Chapter 5

Ultrasound in acute ischemic stroke

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Introduction

The results of non-invasive tests (e.g. ultrasound) can be highly variable, often providing ambiguous results. Although other parameters can be reviewed, calculation of overall accuracy, sensitivity, and specificity as well as positive and negative predictive values are useful to the clinician who is managing the patient.

To calculate these statistics, ultrasound results must be compared with the established gold standards, usually angiography, surgery, or autopsy findings. The simplest statistic compares the outcome of each test as either positive or negative. A true-positive result indicates that both tests are positive. A true-negative result indicates that both tests are negative. A false-positive result means that the gold standard is negative, indicating the absence of disease, while the non-invasive study is positive, indicating the presence of disease. A false-negative result occurs when the non-invasive test indicates the absence of disease but the gold standard is positive. True-positive and true-negative results can be used to calculate sensitivity and specificity. Sensitivity is the ability of a test to correctly diagnose disease. It can be calculated by dividing the number of true-positive tests by the total number of positive results obtained by the gold standard.

Specificity is the ability to diagnose the absence of disease and is calculated by dividing the true negative by the total number of negative results obtained by the gold standard. The positive predictive value (PPV) or likelihood means that disease is present and negative predictive values (NPV) means that disease is not present. Overall accuracy can be calculated by dividing the number of true negatives and true positives by the total number of tests performed. These results are not very specific and can be highly variable, based on the incidence of disease in the patient population. Because the patient population referred to the ultrasound lab is diverse, high levels of sensitivity and specificity help to make the diagnosis optimal.

$$\text{Sensitivity}(\%) = \frac{\text{true positives}}{\text{true positives} + \text{false negatives}} \times 100$$

$$\text{Specificity}(\%) = \frac{\text{true negatives}}{\text{true negatives} + \text{false positives}} \times 100$$

$$\text{Positive predictive value}(\%) = \frac{\text{true positives}}{\text{true positives} + \text{false positives}} \times 100$$

$$\text{Negative predictive value}(\%) = \frac{\text{true negatives}}{\text{true negatives} + \text{false negatives}} \times 100$$

Extracranial ultrasound in acute stroke

The most important diagnostic question in ultrasonography is which extra- and intracranial vessel(s) is/are stenotic or occluded and can it/they be responsible for the clinical symptoms. Note that clinically silent stenotic processes might also influence the cerebral circulation.

Because of the interactions between extra- and intracranial hemodynamics, both extracranial and intracranial ultrasound techniques should be performed in acute stroke. Similarly, clinically silent stenoses should be detected by careful investigation of anterior, posterior, or ipsi- and contralateral vasculature.

Doppler ultrasonography is the primary non-invasive test for evaluating carotid stenosis.

Carotid ultrasonography consists of two steps, imaging and spectral analysis. Images are produced with the brightness-mode (B-mode) technique and

Textbook of Stroke Medicine, Second Edition ed Michael Brainin and Wolf-Dieter Heiss. Published by Cambridge University Press.

sometimes color flow information is superimposed on the grayscale image. By convention, the color of the pulsating artery is red. The echogenicity of an object on the image determines its brightness. An object that rebounds very little of the pulse is hypoechoic. An object that reflects much of the signal, such as calcified plaque, is hyperechoic. Plaques with irregular surface and/or heterogeneous echogenicity are more likely to embolize. Soft plaques present a higher embolic risk than hard plaques. The sonographic characteristics of symptomatic and asymptomatic carotid plaques are different. Symptomatic plaques are more likely to be hypoechoic and highly stenotic while asymptomatic plaques are hyperechoic and moderately stenotic. Evaluation of the surface of the plaque has not been demonstrated to be a satisfactory index of plaque instability.

The degree of stenosis is better measured on the basis of the waveform and spectral analysis of the common carotid artery (CCA) and its major branches, especially the internal carotid artery (ICA). Spectral (velocity) analysis is essential to identify stenosis or occlusion. An important general rule for ultrasound is the greater the degree of stenosis, the higher the velocity. Power Doppler provides color imaging that is independent of direction or velocity of flow and gives an angiographic-like picture of an artery.

Blood flow can be laminar, disturbed, or turbulent. When no stenosis is present, blood flow is laminar. Flow of blood is even, with the fastest flow in the middle and the slowest at the edges of the vessel. When a small degree of stenosis is present, the blood flow becomes disturbed and loses its laminar quality. Even in normal conditions, such flow can be seen around the carotid bulb. With even greater stenosis, the flow can become turbulent [1].

In normal hemodynamics, as vessel length increases so does resistance. With increasing radius, the resistance decreases significantly.

As vessel diameter (and area) decreases, blood velocity increases to maintain volume flow.

The extracranial ultrasound procedure starts with the CCA, ICA and external carotid artery (ECA); at least two or three spectral analyses of each vessel should be obtained. Color imaging and power Doppler may be used but may not necessarily provide additional information.

Note the carotid bifurcation, look for plaques, attempt to characterize the nature of the plaque, and color may be used at this point to identify flow within the artery and potential areas of high velocity.

The CCA can be identified by pulsatile walls, smaller caliber than the jugular vein, and systolic peak and diastolic endpoints in between those of external and internal carotid arteries on spectral analysis. The ECA has a smaller caliber, while the ICA is often posterolateral to the ECA and the ECA may have a superior thyroid artery branch coming off. The ECA has virtually no diastolic flow (i.e. high-resistance vessel) on spectral analysis. The ECA shows positive "temporal tap" (i.e. undulations in waveform with tapping of the temporal artery). Perform spectral analysis and find the highest velocity or frequency. After assessment of the anterior circulation, the sonographer should assess the vertebral circulation. Usually, the C4–C6 segment is accessible. Vertebral arteries can be identified with a probe parallel to the carotid: angle the probe laterally and inferiorly. The vertebral body processes appear as hypoechoic transverse bars. The vertebral artery (VA) runs perpendicular to vertebral processes.

Use of color flow Doppler enables the more rapid identification of vessels (especially the VA) and often helps identify the area of highest velocity, reduces scan time, and may help in diagnosis of arterial occlusion [1].

> Doppler ultrasonography is the primary non-invasive test for evaluating carotid stenosis.
>
> Symptomatic and asymptomatic carotid plaques and the degree of stenosis can be analyzed with ultrasonography by examining the echogenicity of the structures and the velocity of the blood flow.

Identification and classification of ICA stenosis

Mild stenoses (<50%) can be estimated by measurement of area and/or diameter in the cross-sectional and longitudinal image using the B- and color-mode of the ultrasound system. Area measurements in high-grade stenosis are difficult. Diagnosis of severe stenosis is based on hemodynamic parameters (measured by pre-, intra-, and post-stenotic Doppler spectrum analysis).

Investigation of flow direction in the ophthalmic artery is a simple, bedside, ancillary method in suspected ICA stenosis or occlusion (equally severe upper and lower extremity paresis). In a case of hemodynamically significant ICA stenosis or occlusion (proximal to the origin of the ophthalmic artery)

a reversed (extra → intracranial) flow could be detected in the ophthalmic artery.

