Neurovascular ultrasound in emergency settings: diagnostic and therapeutic aspects

Telma Santos, Miguel Veloso, Pedro Barros

Introduction. Neurovascular ultrasound is a non-invasive, portable and fast imaging method that, when performed by an experienced neurosonologist, offers reliable and reproducible information on the morphological and hemodynamic status of cervical and intracranial vessels.

Aim. To review the available evidence regarding the use of this tool in the approach to acute stroke.

Development. Neurovascular ultrasound can be used in one of two ways: diagnostic and therapeutic. Considering the low recanalization rates of internal carotid artery and proximal medial cerebral artery occlusions with intravenous recombinant tissue plasminogen activator (r-tPA), neurovascular ultrasound used shortly in Emergency Department may help to select patients that could benefit from endovascular therapy. Moreover, ultrasound monitorization during intravenous r-tPA treatment allows the analysis of the pattern of arterial recanalization. Cervical ultrasound allows the assessment of the stenosis degree and the composition/surface of an arterial plaque that could, for instance, reveal earlier a candidate for carotid intervention. Finally, the therapeutic potential of ultrasound is also being investigated. Sonothrombolysis and sonolysis, that combine ultrasound technology with r-tPA and use exclusively the ultrasound to lyse the clot, respectively, showed promising results.

Conclusion. Neurovascular ultrasound has greatly expanded to assume an important role in the study of cerebrovascular disorders.

Key words. Brain ischemia. Cerebral arteries. Cerebral infarction. Endovascular procedures. Stroke. Ultrasonography.

Department of Neurology. Centro Hospitalar Vila Nova de Gaia/Espinho. Vila Nova de Gaia, Portugal.

Corresponding author:
Telma Santos MD. Department of Neurology. Centro Hospitalar Vila Nova de Gaia/Espinho. Rua Conceição Fernandes. 4434-502 Vila Nova de Gaia (Portugal).

E-mail:
telma.cristiana.santos@gmail.com

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Introduction

In 1956, Sotomura was the first to use Doppler sonography (DS) to detect blood flow signals from cerebral vessels [1]. Since then, this technique has greatly expanded to assume an important role in the study of cerebrovascular disorders [2]. It is a non-invasive, portable and fast imaging method that, when performed by an experienced observer, offers reliable and reproducible information on the morphological and hemodynamic status of cervical and intracranial vessels [3]. These advantages turn DS an useful diagnostic tool in Emergency Department (ED) to access acute stroke etiology, predict the response to thrombolytic therapy and manage the recanalization procedure [4]. DS is also being investigated as a therapeutic tool in acute stroke settings [4].

The authors aim to review the available evidence regarding the use of ultrasound in the approach to acute stroke. We will first discuss the fundamentals of cervical and transcranial ultrasonography and then, we will describe the diagnostic and therapeutic possibilities of DS in emergency settings with focus on acute stroke management.

Cervical and transcranial ultrasonography

Ultrasonography is based in the propagation of mechanical sound vibrations through the materials, at frequencies between 20 kHz and 1 GHz [5]. DS comprises different imaging modes [5]. The brightness-mode (B-mode) imaging is basically a static cross-sectional display of the transducer image, exhibiting the anatomical organization of the insonated area. Combining the pulsed-wave Doppler function allows the blood flow analysis. The color-flow imaging (CFI) mode uses Doppler flow-velocity information, which is then color-coded based on the speed and direction of flow and overlaid onto the appropriate anatomical site in the B-mode image. This has important practical implications as it exhibits the flow direction and distinguishes a turbulent (pathologic) from a laminar (normal) flow. The power-Doppler mode is a varia-

