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Technical Note

Role of Advanced Hemodynamic Ultrasound Evaluation in the Differential Diagnosis of Middle Cerebral Artery Stenosis: Introducing Morphological Criteria

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Objective: The aim of the work described here was to determine the possible impact of the new technique advanced hemodynamic ultrasound evaluation (AHUSE) in identification of severe intracranial stenosis. Transcranial Doppler (TCD) and transcranial color-coded Doppler (TCCD) provide reliable velocimetric data, the indirect analysis of which allows us to obtain information on the patency of vessels and assumed stenosis range. However, very tight stenoses (>95%) cannot be detected with velocimetric criteria because of spectrum drops and the absence of high velocities, so that the right curve of the Spencer equation cannot be solved. Likewise, high velocities are not detected when analyzing morphologically long stenosis. Furthermore, the current classifications based on velocimetric criteria do not provide any categorization on stenoses with multiple acceleration points (MAPs).
Methods: With this Technical Note we aim to introduce, in addition to velocimetric criteria, more morphological criteria based on TCCD with the algorithm of AHUSE to optimize the characterization of intracranial stenosis (IS). TCCD-AHUSE relies on intensity-based next-generation techniques and can be used to identify IS with MAPs and simultaneously perform a morphological assessment of the stenosis length.
Results: We introduce a new technical ultrasound (U) approach that we tested in a sample of four different types of stenoses combining velocimetric data and AHUSE using Esaote Microvascularization (MicroV) technique to the M1 tract of the middle cerebral artery (MCA).
Conclusion: The authors believe that a multiparametric evaluation is more sensitive and supports the clinician by introducing the morphological concept, not just the velocimetric concept, to differentiate the IS pattern of MCA. The potential for developing a diagnostic/prognostic algorithm is discussed.

Introduction

In relation to the high rate of ischemic events, 15%–38% of which recur within 2 y from first event, and their strong association with intracranial stenosis (IS) ≥70%, the velocimetric assessment of IS has been the subject of numerous studies, initially using transcranial Doppler (TCD) and, subsequently, transcranial color-coded Doppler (TCCD) ultrasound [1–5].

In the absence of an optimized standardization of flow rates, the IS classification remains a challenge. The velocimetric assessment of stenosis of ≤50% and ≥70% was introduced with TCD [6–8]. The velocimetric data were further improved by introducing ratios [7,8]. Through the

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improvement of these criteria, TCCD has played a fundamental role in increasing the accuracy of the angle [9,10], allowing for better reproducibility of the data, particularly with respect to tortuous vessels.

The velocimetric criteria for IS obtained with TCCD have been subject to continuous revisions over time, initially with a cutoff of 50% [11] and then with categorical criteria of <50% (mild stenosis), 50%–69% (moderate stenosis) and ≥70% (severe stenosis) [12,13].

Although the velocimetric spectrum is a strong indicator for the diagnosis of IS, to date a definite set of standardized criteria based only on velocity is still not available [14,15]; diffuse multiple-point stenoses featuring dampened and blunted signals and minimal flow are difficult patterns of IS to investigate with velocimetric only [16,17]. Interestingly, some reports have emphasized not only the degree but also the morphological characterization of the stenosis, such as a long stenosis of ≥50% in the M1 tract or a diffuse stenosis extending beyond the M1 tract [17]. Long stenoses are associated with a higher incidence of ischemic events than point stenoses, as well as more frequent indications for stent treatment [18–20].

Furthermore, there are limitations associated with the color technique, such as the depth of the circle of Willis, which requires low-frequency probes, negatively affecting the morphological resolution of vascular imaging. In addition, the need to analyze slow flows in MCA stenosis with concomitant stenosis outside the M1 segment, especially in the distal M2 branches, or in long stenoses requires a low pulse repetition frequency (PRF), thus increasing the risk of aliasing that compromises examination quality. Finally, the velocimetric criteria suggested in the literature cannot be considered completely valid, because the spectral measurement could be influenced by many factors, such as incorrect angles of insonation, arterial curves, morphological abnormalities upstream or downstream of the analyzed tract, heart pump failure and arrhythmias [21]. Also, stenoses >95% have a sudden decrease in velocity, so the well-known Spencer equation is no longer satisfied for high velocities compared with severe stenosis [22,23].

Power Doppler (PD) is not based on the degree of Doppler shift (which is used for color Doppler images) but on the intensity [24] calculated from the amplitudes of frequency-shifted echoes of the ultrasound (US) return signal and overcomes some of the problems associated with the color technique.

The resulting image is not dependent on flow velocity, direction or angle of insonation, is free of aliasing risk and exhibits greater sensitivity even when evaluating low flows [25].

