Transcranial colour-coded duplex ultrasonography (TCCD): clinical indications

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Summary

This article looks at the "whys and whats" of neurosonology:
– What is neurosonology?
– Why has TCCD become an irreplaceable tool in the treatment of neurological patients?
– Why train neurosonologists?
– What is their role in the Stroke Unit?
– Why is the approach to ictus becoming dynamic?

Introduction

Most Stroke Units currently adopt a basically static approach to patients, which consists mainly of:
– photographing, through CT scan, the situation of the cerebral parenchyma on admission of the patient, and
– carrying out a second CT scan after a few days, which inevitably provides evidence of the ischaemic injury.

In this way nothing is known either about the vascular situation of the Willis polygon on admission (which blood vessel was occluded) or about how and, in particular, *when* the vessel recanalised. The *"time is brain"* concept, and thus the *timing* of recanalisation, is fundamental, because it is easy to imagine that if the vessel recanalises within 3-6-12 hours or more, the necrotic destiny of the involved parenchyma will differ accordingly, as will the patient's prognosis.

Some years ago Alexandrov reported that: "The patients presented with *similar* severity of hemiplegia, but the severity of perfusion deficit and recovery were *dramatically different*". Clearly, the different clinical recovery can be attributed *only* to the different vascular occlusion pattern on admission, and to the different evolution of recanalisation.

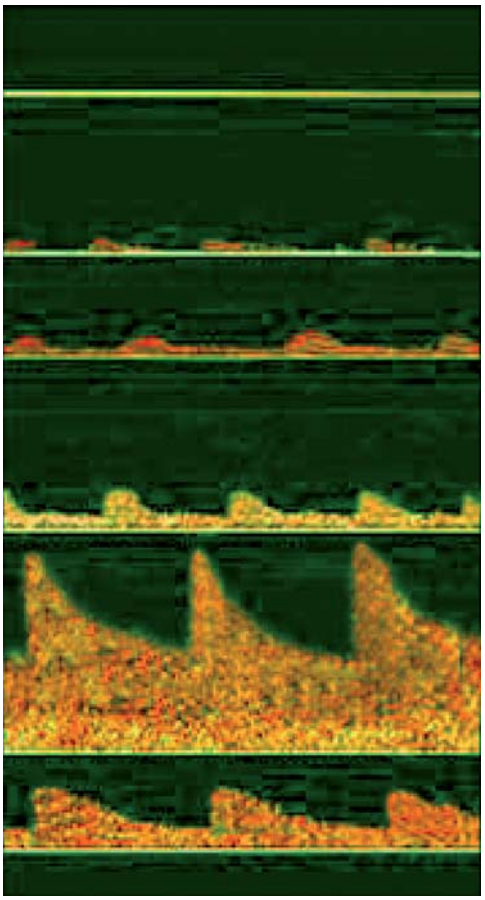
The codification, using TCCD, of reperfusion flowmetric patterns in ischaemic stroke (TIBI patterns) is gaining importance and international appreciation. Demchuk and Alexandrov remarked "Thrombolysis in brain ischemia (TIBI)-transcranial Doppler flow grades predict clinical severity, early recovery and mortality in patients treated with intravenous tissue plasminogen activator".

It follows that a patient with a TIBI 1 six hours after the stroke will have a markedly worse prognosis than a patient with a TIBI 4-5 at the same point in time.

This is where TCCD finds a role in the acute phase of stroke, given that it is the only test allowing us to provide on-line information (in a non-invasive way) about the *dynamic and functional state* of the intracerebral circulation and its modifications, *hour by hour.*

The birth of the last generation instruments with their increasingly advanced two-dimensional imaging, as well as the use of second harmonic frequencies, has enabled us to obtain results that were unimaginable a few years ago.