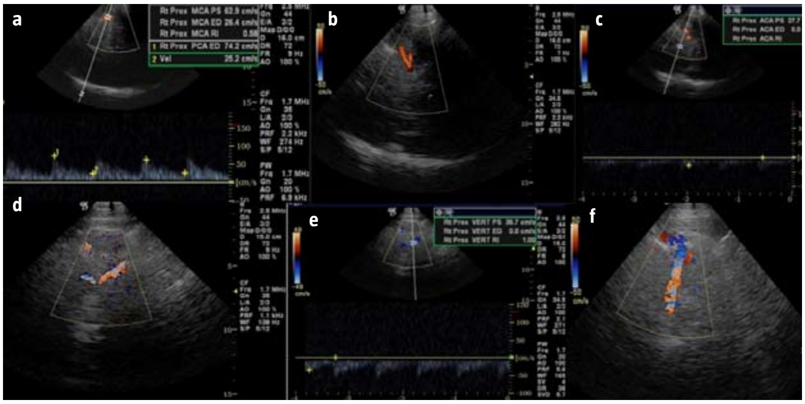


Figure 1. Normal TCD features: a) Proximal ACA; b) Distal MCA (M2); c) Proximal MCA (M1); d) BA; e,f) Right and left VA.

tion of CFI that, instead of offering the mean velocity, it provides information on the amount of flow detected at each point.

Many hemodynamic parameters are registered [6]: peak systolic velocity (PSV), end-diastolic flow velocity (EDV), flow acceleration time, and several indirect or derived parameters such as width or spread of the spectral band of velocities, pulsatility and resistivity index.

After recording flow signals this techniques is able to build a spectral curve for each analyzed vessel [6]. Under normal conditions, the internal carotid artery (ICA) and vertebral artery (VA) spectral curves exhibits a slow deceleration and a higher EDV (low-resistant pattern), in oppositon to the external carotid artery (ECA) that reveals a conspicuous deceleration until lower EDV. These spectral curves may be affected not only by local pathologic conditions (stenosis, occlusion or dissection) but also by distant diseases affecting local vascular resistance (for example, cardiac valvulopathies and heart failure).

Transcranial Doppler ultrasound (TCD) (Fig. 1) consists essentially in using Doppler ultrasound techniques through the skull. When involves imaging techniques it is called transcranial colour-coded sonography (TCCS) [6]. Due to the bone thickness, TCD/TCCS examination is possible only in certain regions, called ‘acoustic windows’, where the skull is thinner. The transtemporal window, the most commonly used, is located above the zigomatic arch near the tragus. It allows the insonation of MCA (middle cerebral artery), ACA (anterior cerebral artery), and PCA (posterior cerebral artery) [7]. The sub-occipital window locates in midline between the occipital bone and transverse process of first cervical vertebra, allowing the insonation of the basilar and vertebral arteries [7]. The submandibular window is located under the angle of the mandible and is used to record the retromandibular portion of ICA [7]. Finally, the orbital approach allows insonation of the ophthalmic arteries and the ICA siphon [7]. However, the examination through the temporal window cannot be done in approximately 25% of patients, predominantly in women and old patients, due to the absence of a proper visualization ‘window’ [7]. This limitation may be overcome by the use of contrast-enhancing agents [7].

Neurovascular ultrasound in emergency department

The initial evaluation of an acute stroke patient requires a concise and expeditious etiologic investigation to enable the prompt introduction of secondary prevention strategies or specific treatment options that have prognostic implications [8].

The computed tomographic angiography (CTA) is a relatively rapid technique performed with a time-optimized bolus of contrast that allows the assessment of the integrity of cerebral vessels [9]. According to several studies, CTA has sensitivity of 92-100% and specificity of 82-100% for the detection of intracranial vessel occlusion, with similar rates for extracranial vessel occlusion/stenosis [9]. This technique has been widely used in acute stroke settings as the ancillary technique to select candidates for endovascular procedures [9]. However, CTA is not available in all hospitals and its use is limited in patients with renal failure or allergy to the contrast.

The ultrasound is an inexpensive, fast, noninvasive tool that is also useful in acute stroke settings [9-12]. In contrast with CTA that reveals the anatomy of cervical and intracranial arteries and their respective lesions, the ultrasound offers information about the hemodynamics of cervical and intracranial circulation [9].

In the setting of acute cerebral ischemia the neurovascular ultrasound may be used in the monitorization of arterial recanalization during and after intravenous thrombolytic therapy, to help in the selection of patients for endovascular treatment and as a therapeutic tool. Furthermore, this technique is also included in the etiologic investigation of an acute stroke. We will describe each topic in the following sections.

