Transcranial Doppler as a Predictor of Ischemic Events in Vertebral Artery Dissection

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ABSTRACT

BACKGROUND AND PURPOSE: **Transcranial Doppler (TCD) helps identify patients with carotid dissections at risk of ischemic events (IEs). There is paucity of data identifying independent predictors of IE in vertebral arterial dissection (VAD). We sought to investigate the clinical and ultrasound predictors of IE.**

METHODS: **Patients with VAD admitted between June 2017 and February 2020 were evaluated clinically and with TCD; sonographic curves, microembolic signals (MES), and the breath-holding index (BHI) test were applied. Covariates found on univariate screen ($P < .25$) were included in a multivariable linear regression to identify independent predictors of IEs.**

RESULTS: **Of 88 patients with 100 VAD, 75 (85.2%) were females with a mean age 37.9 ± 7.5 years. All patients received antiplatelet treatment. TCD monitoring lasted an average of 21 ± 2.1 minutes. TCD was abnormal in 23 cases (26.1%); 21 patients had abnormal sonographic curves in the vertebral/basilar arteries, while in 4 cases, MES were present and in 5 (4.5%), BHI was abnormal. None of the patients with a normal TCD had an IE. Six strokes occurred during follow up. On univariate analysis, male sex, diabetes, dyslipidemia, a previous myocardial infarct, migraine, time of consultation to the ER, bilateral VAD, MES, BHI abnormalities, post stenotic flow in the basilar artery (PFB), and basilar/vertebral velocities were significantly associated with the risk of IEs. In the multivariate analysis, only the presence of PFB was a significant predictor of IE (OR: 68.6, 95% CI 5-937, <.001).**

CONCLUSIONS: **TCD in VAD predicts patients at high risk of IE.**

Keywords: Ultrasound, transcranial Doppler ultrasound, cervical artery dissection, stroke.

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Introduction

Spontaneous cervical arterial dissection is a common cause of stroke in young adults. This condition can present with major recurrent strokes or with only minor symptoms, such as unilateral cervical pain.[1,2]

Transcranial Doppler ultrasonography (TCD) has been shown to be able to identify patients with carotid artery dissection (CAD) that are at high risk of suffering strokes, by detecting those with active microembolism signal (MES) and/or hemodynamic failure, both well-known mechanisms resulting

in cerebral ischemia.[3-5] Analogous data pertaining to vertebral arterial dissection (VAD) are unknown and represent a significant knowledge gap.[6]

In this study, our primary aim was to evaluate the clinical features and abnormalities detected with TCD as potential predictors of the development of ischemic events (IEs) in patients arriving at the emergency room (ER) with spontaneous VAD.

Methods

At our center, if a patient arrives with intense neck pain and/or headache, which is considered different from earlier episodes and that does not respond to analgesics, the neurologist on call evaluates the patient for possible carotid artery or vertebral artery dissection. The following data are obtained: gender age, previous history of hypertension, diabetes, dyslipidemia, heart disease, smoking, migraine, and duration of symptoms (cervical pain, and/or headache, cranial nerve palsy, tinnitus, and Transient ischemic attack (TIA)/stroke). For patients who arrive with clinical symptoms of an acute stroke, neurology evaluation occurs within 15 minutes of presentation. Blood samples are obtained in both groups of patients, following the clinical evaluation, and an ECG is performed. All patients are evaluated with a neuroimaging protocol previously described consisting of a noncontrast brain tomography (CT), a computed tomographic angiography (CTA) of the cervical and intracranial arteries, and a diffusion weighted magnetic resonance imaging study.[7]

VAD is defined as any vertebral artery mural hematoma, aneurysmal dilation, long tapering stenosis, intimal flaps, double lumen, and/or luminal occlusion.[8] If deemed necessary, an MR angiography with cervical MRI T1 fat suppression or conventional angiography images is performed.

VAD is categorized as spontaneous when occurring in the absence of any trauma. Both vertebral arteries are evaluated to determine if the VAD is unilateral or bilateral. The degree of stenosis of the affected artery is calculated by comparing it to a normal segment of the same artery.

