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Additional Information Given to a Multimodal Imaging Stroke Protocol by Transcranial Doppler Ultrasound in the Emergency Room: A Prospective Observational Study

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Key Words
Acute stroke · Ischemic stroke · Ultrasound Doppler sonography · Ultrasound diagnosis

Abstract
Background: Transcranial Doppler (TCD) ultrasound can demonstrate dynamic information. We aimed to evaluate whether TCD generates useful additional information in the emergency room after a multimodal stroke imaging protocol and also whether this modified the management of patients with cerebral infarction. ***Methods:*** Patients admitted between April 2006 and June 2007 with ischemic stroke of less than 24 h were subjected to a protocol consisting of non-contrast brain CT, computed tomography angiography, diffusion-weighted magnetic resonance imaging and then TCD within the following 6 h by an observer blinded to the results of imaging studies. ***Results:*** Seventy-nine patients were included. The imaging protocol was performed 457 (±346) min after stroke symptoms and TCD after 572 (±376) min. TCD provided additional information in 28 cases (35.4%, 95% CI 25.7–46.4). More that one piece of additional information was obtained in 6 patients. The most frequent additional information was collateral pathways. Multivariate analysis demonstrated that intracranial vessel occlusion was the variable most associated with additional information. In 7 patients (8.8%, 95% CI 4.3–17.1), additional information changed management: in 4 an additional angiography was performed, in 2 patients angiography was suspended and in 1 aggressive neurocritical care was indicated. Patients with NIHSS >10 were significantly more likely to have their initial treatment changed (p = 0.004). ***Conclusions:*** TCD can provide additional information to a multimodal acute ischemic stroke imaging protocol in a third of patients. This can result in changes in the management in some of these patients.

Introduction

Transcranial Doppler (TCD) ultrasound is an accurate tool for the diagnosis of arterial occlusions in patients with acute ischemic stroke [1–4]. Due to its dynamic

Research conducted at Clínica Alemana de Santiago.

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characteristics, TCD provides information that other procedures used in the emergency room for the detection of vascular occlusions cannot provide. Examples of this additional information are the detection of collateral pathways, microembolisms and hemodynamic steal of flow of intracranial arteries [5–7].

How much additional information can TCD provide when added to other imaging studies has not been explored in depth and has only been compared to computed tomography angiography (CTA) of intracranial vessels [8, 9].

In this study we aimed to evaluate whether TCD added information to an acute stroke imaging protocol (ASIP) consisting of noncontrast brain computed tomography (CT), CTA and diffusion-weighted magnetic resonance imaging (DWI) and whether any of this additional information helped in changing patient management.

Patients and Methods

Patients admitted with ischemic strokes were prospectively included between April 2006 and June 2007. During this period of time all patients with ischemic stroke who consulted at the emergency room at Clínica Alemana de Santiago were seen by the neurologist on call within the first 15–30 min after arrival. Following clinical evaluation, they were subjected to an ASIP that consisted of CT and, in patients without contraindications (kidney failure, allergy to contrast media or an implanted pacemaker), spiral CTA of intracranial arteries and then DWI. This protocol in our institution takes around 12 min. Additionally patients arriving before 24 h of the onset of symptoms were evaluated with TCD using power motion PMD-100 Spencer Technologies equipment with a 2-MHz probe and a 6-mm sample volume. A standardized, rapid (lasting less than 15 min) insonation protocol was applied [10]. Extracranial vessel examinations were not performed in the emergency room and were usually done on the first 24 h in the stroke unit. All TCD findings were interpreted immediately after insonation by an experienced sonographer certified by the American Society of Neuroimaging who was informed about the patient's main symptoms only, was not the attending physician and was blinded to the results of the ASIP.

Brain CT studies were carried out with a Siemens Sensation 16 multidetector helical scanner. CTA scans were performed with 0.75 mm slice thickness and 0.5 mm intervals during a bolus injection of 80 ml of contrast material, at a rate of 5 ml/s. Two acquisitions were done, the first one during an arterial phase and the second one immediately after a venous phase. Explorations from the C2 level to the vertex were performed. MIP (Maximum Intensity Projection) multiplanar reformats were created in the axial, coronal, and sagittal planes. They were repeated on venous time when an arterial vessel was not contrasted or if there was a significant asymmetrical arterial enhancement. When no distal flow was detected in an artery, an arterial obstruction was diagnosed; in these cases an additional three-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; 32 oblique sections with 5 mm of thickness, without intervals. The diffusion images were obtained with a diffusion weight (b) of 1,000 s/mm^2 and sensitivity gradients of diffusion in planes x, y and z. The neuroradiologist on call informed the CTA and DWI immediately and was unaware of TCD results.

