The Role of TCD in the Evaluation of Acute Stroke

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ABSTRACT

BACKGROUND: The additional information that transcranial Doppler (TCD) can provide as part of a multimodal imaging stroke protocol in the setting of hyper acute strokes has not been evaluated.

METHODS: Consecutive patients admitted between December 2012 and January 2015 with ischemic stroke of less than 4.5 hours of onset were studied as soon as possible with a protocol consisting of noncontrast brain computed tomography, computed tomography angiography of supra-aortic vessels, diffusion-weighted magnetic resonance imaging, and TCD.

RESULTS: Eighty-six patients were included. The imaging protocol was performed 113.9 (±23) minutes after the stroke symptoms appeared and by TCD after 150.2 (±19) minutes. Sixty-six (76.7%) patients were treated with revascularization therapies. TCD provided additional information in 49 cases (56.9.4%, 95 CI 46.4-66.9). More than one piece of additional information was obtained in 17 patients. The most frequent additional information was collateral pathways, information related to patency of vessels, and active microembolization. Multivariate analysis demonstrated that, intracranial vessel occlusion (P <.001) and optimal sonographic windows (P <.004) were the variables associated with additional information. In 15 patients (17.4%; 95 CI 9.4-25.5) the additional information changed the management. In 8 patients endovascular rescue was applied after the failure of intravenous thrombolysis; in 5 patients angiography was suspended and in 2 other cases aggressive neurocritical care was indicated.

CONCLUSIONS: TCD in the first 4.5 hours of acute ischemia can provide additional information to a multimodal acute ischemic stroke imaging protocol, and can induce changes in the management of a proportion of these patients.

Keywords: Acute stroke, ischemic stroke, ultrasound, Doppler sonography.

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Introduction

Transcranial Doppler (TCD) has been shown to be a useful diagnostic tool in the management of acute ischemic stroke (AIS).[1–5] TCD provides information about collateral pathways, microembolisms, degrees of intracranial stenosis, reperfusion, and hemodynamic steal of flow in intracranial arteries which are relevant for the treatment of the patients.[6–11]

When associated with other imaging techniques, TCD complements the information provided by other sources.[5,12] This was demonstrated in studies that included only a limited number of patients in the initial 4.5 hours after an AIS – a period of time when most of the critical and relevant decisions have to be taken. Additionally, most previous studies did not include the immediate evaluation of the cervical arteries, and finally, neurosonographers were blinded to the results of the other imaging techniques – a situation that is not usual in medical practice.

We aimed to evaluate whether TCD added additional information to an acute stroke imaging protocol (ASIP) consisting of noncontrast brain computed tomography (CT), computed tomography angiography of the supra-aortic vessels (CTA) and diffusion-weighted magnetic resonance imaging (DWI) in AIS of less than 4.5 hours of evolution. Furthermore we wanted to elucidate whether this additional information was helpful in the patient's acute care.

Patients and Methods

Consecutive patients admitted to Clínica Alemana de Santiago with hyperacute ischemic strokes (less than 4.5 hours of evolution) were prospectively included between December 2012 and January 2015. When a patient with AIS consulted at the emergency room (ER), a code indicating that a stroke patient had arrived was activated, and the neurologist on call was called. If the duration of the AIS was of less than 6 hours of onset, the neurologist summoned the stroke team: this included the stroke fellow and the ultrasound specialist. Between 8 AM and 6 PM other stroke neurologists also provided assistance. Following the clinical evaluation, blood samples were obtained and the patients were then subjected to an ASIP that

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consisted of a brain CT; in those patients without contraindications (kidney failure, allergy to contrast media or an implanted pacemaker) a spiral CTA of the cervical and intracranial arteries and DWI were performed. Additionally, patients were evaluated with power motion TCD (PMD-100 Spencer Technologies) with a 2 MHz probe and a 6-9 mm sample volume. A standardized, rapid insonation protocol was applied.[1,2] All TCD findings were interpreted immediately by an experienced sonographer.

