas and PWI-DWI mismatch areas.

In **Chapter 3**, the relationship between pretreatment ischemic stroke lesional volume and clinical outcome is studied. Lesional volume was semi-automatically segmented on pretreatment DWI in 298 patients from the THRACE study. Logistic regression was applied to fit the clinical outcome as a function of lesional volume. We demonstrated that pretreatment lesional volume was an independent predictor for functional outcome in acute ischemic stroke with proximal intracranial occlusion. In addition, our results revealed that the clinical benefit of adding mechanical thrombectomy to thrombolysis decreased with the increase of pretreatment lesional volume. Then, we searched for baseline parameters associated with favorable outcome in patients with a large lesional volume (> 70 mL and 100 mL). The results revealed that patients with large pretreatment volume may still benefit from reperfusion therapy, especially those with isolated M1 occlusion or ischemia restricted to the superficial middle cerebral artery (MCA) territory.

In **Chapter 4**, the impact of pretreatment ischemic location on functional outcome after thrombectomy is investigated. 143 ischemic stroke patients who received intravenous thrombolysis plus mechanical thrombectomy in THRACE study were included in this analysis. Ischemic lesions were segmented on pretreatment DWI. Regional ischemic locations were defined based on brain atlases. Ischemia percentage in each region was calculated. Logistic regression and support vector machine were applied to model the influence of age, baseline National Institutes of Health Stroke Scale and lesional volume, as well as stroke location on functional outcome. The results demonstrated the important role of pretreatment lesion location in functional outcome prediction. Compared to using only age, baseline National Institutes of Health Stroke Scale (NIHSS) score and lesional volume, together with the lesion location improved the prediction accuracy of functional outcome (from 70.5% to 77.3%).

In **Chapter 5**, we will give an overall discussion of our work, including the strengths and weaknesses of this work. A conclusion of accomplished work is presented. The implications for future research is addressed in the end.

A summary of the thesis in French will also be presented.

This work was carried out in the laboratory IADI (Imagerie Adaptative Diagnostique et Interventionnelle), under the direction of Professor Jacques Felblinger. This thesis is directed by Professor Serge Bracad and Doctor Gabriela Hossu.

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1. **Xie Y**, Oppenheim C, Guillemin F, Gautheron V, Gory B, Raoult H, Soize S, Felblinger J, Hossu G, Bracad S. Pretreatment Lesional Volume Impacts Clinical Outcome and Thrombectomy Efficacy. *Ann Neurol.* 2018;83(1):178-185. doi: 10.1002/ana.25133.
2. Gautheron V, **Xie Y**, Tisserand M, Raoult H, Soize S, Naggara O, Bourcier R, Richard S, Guillemin F, Bracad S, Oppenheim C. Outcome After Reperfusion Therapies in Patients With Large Baseline Diffusion-Weighted Imaging Stroke Lesions: A THRACE Trial (Mechanical Thrombectomy After Intravenous Alteplase Versus Alteplase Alone After Stroke) Subgroup Analysis. *Stroke.* 2018;49(3):750-753.
3. **Xie Y**, Oster J, Micard E, Chen B, Douros I, Liao L, Soudant M, Felblinger J, Guillemin F, Hossu G, Bracad S. Impact of Pretreatment Ischemic Location on Functional Outcome after Thrombectomy. *Submitted.*
4. **Xie Y**, Liao L, Guillemin F, Chen B, Felblinger J, Hossu G, Bracad S. Role of diffusion and perfusion parameters in predicting tissue viability in acute ischemic stroke. *Submitted.*

The results were presented in the following conferences:

1. **Xie Y**, et al. L'IRM de diffusion et de perfusion dans l'évaluation de la viabilité des tissus cérébraux chez les patients présentant un accident vasculaire cérébral ischémique à la phase aiguë. 44ème congrès annuel de la société française de neuroradiologie. Mar. 22-24, 2017. Oral presentation.
2. **Xie Y**, et al. Impact of pretreatment ischemic location on functional outcome after mechanical thrombectomy in acute ischemic stroke. International stroke conference. Jan. 24-26, 2018. Poster.
3. **Xie Y**, et al. Association between diffusion weighed imaging measured pretreatment ischemic volume and functional outcome in ischemic stroke. ISMRM-ESMRMB. Jun.16-21, 2018. Poster.

Chapter 1

Background and state of the art

1. The brain and ischemic stroke

1.1. The anatomy and vasculature of the brain

The brain, a gelatinous mass, is one of the most complex organs in the body. It is made up of about 86 billion neurons and 85 billion nonneuronal cells (5). The brain is divided into the cerebrum, brainstem, and cerebellum. The cerebrum includes the paired cerebral hemispheres and the diencephalon. The brainstem comprises the midbrain, pons, and medulla (6). The blood supply of the brain depends on two major sources: internal carotid artery (ICA) and vertebral arteries. The ICA gives rise to the anterior and middle cerebral arteries. The vertebral arteries come together at the level of the pons to form the basilar artery, which then divided into posterior cerebral arteries. The circle of Willis provides an important communication between the two major sources and improves the chance of brain to receive blood if one of the arteries is occluded (7). (Figure 1)

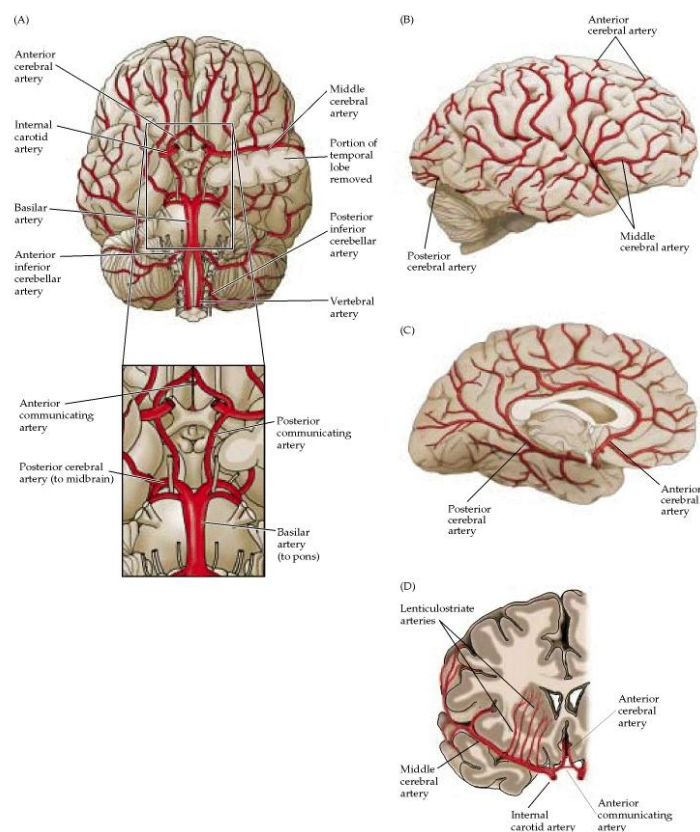


Figure 1. The major arteries of the brain. (A) Ventral view. The enlargement of the boxed area shows the circle of Willis. Lateral (B) and (C) midsagittal views showing anterior, middle,

and posterior cerebral arteries. (D) Idealized frontal section showing course of middle cerebral artery. Ref (7)

1.2. Epidemiology of stroke

Stroke is a “rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin” (8). In 2015, prevalence of stroke was 43.6 million, with 5.2 million people having a first stroke < 65 years of age. Stroke is the second-leading global cause of death, accounting for about 12% of total deaths worldwide (1). With the population aging, the number of patients suffered from stroke will continue to augment.

1.3. Pathophysiology of ischemic stroke

Stroke can be classified into two categories: ischemic and hemorrhagic stroke. Of all the strokes, about 87% are ischemic stroke. It occurs as a result of a thrombotic or embolic occlusion of a cerebral artery, resulting in a corresponding neuron death and loss of neurologic function. Ischemic stroke can be categorized by TOAST (Trial of Org 10172 in Acute Stroke Treatment) subtype classification: large-artery atherosclerosis; cardioembolism; small-vessel occlusion; stroke of other determined etiology; stroke of undetermined etiology (9). About 25~35% of ischemic strokes present with large-artery occlusion.

Sufficient blood supply to the brain tissue is important to maintain the neuronal activity. The energy consumption of brain is high: the brain comprises about 2% of the body mass but consumes about 20% of the total oxygen. With the occlusion of the artery and the decrease of the blood supply, 3 compartments of hypoperfused brain tissue can be distinguished according to the severity of ischemia (Figure 2):

- 1) Ischemic core: tissue with severe hypoperfusion, which is irreversibly infarcted.
- 2) Penumbra: tissue with severe hypoperfusion, which is at the risk of infarction but still have the potential to be salvaged if the blood supply is restored in time.
- 3) Benign oligemia: tissue with moderate hypoperfusion, which is not at the risk of infarction.

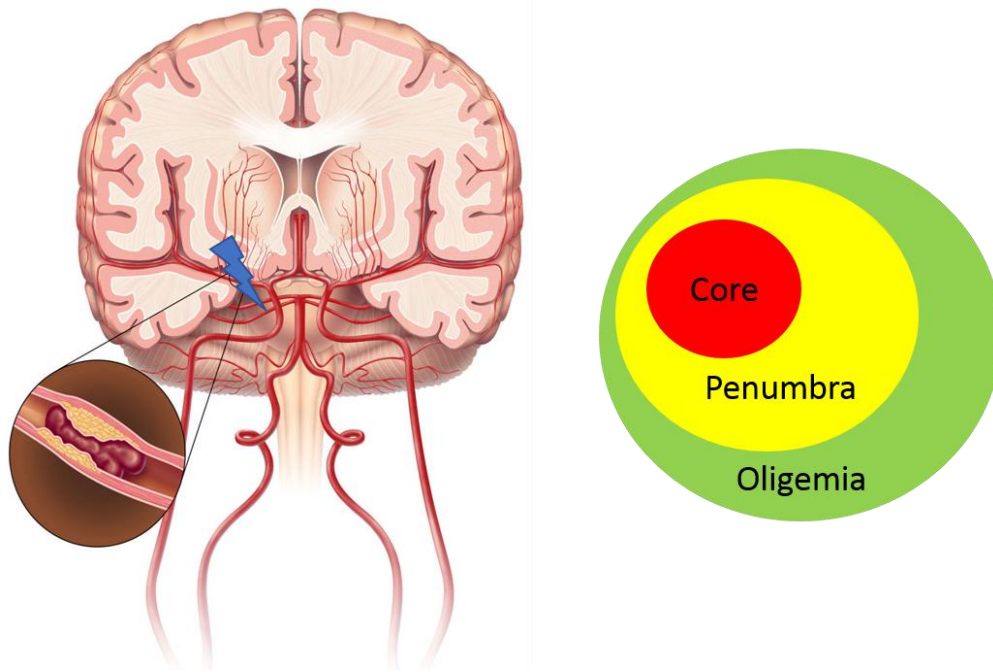


Figure 2. Schema of ischemic core/penumbra/benign oligemia model in ischemic stroke. After the occlusion of artery, 3 compartments of hypoperfused brain tissue can be distinguished according to the severity of ischemia: core, penumbra and oligemia. (Image is modified from <http://www.strokecenter.org/patients/about-stroke/ischemic-stroke/>)

There are two blood flow thresholds for the ischemic brain tissue evaluation: threshold for reversible failure of neuronal electrical function and irreversible failure of energy metabolism and ion pumping. Branston et al. demonstrated that the evoked somatosensory potential recorded in baboon cortex was abolished when local cerebral blood flow (CBF) reduces to 15 mL/100g/min (10). The massive release of intercellular K^+ , which is indicative of ion pump failure, occurs at a further reduced level of CBF (about 6 mL/100g/min) (11). The term “ischemic penumbra” was initially described by Astrup et al. (2). This is a region with blood flow between the upper threshold of electrical failure and the lower threshold of energy failure and ion pump failure. Thus, penumbra is described by electrical silence with normal or only slightly elevated extracellular potassium concentration. The development of penumbra to irreversible morphological damage is determined by the severity and duration of ischemia, and their combined influence (12). Through simultaneous recordings of the cortical neuronal activity and local blood flow, we can depict the residual blood flow and duration of ischemia thresholds for the development of cell damage (13). (Figure 3)

Infarct progression is time dependent: during the acute phase, the injury of the core tissue is a direct consequence of the ischemia-induced energy failure; in the subacute phase, the irreversible damage expands into the penumbra area; in the delayed phase, vasogenic edema, inflammation and programmed cell death may contribute to further damage, which last for several days or even weeks (14).

During the early phase, penumbra has the potential for functional recovery without morphological damage when the CBF is reestablished in a certain time window. It is the principle target for reperfusion treatment.

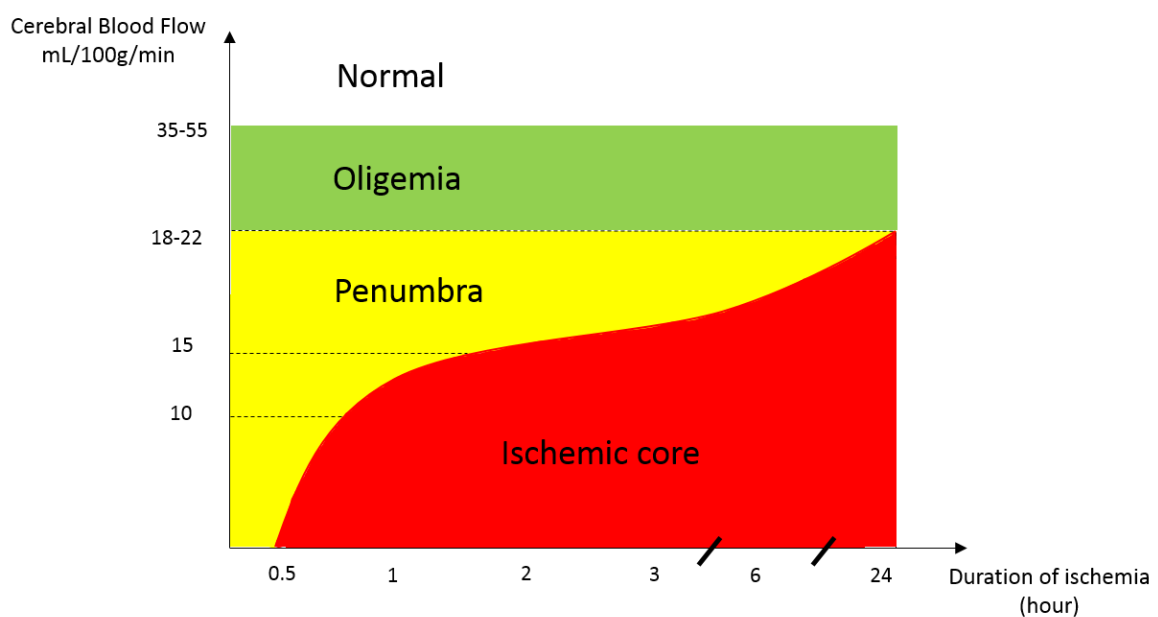


Figure 3. Diagram of cerebral blood flow threshold and duration of ischemia for different tissue compartments in ischemic stroke. Modified according to Heiss W-D (13).

1.4. Treatment of ischemic stroke

The goal of treatment for ischemic stroke is to restore the blood supply at the early phase and to salvage the ischemic penumbra. The term “time is brain” has been widely adopted. A study showed that patient loses 1.9 million neurons each minutes when the stroke is untreated (15). The therapy includes intravenous administration of thrombolytic drugs and the use of various thrombectomy devices under angiographic guidance to remove the thrombus.

NINDS (National Institute of Neurological Disorders and Stroke) trial proved that despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous

rtPA within 3 hours improved the clinical outcome (16). This is the first FDA-approved therapy for acute ischemic stroke. Then ECAS III trial extended the treatment time window to 4.5 hours (17,18). Tenecteplase is a thrombolytic agent which is more specific for fibrin and has a longer half-life compared to Alteplase. Currently, some clinical trials on tenecteplase are underway (3). However, systemic thrombolysis has several limitations, such as the narrow therapeutic time window and contraindications (e.g., recent major surgery, coagulation abnormalities or history of intracranial hemorrhage) (19). Moreover, thrombolysis is much less effective in patients with proximal artery occlusion. Early recanalization after intravenous thrombolysis only occurs in about one third of patients with proximal occlusion (20,21).

Endovascular thrombectomy is a reperfusion strategy different from pharmacologic fibrinolysis. It uses a device to remove the clot directly and restore the blood supply. Results from IRM III, SYNTHESIS, and MR RSCUE trials failed to show the significant benefit of endovascular therapy (22–24). In 2015, 5 landmark clinical trials proved the efficacy of additional endovascular thrombectomy over intravenous rtPA alone in acute ischemic stroke patients with occlusion of the proximal anterior circulation (25–29). The main differences of these 5 trials compared to the early studies are the patient selection criterion (only patients with proximal cerebral artery occlusion were included) and the use of new generation devices. The analysis of the pooled data of these 5 trials demonstrated the benefit of endovascular thrombectomy (30). THRACE study and PISTE study also presented the advantage of mechanical thrombectomy (31,32). A meta-analysis of 21 randomized trials found that endovascular therapy significantly improved functional outcome at 90 days and reduced the mortality (33). A meta-analysis analyzing the 5 landmark trials showed that benefit of thrombectomy became insignificant after 7.3 hours of symptom onset (34). In 2018, DAWN and DEFUSE 3 trials brought new perspective on the treatment window of thrombectomy (35,36). Selected patients up to 24 hours after symptom onset may still benefit from thrombectomy using Trevo clot retriever device. Nowadays, with the development of endovascular thrombectomy, more patients can benefit from treatment.

1.5. Functional assessment scale for the evaluation of ischemic stroke

Assessment scales can help clinicians estimate the severity of ischemic stroke, set realistic therapy strategies and goals. Many assessment tools are available to evaluate ischemic stroke. We will focus on two scales that are most commonly used.

1.5.1. National Institutes of Health Stroke Scale (NIHSS)

The NIHSS was developed in 1989 and is now widely employed in clinical practice and research. It provides a measurement of acute stroke severity by testing various domains of neurological function. The NIHSS is a 15-item scale that incorporates assessment of consciousness, visual fields, eye movement, motor function, sensation, coordination, language, speech and neglect (37). (Appendix 1) It is an ordinal scale from 0 (no impairment) to a maximum of 42. It is a reliable, valid and time efficient assessment tool, for both neurologist and non-neurologist raters. Initial NIHSS score correlates with infarct size, in-hospital neurological and medical complication and 3-month clinical outcome (37–39). However, an important limitation of the NIHSS is that it places emphasis on deficits associated with dominant hemisphere function rather than non-dominant hemisphere function or posterior circulation (40–42). Analysis has shown that patients with right-sided stroke have a low NIHSS score despite substantial DWI lesion volume (41). Besides, an individual can score 0 on the NIHSS, despite having evidence of ischemic stroke, particularly in the posterior circulation territory (42). Overall, NIHSS is a powerful tool for stroke severity evaluation.

1.5.2. Modified Rankin Scale (mRS)

The mRS is a global outcome disability scale that has been widely applied for evaluating functional independence following stroke (43). The mRS is an ordinal scale from 0 to 6, with higher value indicating more severe disability. (Appendix 2) It has been used as a valid and reliable end point in randomized clinical trials (RCTs) (44). However, the mRS has been criticized as an assessment tool accentuating the disability of motor performance rather than other areas of stroke recovery, such as language (45).

2. Utilization of MRI in ischemic stroke evaluation

As previously mentioned, the identification of penumbra is essential for guiding treatment decision-making of ischemic stroke. However, the concept of penumbra is based on experimental models and it is difficult to transfer into non-invasive imaging modalities. Positron emission tomography (PET) has been established as the gold standard to evaluate penumbra (46,47), while it is expensive and impractical for clinical practice. MRI is a useful modality for diagnosing ischemic stroke and determining treatment decision; it is widely used in routine clinical application (4,48).

2.1. Basic concepts of MRI

2.1.1. T1 and T2 relaxation and contrast

The MR measurements can be analyzed in terms of energy transfer. The process of the proton releasing energy that is absorbed from the radiofrequency named as relaxation. Two relaxations times of tissue can be measured: T1 and T2.

The relaxation time T1 is the time required for the longitudinal magnetization (M_z) to return to 63% of its original value following an excitation pulse. In the brain, white matter has a very short T1 and relaxes rapidly. Cerebrospinal fluid (CSF) has a long T1 and relaxes slowly. Gray matter has an intermediate T1. The contrast mechanism that we create an image at a time when T1 curves are widely separated is termed T1-weighted image (49). (Figure 4)

The relaxation time T2 is the time required for the transverse magnetization (M_{xy}) to decay to 37% of its initial value. Different tissue has different values of T2. White matter has a short T2 and dephases rapidly. CSF has a long T2 and dephases slowly. Gray matter has an intermediate T2. T2-weighted image (T2WI) is obtained when T2 curves are widely separated (49). (Figure 5)

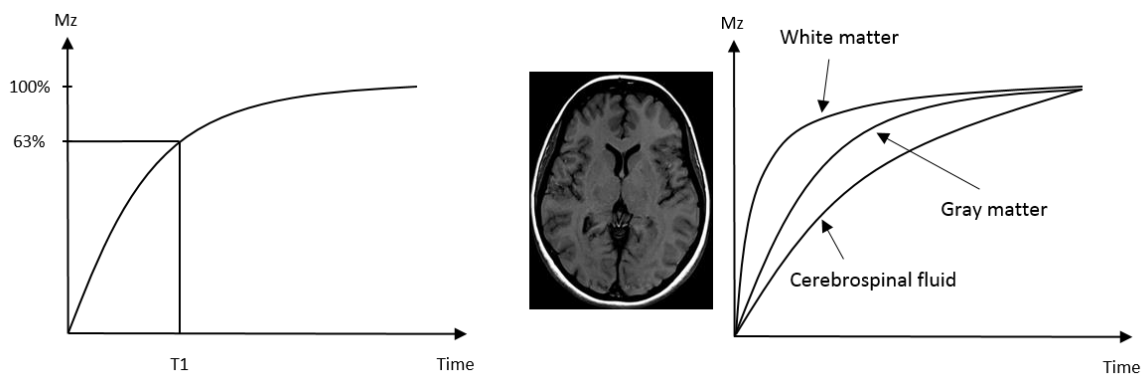


Figure 4. Relaxation of T1 and T1 weighted contrast. T1 is a characteristic of tissue and is defined as the time required for the longitudinal magnetization (M_z) to return to 63% of the original value following an excitation pulse. Different tissue has different T1 characteristic. If an image is obtained at a time when the relaxation curves are widely separated, the contrast is termed T1-weighted contrast. According to (49)

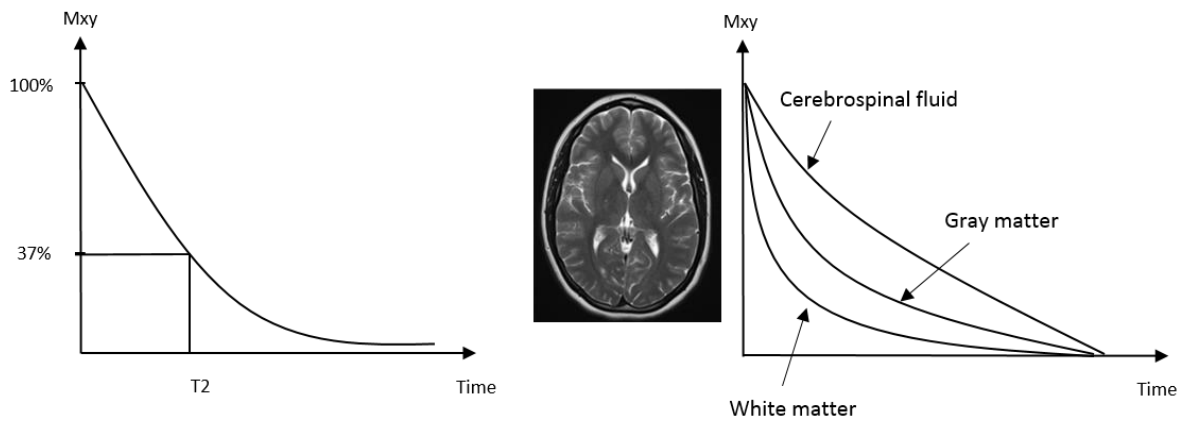


Figure 5. Relaxation of T2 and T2 weighted contrast. T2 is a characteristic of tissue and is defined as the time required for the transverse magnetization (M_{xy}) to decay to 37% of its initial value. Different tissue has different T2 characteristic. If an image is obtained at a time when the relaxation curves are widely separated, the contrast is termed T2-weighted contrast. According to (49)

2.1.2. Spin echo sequence

The spin echo sequence is one of the fundamental MRI pulse sequences. A standard spin echo sequence consists of an excitation pulse (90°), which turns the M_z into M_{xy} (dephase), and a 180° pulse to rephase the spin. The rephasing of the spins formed an “echo” is called a spin echo (49,50). (Figure 6) The spin echo sequence is the base of the typical DWI sequence, which will be presented in the following text.

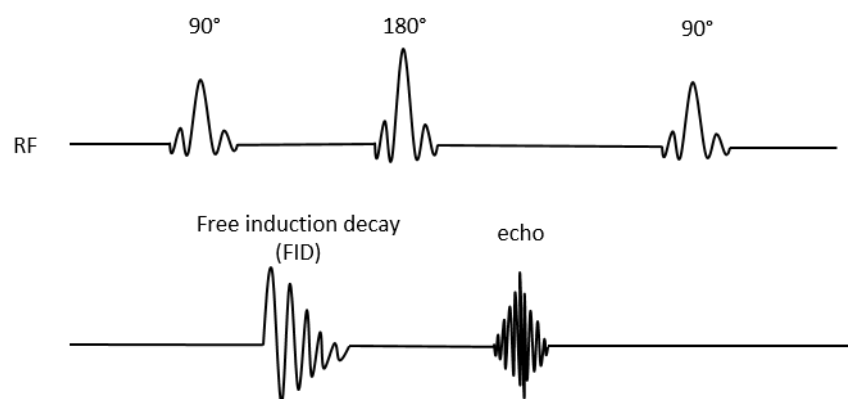


Figure 6. Schema of the spin echo sequence. The application of 90° radiofrequency pulse results in an immediate signal decay (free induction decay, FID). Then the application of 180° radiofrequency pulse will allow the spins to rephase and form an echo. (49)

2.2. Common MRI sequences used in ischemic stroke

2.2.1. DWI

(1). Principle of DWI

The diffusion of the water molecule in tissue follows a pattern according to the tissue organization. The alteration of tissue structure will disturb the water diffusion. Through evaluating the signal changes due to the diffusion alteration, we can detect the abnormalities. In 1965, E. O. Stejskal and J. E. Tanner proposed the sequence of DWI, wherein the diffusion of the water molecules was exploited (51). In 1986, Le Bihan et al. applied DWI on human brain for the first time (52). The most common approach of DWI is to use a spin echo T2-weighted pulse sequence, in which two equal and opposite diffusion gradients were applied before and after the 180° radiofrequency pulse. These gradients successively cause a dephasing and rephasing of the proton of water molecule. (Figure 7) In case of no net movement of proton, both the gradient effects cancel out each other and there will be no signal attenuation. However, in case of the proton diffusion, there will be incomplete rephasing of proton spin and also the signal attenuation. These signal attenuation can be presented on DW images by hyposignal regions (53,54). The signal loss from proton diffusion is given by Stejskal-Tanner equation:

$$S(b) = S_0 e^{-bD}$$

Where $S(b)$ refers to the signal received from the particular gradient value b ; S_0 is the signal strength without diffusion weighting (T2WI), D is the diffusion coefficient. The b -value is given by the equation:

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3)$$

Where γ is the gyromagnetic ratio of hydrogen proton, G is the magnitude of applied diffusion gradient, δ is the duration of the gradient, Δ is the time between the applications of the two gradients.

In order to minimize the effect of patient movement during acquisition, an echo-planar imaging (EPI) technique was used. It samples all the data points necessary for reconstruction of an image after application of a single radiofrequency excitation pulse. The whole k -space is sampled efficiently in a continuous trajectory. (Figure 8)

The true diffusion is the net movement of molecules due to a concentration gradient. However, molecular motion due to pressure gradients, thermal gradients or ionic interactions cannot be differentiated with MRI. Thus, we can only calculate the apparent diffusion coefficient (ADC) (55).

Tissue with high diffusion present as hyposignal on DW images while tissue with restricted diffusion are seen as hypersignal. Clinically, ADC maps, which can quantify diffusion, are derived from DW images with a certain b-value using Stejskal-Tanner equation. An example of DW images and ADC map of an ischemic stroke patient is presented in Figure 9.

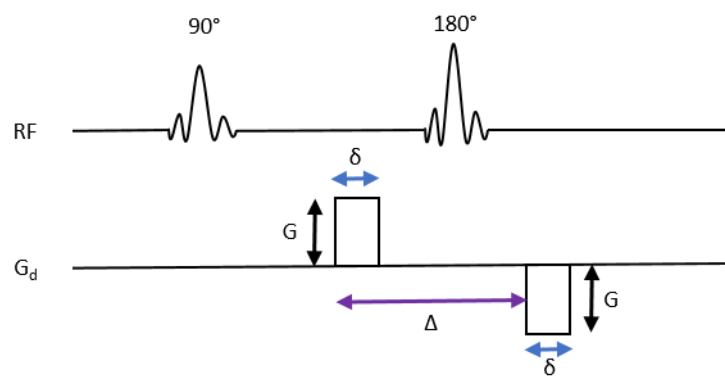


Figure 7. Schema of the diffusion-weighted spin echo sequence. Two diffusion gradient pulses (denoted on diffusion gradient line, G_d) of amplitude G , duration of δ , interval of Δ and opposite in direction, are applied before and after the 180° radiofrequency pulse (denoted on radiofrequency line, RF). Modified according to Chilla et al. (53).

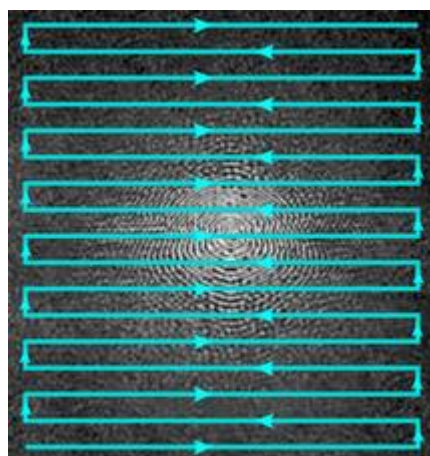


Figure 8. Zig-zag traversal of k-space in EPI technique. The whole k-space is sampled efficiently in a continuous trajectory after application of a single radiofrequency excitation pulse. <<http://mriquestions.com/echo-planar-imaging.html>>

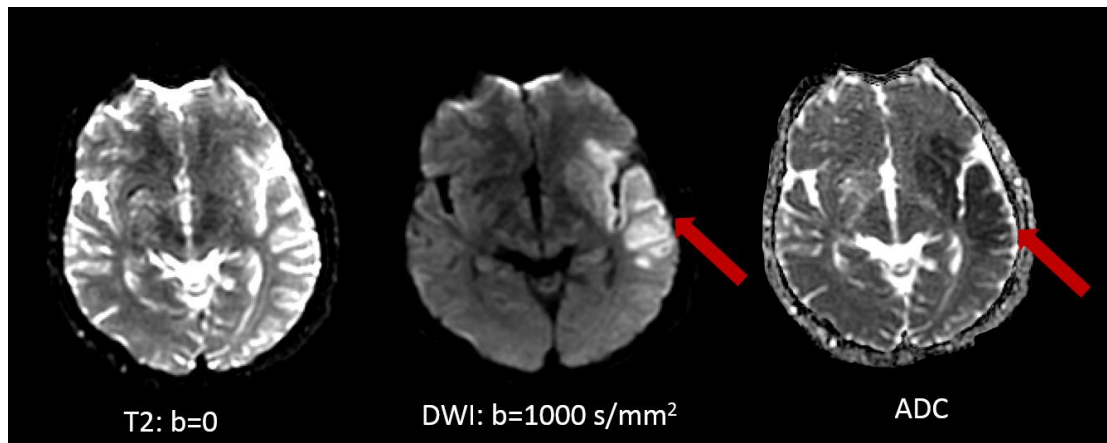


Figure 9. Example of DW image and ADC map in an acute ischemic stroke patient. From the spin echo T2 weighted image with $b=0$ (left), the DW image can be obtained after the application of diffusion gradient with $b=1000 \text{ s/mm}^2$ (middle). On the DW image, the region where water diffusion is high (ex. the cerebrospinal fluid) presents as hyposignal, while region with restrict diffusion (ex. the left insula, lenticular nucleus and inferior temporal lobe as the red arrow indicates) presents as hypersignal. ADC map can be calculated from the previous images by using the Stejskal-Tanner equation (right).

