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14

Neurosonological Evaluation of the Acute Stroke Patients

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1. Introduction

Stroke is a condition with an high mortality rate and a relevant burden of disability and social costs. Indeed it is the third cause of death and the first cause of disability in western countries. About 80% of strokes is ischemic and due to the occlusion of a large or small cerebral artery. Therefore the rationale of thrombolysis is the reopening of the occluded vessel within a short time window from symptoms onset, mainly by using iv rtPA but also by using local delivery of rtPA and/or mechanical disruption of the thrombus. The basic assumption is simple and clear: a large vessel was abruptly occluded and the corresponding brain territory was deprived of oxygenated blood and nutrients. The brain metabolism during ischemia is flow- and time-dependent; there are precise perfusional thresholds for maintaining membrane pump activity; therefore the cell integrity and the duration of neuronal life is related to the time from the vessel occlusion, in a variable combination of individual ischemic tolerance and activation of the collateral circulation. The irreversibly damaged brain tissue is known as ischemic core and the suffering, but still viable, tissue is known as penumbra. The penumbra to core ratio is affected by several factors, but it is widely recognized that both occlusive pattern and time from symptoms onset are strong predictors of the presence of as much viable tissue as needed for the success of the reperfusion treatment. The clinical data and the neurological severity scales, as NIHSS (National Institute of Health Stroke Scale), do not reliably predict if there is a large vessel occlusion and for which extent in single cases. The clinical presentation can be the same for a very proximal large arterial occlusion and for a small perforating artery involvement, but the recanalization rate is strictly dependent on the occlusive pattern. Therefore, because the recanalization is a strong predictor of a good outcome, the prognosis depends on it and it can be early inferred by the diagnosis of the occlusive pattern.

All efforts should be made to achieve the diagnosis of vessel occlusion ad brain perfusion condition as early as possible, in order not only to predict the prognosis but also to tailor the treatment.

In acute stroke time is brain, and therefore the diagnostic steps should be reliable, fast and not time consuming. Ultrasound techniques have these features for other body districts, also for extracranial vessels, but their use for the examination of the intracranial circulation has been hampered for many years, because of the attenuation effect of the skull. In the last twenty years this limitation has been demonstrated to be passed by neurosonological

techniques, Transcranial Doppler (TCD) and Transcranial Colour Coded Duplex Sonography (TCCS). Both these tools are safe, reliable, bedside executable, fast, not expensive and repeatable. Because of these advantages, neurosonology represents an ideal tool to diagnose patients with a focal neurological deficit of suspected vascular origin, particularly in an emergency setting. Furthermore the repeatability and the safety make transcranial Doppler the most suitable tool for monitoring the recanalization, both during a thrombolytic treatment and spontaneously.
In the following sections mainly TCCS will be mentioned and discussed, first because of the undeniable advantage of the B-mode visualization of the brain structures and vascular landmarks, and second because the expertise of our group with this technique and the related literature contributes. In a similar manner our attention will be focused on the anterior circulation stroke.

2. Ultrasound examination of cerebroafferent vessels: Extracranial carotid axis

Ultrasound examination of the extracranial carotid artery (common and internal carotid artery) is a useful and standardized technique and it represents, in patients with a focal neurological symptom, the ideal screening tool for the identification of carotid stenosis and occlusion and the selection of lesions amenable to surgical or endovascular treatment. Atherosclerosis is a relevant cause of transient ischemic attack and stroke, but also non atherosclerotic conditions, like spontaneous cervical artery dissection and arteritis, can be diagnosed and followed-up. In acute stroke patients the involvement of the extracranial carotid axis is the cause of the cerebrovascular event quite in 18%, being the majority of vessel lesions in the intracranial circulation and sometimes both in extracranial and intracranial circulation (Malferrari G et al. 2007). For both atherosclerotic and non-atherosclerotic diseases, the ultrasound findings and the diagnostic criteria has been compared to the neuroradiological findings and criteria in the literature, whereas Digital Subtraction Angiography (DSA) is considered the gold standard.

2.1 Atherosclerotic carotid stenoocclusion

Atherosclerotic involvement of the extracranial carotid artery is not the main cause of vascular lesions in acute stroke patients. It has been reported in about 18% of patients in a 6 hours time window, whereas the intracranial large vessel stenoocclusion accounts for 52.8%. There are two main mechanisms by which the carotid atherosclerotic disease may lead to cerebral infarction: first, an embolic mechanism, as an artery to artery embolism from the plaque rupture; second, an hemodynamic mechanism, because of the blood flow reduction downstream the stenoocclusion. The first one is linearly related to the severity of the carotid stenosis, increasing as the stenosis increases, but the second one is not related to the severity of the stenosis and it depends on multiple factors, as the cerebrovascular reserve, the collateral circulation failure, the time course of the vessel lesion, etc. In many situations the global risk of cerebrovascular events is related to a combination of the two abovementioned mechanisms, because in a territory with an hemodynamic failure, also the clearance of emboli is worse (Caplan L et al. 1998). Ultrasound techniques are suitable to identify carotid lesions and there are several studies in the literature, comparing ultrasound techniques with neuroradiological techniques, but they were conducted mainly in a non acute setting. Very few studies or case series are published, using both neuroradiological and neurosonological

techniques, in the setting of acute stroke, and the main target of these studies was the intracranial disease. Therefore we are somewhat obliged to translate the reliability data of the non acute phase to the acute phase. This process is make easier by the high accuracy of neurosonological grading of carotid stenosis in a symptomatic patient (Chapell F et al., 2009; Wardlaw et al. 2006).

The overall accuracy of ultrasound examination of the internal carotid artery versus neuroradiological techniques was the subject of several studies and the following figure (from Wardlaw et al. 2006, modified) shows the results of a meta-analysis of them for the 70-99% range with the NASCET system.

	DUS	CTA	MRA	CEMRA
70-99% stenosis				
Sensitivity 95% CI	0.89 (0.85-0.92)	0.77 (0.68-0.84)	0.88 (0.82-0.92)	0.94 (0.88-0.97)
Specificity 95% CI	0.84 (0.77-0.89)	0.95 (0.91-0.97)	0.84 (0.76-0.97)	0.93 (0.89-0.96)

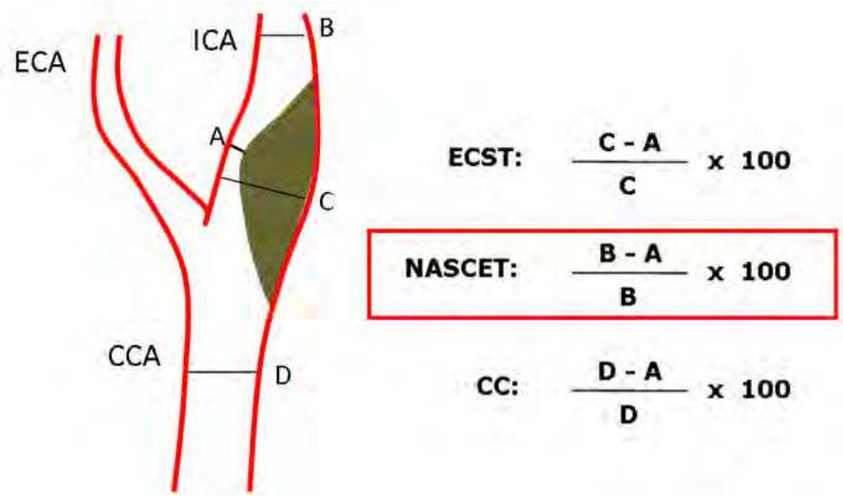
DUS: Doppler UltraSound
CTA: Computed Tomography Angiography
MRA: Magnetic Resonance Angiography
CEMRA: Contrast Enhanced Magnetic Resonance Angiography

Fig. 1. Sensitivity and specificity for the diagnosis of a severe carotid stenosis (ultrasound versus neuroradiological techniques) of non-invasive diagnostic techniques compared to DSA

In the acute setting, even more than in a post-acute management, the main objective is the diagnosis or the exclusion of carotid lesion amenable to surgical or endovascular treatment, according to the current guidelines. Therefore it is relevant to assess the reliability of ultrasound techniques for 70-99% stenosis. In the above cited meta-analysis 41 studies (2541 patients, 4876 arteries) from 1980 to 2004 were included, comparing non-invasive imaging with intra-arterial angiography. The conclusion of this meta-analysis agrees with the common clinical practice of using first-line non-invasive tests, as DUS, for diagnosing 70–99% stenosis. For lesser degrees of stenosis (50–69%) the accuracy of non-invasive techniques is not so high, but again, if surgical indication is well documented for symptomatic carotid stenosis > 70%, the benefit is discussed and very narrow, also for high risk patients, for lesser degrees of stenosis. This categorization is internationally made using the angiographic NASCET grading system (NASCET coll. 1991) and non-invasive imaging techniques should have validated their diagnostic and grading criteria versus the NASCET system.

The ultrasound grading criteria were stated in the Consensus Conference of American Academy of Radiology in 2003 (Grant et al. 2003), but neuroradiological techniques have less shared criteria, based on caliper measurements and ratios, rather than the subjective visual impression. Unfortunately, an implementation of their use in the clinical practice, outside the clinical trials and the evaluation of a central reader, is needed, because the visual impression could be useful only for excluding very tight stenosis, but not for achieving a precise grading (U-King-Im et a. 2007).

In the next figures the grading systems of carotid stenosis and the ultrasound diagnostic criteria are shown.



CCA: commobn carotid artery
ICA: internal carotid artery
ECA: external carotid artery
ECST: European Carotid Surgery Trial
NASCET: North American Symptomatic Carotid Endarterectomy Trial
CC: Common Carotid

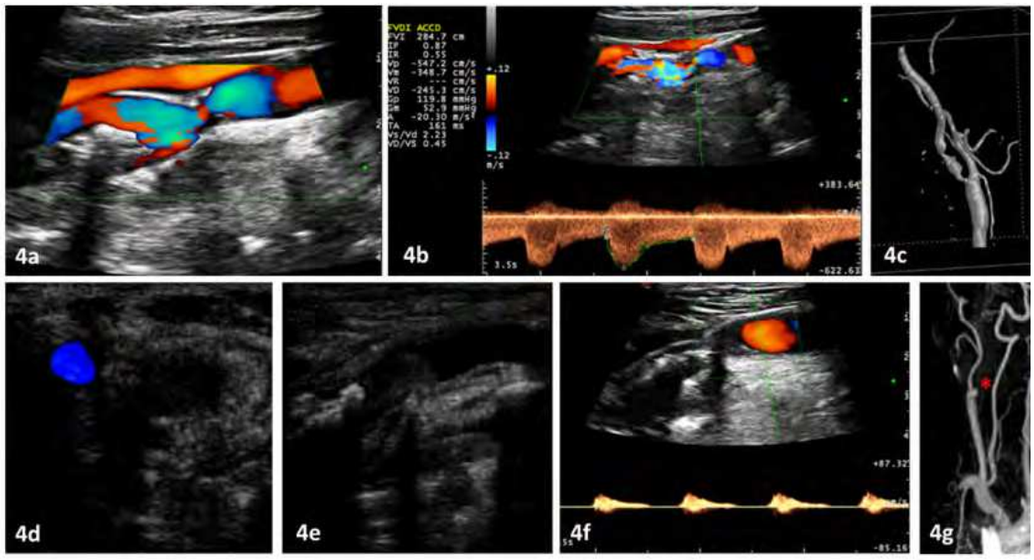
Fig. 2. Schematic drawing of the grading systems of carotid stenosis (NASCET system in the red box)

DEGREE OF STENOSIS	PRIMARY CRITERIA		ADDITIONAL CRITERIA	
	ICA PSV (cm/sec)	STIMA PLACCA (%)	ICA/CCA PSV ratio	ICA EDV (cm/sec)
Normal	< 125	None	< 2	< 40
< 50%	< 125	< 50	< 2	< 40
50-69%	125-230	≥ 50	2-4	40-100
≥ 70%	> 230	≥ 50	> 4	> 100
Near occlusion	High, low or not detectable	Visible	Variable	Variable
Occlusion	Not detectable	Visible, lumen not detectable	Not applicable	Not applicable

Fig. 3. DUS criteria from Grant et al. 2003. These criteria have a 92% sensitivity and a 97% specificity for diagnose a carotid stenosis > 70%

In acute stroke evaluation the finding of a severe carotid stenosis should raise the question of identifying intracranial artery-to-artery embolization as a tandem lesion, in large or small vessels. Sometimes the intracranial occlusion can be missed by imaging, both for spontaneous recanalization and spreading of the clot fragments in the distal vessels, and for the very distal localization, witnessed by the localization of infarcts in the distal cortex of the cerebral hemispheres or in the gray-to white matter junction.