Additional information was defined as: information generated by the TCD only according to the attending neurologist and 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 on the first reading of CTA, information suggesting proximal carotid disease or any other kind of information that TCD provided and was believed to be useful. Changes in management due to the results of TCD were defined as modifications in treatments or studies carried out on the basis of the information generated by the test and defined by the attending physician. TCD results were transmitted to the attending neurologist by the stroke fellow, to avoid any bias generated by contact with the neurosonologist. Stroke subtypes were classified according to the TOAST classification [11].

During the study period, patients eligible for intravenous thrombolytic therapy were treated according to the NINDS trial protocol [12]. Usually intravenous recombinant tissue-type plasminogen activator (rt-PA) bolus was given after CTA and before the patient was transferred to MRI. All patients were monitored with TCD using the CLOTBUST study protocol [13]. During this study in our institution patients who did not recanalize clinically and by TCD after intravenous thrombolysis were offered digital subtraction angiography (DSA), and eventually mechanical or chemical intra-arterial thrombolysis.

The study protocol was reviewed and approved by our institutional ethics and scientific committee. All patients or their relatives gave informed consent.

Analysis

The proportion of additional information and the changes in management resulting from TCD were calculated with their respective 95% CIs.

A univariate analysis was performed using χ^2 for frequency data to study the associations of additional information with: National Institutes of Health Stroke Scale (NIHSS) scores greater or less than 10 points, the presence of occluded vessels in CTA, treatment with intravenous t-PA, etiologic classification, lacunar versus nonlacunar infarction and the presence or absence of temporal windows on TCD. A logistic regression analysis was performed with those variables that were positively associated ($p < 0.05$) in the univariate analysis. Furthermore, in the subset of patients with additional information in which management was changed consequently, a univariate analysis using χ^2 for frequency data was performed dichotomizing again the NIHSS scores greater or less than 10 points, intravenous rt-PA treatment and presence of occluded vessels on CTA. Variables that were statistically significant were tested in a logistic regression model.

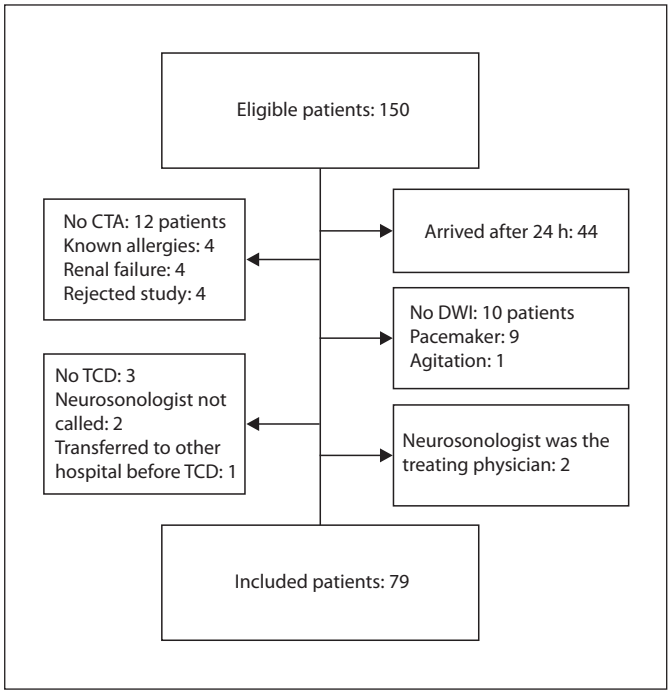

Fig. 1. Flow diagram of the study of additional information given to a multimodal imaging stroke protocol by TCD in the emergency room.

Table 1. Baseline characteristics of the study sample (n = 79 patients) and time to examination

Variables	
Mean age, years (range)	69.7 (42–93)
Male sex	45 (56)
Mean admission NIHSS ± SD	7.4 ± 6.1
Median admission NIHSS range	1–22
Hypertension	54 (68.4)
Diabetes mellitus	26 (32.9)
Hypercholesterolemia	21 (26.6)
Tobacco	25 (31.6)
Ischemic heart disease	17 (21.5)
Mean time from symptom onset to examination ± SD, min	
ASIP[a]	457 ± 346
TCD	572 ± 376

Data shown as number of patients with percent in parentheses unless indicated otherwise.
[a] Brain CT, CTA and DWI.

Results

One hundred and fifty consecutive patients with acute ischemic stroke were seen at the emergency room of Clínica Alemana de Santiago during the study period; of these, 79 (52.6%) were included in this study. The flow diagram of the study and causes of exclusion from analysis are shown in figure 1. The characteristics of the patients evaluated are shown in table 1.