Some of the nervous system neurophysiological exploration methodologies currently in use in neurology are undoubtedly invasive: one need only think of the intense electrical stimuli of MEPs, as well as electomyography which is not always welcomed by patients. In this context, the neurosonological approach to pathologies both of the cerebral vessels and the cerebral parenchyma is undoubtedly original and non-invasive. The strengths of ultrasonology, for several years, have been its repeatability, low costs, and non-invasiveness. If we also consider that the technique can be defined a "bedside examination", it emerges clearly as an irreplaceable examination in most areas of modern neurology.



"ABSENT" Flow
TIBI 0

"MINIMAL" Flow
TIBI 1

"BLUNTED" Flow
TIBI 2

"DUMPENED" Flow
TIBI 3

"STENOTIC" Flow
TIBI 4

"NORMAL" Flow
TIBI 5

Fig. 1 - Thrombolysis and transcranial Doppler flow patterns (TIBI grades).

We must also recall densitometric cerebral studies, which appeared in the literature only a few years ago. The physical features of the microbubbles submitted to an acoustic field are complex and depend on several factors, the most important being the acoustic power of the ultrasonic beam.

- At low powers the microbubbles produce a linear emission frequency in direct relation to the incident one (linear oscillation).
- At higher powers backscattering is produced which results from the radial oscillation of the pressure induced on the surface of the microbubbles. Microbubbles respond differently to positive peaks and negative peaks with loss of symmetry (non-linear oscillation) and 2nd harmonic, sub-harmonic, and ultra harmonic frequencies.
- At even higher powers the microbubbles break, emitting free gases that are quickly eliminated through the lungs.

The advent of the duplex Doppler (TCCD) method has brought undeniable advantages compared to the blind one (transcranial Doppler, TCD). Bi-mode and colourimetric imaging makes it possible not only to detect with absolute certainty the single vessels of the Willis polygon, but also to obtain guided correction, which is necessary for obtaining correct peak systolic velocity (PSV) and peak end diastolic velocity (PEDV) values. The previous difficulties in using equipment with blinded transducers are thus easily overcome: with them, the positioning of the sample volume and consequently the exact determination of the vessel being examined, as well as the insonation angle, were undoubtedly more empirical. Furthermore, if we consider that the Willis polygon shows not only frequent and numerous anatomical variations (e.g., foetal origin of the posterior cerebral artery) but also some tortuosity (kinking etc.) which could simulate and distort velocimetric accelerations, we can easily understand the importance of obtaining imaging which is as correct as possible. Last generation angio-power imaging enables us to solve the problem, just as the use of ultrasound contrast agents allows us to overcome, easily, the difficulties caused by a poor acoustic bone window.

Main clinical indications (1,2)

– Intracranial stenosis and detection of variants of the occlusion pattern
– Study of the collateral compensation circulation circles

– Search for high-intensity transient signals (HITS or micro embolic signals MES) and patent foramen ovale (PFO)
– Diagnosis of brain death
– Determination of cerebrovascular reactivity (intracranial vasomotor reserve)
– Thrombolysis (with rt-PA) and its follow up

Possible future applications (1,2)
– Brain parenchyma sonography
– Cerebral perfusion studies and densitometric curves
– Venous study

The examination can be carried out, technically, with a traditional approach: tanstemporal, transnuchal (suboccipital) or transorbital. It is worth mentioning some variants: transtemporal approach in the coronal plane, particularly useful for studying the siphon (C1 and C2 segments) and the top of the basilar artery; and the approaches by the lateral frontal bone window (LFBV) and paramedian frontal bone window (PMF-BV). In the temporal approach we start the TCCD examination from the orbitomeatal axial plane. First we use the mesencephalic plane, where important sonographic reference points are the "butterfly-like" image of the mesencephalon for the study of the posterior circulation and the lesser sphenoid wing for the middle cerebral artery. Second, by tilting the probe 10 degrees upwards we move to the diencephalic plane where we have, as important reference points (in particular for densitometric studies) the binary image of the third ventricle. Finally, by maximally tilting (30°) the transducer apically we can see the sovradiencephalic plane through the cella media. It has to be noted that, using last generation software, it is possible to detect anatomical formations like the substantia nigra and sometimes the red nucleus. It is no coincidence that studies of substantia nigra echogenicity have recently appeared in the literature. Furthermore, using suitable instruments, we can obtain faithful images which allow us to detect the primary, secondary and even tertiary branches of the middle cerebral artery (see branches 1-2-3-4, Fig. 2).