Patients are hospitalized in the Stroke Unit where they are treated with a daily dose of 100 mg of aspirin and pain therapy as needed. Patients are evaluated with TCD as soon as possible after admission by experienced neurosonographers using a 2-MHz TCD (PMD-150 Spencer Technologies, Seattle, WA), applying a protocol based on criteria of the American Society of Neuroimaging. Flow velocities and pulsatility index (PI) for both vertebral and basilar arteries are recorded. The basilar artery is then monitored for microembolism signals for a minimum of 20 minutes at a depth of 80-100 mm using a hand-held TCD probe through the foraminal window. Microembolism is considered present when signals are consistent with the International Committee on Microembolus guidelines.[9] The results of MES monitoring are counted online, by the specialist on call. Cerebral vasoreactivity is evaluated in the basilar artery using the breath-holding index (BHI) with the patient calm and resting in a supine position; if the patient is unable to hold his/her breath long enough, a second attempt is made 5 minutes later. Impaired vasomotor reactivity is defined as a BHI value $<.69$.[10]

TCD is considered abnormal in the presence of abnormal ultrasonic curves (TIBI 0-4) in one of the three evaluated arteries, presence of MES on the TCD monitoring, or abnormalities in the BHI.[11] Special attention is focused on the presence of a basilar artery with delayed systolic flow acceleration (flattening of the systolic complex with the arrival of maximum frequencies in late systole) and with a PI value $\leq .6$ (basilar artery with post stenotic curve). The specialist performing the TCD was blinded to the conduct of this study.

All patients participating in this study were followed for 90 days, with either face-to-face interviews or by phone. An IE was defined as the appearance of brain focal symptoms in the posterior circulation, lasting longer than 24 hours, with a CT and/or diffusion-weighted imaging (DWI) image compatible with brain ischemia within 90 days of the patient's arrival at the ER. The functional status of stroke patients was assessed by Rankin Stroke Scale (mRS) at 3 months.

Patients were included in the RECCA and DISSECAS registers that are approved by the Ethics Committee of Universidad del Desarrollo, Clínica Alemana de Santiago, and the patients or their relatives provided written informed consent in all cases.

Statistical Analysis

Continuous variables were described using means and standard deviations, while categorical variables were described using frequencies and proportions. An abnormal TCD was defined by the presence of any of the following abnormalities: presence of MES, an abnormal autoregulation test, and abnormal curves in the vertebral or basilar arteries, the presence of a poststenotic curve in the basilar artery, MES or abnormal BHI. A univariate screen was performed using *t*-test for continuous variables and Chi-square for categorical variables; covariates with $P < .25$ were included in a multivariable analysis. This value was used instead of the more classic $P < .05$, because this latter often fails to identify variables known to be important and also has the disadvantage of including variables that could be of questionable importance.

In the multivariable analysis, variables with a significant level of 5% and a coefficient level interval of 95% were considered as significant.[12,13]

All data analyses were performed using STATA version 13.0.

Results

Between June 2017 and February 2020, 93 patients with VAD were evaluated at our center. Of these, 5 patients were excluded (2 were not hospitalized, 2 did not tolerate TCD monitoring, and 1 had a devastating stroke with severe clinical deficit requiring immediate basilar artery thrombectomy). Of the remaining 88 patients comprising the study cohort, 75 (85.2%) were women, mean age was 37.9 ± 7.5 years, 76 had a unilateral VAD, and 12 had bilateral VAD. One patient also experienced bilateral carotid dissections.

Clinical characteristics of the patients included are shown in Table 1.

In 42 (47.7%) patients, the CTA was complemented in the first 48 hours with MR angiography with cervical MRI T1 fat suppression and in 4 cases (4.4%), a conventional angiography was also performed. At the time of TCD, 87 patients were being treated with aspirin and one with clopidogrel due to allergic reactions with aspirin. TCD monitoring was performed in the basilar artery through the transforaminal window at an average depth of 85 mm $\pm$ 3.1. The procedure lasted a mean 21