The mean time (±SD) from symptom onset to ASIP was 457 (±346) min and 572 (±376) min for TCD. TCD examinations were performed before ASIP in 2 cases. Six patients (7.6%) did not have temporal sonographic windows. CTA demonstrated 27 occluded vessels (34.2%). This figure changed according to time to evaluation and initial NIHSS score. Of those patients that were studied within 6 h (n = 42) the median NIHSS score was 7.9 (1–22). When we stratified this group, of those with NIHSS score under 10 (n = 29) only 6 (20%) had arterial occlusions. In contrast, in the group of patients with NIHSS equal to or over 10 points (n = 13), 10 (73%) had an occluded vessel. During the study period, 10 patients were treated with intravenous rt-PA.

In 28 patients (35.4%, 95% CI 25.7–46.4) TCD yielded information that was considered additional by the attending neurologist (table 2). More than one piece of additional information was obtained in 6 patients (7.5%, 95% CI 3.5–15.5). In 3 cases TCD provided false negative results not diagnosing occlusions on 2 vertebral arteries and 1 posterior cerebral artery.

The univariate analysis correlating the presence of additional information with other variables is shown in table 3. Only NIHSS >10 ($p = 0.004$) and the presence of vessel occlusion on CTA ($p < 0.001$) were significantly associated. There was a tendency for additional information to be associated with rt-PA treatment and with nonlacunar strokes, but these variables did not reach statistical significance. In multivariable analysis, vessel occlusion was the only variable associated with additional information obtained by TCD examinations.

Additional information provided by TCD altered the management in the 7 (8.8%, 95% CI 4.3–17.1) cases described in table 4. Figure 2 illustrates a case where TCD findings changed management of the patient.

Discussion

Our study shows the usefulness of adding TCD to the evaluation of acute ischemic strokes in the emergency room, even if the patients already have undergone advanced studies like brain CTA or DWI. TCD generated

Table 2. Additional information given by TCD on 28 patients

Additional information	
Collateral flow	15 (18.9)
Active microembolism	6 (7.6)
Confirms doubtful CTA in patient with MCA trifurcation	3 (3.8)
Confirms occluded MCA M2 branch	n = 2
Discards occluded MCA M2 branch	n = 1
Detects occlusion first not seen by CTA	2 (2.5)
Subclavian steal	1 (1.3)
Information related to patency of vessels	5 (6.3)
Detects proximal carotid stenosis	2 (2.5)

Data shown as number of patients with percent in parentheses.

Table 3. Univariate analysis of predictors of additional information on TCD

Variables	No AI (n = 51)	AI (n = 28)	p
NIHSS <10	43 (84.3)	15 (53.6)	0.004
NIHSS >10	8 (15.7)	13 (46.4)	
Occluded vessel	9 (17.6)	18 (64.3)	<0.001
rt-PA treatment	4 (7.8)	6 (21.4)	0.08
TOAST classification			
Atherothrombotic	3 (5.9)	4 (14.3)	0.2
Cardioembolic	18 (35.3)	9 (31.1)	
Cryptogenic	18 (35.3)	11 (39.3)	
Lacunar	9 (17.6)	1 (3.6)	
Other	3 (5.9)	3 (10.7)	
Nonlacunar stroke	42 (82.4)	27 (96.4)	0.07
Ultrasound temporal windows			
Optimal	47 (92.2)	27 (96.4)	0.3
No window	4 (7.8)	1 (3.6)	

Data shown as number of patients with percent in parentheses.
AI = Additional information.

Table 4. Changes in management determined by TCD

Case	Sex age, years	NIHSS	ASIP findings	TCD findings	Change in management	mRS 3 months after stroke
11	F 18	9	left stroke MCA occlusion	left MCA occlusion, with no recanalization during i.v. rt-PA	DSA angiography and intra-arterial thrombolysis were performed, with recanalization of the occluded artery	0
12	F 84	14	right stroke MCA occlusion	right MCA occlusion that recanalized during diagnostic TCD; NIHSS score decreased from 15 to 4	planned DSA and intra-arterial thrombolysis were not performed	1
33	M 66	13	right stroke MCA M2 occlusion	right M2 occlusion, with important collateral flow from ipsilateral ACA and PCA	aggressive neurocritical care was started	1
40	M 66	19	left stroke MCA occlusion	left MCA occlusion, with no recanalization during i.v. rt-PA	DSA and intra-arterial thrombolysis were performed, with recanalization of the artery	0
51	F 69	15	left MCA stroke no occlusion on circle of Willis	post-stenotic left MCA flow signal and inverted ophthalmic artery suggest proximal left carotid artery disease	DSA was performed and ICA stenosis was found; intensive secondary prevention was begun	1
67	M 83	11	left stroke, CTA with important movement artifacts, possible left terminal M1 stenosis	normal TCD	planned diagnostic DSA was not performed	1
75	F 66	10	right MCA stroke no occlusion on circle of Willis	post-stenotic right MCA flow signal and inverted ophthalmic artery suggest proximal right carotid artery disease	DSA was performed and ICA stenosis was found; intensive secondary prevention was begun	0

mRS = Rankin scale; ACA = anterior cerebral artery; PCA = posterior cerebral artery; ICA = internal carotid artery.