The algorithm generates a parameter that corresponds to the Doppler amplitude and is analyzed by different gray scales that contribute to a high sensitivity for identifying the vessel lumen, and a vessel "continuity" by using high persistence levels, in other words, in assessing the morphology of intracranial vessels [26]. One development in power techniques that is most suitable for studying the cerebral vessels is the TCCD Advanced Hemodynamic Ultrasound Evaluation (TCCD-AHUSE) [27,28].

The aim of the work described here was to highlight the characteristics of TCCD-AHUSE technique and its potential application in grading IS.

Methods

Color flow mode (CFM) techniques and pulse wave Doppler (PWD) methods have filters that eliminate background noise. These filters have a dual function: (i) to eliminate noise and tissue movement artifacts, and (ii) to reconstruct the image through the averaging/interpolation of valid signal information. Image smoothing, color overflow and overestimation of the vessel profile are the results of this type of processing. MicroV has characteristic technical features that differentiate it from color Doppler or power Doppler, such as anticlutter filtering and high signal/noise ratio. The latter allows separation of the blood flow/vessel wall, thus leading to the detection of good low-velocity signals, with an excellent spatial definition, even at deep levels in the brain [27].

The difference between the techniques CFM, PD and MicroV is the degree of processing. CFM requires a higher degree of processing because of the greater involvement of noise and because it overflows more frequently. PD requires a lower degree because the useful signal is amplified (A2) and differentiated from noise. MicroV requires a very low degree of processing because the signal-to-noise ratio is better; in practice, MicroV is more sensitive.

Unlike in TSA, in TCCD, there is the aggravating factor of low frequency; that is, transmitting with a low Doppler frequency (to increase penetration) reduces the detail on the signal. Because of this, filters are required to make a greater contribution in cleaning the signal, resulting in greater smoothing and increased overflow effect. MicroV is the technique that reduces the negative action of filters to a minimum.

The problem with TCCD investigations is the background noise (*i.e.,* from movement of the wall of parenchymal artifacts), only partially solved by adding wall filters. To date, this issue has prevented the use of vessel morphology as an evaluation criterion for IS. The algorithm on which TCCD-AHUSE is based separates flow signals from background noises (Fig. 1), leading to better space resolution when compared with all other TCCD techniques currently used (particularly color methods), as it maintains the signal even at very low flow and limits hyperechoic structure interference. If slender blood vessels and communicating arteries or slender but more superficial M2 or pre-insular vessels are insonated as deep as P2–P3 using the color technique, the PRF needs to be lowered, and aliasing occurs. As a consequence, a vessel can only be analyzed from a spectral point of view. Conversely, the TCCD-AHUSE technique enables the performance of a morphological assessment (Fig. 1) and is suitable both for diagnosing and for monitoring IS because it

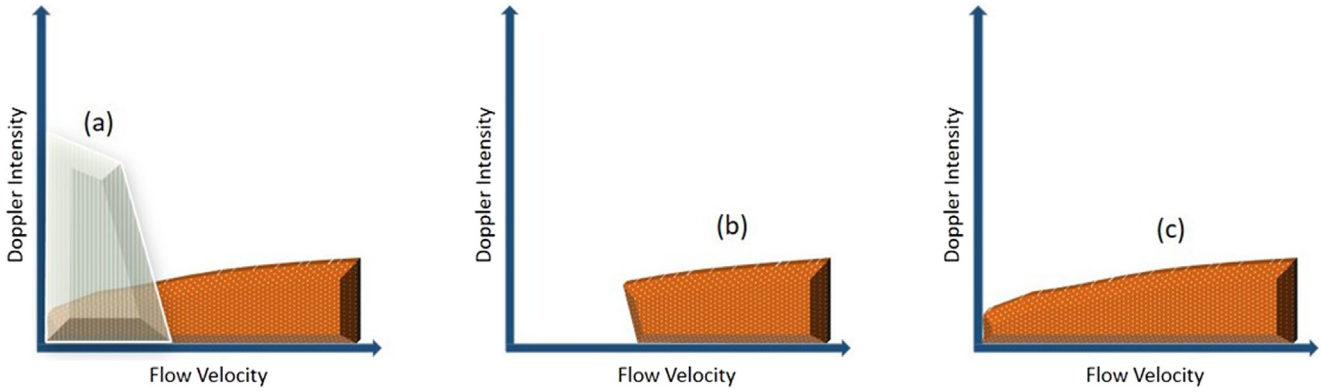

Figure 1. (a) Tissue motion artifact. (b)Vessel flow signal filtered by a conventional Doppler based-algorithm: the conventional filter cut artifacts and the very low flow signals. (c) MicroV algorithm cuts the artifacts but retains the very low flow signals.