If there is a significant hemodynamic finding in carotid arteries in patients with acute stroke within 6 hours, it would be often an acute carotid occlusion or a near occlusion. An acute carotid occlusion may occur for the acute complication of a plaque rupture, as a thrombus above the plaque, regardless the previous presence of a mild stenosis, considering only atherosclerosis. The cause of an acute carotid occlusion may be atherosclerosis, cardiac embolism or dissection, because a carotid plaque is not always clearly detectable. Another possibility is the downstream extension of a thrombus in the petrous or intracranial segment of the internal carotid artery, e.g. from an acute complication of intracranial atherosclerosis. The follow-up of the vessel lesion, if surgically or endovascular untreated, can help to define the diagnosis, because time, morphology and rate of recanalization vary, depending on the cause of the occlusion.
Near occlusion is defined as a stenosis in the range 95-99% with distal reduction of vessel size and flow limitation, typically without the increase of flow velocity of the lesser degrees of stenosis (Bartlett et al. 2006; Thanvi and Robinson 2007).



4a ICA stenosis in power mode; 4b ICA stenosis with the flow waveform; 4 c corresponding 3D reconstruction from CTA; 4d ICA occlusion with hypoechoic luminal thrombus in transverse scanning at the carotid bifurcation (ECA in blue); 4 e corresponding longitudinal scanning in B-mode with the highly hyperechoic plaque and the superimposed organized thrombus; 4g corresponding MRA with the lacking ICA (red asterisk).

Fig. 4. Ultrasound hemodynamic findings of the extracranial carotid axis.

Finally, the ultrasound examination of carotid artery allows to recognize an indirect sign of the hemodynamic involvement of the petrous and/or intracranial segment of the same artery. Indeed, if a middle cerebral artery stenosis or occlusion does not lead to changes in the upstream flow of the carotid artery, because of the distribution of the resistances in the polygon of Willis, a severe stenosis or occlusion of the intrapetrous segment of the internal carotid artery or at the siphon level, has an identifiable consequence on the waveform of the internal carotid artery, as decreased systolic and diastolic flow velocities, increased systolic-diastolic ratio of the flow velocity, and disappearance of the diastolic component of velocity waveform, depending of the increased resistance to the flow downstream. The more

characteristic finding of this situation is the so-called "stump flow" in the extracranial internal carotid artery. A summary of the main ultrasound hemodynamic findings is shown in the fig. 4, compared to neuroradiological imaging.

2.2 Carotid dissection

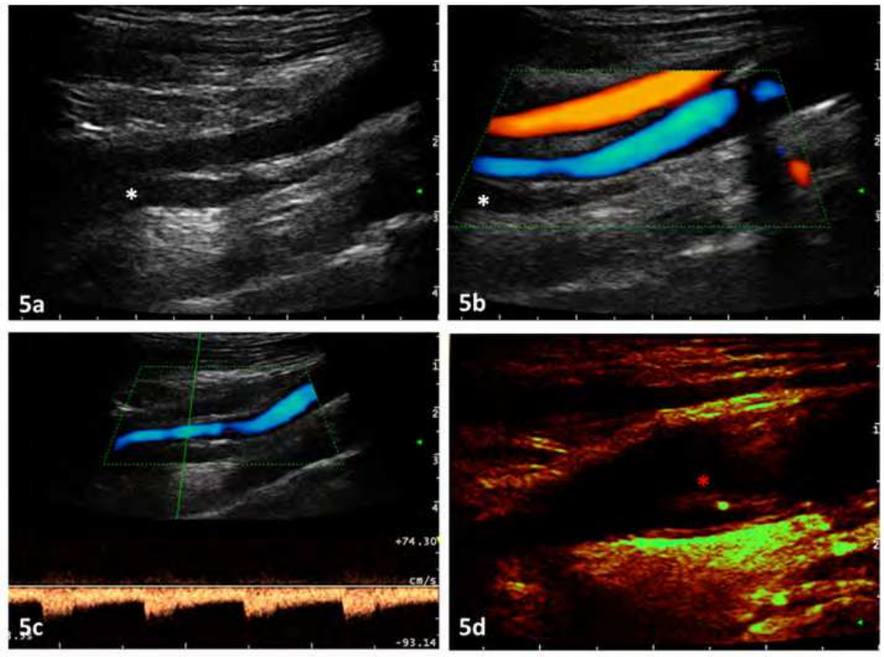
Another cause of stroke, mainly in young patients, is the arterial dissection. It can occur both in extracranial and in intracranial arteries, it is frequently spontaneous and it can start from the intimal or from the adventitial layer of the vessel wall. In the first case the more frequent evolution is a carotid stenosis or occlusion and a potential cerebral damage due not only to hemodynamic factors, but also to artery-to-artery embolism from the clot superimposed on the intimal interruption; in the second case there is a greater likelihood of pseusoaneurysmal evolution with or without rupture (Fusco and Harrigan 2011). Even in a spontaneous dissection, it is often reported a history of trivial or repetitive trauma (1/4 of cases). The gold standard for diagnosis is DSA, but often, when the vessel is partially involved or the mural hematoma is not hemodynamic, magnetic resonance angiography with T2 weighed sections and fat suppression can be almost as much sensitive than DSA. The role of ultrasound examination is discussed, because of the missing petrous carotid segment and of the inability to image or find indirect signs of non-hemodynamic intracranial arterial lesions. The extracranial internal carotid artery is well imaged by ultrasound and therefore a pathologic process is well detectable, if it is located at the carotid bulb and at the origin of internal carotid artery. Unfortunately, a spontaneous extracranial carotid dissection occurs more frequently in the distal segment of the internal carotid artery and sometimes a focal, partial, non-hemodynamic process can be missed by ultrasound examination (Goyal and Derdeyn 2009). Therefore for a reliable evaluation of the sensitivity and specificity of colour-coded duplex ultrasound diagnosis of carotid dissection, it should be taken into account that two different subpopulations exist:

- patients with signs and symptoms of cerebral ischemia in the carotid territory, and
- patients with other complaints or signs (e.g. Horner sign) but without cerebral ischemia.

In the first group, where it can be easily expected an hemodynamic carotid lesion (stenosis or occlusion), the reliability of ultrasound technique is very high. Indeed in a study on 177 young patients with signs of cerebral ischemia in the carotid artery territory, examined by colour duplex ultrasound and MRA, sensitivity, specificity, and positive and negative predictive values for ultrasound diagnosis of spontaneous internal carotid artery dissection, causing carotid territory ischemia, was 96%, 94%, 92%, and 97%, respectively (Benninger et al. 2006).

In the second group, where partial non-hemodynamic arterial lesions are often present, the reliability of ultrasound technique is lower. In patients with isolated Horner syndrome nearly 1/3 of spontaneous internal carotid artery dissection does not have any hemodynamic sign, and therefore was missed by ultrasound (Arnold et al. 2008). Considering both hemodynamic and direct signs, the sensitivity of ultrasound for diagnosis of spontaneous internal carotid artery dissection reaches 90% (Alecu et al. 2007).

In an ultrasound semeiological approach, direct signs of a vessel dissection are the visualization of the intimal flap and/or the intramural hematoma; indirect signs are the hemodynamic relevance of the vessel disease, as stenosis without significant atheromatosis and occlusion by acute thrombosis, or signs of distal stenoocclusion from the flow waveform, as stump flow. Unfortunately the identification of a intimal flap or an intramural hematoma is not a frequent finding, although diagnostic of the dissection (fig. 5).



5a-c are images from the same patient; B-mode (a) and Power-mode (b) longitudinal scanning of ICA with a mural hematoma (white asterisk) without hemodynamic consequences (flow waveform in c). 5d: intimal flap (red asterisk) at the carotid bulb.

Fig. 5. Direct ultrasound findings of carotid dissection.

Ultrasound techniques are also suitable for the monitoring of recanalization in patients with carotid artery dissection, because this disease has an highly dynamic course and it is possible, during days and weeks, to image both recanalization and reocclusion or pseudo-aneurysmal evolution (fig. 6). In a recent study (Nedeltchev et al 2009), of 268 spontaneous internal carotid artery dissections the vessel hemodynamics at presentation was: 7.5% with 50% stenosis, 11.6% with 51% to 80% stenosis, 34.3% with 81% to 99% stenosis, and 46.6% with an occlusion. The sonological follow-up showed normal findings (complete healing of the vessel without residual signs of the dissection on the wall) in 60%, 50% stenosis in 10%, 51% to 80% stenosis in 1%, 81% to 99% stenosis in 10%, and occlusion in 19% of the vessels.

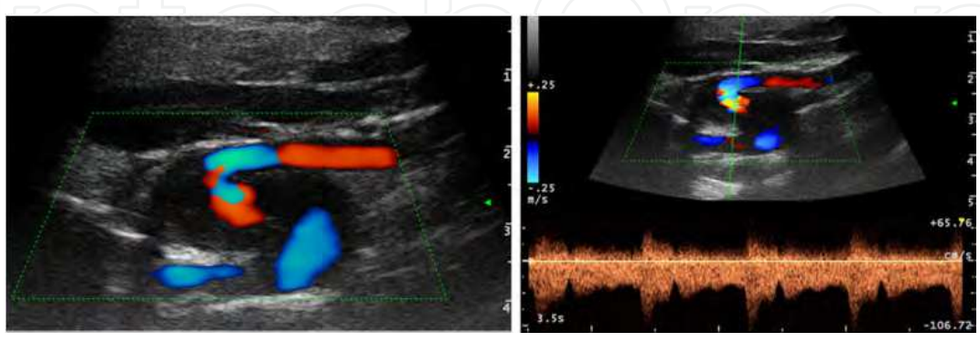
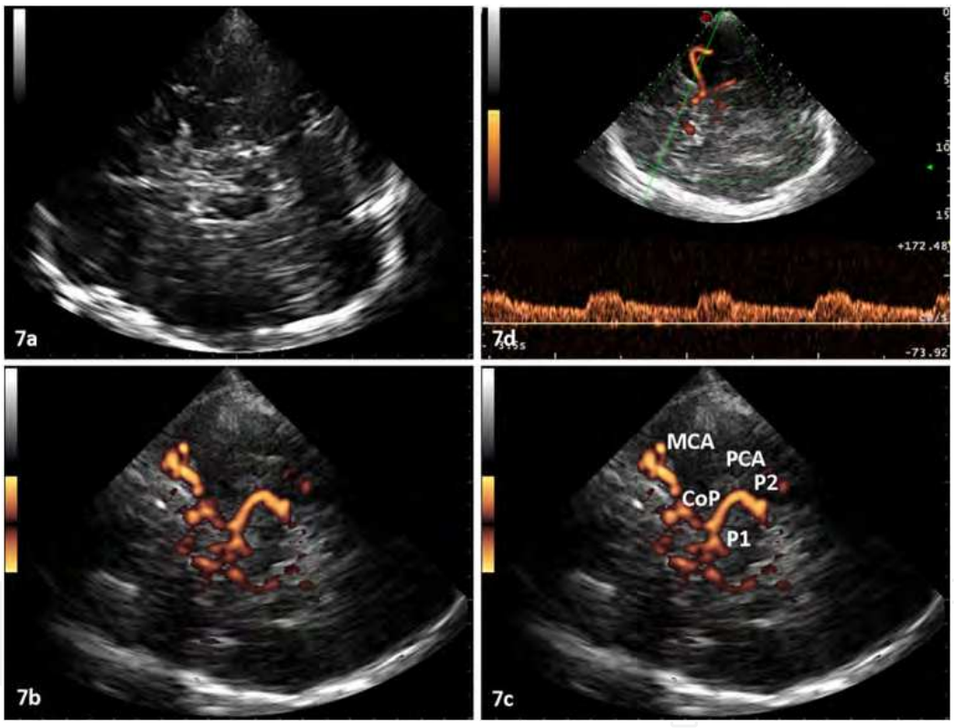


Fig. 6. Pseudo-aneurysmal evolution of a spontaneous internal carotid artery dissection. In the left side Power-mode longitudinal scanning of distal ICA with a partially thrombosed wall enlargement; in the right side corresponding waveform with a minor focal flow acceleration (aliasing in the Colour-mode)

The serial ultrasound examination allowed to define the timing of recanalization: indeed the rate of complete recanalization was 16% at 1 month, 50% at 3 months, and 60% at 6 and 12 months. Therefore the recanalization process occurs mainly within the first six months, regardless the treatment. The main factor that was related to a reduced recanalization rate, was an initial occlusion of the dissected vessel, whereas the absence of stroke symptoms and the presence of local manifestations and signs as the unique clinical presentation, were associated with an increased rate of complete recanalization.

3. Intracranial vessels: TCCS examination

TCCS is a reliable, safe and bedside tool to image intracranial circulation, mainly in acute stroke patients. The natural course of intracranial vessel occlusion is highly dynamic within hours and days and therefore a tool at least so much dynamic is needed in order to monitor the recanalization process.
A basic TCCS scanning is obtained from the temporal bone window in the mesencephalic axial plane, showing the full circle of Willis, as in the figure 7.



a. B-mode evaluation in gray scale with the butterfly shaped midbrain at the midline; b. corresponding Power-mode with the main vessels of the circle of Willis, tagged in c; d. waveform of the flow spectrum of ipsilateral M1 MCA (normal pattern).