Using duplex ultrasound a proximal ICA occlusion (proximal to the origin of the ophthalmic artery, no color-mode signal, and no Doppler flow) can be distinguished from the ICA occlusion distal to the ophthalmic origin (ICA has low flow velocities and a higher pulsatility but preserved diastolic velocity).

Occlusion results in a complete absence of color-flow signal in ICA, and the diagnosis can be confirmed by ultrasound contrast agents.

Some sonographers characterize the degree of stenosis based on diameter or area reduction but estimation of stenosis solely based on this criterion is not reliable. Commonly used methods:

- peak systolic velocities (PSV) and end-diastolic velocities
- ratios of ICA/CCA maximal systolic flow velocity within the ICA stenosis
- maximal systolic flow velocity within the non-affected CCA
- ICA/ICA
- maximal systolic flow velocity within the ICA stenosis
- maximal systolic flow velocity of the non-affected ICA.

The stroke risk depends on more than the degree of carotid artery narrowing (cardiac diseases, age, sex, hypertension, smoking, and plaque structure). Most studies consider carotid stenosis of 60% or greater to be clinically important. In a case of a suspected stenosis not only the intrastenotic but also the flow from vessel segments proximal and distal to a stenosis have to be analyzed. If normal flow signals are present before and behind the suspected lesion significant stenosis can be excluded. The stenosis ranges vary from laboratory to laboratory. When possible, laboratories should perform their own correlations with angiographic measurements for quality control. A consensus statement of the Society of Radiologists in Ultrasound recommended the following criteria for estimating stenosis [2]:

- Normal: ICA PSV <125 cm/s, no plaque or intimal thickening.
- <50% stenosis: ICA PSV <125 cm/s and plaque or intimal thickening.
- 50–69% stenosis: ICA PSV is 125–230 cm/s and plaque is visible.
- >70% stenosis to near occlusion: ICA PSV >230 cm/s and visible plaque and lumen narrowing.
- Near occlusion: a markedly narrowed lumen on color Doppler ultrasound.
- Total occlusion: no detectable patent lumen is seen on grayscale ultrasound, and no flow is seen on spectral, power, and color Doppler ultrasound.

With stenosis over 90% (near occlusion), velocities may actually drop as mechanisms that maintain flow fail. Ratios may be particularly helpful in situations in which cardiovascular factors (e.g. poor ejection fraction) limit the increase in velocity [1].

<50% stenoses ICA/CCA: <2.0.
50–69% stenoses ICA/CCA: 2.0–4.0.
70% stenoses ICA/CCA: >4.0.

Doppler ultrasonography associated with stenosis might result in false-positive/negative results:

- Ipsilateral CCA-to-ICA flow ratios may not be valid in the setting of contralateral ICA occlusion.
- CCA waveforms may have a high-resistance configuration in ipsilateral ICA lesions.
- ICA waveforms may have a high-resistance configuration in ipsilateral distal ICA lesions.
- ICA waveforms may be dampened in ipsilateral CCA lesions.
- Long-segment ICA stenosis may not have high end-diastolic velocity.
- Velocities supersede imaging in grading stenosis.
- Imaging can be used to downgrade stenosis in the setting of turbulence caused by kinking [3].

A recent consensus paper of Neurosonology Research Group of the World Federation of Neurology suggests the use of NASCET method of measuring a stenosis (local diameter narrowing with the diameter distal to the bulb as denominator). Estimation of carotid stenosis should be primarily based on morphological information (B-mode, color flow, or B-flow imaging) in low to moderate degrees of stenosis. In addition to degree of narrowing, plaque thickness, plaque length, and residual lumen should also be reported. The simply velocity measurement (PSV and carotid ratio) in the stenotic area is not sufficient to differentiate a moderate from a severe (≥70% NASCET) stenosis. The reversed flow in the ophthalmic artery (from extracranial to intracranial direction) should also be investigated. The post-stenotic flow velocity distal to flow disturbances is an important diagnostic value, in which a reduction of velocities (comparison with the unaffected contralateral side or absolute reduction) allows additional grading within the category of

severe stenosis. Hemodynamic criteria are appropriate for grading moderate to severe stenoses. Established collateral flow is the most powerful criterion, excluding a less than severe stenosis irrespective of PSV. Special care is recommended for converting Doppler frequencies into velocity by measuring the angle of incidence (Doppler angle). Measurements should be taken using the lowest possible angle of insonation and made in relation to the direction of the jet visualized by color velocity flow and not the vessel course [4].

A carotid occlusion is shown in Figure 5.1.

Morphological measurements (B-mode images and color flow imaging) are the main criteria for low and moderate degrees of stenosis. Most studies consider carotid stenosis of 60% or greater to be clinically important. This equals a peak systolic velocity greater than 125 cm/s. With stenosis greater than 90% (near occlusion), velocities may actually drop as mechanisms that maintain flow fail.

Ratios (maximal systolic flow velocity within the ICA stenosis/maximal systolic flow velocity within the non-affected CCA) may be helpful in situations in which cardiovascular factors (e.g. poor ejection fraction) limit the increase in velocity. Velocity measurements in a stenosis (PSV and carotid ratio) alone are not sufficient to differentiate a moderate from a severe (≥70% NASCET) stenosis.

Additional criteria refer to the effect of a stenosis on pre-stenotic flow (CCA), the extent of post-stenotic flow disturbances, and derived velocity criteria (diastolic peak velocity and the carotid ratio).

The recent American Heart Association /American Stroke Association (AHA/ASA) guideline also recommends that each laboratory should validate its own Doppler criteria for clinically relevant stenosis [5]