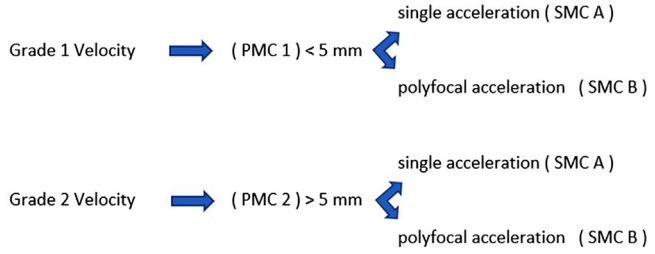

Figure 2. Primary morphological criterion (PMC) and secondary morphological criterion (SMC).

enables better analysis of vessels, minimizing or even excluding CFM vessel-profile overstimation [27,28].

Procedures

The characterization of IS was performed with a three-step assessment as illustrated in Figure 2. In step 1, we measured the velocity of the spectrum flow: peak systolic velocity (PSV), end-diastolic velocity (EDV) and PSV ratios between the stenosis site and its distal segment (*i.e.,* whether the velocity was in line with IS stenosis) [11,12]. In step 2, we assessed the length of the stenosis, that is, whether it was ≤5 mm or >5mm, as the primary morphological criterion (PMC). In step 3, we analyzed the presence of single versus multiple sites of acceleration in the trait of the artery under investigation, indicating irregularity of the vessel wall, as a secondary morphological criterion (SMC). Information from the three-step assessment was then combined into a prognostic risk [18,20,29,30].

In the present work, TCCD and TCCD-AHUSE images were obtained with MyLab 9 eXP, software MicroV (Esaote S.p.A., Genoa, Italy), a machine with transducer multifrequency P 1–5 phased array (wideband electronic single-crystal array) to obtain B-mode (1–5 MHz and a field of view of 16°–93° and maximum depth of 356 mm), TCCD (high penetration, 1.5 MHz), MicroV (1.7–2.0–2.5–3.1 MHz) ultrasound examinations. All examiners were expert level.

Ultrasonography and CTA

Transcranial color-coded Doppler and computed tomographic angiography (CTA) are the techniques most widely used in the emergency setting in patients with acute cerebrovascular events [12]. In the evaluation of intracranial vessels, we analyzed the brain CTA of patients to quantify the degree of MCA stenosis.

Multiplanar reformations (MPRs) and 3-D including orthogonal reconstructions [31] were used to study the major axis of the vessel at the point of most severe stenosis using North American Symptomatic