Fig. 7. TCCS axial scanning from the temporal bone window, mesencephalic plane.

TCCS is a very reliable tool for imaging large intracranial vessels and for diagnosing their occlusion in the acute phase. The current guidelines about its application in clinical practice are not updated from 2004 (Sloan et al. 2004), but further data are now available from clinical studies in acute stroke patients, comparing neurosonology with neuroradiology and documenting the usefulness for monitoring the recanalization and enhance clot lysis. The

clinical indications for TCCS are basically the same of TCD for imaging of large intracranial vessels, but TCCS has the clear advantage to image the brain parenchyma and the intracranial structures, allowing also the application in neurodegenerative disease (mainly extrapiramidal disorders), the diagnosis and monitoring of hemorrhagic parenchymal transformation after treatment, the perfusional evaluation of the microcirculation, etc. The sensitivity and specificity of TCCS is not lesser than the ones of TCD and the established indication for TCD in acute stroke are also applicable to TCCS.
In a recent systematic review (Alexandrov et al. 2010) of TCD application, for patients with acute ischemic symptoms in anterior or posterior circulation who had cranial CT or MRI, the authors stated that "TCD can identify patients with proximal arterial occlusions both in anterior and posterior circulation who have the worst prognosis and can benefit the most from intravenous thrombolysis or rescue intraarterial therapies".

3.1 Advantages and limitations of neurosonology

Neurosonological tools, both TCD and TCCS are reliable and useful in acute stroke patients and have several comparative studies with MRA, CTA or DSA. The advantage of neurosonology in this setting are:

- the virtual absence of contraindications (because of the rarity of adverse reactions against ultrasound contrast agents, whose use is mandatory in about 10% of patients without a suitable temporal bone window) (Baumgartner et al. 1997, Kunz et al. 2006)
- the bedside feasibility
- the very low time consumption with a dedicated examination pathway and a fast-track scanning protocol for extracranial and intracranial arteries, lasting lesser than 15 minutes (Alexandrov et al. 1999)
- the high reliability for the early diagnosis of large artery proximal occlusions in acute stroke patients before thrombolysis; in the above cited article 69% of thrombolysis-eligible patients had a proximal occlusion on TCD (Alexandrov et al. 1999)
- the high reliability for obtain functional and hemodynamic data; in 26% of 130 patients, TCD provided relevant informations, that helped to refine the severity of a stenosis and determine stroke pathogenesis, in addiction to DSA (Alexandrov et al. 1999)
- the repeatability during thrombolytic treatment, to monitor recanalization and help to select patient for a rescue strategy (Saqqur et al. 2005)
- the low cost of examination

Disadvantages are mainly the operator-dependency, but it is notable that all diagnostic techniques somewhat depend on technical skills and expertise of operators, as documented by the intraoperator discordance in grading an extracranial carotid artery stenosis on NASCET study. The early diagnosis of a large vessel occlusion has a great impact on the prognosis of patient and on the choice of the proper treatment. Also in studies with an extended time window for thrombolysis up to 9 hours, because of the mismatch evaluation, only patients with residual large vessel occlusion shown a positive response to treatment and a significant improvement of disability scores (Hacke et al. 2009). Similarly persisting occlusions after reperfusion treatment have worse outcome and this information could be useful to address patients to intra-arterial clot removal or, in some cases, hemicraniectomy.
Sensitivity and specificity of neurosonological diagnosis of intracranial steno-occlusion is very high also compared to DSA (Sloan et al. 2004) (Fig. 8)

	Sensitivity (%)	Specificity (%)
Anterior Circulation	70-90	90-95
Posterior Circulation Occlusion	50-80	80-96
MCA	85-95	90-98
ICA, VA, BA	55-81	96

Fig. 8. Reliability of neurosological techniques vs DSA for diagnosis of intracranial occlusions

It can be noted that the specificity is globally very high, i.e. a negative transcranial examination can reliably exclude a large vessel occlusion, and also the sensitivity for MCA lesion is very good and it is relevant, because most strokes occur in the MCA territory through an MCA main stem occlusion or stenosis.
The reliability of this technique is also very high in the follow-up of stroke, during the monitoring of recanalization (Fig. 9) (Sloan et al. 2004)

	Sensitivity (%)	Specificity (%)
Complete Occlusion	50	100
Partial Occlusion	100	76
Recanalization	91	93

Fig. 9. Reliability of neurosological techniques vs DSA for monitoring recanalization of intracranial occlusions

Also for monitoring the recanalization process the global reliability of TCD is high, and even higher for partial than for complete occlusion. This last feature is well understood if the extremely high dynamicity and temporal resolution of ultrasound techniques is kept in mind, because the serial use of DSA has forcedly time intervals of several hours or days between the successive examinations, and so it is easier to lose the partial recanalization step between occlusion and complete reopening of the vessel. Neurosonological techniques can be applied every minute or hour and therefore also a small variation in vessel patency is well recognized.
Another partial limitation of TCCS (and even more of TCD) is the incomplete evaluation of the internal carotid artery, because of the inability to image the petrous segment. This is a partial limitation, since an hemodynamic lesion in this segment can be inferred by indirect sign, both in extracranial and intracranial ICA, if it is an acute process. The C5-C1 segment of internal carotid artery, according to angiographic terminology, can be explored by TCCS combining the axial and coronal access (Eggers et al. 2009).

3.2 TCCS: How to perform the examination and the consensus statements

TCCS is increasingly used in acute stroke patients, but it should pay for being ten years younger than TCD; therefore there are not clinical shared guidelines, as for TCD, but recently guidelines for its application in clinical trials on acute stroke have been published (Nedelmann et al 2009). Before these guidelines, there was not a systematic consensus on how TCCS examination should be performed in acute stroke patients. Furthermore standardized recommendations are needed to compare the results of TCCS studies from several centres. Therefore a systematic review of the literature on TCCS in acute stroke was performed and the resulting manuscript was corrected and commented by a panel of

international experts with previous publications in the field of TCCS in acute stroke and finally collegially revised.

The examination procedure was carefully described, choosing a basic and comparable insonation modality for the anterior circulation stroke. The main examination plane is the axial transtemporal mesencephalic one (fig. 7), showing a good visualization of the circle of Willis (Malferrari et al. 2007, Wong 2003, Valaikiene et al 2008). A useful information to compare TCCS planes with the corresponding images from neuroradiological techniques, is that the transcranial axial insonation plane is usually different from the axial plane displayed with MR and CT imaging. There are also parenchymal and bone landmarks to identify the vessels and make easier to compare the oblique transcranial images with the neuroradiological images of CT or MR. The transtemporal bone window in the axial insonation plane allows to recognize the main branches of the Willis circle:

- sphenoidal (M1) and insular (M2) segments of the middle cerebral artery
- precommunicating (A1) segment of the anterior cerebral artery
- distal intracranial part of the ICA
- precommunicating (P1) and postcommunicating (P2) segments of the posterior cerebral artery

Also the use of the coronal plane can be useful to localize and distinguish both vessel segments and normal from pathologic conditions (Valaikiene et al 2008).

All segments of all visible arteries should be investigated, not only by Colour- or Power-mode, but especially by spectral Doppler sonography (Zipper and Stolz 2002, Baumgartner 2004, Krejza and Baumgartner 2004).

The way to examine the entire circle of Willis by TCCS, makes unnecessary the orbital bone window, conventionally used by TCD for the exploration of the ophtalmic artery and its branches, as stated in the above cited consensus (Nedelmann et al. 2009) (Fig. 10).

Consensus Statement 1	An adequate interpretation of intracranial findings always requires careful assessment of the extracranial vasculature, because obstructive disease of extracranial vessels may significantly influence or severely compromise intracranial hemodynamics.
Consensus Statement 2	The standard extracranial protocol in the acute stroke setting does not necessarily include evaluation of the ophthalmic artery or supraorbital arteries. In case of relevant ICA pathology, an inverted flow direction in the ophthalmic artery does not provide further information beyond a complete ICA examination. In case of insufficient temporal bone window, evaluation of ophthalmic artery flow direction may be of additional value.

Fig. 10. Statements 1 and 2 from Nedelmann et al 2009

About the main limitation of transcranial Doppler, i.e. the poor acoustic window, the Consensus carefully examined it. Also this review of the literature agreed with the known rate of 10% of patients with cerebrovascular diseases, where the insonation of the basal cerebral arteries is incomplete (Seidel et al. 1995; Kenton et al. 1997; Krejza et al. 2007). In this case the intravenous administration of an ultrasound contrast agent dramatically improves the insonation and therefore increases the number of conclusive ultrasound studies, allowing an adequate diagnosis in 80% to 90% of those patients with insufficient bone window before the contrast agent injection (Zunker et al. 2002; Postert et al. 1999;

Gerriets et al. 1999; Baumgartner et al. 1995; Goertler et al. 1998; Nabavi et al. 1998; Kunz et al. 2002). The shared criterion for defining sufficient the temporal bone window is the adequate displaying of the ipsilateral proximal branches of the circle of Willis, in both Colour- or Power-mode and spectral Doppler. This raises the question of the evaluation of the quality of the insonation window in a case of T-occlusion diagnosis. The Consensus Conference examined also the indication for ultrasouns contrast agents (UCA) in acute stroke in the setting of clinical trials and the Consensus Statement 3 shows the achieved agreement (Fig.11).

Consensus Statement 3	UCA should be used in the setting of clinical trials: • In case of an insufficient temporal acoustic bone window: insufficient signal intensity, or absent visibility of the proximal branches of the circle of Willis. • In cases in which UCA are given at baseline, follow-up examinations should also be performed with UCA. This is important because measured flow velocities may be higher when using UCA (Baumgartner et al. 1997; Khan et al. 2000) • Because of varying availability of UCA in different countries and because of a lack of studies with direct comparison of the different UCA, there are no specific recommendations on the type of UCA. In view of the current literature, application of multiple small boli or continuous intravenous infusion increases the length of the diagnostically useful time window.

Fig. 11. Statements 3 from Nedelmann et al 2009

Another intuitive difference between TCD and TCCS is the possibility of achieving an angle-corrected flow waveform and angle-corrected flow velocity measurements. The relevance of this item comes from the anatomic course of intracranial arteries; indeed the angle between the ultrasound beam and the major intracranial arteries is not the same in each segment of the same artery and between similar segments of the arteries of both sides, mainly in acute stroke patients, because of the time changing mass effect of the ischemic lesion (Eicke et al. 1994). The diagnostic criteria for intracranial stenosis with their velocity threshold are different between TCD and TCCS, because of the angle-corrected measurements with TCCS. Angle corrected threshold have an higher sensitivity to detect arterial narrowing because of stenosis or vasospasm (Baumgartner et al. 1999), and they do not cause a decreased intrarater or interrater reproducibility, as compared to non-corrected measurements (Baumgartner et al. 1994; Maeda et al. 1990; Stolz et al. 2001). These considerations lead to the Consensus Statement 4 and 5 about angle-corrected measurements (Fig. 12).
The focus of this discussion about angle correction is its usefulness to examine patients in the acute phase of stroke, mainly MCA stroke, because the diagnosis of a distal M1 MCA or MCA branches occlusion involves the evaluation of flow velocity differences between MCA of the affected side and MCA of the contralateral side. This is because branch occlusions of MCA cannot be directly imaged by ultrasound and only indirect signs on the flow waveform could be searched, as a reduction of the M1 flow velocity compared to the contralateral side. In the literature there is a prospective TCD study, angiography-controlled, defining the so called asymmetry index without angle correction for the diagnosis of branch occlusions (Zanette et al. 1989). According to this study it is possible to diagnose a condition of multiple MCA branch occlusions (> 3). There is only another study in the literature, addressing this item by contrast-enhanced TCCS and a comparison with angiography (Ogata et al. 2005). Its results were that an end-diastolic velocity of <26 cm/sec

within the M1 segment of MCA, associated with an end-diastolic ratio of < 2.5 between the contralateral and the ipsilateral M1 MCA identified branch occlusion; instead a >2.5 ratio indicated M1 occlusion. The main limitation of this study are the small sample of patients and the lack of specifications on how the criteria relate to the number of affected MCA branches. Another known pitfall is the use of contrast agents, because of the potential increase of flow velocity by 10% to 20% as compared to those assessed without contrast agents (Baumgartner et al. 1997; Khan et al. 2000). Finally it is possible that only the criterion "end-diastolic ratio < 2.5", but not the criterion "end-diastolic MCA velocity < 26 cm/sec" could be useful and exported to non-enhanced TCCS. The definite statement of the Consensus Conference about the diagnosis of MCA branch occlusion is shown in the fig. 13.