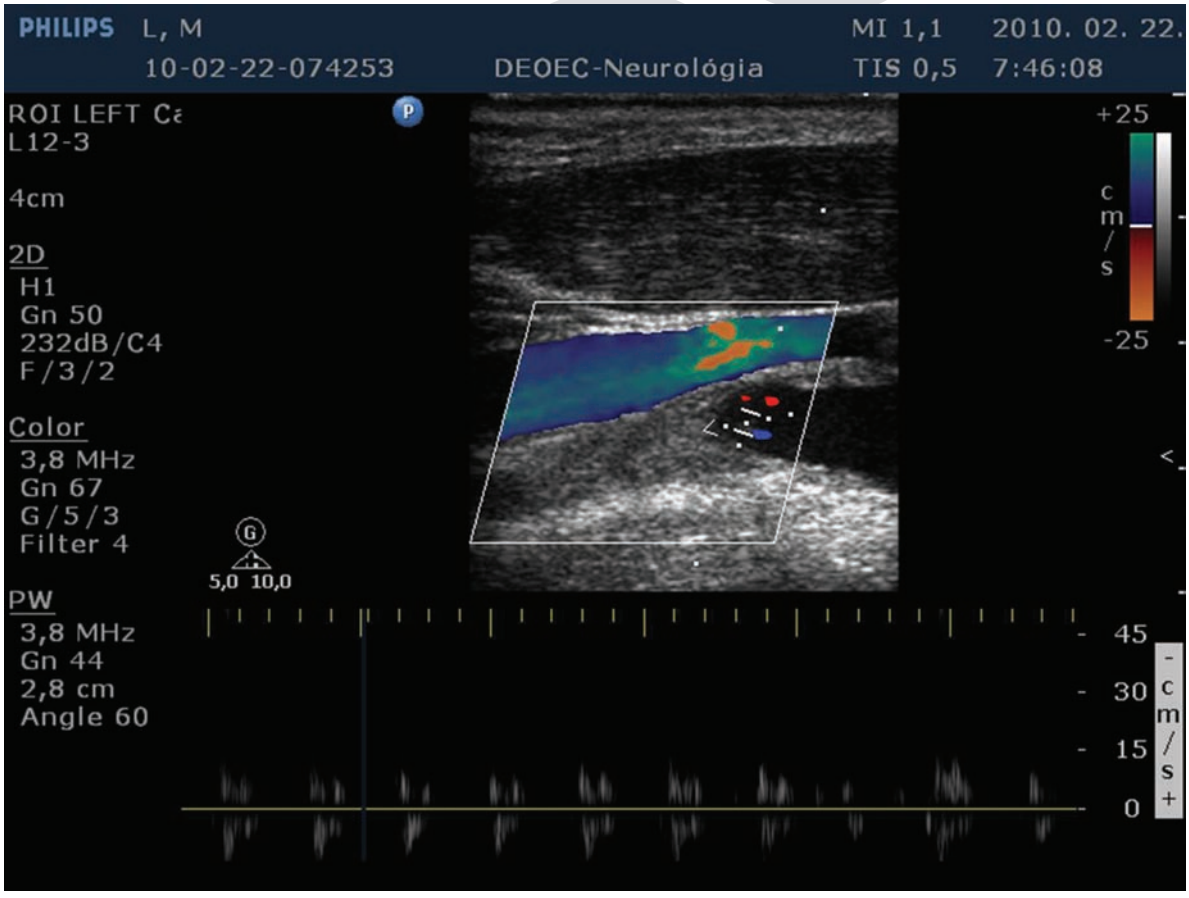

Figure 5.1. A carotid occlusion.

IMT measurement

In the Cardiovascular Health Study, increases in the intimal-medial thickness (IMT) of the carotid artery were associated with an increased risk of myocardial infarction and stroke in older adults without a history of cardiovascular disease [6]. CCA IMT greater than 0.87 mm and ICA IMT greater than 0.90 mm were associated with a progressively increased risk of cardiovascular events. For each 0.20 mm increase in CCA IMT, the risk increased by approximately 27%. For each 0.55 mm increase in ICA IMT, the risk increased approximately 30%.

The following method is suggested by the American Society of Echocardiography and the Society for Vascular Medicine for measuring IMT [7]: (1) use end-diastolic images for IMT measurements; (2) categorization of plaque presence and IMT; (3) avoid use of a single upper limit of normal for IMT because the measure varies with age, sex, and race; and (4) incorporate lumen measurement, particularly when serial measurements are performed, to account for changes in distending pressure.

Treatment with lipid-lowering drugs has been shown to decrease the intimal thickness of the carotid artery. Decrease in the thickness of the intima of the CCA has been correlated directly with successful treatment with drugs that lower serum low-density lipoprotein levels.

A recent consensus paper defines the plaque as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value or demonstrates a thickness 1–1.5 mm as measured from the media–adventitia interface to the intima–lumen interface. Carotid IMT and plaques are different phenotypes indicating increased vascular risk. Plaque presence demonstrates a higher risk and therefore overrides IMT predictive values. However, IMT without plaque remains a significant marker of an increased risk of vascular events and significantly predicts plaque occurrence [8]. A recent, prospective study on more than 600 patients and 2 years follow-up suggests that the progression of stenosis is also a strong risk factor for cerebrovascular events. The IMT was confirmed as a crucial additional measure, with an increased risk by 25% for each 0.1 mm IMT increase [9].

With ultrasound, the intimal-medial thickness [IMT] of the carotid artery can be measured. Increases in the IMT of the carotid artery are associated with an increased risk of myocardial infarction and stroke.

The presence of plaque demonstrates a higher risk and overrides IMT predictive values.

Extracranial vertebral and subclavian arteries

The origin of the VA is one of the most common locations of atherosclerotic stenosis, which is difficult to investigate, especially its origin. Raised flow velocities and spectral broadening can be seen in over 50% of stenoses. A distal extracranial VA occlusion may cause a stump signal or a high pulsatile flow signal with almost absent end-diastolic flow component.

A high grade of subclavian stenosis (>50%) results in increased flow velocities and a turbulent flow. In high-grade subclavian stenosis an alternating flow, or even a retrograde flow, can be detected within the ipsilateral VA. The levels of evidence of the European Federation of Neurological Societies are shown in Table 5.1 [10].

Ultrasound diagnosis of intracranial stenosis and occlusion

Intracranial disease corresponds to approximately 8–10% of acute ischemic stroke, depending on gender and race. Diagnosis is frequently reached through arteriography.

A recent review summarized the existing clinical conditions and standards for which a variety of transcranial Doppler (TCD) tests and monitoring are performed in clinical practice.

TCD has been shown to provide diagnostic and prognostic information that determines patient management decisions in multiple cerebrovascular conditions and periprocedural/surgical monitoring [11, 12].

The consensus confirms the importance of standardized investigation and emphasizes the following aspects:

1. The examiner should follow the course of blood flow in each major branch of the circle of Willis.
2. Identify spectral waveforms at least at two key points per artery,
3. Middle cerebral artery (MCA) signals should be stored as proximal, mid, and distal,
4. VA signals may be stored at 40–50 and 60–70 mm,
5. Basilar artery (BA) signals can be stored as proximal, mid, and distal given the length and variability of velocities in these segments.