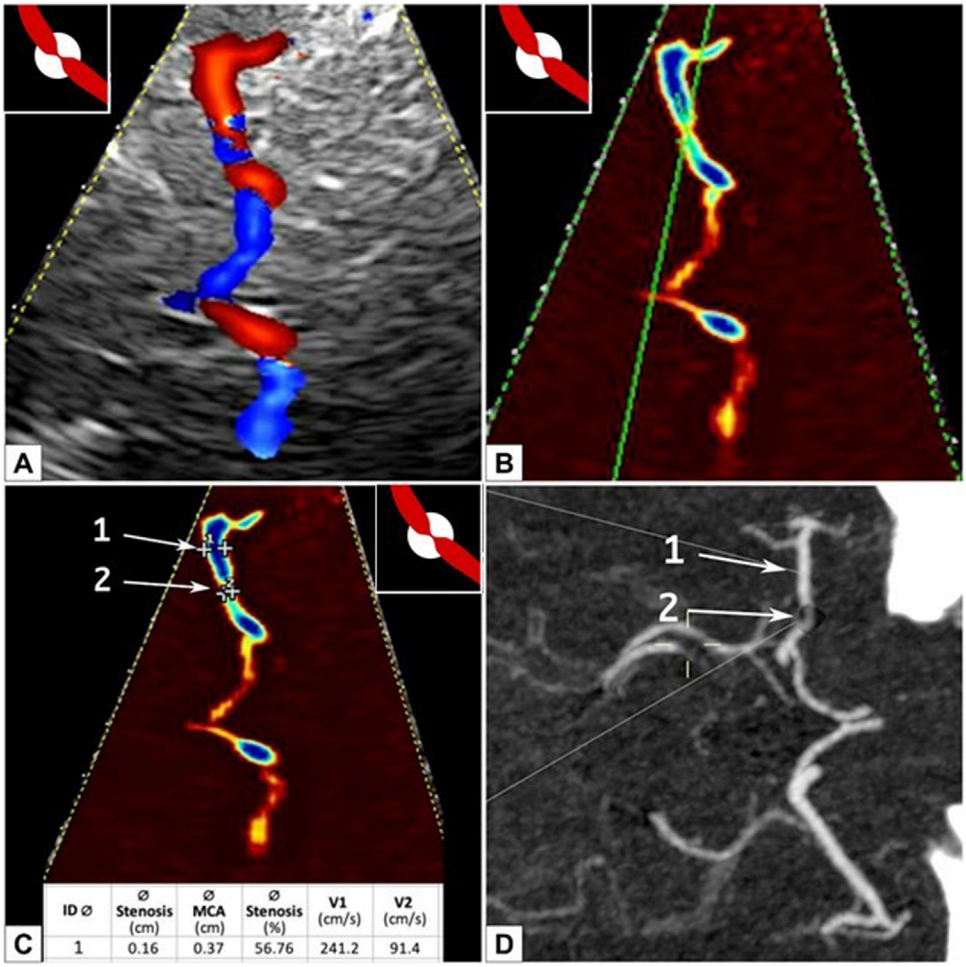

Figure 3. This stenosis characterizes the type: grade 1, primary morphological criterion (PMC) 1, secondary morphological criterion (SMC) A (logo of this type of stenosis at the top of the figure). (a) Color Doppler image: The aliasing color phenomenon is evident in the middle distal tract of M1. (b) Study with MicroV technique. (c) Percentage of morphologic stenosis (distal middle cerebral artery [MCA] is 3.7 mm [*arrow 1*] and stenosis M1 is 1.6 mm [*arrow 2*]) was calculated, applying NASCET criteria with the MicroV modality, as 56.76%, and in the table (lower right) are the corresponding velocities. (d) Computed tomographic angiography: The diameter of the focal stenosis is 1.1 mm (*arrow 2*) and the downstream diameter is 2.5 mm (*arrow 1*), so the percentage stenosis is 56%.

Carotid Endarterectomy Trial (NASCET) [32] criteria with both TCCD-AHUSE (MicroV) and CTA.

After 1 to 14 d, CTA [33] was used to quantify the percentage of MCA stenosis [34]. Only stenoses in the straight tract pre-bifurcation (M1) of the MCA were considered for performing a proper angle-corrected measurement in the TCCD examination.

Thanks to the high morphologic resolution of MicroV mode, we applied NASCET criteria [32,35] as for the neuroradiological examinations [33,34] for ultrasound measurement of degree of stenosis. Exclusion criteria were a poor acoustic window, severe unilateral or bilateral stenosis of the internal carotid artery and atrial fibrillation.

The study was approved by the local ethics committee, and informed consent was obtained from all study participants.

All CTA raters were expert level and blinded to the TCCD-AHUSE results.

Results

We applied the three-step TCCD-AHUSE (MicroV) technique to four intracranial stenoses and found four morphological scenarios, as illustrated in Figure 2, based on the IS length and the presence of single versus multiple stenosis.

In vessels with multiple points of stenosis, the MicroV technique allowed us to guide the gate in the point of major stenosis for a much more accurate velocimetric analysis, when compared with the color survey.

In all four stenoses studied, there was high concordance with the TCCD study performed using the MicroV technique and CTA. Morphologic assessment was computed by applying NASCET criteria to the MicroV technique and CTA (Figs. 3–6).

Discussion

Appropriate assessment and characterization of IS are crucial in identifying the population at higher risk of ischemic stroke. The severity of IS is a reliable predictor of stroke for both symptomatic and asymptomatic individuals, but the number of recurrences is higher in symptomatic patients [1,36]. Detecting and characterizing IS are pivotal in the prevention and management of ischemic stroke, hence the growing need to identify a standardized method for assessing IS, among a number of existing non-invasive and invasive techniques with variable sensitivity and specificity [37]. There are several mechanisms by which IS can cause a stroke, including *in situ* thrombosis, distal plaque rupture embolism, hemodynamic deterioration downstream of the stenosis and occlusion at the origin of a penetrating vessel [5]. These different etiopathological patterns underlie different morphological characteristics of the plaque [38].