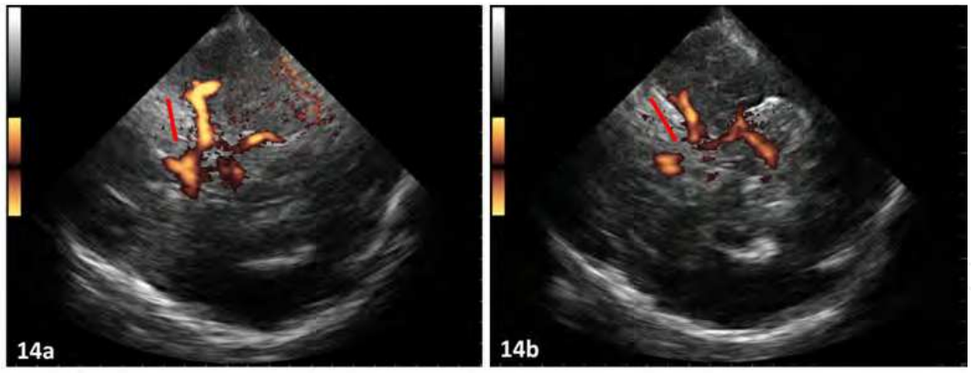
Consensus Statement 4	To prevent inadequate measurements, angle correction should only be applied to velocity measurements when the sample volume can be located in a sufficiently long vessel segment that allows sufficient tracing of the main flow vector (Zipper et al. 2002; Giller et al. 1994). In case of a stenosis being located in a curved arterial segment, angle correction should be omitted, and the ultrasound probe should be repositioned to obtain the smallest insonation angle possible.
Consensus Statement 5	In case of angle-corrected measurements, the correction angle or additional values of uncorrected velocities (that can be calculated from angle corrected velocities and the correction angle) should be provided in publications. This may help to further define the value of angle correction.

Fig. 12. Statements 4 and 5 from Nedelmann et al 2009

Consensus Statement 6	To date, 2 studies have been published that investigated hemodynamics of the M1 segment in MCA branch occlusion. Its solid evaluation requires normal extracranial and contralateral findings as a prerequisite. Angle-corrected TCCS may allow a more accurate approach to detection of MCA branch occlusion. However, the studies discussed were small and one of them used contrast-enhanced TCCS. Therefore, no recommendation can be made regarding which of the criteria should be used in the setting of clinical trials until validation of this specific issue is conducted in a larger study.

Fig. 13. Statements 6 from Nedelmann et al 2009

Angle-corrected measurements are more precise in the acute phase, because, in the presence of a large brain lesion, tissue edema may dynamically modify, expanding and decreasing, mainly within the first hours-days. Therefore a huge lesion in the MCA territory can displace the MCA and vary its course (Krejza et al. 2001) (example in fig. 14). The resulting change of the insonation angle on the affected side is not only different hour by hour or even minute by minute, but also it may lead to a wrong interpretation of the inter-hemispheric differences in flow velocity measurements. However this item requires other dedicated studies and settings to solve the doubts.



a. left side transtemporal insonation; b. right side transtemporal insonation. The red lines show the left and right MCA course.

Fig. 14. TCCS of a patient with acute ischemic stroke in the right MCA territory.

3.3 Scales and measurements in neurosonology

Both in clinical trials and in clinical practice, the course of recanalization has been followed by ultrasound, using shared classification, for achieving a common language and easily compare the results of different centres. The first classification was derived from the angiographic classification, the so-called TICI (Thrombolysis in Cerebral Infarction) scale, which in turn was created beginning from the corresponding coronarographic reperfusion grading system, TIMI (Tomsick 2007). It was called TIBI (Thrombolysis In Brain Ischemia) score and was based on Doppler waveform; it has been widely used for the assessment of initial hemodynamics and recanalization phenomena (Alexandrov, Wojner, Grotta 2004; Demchuk et al. 2001; Molina et al. 2006). Because of the waveform-based being of the scale, it was used primary for TCD examination, and then it was transferred to TCCS, always using only the Doppler spectrum as criterion. TIMI and TICI, being angiography-based, were assumed to assess both features of flow restoration or revascularization: reopening of the originally occluded artery and restoration of effective flow or reperfusion into the distal arterial bed of the originally occluded artery. These two concepts are related each to other but not exactly the same phenomenon, because the reopening of an occluded artery does not mean automatically the restoration of an effective perfusion status in the downstream circulation, due to the duration of ischemia, the efficiency of the collateral circulation, the microembolic load, the viability of tissue, etc. Therefore, also a complete recanalization of the primarily occluded vessel may be associated to variable patterns of distal patency and perfusion/reperfusion ratios (Tomsick 2007).

The TIBI grading system refers only to recanalization process, and not to reperfusion of cerebral tissue. It is a valid and widely used tool to assess recanalization, both for TCD and for TCCS. It is shown in Fig. 15 with some examples of the Doppler spectra corresponding to each grade.

As shown in the fig. 15, this scale comprises 6 different degrees of flow abnormalities. The application of this grading system in clinical practice and in trials is sometimes difficult and there is a broad range of subjectivity, mainly in attributing grade 2 and 3. For this reason in some multicentre trials about ultrasound enhanced thrombolysis, a preliminary training was performed to guarantee the comparability of results. To avoid partially this subjectivity, flow grades are frequently separated into 3 major categories (Burgin et al. 2000), as in the angiographic classification (Fig. 16). These categories are:

- MCA main stem occlusion (TIBI 0–1)
- partial recanalization (TIBI 2–3)
- complete recanalization (TIBI 4–5)

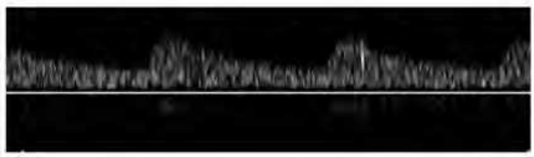
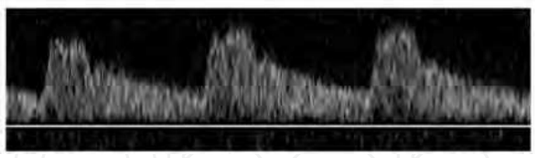
TIBI Flow Grade	Definition	Example
Grade 0 **ABSENT FLOW**	Absent flow signals are defined by the lack of regular pulsatile flow signals despite varying degrees of background noise	
Grade 1 **MINIMAL FLOW**	- systolic spikes of variable velocity and duration - absent diastolic flow during all cardiac cycles - reverberating flow	
Grade 2 **BLUNTED FLOW**	- flattened systolic flow acceleration of variable duration compared to control - positive end diastolic velocity and pulsatility index < 1.2	
Grade 3 **DAMPENED FLOW**	- normal systolic flow acceleration - positive end diastolic velocity - decreased mean flow velocities by 30% compared to control	
Grade 4 **STENOTIC FLOW**	- MFV of >80 cm/s and velocity difference of >30% compared to the control side or - if both affected and comparison sides have MFV <80 cm/s due to low end-diastolic velocity, MFV >30% compared to the control side and signs of turbulence	
Grade 5 **NORMAL FLOW**	- <30% mean velocity difference compared to control - similar waveform shapes compared to control	

Fig. 15. TIBI flow grading system (adapted from Malferrari and Zedde 2008 and Malferrari 2010)

The relevance of this subclassification is that all categories has been externally validated by DSA. But, if this purpose is praiseworthy, it should also considered that only twenty-five patients were examined, half the cases were evaluated by DSA, and the time interval between the two examinations, TCD and DSA, was not short. Indeed TCD was performed at 12+16 hours and angiography at 41+57 hours after stroke onset; only 52% of studies were performed within 3 hours (Burgin et al. 2000). Although this limitations, the authors found that recanalization on TCD had the following accuracy parameters compared with angiography:

- sensitivity 91%
- specificity 93%
- positive predictive value (PPV) 91%

- negative predictive value (NPV) 93%.

As previously stated in the discussion about guidelines (Sloan et al. 2004), to predict partial occlusion (TICI grade II), TCD had an high reliability (sensitivity of 100%, specificity of 76%, PPV of 44%, and NPV of 100%). Also, TCD predicted the presence of complete occlusion on DSA (TICI grade I) with lower, but yet high reliability (sensitivity of 50%, specificity of 100%, PPV of 100%, and NPV of 75%). The conclusions of the authors were that TCD flow signals correlated with angiographic occlusive pattern (Burgin et al. 2000).

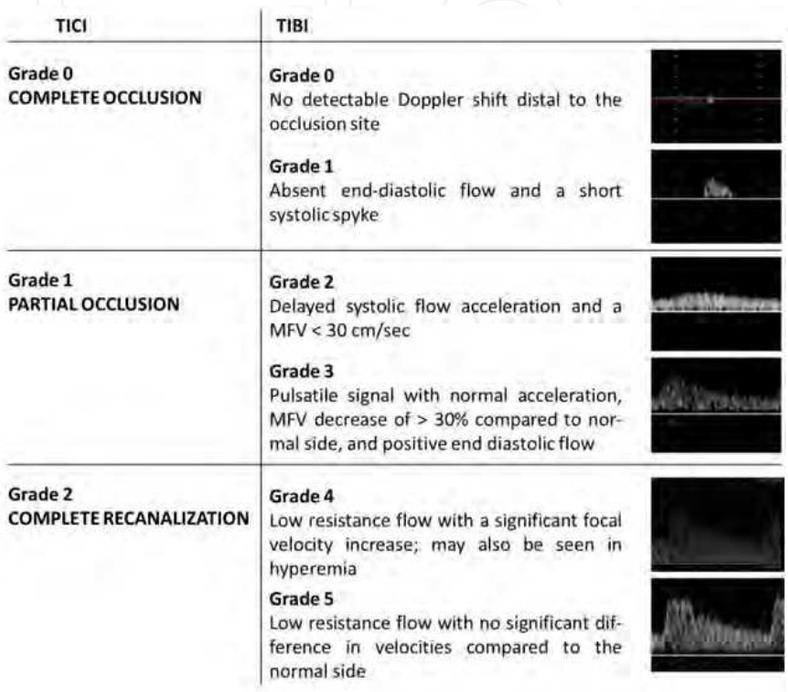


Fig. 16. TIBI flow grading grouping, according to TICI scale (modified from Burgin et al 2000)

The difficulty in differentiation between TIBI grades 1 to 3 (minimal flow, blunted flow, dampened flow) and the limitation of the above cited DSA comparative study (Burgin et al. 2000) raised some questions about the usefulness and the comparability of this grading system in clinical practice. Therefore the authors of the Consensus Conference (Nedelmann et al 2009) noted that, because of the relevant effect of the upstream and downstream arterial status, flow patterns graded by TIBI could not only reflect partial recanalization of the M1 MCA, but also include different hemodynamic situations in a combination of upstream and downstream steno-occlusions (e.g. extracranial or intracranial ICA occlusion, and obstruction of MCA branches). A TIBI flow grade of 2 or 3 may be seen for example in extracranial carotid steno-occlusion without intracranial artery disease, not only during MCA recanalization process.

Based on these considerations, an evolution of the TIBI score into a TCCS-based grading system has been proposed and called COGIF (COnsensus on Grading Intracranial Flow obstruction) score (Nedelmann et al 2009) (Fig. 17).

The purpose of this scoring system is to avoid the interference of previous arterial disease, and it is exclusively based on known hemodynamic changes of the Doppler spectrum, occurring in the acute stage of stroke.

As TIBI score, also COGIF score can be applied for both baseline evaluation and assessment of the spontaneous or treatment-induced recanalization. The score comprise these major grades (fig. 17):

- vessel occlusion (grade 1)
- partial recanalization (grades 2 and 3)
- established perfusion (grade 4).

Each grade is partially different from TIBI corresponding grade, because of the attempt to strongly reduce the subjective interpretation of the Doppler spectrum, mainly for TIBI grades 1 to 3, which are also the ones more affected by downstream and/or upstream arterial status. Furthermore, although the COGIF score, as the TIBI score, is based on the Doppler spectrum for the grading, the first one was designed for TCCS, and then some morphologic findings may play a role in achieving the waveform and in the occlusive pattern diagnosis. This score was proposed in the Consensus Conference (Nedelmann et al. 2009) primary for clinical trials, in order to make easier and reliable the assessment of recanalization grades, but its use is yet under evaluation, because of the lack, at our knowledge, of published prospective studies or retrospective evaluations, using the COGIF score.

COGIF GRADE	HEMODYNAMIC PATTERN	EXAMPLE
Grade 1	No flow	
Grade 2	Low flow velocities without diastolic flow	
Grade 3	Low flow velocities with diastolic flow	
Grade 4	Established perfusion	
	a. Flow velocities equal to controlateral side	
	b. High focal flow velocities (i.e. stenosis)	
	c. High segmental flow velocities (hyperperfusion)	

Fig. 17. COGIF flow grading score: grading, hemodynamic features and examples (modified from Nedelmann et al 2009 and Malferrari et al 2010)

The COGIF score was designed to better follow the recanalization process with its dynamicity and potential alternation of recanalization and reocclusion. Therefore the time course of grades during serial TCCS examination was carefully encoded (Fig. 18).