Intracranial stenosis

Unlike neck stenosis, application of the neurosonological technique in studying intracranial stenosis (IS) is more recent. This helps to explain why intracranial pathology data are underestimated (particularly if we consider that most data derive from studies based only on angiography, an unusual methodology carried out only in selected cases).

Intracranial stenosis: neurosonological features
– Systo-diastolic flowmetric accelerations at vessel stenosis
– Velocimetric deceleration after stenosis
– Bidirectional low- frequency signals during the systole
– Vibrations of the arterial walls with associated "musical murmurs".

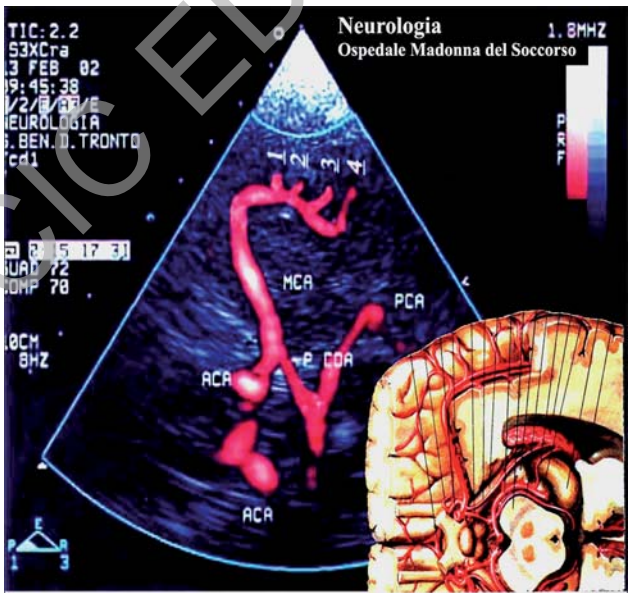


Fig. 2

Several attempts have been made to codify velocimetric peaks. At present the recent study by Baumgartner (3) is the international point of reference. It has determined the PSV values indicating stenosis >50% (compared to angiography).
We can thus assert, without fear of being proved wrong, that looking for intracranial stenosis using last generation software does not present any problems at all. The possibility of highlighting, through "angio" methods, the polygon vessels enables us to study *centimetre by centimetre* every single feature of the vessels. And it is clear that a patient's prognosis will be different if, besides having neck stenosis (for which he may be tested by carotid endarterectomy (CE), he also has a severe middle cerebral artery stenosis (which would surely remain undetected without this examination).
It is necessary to highlight the mainly dynamic and non-static character of IS. It is indeed frequently observed that PSV and PEDV values can vary over time in the course of stenosis.
This finding (also reported in the literature in angiographic studies) explains the *recurrent* presence of the clinical symptoms, but it also confirms the *dynamic* and non-static nature of intracranial stenosis.
Moreover, a further, intriguing possibility offered by this method is its ability to highlight, as well, the morphological pattern of the stenosis (unique, multilobular, etc.) thanks to modern software which shows us (with a good bone window) the arterial and venous vessel walls.