Initially, coronary arteries present plaque growth with outward remodeling of the vessel, whereas in intracranial arteries this situation is of minor impact: 40% coronary versus 6% intracranial [39,40]. We believe that the assessment of IS based only on hemodynamic ultrasound criteria, in which the main parameter is the maximum velocity of the

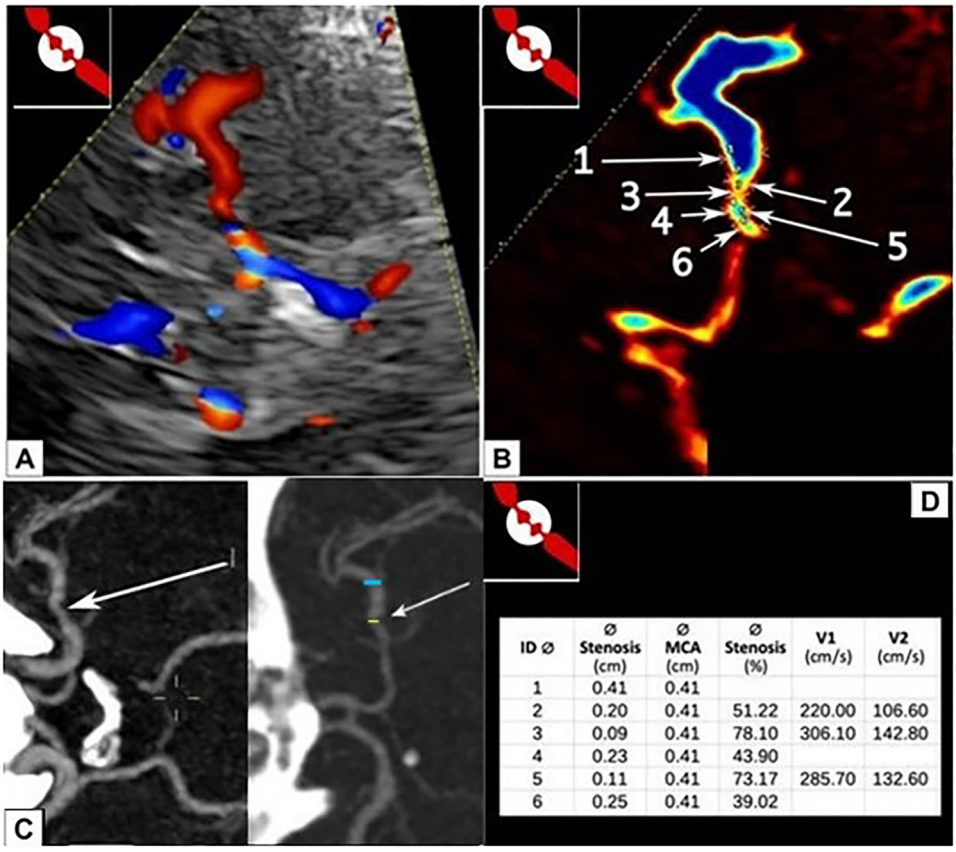

Figure 4. This stenosis characterizes the type: grade 1, primary morphological criterion (PMC) 1, secondary morphological criterion (SMC) B (logo of this type of stenosis at the top of the figure). (a) Color Doppler image: the color aliasing phenomenon in suspected tortuosity of the vessel and the presence of high velocities. (b) MicroV image: multiple stenoses with different percentages of morphological stenosis (*arrows 2–6*) are evident, and the stenoses are <5 mm in length. (c) Corresponding computed tomographic angiography does not reveal the different points of stenosis low level slide, to the left, and up level to the right); the narrowest tract (*yellow line*) of the irregular stenosis of middle cerebral artery (M1) is 1 mm, and the distal tract is 2.4 mm (*blue line*); therefore, the stenosis is 58% and the length is 3.6 mm, less than 5 mm. (d) The table evaluates the accurate velocimetric spectrum as hemodynamic multiple velocimetric acceleration. Transcranial color-coded Doppler: 57.08% (five-point average). CTA: 58.3%. We have a stenosis/distal ratio of 2/2.5, which correlates with 50% to 69% stenosis [13].