Table 5.1. Highlights of the guidelines of the European Federation of Neurological Societies

Domains	Class and level
Ultrasonography is the non-invasive screening technique indicated for the study of vessels involved in causing symptoms of carotid stenosis	Class IV, GCPP
Transcranial Doppler (TCD) is useful for screening for intracranial stenosis and occlusion in patients with cerebrovascular disease	Class II, level B
Transcranial Doppler is very useful for monitoring arterial reperfusion after thrombolysis of acute middle cerebral artery (MCA) occlusions	Class II, level B
Clinical studies have suggested that continuous TCD monitoring in patients with acute MCA occlusion treated with intravenous thrombolysis may improve both early recanalization and clinical outcome	Class II, level A
The presence of embolic signals with carotid stenosis predicts early recurrent stroke risk	Class II, level A
Even in asymptomatic patients, TCD is the only imaging technique that allows detection of circulating emboli	Class II, level A
Asymptomatic embolization is common in acute stroke, particularly in patients with carotid artery disease. In this group the presence of embolic signals has been shown to predict the combined stroke and transient ischemic attack (TIA) risk and more recently the risk of stroke alone	Class II, level A

Source: Masdeu *et al.* [10]

6. Measure the highest velocity signals at each key point.

General characteristics of the investigation are as follows [13–17]:

- About 15% of patients cannot be examined by transcranial color-coded duplex Doppler (TCCD) because of the insufficient acoustic window. Identification rates decline with advancing age.
- The mean velocity analysis is not enough to identify intracranial vessel abnormalities. It must be combined with other parameters such as asymmetry, segmental elevations, spectral analysis, and knowledge of extracranial circulation.
- Either flow velocities (frequency-based TCCD) or the integrated power of the reflected signal (power TCCD) can be coded. The power TCCD does not display information on the flow direction.
- Flow velocities are determined by spectral Doppler sonography using the color Doppler image as a guide to the correct positioning of the Doppler sample volume.
- The angle correction should only be applied to velocity measurements when the sample volume can be located in a straight vessel segment of at least 2 cm length.
- Flow velocities in the arterial as well as in the venous system are higher in women than in men, and decrease with age, whereas the pulsatility index increases.
- Intracranial stenosis: local increase in the peak systolic flow velocities, post-stenotic flow disturbances with low frequency and high-intensity Doppler signals.
- The intracranial vessel is occluded if the color signal is absent in one segment, while other vessels and parenchymal structures can be correctly visualized.
- The accuracy of ultrasound for detecting intracranial stenosis is summarized in Table 5.2.
- The use of contrast material increases the sensitivity and specificity and only 4% of examinations are inconclusive because of insufficient bone windows.
- After application of echo-contrast enhancing agents (ECE) the diagnostic confidence of TCCD for intracranial vessel occlusion is similar to that of magnetic resonance angiography.
- In an acute stroke study the ability of duplex ultrasound to diagnose main stem arterial occlusions within the anterior circulation was between 50% and 60% of studied vessels in unenhanced TCCD but reached 80–90% after intravenous contrast administration.
- The diagnostic strength of contrast-enhanced TCCD can be the highly specific identification of a normal intracranial arterial status. Therefore, if an experienced sonographer detects no abnormalities by using TCCD in a patient with sufficient bone windows, no more imaging is needed.

Table 5.2. Highlights of the American Academy of Neurology recommendations

		Sensitivity (%)	Specificity (%)
Intracranial steno-occlusive disease	• Anterior circulation • Posterior circulation occlusion • MCA • ICA, VA, BA	70–90 50–80 85–95 55–81	90–95 80–96 90–98 96
	TCD is probably useful **(Type B, Class II–III)** for the evaluation of occlusive lesions of intracranial arteries in the basal cisterns (especially the ICA siphon and MCA) The relative value of TCD compared with MR angiography or CT angiography remains to be determined **(Type U)** Data are insufficient to recommend replacement of conventional angiography with TCD **(Type U)**		
Cerebral thrombolysis	• Complete occlusion • Partial occlusion • Recanalization	50 100 91	100 76 93
	TCD is probably useful for monitoring thrombolysis of acute MCA occlusions **(Type B, Class II–III)**. More data are needed to assess the frequency of monitoring for clot dissolution and enhanced recanalization and to influence therapy **(Type U)**		
Cerebral microemboli detection	TCD monitoring is probably useful for the detection of cerebral microembolic signals in a variety of cardiovascular/cerebrovascular disorders/procedures **(Type B, Class II–IV)**. Data do not support the use of this TCD technique for diagnosis or monitoring response to antithrombotic therapy in ischemic cerebrovascular disease **(Type U)**		
TCCS	TCCS is possibly useful **(Type C, Class III)** for the evaluation and monitoring of space-occupying ischemic MCA infarctions. More data are needed to show if it has value vs. CT and MRI scanning and if its use affects clinical outcomes **(Type U)**		
Contrast-enhanced TCCS	(CE)-TCCS may provide information in patients with ischemic cerebrovascular disease and aneurysmal subarachnoid hemorrhage (SAH) **(Type B, Class II–IV)**		
	Its clinical utility vs. CT scanning, conventional angiography, or non-imaging TCD is unclear **(Type U)**		

Type A: established as useful/predictive or not useful/predictive for the given condition in the specified population.
Type B: probably useful/predictive or not useful/predictive for the given condition in the specified population.
Type C: possibly useful/predictive or not useful/predictive for the given condition in the specified population.
Type U: data inadequate or conflicting; given current knowledge, test/predictor unproven.
Class I: evidence provided by prospective study in broad spectrum of persons with suspected condition, using a "gold standard" to define cases, where test is applied in blinded evaluation, and enabling assessment of appropriate tests of diagnostic accuracy.
Class II: evidence provided by prospective study in narrow spectrum of persons with suspected condition or well-designed retrospective study of broad spectrum of persons with suspected condition (by "gold standard") compared to broad spectrum of controls where test is applied in blinded evaluation and enabling assessment of appropriate tests of diagnostic accuracy.
Class III: evidence provided by retrospective study where either persons with established condition or controls are of narrow spectrum, and where test is applied in blinded evaluation.
Class IV: any design where test is not applied in blinded fashion OR evidence provided by expert opinion or descriptive case series.
Source: Sloan *et al.* [14].

- A correctly performed TCD investigation also provides valuable information about the vascular status of the ICA. The presence of collaterals and delayed flow acceleration on TCD usually indicates a hemodynamically significant lesion (>80% ICA stenosis or occlusion).
- The investigation should start on the presumably non-affected side (road map! clinical symptoms).

Table 5.3. Velocity values for ultrasound grading of intracranial stenosis

Stenosis	≥50%	50–80%	≥80%
Middle cerebral artery	≥155 cm/s	≥220	Distal M1/M2-MCA post-stenotic fp A1-ACA and/or P1/P2-PCA↑
Anterior cerebral artery	≥120	≥155	A2-ACA post-stenotic fp ipsilateral M1-MCA and/or contralat. A1↑
Posterior cerebral artery	≥100	≥145	Distal PCA post-stenotic fp ipsilateral M1-MCA↑
Basilar artery	≥100	≥140	Distal BA/PCA post-stenotic fp VA/proximal BA pre-stenotic fp
Vertebral artery	≥90	≥120	Distal VA/BA post-stenotic fp VA extracranial pre-stenotic fp

Fp: flow pattern, ↑ increased velocity as collateral sign.
Source: Modified from Baumgartner [15] and Valdueza *et al.* [16].

- The sonographer looks for a focal velocity rise in a circumscribed vessel segment, and differences between the affected and non-affected sides, extending more than 30 cm/s.
- If a pathological finding is present, the proximal and distal vessel segments should also be evaluated.
- Occlusions are characterized by missing color and Doppler flow signals at the site of the occlusion or reduced flow signals in vessel segments proximal to the occlusion.