Compensation circles
Occlusion of the internal carotid artery (thrombosis, dissection, etc.) has clear repercussions at intracranial level. Yet it must be pointed out that the presence of intracranial obstructions often does not cause sonological alterations at the level of epiaortic vessels, given that the Willis system is an "open" one. It follows that cerebral vascular study must not be limited to the neck examination, since this does not give us any information about what happens downstream, at the polygon level.
In patients with a complete Willis there may be three main possible compensation circles:
– Rehabilitation of the middle cerebral artery through flow inversion in the A1 segment (only in patients with patent anterior communicating artery)
– Inversion of the ophthalmic artery
– Activation of the posterior communicating artery
These modifications, of a *functional* nature, of the cerebral circulation can easily be studied and demonstrated using TCCD. It is evident that in cases of Willis congenital abnormality the possibilities of functional compensation are reduced. These compensatory activations can explain the *different* clinical pictures and *different* follow ups in patients with the *same* occlusive picture at the neck. The compensation pathways in bi-occluded patients (i.e. with occlusion of both internal carotid arteries at the neck) may be numerous as well.

HITS-PFO
The search for HITS is usually carried out on the middle cerebral artery and is particularly recommended in patients with atrial fibrillation, prosthetic cardiac valves, etc. It is worth recalling that a HITS must be included in the area of the spectral flow, otherwise it could be an artefact. Literature on the search for PFO is copious. During the 4th ESNCH meeting, which was held in Venice in 1999, technical criteria to be followed for the PFO search with TCCD, set out in a newsletter, were codified. Data obtained through TCCD are superimposable on those obtained through transoesophageal echocardiography, TEE (i.e. they have the same sensitivity and specificity).

Brain death
The absence of cerebral flow is a useful and sometimes obligatory element in the diagnosis of cerebral death. A progressive increase in intracranial pressure causes a rapid decrease in the diastolic component of the spectral flow up to the inversion in "revers" and the complete disappearance of the diastolic flow. The flowmetric pattern will be characterised by systolic "spikes" followed by diastolic "revers". It is recalled that this pattern must be bilateral and present in more than one vessel to be indicative of brain death.

Cerebrovascular reactivity
Cerebral blood flow is sensitive to pO_2 variations and in particular to pCO_2 ones. The tests used in the determination of cerebral flow variations are numerous: hyperpnoea, apnoea, acetazolamide test, CO_2 inhalation etc. A very easy test, albeit difficult to standardise, is the apnoea test. As we know that the diameter of the large vessels of the cranial base are not subject to variations, each flowmetric change is to be related only to changes in the diameter of the aerterioles: an increase in pCO_2 (apnoea) will cause vasodilatation, while its decrease will cause vasoconstriction. This test enables us to study the so called "functional re-

serve" of the cerebral vessels and thus the cerebral tissues' ability to withstand, or not, further ischaemic injuries. After a stenosis, a vessel appears dilated in search of compensation. The reactivity test will show a reduced or absent compensatory flowmetric variation and thus a situation of extreme compensation with low vasomotor reserve, which does not prevent further ischaemic insults.

Venous study

In addition, the TCCD ultrasound method allows accurate venous intracranial studies to be performed. Several structures can be detected with ultrasound, such as: the deep middle cerebral vein (DMCV), the Rosenthal vein (RV),the vein of Galen (GV), the sphenoparietal sinus (SPaS), the superior sagittal sinus (SSS) (distal part), the straight sinus(SRS),the superior petrosal sinus (SPS),the inferior petrosal sinus (IPS),the transverse sinus (TS), the sigmoid sinus (SS), and the basal venous plexus (BVP).

If the DMCV flows next to the middle cerebral artery, the RV embraces the mesencephalon (peduncles and lamina) and then flows into the GV. As it is a venous circle, many anatomical variants are possible. The DMCV and RV present a flow moving away from the probe, which will thus appear below the zero flow line. The practice of the venous flow study is not an end in itself but can give us important information in cases of intracerebral venous thrombosis (a pathology increasingly frequent in young patients) and arteriovenous malformations.