Table 1. Baseline Characteristics of the Study Sample

Variables	Number
Patients	88
Mean age (years)	37.9 ± 7.6
Female sex (%)	75 (85.2%)
Hypertension (%)	6 (6.8%)
Diabetes mellitus (%)	3 (3.4%)
Hypercholesterolemia (%)	8 (9%)
Tobacco (%)	13 (14.7%)
Ischemic heart disease (%)	2 (2.2%)
Migraine (%)	37 (42%)
Mean time from symptom onset to	
ER minutes (SD)	6,583 ± 7,230
Days	4.5 ± 5
Symptoms	
Neck pain (*n*)	60
Headache and or neck pain (*n*)	5
Headache (*n*)	4
Stroke (*n*)	16
Transient ischemic attack (*n*)	3
Single vertebral dissection (%)	76 (86.4%)
Bilateral vertebral dissection (%)	12 (13.6%)
Right vertebral dissection (*n*)	49
Left vertebral dissection (*n*)	51
Vertebral dissected segment	
VS1	17
VS2	49
VS3	28
VS4	6
Percentage of right vertebral stenosis (%)	57.3 ± 18.1
Percentage of left vertebral stenosis (%)	59.1 ± 19.8
Mean time from symptom onset to	
TCD minutes	7,046 ± 7,196
Days	4.89 ± 5

All the data represent mean ± standard deviation unless otherwise indicated. ER, emergency room; *n*, number; VS, vertebral segment; TCD, transcranial Doppler.

Table 2. Abnormalities Found in Transcranial Doppler of Patients with Vertebral Dissections

Findings	Number of Findings
Vertebral abnormal flow signals	
TIBI 0-1 signals	5
TIBI 2-3 signals	15
TIBI 4	1
Basilar abnormal flow signals	
Post stenotic flow	5
Basilar TIBI 4 flow	1
Microembolic signals	4
Basilar abnormal Breath hold index	5

TIBI, thrombolysis in brain ischemia.

± 2.1 minutes (range 19-27 minutes). The result of this evaluation was considered normal in 65 patients and none of them developed an IE. Twenty-three patients had an abnormal TCD evaluation. Table 2 shows the abnormalities detected. Six patients had multiple abnormal findings: MES were detected in the basilar artery of 4 patients (4.5%) at the time of the examination and these ranged from 1 to 4 microsignals. BHI in the basilar artery was abnormal in 5 cases (5.6%).

In the 23 patients with abnormal TCD, 6 cases (26%) suffered an IE during follow-up; two of these events occurred within the 24 hours of their admission. Three events developed between days 1 and 3 of hospitalization, and 1 patient had an IE on day 14 while at home (however, no changes in the condition of his vertebral arteries was found on a repeated CTA). The six IEs correspond to one case where the patient suffered from a basilar occlusion that was treated with mechanical thrombectomy and whose 3 month mRS was 4. Two other patients had multiple strokes in the posterior circulation and their mRS being in mRS 3 at 3 months. The remaining 3 patients suffered cerebellar strokes and their mRS were 0, 1, and 2 at 3 months. Figure 1A-I illustrates one of these cases.

The results of the univariate analysis investigating the association of IE with clinical and ultrasonographic variables are shown in Tables 3 and 4. In this analysis, male sex ($P = .02$), diabetes mellitus ($P = .11$), hypercholesterolemia ($P = .05$), ischemic heart disease ($P = .06$), and a previous history of migraine ($P = .24$), ischemic brain symptoms ($P < .05$), time of consultation to the ER ($P = .14$), a right ($P = .24$) and left ($P < .05$) VAD, the degree of stenosis of the right VAD ($P = .146$) and left VAD ($P = .23$), and multiple VAD ($P = .168$) met univariate screen test. The existence of MES during basilar monitoring ($P < .05$), basilar flow velocity (cm/second) ($P = .18$), right vertebral velocity (cm/second) ($P < .05$), left vertebral velocity (cm/second) ($P < .05$), post stenotic basilar signal ($P < .000$), and abnormal BHI ($P < .001$) were also variables that reached significance. On multivariate analysis, the only independent determinant of IEs post VAD was poststenotic basilar flow signal (OR: 68.6, 95% CI 5-937, <.001).