4. Anterior circulation stroke

For this chapter anterior circulation stroke was described to show the usefulness and the role of sonological vascular imaging as a guide to treatment and to define the prognosis. Indeed the knowledge of vascular status in acute ischemic stroke have a clear prognostic relevance and it could be used also as a criterion to tailor the treatment and select the best reperfusion strategy for each patient, both in a single modality and in a sequential or

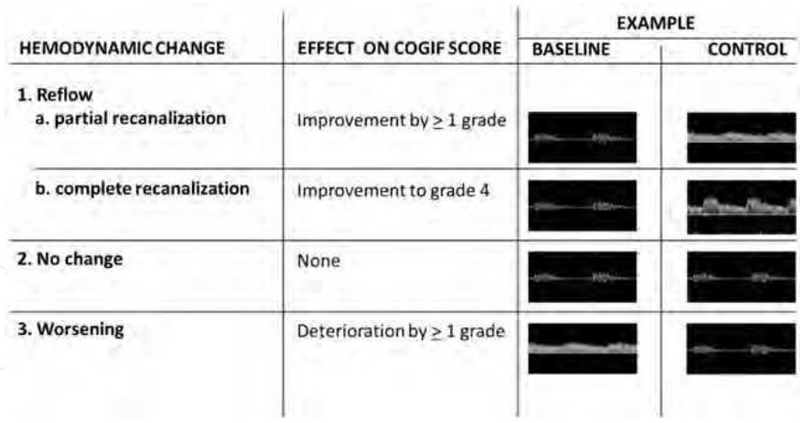


Fig. 18. Hemodynamic changed and COGIF flow grading score (modified from Nedelmann et al 2009)

combined modality. It has been undoubtedly accepted that the occlusive pattern at the presentation is closely related to the outcome of patient, as the recanalization of the primarily occluded vessel and its time course. Another strong predictor of the outcome is the perfusional status of the brain tissue in the downstream of the occluded vessel and it is evaluable mainly by using neuroradiological techniques, MR or CT, but also ultrasound imaging by TCCS and UCA injection may provide some informations about the cerebral perfusion in the MCA territory in acute stroke patients. The combination of the two findings, the occlusive pattern and the perfusional status, could provide a reliable classification of acute stroke patients in terms of the most adequate treatment to reverse the globally poor outcome (Malferrari and Zedde 2008). The following sections are mainly focused on occlusive pattern diagnosis, monitoring of recanalization and perfusional imaging, from the point of view of ultrasound techniques application.

4.1 Occlusive pattern diagnosis

The main studies from which intravenous thrombolysis with recombinant tissue plasminogen activator (rtpA) for stroke achieved an evidence of efficacy (total amount of 2889 patients) (NINDS group 1995; Hacke et al. 1995; Hacke et al. 1998; Clark et al. 1998; Clark et al 2000) did not provide any information about the status of extra- and intracranial vessels before treatment. Therefore it could be hypothesized that a great amount of patients treated with rtPA had a situation of extracranial and intracranial patent vessels. Indeed there is a clearly demonstrated relation between the stroke subtype, according to the Oxfordshire Community Stroke Project Classification (OCSPC), and the occlusive pattern on TCD: Partial or Total Anterior Circulation Strokes (PACIs and TACIs respectively), as expected, are more frequently associated with large vessel disease, as compared with lacunar infarcts (LACIs), where only few patients had an intracranial vessel
lesion (Mead et al. 2000). This last subgroup belongs to Parent Artery Disease (PAD), with the same prognosis of patients with large artery disease.

The relation between the occlusive pattern and the outcome has been demonstrated by several studies, and then it is possible to say that "severe arterial stenosis/occlusion in the early arterial study was highly related with 90-day mortality in an unselected series of patients with stroke" (Ois et al. 2007). This is right non only for severe stroke but also for mild stroke, and it is not related to the imaging technique used. Therefore, if possible, all attempts should be made to diagnose a large-artery intracranial occlusion before

thrombolysis by using neuroradiological techniques or neurosonological ones (TCD or TCCS) (Malferrari and Zedde 2008), without delaying the treatment.
The assumption for this imaging is the close link between the clot burden (i.e. the occlusive pattern) and the extent of brain lesion (i.e. the perfusional status), strongly suggesting the need of diagnosing presence and site of vessel occlusion in the acute phase of stroke. The advantages of neurosonology has been detailed in the previous sections, as widespread availability, easiness of use, the possibility of a repeated bedside examination and monitoring of recanalization, an highest reliability.
Another main advantage of the knowledge of the occlusive pattern before treatment is the possibility of predicting the success of the reperfusion strategy in terms of recanalization rate, because it has been known from the old and recent literature that each occlusive pattern is associated with a different response to rtPA administration (Ringelstein et al. 1992; Trouillas et al. 1998). In the NINDS trial (NINDS group 1995) the subgroup of patients with combined occlusion of ICA and MCA (tandem occlusion) had lesser benefit from thrombolysis than patients with isolated MCA occlusion, particularly in case of branch occlusions, although the clinical presentation and the severity score was the same in the two groups. Another series of 139 patients shown the same results (Del Zoppo et al. 1992), and so on a small study designed for the evaluation of tandem occlusion prognosis (Rubiera et al. 2006) and several studies demonstrated a poor recanalization rate in T-type occlusion (Arnold et al. 2003).
Then there are several occlusive patterns from which it could be expected a different response to thrombolysis: "…the patients presented with similar severity of hemiplegia, but the severity of perfusion deficit and recovery were dramatically different. TCD allows early differentiation of patency and natural history of MCA thromboembolic events. This may have important implications in the decision for thrombolytic therapy…" (Alexandrov et al. 2000).
The neurosonological examination by TCD and TCCS can help in the early diagnostic work-up of patients with acute ischemic stroke (Iannuzzi et al. 1995; Lee et al. 1996; Razumovsky et al. 1999; Alexandrov et al 1999; Garami et al 2003); two studies addressed the reliability of the combined application of ultrasound examination of extracranial and intracranial arteries in acute stroke patients, respectively by TCD and TCCS (Alexandrov et al. 1999; Malferrari et al 2007). This strategy allows to identify the vascular occlusive pattern eligible for treatment (accuracy near to 100%) (IMS study investigators 2004) and a fast-track ultrasound examination protocol has been proposed to diagnose the presence and site of vessel lesion bedside (Alexandrov et al. 1999; Molina et al. 2002; Feldberg et al. 2002), achieving a sensitivity, specificity, positive predictive value and negative predictive value near to 100% (Feldberg et al. 2002; Grant et al. 2003; Demchuk et al. 2001; Burgin et al. 2001; El-Mitwalli et al. 2002; Christou et al 2001).
The occlusive pattern diagnosis was categorized as shown in fig. 19.
There are validated diagnostic criteria for occlusive pattern in acute stroke, both for TCD (Demchuk et al. 2000) and by TCCS (Malferrari et al. 2007) (fig. 20).
Therefore TCD and TCCS are a non-invasive, rapid, reproducible, bedside, reliable tool, to provide useful data on cerebral circulation and then to select patients for reperfusion treatment. Indeed "Ultrasound and other non-invasive tests should be available for the diagnosis of carotid, vertebral artery and intracranial artery stenosis and occlusion" in the acute phase of stroke (European Perspective on Stroke Management, Kjellstrom et al 2007).

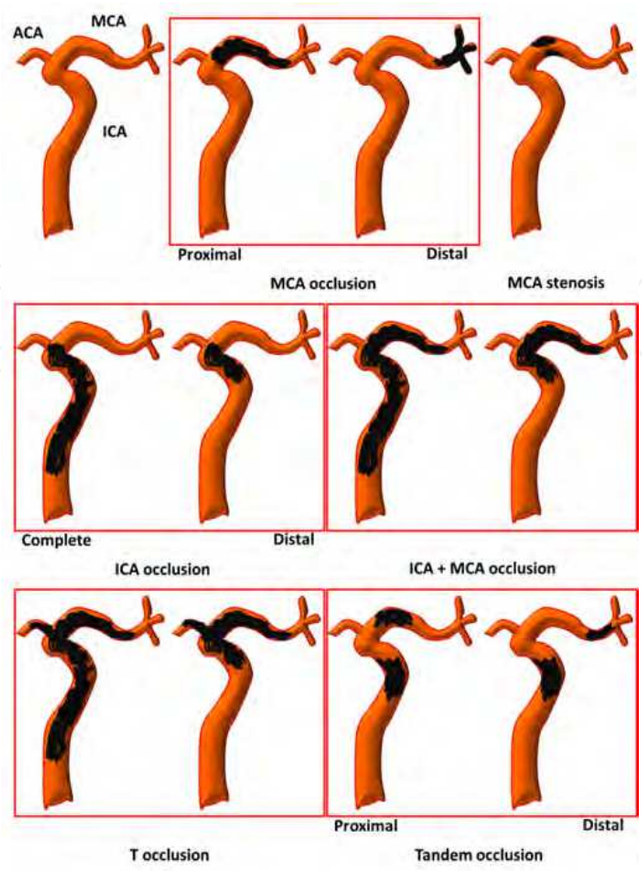


Fig. 19. Occlusive pattern in acute stroke patients.

The step following the diagnosis of occlusive pattern is the assignment of the TIBI or COGIF score, because of the need of a baseline value for monitoring the recanalization. The link between the grading score and the occlusive pattern diagnosis is globally weak, because a single score value matches several occlusive patterns.

Therefore the proposal of the COGIF score (Nedelmann et al. 2009) was associated to the careful analysis of each grade of the score, made by the same authors, both for the diagnosis of arterial occlusion and for the follow-up of recanalization, but mainly for the first one.

The grade 1 (no flow) corresponds to TIBI grade 0 and describes the main spectral finding seen in M1 MCA occlusion (comprising T-occlusion and its variants). The main diagnostic criterion of the M1 MCA occlusion is the absence of a Colour or Power-mode Doppler flow signal and its Doppler spectrum at the proximal MCA main stem (Malferrari et al 2007; Malferrari and Zedde 2008; Malferrari 2010). The absence of Doppler signals may also be caused by an insufficient acoustic bone window, and therefore for a reliable diagnosis of occlusion a sufficient visualization of the other ipsilateral arteries (A1 ACA, C1 ICA, posterior cerebral artery) is requested; sometimes the identification of contralateral arteries of the anterior circulation is also requested (Fig. 21).

The difficulties in the evaluation of MCA versus T occlusions by TCCS born from the lack of angiographically validated criteria. The mostly used diagnostic criterion of carotid T occlusion is detailed in fig. 20, i.e. the absence of colour Doppler flow signal and its Doppler spectrum in M1 MCA, intracranial ICA, and the ipsilateral A1 ACA (Fig. 22). The reliability

of this diagnosis is increased by the simultaneous visualization of the deep middle cerebral vein, the ipsilateral A2 ACA, or the contralateral anterior circulation (Nedelmann et al 2009).

	Intracranial Occlusion Criteria by TCD	Intracranial Occlusion Criteria by TCCS
M1 MCA occlusion	Abnormal Transcranial In Brain Ischemia (TIBI) flow signals were found at a depth of > 45 mm through a temporal bone window, which allow insonation of other intracranial arteries	When no Doppler signal could be obtained in the lateral fissure while the anterior and posterior cerebral arteries (P1 or P2 segment) were sufficiently assessable (Georgiadis et al. 2004)
M2 MCA occlusion	Abnormal TIBI flow signals were found at a depth of < 45 mm or when there were on average > 21% lower mean flow velocities in the ispilateral than in the controlateral M1 MCA, using the Asymmetry Index or Zanette Index (Zanette et al. 1989; Thomassen et al 2005)	Distal occlusions of the MCA (M2) were diagnosed using the interhemispheric asymmetry index with the known threshold of 21% (Zanette et al. 1989) for nonagle-corre4cted measurements and the criterion of end-diastolic ratio < 2.5 between sides for angle-corrected measurements (Ogata et al. 2004)
Terminal ICA occlusion	Abnormal TIBI flow signals were found at a depth of 60 to 70 mm	Whenever a high-resistance signal pattern was recorded on the proximal ICA and if no or minimal signals from M1 and A1 segments were found
Tandem proximal ICA/MCA occlusion	When abnormal TIBI signals at depths 30 to 65 mm were found with signs of collateralization of flow through anterior, posterior communicating, or ophthalmic arteries	Tandem occlusion was classified when there was an occlusion of the extracranial ICA on ECD-SAV, and according to sonographic intracranial criteria previously published by Alexandrov and colleagues (El-Mitwalli et al. 2002)
T-type occlusion		According to the following criteria: (1) absent flow signal of the MCA, ACA, or distal ICA; (2) sufficient temporal bone window, as demonstrated by flow signals in the ipsilateral PCA or contralateral MCA; and (3) resistance profile with increased systolic and decreased end-diastolic velocities (EDV) in the extracranial ipsilateral ICA and CCA. The third criterion was applied only in the absence of < 70% stenosis or occlusion of the extracranial ICA (Georgiadis et al. 2004).
M1 MCA stenosis	Focal mean flow velocity increase of >30% compared with the controlateral MCA	Intracranial stenosis of the proximal and distal MCA were diagnosed according to Baumgartner's criteria (Baumgartner et al. 1999)

Fig. 20. Diagnostic criteria of occlusive pattern in acute stroke patients by TCD and TCCS.