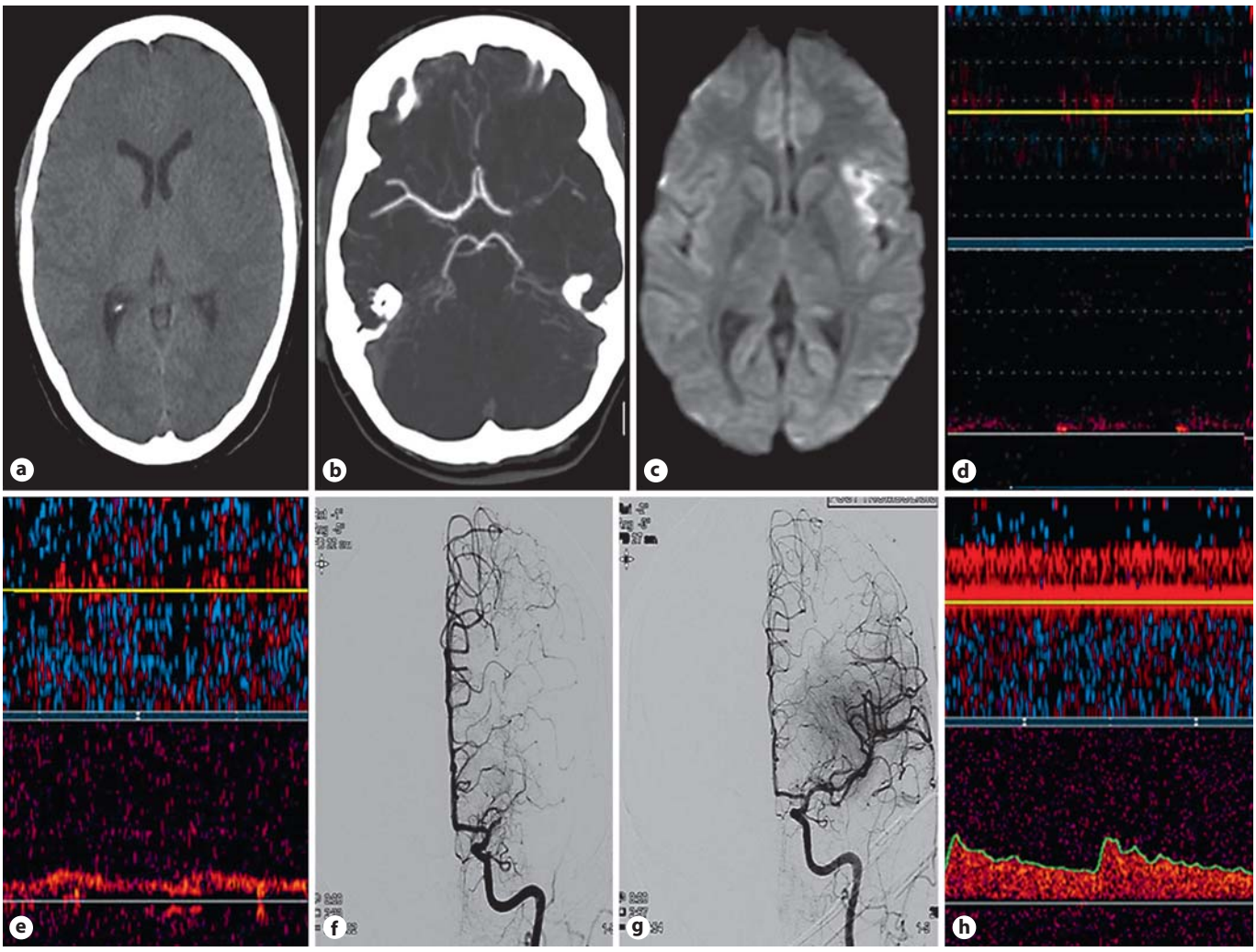

Fig. 2. Case 11, an 18-year-old white female, arrived within 93 min of symptom onset of a left MCA stroke. Initial NIHSS score of 9 points. **a** Brain CT scan demonstrating no abnormalities. **b** CTA showing M1 MCA occlusion. **c** DWI showing small insular ischemic changes. **d** TCD at the beginning of thrombolysis with signal showing occlusion of M1 MCA TIBI-1. **e** TCD at the end of intravenous thrombolysis. The patient had improved by 2 points on the NIHSS scale, but there was minimal improvement on M1 MCA signal to a TIBI-2 flow signal. With these TCD findings the patient was taken to angiography for rescue intra-arterial thrombolysis. **f** Diagnostic angiography demonstrates M1 MCA occlusion, at this point the patient's NIHSS had increased to 11 points. **g** After intra-arterial thrombolysis MCA has normal flow. **h** TCD 20 min after intra-arterial thrombolysis demonstrating normal M1 MCA flow, at this point NIHSS dropped to 5 points.

important additional information in a third of ischemic stroke patients, especially in those who presented with occluded or stenotic intracranial and extracranial arteries; this group of patients frequently had collateral flow that compensated for the obstruction of the affected artery.

In our study TCD yielded more additional information compared to the findings of Tsivgoulis et al. [8] (35.4 vs. 7%), even after using a study protocol that included DWI. This could be related to the fact that we did not include acute transient ischemic attacks, a group of patients who usually have normal TCDs. Furthermore, unlike some of the patients studied by Tsivgoulis et al. [8], who were examined with single-gated TCD, we evaluated all our patients with power mode TCD. This technology increases the speed by which acoustic windows are found and arteries insonated in cases of acute ischemic stroke [14], and can also depict flow signals that complement single-gated TCD [4]. We also had fewer patients with suboptimal temporal windows, which gave us the chance

of more complete studies and probably increased the probabilities of obtaining additional information. Nevertheless, in 3 cases TCD failed to diagnose occlusions of posterior circulation arteries. These are arteries which are more difficult to insonate and in which TCD is less valid [8, 9]. On the other hand, TCD was able to confirm 3 doubtful CTA findings; 2 of these cases were patients with occluded middle cerebral artery (MCA) M2 branches, vessels for which there are no CTA-validated diagnostic criteria. The additional information provided by TCD results from its dynamic characteristics, allowing the detection of opened alternative collateral pathways, active microembolism and information related to the patency of vessels, corresponding to 76.4% of the total additional information