MCA stenosis

Stenoses of the M1-MCA can be graded according to flow velocity, turbulence, and asymmetry into mild, moderate, and high-grade stenoses and all detectable MCA segments should be insonated [14–16].

MCA occlusion

Depending on the location of the occlusion, the Doppler spectrum may be completely absent or reduced. If there is a proximal M1-MCA occlusion no flow signal is seen. In occlusions of the middle part of the MCA, a small orthograde flow with increased pulsatility may be present. In distal M1-MCA occlusion a reduced flow velocity is present with variable pulsatility depending on the presence of a temporal branch.

Distal MCA occlusion, e.g. of a relevant M2-MCA branch or more than one M2 branch, will result in a reduced flow with low velocities and a marked bilateral asymmetry.

Stenosis and occlusion in posterior circulation

Again the typical clinical symptoms of vertebrobasilar insufficiency should orient the sonographer. Alteration of flow velocities and turbulence, at least 30 cm/s flow velocity difference between the right and left sides, may also be useful. A proximal posterior cerebral artery (PCA) occlusion can be diagnosed by absent flow signal. Vertebral stenoses can be diagnosed by flow velocity, profile disturbances, and pre- and post-stenotic flow patterns. Velocity values for mild and severe stenosis are given in Table 5.3. Flow signals in VA occlusion strongly depend on the site of the occlusion, mainly on their relation to the origin of the posterior inferior cerebellar artery (PICA) (proximal or distal). Occlusions distal to the PICA origin will result in mild to moderate flow alterations of the extracranial VA, mainly depending on its diameter and its former relevance in the posterior circulation [16].

Basilar artery stenosis and occlusion

Transforaminal and transtemporal insonation allows the investigation of the total length of the BA. The most distal segment of the BA may be better insonated transtemporally, but the visualization of the distal part of the BA appears to be difficult even using ECE.

Occlusions are difficult to assess and diagnostic certainty depends on the site of the occlusion. A proximal BA occlusion will always result in prestenotic flow alterations of both extracranial VAs [16]. Therefore, apparently normal VA and proximal BA velocities are not sufficient to exclude top of the basilar occlusion.

However, as this cannot exclude the presence of, for example, a fragmented thrombus, ultrasound should always be used together with other diagnostic tools such as CTA, MRA, or DSA in presumed BA pathology.

The highlights of the recommendation of the American Academy of Neurology [14] summarize the accuracy of TCD in intracranial steno-occlusive disorders (Table 5.2).

With transcranial color-coded duplex sonography (TCCD), using low frequencies to penetrate the skull, most intracranial stenoses and occlusions can be detected by combining velocity analysis with other parameters. With the use of echo-contrast enhancing agents (ECE), the sensitivity and specificity can be increased and the diagnostic confidence of contrast-enhanced TCCD for intracranial vessel occlusion can reach that of magnetic resonance angiography.

Fast-track neurovascular ultrasound examination

Recently, a practical algorithm has been published for urgent bedside neurovascular ultrasound examination with carotid/vertebral duplex and TCD in patients with acute stroke [18].

Using such a protocol, urgent TCD studies can be completed and interpreted quickly at the bedside. The expanded fast-track protocol for combined carotid and transcranial ultrasound testing in acute cerebral ischemia is shown in Table 5.4. Below, we highlight the most important details of the algorithm.

The choice of fast-track insonation steps is determined by the clinical localization of ischemic arterial territory. For example, if patients present with MCA symptoms, the insonation begins with the non-affected side. This is followed by locating the MCA on the affected side, with insonation starting at the mid-M1-MCA depth range, usually 50–58 mm. The waveforms and systolic flow acceleration are compared to the non-affected side. If a normal MCA flow is found, the distal MCA segments are insonated (range 40–50 mm); this is followed by proximal MCA and ICA bifurcation assessment (range 60–70 mm) [18]. The non-invasive vascular ultrasound evaluation (NVUE) in patients with acute ischemic stroke has a high yield and accuracy in diagnosing lesions amenable to interventional treatment (LAIT). The ultrasound screening criteria for LAIT are shown in Table 5.5.

TCD has the highest sensitivity (>90%) for acute arterial obstructions located in the proximal MCA and ICAs. TCD has modest sensitivity for posterior circulation lesions if performed without TCCD or contrast enhancement (Table 5.2). However, with a completely normal spectral TCD, there is less than 5% chance that an urgent angiogram will show any acute obstruction [19].

While TCD demonstration of an arterial occlusion helps to determine the ischemic nature of acute focal neurological deficits, a normal TCD result would support a lacunar mechanism.

In summary, bedside ultrasound in acute stroke may identify thrombus presence, determine thrombus location(s), assess collateral supply, find the worst residual flow signal, and monitor recanalization and re-occlusion.

A practical algorithm has been elaborated for urgent bedside neurovascular ultrasound examination with carotid/vertebral duplex and transcranial Doppler in patients with acute stroke.

Emboli monitoring and acute stroke

TCD identifies microembolic signs (MES) in intracranial circulation. The ultrasound distinguishes signal characteristics through embolic materials – solid or gaseous – from erythrocyte flow velocity. Microembolic signals appear as signals of high intensity and short duration within the Doppler spectrum as a result of their different acoustic properties compared to the circulating blood.

A microembolus signal is visible on TCD registration of ACA (Figure 5.2).

MES have been proven to represent solid or gaseous particles within the blood flow. They occur at random within the cardiac cycle and they can be acoustically identified by a characteristic "chirp" sound. Detection of MES can identify patients with stroke or TIA likely to be due to embolism. Potential applications of MES detection include determining the pathophysiology of cerebral ischemia, identifying patients at increased risk for stroke who may benefit from surgical and pharmacological intervention, assessing the effectiveness of novel antiplatelet therapies, and perioperative monitoring to prevent intra- and postoperative stroke.

The methodology includes simultaneous monitoring of both MCAs for at least 30 minutes, with fixed transducers in order to reduce movement artifacts. With two possible embolic sources – cardiogenic and carotid plaque – the identification of MES contributes higher diagnosis accuracy and support for therapy decision-making. MES detection, in addition, acts as a predictor for new cerebral ischemic event recurrence [19–23].

Table 5.4. Fast-track neurovascular ultrasound examination

Use portable devices with bright display overcoming room light. Stand behind patient headrest. Start with TCD because acute occlusion responsible for the neurological deficit is likely to be located intracranially. Extracranial carotid/vertebral duplex may reveal an additional lesion often responsible for intracranial flow disturbance. Fast-track insonation steps follow clinical localization of patient symptoms.