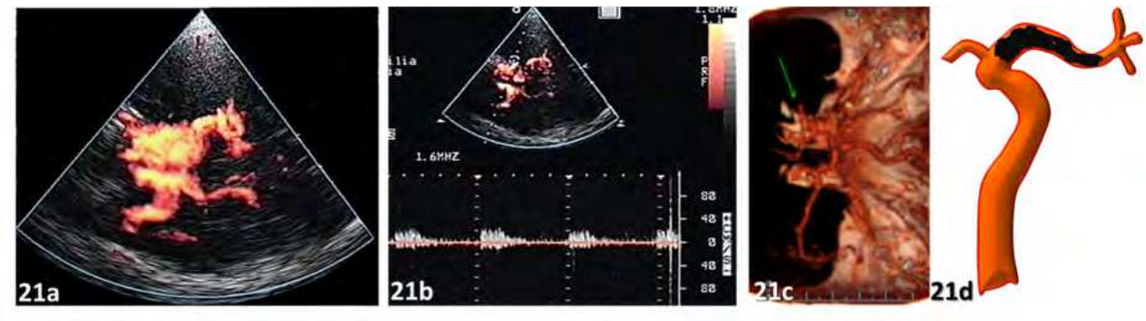


Fig. 21. An example of MCA occlusion by TCCS, compared to CT angiography.

a. TCCS from the temporal bone window in Power-mode with UCA administration: it is well visible the lack of signal in ipsilateral M1 MCA with the sparing of the other vessel of the circle of Willis; b. corresponding Doppler spectrum at MCA origin, with TIBI 2 score and COGIF 2 score; c Tridimensional reconstruction of the intracranial circulation by CT

angiography of the same patient with the lack of M1 MCA (green arrow); d schematic drawing of the occluded artery, as in Fig. 19.

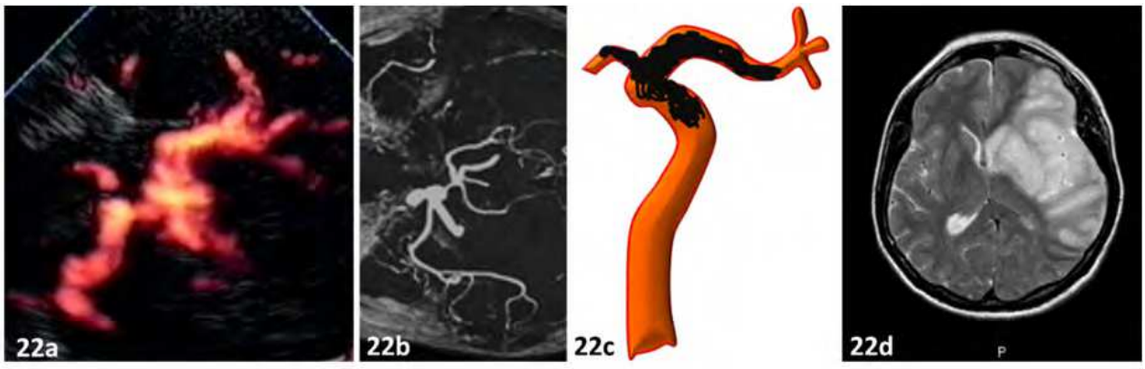


Fig. 22. An example of T occlusion by TCCS, compared to intracranial MR angiography.

a. TCCS from the temporal bone window in Power-mode with UCA administration: it is well visible the lack of signal in ipsilateral M1 MCA, C1 ICA and A1 ACA with the sparing of the posterior cerebral artery and the contralateral anterior circulation; b. MR angiography of the intracranial circulation of the same patient with the corresponding findings; c. schematic drawing of the occluded artery, as in Fig. 19; d. final cerebral infarction at MRI.
In the Consensus Conference these considerations raised other two statements about the diagnostic criterion of T occlusion (Fig. 23).

Consensus Statement 7	If these criteria are fulfilled, it is not necessary to further confirm these diagnoses by use of UCA. A minimal quality standard requires the use of UCA only if insonation conditions are unsatisfactory and a reliable diagnosis is not possible otherwise (see Consensus Statement 3).
Consensus Statement 8	Diagnosis of a carotid T occlusion should be additionally confirmed by presence of decreased flow velocities, in particular end-diastolic, or oscillating flow, in the ipsilateral cervical ICA and common carotid artery in comparison to the contralateral side.

Fig. 23. Consensus Statements 7 and 8 from Nedelmann et al. 2009

4.2 Monitoring of recanalization

As previously outlined, a main prognostic factor in acute stroke patients, treated with rtPA, is the timing of vessel patency restoration. If there have been discussions about the usefulness of vascular imaging before thrombolysis to diagnose the occlusive pattern, there is no doubt that the monitoring of recanalization is useful and widely recommended; for this purpose TCD or TCCS is the preferred technique, because of the known advantages and time resolution. These features make neurosonology a reliable and irreplaceable tool for continuous, real-time monitoring of the beginning, speed, timing and degree of arterial recanalization during thrombolysis (Alexandrov et al. 1999; Malferrari et al 2008). The relation between time of recanalization and outcome is well explained by the attempt of achieve, through the reopening of the occluded artery, the as early as possible restoration of

blood flow mainly in the penumbra (Alexandrov et al 2001; Molina et al. 2004). The residual blood flow signals classification TIBI was described and validated by Alexandrov and coworkers (Demchuk et al 2000b, 2001; Molina et al. 2002) (fig. 15). This classification has been demonstrated to be useful, because the degree of residual flow signals predicts the likelihood of recanalization (Labiche et al. 2003). Patients with TIBI 1 to 3 have a likelihood of recanalization twice more higher than patients with TIBI 0 grade, irrespectively to the occlusion site. This is probably due to the consideration that the detectable residual flow (TIBI 1-3) ensues a better delivery of rtPA to thrombus than the condition of no flow (TIBI 0). Furthermore, an early improvement of blood flow on TCD or TCCS, within 30 min after rt-PA bolus, is related to an higher likelihood of achieving a final complete recanalization and a better outcome (Alexandrov et al. 2001). Then it has been demonstrated that neurosonological technique may distinguish patients who will benefit from thrombolysis, from patients who probably don't. This last subgroup has a poor outcome and the early knowledge of this status could allow to select more aggressive or rescue strategies to achieve the recanalization of the occluded vessel (Saqqur et al. 2006; Sekoranja et al. 2006; Ribo et al. 2006).

In studies defining the impact of recanalization time od an occluded MCA on outcome by TCD monitoring during rtPA treatment (Alexandrov et al. 2001), the timing of arterial reopening was classified into:

- sudden (sudden reappearance of normal flow signal or low resistance stenosis, within 60 s)
- stepwise (flow signal improvement into 1-29 min)
- slow (reappearance of flow signal after 30 min).

In the stepwise group the mean recanalization time of onset was after 17 min from rt-PA bolus and it was complete after 35 min. The complete recanalization was more rapid (mean 10 min) than the partial one (mean 30 min) and recanalization time positively correlated with a favourable clinical outcome. This was also demonstrated in tandem ICA and MCA occlusions (Kim et al. 2005). The slow recanalization pattern and the confimation of TIBI 3 at the end of rtPA administration were poor prognostic factors, related to the persistence of a distal occlusion (Demchuk et al. 2001).

Another useful application of neurosonological examination in the acute stroke, combined with a perfusional approach, is the potential identification of patients treatable beyond the 3 h time window (Ribo et al. 2005).

As expected according to the previous considerations, the time of tPA-induced recanalization, monitored by TCD (Delgado-Mederos et al. 2007) is a strong predictor of the evolution of ischemic lesion at diffusion-weighted imaging (DWI)-MRI (Kidwell et al. 2000; Fiehler et al. 2004) and of the clinical outcome; slow recanalization pattern correlates with greater lesion size and poorer short- and long-term outcomes than sudden and stepwise patterns (Malferrari and Zedde 2008).

DIAS study (Duplex-Sonographic Assessment of the Cerebrovascular Status in Acute Stroke), a German multicentre study, was designed to evaluate the vascular status within 6 h from symptoms onset and to monitor the recanalization after thrombolysis or best medical therapy (Gerriets et al. 2000). Only one of the twelve patients with T occlusion not treated with thrombolysis shown a late spontaneous reperfusion. Also another relevant multicentre study, the NAIS (Study Project of the Neurosonology Research Group of the World Federation of Neurology) (Allendoerfer et al. 2006) had the aim of monitoring the vascular

status within 6 h from symptoms onset and differentiating the several occlusive pattern in extra- and intracranial circulation. Only 32% of the included patients shown a significant extracranial carotid disease and the conclusion of the authors was that it is unlikely that the success of thrombolysis is independent from vascular status, with a statistical significant difference in recanalization between proximal and distal MCA occlusion. Furthermore the "sudden pattern" of recanalization, isolated MCA occlusion, embolic origin of MCA occlusion, are prognostic factors for favourable outcome in patients treated with rtPA within 3 hours and monitored by TCD (Molina et al. 2004 b).

As previously mentioned, the recanalization rate is related to the occlusive pattern. In controlled angiographic trials of intravenous thrombolysis the partial or complete recanalization rate of a previously occluded MCA, is not higher than 25% (Del Zoppo et al. 1998). Trials with intra-arterial thrombolysis had a better recanalization rate (Furlan et al 1999): for example in the PROACT II trial (121 patients), the rate of complete recanalization was 20% and the rate of partial recanalization was 46%, but the median symptom to needle time was 5.3 h and the recanalization, when it occurred, was achieved at > 7 hours from stroke onset.

The sequential bridged strategy of i.v. followed by i.a. thrombolysis, is promising and could be more efficient than each of both single technique, joining the benefit of the rapid administration of i.v. rtPA with the higher recanalization rate of the i.a. treatment (Lewandowski et al. 1999; Flaherty et al. 2005; Lee et al. 2004; Zaidat et al. 2002; Sekoranja et al. 2006).

Several studies described the role of TCD and TCCS as a useful tool for the diagnosis of MCA occlusion and the monitoring of its recanalization and the prognostic value of early arterial recanalization, identified by TCD, was reaffirmed in terms of good outcome at 3 months (Labiche et al. 2003) for:

- 50% of patients with a complete recanalization
- 44% of patients with a partial recanalization
- 22% of patient without recanalization

In this study 20% of patients with proximal MCA occlusion who do not recanalize within 30 min is dead at 3 months.

In the Eligible study (Malferrari et al. 2007; Malferrari and Zedde 2008) the subgroup of patients with MCA stenosis or occlusion had the highest recanalization rate and distal MCA lesions shown a better and earlier recanalization and a significantly lower mortality rate than proximal ones, being patent nearly 50% at 3–6 h, as in the NAIS study (Allendoerfer et al. 2006). The authors conclude that "in acute stroke patients the early identification of a MCA stenosis or occlusion, mainly distal MCA lesions, is a strong predictor of good functional outcome at 3 months". The known differences in the speed and rate of recanalization are probably related to the clot age and composition, because rtPA has a better penetration in fibrin-rich thrombi, likely more recent and embolic, than in platelet-rich thrombi, whose lysis is often slow and partial, with clot fragments moving to the distal smaller vessels and prolonging ischemia (Molina et al. 2004 b; Malferrari and Zedde 2008).

A revision of the data from CLOTBUST study to find out the relationship among the presence and site of vessel lesion and the rate of complete recanalization and clinical recovery was recently made (Saqqur et al. 2007), and its findings were not different from the results of the ELIGIBLE study (Malferrari et al. 2007; Malferrari and Zedde 2008):

- Distal MCA occlusion had an OR of 2 for complete recanalization (44.2%, CI 95: 1.1 to 3.1, P < 0.005)
- Proximal MCA occlusion had an OR of 0.7 (30%, CI 95: 0.4 to 1.1, P < 0.13)
- Terminal ICA had an OR of 0.1 (5.9%, CI 95: 0.015 to 0.8, P < 0.015)
- Tandem cervical ICA/MCA had an OR of 0.7 (27%, CI 95: 0.3 to 1.9, P < 0.5)
- Basilar artery had an OR of 0.96 (30%, CI 95: 0.2 to 4, P < 0.9).