Brain CT studies were carried out with a multidetector helical scanner (Siemens Sensation 64). CTA scans were performed with .75 mm slice thicknesses and .5 mm intervals during a bolus injection of 80 mL of contrast medium at a rate of 5 mL/second. Two acquisitions were made, one in the arterial phase and the other immediately after the venous phase. Evaluations were performed from the aortic arch level to the vertex. MIP (maximum intensity projection) multiplanar reformats were created in the axial, coronal, and sagittal planes. These were repeated during the venous phase to ascertain whether any arterial vessel had not been contrasted or whether there was any important asymmetrical arterial enhancement. When distal flow was not detected in an artery an obstruction was diagnosed; in these cases a 3-dimensional reconstruction study with volume rendering was performed.

DWI examinations were performed with a Signa 1,5-Tesla scanner (General Electric) equipped with echo-speed gradients; the acquisition parameters were: repetition time (TR), 1,000 ms; spin time echo (TE) 73,9 ms; matrix 128×128; field of view 36×23 cm and 32 oblique sections with 5 mm of thickness without intervals. The diffusion images were provided with a diffusion weight of (b) of 1,000 second/mm^2 y and sensitivity gradients of diffusion in planes *X, Y,* and *Z.* The neuroradiologist on call gave an immediate preliminary report about the CTA and DWI and a final diagnosis was made latter.

Additional information was that exclusively generated by the TCD as interpreted by the attending neurologist and was classified as: active microembolism, collateral flow pathways, presence of subclavian steal, changes of patency of vessels during TCD, detection of occlusions or stenosis not detected in the CTA, or any other information that TCD provided and believed to be useful.

Changes in management originated by the TCD were modifications in treatments or studies carried out on the basis of the test and defined by the attending physician. Ultrasound results were immediately transmitted to the attending neurologist on occasion before the neuroradiologist informed the results of the CTA and DWI. Stroke subtypes were diagnosed according to the TOAST classification.[13]

Patients eligible for intravenous (IV) thrombolytic therapy were treated according to the NINDS trial protocol and ECASS III.[14,15] An IV r-TPA bolus was administered after the CT scan before patients were transferred for MRI. Patients were monitored with TCD using the CLOTBUST study protocol.[16] Patients who did not recanalyze as shown by TCD or clinically in the absence of a sonographic window were subjected to digital substraction angiography (DSA) and eventually to mechanical thrombectomy or chemical intraarterial thrombolysis.

The study protocol was reviewed and approved by our Institutional Ethics and Scientific Committee. In all cases patients or their relatives provided informed consent.

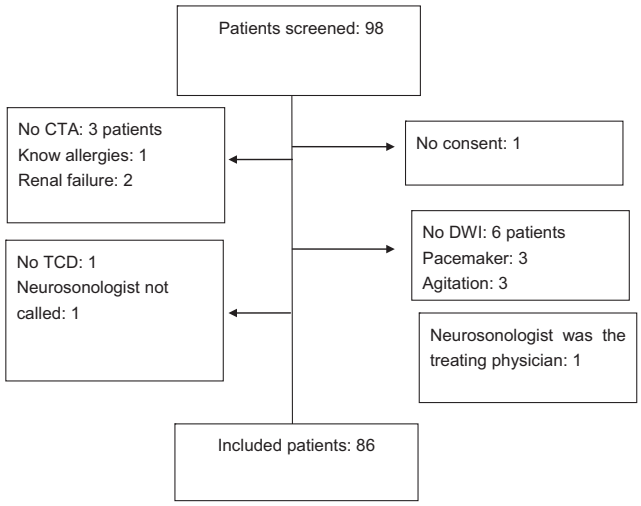

Fig 1. Flow diagram of the study of additional information given to a multimodal imaging stroke protocol by transcranial Doppler in the emergency room.

Analysis

The proportion of additional information and the changes in management resulting from TCD were calculated with 95% confidence intervals.