(2). DWI in ischemic stroke

The time course of signal intensity on DWI and ADC is a dynamic event. Within minutes after ischemia, the decrease of cerebral blood flow causes the disruption of energy metabolism, leading to the failure of the Na^+/K^+ adenosine triphosphates pump and other ion pumps. This leads to loss of ionic gradients and the translocation of water from extracellular to the intracellular compartment (cytotoxic edema, Figure 10). A restriction of water diffusion in extracellular space occurs, which presents as hypersignal on DW images and hyposignal on ADC map (55). This abnormality can be detected in the first hour following the ischemic stroke while there is still no abnormality on the computed tomography (CT) or other sequences on MRI, such as T2 or FLAIR. (Figure 11) After the initial decrease of ADC, there is a gradual increase of ADC value secondary to the cell lysis and vasogenic edema, with a return to the baseline value known as pseudonormalization around 3-10 days post-onset (56). The signal intensity on DW images is maximal at 40 hours after infarction and then gradually normalizes (57). But the normalization of signal intensity on DW images are delayed compared to ADC value, because DW signal is also influenced by T2 effect. During the

chronic stage, there is an increase of water diffusion and also increase in ADC value due to gliosis and cavitation resulted from tissue breakdown.

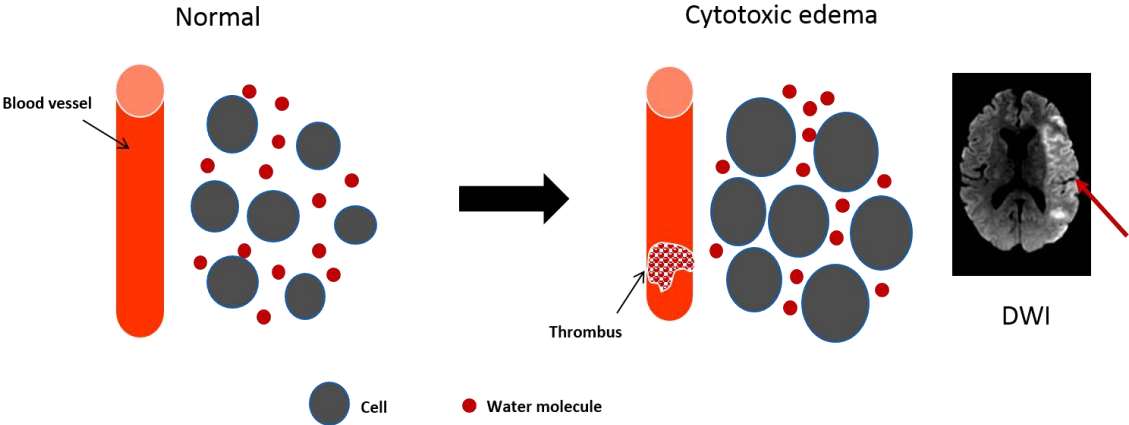


Figure 10. Schema presenting cytotoxic edema after ischemic stroke. The decrease of cerebral blood flow leads to the failure of the Na^+/K^+ adenosine triphosphates. The water molecules translocate from extracellular to the intracellular, causing cell swelling. The water diffusion in extracellular space is restricted, which presents as hypersignal on DW images.

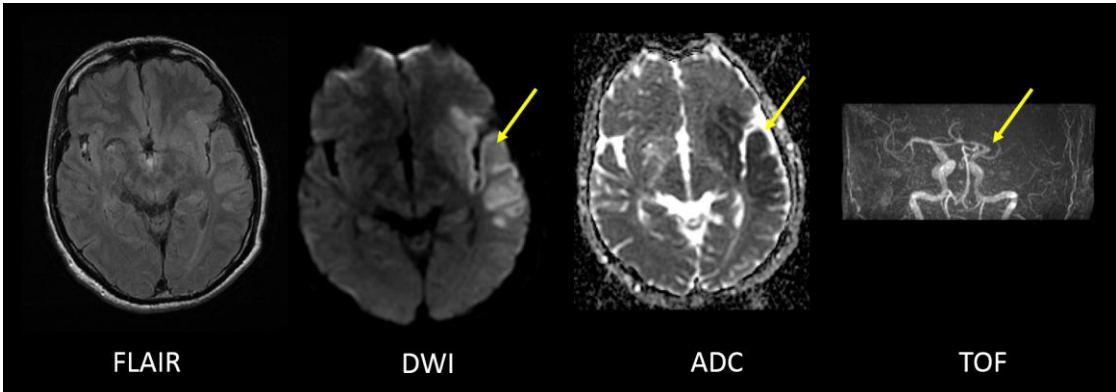


Figure 11. MRI performed 2 hours after the ischemic stroke onset. Only discrete hypersignal can be distinguished in the territory of left MCA on FLAIR sequence. Abnormality can be detected on DWI by distinct hypersignal region (arrow), and on ADC map by hyposignal region (arrow). Time of flight (TOF) sequence shows the occlusion of the left MCA (arrow).

Currently, DWI is the most powerful sequence for diagnosing acute ischemic stroke with high sensitivity and accuracy (58). Its superiority over non-contrast CT at the acute stage (sensitivity 97% vs 40%, specificity 100% vs 92%) and over conventional MRI sequences (sensitivity 58%, specificity 100%) have been demonstrated (59). Studies showed that DWI can efficiently differentiate stroke with stroke mimics, which account for about one quarter of

suspected stroke patients, with different etiologies such as seizure, migraine, brain tumors, etc. (60,61). However, previous studies found that some ischemic stroke patients present false-negative DWI. False-negative DWI is associated with several clinico-radiologic factors. The site of infarction is an important factor: posterior circulation infarct patients are more likely to have negative DWI than anterior circulation infarct patients. Patients with history of smoking, higher initial blood pressure, higher fasting plasma glucose, and longer time to imaging after stroke onset are more likely to have positive DWI lesions (62). Besides, the intensity of magnetic field may also impact DW images, with 1.5 T presenting lower false-negative DWI than 3T (0.6% vs 6.1%) (63). Therefore, it is necessary to combine the DWI and other sequences, as well as the clinical information, before diagnosing the ischemic stroke.

It was widely accepted that DWI lesion indicates the ischemic core or the eventual infarction. However, researchers demonstrated that DWI abnormality could also be reversed, especially in patients with early recanalization. In one study, 3 in 19 patients with acute stroke who underwent intra-arterial thrombolysis presented the reversal of DWI-hyperintense regions (64). In another study, 89/176 (50%) patients exhibited visually-detectable DWI lesion reversal compared to 24-hour images, with a median volume of 2.4 mL (0.5-8). The reversal was significantly greater in patients treated earlier (≤ 3 h). Moreover, the reversal was independently associated with early neurological improvement (65). In a sub study of DEFUSE (Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution) trial, a reversal rate of 43% was reported for the baseline DWI lesion when comparing final infarct volume on FLAIR images obtained at day 30 (66). Moreover, the reversal of the DWI abnormality in patients post thrombolysis was demonstrated to be predictive of favorable clinical outcome (67).

It is worth noting that the definition of DWI reversal is complex. In many cases, the initial DWI reversal is transient. In one study, 8 of 18 patients presented DWI reversal on the immediate post-treatment scan, while only 3 patients had sustained reversal tissue by day 7 (68). In another study, over two-thirds of the DWI lesion reversal captured on 24-hour follow-up MRI is sustained (69). Furthermore, whether the reversal of DWI lesion translates to tissue salvage is questionable. Ringer TM et al. showed that neurons already exhibit evidence of structural damage and stress even though with the normalization of the DWI (70). Li F et al. suggested that even brief period of focal ischemia (e.g. 10 min) and sustained resolve of DWI lesions do not indicate a normal histological outcome (71).

ADC has been proposed to be an indicator to assess the viability of brain tissue. In general, tissue with higher ADC value is more likely to reverse (68). In one study, an ADC threshold of $620 \times 10^{-6} \text{ mm}^2/\text{s}$ was proposed to distinguish ischemic core and penumbra (72). Perfusion-derived parameters were also investigated. The reversal rate was significantly higher in DWI regions with normal perfusion compared to the hypoperfused region (Time to maximum $[T_{\max}] \leq 2\text{s}$) (66). Mean transit time (MTT) has been suggested to improve infarction prediction (73). Currently, there is no consensus on MRI-based tissue viability thresholds for DWI reversal. Apart from the image-derived values, the duration and severity of ischemia and reperfusion status are also important determinants for the tissue reversal.

When the diagnosis of ischemic stroke is established, the volume and the topography of the lesion can help the clinicians to determine the etiology, decide the treatment strategies and predict the clinical outcome.

The Alberta Stroke Program Early CT Score (ASPECTS) (74) is a semi-quantitative method to estimate the infarct size on non-contrast CT scan or DWI at acute phase. A number of studies investigated its role in predicting clinical outcome and guiding patient management. A post-hoc analysis of the PROACT-II study showed that patients with a baseline ASPECTS > 7 were 3 times more likely to have an independent functional outcome with thrombolytic therapy compared with patients with ASPECT ≤ 7 (75). In a similar analysis of IMS-III trial, ASPECTS was also demonstrated as a predictor of outcome and reperfusion. However, it was not able to identify patients likely to benefit from endovascular therapy after routine rtPA (76). Furthermore, a subgroup analysis of the MR CLEAN trial suggested that patients with ASPECTS 5-7 should not be excluded from intra-arterial treatment (77).

Infarct volumes can be measured precisely on initial DWI and ADC. The correlation of initial infarct volume with clinical outcome has been proved by a number of studies (78–80). Evidences showed that DWI lesion volume greater than approximately 70 mL predicted poor clinical outcome regardless of treatment and recanalization status (81–84). For example, Yoo et al. analyzed 54 ischemic stroke patients and reported that all patients with an initial DWI lesion volume $> 72 \text{ mL}$ and an NIHSS score > 20 had poor clinical outcome (82). Schaefer et al. demonstrated 95.6% specificity for DWI $> 70 \text{ mL}$ to predict poor outcome (84). In addition, Yoo et al. studied 34 stroke patients and showed that patients with initial infarcts $> 70 \text{ mL}$ had poor outcome despite a 50% recanalization rate (83). DWI lesion $> 100 \text{ mL}$ was another cut-off empirically used to define the malignant profile in clinical studies (85,86).

Nevertheless, these thresholds were challenged, several studies demonstrated that selected patients with large DWI lesions may still benefit from recanalization (87–91).

Follow-up DWI lesion volume was also proved to be an independent predictor of clinical outcome and was suggested as surrogate marker of outcome in acute stroke trials (92–96). Zaidi et al. analyzed 201 patients with MCA occlusion and suggested that successful recanalization led to improved functional outcomes through a reduction in final infarct volumes. Only age and final infarct volume but not recanalization were found to be independent predictors of outcome (93). Albers et al. analyzed 195 patients and reported that infarct volume at 27 hours was a powerful and independent predictor of 90-day clinical outcome (94). Bucker et al. analyzed images at 24-hour and 1-week for 228 patients from MR CLEAN trial. They found that even though lesion volume growth was common 24-hour post stroke onset, the 24-hour lesion volume was equally strongly associated with functional outcome as the 1-week lesion volume (96).

In addition to the lesion volume, the infarct location has also shown capabilities in stroke assessment and guiding the clinical decision-making. An example of stroke location influencing the functional outcome is presented in Figure 12.

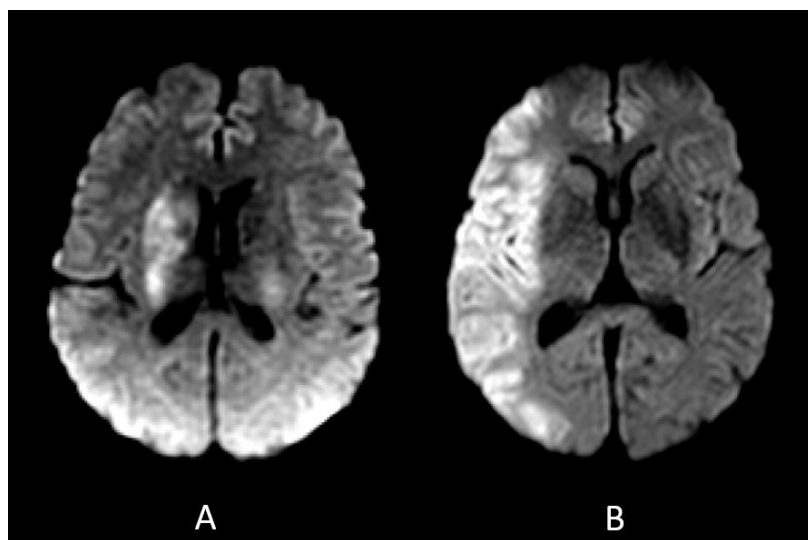


Figure 12. Clinical outcome is associated with stroke location. Initial DWI of two patients with similar initial NIHSS scores but different functional outcomes. A: DWI of a 66-year-old female with ischemic stroke showed restricted diffusion in the right basal ganglia. Admission NIHSS score: 20; mRS at 3 months: 4; lesional volume: 21.7 mL. B: DWI of a 59-year-old

male with ischemic stroke showed restricted diffusion in the right cortical MCA region. Admission NIHSS score: 18; mRS at 3 months: 1; lesional volume: 166.2 mL.

Infarct location are investigated in two aspects: hemispheric involvement and acute infarction location.

Ischemic strokes in different hemispheres can cause distinct deficits depending on the region involved. Studies have shown conflicting results regarding the effect of hemispheric lateralization on stroke outcome. On the one hand, right hemispheric involvement was reported to predict worse functional outcomes. Goto et al. analyzed 183 patients with small or medium-sized infarction and showed that the locomotion outcome was poorer in patients with a right hemispheric infarction: 64.9% of right hemisphere versus 82.1% of left hemisphere stroke patients were able to walk independently after rehabilitation (97). On the other hand, no difference in functional outcome between patients with right or left hemisphere stroke has been demonstrated in other studies (98, 99). Fink et al. analyzed 1644 patients from the Virtual International Stroke Trials Archive. While baseline NIHSS score was higher for left hemisphere patients, no relationship with stroke lateralization and functional outcomes was observed (98). In addition, affected hemisphere lateralization also impacts clinical severity. Fink JN et al. reported that for patients with NIHSS score of 0 to 5, the lesion volume of right hemisphere stroke was greater than that of left-sided lesions (8.8 versus 3.2 mL) (41).

The ASPECTS is one approach that incorporates the precise lesion location to stroke outcomes. Beare R et al. analyzed 185 patients and illustrated the importance of M2 region (MCA cortex lateral to insular ribbon) to disability (100). Phan TG et al. analyzed data from the NINDS rt-PA Study and demonstrated that involvement of M6 region (primary motor cortex / parietal lobe) or lentiform nucleus increases the odds of disability (101). Rangaraju S et al. also demonstrated the importance of the role of right M6 region and left M4 region (superior frontal) in clinical outcome (102). The advantage of ASPECTS is its facility; a trained professional can calculate fast on CT or DWI. There is also effort to calculate ASPECTS automatically (103), which will simplify the process further. However, the ischemic location estimation using ASPECTS is not accurate enough.

More precise assessment of infarct location was investigated in a number of studies. An analysis of patients from MR CLEAN trial demonstrated that the association between infarct volume on follow-up noncontrast CT and clinical outcome was strengthened by accounting

for the mRS relevance of the affected brain areas (104). A pooled analysis of the EPITHET (Echo-planar Imaging Thrombolytic Evaluation Trial) and DEFUSE studies using Classification and Regression Tree demonstrated that the important regions of nonfavorable outcome were: in the left hemisphere, the uncinate fasciculus, the precuneus and the angular gyrus, and in the right hemisphere, the parietal lobe and the putamen (105). Voxel-based method was used in the identification of important infarct location. Payabvash et al. used voxel-based lesion symptom mapping and showed that infarction of insula, lentiform nuclei and middle corona radiata tend to have larger volumes, more severe symptoms and worse outcomes (106). Bentley et al. reported that low recovery rates were associated with lesions to bilateral parietal, right insula, medial frontal, capsule and brainstem (107). Wu et al. analyzed 490 subjects and showed that injury to white matter (corona radiata, internal and external capsules, superior longitudinal fasciculus, and uncinate fasciculus), postcentral gyrus, putamen, and operculum were implicated in poor functional outcome (108). In another study by Cheng et al., corona radiata, internal capsule and insula in both hemispheres, right inferior temporal gyrus and left superior temporal gyrus have been found to influence functional outcome (109). However, even though the integration of infarct location has been suggested to enhance the prediction of clinical outcome, it has not been applied to guide patient management, may be due to the lack of data on pretreatment images.

2.2.2. PWI

(1). Principle of PWI

PWI is another useful sequence for the acute ischemic stroke evaluation. Dynamic susceptibility contrast is one of the main approaches of PWI used in clinic. It involves a rapid intravenous injection of a paramagnetic contrast agent (e.g. gadolinium [Gd] chelate) and a series of measurements of signal during the pass of the bolus through the brain tissue. The model used for perfusion quantification is based on the kinetic for non-diffusible tracers and relies on the assumption that the contrast agent remains intravascular in the presence of an intact brain-blood barrier. The intravascular compartment of contrast agent creates strong, microscopic susceptibility gradients, which causes signal loss in T2- or T2*-weighted MR images until the peak signal change. After the minimum signal is reached, the signal intensity returns gradually to the baseline value (110). The dynamic susceptibility contrast -MRI signal intensity-versus-time curve representing the hemodynamic of the contrast agent is demonstrated in Figure 13.

In dynamic susceptibility contrast -MRI, a bolus of a Gd-based contrast agent can reach the brain approximately 10-15 seconds after the venous injection, creating a signal decrease of about 10-20 seconds or longer. To record the tracer concentration during the first passage, images must be acquired at a fast rate, which is usually of the order of several seconds. Rapid imaging acquisition technique like EPI can be used to achieve fast acquisition (110).

A series of parameters can be calculated for quantifying the perfusion status according to the first pass curve:

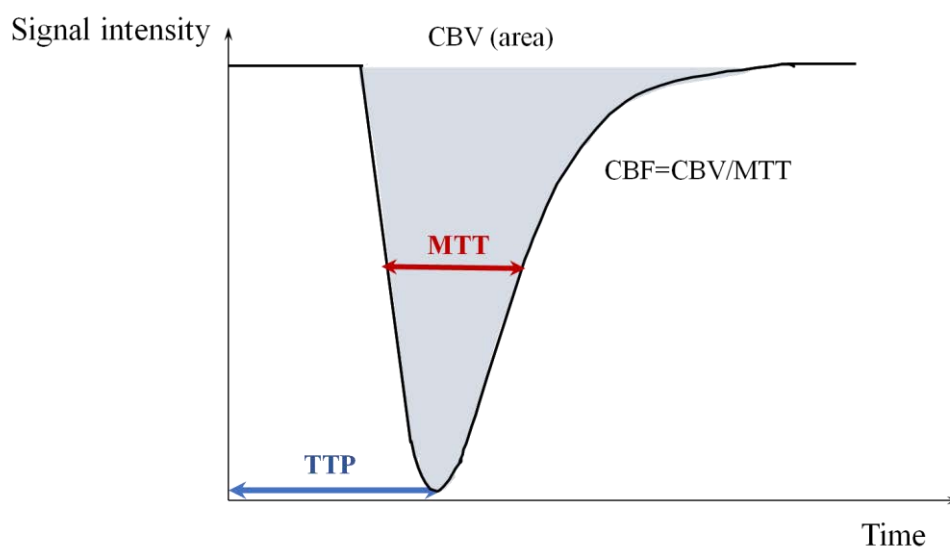
Time to peak (TTP): time corresponding to the maximum value of the contrast agent concentration in the tissue

Mean transit time (MTT): the mean passing time of the contrast agent bolus represented by the time at mid-height of the signal decay curve

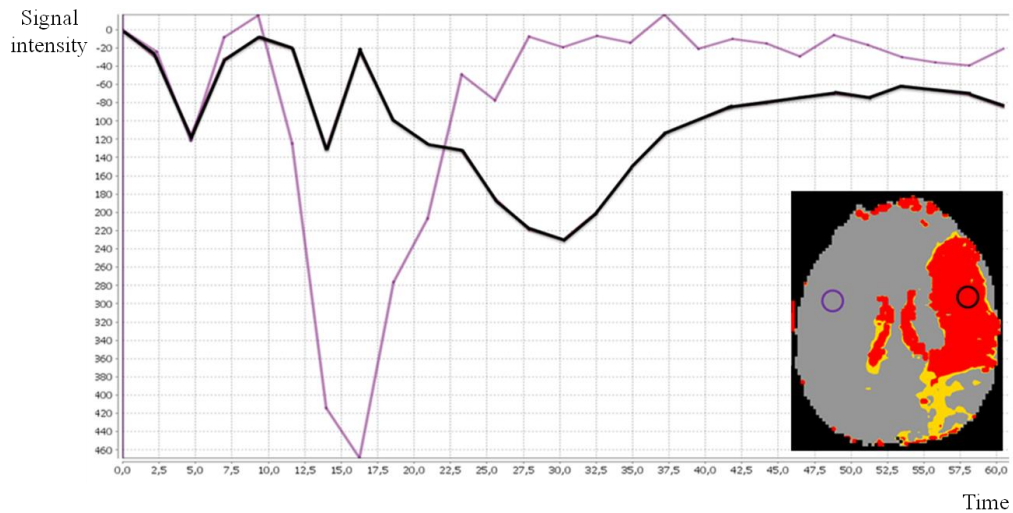
Cerebral blood volume (CBV): the volume of blood in a given amount of brain tissue, it is determined by the area under the signal decay curve

Cerebral blood flow (CBF): the rate at which the blood passes through the brain tissue, it corresponds to the ratio of CBV/MTT

Time to maximum (Tmax): the delay between the contrast agent arrives the tissue and the arterial input function (AIF) after deconvolution (111) (Figure 14)



A



B

Figure 13. A: Diagram demonstrating the hemodynamic of the contrast agent obtained with dynamic susceptibility contrast -MRI. The signal intensity-versus-time curve of the first pass of a bolus of contrast agent is depicted. The MR signal intensity decreases when the contrast agent passing through the microvasculature. After the minimum signal is reached, the signal intensity returns gradually to the baseline value. Several parameters could be calculated according to the curve: TTP, MTT, CBF and CBV.

B: Example of the signal intensity-versus-time curve in an ischemic stroke patient with left MCA occlusion. Compared to the reference region (depicted by the purple curve), the ischemic region (depicted by the black curve) presented prolonged MTT and TTP, and decreased CBV.

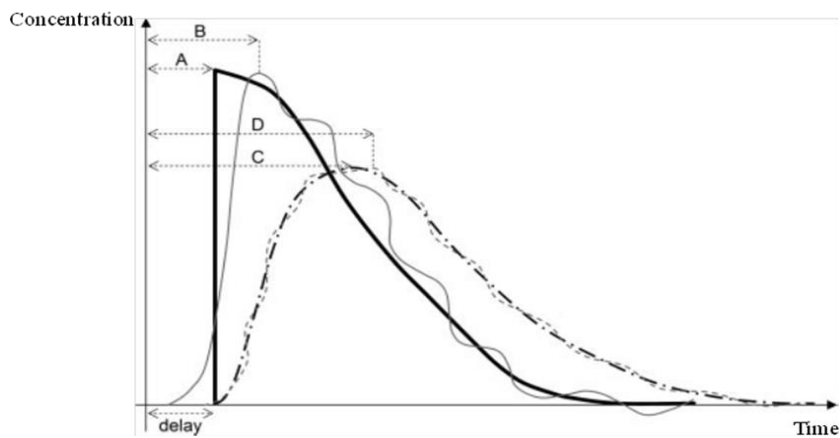


Figure 14. The contrast agent concentration-versus-time curve (after deconvolution). The time delay A represents the ideal Tmax. The time=0 corresponds to the arterial input function arrival time. (111)

(2). PWI in ischemic stroke

PWI is an essential sequence in the diagnostic workup of ischemic stroke to evaluate the perfusion status of brain tissue. The parameters mentioned before can be applied to give insights into the hemodynamic status of tissue. (Figure 15) At the hyperacute phase of ischemic stroke, the cerebral perfusion pressure decreases; CBV can be normal or even slightly increased due to an autoregulatory response; CBF remains normal or decreased depending on the success of the compensating autoregulatory vasodilatation; and MTT/TTP/Tmax will be delayed. The infarcted tissue has decreased CBF/CBV and delayed MTT/TTP/Tmax.

Different PWI parameters are used to distinguish the penumbra and the ischemic core. However, no consensus on the parameter thresholds has been achieved. Tmax is currently the most commonly used parameter to define penumbra. It has the advantage of been measured individually with the use of the AIF. Tmax > 2s was used in EPITHET and DEFUSE study to indicate the hypoperfused brain tissue (85,86). Olivot et al. tested 4 predefined Tmax thresholds to calculate the volume of penumbra. They showed that Tmax delay threshold in the range of 4 to 6 seconds provides the best estimation for the hypoperfused brain tissue in acute phase (112). In a comparative study of PWI and PET, Tmax > 5.5 seconds was demonstrated as the best threshold for penumbra flow (< 20 mL/100 g/min on PET CBF) (113). Tmax > 6 seconds was used in several studies to define the critically hypoperfused tissue (36,114). A threshold of MTT delay > 4 seconds beyond the contralateral hemisphere and TTP > 4 and 6 seconds were applied in other studies to define the hypoperfusion (115,116).

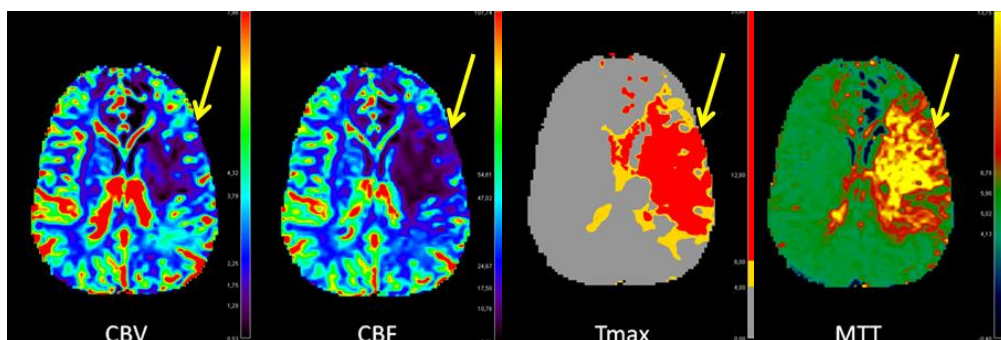


Figure 15. PWI of an ischemic stroke patient with occlusion of left MCA within 4 hours of symptom onset. Different parameter maps are derived: the CBV and CBF are decreased in the left MCA region, while Tmax and MTT are delayed. (Images are post processed by Olea Sphere®)

2.2.3. PWI-DWI mismatch

In general, the hypersignal region on DWI is considered as the ischemic core at the acute stage of stroke, and the hypoperfused region detected on PWI is normally larger than the DWI abnormalities. The difference between the DWI and PWI abnormalities is named PWI-DWI mismatch, which can be used to estimate the penumbra. (Figure 16)

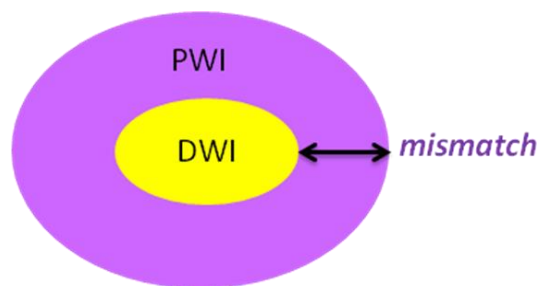


Figure 16. Schema demonstrating the PWI-DWI mismatch. It is a hypoperfused region where signal intensity on DWI is normal.

The criterion for PWI-DWI mismatch is various in different studies:

- DEFUSE/EPITHET: $\text{Volume}_{\text{PWI}}(T_{\text{max}} > 2\text{s}) / \text{V}_{\text{DWI}} > 1.2$; $\text{V}_{\text{PWI}} - \text{V}_{\text{DWI}} > 10\text{mL}$
- DEFUSE 2: $\text{V}_{\text{PWI}}(T_{\text{max}} > 6\text{s}) / \text{V}_{\text{DWI}} > 1.8$; $\text{V}_{\text{PWI}} - \text{V}_{\text{DWI}} > 15\text{mL}$; $\text{V}_{\text{DWI}} < 70 \text{ mL}$; volume of severe hypoperfusion lesion ($T_{\text{max}} > 10\text{s}$) $< 100\text{mL}$
- DEFUSE 3: $\text{V}_{\text{PWI}}(T_{\text{max}} > 6\text{s}) / \text{V}_{\text{DWI}} > 1.8$; $\text{V}_{\text{PWI}} - \text{V}_{\text{DWI}} > 15\text{mL}$; $\text{V}_{\text{DWI}} < 70 \text{ mL}$
- SWIFT PRIME: $\text{V}_{\text{PWI}}(T_{\text{max}} > 6\text{s}) / \text{V}_{\text{DWI}} > 1.8$; $\text{V}_{\text{PWI}} - \text{V}_{\text{DWI}} > 15\text{mL}$; $\text{V}_{\text{DWI}} < 50 \text{ mL}$; volume of severe hypoperfusion lesion ($T_{\text{max}} > 10\text{s}$) $< 100\text{mL}$

PWI-DWI mismatch is useful in selecting appropriate candidate for reperfusion therapy, in order to achieve good clinical outcome and prevent deleterious effects. Studies on PWI-DWI mismatch for stroke patients with thrombolysis and/or thrombectomy are listed in Table 1. EPITHET and DEFUSE are two important studies exploring intravenous thrombolysis using rtPA within 3 to 6 hours of symptom onset. DEFUSE study recruited 74 ischemic stroke

patients and demonstrated that early reperfusion increased the odds of achieving a favorable clinical response only in patients with a PWI-DWI mismatch, and even more in patients with target mismatch profile (i.e. a baseline lesion volume on DWI < 100 mL and lesion volume on PWI < 100 mL defined by Tmax > 8 seconds) (85). EPITHET study analyzed 101 patients and suggested that thrombolysis was associated with lower infarct growth and increased reperfusion in patients with PWI-DWI mismatch (86). Trials on desmoteplase, for example the Desmoteplase In Acute Ischemic Stroke trial (DIAS) (117) and the Dose Escalation of Desmoteplase in Acute Stroke (DEDAS) (118), have also shown positive role of PWI-DWI mismatch in patient selection for achieving better clinical outcome (117,118).

PWI-DWI mismatch can last several hours after symptom onset. Its presence indicates that there exists the brain tissue which can be salvaged, thus may help to extent the treatment window of ischemic stroke. Recently, DEFUSE 3 study used PWI-DWI mismatch as a criteria for recruiting patients for reperfusion treatment 6 to 16 hours after stroke onset, demonstrating that endovascular thrombectomy plus intravenous thrombolysis is the better treatment compared to intravenous thrombolysis alone (36). Overall, PWI-DWI mismatch plays a promising role in selecting stroke patients for reperfusion. However, there is no evidence proving that patients without PWI-DWI mismatch should be excluded from treatment.

Table 1. Trials on PWI-DWI mismatch in patients treated by thrombolysis or thrombectomy

	Study design	Therapy	Time window	Number of patients	Outcome measurement	Main findings
EPITHET	Phase II, RCT; patients treated regardless of MRI findings	Thrombolysis (Alteplase) or placebo	3-6 h	101	infarct growth between DWI and the day 90 T2 lesion; reperfusion, neurological outcome	Alteplase was non-significantly associated with lower infarct growth and significantly associated with increased reperfusion in patients who had mismatch.
DEFUSE	Phase II, open-label study; patients treated regardless of MRI results	Thrombolysis (Alteplase)	3-6 h	74	Early reperfusion on PWI; clinical response assessed by NIHSS score	Early reperfusion was associated with good clinical outcomes in patients with mismatch
DIAS	Phase II, dose-finding randomized trial; only patients with mismatch treated	Thrombolysis (Desmoteplase) or placebo	3-9 h	104	Reperfusion on PWI and clinical outcome	Identification the effectiveness of desmoteplase in patients with mismatch and the safety dose
DEDAS	Similar to DIAS	Thrombolysis (Desmoteplase) or placebo	3-9 h	37	Reperfusion on PWI and clinical outcome	Similar to DIAS
DIAS-2	Phase III, RCT; only patients with mismatch were included	Thrombolysis (Desmoteplase) or placebo	3-9 h	186	Clinical response assessed by NIHSS score	Failed to show a benefit of desmoteplase in stroke patients
SWIFT PRIME	Phase III, RCT; 71 patients were selected by mismatch	Thrombectomy plus thrombolysis or thrombolysis alone	< 6 h	196	Clinical outcome assessed by mRS	Thrombectomy plus thrombolysis resulted in better functional outcomes than thrombolysis alone in patients with proximal arterial occlusion
DEFUSE-3	Phase III, open-label study; only patients with mismatch were included	Thrombectomy plus thrombolysis or thrombolysis alone	6-16 h	182	Clinical outcome assessed by mRS	Similar to SWIFT PRIME

2.2.4. T2-FLAIR sequence

T2-FLAIR image is a common sequence in the standard protocol of ischemic stroke evaluation. It is similar to T2WI but with suppression of CSF, thus it reduces the partial volume caused by CSF. Abnormalities remain bright on FLAIR images while normal CSF is attenuated and presented as hyposignal. It is very sensitive to subacute or chronic ischemic lesions, but its diagnostic value in the first hours of stroke onset is relatively limited. Its role in the acute stroke evaluating is as following.