Ultrasonography in the setting of acute cerebral ischemia

Monitorization of arterial recanalization during and after thrombolytic therapy

In acute ischemic stroke, intravenous r-tPA alteplase is the only FDA-approved therapy to be used in the first four hours and a half from symptoms onset [8]. Several studies revealed low recanalization rates for ICA and proximal MCA occlusions with intravenous recombinant tissue plasminogen activator (r-tPA) [13,14]. The clinical outcome is affected by various factors such as the occlusion site and the time needed to obtain flow recanalization after r-tPA [13]. Therefore, the time to recanalization is considered the strongest predictor of functional outcome, depending on the occlusion site, thrombus composition, thrombus surface area exposed to r-tPA and the required pressure for thrombolytic clot penetration [14].

TCD can be used in ED to assess the arterial recanalization during trombolytic treatment. Alexandrov et al [15] described three patterns of clot dissolution on TCD monitoring: sudden recanalization (abrupt normalization of flow velocity in seconds); stepwise recanalization (progressive improvement in flow velocity lasting less than 30 minutes) and slow recanalization (progressive improvement lasting more than 30 minutes). The first one indicates a rapid and complete restoration of flow and is more commonly found in cardioembolic strokes. Progressive recanalization patterns, in the other hand, indicate proximal clot fragmentation, downstream embolization and continued clot migration. In fact, these patterns have prognostic implications as a sudden recanalization was associated with a higher degree of neurological improvement and better long-term outcome compared to stepwise and slow recanalization [16]. The prognostic significance of MCA flow status was confirmed by a meta-analysis. In fact, a significantly increased mortality (odds ratio: 2.5) is associated with absence of flow in MCA and an early clinical improvement was observed in both initially patent (odds ratio: 11.1) or completely recanalized MCA within 6 h after onset (odds ratio: 5.6) [17].

Furthermore, based on TIMI (thrombolysis in myocardial infartion) flow grade assessment after coronary percutaneous angioplasty [18], the TIBI (thrombolysis in brain ischemia) was adapted to acute stroke [19]. TIBI is a TCD grading system that allows not only the identification and localization of an occlusion, but also the monitorization of recanalization process during thrombolytic treatment. This scale is composed by five grades: grade 0, absent flow signal; grade 1, minimal flow signal; grade 2, blunted flow signal; grade 3, dampened flow signal; grade 4, stenotic flow signal; grade 5, normal flow signal [19]. So, the pre-treatment flow at the occlusion site predicts the likelihood of complete recanalization, time of recanalization and long-term outcome. The persistence of low TIBI category after intravenous thrombolysis can also streamline to further reperfusion [20].

Neurovascular ultrasound may help the decision for intra-arterial therapies

According to AHA guidelines [21] endovascular therapy is a reasonable option in patients who have contraindications to the use of intravenous fibrinolysis (class IIa; level of evidence C). Rescue endovascular therapy is also a reasonable approach in patients with large-artery occlusion who have not responded to intravenous fibrinolysis (class IIb; level of evidence B).

Solitaire FR and Trevo stent retrievers are generally preferred for mechanical thrombolysis. The ability of stent retrievers to improve patient outcomes had not yet been established by Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) [22], International Management of Stroke Trial III [23] and the Local Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) Expansion trials [24]. However, recent trials such as the Multicenter Randomized Clinical Trial of Endovascular Treatment in the Netherlands (MR CLEAN) [25], Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) [26], Solitaire with the Intention for Thrombectomy as Primary Treatment for Acute Ischemic Stroke (SWIFT PRIME) [27], EXtending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy (EXTEND IA) [28] supports the benefit of mechanical thrombolysis. Hence, recently, the Consensus statement on mechanical thrombectomy in acute ischemic stroke (ESO-Karolinska Stroke Update 2014) supports that mechanical thrombectomy, in addition to intravenous thrombolysis within 4.5 hours when eligible, is recommended to treat acute stroke patients with large artery occlusions in the anterior circulation up to 6 hours after symptom onset (grade A, level 1a, KSU grade A).