Univariate analysis was performed using χ^2 for frequency data to study the associations of additional information with cerebrovascular risk factors, NIHSS, the presence of occluded vessels in CTA, revascularization treatment, TOAST etiologic classification, presence or absence of temporal windows on TCD. A logistic regression analysis was performed for those variables that were positively associated ($P<.05$) in the univariate analysis. In the subset of patients in whom additional information induced changes in their management, a univariate analysis using χ^2 for frequency data was performed dichotomizing again with NIHSS, intravenous r-TPA treatment, the presence or absence of temporal windows on TCD, and the presence of occluded vessels on CTA. Variables that were statistically significant were tested in a logistic regression model.

Finally, for those patients that were treated with revascularization therapies, who had intracranial vessel occlusions and a satisfactory sonographic window that allowed TCD monitoring or in whom angiography had been performed, we tested the relationship between successful revascularization and good prognosis at 90 days defined as modified Rankin scale (mRS) ≤ 2 by the test of χ^2.

Results

Ninety-eight consecutive patients with AIS were seen at the ER of Clínica Alemana de Santiago between December 2013 and January of 2015 in the initial 4.5 hours of the onset of symptoms; of these, 87 (88.7%) were included in this study. The flow diagram of the study and the causes of exclusion from the analysis are shown in (Fig 1). The clinical characteristics of these patients appear in Table 1.

The mean time (SD) lapse from symptom onset to the ER was 98.5 (±23) minutes and to ASIP was 113.9 (±28) minutes, while for the TCD it was 150.2 (±19) minutes. In 36 (41.8%)

Table 1. Baseline Characteristics of the Study Sample and Time to Examination

Variables	N = 86
Mean age, years	69.7 (42-93)
Male sex (%)	44 (50.5)
Mean admission NIHSS* (SD)	9. (2.6)
Hypertension (%)	61 (70.1)
Diabetes mellitus (%)	19 (21.8)
Hypercholesterolemia (%)	32 (36.7)
Tobacco (%)	21 (24.1)
Atrial fibrillation (%)	24 (27.5)
Mean time from symptoms onset to examination, minutes (SD)	
ASIP†	113.9 (23) minutes
TCD‡	150.2 (19) minutes

*National Institutes of Health Stroke Scale.
†Brain CT, CTA, and DWI.
‡Transcranial Doppler.

Table 2. Additional Information Given by TCD on 86 Patients

Additional Information	N
Collateral flow	35
Active microembolism	10
Detects occlusion first not seen by CTA	4
Information related to patency of vessels	22
Other information	3

patients the TCD report was delivered to the treating physician before the preliminary ASIP report.

CTA demonstrated 46 intracranial occluded vessels, 9 had severe (≥70%) carotid stenosis; all the patients suffered tandem lesions.

TCD examinations did not demonstrate optimal temporal sonographic windows in 17 (19.7%) patients.

During the study period, 66 (75.8%) patients received reperfusion therapy, 64 were treated with r-tPA, which was followed by intraarterial therapy in 9 patients; in 2 patients this was the initial therapy.

In 49 patients (56.9.4%, 95 CI 46.4-66.9) TCD yielded information that the attending neurologist considered as additional (Table 2); more than one piece of additional information was obtained in 17 cases (19.7%, 95 CI 12.7-19.4); (Fig 2) illustrates a case where TCD findings resulted in additional information. TCD did not yield information that could be considered as confusing.

The results of the univariate analysis of the association between additional information and other variables are shown in Table 3. Hypercholesterolemia ($P = .004$), NIHSS ($P = .005$), intracranial vessel occlusion detected by CTA ($P < .001$) or carotid stenosis, ($P = .009$), optimal ultrasound temporal windows ($P = .057$), and the TOAST etiological classification ($P < .001$), were significantly associated. In multivariate analysis, intracranial vessel occlusion ($P < .000$) and optimal sonographic windows ($P = .004$) were the only variables associated with additional information obtained by TCD.

Additional information resulting from TCD changed the management of 15 (17.4% 95 CI. 9.4-25.5) cases, of these, in 8 patients r-TPA did not restore arterial flow and required endovascular rescue therapy. At the end of their endovenous thrombolytic treatment four of these cases showed mild improvement, 2-3 points in the NIHSS stroke scale. However the occluded vessel did not recanalizate on evaluation by ultrasound, and an occlusion was demonstrated by angiography in all of them. In 6 cases the flow was restored by thrombectomy. After 3 months 5 of these patients were classified in mRS ≤ 2; the remaining reperfused patient was on a mRS score of 4 at 3 months. The 2 patients in whom the arteries could not be opened died from massive strokes.