The FLAIR image can detect the global brain parenchymal lesion, thus providing information on stroke subtype. For example, a patient with high burden of small vessel disease can develop deep perforating stroke.

It has been shown that stroke patients within 6 hours of symptom onset with a visible lesion on DWI but no visible FLAIR lesion, named DWI/FLAIR mismatch, have greater probability to be in a time window 3 hours or less (specificity 93%) (119). (Figure 17) Therefore, DWI/FLAIR mismatch was proposed as an indicator of stroke lesion age in case the onset time is unknown, and to identify those who may benefit from reperfusion therapy. However, the hyperintensities on FLAIR images are sometimes subtle and difficult to distinguish. Caution should be payed when defining the DWI/FLAIR mismatch.

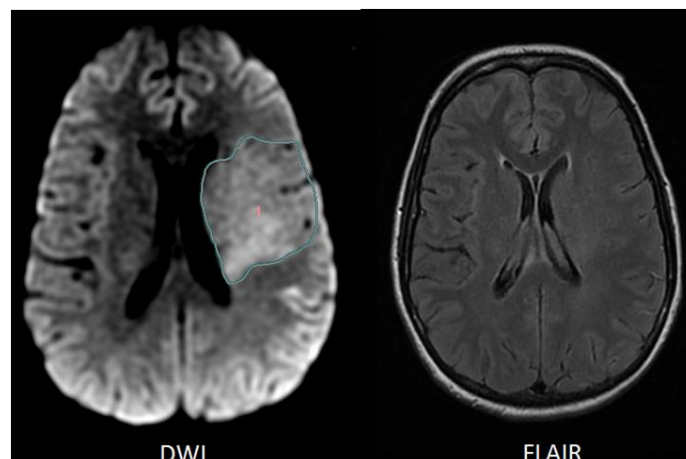


Figure 17. FLAIR and DWI images of an acute ischemic stroke patient imaged after 3 hours of symptom onset. Hypersignal can be detected in the territory of left MCA on DWI, while no obvious hyperintensity is observed on FLAIR image.

Vascular hyperintensities on the T2-FLAIR images is another approach of evaluating acute ischemic stroke. (Figure 18) It is mostly seen in stroke patients with large vessel occlusion and in general is distal to the stenotic artery. It may indicate slow blood flow passing collateral vessels and may be used as a surrogate of collateral status. Hohenhaus et al. demonstrated that the presence of vascular hyperintensities indicated larger ischemic area and proposed that it could be a further surrogate marker for PWI-DWI mismatch and stroke severity (120).

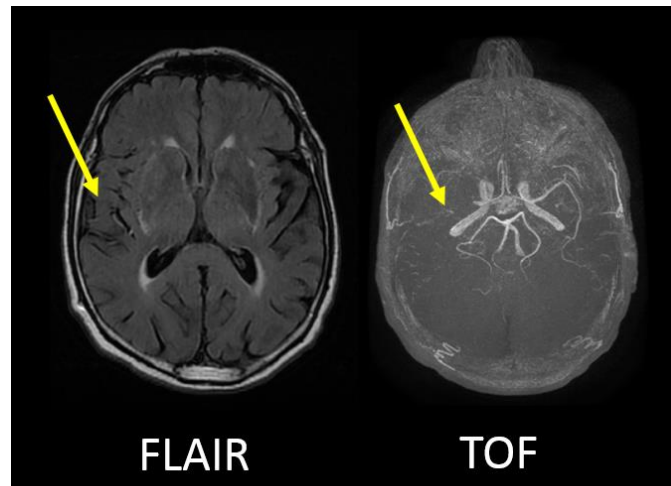


Figure 18. An acute ischemic stroke patient with occlusion of right MCA (shown on TOF). FLAIR image demonstrates the vascular hyperintensities (arrow) in the distal territory of the occluded vessel.

2.2.5. T2*-weighted image

To differentiate ischemic and hemorrhagic stroke, CT is considered as reference imaging modality. However, MRI also has high accuracy in hemorrhagic stroke identification. T2*-weighted image is one of the most important sequences to detect intracranial hemorrhage and intraluminal thrombus formation. The detection of acute hemorrhage is based on the paramagnetic effect of deoxyhemoglobin in the red blood cells, which produces inhomogeneity of the magnetic field and causes a susceptibility effect. Therefore there exists a signal loss on T2*-weighted images (48).

Besides, intraluminal thrombus can be detected within the occluded vessel in the acute phase of ischemic stroke, providing fast diagnosis of acute thrombotic occlusion. (Figure 19)

Finally, T2* is a sensitive sequence to detect the cerebral microbleeds. The microbleeds appear as round hypointense foci because of the paramagnetic effect of hemosiderin. The presence of microbleed is associated with a spontaneous intracerebral hemorrhage and higher probability of hemorrhagic transformation after thrombolytic therapy (121). An example is demonstrated in Figure 20. However, the criterion of microbleed in excluding stroke patients from thrombolytic therapy remains unclear.

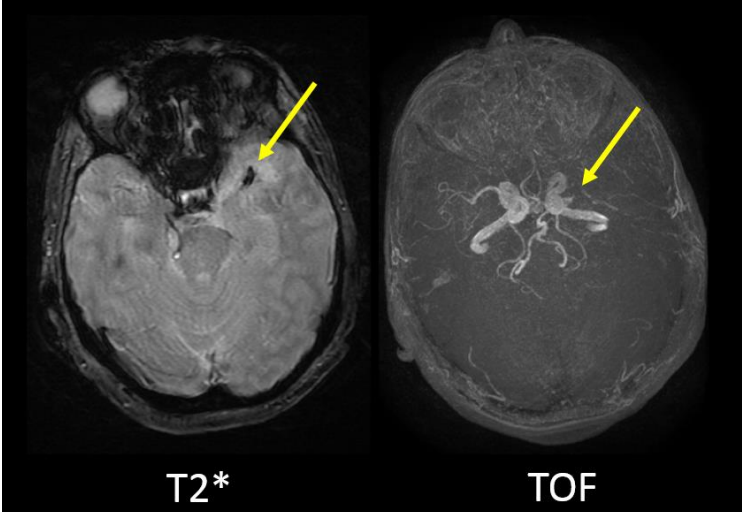


Figure 19. Intraluminal thrombus detected within the left MCA (arrow) on T2* in an acute ischemic stroke patient. TOF demonstrates the occlusion of the left MCA.

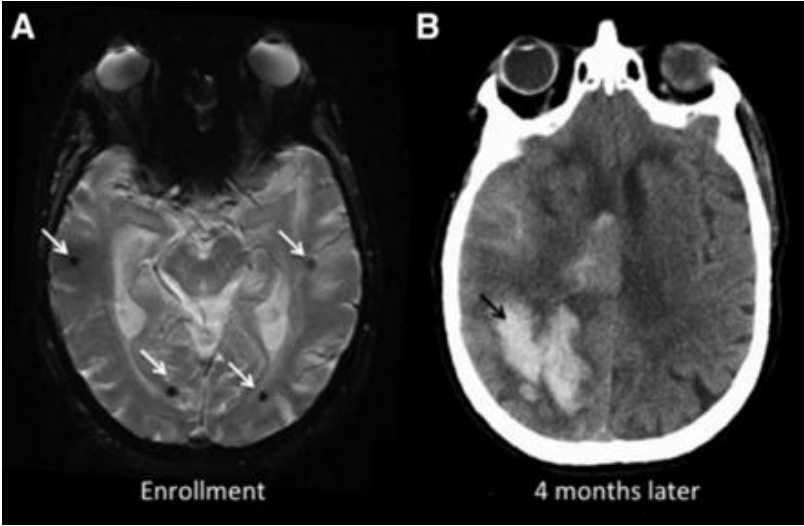


Figure 20. Baseline and follow-up imaging of a lobar microbleed-only patient who later developed intracerebral hemorrhage. An 85-year-old woman with no prior stroke presented multiple isolated lobar microbleeds on MRI (white arrows, A). Four months later, the patient

had a right-sided posterior lobar intracerebral hemorrhage (black arrow, **B**). Image from Etten et al. (121).

2.2.6. MR angiography

MR angiography is an essential sequence performed in stroke diagnosis workup for vascular evaluation. It can demonstrate the location and extension of the vessel occlusion and therefore provide information in patient selection for reperfusion therapy. 3D-time-of-flight (TOF) is a technique widely used in clinic for intracranial vessel assessment, without the need to administer contrast agent. It is based on the phenomenon of flow-related enhancement of spins entering to an imaging volume, which results in increased signal. It is reliable to identify proximal large-vessel occlusion but less powerful in detecting distal artery occlusion or stenosis. Maximum intensity projection (MIP) is a reconstruction technique usually used to create 3D MR angiography. An example of TOF image and MIP projection is presented in Figure 21.

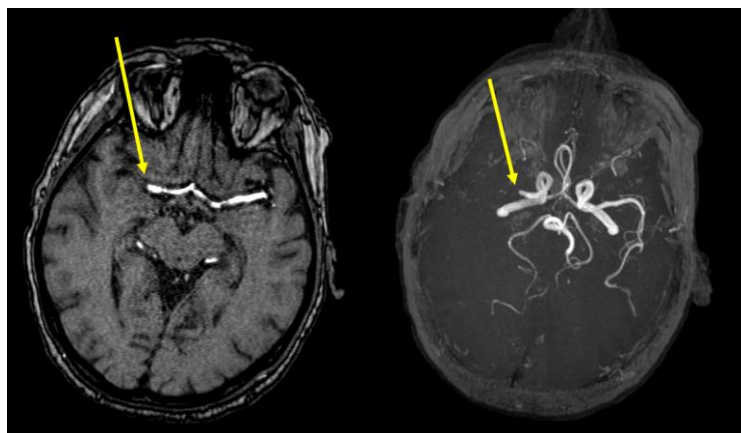


Figure 21. Images demonstrating the occlusion of the proximal right MCA (arrows) in an acute ischemic stroke patient. Left image presents the axial TOF sequence. Right image is the MIP in transverse projection.

3. Synopsis of THRACE study

This thesis is working on the database of the THRACE study. It is a randomized controlled trial done in 26 centers in France from 2010 to 2015.

3.1. Objective

The primary objective of the THRACE study is to compare the standard treatment – intravenous thrombolysis alone – with intravenous thrombolysis plus mechanical

thrombectomy in the acute phase of ischemic stroke due to proximal arterial occlusion. The secondary objective is to determine the cost and effectiveness ratio of these two approaches.

3.2. Patients inclusion

Patients with acute ischemic stroke were eligible for inclusion if they were aged 18 to 80 years; had a NIHSS score of 10 to 25; had an occlusion of the intracranial ICA, the M1 segment of the MCA, or the superior third of the basilar artery confirmed by images; could be administered intravenous thrombolysis within 4h of symptom onset; and if thrombectomy could be initiated within 5 h of symptom onset. The time limit for intravenous thrombolysis initiation was initially within 3 h of symptom onset, then it was extended to 4 h on May 14, 2011 (31). (See Appendix for complete inclusion and exclusion criteria)

3.3. Procedures of the study

Patients were randomized (1:1) as soon as possible during intravenous thrombolysis to receive intravenous thrombolysis and mechanical thrombectomy (IVTMT group) or intravenous thrombolysis alone (IVT group). Randomization was done with a computer-generated sequence at the coordination center by a computer analyst who was masked to the investigation centers and to the patients.

All patients received intravenous thrombolysis as per standard care — i.e., 0.9 mg/kg of alteplase (maximum 90 mg), with an initial bolus of 10% of the total dose, and then infusion of the remaining dose over 60 min, irrespective of group assignment. For the IVTMT group, if patients had clinically significant improvement, defined as a decrease in the NIHSS score of at least 4 points, angiography and thrombectomy were cancelled. Otherwise, angiography was done and followed by thrombectomy if the modified Thrombolysis in Cerebral Infarction (mTICI) grade was less than 2. The mTICI scale scores perfusion from 0 (no perfusion) to 3 (complete antegrade perfusion of the downstream territory).

For baseline images, MRI or CT were done according to the local routine at each participating center. For MRI, the mandatory sequences were DWI, FLAIR, T2*, and TOF. For CT, an acquisition without contrast and CT angiography evaluating the intracranial vessel were necessary. PWI was highly recommended but not mandatory. Follow-up images were obtained at 24h, discharge/day 7. NIHSS score was assessed at baseline, 24h, discharge/day 7, and 3 months. mRS was evaluated at 3 months.

3.4. Main results of THRACE study

402 patients were included in the final analyses of the THRACE study, 202 patients in the IVT group and 200 in the IVTMT group. (Figure 22) The results showed that an approach combining mechanical thrombectomy with standard intravenous thrombolysis provided a significantly higher rate of functional independence at 3 months (defined by a score of 0-2 on mRS) with no evidence of increased mortality than intravenous thrombolysis alone. Bridging therapy seems to be beneficial and should be considered for patients with large-vessel occlusions of the anterior circulation, irrespective of their age, sex, clinical severity, or intracranial location of the occlusion. (31)

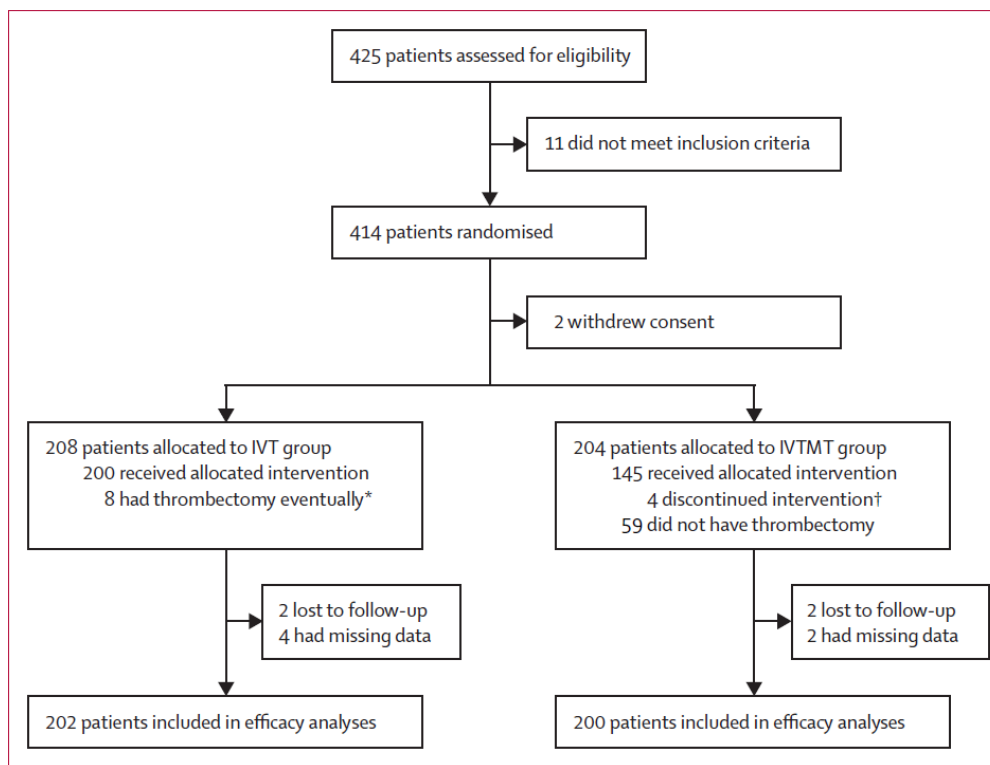


Figure 22. THRACE trial profile. (31)

4. Working environment

4.1. Laboratory IADI

This thesis was carried out in the laboratory IADI, head Pr. Jacques FELBLINGER. It is a component of the university of Lorraine and INSERM (Institut National de la Santé et de la Recherche Médical) U1254 and is located at CHRU (Centre Hospitalier Régional Universitaire) of Nancy Brabois.

4.2. CIC-IT

This thesis is in collaboration with CIC-IT (Centre d'Investigations Cliniques - Innovations Technologiques), a structure specialized in validation and valorization of MRI methods and technologies. Thanks to CIC-IT, I have the access to the database of the THRACE study, and the software that I used for this thesis: Archimed3, ORS[®] (Object Research Systems) Visual[®] (Montreal, Canada), Olea Sphere[®] (Olea Medical SAS, La Ciotat, France), MATLAB (2013a, Mathworks Inc., Sherborn, MA, USA), SPM12 (statistical parametric mapping, Wellcome Trust Center for Neuroimaging, London, United Kingdom). Moreover, the home-made software dedicated to segment the ischemic lesion was developed by CIC-IT.

Chapter 2

The role of MRI in the evaluation of brain tissue viability

Introduction

In this chapter, we will discuss the role of diffusion and perfusion parameters in predicting brain tissue viability in ischemic stroke, in order to provide evidence in selecting patients with salvageable tissue as the target for the reperfusion therapy.

Diffusion and perfusion parameters have been investigated in previous studies for tissue viability prediction. It has been widely accepted that the abnormal hyperintense tissue on DWI are prone to infarction. However, part of this tissue could be salvaged if blood flow is restored at an early time point (122). PWI-DWI mismatch has been proposed to estimate the penumbra and has been used to select appropriate candidates for reperfusion in several clinical trials, though different criteria of mismatch were applied (81, 82, 114, 115). ADC has been suggested for identification of salvageable tissue. Purushotham et al. determined an ADC value of $620 \times 10^{-6} \text{ mm}^2/\text{s}$ (sensitivity 69%, specificity 78%) for discriminating ischemic core from non-core in abnormal hyperintense tissue on DWI using voxel-based analyses (72). However, Loh et al. reported that 13 in 26 ischemic patients presented DWI reversal, no absolute ADC threshold could be identified to predict the fate of tissue (115). Different PWI parameters were also analyzed to evaluate tissue viability. Olivot et al. suggested that $T_{\text{max}} > 2\text{s}$ appeared to provide a reliable estimate of ischemic penumbra (112). Median CBF ranged from 18 to 37 mL/100g/min and MTT from 1.8 to 8.3 seconds relative to the contralateral side were suggested in other studies to identify the tissue at risk (123). However, the perfusion parameters are highly variable and their thresholds are lack for consistency among studies. This is mainly because of the small sample size, the different definition of tissue status, the different physiological condition between brain tissue (grey matter and white matter) and among different subjects, and also the dynamic process of ischemic stroke. Currently, there has been no consensus on MRI-based tissue viability thresholds in ischemic stroke.

In order to investigate the role of the diffusion and perfusion parameters in tissue viability prediction, we analyzed patients in the THRACE study who underwent baseline DWI/PWI and day-7 MRI/CT. We analyzed both the initial abnormal DWI hyperintensity region and the PWI-DWI mismatch region, to study the parameters for salvageable tissue prediction.

Predicting tissue viability in ischemic stroke with diffusion and perfusion MRI

Rationale and Objectives: Identification of salvageable tissue is crucial for acute ischemic stroke evaluation. MRI could be very useful but its role has not been fully established. We aimed to assess whether parameters of diffusion-weighted imaging and perfusion-weighted imaging could predict tissue viability.

Patients and Methods: 36 ischemic stroke patients who underwent baseline MRI and day-7 images were included. Both initial abnormal diffusion areas and perfusion-diffusion mismatch areas were separated into parts which presented as normal tissue on day-7 images and those which evolved into infarction. The roles of diffusion and perfusion parameters in predicting tissue viability were analyzed at region-of-interest level. Receiving operating characteristic curves were performed to select appropriate parameters and determine the optimal thresholds.

Results: 7/36 patients presented normalized tissue in initial abnormal diffusion areas. 34/36 patients had normalized tissue in mismatch areas. In initial abnormal diffusion areas, the area under the curve of absolute apparent diffusion coefficient, relative apparent diffusion coefficient, relative cerebral blood flow and relative cerebral blood volume were 0.79, 0.81, 0.76 and 0.75; the thresholds of $623 \times 10^{-6} \text{ mm}^2/\text{s}$, 0.80, 0.47 and 0.82 were selected to identify salvageable tissue, respectively. In perfusion-diffusion mismatch areas, the area under the curve of absolute apparent diffusion coefficient, relative apparent diffusion coefficient and relative cerebral blood flow were 0.75, 0.72 and 0.68, with thresholds of $785 \times 10^{-6} \text{ mm}^2/\text{s}$, 0.98 and 0.63 selected, respectively.

Conclusion: Our study suggested that apparent diffusion coefficient and relative cerebral blood flow were optimal candidates for tissue viability prediction in acute ischemic stroke, in both initial abnormal diffusion areas and perfusion-diffusion mismatch areas.

Keywords: Stroke; Magnetic resonance imaging; Diffusion Magnetic Resonance Imaging; Cerebrovascular Circulation; Tissue survival

Introduction

Magnetic resonance imaging (MRI) is increasingly used in ischemic stroke assessment. Diffusion-weighted imaging (DWI) has been established as the most accurate technique for acute ischemic stroke diagnosis.¹ Perfusion-weighted imaging (PWI) may complete the stroke evaluation by providing tissue microcirculation information.²

Ischemic penumbra is a region at the risk of infarction but still has the potential to be salvaged.³ As the target of acute phase treatment, penumbra evaluation is of great clinical importance. PWI-DWI mismatch has been assumed to represent the penumbra and has been included as an evaluation index for patient selection in several clinical trials.⁴⁻⁷ However, the substitution of penumbra by PWI-DWI mismatch remains uncertain. On the one hand, the initial DWI hyperintensity area consists not only the irreversibly damaged “core”, but also tissue at risk which could be salvaged if blood flow is restored at an early time point.⁸ On the other hand, PWI abnormality often overestimate the penumbra by including oligemia.⁹ Therefore, tissue viability should be assessed more precisely other than PWI-DWI mismatch.

Apparent diffusion coefficient (ADC) has been proposed to differentiate tissue at risk and the ischemic core. Purushotham et al. suggested a threshold of $620 \times 10^{-6} \text{mm}^2/\text{s}$ for delineation of ischemic core.¹⁰ However, this point of view was challenged, previous study has demonstrated that the fate of tissue could not be predicted based on the ADC value alone.¹¹ Widely-varied thresholds of different perfusion parameters were presented to evaluate tissue viability. Cerebral blood flow (CBF) ranged from 18 to 37 mL/100g/min and mean transit time (MTT) ranged from 1.8 to 8.3 seconds relative to the contralateral side were reported to identify the tissue at risk.¹² A threshold of $T_{\text{max}} > 2\text{s}$ delay was demonstrated to be a reliable estimate of ischemic penumbra.¹³ Currently, there is no consensus on MRI-based tissue viability thresholds in ischemic stroke.

In our study, we sought proper diffusion and perfusion parameters which could predict tissue viability in both initial abnormal diffusion areas and PWI-DWI mismatch areas. We analyzed acute ischemic stroke patients due to proximal intracranial arterial occlusion. These patients generally present more severe clinical symptoms and carry a worse prognosis, thus the treatment decision needs to be made properly and immediately.

Materials and methods

Patient Selection

We analyzed patients in the THRACE study (Clinical Trial Registration-URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01062698), a multicentric study in France underwent from 2009 to 2015, comparing intravenous thrombolysis plus mechanical thrombectomy and intravenous thrombolysis alone in patients with acute ischemic stroke due to proximal arterial occlusion, aged 18 to 80 years, and with a NIHSS (National Institutes of Health Stroke Scale) score of 10 to 25. The study design and patient inclusion criteria have been described in detail previously.¹⁴ The study protocol was approved by the CPP (Comité de Protection des Personnes) III Nord Est Ethics Committee and the research boards of the participating centers. All patients or their legal representatives provided written informed consent. In this study, we included patients who received baseline MRI exam, including DWI, PWI, fluid attenuation inversion recovery (FLAIR) and time-of-flight MR angiography, followed by MRI or computed tomography (CT) on day-7.

In 412 patients included in the THRACE study, 36 patients finally met the inclusion criteria of our work (Figure 23). Compare to the final sample, excluded patients were similar in terms of age, sex, baseline NIHSS score and time from stroke onset to imaging. All the included patients received intravenous thrombolysis, 12 patients also received an additional mechanical thrombectomy.

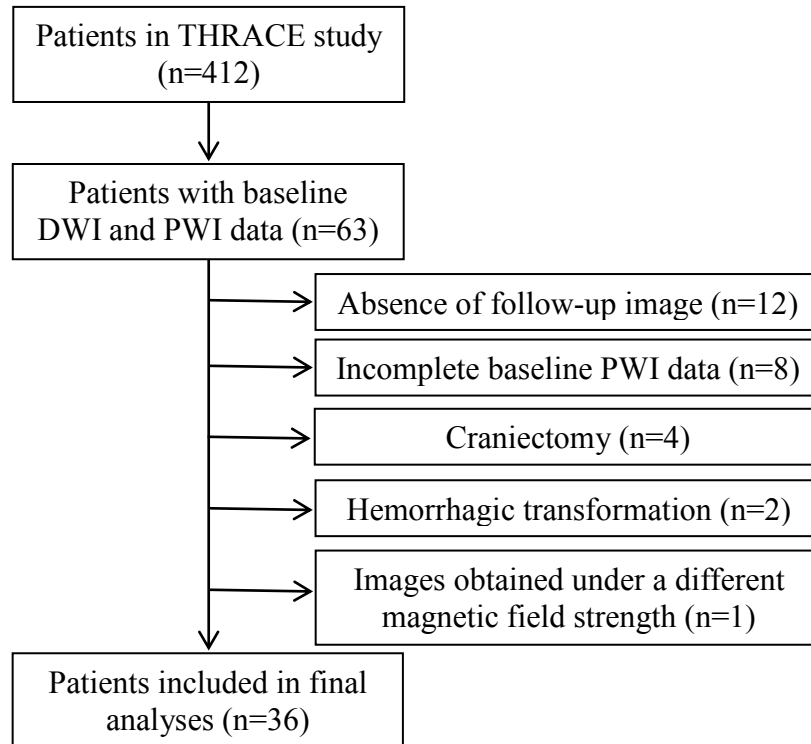


Figure 23. Patient selection flowchart. DWI: diffusion-weighted imaging; PWI: perfusion-weighted imaging

Imaging protocol

Imaging was performed according to the established local routine. MRI was performed on 1.5T MR Scanners (Signa HDxt, General Electric Healthcare, WI, USA; Intera/Achieva, Philips medical systems, Best, the Netherlands). The baseline DWI was performed using a single-shot, pulsed gradient spin echo (PGSE) sequence with echo planar imaging (EPI) read-out (b-value 0 and 1000s/mm²). The baseline PWI data were acquired after a bolus of intravenous gadolinium by using the dynamic susceptibility contrast technique and a single-shot, gradient echo EPI sequence. Day-7 FLAIR sequence was performed in 7 patients to assess the final infarction. The rest 29 patients were evaluated by CT. CT images were non-contrast-enhanced with reconstruction matrix 512×512, resolution 0.4×0.4×1.0mm³ ~ 0.4×0.4×2.5mm³. (LightSpeed VCT, GE medical system, WI, USA; SOMATOM Sensation 16, Siemens AG, Forchheim, Germany; Aquilion ONE, Toshiba, Japan). More details about MRI sequence parameters are listed in Table 2.

Table 2. Parameters of MRI sequences

Sequence	Manufacturer	TE/TR (ms)	slice thickness/gap (mm)	acquisition matrix	field of view (cm ²)
Baseline DWI	GE	82~102/6100~8300*	4~6/0~2*	128×128	24×24~29×29*
	Philips	70~106/2700~3605*	5/1	88×112~127×152*	23×23/24×24
Baseline PWI	GE	30~60/2000~2400*	5~6/0~1*	64×96~96×128*	24×24~28×28*
	Philips	30~40/627~2021*	5~6/0~1*	88×88~86×128*	22×22/23×23
Day-7 FLAIR	GE	152~174/8377~8402*	5~6/0~1*	192×256	24×24
	Philips	140/11000	5/1	186×256	23×23

MRI: Magnetic Resonance Imaging; DWI: Diffusion-Weighted Imaging; PWI: Perfusion-Weighted Imaging; FLAIR: Fluid Attenuation Inversion Recovery. *: ranges of parameter values are presented.

Imaging data analysis

Baseline MRI and day-7 images from the same patient were co-registered by ORS[®] (Object Research Systems) Visual[®] (Montreal, Canada). An experienced neuroradiologist (with experience of reading stroke imaging >5 years, reader 1) checked all the registration results in order to ensure adequate alignment. Post processing of DWI and PWI data was performed in Olea Sphere[®] (Olea Medical SAS, La Ciotat, France). ADC maps were calculated based on DWI data. MTT, CBF, cerebral blood volume (CBV) and Tmax (time to peak of the deconvolved tissue residue function) maps were calculated from PWI data.

The experienced neuroradiologist (reader 1) and a junior neurologist (with experience of reading stroke imaging <5 years) (reader 2), blind to the clinical information, read all the images separately, and manually outlined the 2D abnormal regions on all the pathological slices of the post processed DWI and PWI data as well as coregistered day-7 images. The window level was set to its maximal visual extent of each volume. The criteria to define the abnormal regions in the images were: (1). the abnormal hyperintense areas on baseline DWI which correspond to a decreased ADC value; (2). the hypoperfused tissue on baseline Tmax maps (Tmax > 6s), as proposed by previous study;¹³ (3). the abnormal hyperintensity on day-7 FLAIR images or hypodense areas on day-7 CT data. Baseline FLAIR images were used as references to solve the confusion brought by the "T2 shine-through" effect when delineating

abnormal hyperintense areas on baseline DWI. The PWI-DWI mismatch profile criteria corresponded to $\text{Volume}_{\text{PWI}} / \text{Volume}_{\text{DWI}} > 1.2$ and $\text{Volume}_{\text{PWI}} - \text{Volume}_{\text{DWI}} \geq 10\text{mL}$, according to the criteria used in DEFUSE and EPITHET studies.^{5,6}

Four types of regions of interest (ROIs) were derived from the abovementioned abnormal regions: the initial abnormal diffusion areas which appeared as normal tissue on day-7 image (*DN*) and which evolved into infarction (*DI*), the PWI-DWI mismatch areas which appeared as normal tissue on day-7 image (*MN*) and which evolved into infarction (*MI*). For each types of ROI, mirror regions were drawn in the contralateral hemisphere. All the voxels with $\text{ADC} < 200 \times 10^{-6} \text{ mm}^2/\text{s}$ or $> 1200 \times 10^{-6} \text{ mm}^2/\text{s}$ were considered as artifacts or cerebrospinal fluid and were eliminated. Examples of the ROIs were illustrated in Figure 24.

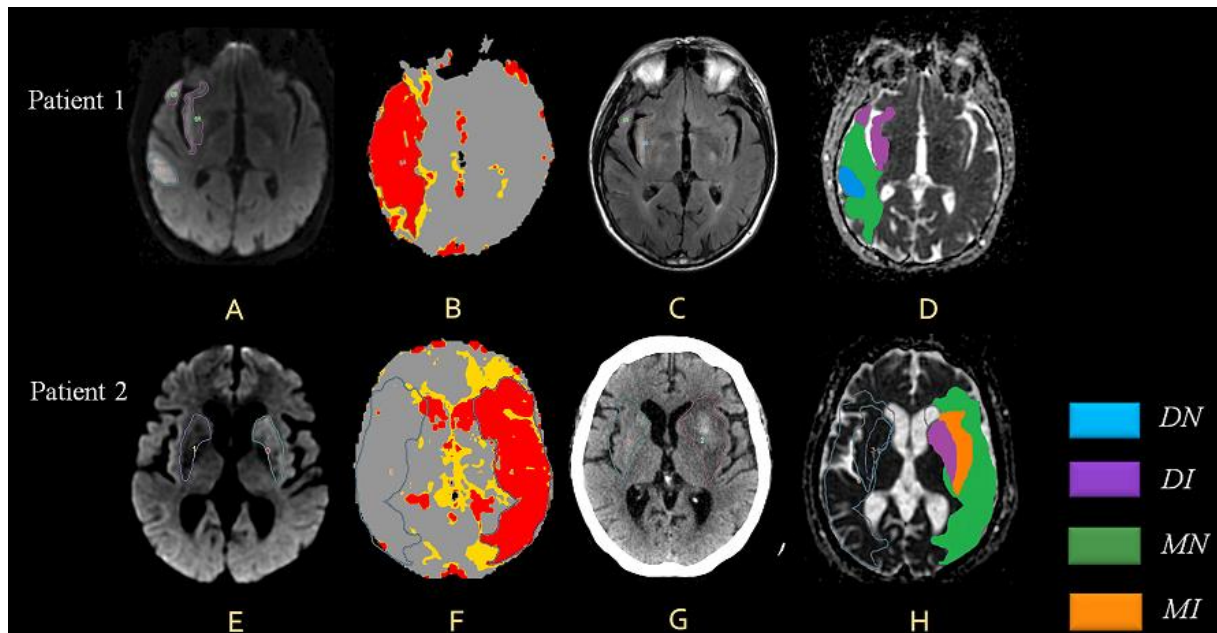


Figure 24. Examples of ROIs. Abnormal regions outlined on baseline DWI data (A, E), Tmax maps (B, F) and day-7 FLAIR/CT images (C, G) in two patients. ROIs derived from these abnormal regions are presented in D and H.