So, TCD allows the diagnosis of intracranial arterial occlusion and define persisting occlusions after intravenous r-tPA which were suggested to further benefit from combined intraarterial/endovascular treatment [29,30].

Therapeutic aspects: sonothrombolysis and sonolysis

Sonothrombolysis consists in the continuous ultrasound sonation of an intra-arterial occlusive thrombus during systemic or local intra-arterial thrombolysis to enhance recanalization and tissue reperfusion [31]. Sonolysis is defined by the use of this technology as the sole thrombolytic therapy [3].

The use of ultrasound with a therapeutic aim is well-known and has various indications such as phacoemulsification in cataract surgery, lithotripsy in treatment of kidney stones and acceleration of wound healing [32]. The mechanical effect of ultrasound on endothelium increase the transport of r-tPA into the thrombus, promotes the opening and cleavage of the fibrin polymers and improves the binding affinity of r-tPA to fibrin [33]. Ultrasound-enhanced thrombolysis can be further amplified by adding gaseous microbubbles with contrast agents [34]. Ultrasound cause these small microspheres to oscillate and progressively absorb energy that accelerate the clot-dissolving effect [35]. A potential adverse event related to the use of these microspheres is intracerebral hemorrage. However, published trials used different microbubbles (eg, galactose, lipid, albumin shells) with different protocols that emphasizes the need for further studies to access microbubble composition with a more reasonable risk-benefit profile [36].

Moreover, the use of ultrasound in combination with thrombolytic agents may also potentially increase bleeding complications, but this is still uncertain [36].

A meta-analysis [37] concluded that the exposure to any diagnostic high-frequency ultrasound with or without microbubbles could more than double the likelihood of tPA-induced recanalization and increase the likelihood of functional independence after stroke. The authors also concluded that the spontaneous cerebral haemorrage risk was higher with low-frequency ultrasound.

A recent Cochrane review [38] also showed benefit. Regarding the primary outcome, defined by death/dependency at three months, patients treated with adjunctive sonothrombolysis were less likely to be dead or disabled at three months (odds ratio: 0.50; 95% confidence interval: 0.27-0.91). Moreover, recanalization failure was also lower in the sonothrombolysis group and no significant difference was found concerning mortality and cerebral haemorrhage.

The recent development of operator-independent ultrasound devices aims to expand the use of this technique to centers without specialized operators [36]. Preliminary results revealed a complete recanalization rate of 40% that is comparable with that that occurred in the CLOTBUST trial which utilized operator-dependent hand-held technology [30]. Consequently, a multicenter phase III trial called CLOTBUST-ER (Combined Lysis of Thrombus using 2 MHz PW Ultrasound and Systemic TPA for Emergent Revascularization) using an operator-independent ultrasound device was settled [36].

Regarding sonolysis, Cintas et al [39] performed continuous TCCD monitoring in six consecutive patients with acute MCA main stem occlusion and observed that five patients presented partial recanalization (defined by blunted waveforms). The authors also reported that the mean time to the beginning of recanalization was 17.2 ± 9.6 minutes and concluded that sonolysis may be a promising technique. However, the sample size was small and the study did not included a control group, which enhances the need for further studies.

Ultrasonography in acute stroke etiologic investigation

The ultrasound has a critical value in the stroke etiologic investigation. This investigation should be done rapidly and effectively as it may determine the need for an additional intervention, such as carotid stenting/endarterectomy for large-vessel disease [8]. Moreover, the recurrence risk is higher in the first days enhancing the need for an early investigation.