In 5 patients angiography was avoided because they already had experimented arterial reperfusion on ultrasound, 3 of them did not demonstrated any changes of NIHSS at the end of r-TPA; at 3 months, 4 of them were on a mRS ≤ 2 and the remaining patient was at a mRS of 4 on day 90.

Finally, neurointensive care therapies were increased in 2 cases that had contraindications for reperfusion management. They presented distal branch occlusions in the middle cerebral artery but with very good collateral flow on TCD. With flat head position, induced hypertension and volume expansion, important increases in flow velocity in the affected artery and collateral pathways resulted. Both patients had a final mRS of 2 on day 90.

The only variable that resulted in significant changes in management was the presence of an occluded vessel ($P < .000$). *None of those patients whose clinical treatment was modified based on the information provided by the TCD manifested orthostatic hypoperfusion syndrome.*

Of the 66 patients that were treated with reperfusion therapies, 9 had suboptimal sonographic windows that did not allow TCD monitoring while 15 other cases did not demonstrate intracranial vessel occlusions. Of the remaining 42 patients, reperfusion was achieved in 28 patients with good prognosis in 19 of them. Of the 14 patients that did not revascularize their obstructed arteries only 3 of them were considered to have good prognosis. Arterial reperfusion was associated with good prognosis at 3 months ($P = .004$).

Discussion

The first hours after an AIS are the most critical, when most of the treatments with greater clinical impact are applied, like the use of intravenous thrombolytics or endovascular treatments. Our study demonstrates that even if patients have been already studied with advanced neuroimaging vascular techniques like brain and cervical CTA, TCD at this time may provide additional useful information in 1 out of 2 patients, and changes in management are indicated in 1 out of 6 cases.

In this study TCD yielded more additional information than in previous ones,[5,12] even after a more complete imaging protocol had been used that included for the first time the evaluation by CTA of cervical vessels and the presence of a higher number of suboptimal temporal windows than in previous studies (20%). Probably our results depend on several variables; firstly, compared to previous studies,[5,12] were the amount of additional information provided by TCD ranged between 7 and 35.4%, the neurosonologists in this study were not blinded to the results of any other imaging studies, as is usual in clinical practice. This may guide neurosonographers to an improved use of ultrasound. Not infrequently, in the current experience the results of TCD were provided to the attending physicians before the