Patient 1: this slice presents the initial abnormal diffusion area with normal intensity on day-7 FLAIR image (*DN*: blue) and which evolved into infarction (*DI*: violet), also the PWI-DWI mismatch area with normal intensity on day-7 FLAIR image (*MN*: green).

Patient 2: besides *DI* and *MN*, this slice presents the PWI-DWI mismatch area which evolved into infarction (*MI*: orange).

ROI-based parameter value comparison

Mean value of ADC (ADC_{mean}), MTT (MTT_{mean}), CBV (CBV_{mean}) and CBF (CBF_{mean}) were calculated for each ROI and the symmetric regions. By dividing the values in each ROI and their corresponding symmetric region, the lesion-contralateral ratios (rADC, rMTT, rCBV and rCBF) were obtained. Parameters in ROIs evolving into infarction on day-7 image were compared with those which did not.

Receiving operating characteristic (ROC) curve analysis

ROC curves of parameters which presented significant difference in ROI-based comparison were plotted, in initial abnormal diffusion areas and in mismatch areas separately. Area under the ROC curve (AUC) was calculated for each parameter. The optimal parameter thresholds distinguishing the regions evolved into infarction and which normalized were selected.

Statistical analysis

Categorical variables were presented as proportions; continuous variables were tested for normality and presented as mean \pm SD if normally distributed, or as median and interquartile range (IQR) if not. Comparisons of ROI-based parameter values were performed by Wilcoxon test. *P*-values were two-sided and $p=0.05$ was chosen as the significance level. ROC curves were plotted by R package pROC.¹⁵ The optimal parameter thresholds were determined by Youden index.¹⁶ To evaluate the reproducibility of two readers, we calculated the intraclass correlation coefficient of ADC_{mean} in each category of ROI. Statistical analyses were performed using statistical software R (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

The included 36 patients were composed of 14 women and 22 men with median age of 71 (IQR 59-77) years. The baseline characteristics were presented in Table 3. 7/36 (19.4%) patients had *DN* tissue, with a volume of 5.29 (IQR 3.35-8.39) mL (i.e. 5.6% of the initial diffusion abnormal areas). 34/36 (94.4%) patients presented *MN* tissue, with a volume of 44.34 (IQR 31.02-61.22) mL (i.e. 72.6% of the mismatch areas).

Table 3. Baseline characteristics of ischemic stroke patients (n=36)

Baseline characteristics	
Age, years	71 (59-77)
Women	14/36 (38.9)
Cardiovascular risk factors	
Arterial hypertension	19/36 (52.8)
Diabetes	4/36 (11.1)
Hypercholesterolemia	18/30 (60.0)
Active smoking	12/31 (38.7)
Baseline NIHSS score	17 (13-20)
Time from stroke onset to baseline imaging, min	110 (93-136)

Continuous variables are presented as median (interquartile range); categorical variables are presented as no. (%). NIHSS: National Institutes of Health Stroke Scale.

ROI-based parameter value comparison

Intraclass correlation coefficient of ROI-based ADC_{mean} between two readers was 0.98 with 95% confidence interval (CI) 0.96-0.99. Accordingly, the following results are based on measurements obtained by reader 1. ADC_{mean} , rADC, rCBF and rCBV were significantly different between *DI* and *DN*: ADC_{mean} was $617.14 \pm 54.74 \times 10^{-6}$ mm²/s in *DI* and $677.21 \pm 65.67 \times 10^{-6}$ mm²/s in *DN* ($p=0.02$); rADC was 0.76 ± 0.05 and 0.84 ± 0.08 respectively ($p=0.01$); rCBF was 0.49 ± 0.15 and 0.63 ± 0.14 respectively ($p=0.03$); rCBV was 0.80 ± 0.32 and 1.04 ± 0.28 respectively ($p=0.04$). ADC_{mean} , rADC and rCBF were significantly different in *MI* and *MN*: ADC_{mean} was $783.04 \pm 37.40 \times 10^{-6}$ mm²/s in *MI* and $821.99 \pm 39.73 \times 10^{-6}$ mm²/s in *MN* ($p=0.001$); rADC was 0.95 ± 0.05 and 0.99 ± 0.04 respectively ($p=0.01$); rCBF was 0.63 ± 0.18 and 0.71 ± 0.16 respectively ($p=0.02$). The other parameters showed no significant differences. Results are listed in Table 4.

Table 4. Parameter values in different ROIs

	ADC _{mean} (10 ⁻⁶ mm ² /s)	rADC	rCBF	rCBV	rMTT
<i>DI</i>	617.14±54.74	0.76±0.05	0.49±0.15	0.80±0.32	1.76±0.63
<i>DN</i>	677.21±65.67	0.84±0.08	0.63±0.14	1.04±0.28	1.79±0.38
mean difference	-56.10	-0.09	-0.14	-0.28	0.00
95% CI of mean difference	[-112.49, -10.59]	[-0.15, -0.02]	[-0.27, -0.03]	[-0.52, 0.00]	[-0.48, 0.47]
<i>p</i> value	0.02*	0.01*	0.03*	0.04*	1
<i>MI</i>	783.04±37.40	0.95±0.05	0.63±0.18	1.02±0.26	1.88±0.63
<i>MN</i>	821.99±39.73	0.99±0.04	0.71±0.16	1.12±0.44	1.77±0.67
mean difference	-39.17	-0.03	-0.11	-0.08	0.14
95% CI of mean difference	[-60.60, -13.37]	[-0.05, -0.01]	[-0.18, -0.01]	[-0.18, 0.03]	[-0.12, 0.41]
<i>p</i> value	0.001*	0.01*	0.02*	0.15	0.34

ROI: Region of interest; *DI*: the initial abnormal diffusion areas which evolved into infarction on day-7 image; *DN*: the initial abnormal diffusion areas which appeared as normal tissue on day-7 image; *MI*: the PWI-DWI mismatch areas which evolved into infarction on day-7 image; *MN*: the PWI-DWI mismatch areas which appeared as normal tissue on day-7 image; CI: confidence interval; Parameter values are presented as mean ± SD; *: *p* value<0.05

ROC curve analysis

ROC curves of parameters in initial abnormal diffusion areas are presented in Figure 25. AUC of each parameter were as follows: ADC_{mean}: 0.79 (95% CI 0.60-0.98); rADC: 0.81 (95% CI 0.61-0.99); rCBF: 0.76 (95% CI 0.58-0.94); rCBV: 0.75 (95% CI 0.55-0.94). Thresholds calculated by Youden index were 623×10⁻⁶ mm²/s for ADC_{mean} (sensitivity(Se) 86%, specificity(Sp) 63%, positive predictive value (PPV) 32% and negative predictive value (NPV) 96%); 0.80 for rADC (Se 71%, Sp 83%, PPV 45% and NPV 94%); 0.47 for rCBF (Se 100%, Sp 54%, PPV 30% and NPV 100%); 0.82 for rCBV (Se 86%, Sp 63%, PPV 32% and NPV 96%).

ROC curves of parameters in PWI-DWI mismatch areas are shown in Figure 26. AUC of each parameter were as follows: ADC_{mean}: 0.75 (95% CI 0.62-0.89); rADC: 0.72 (95% CI 0.58-

0.86); rCBF: 0.68 (95% CI 0.53-0.84). Thresholds calculated by Youden index were 785×10^{-6} mm²/s for ADC_{mean} (Se 91%, Sp 57%, PPV 78% and NPV 80%); 0.98 for rADC (Se 65%, Sp 76%, PPV 81% and NPV 57%); 0.63 for rCBF (Se 76%, Sp 67%, PPV 79% and NPV 64%).

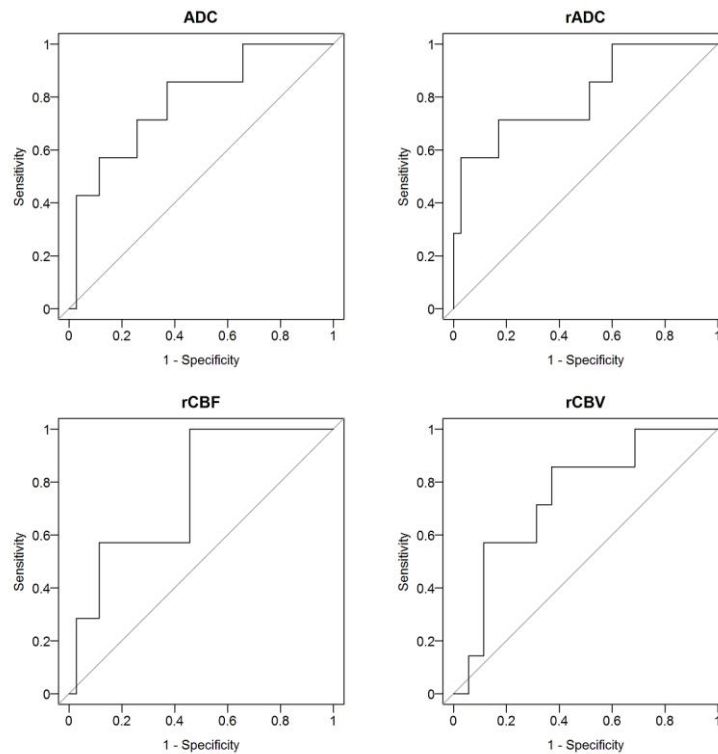


Figure 25. ROC curves showing the role of different parameters in distinguishing the regions presented as normal tissue on day-7 images and those evolved into infarction in initial abnormal diffusion areas. Top left (ADC): AUC 0.79 (95% CI 0.60-0.98); Top right (rADC): AUC 0.81 (95% CI 0.61-1); Bottom left (rCBF): AUC 0.76 (95% CI 0.58-0.94); Bottom right (rCBV): AUC 0.75 (95% CI 0.55-0.94)

ADC: apparent diffusion coefficient; CBF: cerebral blood flow; CBV: cerebral blood volume; ROC: receiving operating characteristic; AUC: area under the ROC curve; CI: confidence interval.

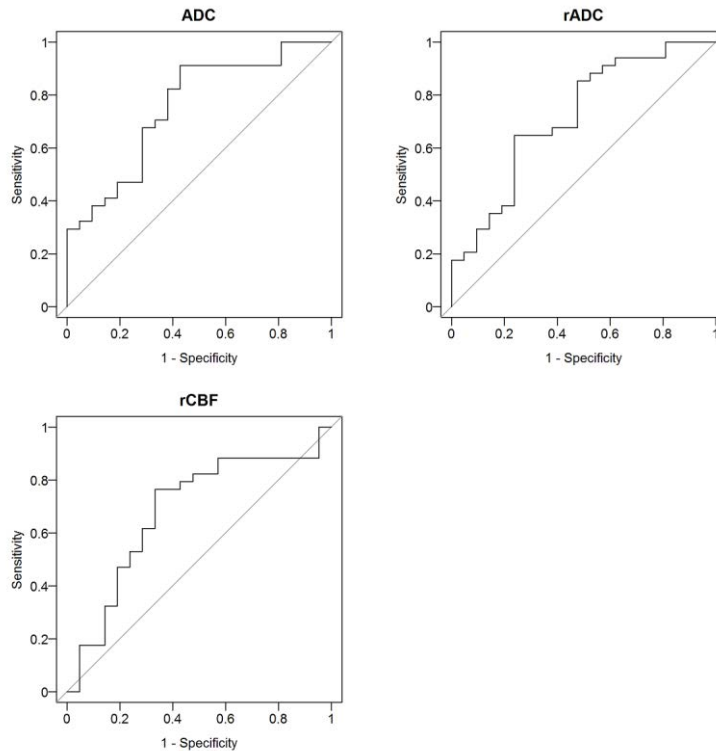


Figure 26. ROC curves showing the role of different parameters in distinguishing the regions presented as normal tissue on day-7 images and those evolved into infarction in PWI-DWI mismatch areas. Top left (ADC): AUC 0.75 (95% CI 0.62-0.89); Top right (rADC): AUC 0.72 (95% CI 0.58-0.86); Bottom left: rCBF; AUC 0.68 (95% CI 0.53-0.84).

ADC: apparent diffusion coefficient; CBF: cerebral blood flow; ROC: receiving operating characteristic; AUC: area under the ROC curve; CI: confidence interval.

Discussion

The role of MRI in tissue viability prediction in acute ischemic stroke is promising. It can help the clinicians to select appropriate patients for treatment. Our work investigated tissue viability in both initial abnormal diffusion areas and PWI-DWI mismatch areas, and suggested that ADC and rCBF may be optimal candidate for tissue viability prediction.

Tissue viability in initial abnormal diffusion areas

Combined positron emission tomography (PET)-MRI studies have suggested that DWI lesions reflect variable metabolic disruption, thus may not always represent irreversibly damaged tissue.¹⁷ The proportion of patients presenting normalization of abnormal diffusion

areas (19.4%) was close to another study (19.7%)⁸, but lower than 50% demonstrated by Labeyrie et al.¹⁸ and 67% reported by *Loh et al.*¹¹. The proportion of initial diffusion abnormal area presenting normalization (5.6%) was lower than 11% reported by Labeyrie et al.¹⁸ Recent animal study also demonstrated a higher proportion of diffusion lesion reversal (8.3-51.9% for early reversal and 41.7-77.8% for sustained reversal).¹⁹

Both diffusion and perfusion parameters showed relevance in distinguishing the regions that evolved into infarction with those which did not. The effective role of ADC value was in line with the previous results.^{8,10,20} ROC analysis showed that rADC and ADC_{mean} are the most promising parameters. The optimal ADC_{mean} threshold was in accordance with *Purushotham's* study who proposed 620×10^{-6} mm²/s, although voxel-based method was used by them.¹⁰ The rADC threshold of 0.80 determined in our study was similar to the result of an animal study, in which rADC of 0.77 was decided as a good estimate for the breakdown of energy metabolism.²¹

PWI parameters were investigated in previous studies for their potential value to predict tissue viability in DWI lesions. Carrera et al. proposed that MTT may improve infarction prediction within DWI lesions.²² While another study presented that CBV maps could not reliably substitute for DWI in identifying the infarct core.²³ Nevertheless, these studies only assessed one parameter. Our results indicated that the prediction of initial abnormal diffusion tissue destiny could be improved by applying rCBF or rCBV thresholds. Voxel-based analyses on large sample studies are needed to confirm the role of PWI parameters in ischemic core assessment.

Tissue viability in PWI-DWI mismatch areas

The introduction of PWI-DWI mismatch as a surrogate marker of penumbra has opened a new perspective in stroke imaging. Compared to initial abnormal diffusion areas, higher frequency of normalization in mismatch areas in our cohort could be explained by stroke pathophysiology. DWI lesions occurred in regions of maximal perfusion deficit and thus had less opportunity for recovery.²⁴

Previous comparative PET-MRI studies detected different PWI parameters for estimating penumbral flow thresholds, Tmax (> 5.5 seconds), CBF (< 21.7 mL/100g/min) and time to peak (TTP, > 4.2 seconds) have been proposed.^{25,26} Numerous thresholds for distinguishing

tissue “at risk” and “not at risk” were presented without consensus, with rCBF value ranged from 0.58 to 0.61,¹² which was similar with the value suggested in our study (0.63).

The role of ADC value was usually investigated within DWI lesion. Our results revealed that ADC could also be implicated in the prediction of tissue viability in mismatch area, even better than perfusion derived parameters. Our results was similar with previous study which proposed a ADC threshold of $803 \times 10^{-6} \text{ mm}^2/\text{s}$ as the best discriminator for viable tissue in mismatch area.²⁰ ADC is a quantitative measurement of water diffusion, which decreases at the acute phase of stroke because of a net shift of water from the extracellular to intracellular space. We could infer that PWI-DWI mismatch area also present various degrees of decreased ADC value, but without evident intensity alteration on DWI.

Our study has the following limitations. Firstly, CT was used in the majority of our patients to evaluate the final infarct. Although tracing the abnormal hypodensity manually on CT was reported to be reproducible in measuring infarct volume,²⁷ it would be more precise using MRI. Secondly, our sample is rather small and the imaging parameters are heterogeneous. The primary objective of THRACE study was the evaluation of stroke treatment and imaging was done according to the established local routine. In our sub-study we only focused on patients who had baseline DWI and PWI and follow-up day-7 images. The variation of imaging parameter could be a source of bias; on the other hand, it approaches the real situation of clinical practice. Thirdly, tissue viability was analyzed regardless of other confounding factors, such as collateral circulation and reperfusion status, due to the absence of angiography for patients in intravenous thrombolysis group. Lastly, metabolic status is different between brain compartments, with white matter more resistant to ischemia than grey matter.^{28,29} Considering them separately could improve the accuracy of viable tissue identification.

Conclusions

Our study proposed that ADC and rCBF may be optimal candidates in predicting tissue viability in acute ischemic stroke. Tissue with higher ADC value and higher rCBF value tended to normalize in initial abnormal diffusion areas and in PWI-DWI mismatch areas.

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Discussion

Our study investigated the role of DWI and PWI for brain tissue viability prediction in acute ischemic stroke patients, in initial abnormal diffusion areas and PWI-DWI mismatch areas separately.

Our results confirmed the DWI reversal phenomenon: 19.4% patients in our cohort presented DWI lesion normalization. We further proposed thresholds of ADC and perfusion-derived parameters (rCBF and rCBV) to distinguish the salvageable tissue in initial abnormal areas.

PWI-DWI mismatch has been considered as a surrogate of PET-derived parameter to identify the penumbra. Studies has suggested that PWI-DWI mismatch was able to identify patients that were likely to benefit from reperfusion therapy (85,86). Mismatch has been applied as a criterion for patient selection (36). However, it has several uncertainties. Firstly, the identification of ischemic core on DWI is not normative. Clinically, ischemic core is mainly visually estimated on DWI. However, lesion estimation on DW images is susceptible to artifacts, influenced by T2 shine-through effect and contrast window, and is also operator-dependent. ADC is a more reliable parameter for lesion delineation and has been used in commercial software for automatic lesion segmentation (124). Our results revealed that the appropriate ADC threshold can identify the ischemic core with fair sensitivity and specificity. Secondly, DWI reversal is a common phenomenon, thus DWI abnormality does not always represent ischemic core. Thirdly, the lack of standardization of methodology to PW images acquisition, post-processing algorithms, and the perfusion parameters to define hypoperfused tissue, give rise to different PWI-DWI mismatch evaluation. Lastly, PWI abnormality region cannot be clearly differentiated from oligemia. The PWI-DWI mismatch has been reported to overestimate the penumbra (116). Therefore, considering PWI-DWI mismatch region as penumbra seems unadvisable.

Our results revealed that rCBF was a promising parameter for tissue viability evaluation in PWI-DWI mismatch region. It is worth noting that ADC is also a candidate for tissue viability prediction in mismatch area in our cohort. We could infer that PWI-DWI mismatch area also present various degrees of decreased ADC value, but without evident intensity alteration on DWI.

There are some strong points in our studies.

1. We analyzed patients from a multicenter randomized controlled trial, which can minimize the sampling bias. Even though the image acquisition parameters are heterogeneous, it approaches the real situation of clinical practice.
2. Various diffusion- and perfusion-derived parameters were analyzed and appropriate ones were selected for tissue viability prediction using ROC curve analysis.
3. Both initial abnormal diffusion areas and PWI-DWI mismatch areas were analyzed, providing a comprehensive description of brain tissue.

However, several limitations exist in our research:

1. Baseline PWI was not a mandatory sequence for patients in the THRACE study, which gave rise to a small sample size in our study.
2. CT was used in the majority of the included patients (29 in 36 patients) to evaluate the final infarct. CT is less precise than MRI when delineating final infarction.
3. Tissue viability was analyzed regardless of other important confounding factors, such as collateral circulation and reperfusion status, due to the absence of angiography for patients in IVT group.
4. We did not analyze the image-based parameter thresholds to distinguish oligemia tissue from penumbra in PWI-DWI mismatch area.
5. Region-of-interest-based method was used in our study. Voxel-based analysis with large sample size will help to confirm our results and may provide more robust evidence on tissue viability assessment by image-based parameters.

In conclusion, our study provided new evidences in brain tissue prediction in acute ischemic stroke. Diffusion and perfusion-derived parameters have shown to be promising. However, it should be pointed out that the fate of the tissue cannot be determined by the image-based parameters alone. Other factors, such as reperfusion status and the time point of imaging, should also be taken into account. Moreover, functional outcome should be analyzed in the future study to understand whether using image-based parameters in tissue viability prediction and patient selection can actually benefit in terms of patient living quality after therapy.

Résumé en français

Rôle des paramètres de diffusion et de perfusion dans la prédiction de la viabilité des tissus chez les patients présentant un AVC ischémique aigu

Contexte et objectif

L'objectif du traitement de l'AVC (accident vasculaire cérébral) ischémique est de récupérer les tissus en risque d'infarctus mais qui ont la possibilité d'être récupérés. L'identification des tissus récupérables est cruciale pour l'évaluation de l'AVC ischémique aigu. L'IRM pourrait être très utile dans ce domaine, mais son rôle n'a pas été complètement établi. Nous avons cherché à déterminer si les paramètres de diffusion et de perfusion pouvaient prédire la viabilité des tissus cérébraux.

Méthode

Nous avons analysé les patients présentant un AVC ischémique avec occlusion artérielle intracrânienne proximale antérieure qui ont eu une DWI et PWI à l'inclusion et une imagerie au 7^{ème} jour. Les DWI et PWI à l'inclusion et les imageries au 7^{ème} jour d'un même patient ont été recalées en utilisant le logiciel ORS Visual[®]. Le post-traitement des DWI et PWI ont été réalisés sur Olea Sphere[®]. La segmentation des lésions a été faite manuellement. 4 types de ROI (*region of interest*) ont été définies : la zone anormale en DWI qui devient normale en imagerie au 7^{ème} jour (*DN*) et celles qui évoluent en infarctus (*DI*) ; la zone de mismatch PWI-DWI qui devient normale au 7^{ème} jour (*MN*) et celles qui évoluent en infarctus (*MI*). Le coefficient apparent de diffusion (*apparent diffusion coefficient*, ADC) et les paramètres de perfusion (le débit sanguin cérébral [DSC], le volume sanguin cérébral [VSC] et le temps de transit moyen [TTM]) ont été comparés au niveau des ROI. Les courbes ROC (*receiving operating characteristic*) et l'aire sous la courbe (*area under the curve*, AUC) ont été calculés, pour sélectionner les paramètres et déterminer leurs seuils optimaux pour distinguer les tissus normalisés et les tissus infarctés. Les analyses statistiques ont été faites avec logiciel R.

Résultat

36 patients ont été inclus dans cette sous-étude de THRACE. 7/36 (19,4%) patients présentaient un tissu *DN*, avec un volume de 5,29 mL (IQR 3,35-8,39). 34/36 (94,4%) patients présentaient un tissu *MN*, avec un volume de 44,34 mL (IQR 31,02-61,22). L'ADC absolu, l'ADC relatif (rADC), le DSC relatif (rDSC) et le VSC relatif (rVSC) présentaient des différences significatives entre *DI* et *DN*. L'ADC absolu, le rADC et le rDSC présentaient des différences significatives entre *MI* et *MN*.

Dans les zones anormales en DWI initiale, l'ADC absolu avait une AUC de 0,79 (95% IC 0,60-0,98) ; le rADC avait une AUC de 0,81 (95% IC 0,61-1) ; le rDSC avait une AUC de 0,76 (95% IC 0,58-0,94) ; rVSC avait une AUC de 0,75 (95% IC 0,55-0,94). Les seuils de $623 \times 10^{-6} \text{ mm}^2/\text{s}$ (ADC), 0,80 (rADC), 0,47 (rDSC) et 0,82 (rVSC) ont été choisis pour prédire la viabilité du tissu.

Dans les zones de *mismatch* PWI-DWI: l'ADC absolu avait une AUC de 0,75 (95% IC 0,62-0,89); le rADC avait une AUC de 0,72 (95% IC 0,58-0,86) ; le rCBF avait une AUC de 0,68 (95% IC 0,53-0,84). Les seuils de $785 \times 10^{-6} \text{ mm}^2/\text{s}$ (ADC), 0,98 (rADC) et 0,63 (rDSC) ont été choisis pour prédire la viabilité du tissu.

Discussion

Cette étude a montré que les paramètres de diffusion et de perfusion peuvent prédire la viabilité des tissus cérébraux en cas d'AVC ischémique. Dans les zones anormales en DWI initiale, le rôle de l'ADC dans la prédiction de la viabilité de tissus sont en accord avec les études précédentes (72,125). Le rDSC et le rVSC sont aussi des paramètres utiles, mais moins prometteurs que l'ADC. Dans les zones de *mismatch* PWI-DWI, le seuil de rDSC proposé pour distinguer les tissus récupérables correspond aux seuils proposés dans l'étude précédente (123). Le rADC et l'ADC absolu sont aussi des paramètres prometteurs. Cependant, nous devons souligner que le devenir du tissu ne peut pas être déterminé seulement par les paramètres basés sur l'imagerie. D'autres facteurs, tels que l'état de reperfusion, doivent également être pris en compte. De plus, les résultats fonctionnels doivent être analysés, pour comprendre si la sélection des patients à partir des paramètres d'imagerie peut bénéficier en termes de qualité de vie des patients.

Chapter 3

Pretreatment ischemic stroke lesional volume and clinical outcome

Introduction

In this chapter, we will discuss the association between the pretreatment lesional volume measured on DWI and clinical outcome, and estimate the impact of lesional volume on mechanical thrombectomy (MT) efficacy. Then, we will focus on the patients with large pretreatment volume and investigate the association between the baseline parameters and clinical outcome.

Firstly, we analyzed the effect of pretreatment lesional volume on clinical outcome. In previous studies, lesional volume has been suggested to be related with clinical outcome in ischemic stroke. Nighoghossian et al. demonstrated that in ischemic stroke patients treated with rtPA, the baseline DWI abnormality volume was well correlated with a day-60 NIHSS score ($r=0.58$, $p=0.001$), it remained to be an independent factor for clinical outcome after multiple linear regression (78). Olivot et al. analyzed 139 patients with complete occlusion of ICA or MCA treated by endovascular therapy and showed that higher volume was associated with less favorable outcome, which is defined by a mRS 3-6 (adjusted odds ratio 0.55; 95% CI 0.31-0.96) (87). Thresholds above which patients will not benefit from the treatment were proposed by previous studies (77–81). 70 mL and 100 mL are two thresholds widely proposed. However, most of the data were from single-center studies. In several randomized controlled clinical trials, the lesional volume was estimated on CT or MRI using ASPECT score or volumetric methods. Patients with large pretreatment infarct core were excluded (24–27, 31). The exclusion criteria of the THRACE study did not take infarct core volume into consideration, providing a unique opportunity to study the association between pretreatment lesional volume and clinical outcome.

Furthermore, we investigated the impact of lesional volume on MT efficacy. MT has been considered as a standard therapy for ischemic stroke patients with occlusion of proximal circulation. Intuitively, the large lesional volume will have a negative effect on therapy, including MT; however, the relationship remains unclear. It is valuable and necessary to study this aspect.



Then, we analyzed patients with large pretreatment lesional volume (> 70 mL or > 100 mL) in the THRACE study. Although larger infarct volume has been suggested to be associated with less favorable outcome, these patients may still benefit from recanalization (87). We searched

for baseline parameters which were associated with favorable outcome in patients with large volume, in order to select patients who could benefit from reperfusion therapy.

Two articles have been published based on this part of work:

1. **Xie Y**, Oppenheim C, Guillemin F, Gautheron V, Gory B, Raoult H, Soize S, Felblinger J, Hossu G, Bracard S. Pretreatment Lesional Volume Impacts Clinical Outcome and Thrombectomy Efficacy. *Ann Neurol*. 2018;83(1):178-185. doi: 10.1002/ana.25133.
2. Gautheron V, **Xie Y**, Tisserand M, Raoult H, Soize S, Naggara O, Bourcier R, Richard S, Guillemin F, Bracard S, Oppenheim C. Outcome After Reperfusion Therapies in Patients With Large Baseline Diffusion-Weighted Imaging Stroke Lesions: A THRACE Trial (Mechanical Thrombectomy After Intravenous Alteplase Versus Alteplase Alone After Stroke) Subgroup Analysis. *Stroke*. 2018;49(3):750-3.

Pretreatment Lesional Volume Impacts Clinical Outcome and Thrombectomy Efficacy

Yu Xie, MD, MSc,¹ Catherine Oppenheim, MD, PhD,²
Francis Guillemin, MD, PhD,³ Vincent Gautheron, MD,²
Benjamin Gory, MD, PhD ,⁴ H el ene Raoult, MD, PhD,⁵
S ebastien Soize, MD, PhD,⁶ Jacques Felblinger, PhD,^{1,7}
Gabriela Hossu, PhD,⁷ and Serge Bracard, MD ^{1,8};
on behalf of the THRACE investigators

Objective: We aimed to characterize the association between pretreatment lesional volume measured on diffusion-weighted images and functional outcome, and estimate the impact on thrombectomy efficacy for ischemic stroke with anterior proximal intracranial arterial occlusion.

Methods: Anterior circulation ischemic stroke patients who had pretreatment diffusion-weighted imaging in the THRACE study were included. Lesional volume was semiautomatically segmented. Logistic regression was applied to model clinical outcome as a function of lesional volume. Outcomes included functional independence (modified Rankin Scale [mRS] 0–2), degree of disability (ordinal mRS 0–6), and mortality at 3 months.

Results: Of 298 included patients, with median lesional volume 17.2ml (interquartile range [IQR], 9.2–51.8) and median mRS 2 (IQR, 1–4), 51.0% achieved functional independence. Increased lesional volume was an independent predictor for a lower probability of functional independence (odds ratio [OR], 0.90 [95% confidence interval {CI}, 0.81–0.99] per 10ml; $p < 0.001$), a less favorable degree of disability (common OR, 0.86 [95% CI, 0.81–0.90] per 10ml; $p < 0.001$), and a higher mortality rate (OR, 1.21 [95% CI, 1.08–1.37] per 10ml; $p < 0.001$). For additional thrombectomy, the number of patients needed to treat to achieve functional independence in 1 patient increased with lesional volume (10 for a volume of 80ml; 15 for 135ml). No significant treatment-by-dichotomized volume interaction for functional independence and mortality was observed.

Interpretation: Pretreatment lesional volume is an independent predictor for functional outcome in acute ischemic stroke with proximal intracranial occlusion. The clinical benefit of adding mechanical thrombectomy to thrombolysis decreased with the increase of lesional volume.

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Recent randomized clinical trials have demonstrated the clinical benefit of mechanical thrombectomy (MT) in acute ischemic stroke patients with anterior

circulation proximal intracranial occlusions.^{1–8} In the majority of these trials, patients were evaluated with computed tomography (CT) and selected by

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Corresponding Author: Pr Serge Bracard, Department of Diagnostic and Interventional Neuroradiology, University Hospital of Nancy, 54035 Nancy, France. E-mail: s.bracard@chru-nancy.fr

From the ¹IADI, U1254, INSERM, Universit e de Lorraine, CHRU Nancy, Nancy, France; ²Department of Neuroradiology, Sainte-Anne Hospital and Paris-Descartes University, INSERM U894, Paris, France; ³CIC 1433 Epid emiologie Clinique, INSERM, Universit e de Lorraine, CHRU Nancy, Nancy, France; ⁴INSERM U1237, “Physiopathology and Imaging for Neurological Disorders (PhIND)”, GIP Cyceron, Caen, France; ⁵Department of Neuroradiology, University Hospital of Rennes, Rennes, France; ⁶Department of Neuroradiology, University Hospital of Reims, Reims, France; ⁷CIC 1433 Innovation Technologique, INSERM, Universit e de Lorraine, CHRU Nancy, Nancy, France; and ⁸Department of Diagnostic and Interventional Neuroradiology, CHRU Nancy, Nancy, France

Please see a supplementary file for the list of THRACE study investigators and their affiliations.

Additional supporting information can be found in the online version of this article.