In this study patients with TIBI 0 grade had less probability of complete recanalization than patients with TIBI 3 (ORadj: 0.256, CI 95: 0.11 to 0.595, P < 0.002).

In the CLOTBUST study (Alexandrov et al. 2004 b) the continuous TCD monitoring (i.e. exposure to ultrasound) was a positive predictor for complete recanalization (ORadj: 3.02, CI95: 1.396 to 6.514, P < 0.005). NIHSS score < 2 at 24 h was achieved in 22% of patients, so categorized in terms of the occlusive pattern:

- distal MCA occlusion 33%
- tandem cervical ICA/MCA occlusion 24%
- proximal MCA occlusion 16%

It is notable that none of the patients with T occlusion had dramatic recovery (0%) (P < 0.003).

Modified Rankin Scale score <1 was achieved in 35% of patients, so categorized in terms of the occlusive pattern:

- distal MCA occlusion 52%
- proximal MCA occlusion 25%
- tandem cervical ICA/MCA occlusion 21%
- T occlusion 18%

The likelihood of a good long-term outcome was twice higher for patients with distal MCA occlusion than for patients with proximal MCA occlusions (OR: 2.1, CI 95: 1.1 to 4, P < .025).

The authors conclude that the "clinical response to thrombolysis is influenced by the site of occlusion" and "patients with no detectable residual flow signals as well as those with terminal internal carotid artery occlusions are least likely to respond early or long term" (Alexandrov et al. 2004b; Saqqur et al. 2007).

Also the Eligible study (Malferrari et al. 2007) shown that the clinical recovery at both 24 h and 3 months is influenced by the site of occlusion.

CLOTBUST (Alexandrov et al. 2004b; Saqqur et al. 2007), NAIS (Allendoerfer et al. 2006) and ELIGIBLE (Malferrari et al. 2007; Malferrari and Zedde 2008) studies demonstrated the high predictive value of neurosonology for identifying proximal MCA occlusion. The CLOTBUST authors (Alexandrov et al. 2004b; Saqqur et al. 2007) proposed TCD as a screening tool for i.v./i.a. thrombolysis. A similar proposal has been made for TCCS by an interesting but small clinical study (Sekoranja et al. 2006), where the patients with partial or complete MCA recanalization at 30 min from the onset of i.v. thrombolysis showed an higher rate of positive outcome at 24 h and at 3 months than patients with none recanalization. In this latter subgroup the subsequent i.a. thrombolysis with the residual amount of rtPA was performed and provided a substantial benefit. Therefore, 56% of patients treated with combined i.v./i.a. thrombolysis achieved a good outcome at 3 months (mRS 0-2), compared with 22% of a previous study (Labiche et al. 2003) in patients with no recanalization with i.v. thrombolysis.

As in the TCD studies (Saqqur et al. 2005), this TCCS experience (Sekoranja et al. 2006) found that TIBI classification, defined by TCCS, was reliably related with the corresponding TIMI angiographic grades. Therefore neurosonological techniques, both TCD and TCCS, can

be "a suitable noninvasive tool for selecting patient with persistent arterial occlusions despite initial i.v. rtPA treatment with an i.v. /i.a. protocol" (Saqqur et al. 2005).

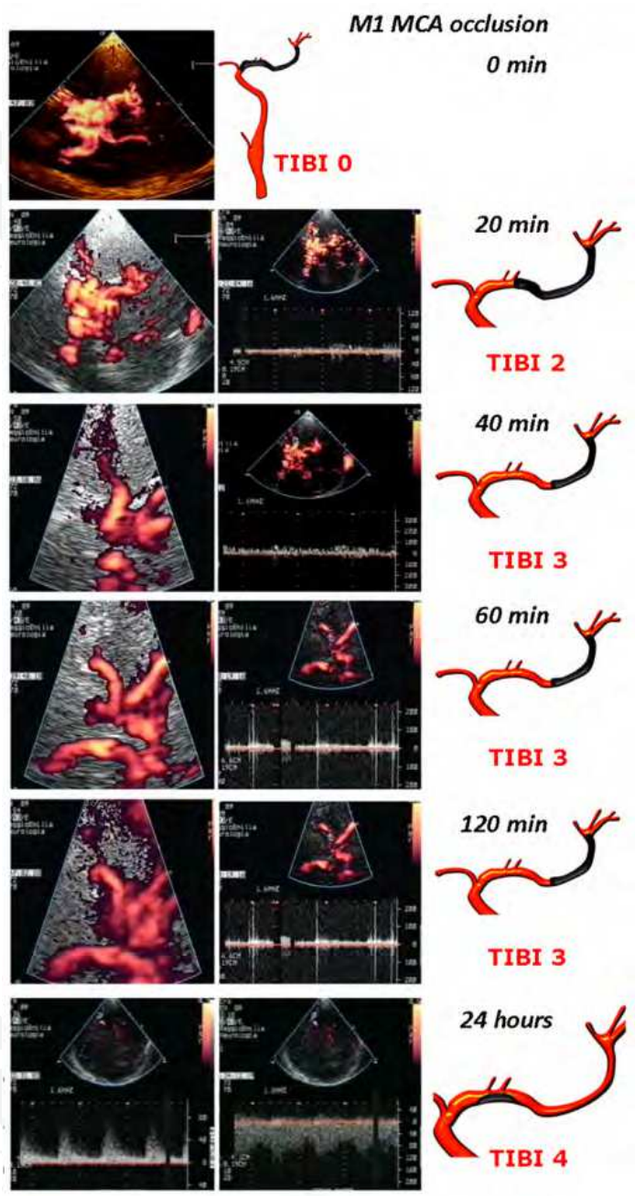


Fig. 24. From top to bottom a sequential TCCS examination of a patient with MCA occlusion and contraindication to thrombolysis. In the right side the corresponding drawings (adapted from Malferrari 2010) and TIBI flow grades.

This is mainly true for vascular occlusive patterns known and accepted for being prognostically poor, i.e. tandem occlusions of ICA and proximal MCA and T occlusions (Fig. 14). It has been known that tandem occlusions of ICA and proximal MCA have a poorest response to i.v. thrombolysis and are associated with an early (within 7 days) mortality rate, as high as 18%, but also 80% of the survivors have a severe disability (mRS > 2) (Rubiera et

al. 2006). T occlusions have similar, if not poorer, mortality and disability rates and a recanalization rate of 31% at 3 days with i.v. thrombolysis (almost all were late or slow recanalizations) (Linfante et al. 2002). This is because of the broader clot burden with lesser collateral circle (Jansen et al. 1995; von Kummer et al. 1995; Christou et al. 2002).
An example of a slow recanalization process is in Fig. shown in Fig. 24.
After the literature review about clinical practice, it is useful to consider the TCCS score, COGIF (Nedelmann et al. 2009) for the potential pitfalls of the recanalization monitoring in clinical trials, i.e. for grade > 2.
Grades 2 and 3 define the low flow situation and it may be determined by different pathological conditions. Low-flow phenomena in the M1 MCA are a main feature of a partial recanalization or T occlusion or tandem pattern, because of an upstream or downstream obstruction (i.e., distal main stem or MCA branch occlusions). The differentiation of these conditions from partial recanalization is well addressed by the Consensus Conference, as summarized in Fig. 25.

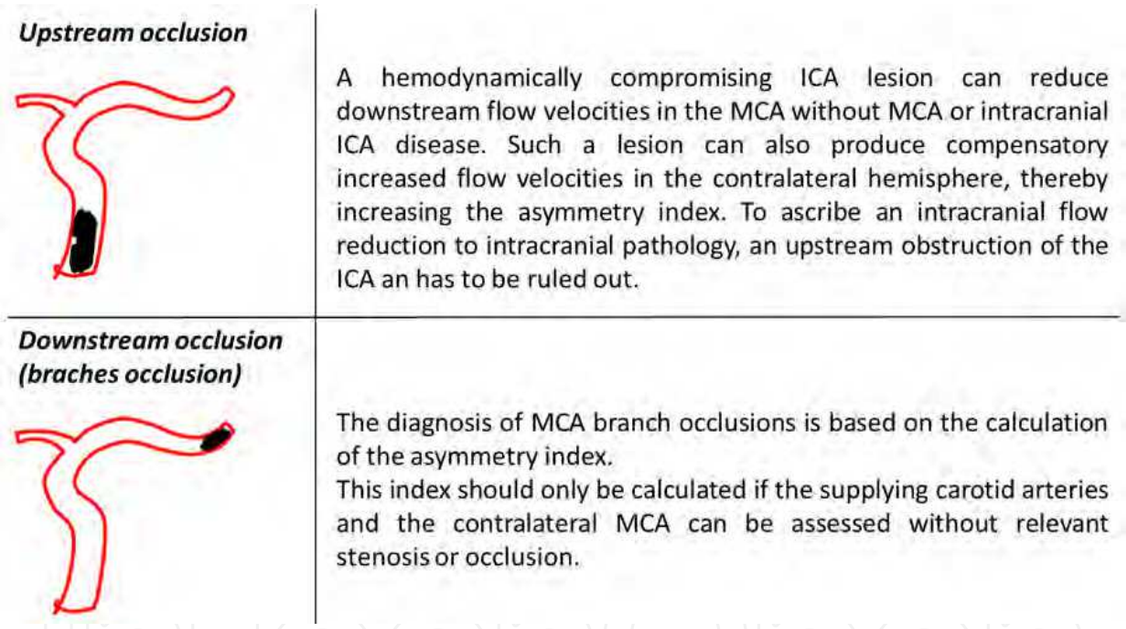


Fig. 25. The influence of upstream and downstream occlusions on low-flow status in COGIF score (modified, from Nedelmann et al. 2009)

In the COGIF score, low-flow velocities without diastolic flow (grade 2: residual flow), are distinguished from complete obstruction (grade 1: no flow), because residual flow signals are associated with improved results of thrombolysis (Labiche et al. 2003; Saqqur et al. 2008). The grade 4 (established perfusion) comprises different hemodynamic situations: normal flow (4a), stenotic flow (4b), and high-flow velocities in hyperperfusion (4c). This grouping was determined by the thought that distinguishing high-flow velocities from normal-flow velocities is not so relevant for defining a reestablishment of sufficient hemispheric perfusion.
About the differentiation between grade 4 b and 4 c the statement 9 is well explicative (fig. 26).

Consensus Statement 9	In a prospective study, TCCS data were correlated with digital subtraction angiography. Criteria based on this study allowed for the reliable assessment of > 50% and < 50% basal cerebral artery diameter narrowing. They should be applied for the detection and follow-up of intracranial stenoses. However, these criteria have not been validated in the setting of acute stroke. Reactive hyperperfusion may possibly lead to overestimation of the degree of intracranial stenosis.

Fig. 26. Consensus Statement 9 (from Nedelmann et al. 2009)

4.3 Perfusional ultrasound imaging

As previously mentioned at the beginning of this section, both vascular and perfusional informations are relevant to define the prognosis of acute stroke patients and the success of treatment, because the reopening of the occluded vessel is not equal to the reperfusion of the affected brain tissue. Neuroradiological imaging, with the concept of core/penumbra mismatch, raised some questions about the reliability and the usefulness of these data before thrombolysis, but there are several logistic limitation to the wide use of this techniques, besides some contraindications (to the technique, as for patients with pacemakers in MRI, or to the contrast medium, as for CT). Ultrasound techniques, namely TCCS with UCA administration and harmonic imaging, are safe and bedside executable, but their reliability for evaluating the brain perfusional status has not been demonstrated and there are not validated thresholds for core (brain tissue irreversibly harmed and not salvageable by any treatment) and penumbra (brain tissue surrounding the core and hypoperfused, likely not irreversibly harmed, and therefore potentially salvageable by reperfusion). Although these limitations, TCCS can help the clinician to decide in the acute stroke setting, where other techniques are not available or reliable (as for patients with severe arterial disease on both sides).

The purpose of this imaging strategy is the selection of patients for reperfusion treatment, i.v. or i.a., in order to improve its safety and efficacy, decreasing the hemorrhagic complications. This strategy could theoretically lead to overcome the concept of a fixed time window.

In clinical practice, there are two established imaging techniques to distinguish core from penumbra, MRI and contrast CT. The first technique diagnoses the core by using DWI and the penumbra by using perfusion-weighted imaging (PWI); the second one uses CT cerebral blood volume imaging for the core and PWI for the penumbra.

Also ultrasound techniques allow to perform a perfusional study of the brain parenchyma, depicting the blood flow in the microcirculation (Malferrari and Zedde 2008). This non-invasive tool can assess the perfusion deficits in acute stroke patients, although the lack of validated threshold in comparison with conventional neuroradiological methods.