A. Clinical diagnosis of cerebral ischemia in the anterior circulation

STEP 1: Transcranial Doppler

1. If time permits, begin insonation on the non-affected side to establish the temporal window, normal MCA waveform (M1 depth 45–65 mm, M2 30–45 mm) and velocity for comparison with the affected side.
2. If short on time, start on the affected side: first assess MCA at 50 mm. If no signals detected, increase the depth to 62 mm. If an anterograde flow signal is found, reduce the depth to trace the MCA stem or identify the worst residual flow signal. Search for possible flow diversion to the ACA, PCA, or M2 MCA. Evaluate and compare waveform shapes and systolic flow acceleration.
3. Continue on the affected side (transorbital window). Check flow direction and pulsatility in the OA at depths 40–50 mm followed by ICA siphon at depths 55–65 mm.
4. If time permits or in patients with pure motor or sensory deficits, evaluate BA (depth 80–100 mm) and terminal VA (40–80 mm).

STEP 2: Carotid/vertebral duplex

1. Start on the affected side in transverse B-mode planes followed by color or power-mode sweep from proximal to distal carotid segments. Identify CCA and its bifurcation on B-mode and flow-carrying lumens.
2. Document if ICA (or CCA) has a lesion on B-mode and corresponding disturbances on flow images. In patients with concomitant chest pain, evaluate CCA as close to the origin as possible.
3. Perform angle-corrected spectral velocity measurements in the mid-to-distal CCA, ICA and external carotid artery.
4. If time permits or in patients with pure motor or sensory deficits, examine cervical portion of the vertebral arteries (longitudinal B-mode, color or power mode, spectral Doppler) on the affected side.
5. If time permits, perform transverse and longitudinal scanning of the arteries on the non-affected side.

B. Clinical diagnosis of cerebral ischemia in the posterior circulation

STEP 1: Transcranial Doppler

1. Start suboccipital insonation at 75 mm (VA junction) and identify BA flow at 80–100 mm.
2. If abnormal signals present at 75–100 mm, find the terminal VA (40–80 mm) on the non-affected side for comparison and evaluate the terminal VA on the affected side at similar depths.
3. Continue with transtemporal examination to identify PCA (55–75 mm) and possible collateral flow through the posterior communicating artery (check both sides).
4. If time permits, evaluate both MCAs and ACAs (60–75 mm) for possible compensatory velocity increase as an indirect sign of basilar artery obstruction.

STEP 2: Vertebral/carotid duplex ultrasound

1. Start on the affected side by locating CCA using longitudinal B-mode plane, and turn transducer downward to visualize shadows from transverse processes of midcervical vertebrae.
2. Apply color or power modes and spectral Doppler to identify flow in intratransverse VA segments.
3. Follow VA course to its origin and obtain Doppler spectra. Perform similar examination on other side.
4. If time permits, perform bilateral duplex examination of the CCA, ICA and external carotid artery as described above.

OA = ophthalmic artery.

Source: Reproduced with permission from Chernyshev *et al*. [17].

At present, monitoring of microembolisms is useful for patients with non-defined acute ischemic stroke, and for determining which is of probable cardio- or carotid-embolic etiology.

Simultaneous monitoring for MES in different vessels may help identify the active embolic source (cardiac? carotid?). Simultaneous monitoring above (i.e. MCA) and below (i.e. CCA) an ICA stenosis is

Table 5.5. Ultrasound screening criteria for lesions amenable for intervention

Lesion location	TCD criteria (at least one present)	CD criteria
M1/M2 MCA	*Primary:* TIBI grades 0–4 (absent, minimal, blunted, dampened, or stenotic) at depths <45 mm (M2) and 45–65 mm (M1)	Extracranial findings may be normal or may show decreased ICA velocity on the side of the lesion
	Secondary: Flow diversion to ACA, PCA, or M2 Increased resistance in ipsilateral TICA Embolic signals in MCA Turbulence, disturbed flow at stenosis Nonharmonic and harmonic covibrations (bruit or pure musical tones)	
TICA	*Primary:* TIBI grades 0–4 at 60–70 mm Increased velocities suggest anterior cross-filling or collateral flow in posterior communicating artery	Decreased ICA velocity unilateral to lesion or normal extracranial findings
	Secondary: Embolic signals in unilateral MCA Blunted unilateral MCA, MFV >20 cm/s	
Proximal ICA	*Primary:* Increased flow velocities suggest anterior cross-filling through ACommA or collateral flow through PCommA Reversed OA Delayed systolic flow acceleration in or blunted ipsilateral MCA, MFV >20 cm/s	B-mode evidence of a lesion in ICA ± CCA; Flow imaging evidence of no flow or residual lumen
	Secondary:	ICA >50% stenosis PSV >125 cm/s EDV >40 cm/s ICA/CCA PSV ratio >2
	Embolic signals in unilateral MCA Normal OA direction due to retrograde filling of siphon	ICA near-occlusion or occlusion Blunted, minimal, reverberating, or absent spectral Doppler waveforms in ICA
Tandem ICA/ MCA stenosis/ occlusion	*Primary:* TIBI grades 0–4 and: Increased velocities in contralateral ACA, MCA, or unilateral PCommA or: Reversed unilateral OA	B-mode evidence of a lesion in ICA ± CCA; or: Flow imaging evidence of residual lumen or no flow ICA >50% stenosis PSV >125 cm/s EDV >40 cm/s ICA/CCA PSV ratio >2

Table 5.5. (*cont.*)

Lesion location	TCD criteria (at least one present)	CD criteria
	Secondary: Delayed systolic flow acceleration in proximal MCA or TICA	ICA near-occlusion or occlusion
	Embolic signals in proximal MCA or TICA	Blunted, minimal, reverberating, or absent spectral Doppler waveforms in ICA
Basilar artery	*Primary:* TIBI flow grades 0–4 at 75–100 mm	Extracranial findings may be normal or showing decreased VA velocities or VA occlusion
	Secondary: Flow velocity increase in terminal VA and branches, MCAs, or PcommAs High resistance flow signals in VA(s) Reversed flow direction in distal basilar artery (85 mm)	
Vertebral artery	*Primary (intracranial VA occlusion):* TIBI flow grades 0–4 at 40–75 mm Primary (extracranial VA occlusion) Absent, minimal, or reversed high resistance flow signals in unilateral terminal VA	Extracranial findings may be normal (intracranial VA lesion) or showing decreased VA velocities or VA occlusion
	Secondary: Embolic signals increased velocities or low pulsatility in contralateral VA	

TICA = terminal internal carotid artery; TIBI = thrombolysis in brain infarction; MFV = mean flow velocity; ACommA = anterior communicating artery; PCommA = posterior communicating artery; OA = ophthalmic artery; EDV = end-diastolic velocity; CD = cervical duplex.

Source: Reproduced with permission from Chernyshev *et al*. [18].

another possible way of differentiating between artery-to-artery and cardiogenic embolism.

The frequency of MES in acute stroke shows a wide range, from 10% to 70%, probably due to different therapies, different criteria for MES detection, or different elapsed times after stroke. Some investigators used single registration, others serial measurements. The incidence of MES is maximal in the first week after stroke. The occurrence of MES showed more prevalence in completed stroke than in patients with TIA, and in symptomatic than asymptomatic hemispheres and a discrete subcortical or cortical pattern of infarction on computed tomography (CT) compared with a hemodynamic or small-vessel pattern.