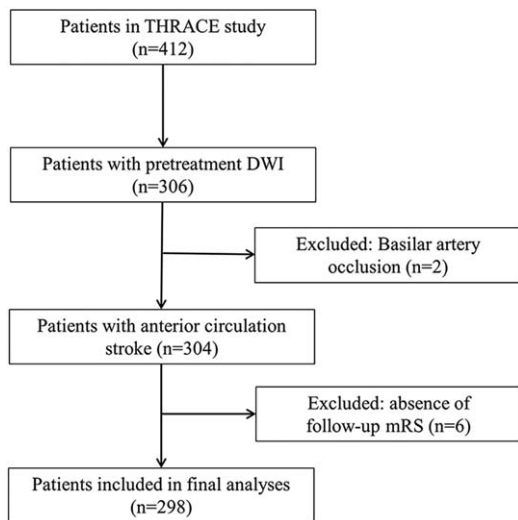


FIGURE 1: Patient selection flowchart. DWI = diffusion-weighted imaging; mRS = modified Rankin Scale.

pretreatment ASPECTS (Alberta Stroke Program Early CT Score) threshold, and patients with large stroke volume were excluded. Infarct volume at follow-up was shown to be a prognostic biomarker^{9–11}; however, uncertainty remained as to the optimal baseline imaging profile for favorable clinical outcome after MT. Extensive data from previous studies support diffusion-weighted imaging (DWI) as the most accurate imaging sequence available for estimating the ischemic core in acute ischemic stroke patients.¹² To date, evidence with regard to the association between pretreatment lesional volume measured on DWI and functional outcome is relatively weak and is limited to retrospective single-center studies and thrombolysis therapy.^{13–16} Moreover, the effect of pretreatment lesional volume on the benefit of MT has yet to be determined.

The THRACE study⁶ provided a unique opportunity to evaluate the association between pretreatment lesional volume measured on DWI and both functional outcome and MT efficacy, because of the use of DWI in pretreatment imaging in a large proportion of patients and the absence of exclusion criteria on the basis of pretreatment lesional volume.

In this substudy, we aimed to characterize the relationship between pretreatment lesional volume measured on DWI and the functional outcome of ischemic stroke, and estimate the impact of pretreatment lesional volume on MT efficacy for acute ischemic stroke due to proximal intracranial arterial occlusion.

Patients and Methods

Study Design and Participants

The THRACE study (Clinical Trial Registration-URL: <http://www.clinicaltrials.gov>; unique identifier: NCT01062698) was a

randomized, controlled trial done in 26 centers in France, comparing intravenous thrombolysis plus MT (IVTMT) and intravenous thrombolysis alone (IVT) in patients with acute ischemic stroke attributed to proximal arterial occlusion, aged 18 to 80 years, and with an NIHSS (National Institutes of Health Stroke Scale) score of 10 to 25. The study design and patient inclusion criteria have been described in detail previously.⁶ The study protocol was approved by the CPP (Comité de Protection des Personnes) Est III Ethics Committee and the research boards of the participating centers. All patients or their legal representatives provided written informed consent. In our THRACE substudy, we included anterior circulation stroke patients who had pretreatment DWI.

Imaging and Clinical Assessment

Pretreatment infarct lesions were semiautomatically segmented by Olea Sphere (Olea Medical SAS, La Ciotat, France) after applying a threshold of apparent diffusion coefficient (ADC) of $0.6 \times 10^{-3} \text{ mm}^2/\text{s}$ on ADC maps,^{17–19} which were calculated from DWI acquisitions. All the lesion masks were confirmed by two neuroradiologists and were manually corrected, if necessary.

Demographic and clinical data and functional outcome were extracted from the THRACE database. Primary outcome was the proportion of patients achieving functional independence at 3 months, defined by a score of 0 to 2 on the modified Rankin Scale (mRS; ranging from 0 [no symptoms] to 6 [death]). Secondary outcomes were (1) degree of disability at 3 months, assessed by the ordinal mRS from 0 to 6 with ranks 5 and 6 combined into a single category, and (2) mortality at 3 months. Cerebral reperfusion was assessed by angiography and reviewed by three experienced interventional neuroradiologists under a consensus evaluation for patients who received thrombectomy. Substantial reperfusion was defined as a modified Thrombolysis in Cerebral Infarction (mTICI) scale score of 2b or 3, corresponding to reperfusion of at least 50% of the affected vascular territory.

Statistical Analysis

Baseline characteristics and functional outcome were compared between patients in the IVT group and the IVTMT group. Non-Gaussian continuous variables are presented as median and interquartile range (IQR) while categorical variables are presented as proportions. Comparisons were performed by Wilcoxon test and chi-square test, respectively. p values were two-sided and $p = 0.05$ was chosen as the significance level.

ASSOCIATION BETWEEN PRETREATMENT LESIONAL VOLUME AND FUNCTIONAL OUTCOME. Univariate and multivariate logistic analyses evaluated the association between lesional volume and clinical outcomes (binomial logistic regression for binarized mRS and ordinal logistic regression for ordinal mRS). Factors that had predictive value for clinical outcome in the main THRACE study⁶ (age, baseline NIHSS score, occlusion location, ASPECTS, blood glucose, and Fazekas score) were included as covariates in the present analysis. Variables with a p value <0.20 in univariate analysis were included in the multivariate model. The final model was

TABLE 1. Demographic and Clinical Baseline Characteristics of Patients

	All Patients (n = 304)	IVT Group (n = 155)	IVTMT Group (n = 149)	p
Age, years	67 (54–74)	68 (54–75)	67 (54–74)	0.64
Male sex	159/304 (52.3)	72/155 (46.5)	87/149 (58.4)	0.05
Diabetes mellitus	31/301 (10.3)	21/155 (13.5)	10/146 (6.8)	0.09
Hypertension	155/301 (51.5)	86/155 (55.5)	69/146 (47.3)	0.19
Tobacco (current or past)	117/274 (42.7)	56/142 (39.4)	61/132 (46.2)	0.31
Hypercholesterolemia	142/271 (52.4)	80/142 (56.3)	62/129 (48.1)	0.21
Coronary disease	42/290 (14.5)	22/148 (14.9)	20/142 (14.1)	0.98
History of stroke	19/294 (6.5)	10/153 (6.5)	9/141(6.4)	0.99
Admission blood glucose, g/l	1.2 (1.0–1.4)	1.2 (1.0–1.4)	1.2 (1.0–1.4)	0.69
Admission NIHSS score	18 (14–20)	17 (14–21)	18 (14–20)	0.83
Time from stroke onset to imaging, min	114 (89–139)	113 (92–140)	114 (86–139)	0.54
Time from stroke onset to randomization, min	166 (139–195)	168 (138–198)	165 (143–194)	0.72
Occlusion location, ICA:M1	47:257	31:124	16:133	0.04*
ASPECT score	7 (5–9)	7 (5–9)	7 (6–8)	0.89
Fazekas score	1 (0–1)	1 (0–2)	1 (0–1)	0.11
Infarct laterality, left hemisphere	145/304 (47.7)	69/155 (44.5)	76/149 (51.0)	0.31

Continuous variables are presented as median (interquartile range); categorical variables are presented as no. (%).
* $p < 0.05$.
IVT = intravenous thrombolysis; IVTMT = intravenous thrombolysis plus mechanical thrombectomy; NIHSS = National Institutes of Health Stroke Scale; ICA = intracranial internal carotid artery; M1 = proximal portion of middle cerebral artery; ASPECT = Alberta Stroke Program Early CT Score.

selected using Akaike's information criterion (AIC). Adjusted odds ratios (ORs) or common odds ratios (cORs) with 95% confidence intervals (CIs) were calculated. The estimated probability of achieving functional independence according to age, baseline NIHSS score, and lesional volume for each patient was depicted by three-dimensional scatterplots. Fitted surfaces were added to describe the association between age, baseline NIHSS score, and lesional volume on the likelihood of functional independence. The reperfusion status was also included in the model in a per-protocol analysis of the IVTMT group (patients assigned to the IVTMT group who did not have thrombectomy were excluded from the analysis).

ASSOCIATION BETWEEN PRETREATMENT LESIONAL VOLUME AND THROMBECTOMY EFFICACY ON FUNCTIONAL OUTCOME. The association between pretreatment lesional volume and functional independence was evaluated in the IVTMT group and compared with the IVT group. The number needed to treat (NNT)²⁰ was calculated to estimate the number of patients needed to treat to obtain 1 patient

achieving functional independence after thrombectomy through the range of lesional volume. The interaction of treatment-by-dichotomized lesional volume for functional independence and mortality was assessed with two volume thresholds suggested in previous studies: 70 and 100ml.^{15,21} All the statistical analyses were performed using statistical software R (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 412 patients in the THRACE study, 304 met the inclusion criteria (106 patients without pretreatment DWI examination and 2 with basilar artery occlusion were excluded; Fig 1), including 155 (51.0%) patients in the IVT group and 149 (49.0%) in the IVTMT group. The cohort was composed of 159 (52.3%) men and had a median age of 67 (IQR, 54–74) years. Baseline characteristics of the included patients are presented in Table 1. No significant differences in baseline characteristics were

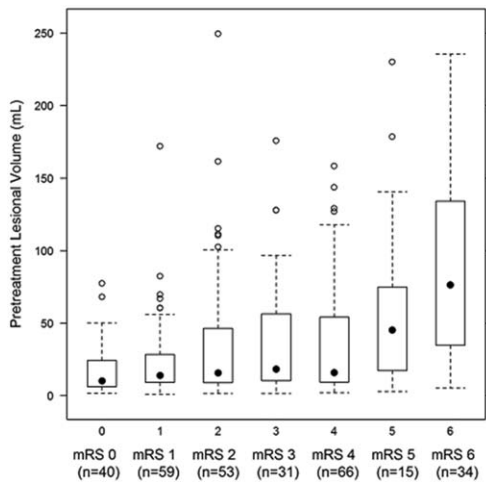


FIGURE 2: Box-and-whisker plot showing the distribution of the pretreatment lesional volume for each modified Rankin Scale (mRS) category. The boundaries of the box indicate the 25th and 75th percentiles and the black dots indicate the median values. The whiskers represent the lowest and highest values in the 25th percentile minus 1.5 interquartile range (IQR) and 75th percentile plus 1.5 IQR, respectively. Circles indicate outliers.

observed between the two groups except for the occlusion location.

Furthermore, 6 patients without follow-up mRS evaluation were excluded, leaving 298 patients (IVTMT group, n = 148; IVT group, n = 150) for the subsequent analyses (median age, 67 years [IQR, 54–74]; women, 47.3%).

Association Between Pretreatment Lesional Volume and Functional Outcome

For the 298 patients, median pretreatment lesional volume was 17.2ml (IQR, 9.2–51.8) and median mRS was 2 (IQR, 1–4), with 152 (51.0%) achieving functional independence at 3 months. The distribution of lesional volume for each mRS category is shown in Figure 2. Increased ordinal mRS was associated with a larger lesional volume (Spearman’s ρ correlation coefficient, 0.34; $p < 0.0001$). Best regression models for the association between pretreatment lesional volume and functional outcomes and death are presented in Table 2. Lesional volume, together with age, baseline NIHSS score, intracranial occlusion location, and blood glucose level, were independent predictors for both functional independence and degree of disability. ASPECTS was not chosen to be part of the final regression model after the model selection using the AIC. The probability of achieving functional independence decreased with the increase of lesional volume (per 10ml: OR, 0.90; 95% CI, 0.81–0.99; $p < 0.001$). The degree of disability increased with the increase of lesional volume (per 10ml: cOR, 0.86; 95% CI, 0.81–0.90; $p < 0.001$). The associations between lesional volume, age, baseline NIHSS score, and adjusted probability of functional independence were depicted by three-dimensional scatterplots with fitted surfaces (Fig 3). The mortality rate increased with the increase of lesional volume (per 10ml: OR, 1.21; 95% CI, 1.08–1.37; $p < 0.001$). When the reperfusion status was included as covariate in the per-protocol

TABLE 2. Multivariate Logistic Models for the Association Between Pretreatment lesional volume with Functional Independence, Degree of Disability, and Mortality at 3 Months

	OR (95% CI) for Functional Independence	<i>p</i>	cOR (95% CI) for Degree of Disability	<i>p</i>	OR (95% CI) for Mortality	<i>p</i>
Age	0.96 (0.93–0.98)	0.001	0.97 (0.95–0.99)	0.001	1.06 (1.02–1.11)	0.002
Baseline NIHSS score	0.89 (0.83–0.95)	0.001	0.91 (0.86–0.96)	0.001		
Occlusion location (M1)	3.03 (1.31–7.52)	0.011	2.04 (1.12–3.72)	0.020		
Blood glucose level	0.38 (0.17–0.81)	0.020	0.62 (0.37–0.99)	0.054		
Fazekas score	0.76 (0.55–1.04)	0.099	0.84 (0.65–1.08)	0.171		
Lesional volume (per 10ml)	0.90 (0.80–0.99)	<0.001	0.86 (0.81–0.90)	<0.001	1.21 (1.08–1.37)	<0.001

Functional independence was defined by a modified Rankin Scale score 0 to 2 at 3 months. Degree of disability was assessed by ordinal modified Rankin Scale scores ranging from 0 to 6, with ranks 5 and 6 combined into a single category. Patients with missing values (n = 12) were excluded from this analysis.
 NIHSS = National Institutes of Health Stroke Scale; M1 = proximal portion of middle cerebral artery; OR = odds ratio; cOR = common odds ratio; CI = confidence interval.

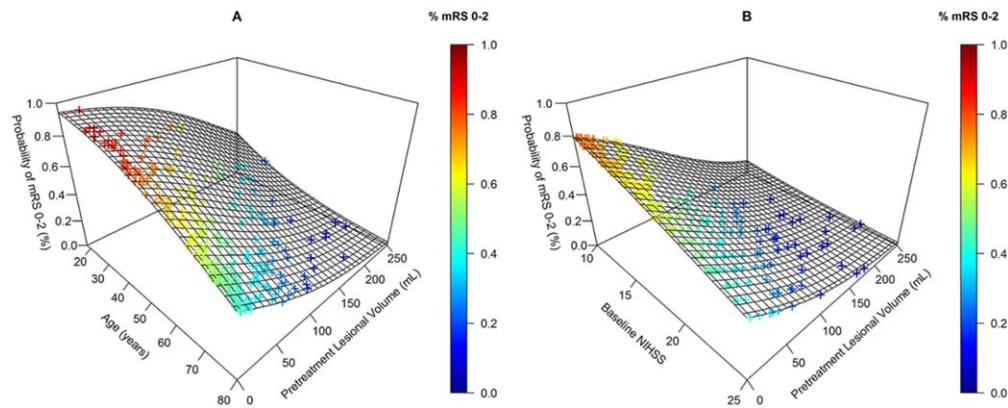


FIGURE 3: Three-dimensional scatterplots with fitted surfaces illustrating the association between age (A) or baseline NIHSS score (B), and pretreatment lesional volume, and adjusted probability of functional independence (mRS 0–2) at 3 months. The colored crosses indicate the estimated probability of functional independence for each patient in our cohort. mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale.

analysis ($n = 100$), the increase of lesional volume was still associated with a decreased probability of functional independence (per 10ml: OR, 0.87; 95% CI, 0.75–0.99; $p = 0.05$) and an increased degree of disability (per 10ml: cOR, 0.90; 95% CI, 0.80–0.99; $p = 0.04$).

Association Between Pretreatment Lesional Volume and Thrombectomy Efficacy on Functional Outcome

The median pretreatment lesional volume was 18.4ml (IQR, 9.9–45.3) in the IVTMT group, and 15.5ml (IQR, 8.7–60.1) in the IVT group ($p = 0.96$). The median NIHSS score at 24 hours was 9 (IQR, 4–18) in the IVTMT group, and 12 (IQR, 6–19) in the IVT group ($p = 0.08$). The median mRS was 2 (IQR, 1–4) in the IVTMT group, and 3 (IQR, 1–4) in the IVT group ($p = 0.21$). Compared to IVT alone, IVTMT increased the proportion of patients achieving functional independence by 11.4% (95% CI [–0.5; 23.4]; $p = 0.06$). In the IVTMT group, 46 (63.9%) of 72 patients achieving substantial reperfusion and 7 (25.0%) of 28 without substantial reperfusion had functional independence at 3 months. Substantial reperfusion increased the proportion of patients achieving functional independence by 38.9% (95% CI [16.9; 60.9]; $p = 0.001$). With the increase of pretreatment lesional volume, the probability of achieving functional independence decreased in both the IVTMT group and the IVT group (Fig 4). Adjusted OR for lesional volume per 10 mL was 0.87 (95% CI, 0.77–0.98; $p = 0.02$) in the IVTMT group, 0.89 (95% CI, 0.80–0.97; $p = 0.01$) in the IVT group and 0.82 (95% CI, 0.66–0.98; $p = 0.047$) for patients in the IVTMT group who achieved substantial reperfusion. The NNT for 1 patient achieving functional independence through IVTMT increased with pretreatment lesional volume:

from 10 with a lesional volume of approximately 80ml to 15 with 135ml and 20 with 160ml (Fig 5).

In the pretreatment lesional volume ≤ 70 mL subgroup ($n = 245$), additional MT increased the proportion of patients achieving functional independence by 10.5% (95% CI [–2.7; 23.7]; $p = 0.13$), and by 1.9% (95% CI [–23.2; 27.0]; $p = 0.99$) for pretreatment lesional volume

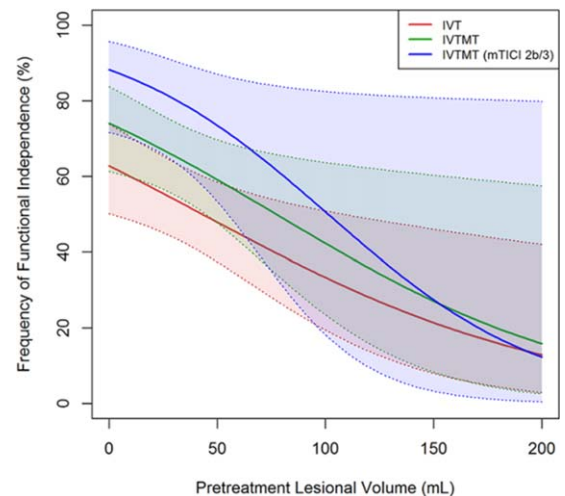


FIGURE 4: Probability of functional independence according to pretreatment lesional volume, by treatment group. Curves were obtained from binomial logistic regression of functional independence (defined by modified Rankin Score 0–2) at 3 months on pretreatment lesional volume as a continuous variable, adjusted for age, baseline NIHSS score, occlusion location of proximal portion of middle cerebral artery, and blood glucose level. The solid lines showed the model results from the logistic regression analysis, with 95% CIs shown in the color-corresponding dashed lines. Red lines indicate patients in intravenous thrombolysis (IVT) group; green lines indicate patients in intravenous thrombolysis plus mechanical thrombectomy (IVTMT) group; blue line indicates patients in IVTMT group who achieved substantial reperfusion (modified Thrombolysis in Cerebral Infarction [mTICI] Scale score 2b or 3). CI = confidence interval; NIHSS = National Institutes of Health Stroke Scale.

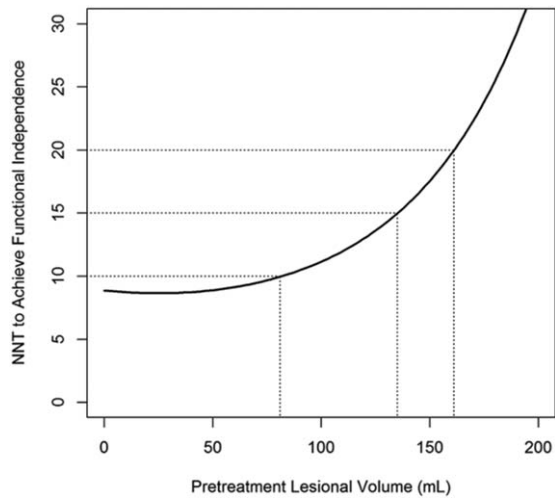


FIGURE 5: Number needed to treat (NNT) for 1 patient achieving functional independence (mRS 0–2) through mechanical thrombectomy according to pretreatment lesional volume. Lesional volume was treated as a continuous variable; the model was adjusted for age, baseline NIHSS score, occlusion location of proximal portion of middle cerebral artery, and blood glucose level. The corresponding lesional volume when NNT was 10, 15, and 20 are shown by dotted lines. mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale.

>70ml (n = 53). The increased proportion was 9.2% (95% CI [-3.6; 22.0]; *p* = 0.17) for pretreatment lesional volume ≤100ml (n = 261), and 5.0% (95% CI [-29.1;

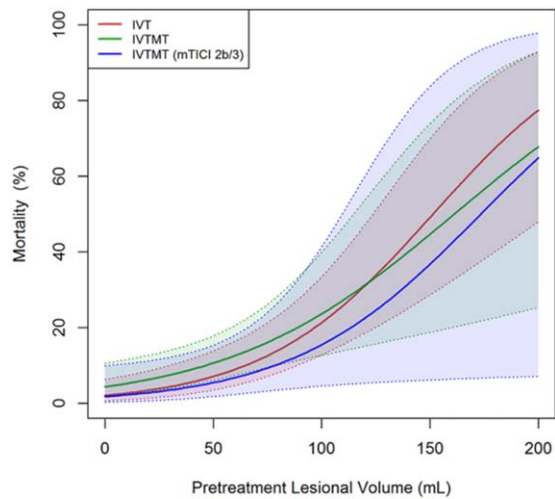


FIGURE 6: Probability of mortality according to pretreatment lesional volume, by treatment group. Curves were obtained from binomial logistic regression of mortality on pretreatment lesional volume as a continuous variable, adjusted for age. The solid lines show the model results from the logistic regression analysis, with 95% CIs shown in the color-corresponding dotted lines. Red lines indicate patients in the intravenous thrombolysis (IVT) group; green lines indicate patients in the intravenous thrombolysis plus mechanical thrombectomy (IVTMT) group; blue line indicates patients in the IVTMT group who achieved substantial reperfusion (modified Thrombolysis in Cerebral Infarction [mTICI] Scale score 2b or 3). CI = confidence interval.

39.1]; *p* = 0.99) for pretreatment lesional volume >100ml (n = 37). We noted no significant treatment-by-dichotomized lesional volume interaction for functional independence (dichotomized by pretreatment lesional volume of 70ml: OR, 0.99; 95% CI, 0.19–5.42, *p* = 0.99; dichotomized by pretreatment lesional volume of 100ml: OR, 0.98; 95% CI, 0.16–6.74; *p* = 0.99). Besides, NNT for 1 patient achieving functional independence through MT compared with thrombolysis alone was similar for patients who had pretreatment lesional volume ≤70ml or ≤100ml (Fig 5).

The mortality rate was 10.8% (16 of 148) in the IVTMT group and 12.0% (18 of 150) in the IVT group (*p* = 0.89). After adjustment for age, the mortality rate increased with the increase of pretreatment lesional volume (per 10ml: IVTMT group: OR, 1.21; 95% CI, 1.07–1.38; *p* = 0.003; IVT group: OR, 1.29; 95% CI, 1.17–1.45; *p* < 0.001; IVTMT group patients with substantial reperfusion: OR, 1.26; 95% CI, 1.01–1.60; *p* = 0.04; Fig 6). No significant treatment-by-dichotomized pretreatment lesional volume interaction was observed for mortality (dichotomized by pretreatment lesional volume of 70ml: OR, 0.42; 95% CI, 0.08–2.12; *p* = 0.30; dichotomized by pretreatment lesional volume of 100ml: OR, 0.23; 95% CI, 0.03–1.39; *p* = 0.12).

Discussion

Our study emphasizes the importance of pretreatment lesional volume to predict disability and mortality at 3 months in patients with acute ischemic stroke attributed to proximal intracranial arterial occlusion. Prediction of clinical outcome at the acute stage of ischemic stroke has a number of clinical benefits, ranging from determining optimal therapeutic intervention to informing patients and their family of possible consequences, as well as optimizing patient inclusion criteria for clinical trials.

DWI has been established as the most useful imaging sequence for estimating the ischemic core at the acute stage, because of its high diagnostic sensitivity and specificity, as well as its nonionizing nature.¹² The results of our THRACE substudy could have implications for clinical routine on account of the semiautomatic volumetric assessment for ischemic lesions in a large population, which was reliable and also easily applicable in a clinical setting. Moreover, patients in the IVTMT group were treated with last-generation MT devices and achieved a high proportion of early reperfusion.

Our study produced four main findings. First, as expected, pretreatment lesional volume was an independent predictor for clinical disability and mortality in our

cohort, even when reperfusion status was taken into consideration (in the IVTMT group). This result was in accord with previous studies.^{13–15} In a retrospective analysis of the Bernese stroke registry, including magnetic resonance imaging (MRI) triage of stroke patients, Gilgen et al¹⁴ observed that the volume of DWI lesions was an independent predictor of unfavorable outcome and survival. The three-dimensional scatterplots with fitted surfaces in our study also illustrate the clear association between pretreatment lesional volume and functional independence at 3 months, according to age and initial stroke severity. Even with young age and mild neurological deficit, which are two well-known predictive factors for a favorable functional outcome,²² the probability of achieving functional independence was lower in patients with a large pretreatment lesional volume.

Second, with the increase of pretreatment lesional volume, the NNT to obtain 1 patient achieving 3-month functional independence with IVTMT increased, indicating that the benefit of adding MT to thrombolysis decreased. Also of note, the proportion of patients achieving functional independence in the IVTMT group was always superior to that in the IVT group. Therefore, we can infer the benefit of thrombectomy regardless of pretreatment lesional volume.

Third, previous studies have suggested that patients with a pretreatment lesional volume superior to 70ml present a poorer outcome,^{15,16} and 100ml has also been proposed as a potential threshold for patient selection.²¹ After dichotomizing patients by lesional volume of 70 and 100ml, we observed a trend of greater benefit of MT in the subgroups with the smaller volume. However, the nonsignificant treatment-by-dichotomized lesional volume interaction for functional independence and mortality suggests that excluding patients based on a simple volume threshold would be unadvisable. It is worth noting that although patients with a large pretreatment lesional volume represented a small proportion of our cohort (53 patients with pretreatment lesional volume >70ml), our results were robust because of the absence of exclusion criteria based on pretreatment lesional volume. Our result is similar to that of a subgroup analysis of the MR CLEAN trial, which found that patients with relatively large estimated pretreatment lesional volume (evaluated by ASPECTS) should be treated, but they included only 30 patients with CT ASPECTS <5.²³

Fourth, we confirmed the importance of substantial reperfusion for a favorable functional outcome, as previously reported elsewhere.^{13,14} Gilgen et al¹⁴ reported that a favorable outcome was achieved in every third patient with DWI lesions >70ml after successful reperfusion,

but in only every 12th patient after poor or failed reperfusion. Olivot et al¹³ also proved that complete recanalization was associated with a more favorable outcome; however, patients were mainly treated with thrombolysis. In our study, substantial reperfusion significantly increased the proportion of patients achieving functional independence. However, reperfusion status was only investigated in a per-protocol analysis of the IVTMT group, because of the absence of this information for patients in the IVT group and for patients in the IVTMT group who did not receive thrombectomy, because they were not monitored with angiography.

Our study has several limitations. First, a relatively smaller treatment effect of MT than in other randomized clinical trials was observed in the THRACE study, likely attributed to the shorter randomization delay and longer time to groin puncture. We only selected a part of the patients, which might explain the nonsignificant effect of MT on functional independence in our cohort. Moreover, the small number of patients with a large pretreatment lesional volume in our cohort may have resulted in a misestimate of the treatment-by-dichotomized lesional volume interaction. Despite this limitation, our results were robust on account of the absence of exclusion criteria based on pretreatment lesional volume. Second, we selected predefined lesional volume thresholds (70 and 100ml) to test treatment-by-volume interaction according to previous studies; the question of a cohort-specific threshold should be investigated. Third, standardized follow-up data at 24 hours are not available in THRACE. This is because imaging modality in THRACE study was determined according to the local routine at each participating center. A majority of the patients only received follow-up CT examinations at 24 hours instead of MRI. In the end, we only analyzed patients who had pretreatment DWI in the THRACE study. However, CT remains the routine first-line modality in acute stroke evaluation, because it is faster and is easier to access in most of the stroke centers. A further substudy of the THRACE trial is planned to elucidate the influence of the two imaging modalities on clinical outcome.

In conclusion, the results of this subgroup analysis of the THRACE study confirmed the independent value of pretreatment lesional volume in predicting functional outcome in ischemic stroke patients post-MT. The clinical benefit of adding MT to thrombolysis decreased as the pretreatment lesional volume increased. However, excluding patients from treatment according to simple pretreatment lesional volume thresholds would appear unadvisable.

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Author Contributions

Y.X., C.O., F.G., and S.B. contributed to the conception and design of the study. Acquisition and analysis of data were performed by Y.X., C.O., F.G., V.G., H.R., S.S., G.H., and S.B. Y.X., C.O., F.G., B.G., J.F., and S.B. drafted text and/or prepared figures.

Potential Conflicts of Interest

Nothing to report.

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Outcome After Reperfusion Therapies in Patients With Large Baseline Diffusion-Weighted Imaging Stroke Lesions A THRACE Trial (Mechanical Thrombectomy After Intravenous Alteplase Versus Alteplase Alone After Stroke) Subgroup Analysis

Vincent Gautheron, MD; Yu Xie, MD; Marie Tisserand, PhD; H el ene Raoult, PhD;
S ebastien Soize, MD; Olivier Naggara, PhD; Romain Bourcier, MD; S ebastien Richard, PhD;
Francis Guillemin, PhD; Serge Bracard, PhD; Catherine Oppenheim, PhD

Background and Purpose—Stroke patients with large diffusion-weighted imaging (DWI) volumes are often excluded from reperfusion because of reckoned futility. In those with DWI_{volume} >70 mL, included in the THRACE trial (Mechanical Thrombectomy After Intravenous Alteplase Versus Alteplase Alone After Stroke), we report the associations between baseline parameters and outcome.

Methods—We examined 304 patients with anterior circulation stroke and pretreatment magnetic resonance imaging. Variables were extracted from the THRACE database, and DWI volumes were measured semiautomatically.

Results—Among 53 patients with DWI_{volume} >70 mL, 12 had favorable outcome (modified Rankin Scale score, ≤2) at 3 months; they had less coronary disease (0/12 versus 12/38; *P*=0.046) and less history of smoking (1/10 versus 12/31; *P*=0.013) than patients with modified Rankin Scale score >2. None of the 8 patients >75 years of age reached modified Rankin Scale score ≤2. Favorable outcome occurred in 12 of 37 M1-occluded patients but in 0 of 16 internal carotid-T/L-occluded patients (*P*=0.010). Favorable outcome was more frequent (6/13) when DWI lesion was limited to the superficial middle cerebral artery territory than when it extended to the deep middle cerebral artery territory (6/40; *P*=0.050).

Conclusions—Stroke patients with DWI lesion >70 mL may benefit from reperfusion therapy, especially those with isolated M1 occlusion or ischemia restricted to the superficial middle cerebral artery territory. The benefit of treatment seems questionable for patients with carotid occlusion or lesion extending to the deep middle cerebral artery territory. (*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.020244.)

Key Words: ischemia ■ magnetic resonance imaging ■ outcome ■ recanalization ■ stroke

The prognosis of acute ischemic stroke because of large vessel occlusion with large baseline lesion's volume is known to be ominous. Because clinical benefit is uncertain,^{1,2} these patients were excluded or underrepresented in recent thrombectomy trials.³ In the THRACE trial (Mechanical Thrombectomy After Intravenous Alteplase Versus Alteplase Alone After Stroke),⁴ patients were not selected by lesion size. Consequently, 57 patients had large lesion based on low (<5) Alberta Stroke Program Early CT Score (ASPECTS).⁴ Interestingly, 17 patients had 3-month favorable outcome (modified Rankin Scale [mRS] score, ≤2), suggesting they may actually derive benefit from reperfusion, in line with previous mono- and bicenter studies.⁵⁻⁸ Ischemic lesion volume is more accurately assessed by direct diffusion-weighted imaging

(DWI) measurements than by ASPECTS.⁹ Using magnetic resonance imaging-selected patients of the THRACE trial, we searched for baseline parameters associated with favorable outcome in those with large DWI lesions, focusing on pre-defined 70- and 100-mL cutoffs.^{2,6-8,10}

Patients and Methods

THRACE⁴—a multicenter randomized controlled trial in France— included patients 18 to 80 years of age with acute ischemic stroke because of proximal occlusion, randomly assigned to receive either intravenous thrombolysis or thrombolysis plus thrombectomy. We selected patients with anterior circulation stroke and occlusion of the intracranial internal carotid artery (ICA) or M1 portion of the middle cerebral artery (MCA) on pretreatment magnetic resonance imaging. DWI_{volume} was determined semiautomatically on Olea Sphere (V3.0;

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From the Department of Neuroradiology, INSERM U894, Sainte-Anne Hospital, Universit e Paris Descartes, France (V.G., O.N., C.O.); Department of Neuroradiology, INSERM U947 (Y.X., S.B.), Department of Neurology (S.R.), and INSERM U1116, CIC-P1433 (S.R., F.G.), Lorraine University, Nancy, France; Department of Neuroradiology, Foch Hospital, Suresnes, France (M.T.); Department of Neuroradiology, CHU Rennes, France (H.R.); Department of Neuroradiology, CHU de Reims, France (S.R.); and Department of Neuroradiology, CHU de Nantes, France (R.B.).