Discussion

This study is the first to identify clinical and TCD criteria that independently predict IE in patients with VAD. In CAD, TCD has been able to identify patients at high risk of a stroke even if they seek care for symptoms that do not appear dangerous initially, such as headache or cervical pain.[5] The presence of MES in the territory of the middle cerebral artery,[3-5] specially if associated with abnormalities in the BHI,[5] carries the higher risk as it represents the simultaneous existence of arterial-arterial embolism with occlusion of proximal and distal cerebral arterial branches causing decreases of perfusion in border-zone arterial regions and reductions of the clearance of the clots migrating to distal arterial branches.[14]

Our first findings suggest that patients with a normal TCD evaluation (normal vertebral and basilar spectral curves, no active MES, and normal BHI) have a low risk of IE. TCD has moderate sensitivity, but high specificity for detecting stenosis in both vertebral and basilar arteries when compared to angio-DSA and CTA,[15,16] this means that TCD probably detects the most critical arterial stenosis and misses those stenosis that are not relevant and that could be easily compensated by the network of collaterals of the posterior circulation. A normal evaluation also implies the absence of arterial-arterial embolism represented by the existence of MES, a well-known mechanism of ischemia in CAD[3-5] and adequate autoregulation and collateral flow represented by a normal BHI.[5] A second important finding of our experience is that 1 in 4 patients who had an abnormal TCD will eventually develop a stroke. In this group of patients, the only variable associated with the risk of IE was a post stenotic basilar artery flow signal. This finding demonstrates the inability of both vertebral arteries to support an adequate blood flow to the basilar artery in the presence of