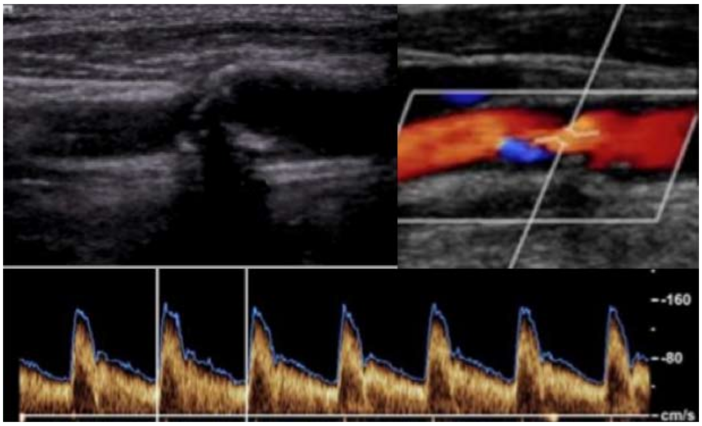
An atheromatous plaque is by definition a focal structure encroaching into the arterial lumen with at least 0.5 mm, 50% of the surrounding intima-media thickness or demonstrating a thickness > 1.5 mm as measured from the intima-lumen interface to the media-adventitia interface [40]. Cervical Doppler ultrasound (CDU) allows the plaque characterization regarding to number (single/multiple), location, shape, size, echogenicity, surface, texture (homogeneous or heterogeneous) and to the stenosis degree [41]. Several studies suggest that anechogenic lipid-rich, heterogeneous and plaques with surface irregularities/ulceration carry a more significant risk of neurologic events (transient ischemic attack/stroke) [42-46]. The most significant sonographic features of a severe ICA stenosis are: a ≥ 70% lumen diameter reduction of visible plaque at gray-scale imaging and PSV greater than 230 cm/s, spectral broadening, color aliasing and post-stenosis turbulence [47]. Serena et al [48] described the proposed cut-off values to diagnose and quantify a carotid stenosis. This estimation is extremely important as it is correlated with the risk of neurologic events. In the case of a near-occlusion the PSV may be high, low or undetectable [48]. Total ICA occlusion is diagnosed by the direct visualization of a thrombus at gray-scale imaging, absent flow at color Doppler imaging and damped resistive flow in CCA at pulsed-wave Doppler imaging [49]. This is also important because near-occlusion patients may be surgical candidates.

Atherosclerotic stenosis of the major intracranial arteries is probably the most common cause of stroke worldwide [50], accounting for 8-10% ischemic strokes in North America [50] and 30-50% in Asia [51]. Although the digital-subtraction angiography is considered the gold-standard diagnostic method [52], TCD may be extremely useful. TCCD diagnosis is usually based on finding flow acceleration and spectral broadening on intracranial stenosis site, or a combination of low mean flow velocity and high PI in the case of a severe or long stenosis [53]. An occlusion is suspected by the absence of color or power flow signal with absent/minimal flow on Doppler spectrum [53].

Due to the absence of internationally accepted diagnostic criteria for intracranial stenosis, authors usually rely on velocity criteria such as the ones proposed by Baumgartner et al [3]. However, diagnosing intracranial stenosis based solely on velocity criteria may be misleading in hyperdynamic states, after intravenous contrast agents and in the presence of collateral compensation [53]. Consequently, we should also consider the following criteria: focal velocity increasing (more than 30 cm/s compared to the contralateral side), absence of laminar flow, changed pre and post-stenotic flow, collateral compensation and narrowing/aliasing in color mode (Fig. 2) [53]. This technique has a sensitivity of 70% and 50-80% and a specificity of 90-95% and 80-96% for anterior and posterior circulation territory examination, respectively [53].

Color DS also allows the diagnosis of an arterial dissection. The main CDU features are: luminal flap or false lumen (the most specific sign); bulbar or proximal ICA hematoma or low-reflective thrombus with or without narrowed true lumen; bulb and ICA origin with high-resistance flow pattern to a stenotic hematoma in the cervical ICA segment not explored directly [48]. Although non-specific, the last feature is the most frequently observed. Likewise, the specific signs of VA dissection, such as segmental vessel dilation with an eccentric channel are rarely encountered.

Figura 2. 50-70% ACI stenosis (PSV 160 cm/s; EDV 80.4 cm/s; ratio PSV ACI/PSV ACC: 2.1).