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Correspondence to Catherine Oppenheim, PhD, Department of Neuroradiology, INSERM U894, Sainte-Anne Hospital, Universit e Paris Descartes, CH Sainte-Anne, 1 rue Cabanis, 75014 Paris, France. E-mail c.oppenheim@ch-sainte-anne.fr

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Olea Medical, La Ciotat, France). After motion correction and cerebrospinal fluid masking, a threshold of apparent diffusion coefficient $<0.6 \times 10^{-3} \text{ mm}^2/\text{s}$ was applied to the ADC map, with manual adjustment of lesion boundaries in consensus by 2 neuroradiologists when appropriate. Other variables were extracted from the THRACE database. DWI lesions of the MCA territory were classified as deep when involving the caudate, lentiform nuclei or internal capsule or superficial, otherwise. Patients with mRS score ≤ 2 and > 2 were compared in the DWI_{volume} >70 - and >100 -mL subgroups in univariate analysis (Student *t* test or Mann–Whitney *U* test for quantitative variables and χ^2 test or Fisher exact test for qualitative variables). Inclusion/exclusion criteria and ethics statement of THRACE trial⁴ are provided in Methods in the [online-only Data Supplement](#). The data that support the findings of this study are available from the corresponding author on reasonable request.

Results

Among 414 randomized patients in the THRACE trial, 110 were excluded (108 without pretreatment magnetic resonance imaging, 2 vertebrobasilar strokes). Of the 304 included patients, 56 (18.4%) presented DWI_{volume} >70 mL and 37 (12.5%) >100 mL. A comparison between patients with DWI_{volume} ≤ 70 mL and those with DWI_{volume} >70 mL is provided in Table I in the [online-only Data Supplement](#).

In patients with DWI_{volume} >70 mL, 12 of 53 had 3-month mRS score ≤ 2 (3 patients lost to follow-up; Table). Patients with mRS score ≤ 2 had less coronary disease (0/12 versus 12/38; $P=0.046$) and less history of smoking (1/10 versus 12/31; $P=0.013$). All 8 patients >75 years of age had 3-month mRS score >2 . Favorable outcome occurred in 12 of 37 patients with M1 occlusions but in none of the 16 ICA-T/L occlusions ($P=0.010$). This difference in outcome was not explained by concomitant anterior cerebral arterial territory lesions that were equally observed in M1- (5/37) and ICA- (2/16) occluded patients. Favorable outcome was more frequent in patients with DWI lesion limited to the superficial MCA territory (6/13) than when it also involved the deep MCA territory (6/40; $P=0.050$; Figure). Six of 10 patients with M1 occlusion and DWI lesion limited to the superficial MCA territory had favorable outcome. In patients with DWI_{volume} >70 mL, lesion lateralization and randomization group did not differ between those with favorable and unfavorable outcomes. In an intention-to-treat analysis (3 patients with missing 3-month mRS score considered as unfavorable outcome), patients with mRS score ≤ 2 had less coronary disease, higher DWI-ASPECTS, and less ICA-T/L occlusion (Table II in the [online-only Data Supplement](#)). In the DWI_{volume} >100 -mL subgroup, 8 of 37 patients had an mRS score ≤ 2 . All significant associations observed in the DWI_{volume} >70 mL-subgroup were maintained except for coronary disease.

Discussion

In the THRACE population, 12 of 53 patients achieved favorable outcome, despite pretreatment DWI_{volume} >70 mL. This result is similar to rates reported by others using DWI_{volume} >70 mL^{6–8} or core >70 mL on computed tomographic perfusion maps,¹¹ despite disparities in the administered treatment. Our results question the 70-mL cutoff reliability because the proportion of patients with favorable outcome was similar in the >100 - and >70 -mL subgroups, in line with others.⁶ Interestingly, above the 70- or 100-mL cutoff, DWI_{volume} was not significantly different

Table. Three-Month Outcome in Patients With DWI_{volume} >70 mL

	mRS Score ≤ 2 , n=12	mRS Score > 2 , n=41	P Value
Age, y	53.5 [44.2–68]	65 [50–72.5]	0.149
Women	3/12 (25)	18/41 (43.9)	0.239
Hypertension	5/12 (41.7)	20/41 (48.8)	0.664
History of smoking	1/10 (10)	12/31 (38.7)	0.013
Hypercholesterolemia	8/12 (66.7)	16/35 (45.7)	0.210
Diabetes mellitus	0/12 (0)	8/41 (19.5)	0.097
Coronary disease	0/12 (0)	11/38 (29)	0.046
Baseline glycemia, g/L	1.2 [1–1.3]	1.3 [1.1–1.5]	0.285
Baseline NIHSS score	18.5 [18–21.7]	20 [18.5–22]	0.691
Left hemisphere	5/12 (41.7)	25/41 (61)	0.235
ICA-T/L occlusion	0/12 (0)	16/41 (39)	0.010
Deep and superficial MCA territory	6/12 (50)	34/41 (82.9)	0.050
DWI-ASPECTS	4.5 [3–5.7]	3 [2–5]	0.033
DWI _{volume} , mL	106.4 [85.5–149.8]	127.7 [91.0–163.4]	0.548
Onset-to-MRI delay, min	106.5 [80.5–120]	116 [95.5–138.5]	0.254
Onset-to-thrombolysis delay, min	146.4 [114–170.4]	153 [133.8–172.8]	0.343
Thrombolysis and thrombectomy	5/12 (41.7)	16/41 (39.0)	0.958
Reperfusion mTICI 2b-3	2/4 (50)	5/13 (38.5)	0.682
Any 24-h hemorrhage	0/12 (0)	13/40 (32.5)	0.024
Symptomatic 24-h hemorrhage	0/12 (0)	3/35 (8.6)	0.560

Data are presented as n (%) or median [IQR]. ASPECTS indicates Alberta Stroke Program Early CT Score; DWI, diffusion-weighted imaging; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; mRS, modified Rankin scale; mTICI, modified treatment in cerebral infarction; and NIHSS, National Institutes of Health Stroke Scale.

between patients with and without favorable outcomes, suggesting that a simple DWI_{volume} cutoff is insufficient to exclude patients for treatment.⁶ As in 2 previous studies,^{6,11} all patients >75 years of age with large baseline volumes had unfavorable outcome, suggesting that age could be an additional factor to guide treatment decision-making. Risk factors for atherosclerosis including history of smoking and coronary disease were more frequent in patients with unfavorable outcome. This may be because of a poorer collateral network, lower fibrin clot permeability, more difficult access to the clot during catheterization, and thus higher risk of infarct growth.

An original although expected finding was the association between unfavorable outcome and deep MCA territory involvement. The capsulostratial regions play a key prognostic role in motor recovery and because of their small size, weigh more in ASPECTS than in DWI_{volume}. This likely explains why, in large DWI lesions, ASPECTS remained associated with outcome, whereas DWI_{volume} did not. ASPECTS is also

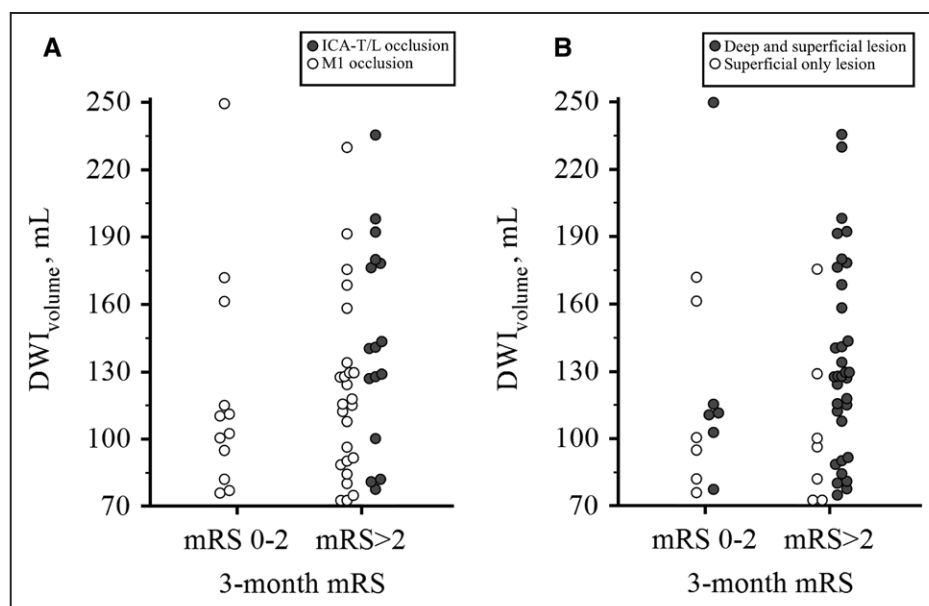


Figure. Baseline diffusion-weighted imaging (DWI) volume and 3-mo outcome (modified Rankin Scale [mRS] score >2, unfavorable) in the 53 patients with $DWI_{\text{volume}} > 70$ mL according to (A) occlusion site, (B) involvement of the deep or superficial middle cerebral artery territory. ICA indicates internal carotid artery.

independent of the total brain volume, while a given lesion volume could have a different clinical meaning in young patients without brain atrophy than in older patients, in whom 70 mL of tissue represents a larger proportion of the entire brain. The frequent involvement of deep MCA territory likely explains the higher frequency of any type of hemorrhagic transformation in patients with unfavorable outcome because deep MCA infarcts are prone to petechial hemorrhage after recanalization.¹²

Finally, ICA-T/L occlusion is a well-known factor of poor outcome after stroke,¹³ but this association has never been studied in patients with $DWI_{\text{volume}} > 70$ mL. Strikingly, none of the 16 patients with ICA occlusion had favorable outcome, which conversely occurred in one third of patients with M1 occlusion. In the only study reporting poor outcome in all 6 $DWI_{\text{volume}} > 70$ mL patients, despite successful reperfusion in 3 of them, all had an ICA occlusion.²

Our study has several limitations: (1) given the THRACE trial design, reperfusion status, which plays a major role in predicting outcome,⁵⁻⁸ was lacking in patients who did not receive thrombectomy; (2) we did not differentiate between ICA-T and ICA-L occlusions or between proximal and distal M1 occlusions; (3) our results do not apply to patients imaged well beyond the IV-thrombolysis time window because magnetic resonance imaging was obtained within 4 hours after onset. Likely, DWI lesions have different tissue fate and prognosis value if captured at an early time point or later on, owing to the DWI reversibility phenomenon that is more frequent and sizeable in the early time frame^{8,14}; and (4) although multicenter and prospective, the THRACE trial was not designed for the purpose of our analysis, which does not allow conclusions to be made about the optimal treatment in large DWI lesions. The small sample size precluded multivariate analysis. Pooled analysis of studies with large DWI will help clarify which of the above parameters are independent prognostic factors. Planned randomized studies for patients with large

infarcts will help elucidate the link between early reperfusion and outcome.

Our multicenter data suggest that patients with M1 occlusion or ischemia restricted to the superficial MCA territory may benefit from reperfusion therapies, despite large DWI lesion. Conversely, the benefit seems questionable for patients with carotid occlusion or DWI lesion extending to the deep MCA territory. Validation in larger cohorts is warranted.

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Disclosures

None.

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Stroke

SUPPLEMENTAL TABLES

Online supplemental Table I. Baseline characteristics and outcomes

	All population n=304	DWI-volume\leq70mL n=248	DWI-volume$>$70mL n=56	P-value
Age, years	67 [54-74]	68 [55-75]	61.5 [45.5-70.8]	0.016
Women	145/304 (47.7)	123/248 (49.7)	22/56 (39.3)	0.163
Hypertension	155/301 (51.5)	128/245 (52.2)	27/56 (48.2)	0.586
Past smoking	51/264 (19.3)	38/220 (17.3)	13/44 (29.6)	0.06
Hypercholesterolemia	142/271 (52.4)	117/221 (53)	25/50 (50.0)	0.707
Diabetes mellitus	31/301 (10.3)	22/245 (9)	9/56 (16.0)	0.115
Coronary disease	42/290 (14.5)	30/237 (12.7)	12/53 (22.6)	0.062
Baseline glycemia, g/L	1.17 [1.0-1.4]	1.16 [1.0-1.4]	1.20 [1.0-1.4]	1.000
Baseline NIHSS score	18 [14-20]	17 [13-20]	19.5 [18-22]	<0.001
Left hemisphere	145/304 (47.8)	115/248 (46.4)	30/56 (53.6)	0.330
ICA-T/-L occlusion	47/304 (15.5)	31/248 (12.5)	16/56 (28.6)	0.003
MCA ischemic territory lesion				
Superficial	208/304 (68.4)	153/248 (61.7)	56/56 (100)	<0.001
Deep and superficial	173/304 (56.9)	131/248 (52.8)	42/56 (75.0)	0.003
DWI-ASPECTS	7 [5-9]	8 [6-9]	3 [2-5]	<0.001
DWI _{volume} , mL	17.2 [9.3-52.5]	13.90 [7.3-29.1]	115.48 [89.2-154.5]	<0.001
Onset-to-MRI delay, min	114 [90-138]	114 [90-138]	114 [96-138]	0.522
Onset-to-thrombolysis delay, min	150 [126-180]	150 [120-180]	156 [126-174]	0.703
Thrombolysis and thrombectomy	149/304 (49.0)	92/248 (37.1)	20/56 (35.7)	0.846
Reperfusion mTICI 2b-3	74/104 (71.2)	22/86 (25.6)	7/18 (38.9)	0.252
mRS score 0-2	142/298 (51.0)	140/245 (57.1)	12/53 (22.6)	<0.001
Death	34/298 (11.4)	15/245 (6.1)	18/53 (34.0)	<0.001
Any 24hr hemorrhage	45/295 (15.2)	32/241 (13.3)	13/54 (24.1)	0.046
Symptomatic 24hr hemorrhage	6/282 (2.1)	3/233 (1.3)	3/49 (6.1)	0.067

Data are presented as n/N(%) or median [IQR]. mRS, modified Rankin Scale; mTICI, modified treatment in cerebral infarction; ICA, internal carotid artery; MCA, middle cerebral artery; ASPECTS, Alberta Stroke Program Early CT-Score. P-values were calculated between DWI_{volume \leq 70mL} and DWI_{volume $>$ 70mL} groups.

Online supplemental Table II. 3-month outcome in Patients with DWI_{volume}>70mL. Intention-to-treat analysis*

	mRS≤2, n=12	mRS>2, n=44	P-value
Age, years	53.5 [44.2-68]	65 [49.5-73.8]	0.159
Women	3/12 (25)	19/44 (43.2)	0.329
Hypertension	5/12 (41.7)	22/44 (50)	0.748
History of smoking	1/10 (10)	12/34 (35.3)	0.237
Hypercholesterolemia	8/12 (66.7)	17/38 (44.7)	0.321
Diabetes mellitus	0/12 (0)	9/44 (19.5)	0.180
Coronary disease	0/12 (0)	12/41 (29.3)	0.048
Baseline glycemia, g/L	1.2 [1-1.3]	1.3 [1-1.5]	0.214
Baseline NIHSS score	18.5 [18-21.7]	20 [18-22]	0.740
Left hemisphere	5/12 (41.7)	25/44 (56.8)	0.515
ICA-T/-L occlusion	0/12 (0)	16/44 (36.4)	0.012
Deep and superficial MCA territory	6/12 (50)	36/44 (81.8)	0.054
DWI-ASPECTS	4.5 [3-5.7]	3 [2-5]	0.033
DWI _{volume} , mL	106.4 [85.5-149.8]	125.6 [89.1-154.5]	0.448
Onset-to-MRI delay, min	106.5 [80.5-120]	115 [94.3-138.8]	0.281
Onset-to-thrombolysis delay, min	146.4 [114-170.4]	153 [129.2-173.7]	0.522
Thrombolysis and thrombectomy	5/12 (41.7)	17/44 (38.6)	1
Reperfusion mTICI 2b-3	2/4 (50)	5/14 (35.7)	1
Any 24hr hemorrhage	0/12 (0)	13/42 (31)	0.050
Symptomatic 24hr hemorrhage	0/12 (0)	3/37 (8.1)	0.566

Data are presented as n/N (%) or median [IQR]. mRS, modified Rankin Scale; mTICI, modified treatment in cerebral infarction; ICA, internal carotid artery; MCA, middle cerebral artery; ASPECTS, Alberta Stroke Program Early CT-Score. *Three patients with missing 3-month mRS are considered in the unfavorable outcome group.

Discussion

Our results suggested that increased pretreatment lesional volume was an independent predictor for unfavorable clinical outcome and mortality in acute ischemic stroke patients with anterior proximal intracranial arterial occlusion after IVT or IVTMT. The clinical benefit of adding mechanical thrombectomy decreased with the increase of lesional volume. Meanwhile, we indicated that certain patients with large lesional volume may still benefit from reperfusion therapy.

The strong points in our studies are:

1. The data was extracted from a multicenter randomized controlled trial, and the sample size for investigating the association between lesional volume with clinical outcome was relatively large, which premised the reliability and the representativeness of our results. In addition, the absence of exclusion criteria on the basis of pretreatment lesional volume in the THRACE study provided a unique opportunity for studying the impact of lesional volume in stroke, especially in patients with large lesional volume.
2. DWI, which is considered as the most accurate sequence available in the assessment of ischemic lesion in acute phase, was analyzed in our studies.
3. Automatic segmentation method was used for lesion detection, which is efficient, reproducible and easy for clinical application.
4. To the extent of our knowledge, our study is the first to investigate the benefit of adding thrombectomy to thrombolysis according to the size of lesional volume. Our results indicated that the benefit of thrombectomy decreased with the increase of lesional volume.
5. We selected 70 mL and 100 mL as predefined large volume thresholds, both having been widely suggested in previous studies. Our results suggested that volume threshold should not be used alone as the patient exclusion criterion for therapy selection.

However, several limitations lie in our research:

1. The main objective of the THRACE study was to compare the IVT with IVTMT in acute ischemic stroke; our results were obtained from the retrospective sub-studies, which may introduce bias in the results. Moreover, our results have no implication in selecting the optimal treatment method according to pretreatment lesional volume for stroke patients. In order to achieve this purpose, prospective studies are needed.
2. Reperfusion status was not available in patients who received IVT in the THRACE study. Therefore, it was not taken into account when analyzing the relationship between lesional volume and clinical outcome. However, reperfusion is an important factor for clinical outcome. Olivot et al. demonstrated that compared to patients with no recanalization, the OR of favorable clinical outcome was 2.96 (95% CI, 0.95-9.25) for partial recanalization and 11.85 (95% CI, 4.06-34.57) for complete recanalization (87). Our results also showed that substantial reperfusion increased the proportion of patients achieving functional independence by 38.9% (95% CI, 16.9-60.9; $p=0.001$) in IVTMT subgroup patients. However, the importance of reperfusion in the IVT group was not analyzed in our study due to the lack of angiography in this part of patients.
3. The number of patients who had large lesional volume is small, which precluded the multivariate analysis for exploring the independent factors associated with favorable clinical outcome in these patients. Therefore, the conclusion of our subgroup study should be interpreted with caution.
4. Previous researches reported that large lesional volume indicated a higher risk of symptomatic intracranial hemorrhage (sICH) (88). sICH was a rare event in the THRACE study: only 7 patients in the whole cohort presented sICH. Of the 298 patients included in our analyses, 2 of 5 patients who presented sICH had pretreatment lesional volume > 70 mL. We did not perform statistical analyses due to small sample.
5. Our results do not apply to patients imaged beyond the time window of IVT, because all the patients in the THRACE study were included within 4 hours after the symptom onset. Recent studies suggested that selected ischemic stroke patients within 24 hours can still benefit from thrombectomy (35, 36). Further studies are needed to investigate the association between lesional volume and clinical outcome in patients after 4 hours of stroke onset. Furthermore, our results only fit for ischemic stroke patients with occlusion

of proximal intracranial artery in the anterior circulation. The association between lesional volume and clinical outcome in stroke patients with posterior circulation occlusion need additional study.

In conclusion, our studies provided new evidences on the association between lesional volume and clinical outcome in acute ischemic stroke. Pretreatment lesional volume is an independent predictor for functional outcome in acute ischemic stroke with proximal intracranial occlusion. Meanwhile, excluding patients only according to their lesional volume is unadvisable. Further studies are still needed to investigate the role of lesional volume in guiding patient selection for treatment.

Résumé en français

Impact du volume lésionnel prétraitement sur le résultat clinique et l'efficacité de la thrombectomie mécanique chez les patients présentant un AVC ischémique

Contexte et objectif

Il a été prouvé que le volume lésionnel était associé au résultat clinique après une thrombolyse. Cependant, actuellement, les données sur l'association entre le volume lésionnel prétraitement et le résultat clinique après une thrombectomie sont relativement faibles, et la plus part sont monocentriques. Nous avons cherché à caractériser dans ce travail l'association entre le volume lésionnel prétraitement mesuré sur l'IRM de diffusion et le résultat fonctionnel à 3 mois, et à estimer l'impact du volume lésionnel sur l'efficacité de la thrombectomie mécanique pour l'AVC ischémique avec occlusion artérielle intracrânienne proximale antérieure.

Dans la pratique clinique courante, la thérapie de reperfusion n'est généralement pas prise en compte chez les patients ayant un gros volume lésionnel, en raison du faible apport de bénéfice. Néanmoins, il existe des preuves de succès du traitement chez ces patients. Nous explorons ici les associations entre les paramètres de base et les résultats cliniques chez les patients dont le volume en DWI est important dans l'étude THRACE.

Méthode

L'étude a porté sur les patients présentant un AVC ischémique avec occlusion artérielle intracrânienne proximale antérieure. Les lésions ischémiques en DWI prétraitement ont été automatiquement segmentées avec le logiciel Olea Sphere® en appliquant un seuil d'ADC de $0,6 \times 10^{-3}$ mm²/s sur la cartographie d'ADC et corrigées par un neuroradiologue expérimenté. L'évolution fonctionnelle a été évaluée par le score mRS dichotomisé (0-2 indiquent un résultat favorable et 3-6 indiquent un résultat défavorable) et par le score mRS ordinal. Des analyses logistiques univariées et multivariées ont été faites pour évaluer les associations entre le VLP (volume lésionnel prétraitement) et le résultat fonctionnel, ainsi que l'efficacité de la thrombectomie.

De plus, les facteurs prédictifs d'un bon résultat fonctionnel chez les patients ayant un gros volume (volume en DWI >70 mL ou 100 mL) ont été cherchés. Les lésions du territoire de l'artère cérébrale moyenne (ACM) ont été classées comme étant profondes lorsqu'elles impliquent le noyau caudé, le noyau lenticulaire ou le capsule interne, ou superficielle, sinon.

Du fait de la faible taille de l'échantillon (53 patients), seulement l'analyse univariée a été réalisée pour étudier l'association entre les facteurs et le résultat fonctionnel.

Résultats

298 patients ont été analysés pour chercher l'association entre le VLP et le résultat clinique, dont 148 dans le groupe IVTMT. Le VLP moyen était de 17,2 mL (IQR 9,2-51,8). Le mRS à 3 mois était de 2 (IQR 1-4). 51% des patients atteignaient un mRS 0-2 à 3 mois.

1. Pour l'association entre le VLP et le résultat clinique

- Une augmentation du mRS a été associée à un VLP plus grand, le coefficient de corrélation de Spearman était de 0,34 ($p < 0,0001$).
- L'analyse logistique multivariée a montré que les facteurs pronostiques indépendants de l'indépendance fonctionnelle étaient : le VLP, l'âge, le score NIHSS, le site de l'occlusion et la glycémie. Les facteurs pronostiques indépendants pour le degré d'invalidité étaient : le VLP, l'âge, le score NIHSS et le site de l'occlusion. Les facteurs pronostiques indépendants pour la mortalité étaient le VLP et l'âge.
- La probabilité d'obtenir l'indépendance fonctionnelle diminuait avec l'augmentation de l'âge, du score NIHSS et du VLP.

2. Pour l'association entre le VLP et l'efficacité de la thrombectomie mécanique

- Il n'y avait pas de différence significative pour le VLP, le mRS à 3 mois et le score NIHSS à 24 heures entre les groupes IVT et IVTMT.
- Par rapport à l'IVT seule, l'IVTMT augmentait (non significativement) la proportion de patients atteignant un mRS 0-2 de 11,4% (95% IC [-0,5; 23,4]; $p=0,06$).
- Dans le groupe IVTMT, la recanalisation augmentait la proportion de patients atteignant un mRS 0-2 de 38,9% (95% IC [16,9; 60,9]; $p=0,001$).
- La probabilité d'atteindre un mRS 0-2 diminuait avec l'augmentation du VLP (par 10mL): pour le groupe IVTMT: OR 0,87 (95% IC [0,77-0,98], $p=0,02$) ; pour le groupe IVT: OR 0,89 (95% IC [0,80-0,97], $p=0,01$); pour le groupe IVTMT avec un mTICI 2b/3: OR 0,82 (95% IC [0,66-0,98], $p=0,047$).
- Le nombre nécessaire à traiter (*number needed to treat*, NNT) pour un patient atteignant l'indépendance fonctionnelle par thrombectomie mécanique augmentait avec l'augmentation du VLP.
- La probabilité de mortalité augmentait avec l'augmentation du VLP (par 10mL). Pour le groupe IVTMT nous avons obtenu un OR de 1,21 (95% IC [1,07-1,38], $p=0,003$) ;

pour le groupe IVT OR 1,29 (95% IC [1,17-1,45], $p < 0,001$) ; et pour le groupe IVTMT avec mTICI 2b/3 OR 1,26 (95% IC [1,01-1,60], $p = 0,04$).

- Nous n'avons pas observé d'interaction significative entre le traitement et le VLP dichotomisé (70 mL et 100 mL) pour l'indépendance fonctionnelle et la mortalité.
3. Pour l'association entre les caractéristiques initiales et le résultat fonctionnel chez les patients avec un gros VLP
- 53 patients présentaient un VLP en DWI > 70 mL. Les patients avec un résultat favorable (12 patients) avaient moins de maladies coronariennes (0/12 contre 12/38 ; $P = 0,046$; 3 patients avec valeurs manquantes) et moins d'antécédents de tabagisme (1/10 contre 12/31 ; $P = 0,013$; 12 patients avec valeurs manquantes) que ceux ayant un résultat défavorable (soit 41 patients). Aucun des 8 patients âgés de plus de 75 ans n'a atteint un mRS ≤ 2 .
 - Des résultats favorables ont été observés chez 12 des 37 patients avec occlusion M1, mais chez aucun des 16 patients avec occlusion de la carotide interne-T/L ($P = 0,010$). Le résultat favorable était plus fréquent (6/13) lorsque la lésion était limitée au territoire ACM superficielle que lorsqu'elle s'étendait au territoire ACM profonde (6/40 ; $P = 0,050$).

Discussion

Notre travail a montré que le VLP était un prédicteur indépendant de l'invalidité et de la mortalité à 3 mois, même lorsque le statut de reperfusion était pris en considération. Ce résultat est en accord avec les études précédentes (83,87,88). De plus, un bénéfice lié à l'ajout de la thrombectomie à la thrombolyse pour tous les patients a été observé ; mais celui-ci diminuait avec l'augmentation du VLP. Nos résultats ont montré que l'exclusion des patients ayant un VLP supérieur aux seuils étudiés (70 mL et 100 mL) au traitement n'était pas raisonnable. L'importance de la reperfusion substantielle pour un résultat fonctionnel favorable a été confirmée dans notre cohorte, comme indiqué dans les études précédentes (87,88).

De plus, les patients ayant un gros VLP ont pu aussi bénéficier d'un traitement de reperfusion, en particulier ceux qui présentaient une occlusion M1 isolée ou une ischémie limitée au territoire ACM superficiel. Le bénéfice du traitement pour les patients présentant une occlusion carotidienne ou une lésion s'étendant jusqu'au territoire MCA profonde restait à discuter.

Chapter 4

Ischemic stroke lesional location and functional outcome

Introduction

In this chapter, we will discuss the association between pretreatment lesion location estimated on DWI and functional outcome after mechanical thrombectomy in ischemic stroke patients.

Several clinical and imaging characteristics have been suggested to predict functional outcome of ischemic stroke. Lower age and less stroke severity, measured by NIHSS score, have been proved to be independent predictors of favorable outcome (126). Age and NIH Stroke Scale (SPAN) index by combining age in years plus $\text{NIHSS} \geq 100$ was created by Gustavo et al. to estimate the clinical response after rtPA for acute ischemic stroke. The benefit of rtPA was present only in SPAN-100-negative patients (127). Infarct volume and ASPECT, assessed on CT or MRI, also presented important value in outcome prediction, both in patients after intravenous thrombolysis and thrombectomy (88,126,128,129). However, final infarct volume was reported to be moderately correlated with brain function ($r=0.3$ to 0.6 in different outcome assessment scale) (130,131).

Stroke location is another useful radiological feature for outcome prediction. Stroke can affect any part of the brain in the occluded arterial territory and often includes different functional areas. Some areas are more eloquent than others in functional outcome assessment. For example, internal capsule, as a part of corticospinal tract, could induce severe motor deficits if damaged, and affect functional outcome. However, cortical stroke is linked to functional deficits to a lesser extent. Menezes et al. developed atlases consisting location-weighted values indicating the relative importance in terms of neurological deficit for every voxel of the brain, and showed that the addition of location resulted in a significantly better correlation with clinical deficit severity than volume alone (from $r=0.62$ to $r=0.79$) (131). A number of studies explored the important infarct location using region-based or voxel-based analyses, suggesting several important regions in predicting stroke outcome (106–109). However, these studies analyzed lesion location only on post-treatment images. Little evidence could be found with regard to pretreatment data. This is probably due to the concern that lesion evolves variably after treatment depending on time and recanalization status. In order to incorporate the lesion location as a parameter in treatment decision making, it is necessary to study the association between pretreatment lesion location and clinical outcome.

Patients in THRACE study who underwent baseline DWI exam and who were treated by mechanical thrombectomy were included in our work.

The objective of this study is to investigate the predictive value of pretreatment DWI-measured lesion location on functional outcome at 3 months. Models were built by logistic regression and support vector machine (SVM) for functional outcome prediction. Logistic regression is similar to linear regression, but it uses a logit transformation of the binomial response variable (132). SVM (133) is a supervised machine learning algorithm which takes a set of input data and builds a model predicting the possible classes comprises the input data, making it a non-probabilistic linear classifier. Then the model can be used to assign new data into one category or the other. First prediction models included age, initial NIHSS score and total lesional volume. The first models were then retrained by including the ischemic percentage in each brain regions and by automatically selecting the best subset variables. 10-fold cross validation was performed to assess the generalizability of our models. The models were evaluated using the prediction accuracy. Furthermore, important brain regions which are associated with functional outcome were selected automatically by the model.

Impact of Pretreatment Ischemic Location on Functional Outcome after Thrombectomy

Abstract

Objective: To evaluate the impact of pretreatment ischemic location on functional outcome in anterior circulation ischemic stroke treated by mechanical thrombectomy.

Methods: Ischemic stroke patients who received intravenous thrombolysis plus mechanical thrombectomy in the THRACE study were included. Ischemic lesions were semi-automatically segmented on pretreatment diffusion-weighted imaging and registered on brain atlases. Percentage of ischemic tissue in each region was calculated. Statistical models were built to analyze the predictors of functional outcome (3-month modified Rankin Scale). The investigated parameters included: age, baseline National Institutes of Health Stroke Scale score and lesional volume (3-parameter model, M_{p3}), together with the ischemic percentage in each region (4-parameter model, M_{p4}). Logistic regression and support vector machine were applied to build the model.

Results: Of 143 included patients, with median ischemic volume 20.5 mL (interquartile range 10.3-51.0), 51.4% had left-hemisphere stroke. Functional outcome was comparable for left- and right-hemispheric stroke. Support vector machine with radial basis functions outperformed logistic regression in prediction accuracy. Support vector machine- M_{p3} demonstrated an accuracy of 70.5%, while M_{p4} achieved a higher accuracy of 77.3%. The lesional volume did not persist as an independent predictor in M_{p4} . Regions with important impacts in outcome prediction were: in left hemisphere, uncinate fasciculus, postcentral gyrus, putamen, middle occipital gyrus, supramarginal gyrus, posterior corona radiata; in right hemisphere, uncinate fasciculus, paracentral lobule, temporal pole, hippocampus, inferior occipital gyrus, middle temporal gyrus, pallidum and anterior limb of internal capsule.

Interpretation: Pretreatment ischemic location provided important prognostic information for functional outcome.