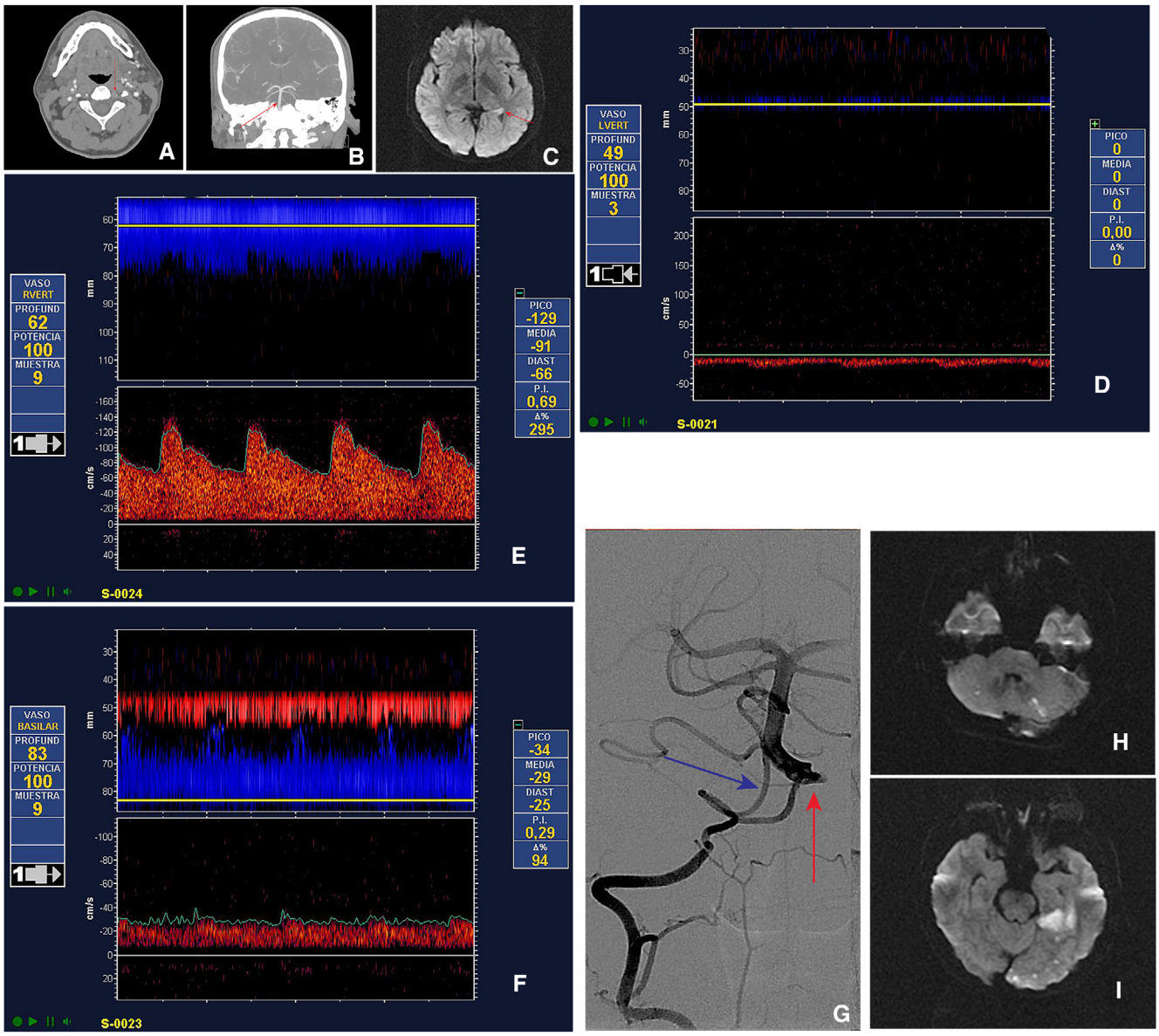

Fig 1. (A-I) A 38-year-old male, with 20 hours of intense cervical pain. Twelve hours before arrival to the emergency room (ER), he developed mild aphasia, dysarthria, and right side numbness. On arrival to the ER, his National institute of Health Stroke Scale (NIHSS) is 5.
(A) CTA demonstrated a left vertebral dissection (red arrow)
(B) CTA shows a normal and well-contrasted basilar artery (red arrow).
(C) DWI carried out a few minutes later shows a small left posterior cerebral artery stroke (red arrow).
(D)TCD 20 minutes later in the ER demonstrated an occlusion (thrombolysis in brain ischemia flow grade of 2 flow) of the left vertebral artery.
(E) TCD of the right vertebral artery demonstrating elevated velocity in all its extension compatible with collateral flow.
(F) TCD of basilar artery demonstrated a post stenotic flow signal, with a very low PI. The breath hold index was abnormal with almost no increases in velocities after 30 seconds of breath holding, from a basal velocity of 28 to 29 cm/second; the BHI value was under .69. Embolization was detected during this test.
(G) Angiography 1 hour after the TCD demonstrated left vertebral occlusion (red arrow) with basilar filling from a nondominant right vertebral artery (blue arrow), basilar artery is well contrasted. No endovascular treatment was done, due a high risk of a massive basilar embolism according to the neuroradiologist.
(H and I). The patient developed abrupt moderate aphasia, right hemianopsia, and right hemiparesis, with important vomiting NIHSS increased to 14 points. DWI demonstrated multiple strokes in the posterior circulation and a new CTA was not different from the one from the images A and B.
[Color figure can be viewed at wileyonlinelibrary.com]

a proximal stenosis or occlusion. The absence of an association between MES and IE could be due to the low frequency of these findings in our patients. This may be secondary to the low incidence of patients admitted with a stroke in our study population, whereas in studies of CAD, patients with stroke more frequently suffered MES.[4] Another potential explanation could be late consultations by our patients compared to those in studies of CAD.[5] Finally, our patients were already under treatment with antiplatelets drugs and had a shorter MES monitoring than those conducted in studies of CAD,[4] but an

Table 3. Univariate Analysis of Clinical Predictors of Ischemic Events in Patients with Vertebral Dissections

Variables	Patients VAD No IE	Patients VAD With IE	*P*
Number of cases	82	6	
Mean age (years)	37.7 ± 78	41.1	.28
Sex (male, *n*)	10	3	.02
Hypertension (*n*)	5	1	.34
Diabetes mellitus (*n*)	2	1	.11
Hypercholesterolemia (*n*)	6	2	.05
Tobacco (*n*)	12	1	.89
Ischemic heart disease (*n*)	1	1	.06
Migraine (*n*)	33	4	.24
Consulting symptoms			.005
Transient ischemic attack or stroke (*n*)	14	5	
Headache and or neck pain (*n*)	68	1	
Mean time from symptom onset to			
ER minutes	6,879.5 ± 7,344	2,544 ± 3,844	.149
Days	4.7 days	3.6 days	
Right vertebral affected CTA	48	2	.24
Left vertebral affected CTA	44	6	.001
Vertebral segment compromised CTA			.26
VS1	14	1	
VS2	47	6	
VS3	24	1	
VS4	6	0	
Degree of vertebral stenosis CTA (%)			
Right vertebral artery			
Mean	56 ± 17	80 ± 2	.146
Median	50	80	
Left vertebral artery			
Mean	57 ± 19	68 ± 24	.23
Median	50	50	
Multiple vertebral arterial dissections	10	2	.168

All the data represent mean ± standard deviation unless otherwise indicated.
VAD, vertebral arterial dissection; IE, ischemic event; *n*, number, ER, emergency room; CTA, computed tomographic angiography; VS, vertebral segment.