demonstrated by TCD in our study. This is similar to what has been described previously [8, 15]. Interestingly, we found that TCD modified the management of 9% of the patients evaluated, even if they already had been studied with CTA and DWI. TCD has also been previously found to change the management of patients with subarachnoid hemorrhage and of those under treatment in neurointensive care [16, 17], but not of patients with acute ischemic strokes. Patients with high NIHSS scores were the ones that benefited the most from TCD studies. They usually have intra- or extracranial stenosis and occlusions and could be candidates for revascularization or rescue therapies [18, 19]. In our series, all the changes in management determined by TCD were in those patients in whom intravenous rt-PA had failed or in whom there was a high degree of suspicion of an occluded or stenosed artery. These are patients in whom ultrasound studies have demonstrated great correlation with DSA, having a poor prognosis with a high probability of clinical deterioration [19–21], and in which TCD has been found to be a useful tool for intra-arterial thrombolysis rescue [18]. Due to its dynamic characteristics, TCD can add to CTA the ability to detect the time of recanalization, arterial reocclusions, demonstration of the worst residual flow at the site of an occlusion and as a predictive tool for the response to thrombolysis or the risk of intracerebral hemorrhage [19, 21–24]. Ultrasound as a noninvasive screening test is also able to predict outcome in the acute phase and follow-up of acute stroke patients [20, 25, 26] and to diagnose diffuse intracranial disease [27]. TCD has some disadvantages as a diagnostic technique, being operator-dependent and having a percentage of inadequate temporal windows that has been calculated to be between 5 and 38% [28, 29].

The main strengths of our study are that it was conducted in a clinical setting in consecutive patients with acute ischemic strokes, regardless of their acoustic windows. However, our study also has some limitations: it included a small sample size and our ASIP did not include cervical carotid and vertebral CTA which, if performed routinely, could decrease the amount of additional information and the changes in management generated by TCD. There were patients that were treated according to the CLOTBUST protocol and had additional monitoring during diagnostic TCD, which probably produced bias towards more information and changes in management.

Conclusions

In patients with acute stroke and an imaging protocol consisting of noncontrast CT, intracranial CTA and DWI, TCD can generate additional information in a number of patients, especially in those with arterial occlusions, and may promote changes in the management of some of them.

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