Some authors have demonstrated that MES occur predominantly in patients with large-vessel territory stroke patterns and cases of artery-to-artery or cardiogenic embolism with persisting deficit. In contrast, MES are only occasionally detected in patients with small-vessel infarctions.

In addition, TCD monitoring may help to discriminate between different potential sources of embolism (i.e. artery-to-artery or cardioembolic strokes). Different types of emboli (i.e. cardiac or carotid) have different acoustic properties and ultrasonic characteristics, based on composition and size, which could permit differentiation.

MES detection by TCD in carotid endarterectomy (CEA) candidates may allow identification of a particularly high-risk group of patients who merit an early intervention or, if this is not possible, more aggressive antithrombotic therapy. The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis Study (CARESS) also revealed that the combination of clopidogrel and aspirin was associated with a marked reduction in MES, compared with aspirin alone (e.g. clopidogrel + aspirin versus aspirin) [24].

A recent meta-analysis confirmed the usefulness of MES detection by TCD sonography. MES are a frequent finding in varying sources of arterial brain

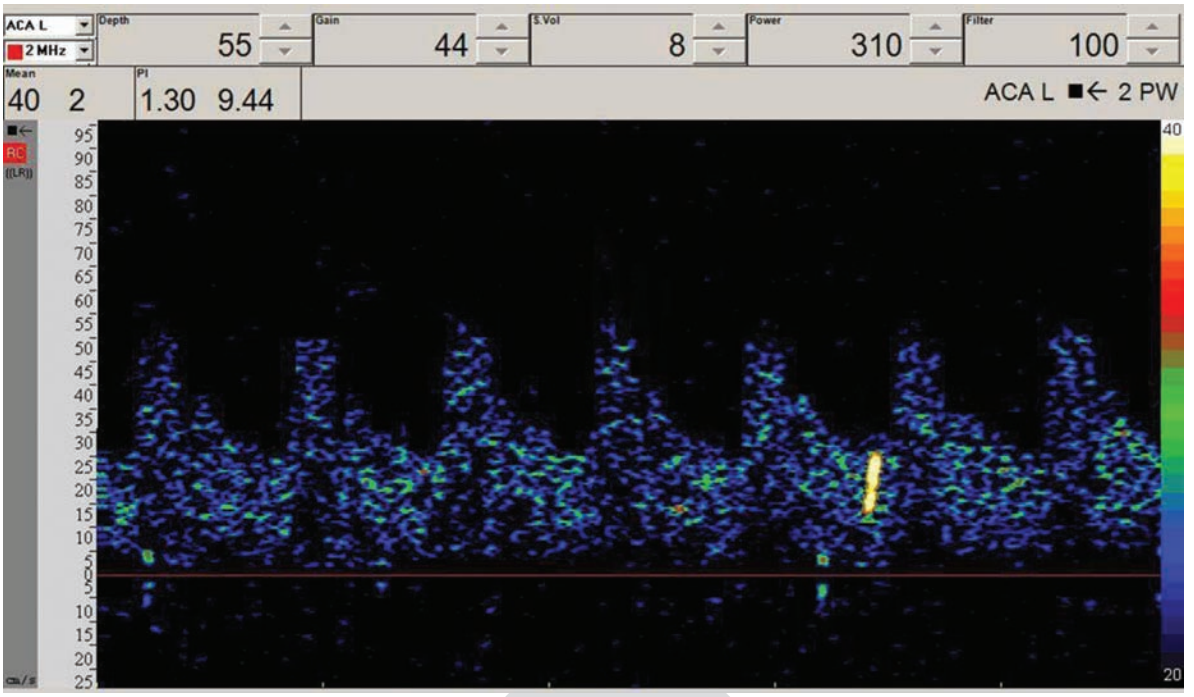

Figure 5.2. A microembolus signal visible on transcranial Doppler registration of anterior cerebral artery.

embolism and MES detection is useful for risk stratification in patients with carotid stenosis [25].

Numerous studies, including a prospective observational one (asymptomatic carotid emboli study [ACES]), proved that TCD can be used to identify patients who are at a higher risk of stroke and TIA. The meta-analyses of ACES with previous studies confirmed the association of embolic signals with future risk of ipsilateral stroke and TIA [25].

> TCD identifies MES (microembolic signs) in intracranial circulation. Detection of MES can identify patients with stroke or TIA likely to be due to embolism, acts as a predictor for new cerebral ischemic event recurrence, and can influence therapy decision-making.

Diagnostic brain perfusion imaging in stroke patients

The availability of new ultrasound contrast agents (UCAs) and the development of contrast-specific imaging modalities have established the application of ultrasound in stroke patients for visualization of brain perfusion deficits. The UCAs consist of micro bubbles composed of a gas that is associated with various types of shells for stabilization. Because of their small size, they can pass through the microcirculation. There are interactions between ultrasound and microbubbles: at low ultrasound energies UCA microbubbles produce resonance, emitting ultrasound waves at multiples of the insonated fundamental frequency.

The new microbubbles (e.g. SonoVue) generate a nonlinear response at low acoustic power without destruction, thus being particularly suitable for real-time imaging. Harmonic imaging differentiates echoes from microbubbles from those coming from tissue. The insonated tissue responds at the fundamental frequency, while resonating microbubbles cause scattering of multiples of the fundamental frequency – the harmonic frequencies.

Real-time visualization of middle cerebral artery infarction

Perfusion harmonic imaging after SonoVue bolus injection can be used in patients with acute stroke. In the early phase of acute ischemic stroke, bolus imaging after SonoVue injection is useful for analyzing cerebral perfusion deficits at the patient's bedside.

The ultrasound imaging data correlate well with the definite area of infarction and outcome after ischemic stroke. Ultrasound perfusion imaging (UPI) with SonoVue has allowed measurements not only in ischemic stroke but also in intracerebral hemorrhages, due to a characteristic reduction of contrast reaching the lesion.

The real-time UPI can detect hemodynamic impairment in acute MCA occlusion and subsequent improvement following arterial recanalization. This offers the chance for bedside monitoring of the hemodynamic compromise (e.g. during therapeutic interventions such as systemic thrombolysis [27]. In spite of continuous effort, perfusion imaging in acute stroke is still in the experimental phase [28–31].

> New ultrasound contrast agents (UCAs) that can pass through the microcirculation and the development of contrast-specific imaging modalities make it possible to use ultrasound for the visualization of brain perfusion deficits.

Prognostic value of ultrasound in acute stroke

During recent years, ultrasound has become an important non-invasive imaging technique for bedside monitoring of acute stroke therapy and prognosis. By providing valuable information on temporal patterns of recanalization, ultrasound monitoring may assist in the selection of patients for additional pharmacological or interventional treatment. Ultrasound also has an important prognostic role in acute stroke. A prospective, multicenter, randomized study confirmed that a normal MCA finding is predictive of a good functional outcome in more than two-thirds of subjects. After adjustment for age, neurological deficit on admission, CT scan results, and pre-existing risk factors, ultrasound findings remained the only independent predictor of outcomes [32].