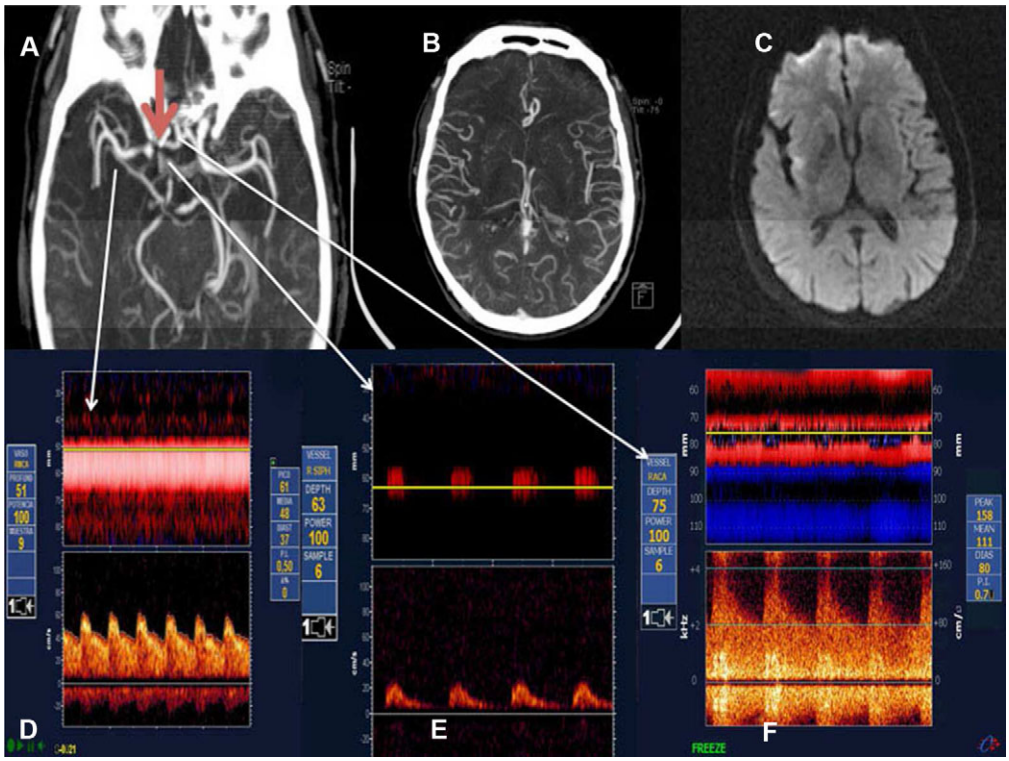

Fig 2. Case 19, 78-year-old male, arrived within 30 minutes of symptom onset of a right side MCA stroke. Initial NIHSS score of 2 points. (A) CTA interpreted as normal by the neuroradiologist on call; the red arrow demonstrates a short right terminal carotid occlusion. (B) CTA demonstrates symmetrical filling of both MCA territories, which may be due to collateral flow. (C) DWI showing small insular ischemic changes. (D) TCD at the beginning of thrombolysis demonstrates a middle cerebral artery with good flow velocity but with low pulsatility index suggesting post stenotic flow, and a proximal vascular lesion. (E) Occlusion of right terminal carotid as revealed by the TCD. (F) Inverted, high velocity flow in the right anterior cerebral artery compatible with anterior cross filling (collateral flow).

Table 3. Univariate Analysis of Predictors of Additional Information (AI) on TCD

Variables	No AI* $N = 37$	AI $N = 49$	P
Hypertension (%)	23 (26.7)	37 (43)	.237
Diabetes mellitus (%)	9 (10.4)	10(11.6)	.79
Tobacco (%)	6 (6.9)	15 (17.4)	.138
Hypercholesterolemia (%)	11 (12.7)	21(24.4)	.263
Heart failure (%)	2 (5.4)	4 (4.6)	.69
Atrial fibrillation (%)	7(8.1)	17 (19.7)	.14
Mean NIHSS	6.6	12.8	.005
Intracranial stenosis or occlusion (%)	4 (4.6)	42 (48.8)	.000
Carotid stenosis or occlusion (%)	0	9 (10.4)	.009
Revascularization therapy (%)	27 (31)	39 (45.3)	.223
Ultrasound temporal windows			
Optimal	11 (12.7)	43 (50)	.057
No window (%)	26 (30.2)	6(6.9)	
TOAST classification (%)			
Large-artery atherosclerosis	0(0)	10 (11.6)	.000
Cardioembolic	9 (10.4)	20 (23.2)	
Cryptogenic	18 (20.9)	16(16.6)	
Lacunar	8 (9.3)	0 (0)	
Other	2 (2.3)	3 (3.4)	
Nonlacunar stroke	29 (33.7)	49 (56.9)	.002

*AI = Additional Information

CTA report was produced; this could be an important factor but it does not explain the totality of our results.