Thrombolysis

Being able to lyse a newly formed thrombus in order to obtain rehabilitation of the vessel and prevent the most likely consequences of the stroke is, without doubt, the aim of neurosonology in acute ischaemic stroke patients. While thrombolysis at cardiac level is already a standard procedure, its application at cerebral level is still being studied. Several studies in this field have set out to validate a possible 3-6-hour therapeutic window. We recall, in addition to the NINDS study, the SITS-MOST study which paved the way for the application of rt-PA within three hours, in Italy too. At the same time, ultrasonology studies have been conducted and have shown the importance of TCCD in the selection of patients eligible for thrombolysis: Dr Reutern's NAIS study (Neurosonology in Acute Ischaemic Stroke,) and the Italian ELIGIBLE study (coordinated by S.I.N.V.), in which our centre has taken part.

These studies have clearly demonstrated that TCCD in the course of ischaemic stroke will serve for the early detection of:

– possible variants of the intracranical occlusion pattern (patency of the anterior communicating cerebral artery and inverted flow in A1 segment?, siphon occlusion?, T occlusion?, distal/proximal MCA occlusion? etc.), thereby furnishing invaluable information for the thrombolytic approach (with rt-PA), as well as documenting
– the time of the reperfusion of the vessel ("timing" concept)
– the flowmetric recanalisation (TIBI) patterns (which, as we know, give outcome information).

Confirming all of this is a growing body of data in the literature. And it can be seen to be even more important if we consider that patients with *the same* neuroradiological picture on Stroke Unit admission brain CT scan and *the same* NIH values may meet with *completely different outcomes.*

Furthermore, the literature contains several studies of the direct effect of prolonged thrombus exposure to high-intensity ultrasound, with possible lysis of the thrombus itself (sonothrombolysis). The contemporaneous use of the second-generation contrast agents has highlighted a possible strengthening of the ultrasound beam's thrombolytic effect, which is associated with a higher cerebral vessel recanalisation rate in the course of ischaemic stroke.

Densitometric study

Finally, the cerebral perfusion study (4-7) deserves a separate mention. It is made possible by a second-generation ultrasound contrast agent (Sonovue®) and by last generation, second harmonic-equipped devices that allow us to highlight the contrast diffusion at the cerebral parenchyma level, and also to perform wash-IN and wash-OUT curves relative to particular areas of the cerebral parenchyma (regions of interest, ROIs).

Perfusion studies and densitometric IN and OUT curves with use of ultrasound contrast can surely open up new possibilities in the study of cerebral parenchyma in the course of acute ischaemic stroke. Needless to say that whereas MRI and PET are considered "gold standard" methodologies in the study of cerebral neuroradiological perfusion, their routine use in the course of acute ischaemic stroke is neither possible nor feasible for the time being, for obvious reasons. On the contrary, the information we can obtain through the densitometric study show this to be a valuable and effective resource.

The information provided by the densitometric study (visualisation of the presence and extent of

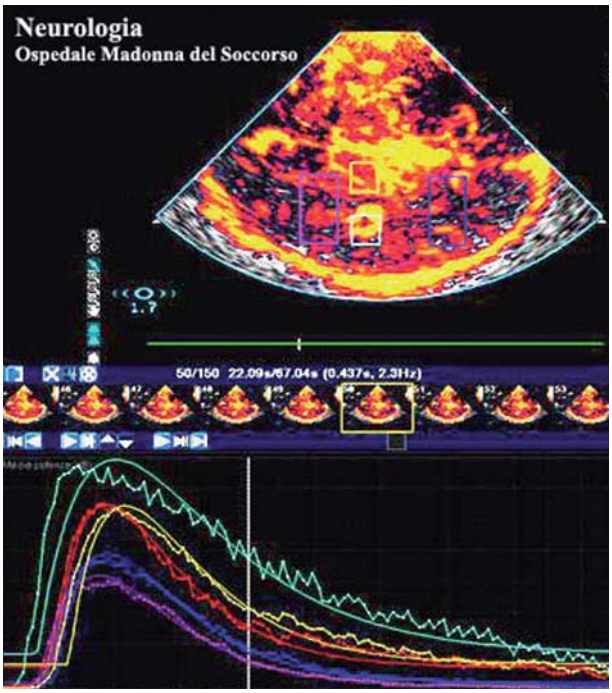


Fig. 3 - Healthy hemisphere: ROIs and correspondent IN-OUT curves: normal data.