Table 4. Univariate Analysis of Ultrasonographic Predictors of Ischemic Events in Patients with Vertebral Dissections

Variables	Patients VAD No IE	Patients VAD With IE	*P*
Number of cases	82	6	
Mean time from symptom onset to TCD, minutes	7,352 ± 7,293	2,857 ± 4,175	
TCD evaluation			.02
		0	
Normal	65	0	
Abnormal TCD	17	6	NV
			.000
Presence of MES	2	2	.008
Basilar artery velocity cm/second	44.2 ± 7.8	49 ± 24.2	.185
Basilar PI	.89 ± .9	.75 ± .49	.59
Right vertebral artery velocity cm/second	36.6 ± 12.9	63.8 ± 41.9	.007
Right vertebral PI	.8 ± .36	.73 ± .29	.66
Left vertebral artery velocity cm/second	36.8 ± 11.8	21.1 ± 11.6	.005
Left vertebral artery PI	.79 ± .34	1 ± 1	.26
Abnormal breath hold index	2	3	.001
Post stenotic basilar signal	2	3	.000

All the data represent mean ± standard deviation unless otherwise indicated.
VAD, vertebral arterial dissection; IE, ischemic event; TCD, transcranial Doppler; NV, without variability; MES, microembolic signals; PI, pulsatility index.

experience with 11 patients also found a small percentage of MES in patients with VAD, even with longer monitoring that ours.[6]

The absence of abnormalities of autoregulation as a risk factor for strokes in our patients with VAD has been previously demonstrated in CAD where the BHI was abnormal in almost 1 out of every 3 patients, but most of them did not suffer an IE.[5] In our study, BHI abnormalities were observed in fewer than 5% of the cases, and this could be due to the fact that the posterior circulation has extensive collaterals from the cerebellar arteries and even from the occipital arteries, but also maybe the BHI is not the optimal method to evaluate autoregulation on this type

of patients as only small studies demonstrated its validity.[17] The coexistence of cases with both MES and abnormities of BHI was even less frequent and the interactions between these two aspects could not be analyzed properly.

TCD could identify in patients affected by VAD those with low risk of stroke, represented by those who had normal ultrasound curves in both the vertebral and basilar arteries, and who also had a normal 20 minutes monitoring for MES and normal BHI. On the other hand, there is a high-risk group of patients with VAD that probably requires more aggressive treatments, including dual antiplatelet drugs or anticoagulation,[18] Tirofibam,[19] or even stenting in some cases.[20]

This study has several limitations. It represents the experience of a single center. The unusually high frequency of patients presenting with isolated neck pain in our series may reflect a recruitment bias because we carry out imaging of the cervical arteries in any patient with recent pain and/or headache of unknown cause. TCD monitoring is difficult to be performed for longer than 20 minutes through the transforaminal window due to the use of a hand-held probe technique. It is possible that patients could benefit from longer MES monitoring and that BHI test in the basilar artery could not be the most appropriate method to evaluate autoregulation in the posterior circulation. We did not measure CO_2 during the BHI. We did not have any case of subarachnoid hemorrhage during the study period due to VAD, and maybe our findings could not extrapolate to this particular group of patients. Our results may not be applicable to other ultrasound techniques, such as Duplex sonography, which is capable of providing information about the vessel wall of the dissected artery, which may be of equal or greater relevance than the TCD findings. Finally, less than 50% of our patients were evaluated by MRA with cervical MRI T1 fat suppression, which is able to demonstrate the wall hematoma of a cervical arterial dissection due to the change of hemoglobin to methemoglobin. This is easy to diagnose by a radiologist or a neurologist, whereas CTA is more limited.[21,22]

Nonetheless, this study addresses an important knowledge gap and adds to our understanding of how TCD findings can be interpreted and predictive in the setting of VAD. The study is prospective and relatively large compared to the previous work.

In conclusion, TCD is a useful tool in patients presenting with VAD and can help to identify a high-risk group of patients with that likely benefit from more aggressive treatments and are represented by those with abnormal TCD evaluations, especially if they had poststenotic flow in the basilar artery.

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