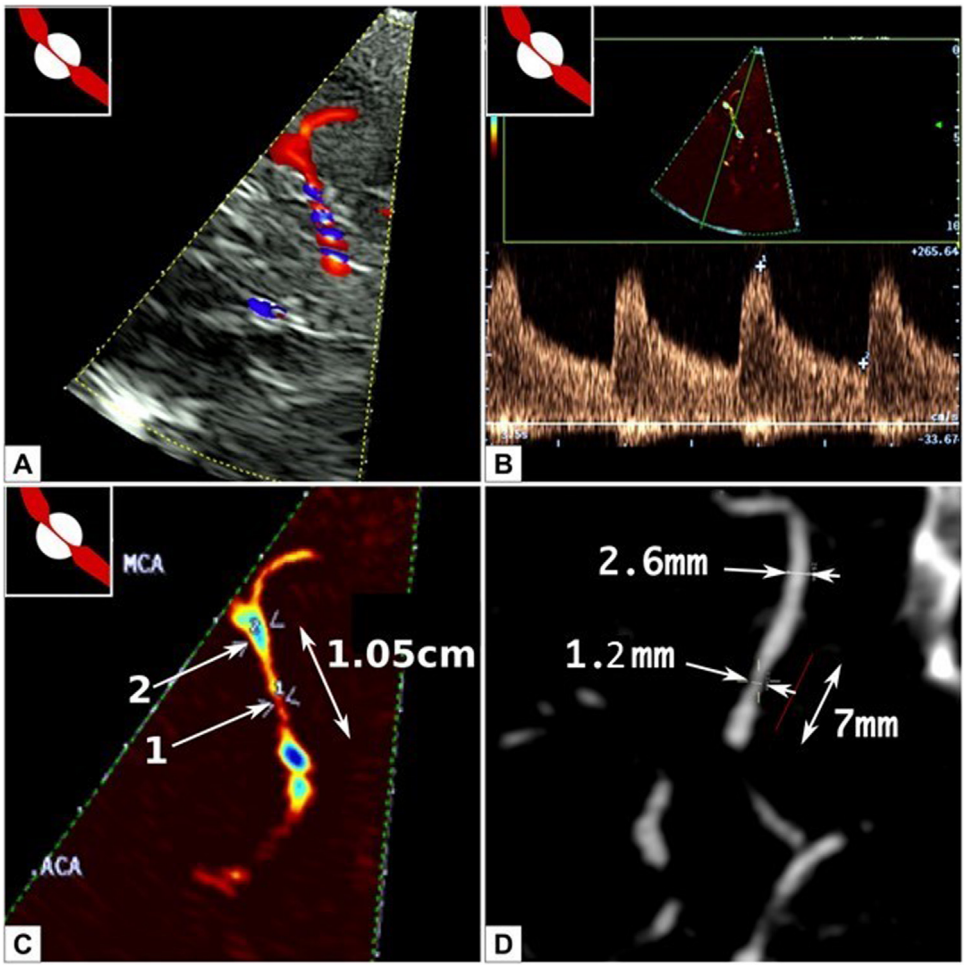

Figure 5. This stenosis characterizes the type: grade 2, primary morphological criterion (PMC) 2, secondary morphological criterion (SMC) A (a logo of this type of stenosis is at the top of the figure). (a) The aliasing phenomenon is serially detectable in the color Doppler image. (b) The spectrum detects high velocity: systolic peak 265 cm/s. (c) Table evaluates: morphologic stenosis percentage calculated in the MicroV modality (54 %); stenosis length >5 mm (10.5 mm) and a regular surface measured in the same MicroV modality. (d) Corresponding CTA

stenosis point, is currently insufficient because of the clinical implications and technical limitations of this approach and the feature of plaque.

Spectral data can be influenced by many factors, such as incorrect angles of insonation, the tortuous nature of intracranial vasculature, morphological abnormalities upstream or downstream of the analyzed vessel, cardiac pump insufficiency and arrhythmias and vessel thinness, all potentially affecting the velocimetric criteria [10]. Furthermore, color technique [28] overestimates vessel diameter because of both background noise and aliasing in stenosis, and this is of less relevance in morphological evaluations.

Another limitation of classifications based on velocity criteria alone is that when evaluating very narrow stenoses characterized by low-velocity spectra, the first criterion, that is, high velocity, is no longer fulfilled, solving the Spencer equation [22,23].

Also, as for long and diffuse stenoses, a dampened or blunted blood flow can be observed instead of an acceleration in systolic velocity. The need to analyze slow flows, especially in distal branches, and the depth of the Willis circle require low PRF, which increases the risks of aliasing and of impairing examination quality.

Morphological imaging has always been considered pivotal in neuroradiological techniques.

However, minimally or non-invasive technologies such as MRA and CTA may have some limitations. MRA does not imply radiation and invasiveness, but it has lower sensitivity than digital subtraction angiography (DSA) and CTA and greater sensitivity to artifacts, with potential overestimation of stenosis. Even with the use of contrast agent, MRA features [41,42] lower levels of accuracy than DSA [30]. High-resolution MRI makes new assessments possible by highlighting a necrotic core in T1-weighted fat-suppressed images and increased focal contrast enhancement, identifying a stenosis with vulnerable plaque with a concomitant site of inflammation [43–45]. CTA has some limitations because it exposes patients to radiation, requires potentially allergenic and nephrotoxic contrast agents, has unsatisfactory resolution power for vessels <0.7 mm in diameter and has reduced accuracy in stenosis quantification for vessels <2 mm in diameter [34] or in the presence of arterial wall calcifications.