Introduction

An accurate prediction of functional outcome at acute stage of ischemic stroke is important for personalized treatment decision-making and early rehabilitation strategies, and informing patients and their family of possible outcome, as well as optimizing patient inclusion criteria and end-point for clinical trials.^{1,2}

Several clinical and imaging features have been proposed as appropriate candidates to predict post-stroke functional outcome, with the most robust among them being age, initial stroke severity which is evaluated by the National Institutes of Health Stroke Scale (NIHSS) score, and infarct volume.³⁻⁷

Recently, a growing number of studies proposed infarct location on posttreatment imaging as an additional prognostic factor for stroke outcome.⁸⁻¹¹ However, little evidence have been found with regard to pretreatment ischemic location, probably because lesion evolves very fast in the acute stage of stroke onset. Moreover, some important factors, such as age, NIHSS score and lesional volume, have often not been taken into consideration in clinical studies.^{8,9} Randomized clinical trials have demonstrated the benefit of mechanical thrombectomy in acute ischemic stroke patients with anterior circulation proximal intracranial occlusions.¹²⁻¹⁹ Therefore, it is of great clinical interest to investigate the pretreatment imaging profile in patients who received mechanical thrombectomy.

In this study, we investigated whether the pretreatment (< 4.5h of stroke onset) ischemic location could provide additional prediction value on functional outcome at 3 months after mechanical thrombectomy. The ischemic location was analyzed at both the hemispheric scale and the atlas-based regional scale. Logistic regression²⁰ and support vector machine²¹ (SVM) techniques were used in the regional scale investigation.

Patients and Methods

Patient Selection and Clinical Assessment

We analyzed patients in the THRombectomie des Artères CÉrebrales (THRACE) trial (Clinical Trial Registration-URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01062698), a randomized controlled multicenter trial in France between 2009 and 2015, aiming at comparing intravenous thrombolysis plus mechanical thrombectomy (IVTMT) and intravenous thrombolysis alone (IVT) in patients with acute ischemic stroke due to proximal arterial occlusion, aged 18-80 and with a NIHSS score of 10 to 25. The study design and patient inclusion criteria have been described in detail previously.¹⁷ The study protocol was approved by the CPP (Comité de Protection des Personnes) Est III Ethics Committee and the research boards of the participating centers. All patients or their legal representatives provided written informed consent. In this work, we selected patients assigned in the IVTMT group who had an anterior circulation occlusion and qualified pretreatment diffusion-weighted imaging (DWI) data. We excluded patients with severe atrophy or hydrocephaly which could cause inaccurate ischemic location assessment.

Demographic and clinical data and functional outcome were extracted from the THRACE database. Functional outcome at 3 months was measured by modified Rankin Scale (mRS), which consists of 7 grades: from 0 (no symptoms) to 6 (death). mRS was dichotomized into 0-2 versus 3-6, with 0-2 indicating functional independence.

Image Acquisition, Segmentation and Normalization

Pretreatment DWI data were acquired on 1.5T or 3T MRI scanners (General Electric Healthcare, WI, USA; Philips medical systems, Best, The Netherlands; Siemens, Erlangen, Germany) according to the established local routines.

Ischemic lesions were segmented semi-automatically with our own developed software after applying a threshold of apparent diffusion coefficient (ADC) $< 615 \times 10^{-6} \text{mm}^2/\text{s}$ on ADC maps.²² The generated lesion masks were then normalized to standard Montreal Neurological Institute space using statistical parametric mapping software (SPM12, Wellcome Trust Center for Neuroimaging, London, United Kingdom). All the image post-processing results were checked by a junior neurologist (with experience of reading stroke images < 5 years) and an

experienced neuroradiologist (with experience of reading stroke images > 5 years), both blind to clinical information.

Regional Ischemic Location Determination

Regional ischemic location was determined according to Automated Anatomical Labeling²³ (AAL) (as gray matter atlas) and Johns Hopkins University-WhiteMatter-labels-1mm (JHU-WM) atlas (for white matter tracks) available in the MRICron software package (<http://people.cas.sc.edu/rorden/mricron/index.html>). The determination of ischemic location was performed in MATLAB (<https://www.mathworks.com/products/matlab.html>, Mathworks Inc., Sherborn, MA, USA). The ischemic percentage in each anatomical region was calculated.

Prediction Model Building

Two machine learning approaches, logistic regression (linear model) and SVM with radial basis functions (non-linear model), were used to build prediction models. These two approaches were first tested using only conventional parameters (age, baseline NIHSS score and lesional volume) to build 3-parameter models (LogReg-M_{p3} model and SVM-M_{p3} model). The M_{p3} prediction models were then retrained by including the ischemic percentage in each brain regions and by automatically selecting the best subset of parameters using either a least absolute shrinkage and selection operator (LASSO) regularization²⁴ for the logistic regression or a feature ranking method²⁵ for the SVM (4-parameter models: LogReg-M_{p4} model and SVM-M_{p4} model). F₁ score was used to measure the impact of adding features to the model on prediction performance (The F₁ score is a measure of a test's accuracy. It is the harmonic average of the precision and recall, where it reaches its best value at 1 and worst at 0). In order to assess the generalizability of our models, a repeated cross validation was performed for each model, which means that the dataset was divided in ten subsets. The models were then trained on nine subsets and tested on the remaining one. This process was repeated so to use all ten subsets for evaluation in order to get one accuracy score. The random division of subsets was repeated hundred times, providing 100 accuracy scores for each model.

Statistical Analysis

Baseline characteristics and functional outcome were compared between left- and right-hemisphere stroke patients. Continuous variables were tested for normality by Shapiro-Wilk

test and described in the form of mean and standard deviation (SD) if normally distributed, or in the form of median and interquartile range (IQR) if not. Categorical variables were expressed as proportions. Two-sided comparisons were performed by Wilcoxon test and chi-square test, respectively. The assessment of the difference between the accuracy scores using different prediction models is evaluated by Wilcoxon test. $\alpha=0.05$ was chosen as the significance level.

The data analysis process is presented in Figure 27. All the statistical analyses were performed using statistical software R (R Foundation for Statistical Computing, Vienna, Austria) and MATLAB (<https://www.mathworks.com/products/matlab.html>, Mathworks Inc., Sherborn, MA, USA). The LIBSVM package was used for the implementation of SVM models.²⁶

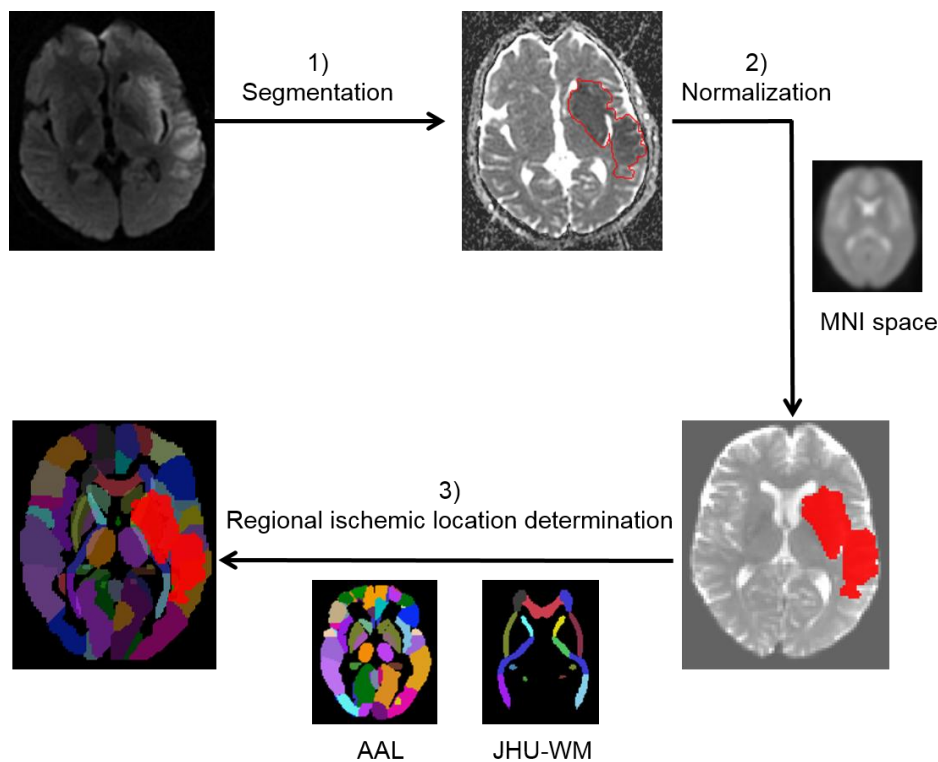


Figure 27. Workflow of lesion location determination: 1) Ischemic lesions were segmented semi-automatically. 2) The generated lesion masks were then normalized to standard Montreal Neurological Institute space using SPM12. 3) The regional ischemic location was determined according to Automated Anatomical Labeling and Johns Hopkins University-WhiteMatter-labels-1mm atlas. (MNI = Montreal Neurological Institute; AAL = Automated Anatomical Labeling atlas; JHU-WM = Johns Hopkins University-WhiteMatter-labels-1mm atlas.)

Results

Patient Characteristics

Overall, 143 acute stroke patients (59 female and 84 male) met the inclusion criteria in our study (Figure 28). The cohort had a median age of 66 (IQR 54-74). Median ischemic volume was 20.5 mL (IQR 10.3-51.0). 74 (51.7%) patients had left-hemisphere stroke.

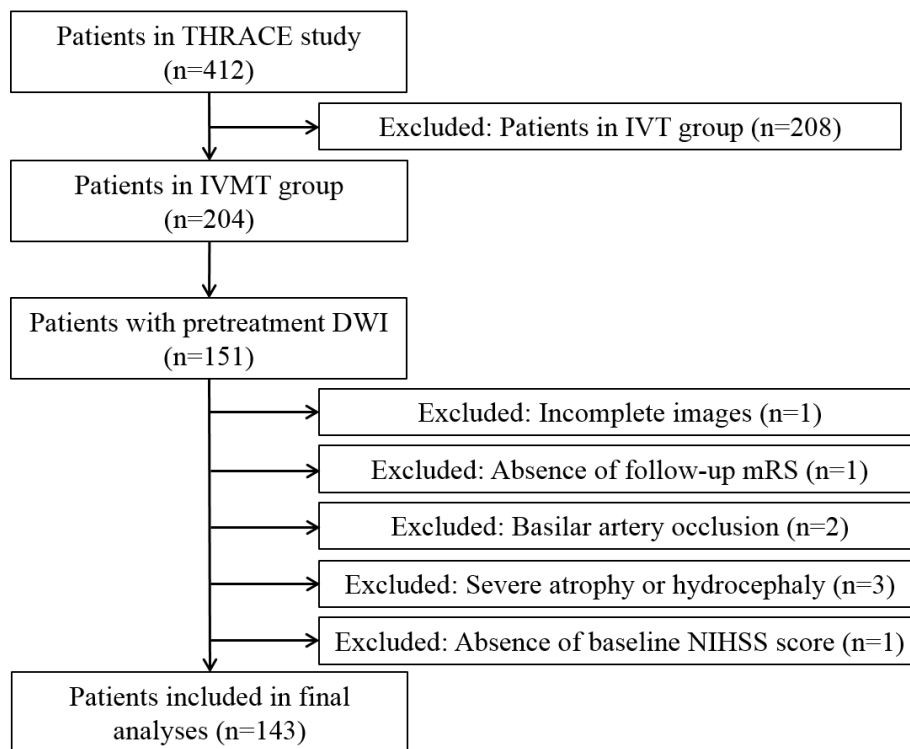


Figure 28. Patient selection flowchart. IVT = intravenous thrombolysis; IVTMT = intravenous thrombolysis plus mechanical thrombectomy; DWI = diffusion-weighted imaging; mRS = modified Rankin Scale.

Effect of Hemispheric Lateralization on Functional Outcome

Baseline characteristics and functional outcome of the left- and right-hemisphere stroke patients are listed in Table 5. Baseline NIHSS score was significantly higher in the left-hemisphere stroke patients than in the right-hemispheric patients ($p < 0.001$). Functional outcome at 3 months was comparable for stroke in either hemisphere.

Table 5. Baseline characteristics and functional outcome of left- vs right-hemisphere stroke patients

	Left hemisphere (n=74)	Right hemisphere (n=69)	<i>p</i>
Age, years	64(52-74)	68(57-73)	0.34
Sex, female/male	31/43	28/41	0.99
Diabetes mellitus	4/73 (5.5%)	4/68(5.9%)	0.99
Hypertension	33/74(44.6%)	33/67(49.3%)	0.70
Smoking (current or past)	36/63(57.1%)	23/64(35.9%)	0.03*
Hypercholesterolemia	34/62(54.7%)	26/63(41.3%)	0.18
Coronary disease	7/70(10.0%)	10/67(14.9%)	0.54
History of stroke	4/71(56.3%)	4/65(61.5%)	0.99
Admission glucose, g/L	1.2(1.0-1.5)	1.2(1.0-1.4)	0.62
Baseline NIHSS score	20(18-22)	15(12-17)	<0.001*
Time from stroke onset to imaging, min	113(85-143)	116(93-127)	0.65
Time from stroke onset to randomization, min	173(143-202)	161(142-183)	0.13
Occlusion location, ICA:M1	10:64	5:64	0.34
ASPECT score	7(5-8)	7(6-8)	0.04*
Fazekas score	0(0-1)	1(0-1)	0.10
Functional outcome (mRS)	2(1-4)	2(1-4)	0.33
Favorable functional outcome (mRS≤2)	40/74 (54%)	42/69 (61%)	0.51
Ischemic volume, mL	21.6(11.1-54.4)	19.2(10.2-32.7)	0.51

Quantitative data are presented in median (interquartile range); qualitative data are presented by no. (%). NIHSS = National Institutes of Health Stroke Scale; ICA = intracranial internal carotid artery; M1 = proximal portion of middle cerebral artery; ASPECT = Alberta Stroke Program Early CT Score; mRS = modified Rankin Scale. * = *p* value < 0.05.

Effect of Ischemic Topography on Functional Outcome

Table 6 assembles the accuracy of the four different models. It can be seen that a linear model using only conventional parameters (LogReg-M_{p3} model) reached an accuracy of 70.1%, which was similar to 70.5% of the nonlinear model (SVM-M_{p3} model). Adding the ischemic percentage in each brain regions led to an increased accuracy, with an accuracy of 73.3% (increment of 3.2%) for the linear model (LogReg-M_{p4} model) and an accuracy of 77.3% (increment of 6.8%) for the nonlinear model (SVM-M_{p4} model). The accuracy of SVM-M_{p4} model was significantly higher than LogReg-M_{p4} model ($p < 0.001$). It can also be noted that the lesional volume was not selected as a predictor by the automated approach in the SVM-M_{p4} model. The Figure 29 illustrated that the model reached the highest performance on the validation set when using 16 features. Regions with important impacts in functional outcome prediction and their function were: in left hemisphere, uncinate fasciculus, postcentral gyrus, putamen, middle occipital gyrus, supramarginal gyrus, posterior corona radiata; in right hemisphere, uncinate fasciculus, paracentral lobule, temporal pole, hippocampus, inferior occipital gyrus, middle temporal gyrus, pallidum and anterior limb of internal capsule.

Table 6. Accuracy of different models using repeated cross fold validation

Model	LogReg-M _{p3}	LogReg-M _{p4}	SVM-M _{p3}	SVM-M _{p4}
Accuracy (Mean ± SD)	70.1% ± 1.0	73.3% ± 1.0	70.5% ± 1.8	77.3% ± 1.4

Age, baseline National Institutes of Health Stroke Scale and lesional volume were included in 3-parameter models (LogReg-M_{p3} and SVM-M_{p3}) for outcome prediction. Ischemic percentage in each brain region was also included in 4-parameter models (LogReg-M_{p4} and SVM-M_{p4}). LogReg = logistic regression; SVM = support vector machine; SD = standard deviation

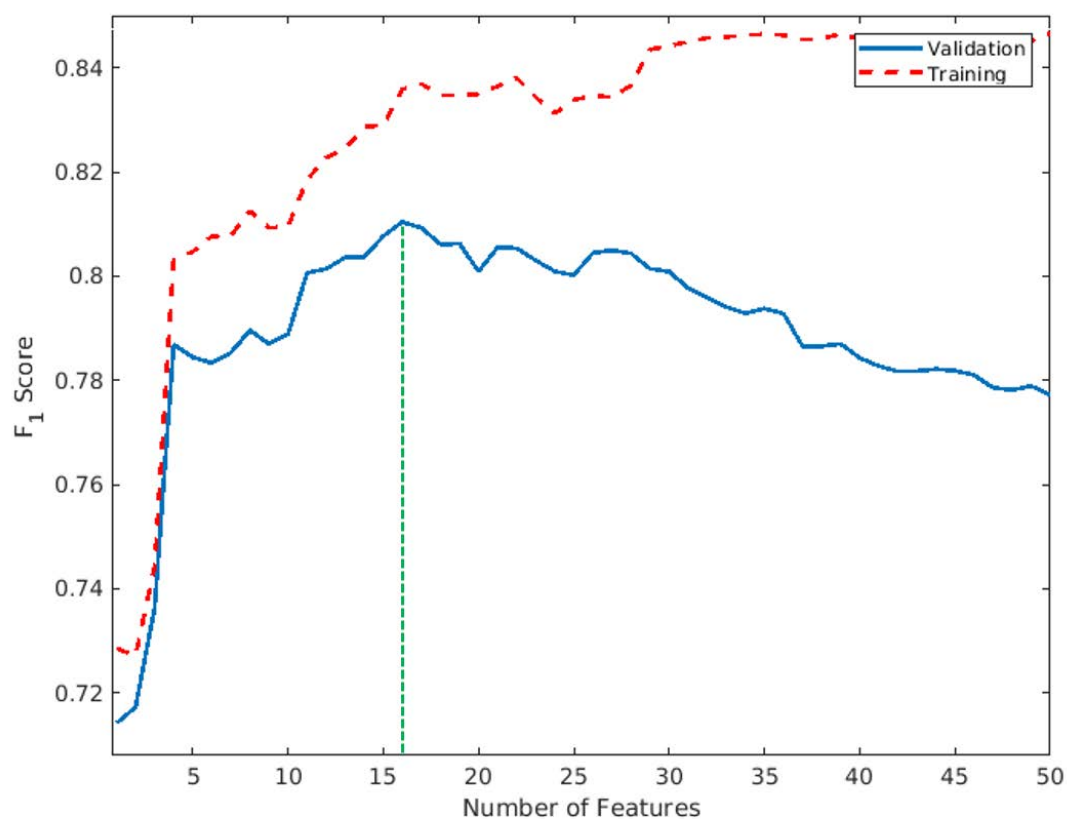


Figure 29. F₁ score obtained on the average training (red dotted line) and validation (blue line) sets during cross-validation performed by SVM after adding different features. The model reaches the highest performance on the validation set when using 16 features (green dotted line). SVM = support vector machine.

Discussion

To the best of our knowledge, our work was the first attempt of identifying the additional prognostic value of pretreatment ischemic location on functional outcome, compared to the conventional parameters (age, baseline NIHSS score and lesional volume). We investigated both hemispheric lateralization and atlas-based regional location effect on functional outcome. Furthermore, a nonlinear machine learning method was utilized in our study as such an approach can allow a better classification than using linear models, especially when incorporating additional features (percentage of ischemic tissue in each brain regions).

From the perspective of hemispheric scale, our results suggested that ischemia hemispheric lateralization did not impact significantly on functional outcome. This was in line with a previous study which demonstrated that there was no difference in functional outcome

between patients with right or left hemisphere stroke.²⁷ Our results supported the reliable value of mRS in functional outcome evaluation in both hemispheric stroke patients. However, the baseline NIHSS score in right-hemisphere stroke patients was significantly lower than those with left-sided stroke in our analysis, indicating that NIHSS score placed greater emphasis on left-hemisphere dysfunction, in line with previous research.²⁸ Therefore, ischemic lateralization should be taken into consideration when evaluating stroke severity.

At the atlas-based regional scale, ischemic location was demonstrated to be able to provide additional prediction value for functional outcome. 14 regions, which are involved in cognitive function, motor and sensory function and visual function, were demonstrated to play important roles in outcome prediction.

Uncinate fasciculus is involved in various types of memory, language, social-emotional processing tasks and executive function.²⁹⁻³¹ The important predictive value of uncinated fasciculus on functional outcome is in accordance with the results demonstrated by Yassi et al.⁹ Right temporal lobe was reported to be implicated in semantic dementia, behavior and socioemotional functioning.³² Hippocampus is essential for the storage of long-term memory. The anterior limb of internal capsule is an important thalamo-frontal white matter tract, and it has been reported to be related to depression, diabetes and schizophrenia.^{33,34} These regions were also showed in others studies in outcome prediction.⁸⁻¹⁰ We infer that lesions in the above-mentioned regions could impact the post-stroke rehabilitation, thereby influence functional outcome at 3 months.

Putamen is a part of the striatum, which receives input from cortical areas and thalamic nuclei and sends signal to other components of basal ganglia. The pallidum is an output nuclei of the basal ganglia. Both putamen and pallidum participate in the direct and indirect pathways of movement, and their damage could cause hypokinetic or hyperkinetic disorders.³⁵ Lesion in corona radiata, which is a part of the corticospinal tract, was associated with poorer functional outcome in our cohort. Our findings consist with the previous studies which suggested the importance of motor pathway in stroke functional outcome prediction.⁸⁻¹⁰ The mRS broadly assesses the degree of disability, emphasizing physical impairment.³⁶ Our results, therefore, highlight the important association between motor function and mRS.

Postcentral gyrus is the primary somatosensory cortex, which also exerts a critical role in the initiation and execution of purposive movements.³⁷ Paracentral lobule, which connects the medial portion of the precentral and postcentral gyri, controls the motor and sensory innervation. Supramarginal gyrus is a part of the somatosensory association cortex, and plays a critical role in ideomotor transformations: the integration of conceptual knowledge and

motor representations into meaningful actions.³⁸ It could be inferred that damage in somatosensory cortex restrains the convection of kinaesthetic input to motor areas, therefore impacts the functional outcome. This finding is in line with a previous study which supported a critical role of somatosensory cortices in motor skill recovery.³⁹

Visual feedback could partly substitute for somatosensory information thus counteract the motor task deficit.³⁷ This could explain why regions in the occipital lobe, where the visual processing center locates, were involved in functional outcome prediction in our study.

However, certain regions which were implicated in poor outcome prediction in previous studies did not present important value in our study, such as external capsule, insula and left superior temporal gyrus.⁸⁻¹⁰ This may be due to the fact that ischemic location was evaluated within 4.5 hours after stroke onset in our study, while the other studies performed imaging on day 2 or 3. The dynamic process of ischemia, especially at the hyperacute phase, could result in lesion location evolution.

mRS has been considered as a functional disability assessment tool which mainly emphasizes motor recovery.⁴⁰ Our findings, however, demonstrated that brain regions associated with mRS were involved in various aspects of neurological functionalities. It could be explained by the fact that nonphysical functions, such as somatosensory, cognition and poststroke mood disturbance, would impact the rehabilitation process, thus further effect functional outcome at 3 month.⁴¹

Moreover, our results questioned the importance of lesional volume in predicting functional outcome. Lesional volume has been proposed as an independent predictor for functional outcome in acute ischemic stroke. However, using lesional volume as the only criterion to exclude patients from therapy was unadvisable.^{6,7} We could infer from our study that, in addition to lesional volume, the integration of lesional location is important in outcome prediction.

Our results also shed new lights on the application of machine learning method in stroke outcome prediction. Machine learning approaches have already been proposed for stroke outcome prediction using different parameters, such as baseline NIHSS score, intracerebral hemorrhage transformation, recanalization success and age, which obtained a promising accuracy (approaching 70%).⁴² Our work improved the prediction accuracy by 6.8% after adding the lesional location to the model. Such model may be useful in outcome prediction and clinical decision making.

Limitations also exist in our study. We tried to recruit homogeneous patients without bias related to treatment, giving rise to relatively small sample size. Due to lack of age matched

atlas, we applied young-adults-derived atlas on elderly patients. This might cause potential bias; therefore, we checked all the normalized images and excluded problematic ones. Information of handedness, which influences function lateralization, was unavailable in our cohort, which may impact the function outcome as well. Also, due to the lack of information in THRACE study, we could not evaluate modality-specific outcome to investigate implication of regions in special function, which could help for guiding rehabilitation therapies.

In conclusion, our study suggested that pretreatment ischemic location could provide important prognostic values for functional outcome in acute stroke, in addition to age, baseline NIHSS score and ischemic volume. Moreover, an advanced model incorporating ischemic location information using SVM technique was developed for multifactorial stroke outcome prediction.

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Discussion

Our study investigated the role of pretreatment ischemic location for functional outcome prediction in acute ischemic stroke. From the perspective of hemispheric scale, our results suggested that ischemia hemispheric lateralization did not impact significantly on functional outcome. While from the atlas-based regional scale, our results demonstrated that the lesional location provided important prognostic value, resulting in an increment of prediction precision of 6.8 points (from 70.5% to 77.3%). Additionally, our results questioned the importance of lesional volume in predicting functional outcome. Furthermore, we demonstrated an advanced model incorporating ischemic location information using SVM technique for predicting stroke outcome.

The strong points in our studies are:

1. This is the first study of investigating pretreatment ischemic location in predicting functional outcome, which could shed light into the clinical practice to guide treatment approaches.
2. Our sample was homogeneous. Data were extracted from a multicenter trial, and all patients received the same therapy.
3. Logistic regression and SVM were both applied for building model. There has been growing interest in applying machine learning techniques in predicting stroke outcome, with the advantage of easily incorporating large-scale data and newly available data (134). Our results provided new evidence on the application of machine learning in stroke outcome prediction. Furthermore, a 10-fold cross-validation method was performed to assess the generalizability of our models.

There are the following limitations in our research:

1. Our study sample is relatively small because of the consideration of selecting homogeneous patients.
2. Automated Anatomical Labeling atlas is a parcellation of the spatially normalized high-resolution T1 volume of a single young man provided by the Montreal Neurological

Institute database. Johns Hopkins University-WhiteMatter-labels-1mm atlas was derived from group-averaged young adult subjects. Application of these atlases on elderly patients could cause normalization bias. Therefore, we have carefully checked the normalized images to reduce the bias. Besides, despite the large number of the regions, there are still some areas where both atlases do not cover.

3. The information of handedness, which influences function lateralization, was unavailable in our cohort.
4. mRS is used to assess the degree of disability, which could be affected by different brain functions. The modality-specific outcome, such as motor-recovery, language or cognitive outcome should be investigated to understand the role of lesion location.

In conclusion, our work showed the important role of pretreatment lesion location in functional outcome prediction at 3 months. Early identification of patients at a risk of poor clinical outcome is useful for patient selection in clinical trials, decision of aggressive intervention and strategy of post-stroke rehabilitation. According to the results of our study, the lesion location should also be taken into account when predicting clinical outcome. However, there are definitely more investigations to carry on before using the pretreatment lesion location in guiding patient therapy in clinical practice.

Résumé en français

Relation entre la topographie lésionnelle prétraitement et le résultat clinique chez les patients présentant un AVC ischémique traité par thrombectomie mécanique

Contexte et objectif

La prédiction précoce du résultat clinique est importante pour la décision du traitement chez les patients ayant un AVC ischémique. Il a été prouvé que l'âge, le score NIHSS et le volume lésionnel étaient associés au résultat clinique. Récemment, la localisation de la lésion a été démontrée comme étant un autre prédicteur prometteur. Néanmoins, peu de données peuvent être trouvées sur la localisation prétraitement. L'objectif de ce travail est d'évaluer le gain lié à l'ajout de la localisation lésionnelle prétraitement mesurée sur la DWI initiale dans la prédiction du résultat clinique.

Méthode

Cette sous étude a porté sur les patients présentant un AVC ischémique avec occlusion de la circulation antérieure dans le groupe IVTMT. Les lésions ischémiques en DWI prétraitement ont été automatiquement segmentées par un logiciel développé au CIC-IT. Le masque de lésion a été normalisé dans l'espace standard MNI152 avec SPM12 (*statistical parametric mapping*). L'atlas Automated Anatomical Labeling (AAL), pour la substance grise, et l'atlas Johns Hopkins University-WhiteMatter-labels-1mm (JHU-WM), pour la substance blanche, ont été utilisés pour identifier et labéliser automatiquement les localisations des lésions. Le pourcentage de lésions dans chaque région identifiée a été calculé. Des outils de régression logistique et de machine à vecteurs de support ont été utilisés pour construire les modèles prédisant le résultat clinique à 3 mois, à partir de l'âge, le score NIHSS initial et le volume lésionnel total, sans ou avec les données de la localisation lésionnelle. Le résultat clinique a été mesuré par le score de Rankin modifié à 3 mois.

Résultat

143 patients ont été inclus dans cette sous-étude. Le volume lésionnel moyen des patients était 20,5 mL (IQR 10,3-51,0). 74 patients présentent un AVC dans l'hémisphère gauche. Le score NIHSS initial était significativement plus élevé chez les patients avec ischémie dans

l'hémisphère gauche ($p < 0,001$) par rapport à ceux dans l'hémisphère droit (69 patients). Les prévalences d'atteindre un mRS 0-2 à 3 mois sont comparables entre les deux hémisphères. La machine à vecteurs de support est supérieure que la régression logistique en ce qui concerne la précision prédictive. Le modèle de la machine à vecteurs de support incluant l'âge, le score NIHSS initial et le volume lésionnel total a démontré une précision de 70,5%. Lorsque nous avons inclut le pourcentage ischémique dans chaque région dans le modèle, le volume lésionnel n'a pas persisté en tant que prédicteur. Ce dernier modèle a atteint une précision supérieure de 77,3%. Les régions importantes dans la prédiction du résultat fonctionnel sont les suivantes : dans l'hémisphère gauche, le faisceau unciné, le gyrus postcentral, le putamen, le gyrus supramarginal, le corona radiata postérieur, le gyrus occipital moyen ; dans l'hémisphère droit, le faisceau unciné, le lobule paracentral, le pôle temporal, le pallidum, le bras antérieur de la capsule interne et le gyrus occipital inférieur.

Discussion

Premièrement, nos résultats ont montré que la latéralisation ischémique n'a pas d'impact sur le résultat clinique. Deuxièmement, la localisation lésionnelle définie par l'atlas a ajouté une valeur additionnelle dans la prédiction du devenir fonctionnel. Les régions importantes dans la prédiction comprennent non seulement des régions qui s'occupent de la motricité, comme le corona radiata, mais aussi des régions qui jouent un rôle dans la cognition ou la fonction somatosensorielle. Cela pourrait s'expliquer par le fait que des fonctions non physiques, telles que les troubles somatosensoriels, cognitifs et du moral après AVC, auraient un impact sur la rééducation, affectant ainsi davantage les résultats fonctionnels à 3 mois. Troisièmement, nos résultats ont mis en doute l'importance du volume lésionnel dans la prédiction du résultat fonctionnel. Ce résultat a consentit qu'il n'est pas raisonnable d'exclure les patients pour des thérapies seulement en fonction du volume lésionnel. Enfin, nous avons apporté également une nouvelle preuve sur l'application de l'apprentissage automatique dans la construction d'un modèle prédictif des résultats clinique de l'AVC.

En conclusion, nous avons mis en évidence que la localisation ischémique prétraitement était un facteur prédictif du pronostic fonctionnel à 3 mois chez les patients présentant un AVC ischémique après le traitement IVTMT.

Chapter 5

General discussion

Summary of the results

In this thesis, we provided new evidences on the application of MRI in acute ischemic stroke evaluation, focusing on DWI and PWI. Our results yielded findings in three aspects:

1. We demonstrated that pretreatment DWI- and PWI-derived parameters were able to predict brain tissue viability. ADC and rCBF presented the most promising values, in both initial abnormal diffusion areas and PWI-DWI mismatch areas. Thresholds of parameters for distinguishing salvageable tissue suggested by our results were: ADC $623 \times 10^{-6} \text{ mm}^2/\text{s}$, rADC 0.80 and rCBF 0.47 in initial abnormal diffusion areas; $785 \times 10^{-6} \text{ mm}^2/\text{s}$, 0.98 and 0.63 relatively in mismatch areas.
2. We analyzed the role of pretreatment DWI lesional volume in predicting clinical outcome. We confirmed that increased lesional volume was an independent predictor for unfavorable outcome, in patients after IVT or IVTMT. However, volume thresholds (70 mL and 100 mL) for excluding patients from reperfusion therapy as suggested in the previous studies were unadvisable according to our results. Patients with large lesional volume could still benefit from therapy. Moreover, our results showed for the first time that the clinical benefit of adding mechanical thrombectomy decreased with the increase of lesional volume.
3. Our results showed that pretreatment ischemic location measured on DWI provided important prognostic value for functional outcome, in addition to age, baseline NIHSS score and ischemic volume. When including lesion location in the prediction model, lesional volume did not persist as an independent predictive factor. Besides, we developed an appropriate model based on SVM for multifactorial stroke outcome prediction.