Also, in contrast with the experience of Tsivgoulis et al, we excluded from our protocol those patients with acute transient ischemic attacks who usually have normal TCDs. Finally as we evaluated the patients in their first few hours of onset of their symptoms, while previous studies included patients in the first day of evolution,[5,12] our chances of detecting arterial occlusions was higher. Finding an arterial obstruction by TCD has been shown to be an important variable that correlates with the detecting of additional information.[5]

The statistically significant variables that resulted in additional information by TCD, were our ability to carry out a technically satisfactory neurosonographic study, with a good sonographic window, and the detection of an occluded vessel by CTA, which is frequently associated on TCD with the presence of collateral flow (flow diversion). Arteries can remain open, may reocclude or experience no change in their status during thrombolytic therapy. Two of these findings, collateral flow and arterial flow, represented the most frequent additional information provided by TCD. These results had some similarity with those of our previous study, carried out during the first 24 hours of evolution of AIS,[5] in which vessel occlusion was the only variable associated with the additional information obtained by TCD. In that study there was a lower proportion of suboptimal sonographic temporal windows and probably for this reason the presence of optimal temporal windows did not reach statistical significance.

Additional information by TCD results from its dynamic characteristics allowing the detection of alternative collateral pathways, active microembolism and the patency of vessels – accounting these for the 90% of the additional information in this study.

TCD leads to modifications of management in 17% of the patients. Most of these changes depend on the possibility to provide intraarterial rescue therapies, according to the monitoring of the condition of the occluded vessel during r-TPA treatment; indeed the only statistical variable resulting in changes in management was the presence of an occluded intracranial artery. The persistence of an occluded artery after r-TPA treatment correlates not only with a worse prognosis at 3 months but also increases the risk of symptomatic brain hemorrhage during the first 72 hours of evolution.[17]

Thrombectomy has been recently shown to be an important therapeutic tool in AIS. Initial studies comparing r-TPA and intravascular therapies demonstrated negative results.[18–20] One of the strongest criticisms to these studies was that they did not require the demonstration of an occluded intracranial vessel before admitting the patients to the angiography suit.[21] Recent studies with positive results demonstrated the importance of having an intracranial occluded vessel demonstrated before conducting intraarterial revascularization.[22–26]

For the diagnosis of intracranial occlusions in patients with AIS, TCD has the advantage of considerable accuracy compared to angiography[1] and CTA;[12,27] it also can detect occlusions not detected in the first reading of CTA in the anterior circulation (5), which also happened in our study. TCD may miss some occlusions in the posterior circulation,[12,27] while CTA may miss some of them in the anterior brain vessels.[5] We think that both techniques are complementary in the acute setting of an ischemic stroke, where missing an occluded vessel could mean not applying endovascular therapies to patients who could have contraindications for r-TPA or who did not reperfuse with intravenous thrombolytic. TCD monitoring of endovascular procedures is also helpful as it may detect reocclusions, hyperperfusion syndromes, or thromboembolism events in nearly half of all procedures.[28]

In our experience TCD could be a useful tool in deciding which patients should be programmed for intravascular rescue after r-TPA treatment, as demonstrated previously by Saqqur et al.[29] Angiography is an expensive and invasive test, that sometimes could have complications;[30] it is not practical to offer it to every patient treated with r-TPA and to base this decision purely on clinical grounds could be complicated, as in some patients even if the arterial perfusion is restored their NIHSS score is not improved.[31]

TCD can accurately predict brain artery recanalization in real time compared to angiography,[9] and could be used to avoid unnecessary angiography when it demonstrates regression of the treated occlusion, an element that is associated with better prognosis like in our study.[21–26] Finally TCD could be used to monitor the effects of other treatments that could increase collateral flow in the brain.[32]

The absence of a sonographic window, which in this study was very high, could be avoided with the use of neurosonographic contrast media.[33]

We postulate that TCD in patients with AIS in the first hours of evolution has an important role even if these patients have been subjected to other advanced diagnostic neuroimaging techniques.

The main strengths of our study are that it was conducted consecutively in a clinical setting in patients with AIS, independently of their acoustic windows. However, our study also has some limitations: it included a small sample size, and TCD had some disadvantages, as it is an operator-dependent diagnostic technique with a percentage of inadequate temporal windows. Due to the small size of our sample, a multivariate analysis for elements defining better prognosis is difficult.

Conclusions

In patients with hyperacute stroke and an imaging protocol consisting of noncontrast CT, CTA, and DWI; TCD generates useful additional information in half of the cases and may promote changes in the management in 17% of them, especially in those with arterial occlusions.

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