Several studies have investigated the concordance between CTA and TCCD, but only by means of color Doppler techniques [46,47], without adopting newest-generation ultrasound systems. A strong correlation between stenoses assessed with TCCD and CTA is reported for severe stenoses with ≥70% occlusion [12].

Transcranial color-coded Doppler and CTA are currently used in clinical practice (the gold standard remains DSA) and have a high sensitivity and positive predictive value (PPV) for stenoses >70%, whereas CTA is used less often than TCCD for smaller stenoses [12,30,34,46,47] (although, currently, there aren't many studies comparing the two methods).

The main advantage of TCCD-AHUSE (MicroV) technology is that it can detect stenoses with higher sensitivity and spatial resolution and, in

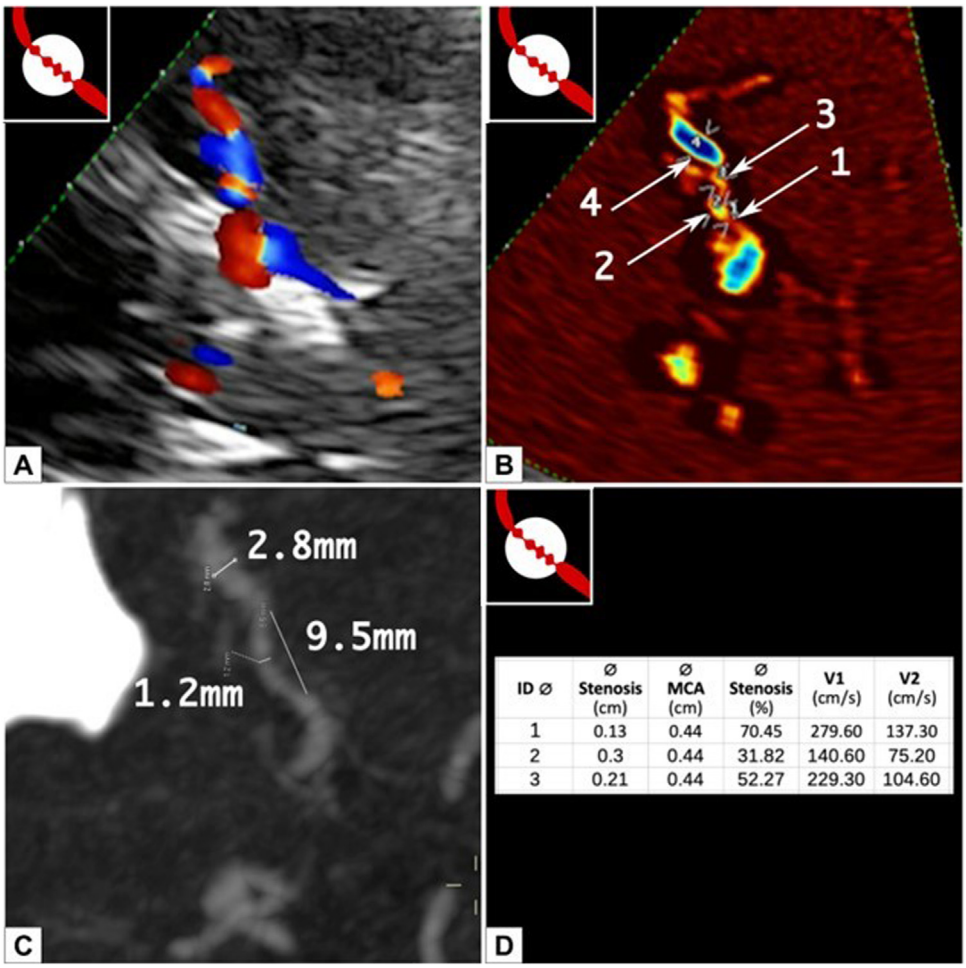

Figure 6. This stenosis characterizes the type: grade 2, primary morphological criterion (PMC) 2, secondary morphological criterion (SMC) B (a logo of this type of stenosis is at the top of the figure). (a) Color Doppler image: the aliasing phenomenon is evident in different parts of the vessel, an expression of a probable tortuous course. (b) MicroV image: irregular lesion, >5 mm in length, with multiple stenoses with an irregular surface. May exhibit several characteristics that can be detected in MicroV as hemodynamic accelerations and/or downstream spectrum falls and correlates with morphological evaluations. (c) Computed tomographic angiography with the *arrow* pointing to the stenosis. The narrowest tract of the irregular stenosis of M1 is 1.2 mm, and that of the distal tract is 2.8 mm; therefore, the percentage stenosis is 58% and the length is 9.5 mm. (d) The diameters at different points of stenosis are calculated, and then the percentage stenosis is obtained with reference to the diameter calculated downstream of the distal tract of the middle cerebral artery; the velocimetric spectrum of a stenosis >5 mm.

combination with velocimetric spectral signal, can improve accuracy [27,28].