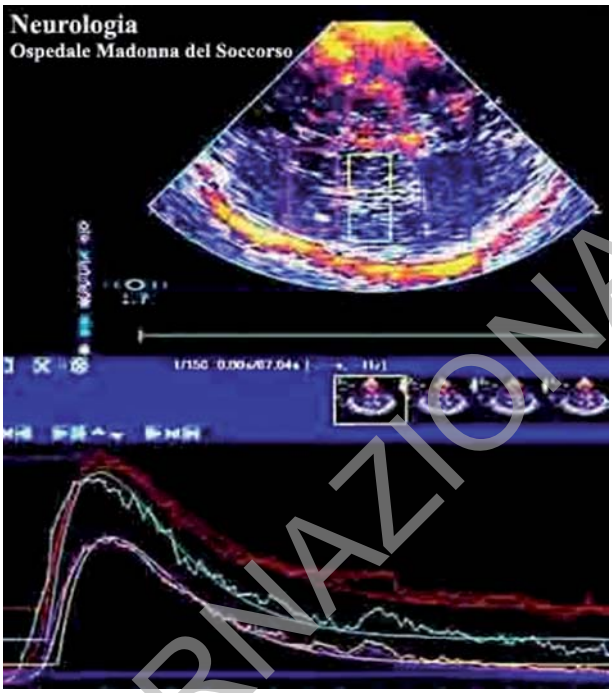


Fig. 4 - Contralateral diseased hemisphere: note the blue ROI and corresponding *flat* IN-OUT curve: area with *absent perfusion*.

reduced/absent perfusion area) acquires particular importance when the CT scan examination is still *negative* (the CT-scan delay in detecting ischaemic-necrotic areas within the very first hours is well known). The acquired digital imaging can be processed with the pertinent study of the ROIs. In the last generation instruments it is possible not only to position the ROI where we like, but also to determine the shape and extent of the ROI itself, but this is done only on the basis of the previously acquired perfusion imaging. Clearly, points of reference are crucial in the acquisition of this information (without them, we cannot know the level of the insonation plane we are using, or position the ROI with scientific-anatomical precision). In this regard, "double binary" imaging of the third ventricle with, at the back, the small, often hyperechogenic (because of calcification) area corresponding to the epiphysis is crucially important. On the sides we look for the hypoechogenic area of the two thalami and, if possible, the areas of the caudate and lenticular nucleus. Only then can we accurately position the ROI. Under normal conditions in each curve we will be able to detect a very rapid rise phase (IN) culminating in a peak, indicative of the contrast arrival, followed by the more or less rapid phase of contrast diffusion and elimination (OUT). In each curve we will be able to detect important parameters (time-to-peak, peak intensity, peak width, area under the curve, etc.). These curves can provide us with an indirect, *semi-quantitative* index of the perfusion in the ROIs. Perfusion studies can clearly be extended not only to ischaemic, but also to degenerative pathologies, and to patients with brain death etc.

Conclusions

Stroke is changing from a "static" into a highly "dynamic and functional" pathology. The patient reaching the Stroke Unit does not remain the same but undergoes, continuously, flowmetric and dynamic modifications that have a major impact on his outcome. These modifications can be studied "on-line" only by means of TCCD. Using this method, we can see the recanalisation patterns in stroke patients and detect their dynamic variations (TIBI 0,TIBI 1 ... etc.) hour by hour in a non-invasive way.
For this reason, it is not reasonable to use repeated angio-CT studies to document vessel recanalisation (also because of the high doses of radiation delivered in this way). Modern neurosonology has a wide spectrum of application for the study of cerebral pathology. Moreover, brain parenchyma sonography, perfusional studies and venous studies are undoubtedly destined to give us some interesting surprises in the very near future.

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