Strengths

This thesis has the following strengths:

1. We comprehensively investigated the role of pretreatment MRI in evaluating ischemic stroke, including tissue viability prediction and clinical outcome prediction. The impact of both lesional volume and lesional location were analyzed.
2. We analyzed patients from a multicenter randomized controlled trial, which premised the representativeness of our sample and the reliability of our results.
3. Due to the concern of dynamic lesion evaluation after the treatment, previous studies focused on the association between post-treatment imaging profiles and clinical outcome. However, the results on post-treatment imaging could not guide patient selection for treatment. Our results were all based on the pretreatment data, thus could provide useful evidence for patient treatment decision making.
4. Ischemic lesions were segmented automatically, which is time-efficient, reliable, reproducible, less operator-dependent and easy for clinical application.
5. Factors which had potential predictive value for clinical outcome (age, baseline NIHSS score, occlusion location, ASPECTS, blood glucose and Fazekas score) were included as covariates in the statistical model when studying the role of lesional volume. Age, baseline NIHSS score and lesional volume were also included when investigating the predictive value of lesion location.
6. Two machine learning approaches were applied to build models for stroke outcome prediction: logistic regression (linear model) and SVM (nonlinear model). Machine learning has been used more and more recently to help solving diagnostic and prognostic problems in a variety of medical domains. Our results provided new evidence on the application of machine learning in stroke outcome prediction.

Weaknesses

This thesis has the following weaknesses:

1. The sample size was relatively small, in the sub study of tissue viability prediction using MRI-derived parameters, the clinical outcome prediction in case of large volume and the clinical outcome prediction using lesional location. Small sample size limited more comprehensive analyses.
2. Although the THRACE study is a prospective trial, its primary objective was to evaluate different treatment methods (IVT and IVTMT) in acute ischemic stroke patients. All the sub studies carried out in this thesis were retrospective. Therefore, we should be prudent in causal inference.
3. Imaging in the THRACE study was done according to the established local routine. Imaging modalities and image acquisition parameters were heterogeneous among patients. This could be a source of bias in our results. Moreover, due to the lack of the follow-up MRI evaluation of a big percentage of the THRACE study patients (84 patients [20.4%] had DWI data both at baseline and 24h; 44 patients [10.7%] had DWI data at baseline, 24h and day-7), we did not discuss the association among baseline imaging, follow-up imaging and clinical outcome.
4. Reperfusion status was not available for the patients who received IVT in the THRACE study. Nevertheless, reperfusion is an important factor of the fate of brain tissue and of predicting clinical outcome.
5. The results of this thesis only apply to ischemic stroke patients with occlusion of proximal intracranial artery in anterior circulation. Stroke patients due to small artery occlusion, cardioembolism or other causes as well as patients with posterior circulation occlusion were out of scope of our discussion.
6. All the patients in the THRACE study received IVT within 4 hours and those in the IVTMT group received thrombectomy within 5 hours after stroke onset. Investigation of

tissue viability and clinical outcome prediction in stroke patients beyond these time windows will provide valuable information in clinical practice.

Implications for the future research

MRI is valuable for diagnosing ischemic stroke and for determining treatment strategies in the acute phase. This thesis analyzed its role in predicting tissue viability and clinical outcome. In the future, the following issues are needed to be addressed.

1. Other MRI sequences, apart from the sequences that we discussed in this work, should also be considered in the acute ischemic stroke evaluation, such as SWI (susceptibility-weighted imaging) and SWAN (susceptibility-weighted angiography) sequences. SWI uses paramagnetic susceptibility effects to study metabolic changes in hypoperfused brain tissue. DWI-SWI mismatch has been proposed as a good marker for evaluating the ischemic penumbra. Besides, it can determine the position of an arterial thrombus (135). SWAN is a novel 3D gradient echo multi-echo T2*-weighted sequence. It allows high-resolution visualization of both cerebral arteries and veins (136). Both SWI and SWAN evaluate the vessel status without application of contrast agent, therefore considering safety issues, they are more appropriate compared to perfusion-weighted imaging or angiography which need injection of contrast agent.
2. Although there are many studies analyzing the use of MRI for tissue outcome prediction, no consistent parameters and values have been proposed. This is due to the following reasons: First, the definition of “non-viable”/“at risk”/“not at risk” tissue states are different from study to study (123). Second, the sample size of the studies are small. Third, the imaging acquisition parameter and post processing method for PWI were heterogeneous; perfusion-derived parameters and thresholds for defining hypoperfusion were variable. Fourth, these studies were not able to conclude whether the use of MRI for tissue viability evaluation could improve the clinical outcome, due to the lack of the outcome data. Prospective studies in large sample size, using standardized MRI acquisition protocol, especially PWI settings, are required for the tissue viability prediction. Clinical outcome should also be taken into consideration. This would improve the precision of penumbra assessment using MRI, thus guide treatment decision making in acute stroke patients.

3. The metabolic status is different between the white matter and the grey matter. Therefore, considering the white matter and the grey matter separately will be valuable in tissue viability prediction using MRI-derived parameters.
4. Ageing and leukoaraiosis should be taken into account when defining the parameter thresholds for tissue viability evaluation, because they will impact the cerebral perfusion.
5. Voxel-based analysis is thought to be more precise than ROI-based analysis, and thus imaging analysis could be done in voxel-based level, both for the tissue viability assessment and lesion location investigation.
6. The reperfusion status and the collateral circulation are essential for tissue viability and clinical outcome; this information should be considered in the future research.
7. Ischemic stroke has been considered as a dynamic process. The image-derived parameters for the tissue viability assessment differ at different time points. In order to obtain meaningful statistical results, it is necessary to perform MRI at different time points using a larger patient population. Experiments with MRI at more time points using stroke animal models may also provide useful information.
8. Noncontrast CT is not an ideal modality for follow-up imaging when we investigate the tissue viability, because of its low ability for ischemic lesion delineation and the inaccuracy for image coregistration with baseline MRI. Thus, to apply a MRI-based systemic baseline imaging and follow-up is necessary for a more precise evaluation.
9. The lesional volume and ischemic location on follow-up images as well as initial images should both be analyzed, to evaluate whether the final volume and location could be predicted from the initial images.
10. Stroke outcome prediction is an extremely complex task, and is influenced by numerous factors. There has been increasing interest on machine learning technique. It has been used in the identification of potentially salvageable tissue and in predicting stroke outcome (134,137). To our knowledge, there is no comprehensive multifactorial model, incorporating extensive clinical features, imaging characteristics and even genetic factors, for stroke outcome prediction with machine learning. Hence, future work should also include developing predictive multifactorial models using advanced machine learning techniques with various data from a larger stroke patient population.

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Résumé de la thèse en français

Introduction

L'AVC est la deuxième cause de mortalité dans le monde dont 87% est d'origine ischémique (1). En cas d'AVC ischémique, les occlusions des artères provoquent la diminution du DSC qui irrigue le cerveau, entraînent une mort neuronale et une perte de fonction neurologique. Deux seuils de DSC peuvent être différenciés pour mesurer la viabilité des tissus cérébraux: 1). seuil de défaillance réversible de la fonction électrique neuronale; 2). seuil de défaillance irréversible du métabolisme énergétique et de la pompe ionique. Des études ont montré que le potentiel évoqué somatosensoriel enregistré dans le cortex du babouin a été aboli lorsque le DSC était réduit à 15 mL/100g/min (2). La libération massive de potassium intercellulaire, qui indique une défaillance de la pompe ionique, se produit à environ 6 mL/100g/min (3). Trois compartiments peuvent être distingués selon les seuils de DSC: le cœur de l'ischémie, la pénombre et l'oligémie. La pénombre est une région où le DSC se situe entre le seuil supérieur de défaillance électrique et le seuil inférieur de défaillance d'énergie et de la pompe ionique. C'est une région au risque d'infarctus mais avec la possibilité d'être récupérée lorsque le DSC est rétabli à temps. L'évolution de la pénombre dépend de la gravité et de la durée de l'ischémie (4). La pénombre est la cible du traitement de reperfusion.

Le but du traitement de l'AVC ischémique est de rétablir le flux sanguin et d'obtenir la revascularisation du parenchyme cérébral en souffrance. Deux traitements ont montré leur efficacité: la thrombolyse par voie intraveineuse en utilisant du rt-PA (*recombinant tissue plasminogen activator*) et la thrombectomie mécanique par voie intra-artérielle. La thrombolyse intraveineuse était la première thérapie approuvée par la FDA. Néanmoins, elle a plusieurs limites, telle que la fenêtre temporelle thérapeutique étroite (dans les 4,5h après le début de l'AVC), les contre-indications (par exemple, chirurgie majeure récente, anomalies de la coagulation ou antécédents d'hémorragie intracrânienne) et l'inefficacité chez les patients présentant une occlusion de l'artère proximale. Depuis 2015, des essais cliniques randomisés ont prouvé l'efficacité d'une thrombectomie mécanique supplémentaire par rapport à la thrombolyse intraveineuse seule chez les patients atteints d'AVC ischémique avec occlusion de la circulation antérieure proximale (5–11).

Bien que de grands progrès aient été réalisés pour le traitement de l'AVC ischémique, deux questions ne sont pas résolues actuellement : 1. Comment prédire le pronostic tissulaire cérébral en phase aiguë ? 2. Comment choisir les « bons » candidats aux traitements, afin d'éviter des traitements inutiles, voire délétères ?

L'imagerie par résonance magnétique (IRM) joue un rôle important dans l'évaluation de l'AVC ischémique à la phase aiguë. L'IRM de diffusion (*diffusion weighted imaging*, DWI), qui mesure des mouvements microscopiques des molécules d'eau, est la séquence la plus sensible et fiable pour détecter la lésion ischémique aiguë (12). Le coefficient de diffusion apparent (*apparent diffusion coefficient*, ADC) peut être calculé à partir des données de diffusion. Les lésions ischémiques aiguës présentent un hypersignal en DWI et un hyposignal sur la cartographie d'ADC. L'IRM de perfusion (*perfusion weighed imaging*, PWI) étudie la microvascularisation cérébrale en utilisant un agent de contraste (ex. gadolinium). On exploite le premier passage d'un bolus de gadolinium et on obtient différents paramètres de perfusion pour décrire la perfusion cérébrale: TTP (*Time to Peak*), TTM, VSC (volume sanguin cérébral), DSC, Tmax.

En général, les anomalies en DWI représentent le cœur de l'ischémie qui évolue à infarctus définitivement et les anomalies sur PWI représentent le tissu cérébral hypoperfusé. Ainsi le territoire hypoperfusé sans hypersignal diffusion, ce que l'on appelle le *mismatch* PWI-DWI, permet d'évaluer la pénombre ischémique. Le *mismatch* PWI-DWI est aussi un outil pour la sélection de patients pour traitement dans les études cliniques (5,13). Néanmoins, la substitution de pénombre par le *mismatch* est contestée. Les principaux aspects à considérer sont: 1). Beaucoup d'études ont montré qu'une partie d'anomalies en DWI pourraient être récupérées, appartenant à la pénombre, en particulier chez les patients avec une recanalisation précoce (14,15). Mais actuellement il n'existe pas de consensus sur les seuils basés sur la DWI pour estimer la réversibilité des tissus. 2). La région hypoperfusée en PWI comprend souvent du tissu d'oligémie. 3). La PWI pourrait varier beaucoup du fait des techniques d'acquisition et de posttraitement des imageries. En plus, il n'existe pas de standardisation des paramètres ni de seuils permettant de définir le tissu hypoperfusé en PWI. Actuellement, le seuil de réversibilité du tissu dans le *mismatch* PWI-DWI reste à étudier.

Le volume lésionnel en DWI a été proposé comme un facteur pronostic du devenir clinique chez les patients d'AVC ischémique (16–19). Il a été utilisé dans certaines études cliniques pour choisir les patients aux traitements. Les patients qui présentent un gros volume lésionnel

ont été exclus aux traitements dans beaucoup d'études (24–27, 31). Un seuil de volume lésionnel initial supérieur à 70 mL a été proposé comme seuil associé à un mauvais résultat clinique (20).

La topographie des lésions ischémiques est aussi un facteur important pour la prédiction du résultat clinique. Beaucoup d'études ont montré l'importance de différentes régions dans la prédiction du résultat clinique (21–25). Mais la localisation n'a pas été appliquée pour guider le traitement initial des patients, dû au manque de données sur les imageries avant traitement.

Actuellement, les données sur le rôle de l'imagerie prétraitement dans la prédiction du résultat clinique sont insuffisantes ou sont souvent étudiées dans les études mono-centriques. D'ailleurs, avec le développement de la thrombectomie mécanique, il est intéressant et nécessaire d'explorer le rôle pronostique de DWI chez les patients traités par thrombectomie.

Objectifs du travail

Les objectifs principaux de cette thèse étaient :

1. Évaluer les paramètres de diffusion et de perfusion dans la prédiction de la viabilité des tissus cérébraux.
2. Caractériser l'association entre le VLP mesuré en diffusion et le résultat fonctionnel (à 3 mois), et estimer l'impact du volume lésionnel sur l'efficacité de la thrombectomie mécanique. Identifier des facteurs associés au résultat fonctionnel favorable chez les patients ayant un gros volume lésionnel.
3. Rechercher l'association entre la topographie lésionnelle prétraitement mesurée en diffusion et le résultat fonctionnel.

Population étudiée

L'étude THRACE est une étude contrôlée, multicentrique et randomisée, qui a inclut 412 patients présentant un AVC ischémique aigu dans 26 centres en France entre 2010 et 2015 (10). Cette étude dont l'investigateur principal est le Pr. Serge Bracard, a été promue par le CHRU de Nancy. L'objectif principal de cette étude était de déterminer si une approche combinée thrombolyse intraveineuse et thrombectomie mécanique (IVTMT) est supérieure au traitement standard par thrombolyse intraveineuse (IVT). Les critères d'inclusion des patients étaient :

- 1). Âge de 18-80 ans ;

- 2). Début des symptômes datant de <4h ;
- 3). Score NIHSS de 10 à 25 ;
- 4). Occlusion de la carotide intracrânienne, de l'artère cérébrale moyenne (M1) ou du tiers supérieur du tronc cérébral.

Cette thèse analyse des patients de l'étude THRACE qui ont eu une IRM à l'inclusion et qui se conforment aux autres critères dans chaque sous-étude.

Résultat

Nos travaux ont fourni des résultats sous trois aspects:

1. Nous avons démontré que les paramètres dérivés du prétraitement DWI et PWI étaient capables de prédire la viabilité des tissus cérébraux. L'ADC et le rDSC présentaient les valeurs les plus prometteuses, à la fois dans les zones anormales en DWI initiale et dans les zones de *mismatch* PWI-DWI. Les seuils de paramètres permettant de distinguer les tissus récupérables suggérés par nos résultats sont de: 623×10^{-6} mm²/s (ADC), 0,80 (rADC), 0,47 (rDSC) et 0,82 (rVSC) dans les zones anormales en DWI initiale; 785×10^{-6} mm²/s (ADC), 0,98 (rADC) et 0,63(rDSC) dans les zones de *mismatch* PWI-DWI.
2. Nous avons analysé le rôle du volume lésionnel prétraitement en DWI dans la prédiction du résultat clinique. Nous avons confirmé que l'augmentation du volume lésionnel était un facteur prédictif indépendant de résultats défavorables chez les patients après traitement. Cependant, les seuils de volume (70 ml et 100 ml) pour exclure les patients du traitement, comme suggéré dans les études précédentes, étaient déconseillés. Les patients avec un grand volume pourraient encore bénéficier d'un traitement. De plus, nos résultats ont montré pour la première fois que le bénéfice clinique de l'ajout d'une thrombectomie mécanique diminuait avec l'augmentation du volume lésionnel.
3. Nos résultats ont montré que la localisation ischémique prétraitement mesurée sur la DWI fournissait une valeur pronostique importante pour le résultat fonctionnel. Lorsque l'on inclut la localisation lésionnelle dans le modèle de prédiction, le volume lésionnel n'a pas persisté en tant que facteur prédictif indépendant. En outre, nous avons développé un modèle approprié basé sur la SVM pour la prédiction des résultats cliniques d'AVC.

Discussion et perspective

Nos travaux, basés sur l'étude THRACE, en analysant l'IRM à la phase aiguë de l'AVC ischémique, ont permis de mieux comprendre le rôle de l'IRM prétraitement dans l'évaluation de réversibilité tissulaire et dans la prédiction du résultat clinique. Les résultats peuvent être utilisés en clinique dans la prise en charge de l'AVC ischémique aigu afin de :

1. prédire la viabilité des tissus en fonction des résultats de l'IRM en phase aiguë et adapter la décision thérapeutique à l'horloge tissulaire ;
2. prédire quels sont les « bons » candidats aux traitements de revascularisation, dans le but d'éviter des traitements inutiles, voire délétères.

Cette thèse a les points forts suivants:

1. Nous avons étudié le rôle de l'IRM prétraitement dans l'évaluation de l'AVC ischémique sous différents aspects, y compris la prédiction de la viabilité des tissus et la prédiction des résultats cliniques. L'impact du volume lésionnel et de la localisation lésionnelle a été analysé.
2. Nous avons analysé les patients d'une étude randomisée multicentrique, qui assure la représentativité de notre échantillon et la fiabilité de nos résultats.
3. Des études précédentes se sont concentrées sur l'association des profils d'imagerie post-traitement et les résultats cliniques. Cependant, les résultats de l'imagerie post-traitement n'ont pas pu guider la sélection du patient pour le traitement. Nos résultats étaient tous basés sur les données prétraitement, ce qui pourrait fournir des preuves utiles pour la prise de décision thérapeutique des patients.
4. Les lésions ischémiques ont été segmentées automatiquement, ce qui est efficace, fiable, reproductible, moins dépendant de l'opérateur et facile pour une application clinique.
5. Les facteurs ayant une valeur prédictive potentielle du résultat clinique (âge, score NIHSS initial, localisation de l'occlusion, ASPECTS, glycémie et score de Fazekas) ont été inclus comme covariables dans le modèle statistique lors de l'étude du rôle du volume lésionnel. L'âge, le score NIHSS initial et le volume lésionnel ont également été inclus lors de l'étude de la valeur prédictive de la localisation de la lésion.

6. Deux approches d'apprentissage automatique ont été appliquées pour construire des modèles prédictifs: la régression logistique (modèle linéaire) et le SVM (modèle non linéaire). L'apprentissage automatique a été utilisé de plus en plus récemment pour aider à résoudre les problèmes de diagnostic et de pronostic dans divers domaines médicaux. Nos résultats ont fourni de nouvelles preuves sur l'application de l'apprentissage automatique dans la prédiction des résultats de l'AVC.

Cette thèse présente les faiblesses suivantes:

1. L'échantillon était relativement petit dans les sous-études, ce qui a empêché des analyses plus complètes. Par exemple, nous n'avons pas pu effectuer des régressions multivariées lorsque nous avons analysé les facteurs associés à résultat clinique chez les patients avec un gros volume.
2. Bien que l'étude THRACE soit une étude prospective, son objectif principal était d'évaluer différentes méthodes de traitement (IVT et IVTMT) chez les patients ayant subi un AVC ischémique aigu. Toutes les sous-études réalisées dans cette thèse étaient rétrospectives. Par conséquent, nous devrions être prudents dans l'inférence causale.
3. Les modalités d'imagerie et les paramètres d'acquisition dans l'étude THRACE ont été réalisés selon la routine locale établie ; donc ils étaient hétérogènes chez les patients. Cela pourrait être une source de biais dans nos résultats. En outre, en raison de l'absence d'IRM de suivi chez un grand pourcentage des patients dans l'étude THRACE, nous n'avons pas analysé l'association de l'imagerie de suivi et les résultats cliniques.
4. Le statut de reperfusion n'était pas disponible pour les patients ayant reçu seulement une thrombolyse intraveineuse dans l'étude THRACE. Néanmoins, la reperfusion est un facteur important du devenir des tissus cérébraux et de la prédiction des résultats cliniques.
5. Les résultats de cette thèse ne concernent que les patients ayant subi un AVC ischémique avec occlusion de l'artère intracrânienne proximale dans la circulation antérieure. Les patients d'AVC ischémique à cause d'une occlusion de la circulation postérieure, ainsi que l'occlusion des petites artères, d'origine cardioembolie ou d'autres causes, étaient hors de la portée de notre discussion.

6. Tous les patients de l'étude THRACE ont reçu une IVT dans les 4 heures et ceux du groupe IVTMT ont reçu une thrombectomie dans les 5 heures suivant les symptômes. L'étude de la viabilité des tissus et de la prédiction des résultats cliniques chez les patients ayant subi un AVC au-delà de ces fenêtres fournirait des informations précieuses dans la pratique clinique.

Dans les recherches à venir, les questions suivantes doivent être étudiées et approfondies :

1. Hormis les séquences qui ont été discutées dans notre travail, d'autres séquences peuvent avoir un intérêt dans l'évaluation de l'AVC ischémique. Par exemple, la séquence SWI (imagerie de susceptibilité magnétique) et la séquence SWAN (*susceptibility-weighted angiography*). Ces deux séquences évaluent les vaisseaux sanguins sans injection du produit de contraste. Donc, elles sont plus appropriées d'un point de vue sécurité par rapport à l'imagerie de perfusion ou l'angiographie nécessitant du produit de contraste.
2. Bien qu'il y ait beaucoup de recherches sur la prédiction de la viabilité des tissus en utilisant l'imagerie, aucun paramètre ni de seuil de paramètre concordants ont été proposés. Tout d'abord, il est nécessaire d'unifier la définition du statut des tissus dans les études. Deuxièmement, il faut élargir l'échantillon des études. Troisièmement, les paramètres d'acquisition d'imagerie et la méthode de post-traitement pour la séquence PWI devraient être davantage standardisés. De plus, le résultat clinique devrait être pris en compte, afin d'étudier si l'utilisation de l'IRM pour prédire la viabilité des tissus peut être bénéfique sur le résultat clinique des patients.
3. Les métabolismes de la substance blanche et de la substance grise sont différents. La substance blanche est plus résistante à l'ischémie. Ainsi il serait intéressant de différencier ces deux parties. De plus, la perfusion parenchymateuse diminuant avec l'âge et la leucoaraiose, il apparaît nécessaire de prendre cet aspect en considération quant à l'analyse.
4. L'analyse au niveau du voxel pourrait fournir les informations plus en détail par rapport à l'analyse au niveau de régions cérébrales. Il serait également intéressant de l'utiliser pour étudier la viabilité du tissu et le rôle prédictif de la localisation lésionnelle.

5. Le statut de la reperfusion et de la circulation collatérale sont importants pour la viabilité des tissus. Il faut donc les évaluer lors d'études de recherche clinique et les prendre en considération dans l'analyse.
6. L'AVC ischémique a été considéré comme un processus dynamique. Les paramètres dérivés de l'image pour l'évaluation de la viabilité des tissus varient à différents moments. Afin d'obtenir des résultats statistiques significatifs, il serait nécessaire d'effectuer une IRM à différents moments sur un grand échantillon de patients présentant des lésions autant que possible homogènes. Des expérimentations en utilisant des modèles animaux à plusieurs points de temps peuvent également fournir des informations utiles.
7. L'application d'IRM pour les imageries initiales et aussi les imageries de suivi chez les patients d'AVC ischémique peuvent fournir une évaluation plus précise.
8. La prédiction du résultat clinique de l'AVC est une tâche extrêmement complexe. La technique d'apprentissage automatique suscitait un intérêt croissant. À notre connaissance, il n'existe pas de modèle multifactoriel complet, intégrant des caractéristiques cliniques étendues, des caractéristiques d'imagerie et même des facteurs génétiques, pour la prédiction des résultats cliniques d'AVC ischémique. Par conséquent, les travaux futurs devront comprendre également le développement des modèles multifactoriels prédictifs, en appliquant des techniques avancées d'apprentissage automatique et en utilisant diverses données provenant d'une population victime d'AVC ischémique.

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Appendix

NIHSS

Instructions	Scale definition
<p>1a. Level of consciousness : The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A "3" is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.</p>	<p>0 = Alert; keenly responsive 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped) 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic</p>
<p>1b. LOC Questions: The patient is asked the month and his/her age. Aphasic and stuporous patients who do not comprehend the questions will score "2". Patients unable to speak because of endotracheal intubation, orotracheal trauma, and severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a "1".</p>	<p>0 = Answers both questions correctly 1 = Answers one question correctly 2 = Answers neither question correctly</p>
<p>1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one-step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to commands, the task should be demonstrated to them and score the result. Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands.</p>	<p>0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly</p>
<p>2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but calorie testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be "1". If a patient has an isolated peripheral nerve paresis score a "1". Gaze is testable in all aphasic patient. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eyes contact and then</p>	<p>0 = Normal 1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver</p>

<p>moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.</p>	
<p>3. Visual: Visual fields are tested by confrontation, using finger counting or visual threat as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrant anopia is found. If patient is blind from any cause, score "3." Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a "1" and the results are used to answer question #11.</p>	<p>0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind, including cortical blindness)</p>
<p>4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma /bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.</p>	<p>0 = Normal symmetrical movement 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling) 2 = Partial paralysis (total or near total paralysis of lower face) 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)</p>
<p>5 & 6. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90° (if sitting) or 45° (if supine) and the leg 30° (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "9" and the examiner must clearly write the explanation for scoring as a "9".</p>	<p>0 = No drift, limb holds 90° (or 45°) for full 10 seconds 1 = Drift, limb holds 90° (or 45°), but drifts down before full 10 seconds; does not hit bed or other support 2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90° (or 45°), drifts down to bed, but has some effort against gravity 3 = No effort against gravity, limb falls 4 = No movement 9 = Amputation, joint fusion explain: ____ 5a. Left Arm ____ 5b. Right Arm ____</p> <p>0 = No drift, leg holds 30° for full 5 sec 1 = Drift, leg falls by the end of the 5 second period but does not hit bed. 2 = Some effort against gravity, leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity, leg falls to bed immediately</p>

	<p>4 = No movement 9 = Amputation, joint fusion explain: ____ 6a. Left Leg ____ 6b. Right Leg ____</p>
<p>7. Limb Ataxia:</p> <p>Test with eyes open. In case of visual defect, insure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "9", and the examiner must clearly write the explanation for not scoring. In case of blindness test by touching nose from extended arm position.</p>	<p>0 = Absent 1 = Present in one limb 2 = Present in two limbs</p>
<p>8. Sensory:</p> <p>Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic score 2. Patients in coma (item 1a=3) are arbitrarily given a 2 on this item.</p>	<p>0 = Normal; no sensory loss 1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm and leg</p>
<p>9. Best Language:</p> <p>The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a=3) will arbitrarily score 3 on this item. The</p>	<p>0 = No aphasia, normal 1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning and guessing by the listener.</p>

<p>examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one step commands.</p>	<p>3 = Mute, global aphasia; no usable speech or auditory comprehension</p>
<p>10. Dysarthria: If patient is thought to be normal an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barrier to producing speech, may the item be scored "9", and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested.</p>	<p>0 = Normal 1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty 2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric 9 = Intubated or other physical barrier, explain</p>
<p>11. Extinction and Inattention (Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.</p>	<p>0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities 2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.</p>

mRS

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Inclusion and Exclusion criteria for THRACE study

Inclusion criteria:

- Age 18 to 80 years
- No more than 4 hours since symptom onset
- NIHSS score ≥ 10 and ≤ 25
- Occlusion of the intra cranial ICA, the initial segment of MCA (M1 segment) or the superior third of the basilar artery.

Exclusion criteria:

- General or acute ischemic stroke-specific contraindications to alteplase according to French guidelines* (see below);
- Treatment initiated more than four hours after ischemic stroke symptom onset or when the time of symptom onset is unknown;
- Any conditions that may be life-threatening within the following three months;
- Any situations making patient follow-up impossible (patients who are homeless, foreigners, etc.);
- History of iliofemoral surgery and by extension any local conditions making femoral catheterization impossible;
- Occlusion or preocclusive stenosis of the cervical segment of the ICA ipsilateral to the lesion;
- Hyperdensities or other signal abnormalities suggesting hemorrhage regardless of severity;
- Intracranial tumours other than small meningiomas;
- Infarct with a mass effect causing midline shift already visible on CT or MRI FLAIR indicating an error in amount of time since symptom onset;
- Contraindications specific to the employed thrombectomy system.

* Contraindications to alteplase in the ACTILYSE[®] marketing authorization:

- Hypersensitivity to the active substance or to any of the excipients.
- In cases where there is a high risk of haemorrhage: significant bleeding disorder at present or within the past 6 months; known haemorrhagic diathesis; concomitant administration of

oral anticoagulants (e.g. warfarin); manifest or recent severe or dangerous bleeding ; known history of or suspected intracranial haemorrhage; suspected subarachnoid haemorrhage or condition after subarachnoid haemorrhage from aneurysm; any history of central nervous system damage (e.g. neoplasm, aneurysm, intracranial or spinal surgery); recent (less than 10 days) traumatic external cardiac massage; obstetrical delivery; recent puncture of a non-compressible blood vessel (e.g. subclavian or jugular vein puncture); severe uncontrolled arterial hypertension; bacterial endocarditis; pericarditis; acute pancreatitis; documented ulcerative gastrointestinal disease during the last 3 month; oesophageal varices; arterial-aneurysm; arterial or venous malformations; neoplasm with increased bleeding risk; severe liver disease (including hepatic failure, cirrhosis, portal hypertension and active hepatitis); major surgery or significant trauma in past 3 months.

Additional contraindications in acute ischemic stroke:

- symptoms of ischemic attack beginning more than 3 hours prior to infusion start or when time of symptom onset is unknown
- minor neurological deficit or symptoms rapidly improving before start of infusion
- severe stroke as assessed clinically (e.g. NIHSS > 25) and/or by imaging
- seizure at onset of stroke
- evidence of intracranial hemorrhage (ICH) on the CT scan
- symptoms suggestive of subarachnoid hemorrhage, even if CT scan is normal
- administration of heparin within the previous 48 hours and a thromboplastin time exceeding the upper limit of normal
- diabetic patients with any history of prior stroke within the last 3 months
- platelet count below 100000/mm³
- systolic blood pressure > 185 mmHg or diastolic BP > 110 mmHg, or aggressive management (intravenous pharmacotherapy) necessary to reduce BP to these limits
- blood glucose less than 50 or greater than 400 mg/dl

ACTILYSE® is not indicated for the treatment of acute stroke in pediatric patients under 18 years or adults over 80 years of age.

Abstract

MRI plays an important role in evaluating ischemic stroke and determining the treatment strategies. Diffusion weighted imaging and perfusion weighted imaging are two essential sequences in ischemic stroke assessment. The principal objective of this work was to study the predictive role of MRI in ischemic stroke, including the role of MRI-derived parameters in tissue viability prediction; the relationship of the ischemic lesional volume and the functional outcome and mechanical thrombectomy efficacy; and the impact of the pretreatment ischemic location on functional outcome after mechanical thrombectomy. Our results suggested that apparent diffusion coefficient and relative cerebral blood flow were potential candidates to predict tissue viability; pretreatment lesional volume was an independent predictor for functional outcome; the clinical benefit of adding mechanical thrombectomy to thrombolysis decreased with the increase of lesional volume; however, patients with large lesional volume could still benefit from reperfusion treatment; the pretreatment ischemic location provided important prognostic information for functional outcome. The overall results of the thesis provided a better understanding of the role of MRI in acute ischemic stroke assessment, especially in patients treated with mechanical thrombectomy. Our work provided new perspective in clinical application of MRI and suggested future research of ischemic stroke imaging.

Key words: Stroke; magnetic resonance imaging; diffusion magnetic resonance imaging; perfusion imaging; thrombolytic therapy; thrombectomy

Résumé

L'IRM joue un rôle important dans l'évaluation de l'AVC ischémique et la détermination des stratégies de traitement. L'IRM de diffusion et l'IRM de perfusion sont deux séquences essentielles dans l'évaluation de l'AVC ischémique. L'objectif principal de ce travail était d'explorer le rôle prédictif de l'IRM dans l'AVC ischémique, y compris le rôle des paramètres dérivés de l'IRM dans la prédiction de la viabilité des tissus ; la relation entre le volume lésionnel ischémique pré-traitement et le résultat fonctionnel ainsi que l'efficacité de la thrombectomie mécanique ; l'impact de la localisation ischémique pré-traitement sur le résultat fonctionnel après une thrombectomie mécanique. Nos résultats ont montré que le coefficient de diffusion apparent et le débit sanguin cérébral relatif étaient des candidats potentiels pour prédire la viabilité des tissus ; le volume lésionnel de prétraitement était un prédicteur indépendant pour le résultat fonctionnel ; le bénéfice clinique de l'adjonction de la thrombectomie mécanique à la thrombolyse diminuait avec l'augmentation du volume lésionnel; les patients ayant un gros volume lésionnel peuvent encore bénéficier du traitement ; la localisation ischémique a fourni également des informations pronostics importantes pour le résultat fonctionnel. Les résultats globaux de la thèse ont permis de mieux comprendre le rôle de l'IRM dans l'évaluation de l'AVC ischémique aigu, en particulier chez les patients traités par thrombectomie mécanique. Notre travail a fourni une nouvelle perspective dans l'application clinique de l'IRM et a permis de suggérer de futures recherches sur l'imagerie cérébrale ischémique.

Mots-clés: Accident vasculaire cérébral; imagerie par résonance magnétique; imagerie par résonance magnétique de diffusion; imagerie de perfusion; thérapie thrombolytique; thrombectomie