Practical algorithm for neurovascular emergency assessment

When performed by an experienced neurologist with a standardized and validated protocol, which should include both TCD and cervical duplex, neurosonological evaluation does not result in any delay in the acute stroke management [53,54]. A practical algorithm was proposed for the urgent bedside ultrasound examination with carotid/vertebral duplex and transcranial Doppler in patients with acute stroke [54-56].

The algorithm determines that the ultrasound examination should start by the location suggested by the clinical symptoms. For instance, in a case of an anterior circulation syndrome the insonation begins with TCD examination of MCA preferentially in non-affected side, that is followed by the examination of contralateral one. The insonation may start at 50 mm depth and the waveforms and systolic flow velocities are compared with the non-affected side. If a normal MCA flow is found, the distal MCA segments are insonated (range: 40-50 mm); this is followed by proximal MCA and ICA bifurcation assessment (range: 60-70 mm) [54-56]. In the case a posterior circulation syndrome, the algorithm suggest to start with suboccipital insonation at 75 mm to analyze the VA junction and then BA flow at 80-100 mm. If abnormal signals were present at 75-100 mm, observers should proceed to terminal VA (40-80 mm) on the non-affected side for comparison [54-56]. In addiction, these authors also propose screening criteria for lesions amenable for intervention.

Using such a protocol urgent TCD studies can be completed and interpreted quickly at the bedside. TCD has the highest sensitivity (> 90%) for acute arterial obstructions located in the proximal MCA and ICA. However, for posterior circulation lesions the sensitivity is modest (55-60%) [54-56].

Conclusion

Recently, ultrasonography application in neurovascular disorders have greatly expanded. Color DS and TCCD are inexpensive, fast, noninvasive and reliable tools to evaluate the cervical and intracranial arteries and may be considered the stethoscopes of the neurologists that manage acute stroke.

In acute stroke settings, neurovascular ultrasound can be used with diagnostic and therapeutic purposes. TCD may assist the patient selection for mechanical thrombectomy and, when performed during r-tPA infusion, allows the monitorization of arterial recanalization.

Moreover, CDU assess the stenosis degree and the composition/surface of an arterial plaque that could, for instance, reveal earlier a patient with an indication for a carotid angioplasty or endarterectomy.

Sonothrombolysis and sonolysis are emerging techniques that expand the therapeutic potential of ultrasonography.

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Ecografía neurovascular en urgencias: aspectos diagnósticos y terapéuticos

Introducción. La ecografía neurovascular es una técnica de diagnóstico por imágenes rápida, portátil e incruenta que en manos de un ecografista experimentado aporta información reproducible y fiable acerca del estado hemodinámico y morfológico de los vasos craneales y cervicales.

Objetivo. Revisar los datos disponibles sobre el uso de esta herramienta en el abordaje del ictus isquémico agudo.

Desarrollo. La ecografía neurovascular se divide en dos modalidades de uso: diagnóstica y terapéutica. A la luz de los bajos porcentajes de recanalización de las oclusiones de la arteria carótida interna y del segmento proximal de la arteria cerebral media logradas por el activador del plasminógeno tisular recombinante (r-tPA) por vía intravenosa, el uso diligente de la ecografía neurovascular en el servicio de urgencias ayuda a dirimir qué pacientes son susceptibles de beneficiarse del tratamiento endovascular. Asimismo, la vigilancia ecográfica durante el curso del tratamiento con el r-tPA permite analizar la evolución de la recanalización arterial. La ecografía cervical permite valorar el grado de estenosis y la composición o la superficie de la placa arterial, extremos que, por ejemplo, pueden indicar la idoneidad de una intervención carotídea. Por último, también se está investigando el potencial terapéutico de la ecografía. La sonotrombólisis y la sonólisis, la primera combinando el r-tPA con las ondas ultrasónicas y la segunda sirviéndose únicamente de ellas como medio para lisar el trombo, han evidenciado hasta el momento resultados alentadores.

Conclusión. La ecografía neurovascular ha progresado enormemente hasta adquirir un protagonismo destacado en el estudio de los trastornos cerebrovasculares.

Palabras clave. Arterias cerebrales. Ecografía. Ictus. Infarto cerebral. Isquemia cerebral. Procedimientos endovasculares.