The optimization of this concept was achieved by routine use of second generation UCA (for European countries, because UCA are not approved for neurosonological application in the USA) and harmonic imaging, that allow a real time dynamic study of cerebral circulation. It is possible to achieve an early visualization of the estimated size of the ischemic area in the acute phase, with minimal or no signs at the basal unenhanced CT (Seidel et al. 2004; Wiesman et al. 2004; Meyer-Wiethe et al. 2007). Ultrasound perfusion, like perfusional studies by CT and MRI, is based on dilution theory and allows to obtain wash-in and wash-

out curves into selected areas of cerebral parenchyma or ROIs (Region of Interest) (Malferrari and Zedde 2008) (Fig. 27).

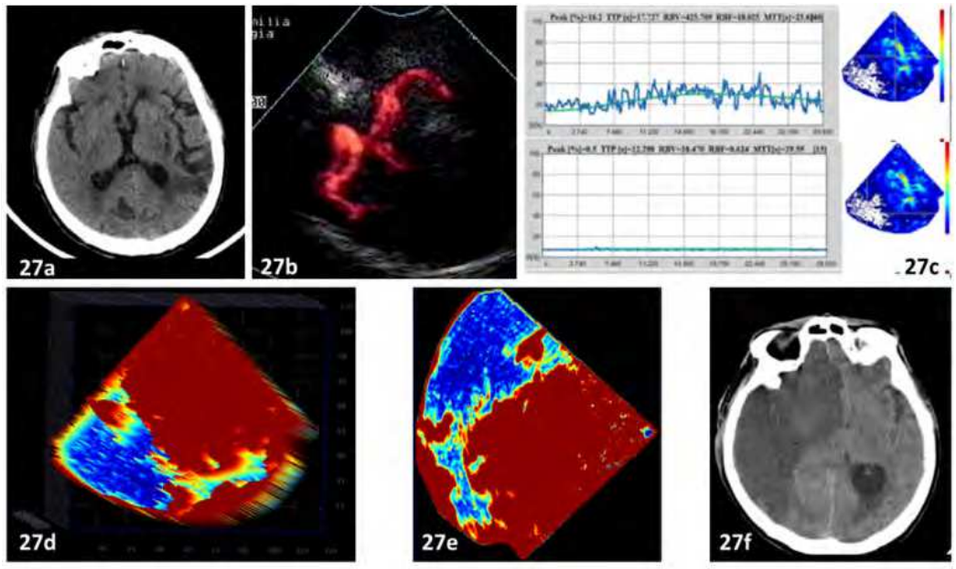


Fig. 27. An example of Ultrasound Perfusional Imaging.

a. unenhanced brain CT at the baseline; b. TCCS from the right temporal window with a diagnosis of a T occlusion; c. ultrasound perfusional curves (normal hemisphere in the upper half and flattened curves of the affected hemisphere in the lower half); d. tridimensional perfusional map with a broad area of hypoperfusion (blue); e. 90° rotated bidimensional map to make easier to compare it with the CT; f. 24 hours unenhanced brain CT with a perfectly corresponding ischemic lesion.

Another recent application of TCCS is the monitoring of the hemorrhagic transformation after thrombolysis for acute stroke of the anterior circulation (Seidel et al. 2009). An example of this application is showed in Fig. 28.

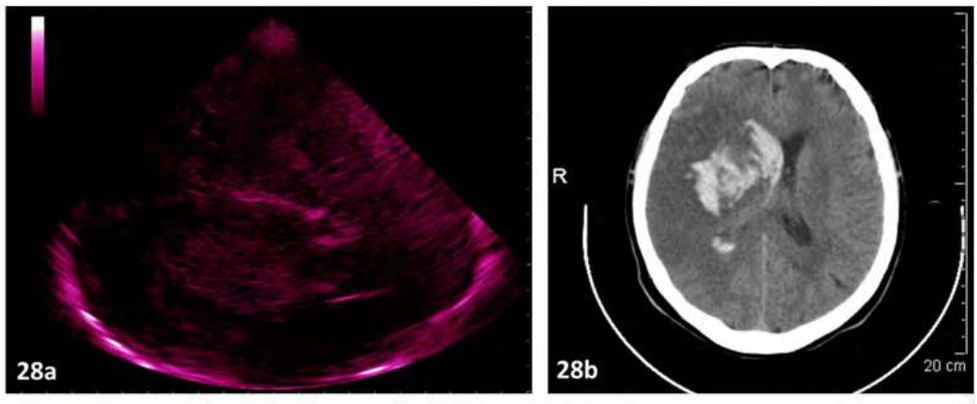


Fig. 28. Parenchymal haemorrhage after thrombolysis.

a. TCCS from the left temporal window, showing the rounded hyperechoic hemorrhagic lesion in the contralateral hemisphere; b. corresponding unenhanced brain CT.

5. Focus on intracranial stenosis

Intracranial atherosclerosis is an often neglected cause of stroke but it represents the first cause of ischemic stroke in the world (Gorelick et al. 2008). Not only atherosclerosis may cause an intracranial stenosis, but it is certainly the most frequent cause and also in the white population, in patients with multiple vascular risk factors.

Some relevant aspects of intracranial large artery disease, as recently stated and summarized (Gorelick et al. 2008), are:

- the magnitude of the public health problem;
- the risk of stroke and other cardiovascular diseases associated with intracranial occlusive disease;
- the etiology;
- medication and non-medication approaches to treatment and prevention;
- gaps in our understanding of intracranial occlusive disease and possible next steps to unravel enigmas related to this disorder.

The evaluation of the intracranial atherosclerosis and stenosis has addressed in the literature mainly in the setting of the post-acute phase and the diagnostic criteria for all techniques are not directly applicable in the acute phase; for example the TCCS criteria (Baumgartner et al. 1999) were selected and validated in a stable situation, because of the frequent presence of a transient intracranial stenosis (TIBI grade 4 and COGIF grade 4b) during the recanalization process of an occluded intracranial artery; therefore it is not possible to define criteria for a dynamically changing situation and the persistence of the stenosis days and weeks after the acute phase may more reliably indicate the intracranial atherosclerosis as the cause of the cerebrovascular event (Nedelmann et al. 2009; Malferrari et al. 2007; Malferrari et al. 2008).

Because of these considerations, the diagnosis of intracranial stenosis is not a main item in the ultrasound monitoring of the acute phase of ischemic stroke. Nevertheless it is useful to outline a neglected aspect of intracranial stenosis, as previously mentioned, i.e. the PAD subgroup (patients with clinical and radiological manifestations of lacunar infarction as a result of intracranial large artery atherosclerosis, mainly in MCA, located near the origin of perforating branches and therefore occluding them by direct clot growth of artery-to-artery embolism) (Bang et al. 2002) (Fig. 29).

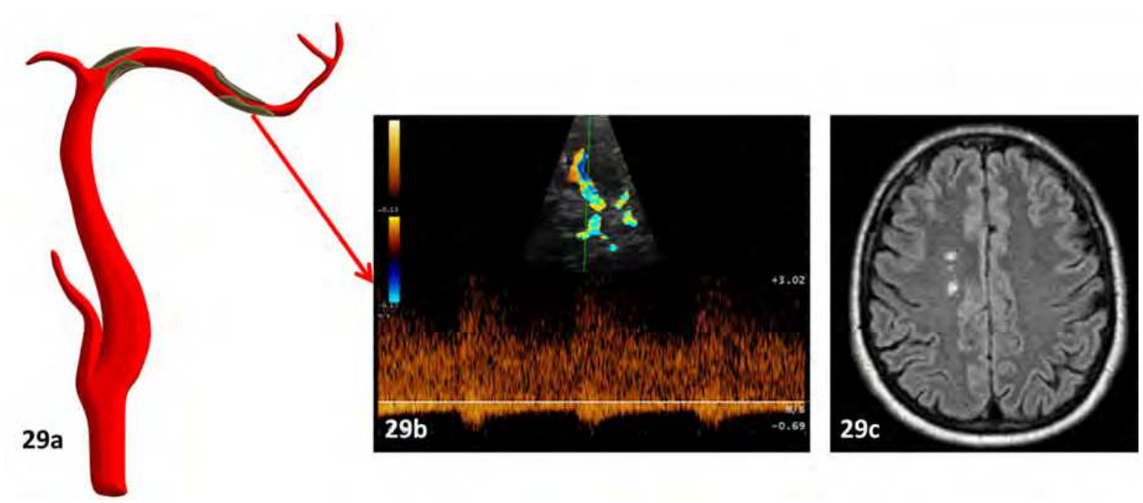


Fig. 29. PAD example.

a. schematic drawing of proximal and distal atherosclerosis of M1 MCA; b. corresponding TCCS from the right temporal window, with the Doppler spectrum and a clear increase of the flow velocity; c. MRI with ischemic lesions in the centrum semiovale of lacunar size.

6. Ultrasound-assisted thrombolysis

In the last decade a considerable amount of experimental and pilot clinical studies on stroke patients addressed the matter of ultrasound-assisted thrombolysis. The in vitro experience and the studies on animal models demonstrated that ultrasounds at frequencies in the 20 KHz -1 MHz range, lower than the ones usually available for diagnostic purposes, can potentiate the action of endogenous or exogenous tPA (Malferrari and Zedde 2008), leading to design a human study with a specific therapeutic ultrasound machine (Daffershofer et al. 2005) with the premature stop of the enrolment because of the increased rate of hemorrhage. This study caused a mild slowdown in the TCCS application on this field, although the good results of the above-mentioned CLOTBUST study with TCD (Alexandorv et al. 2004b).

The phenomena by which ultrasounds enhance thrombolysis is the increased delivery of rtPA into the fibrin clot and the breaking of the tight binding of fibrin itself, therefore providing a greater surface for thrombolytic drugs action, by cavitation, starting from the tissue and blood microbubbles (Alexandrov 2009).

The association of the UCA administration provides a great amount of right-sized microbubbles and then makes easier the clot fragmentation by the cavitation and thermal effects of ultrasound waves. This process happens by using the same ultrasound machines available for clinical purposes and the frequencies of the diagnostic transcranial doppler (1-2 MHz) (Malferrari and Zedde 2008). Microbubbles lower the ultrasound-induced cavitation threshold and dramatically increase the lytic action of ultrasounds. Several microbubbles has been used in experimental studies and some kind of not commercially available microbubbles also for human studies (Molina et al. 2009). The CLOTBUST study (Alexandrov et al. 2004b) evaluated the combined effect of rtPA administration within 3 h from symptom onset and TCD continuous monitoring at 2 MHz (diagnostic parameters), achieving a recanalization rate of 36% and an hemorrhagic transformation rate of 9%, not significantly different in comparison with the hemorrhagic rate of non-monitored patients. Other authors used TCCS for the same purposes with a diagnostic setting, with or without rtPA administration, confirming these findings (Cintas et al. 2002; Eggers et al. 2008).

The data about ultrasound-enhanced thrombolysis has been recently analysed in a meta-analysis (Tsivgoulis et al. 2010) and the results were comforting, regarding the safety of sonothrombolysis with high frequency ultrasounds, with or without UCA. This modality of sonothrombolysis "is associated with a nearly 3-fold increased likelihood of complete recanalization and 2-fold higher likelihood of functional independence at 3 months" (Tsivgoulis et al. 2010).

The limitations are certainly the small number of patients included, particularly in sonothrombolysis studies using TCCS, and other studies are needed.

7. Conclusion

Neurosonology is a safe, reliable and useful technique for evaluate acute stroke patients It may provide relevant information about the prognosis and guide the selection of the most adequate treatment for each patient. The recent development of intrinsic therapeutic

perspectives, as ultrasound-enhanced thrombolysis, make even more recommendable its use in this setting.

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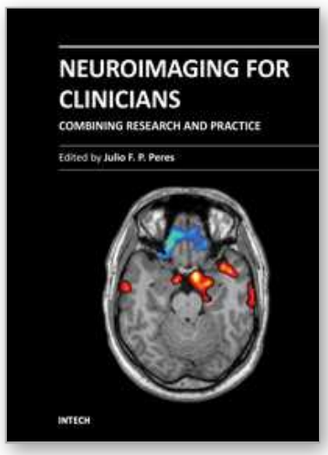

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Neuroimaging for clinicians sourced 19 chapters from some of the world's top brain-imaging researchers and clinicians to provide a timely review of the state of the art in neuroimaging, covering radiology, neurology, psychiatry, psychology, and geriatrics. Contributors from China, Brazil, France, Germany, Italy, Japan, Macedonia, Poland, Spain, South Africa, and the United States of America have collaborated enthusiastically and efficiently to create this reader-friendly but comprehensive work covering the diagnosis, pathophysiology, and effective treatment of several common health conditions, with many explanatory figures, tables and boxes to enhance legibility and make the book clinically useful. Countless hours have gone into writing these chapters, and our profound appreciation is in order for their consistent advice on the use of neuroimaging in diagnostic work-ups for conditions such as acute stroke, cell biology, ciliopathies, cognitive integration, dementia and other amnestic disorders, Post-Traumatic Stress Disorder, and many more

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