MicroV is a power Doppler-based method, so it works on signal intensity and not on velocity and direction like color Doppler with a unique algorithm that works differently from common wall filters.

Evaluations of PSV, EDV and PSV ratios [7,13] between the stenosis site and its distal segment are, however, carried out by applying the power Doppler method, with the aim of combining this analytical reference information with the morphological information of MicroV, which allows us to visualize more precisely the anatomy of the flow; AHUSE is an improvement to be used only in association with the "classic" parameters. This morphological technique allows us to differentiate focal from linear stenoses, to discriminate stenosis length (*i.e.,* >5 mm or <5 mm) and to guide the gate to the point of major stenosis for a much more accurate velocimetric analysis, when compared with the color survey.

To the best of our knowledge, this is the first time TCCD-AHUSE technology has been used for an innovative characterization of IS. We report on four different patterns of IS potentially associated with high cerebrovascular risk and open new perspectives in IS classification. The stratification of IS degree, considering both hemodynamic and morphologic aspects, is of utmost importance not only for diagnostic, but also for therapeutic implications (*e.g.,* best medical therapy vs. endovascular treatment) [19], by virtue of a dynamic process and under, occasionally, unstable conditions. In addition, other findings such as distal microembolic signals (MESs) should be included to appropriately predict IS severity, in the light of their documented negative prognostic role [48].

The combination of high velocities in multiple points and a length >5 mm suggests that the patient is possibly at higher cerebrovascular risk [18,20,29,30].

A limitation of TCCD-AHUSE technology is that by cutting background noise, B-mode assessment cannot be performed simultaneously. Furthermore, the classification we propose may have weaknesses in detecting emboli, which deserves long-lasting monitoring.

Another limitation of concern in very severe stenosis is caused by the reduction in flow volume distally; the vessel collapses and this leads to the calculation of a less severe stenosis according to NASCET criteria. This limitation is already very well recognized on the basis of reports on the grading of carotid stenosis, with the knowledge that internationally all major classifications use NASCET criteria [49,50].

With respect to the difficulties that exist in relating, in the classifications of carotid stenosis [51,52], an angiographic criterion to a US criterion [53], we believe that AHUSE is a further aid in this debate at the intracranial level. The flow, detected by the Doppler spectrum, correlates with the reduction in area; therefore, the flow velocity, the spectrum, correlates with the vessel restriction.

The velocity of the blood column provides information on flow resistance and, thus, indirectly on the "area reduction-increase" and information on the flow rate. Flow rate and flow velocity are not the same value but correlate with each other. TCCD and TCD could provide indirect information on the state of the vascular reserve in areas distal to the IS and the possible activation of vasoreactivity, which could also influence the velocity and, relatively, even the distal diameter to the stenosis and influence the NASCET value [49,53] (indirectly because it is mainly the microcirculation that is involved) [54]. For these reasons we believe that it is correct to use multiparametric evaluations in quantifying IS, including also the value of the ratios and activation of collateral circles that are already known [7,12,13,30,55].

With this in mind, we wanted to include, in addition to the classic parameters, AHUSE as another possible parameter that should be considered to better detect stenosis. Likewise, more advanced US research, for example, ultrasound localization microscopy (ULM), provided the first results on humans, an attempt to give more value to the morphology of intracranial vessels [56], which allows direct assessment of microcirculation.

Limitations of the study are the small sample size of the case series, the descriptive nature of statistics (we need to further explore our four MicroV IS patterns inn a wider population to validate them), which should imply correlations with other assessment methods such as DSA or allowing for tuning neurosonology and neuroradiology images. The virtual navigator (VN) allows the real-time display of US images with neuroradiological examinations [57,58].

Conclusions

The TCCD-AHUSE technology embodies the most appropriate model of morphofunctional examination in line with the latest US acquisitions, combining colorimetric and morphologic representations with velocimetric spectral analysis, minimizing or even excluding CFM vessel-profile overestimation and proposing (although there are currently no extensive correlation studies with neuroradiological investigations) a novel real-time angiogram-like imaging, in addition to the other velocity parameters already known.

Conflict of interest

The authors declare no competing interests.

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Data availability statement

MicroV is a confidential Esaote technology.

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