The analysis of flow signal changes during thrombolysis acquired by TCD further confirmed the prognostic value of transcranial ultrasound. Acute arterial occlusion is a dynamic process since a thrombus can propagate and break up, thereby changing the degree of arterial obstruction and affecting the correlation between TCD and angiography.

A complete occlusion should not produce any detectable flow signals. However, in reality, some residual flow around the thrombus is often present. The Thrombolysis in Brain Ischemia (TIBI) flow-grading system was developed to evaluate residual flow non-invasively and monitor thrombus dissolution in real time [33]:

- Grade 0: absent flow.
- Grade 1: minimal flow.
- Grade 2: blunted flow.
- Grade 3: dampened flow.
- Grade 4: stenotic flow.
- Grade 5: normal flow.

(TIBI 0 and 1 refer to proximal occlusion, TIBI 2 and 3 to distal occlusion, and TIBI 4 to recanalization.)

Applying these criteria in acute stroke the TIBI classification correlates with initial stroke severity, clinical recovery, and mortality in patients treated with recombinant tissue plasminogen activator (rtPA). The grading system can be used also to analyze recanalization patterns.

The waveform changes ($0 \rightarrow 5$) correlate well with clinical improvement and a rapid arterial recanalization is associated with better short-term improvement, whereas slow flow improvement and dampened flow signals are less favorable prognostic signs [33].

Even incomplete or minimal recanalization determined 24 hours after stroke onset results in more favorable outcome compared with persistent occlusion [34].

Reperfusion is important for prognosis. Both partial and full early reperfusion led to a lesser extent of neurological deficits irrespective of whether this occurred early or in the 6- to 24-hour interval.

Progressive deterioration after stroke due to cerebral edema, thrombus propagation, or hemodynamic impairment is closely linked to extra- and intracranial occlusive disease. TCCD is also useful for the evaluation of combined intravenous (i.v.)–intra-arterial (i.a.) thrombolysis. Patients receiving combined i.v.–i.a. thrombolysis show greater improvement in flow signal and higher incidence of complete MCA recanalization compared with those receiving i.v. thrombolysis, especially when the MCA was occluded or had only minimal flow [35].

Patients with distal MCA occlusion are twice as likely to have a good long-term outcome as patients with proximal MCA occlusion. Patients with no detectable residual flow signals as well as those with terminal ICA occlusions are least likely to respond early or long term. The distal MCA occlusions are more likely to recanalize with i.v. rtPA therapy; terminal ICA occlusions were the least likely to

recanalize or have clinical recovery with i.v. rtPA compared with other occlusion locations [36].

Alexandrov *et al.* [37] described the patterns of the speed of clot dissolution during continuous TCD monitoring: sudden recanalization (abrupt normalization of flow velocity in a few seconds), stepwise recanalization as a progressive improvement in flow velocity lasting less than 30 minutes, and slow recanalization as a progressive improvement in flow velocity lasting more than 30 minutes. Sudden recanalization reflects rapid and complete restoration of flow, while stepwise and slow recanalization indicate proximal clot fragmentation, downstream embolization, and continued clot migration. Sudden recanalization was associated with a higher degree of neurological improvement and better long-term outcome than stepwise or slow recanalization.

A tandem ICA/MCA occlusion independently predicted a poor response to thrombolysis in patients with a proximal MCA clot, but not in those with a distal MCA clot [38].

Ultrasound has an important prognostic role in acute stroke and can be used to monitor thrombus dissolution during thrombolysis.

Ultrasound accelerated thrombolysis and microbubbles

TCD can be used not only for diagnostic and prognostic purposes, but also for therapy. The ultrasound enhances the enzymatic thrombolysis, increasing the transport of rtPA into the thrombus and improving the binding affinity, and provides a unique opportunity to detect the recanalization during and after rtPA administration.

Continuous monitoring with 2 MHz TCD in combination with standard i.v. rtPA therapy results in significantly higher recanalization rate or dramatic recovery than i.v. rtPA therapy without TCD monitoring. In the CLOTBUST trial, 126 patients were randomly assigned to receive continuous TCD monitoring or placebo in addition to i.v. rtPA. Complete recanalization or dramatic clinical recovery within 2 hours after the administration of a rtPA bolus occurred in 49% of the target group as compared to 30% in the control group ($P = 0.03$). Only 4.8% of patients developed symptomatic intracerebral hemorrhage. These results showed the positive effects of 2 MHz continuous TCD monitoring in acute stroke, with no increase in the rate of intracerebral hemorrhage [39].

Recently, combining rtPA, ultrasound, and gaseous microbubbles showed signs of further enhancing arterial recanalization. Although these microbubbles, previously known as diagnostic microbubbles or gaseous microspheres, were originally designed to improve conventional ultrasound images, facilitation of thrombolysis is now emerging as a new treatment application for this technology. Newer-generation bubbles use specific phospholipid molecules that, when exposed to mechanical agitation, arrange themselves in nanobubbles with a consistent 1–2 μm (or even less) diameter. When injected intravenously, nanobubbles carry gas through the circulation. As the bubbles approach and permeate through the thrombus, they can be detected and activated by the ultrasound energy. Upon encountering an ultrasound pressure wave, the phospholipid shell breaks up and releases gas. The result is bubble-induced cavitation with fluid jets that erode the thrombus surface. In the presence of rtPA, this erosion increases the surface area for thrombolytic action and accelerates lysis of clots [40]. Recent studies evaluated the effects of administration of microbubbles on the initial MCA recanalization during systemic thrombolysis and continuous 2 MHz pulsed-wave TCD monitoring. The complete recanalization rate was significantly higher in the rtPA + ultrasound + microbubbles group (55%) than in the rtPA/ultrasound (41%) and rtPA (24%) groups [40] with no increase in symptomatic intracranial hemorrhage after systemic thrombolysis.

A Cochrane analysis indicated that sonothrombolysis produces a significant increase of recanalization rate associated with a non-significant increase of hemorrhagic transformation of the cerebral infarction [41]. There was also a statistically significant clinical improvement at the three-month follow-up in terms of death plus disability rate.

The concomitant use of microbubbles and ultrasound may increase the frequency of asymptomatic and symptomatic cerebral hemorrhage, but the small size of the evaluated population means that these conclusions are not reliable.

The use of any sonothrombolysis plus rtPA versus rtPA alone allowed a statistically significant reduction of death plus disability rate at 3 months in the sonothrombolysis group in comparison to rtPA alone, but with a wide confidence interval.

A significant improvement in the recanalization rate (any degree) was also attained. However, the

incidence of cerebral hemorrhage increased, although this result was not statistically significant [40]. The Cochrane analysis [41] urges further investigations with sonothrombolysis, similarly to the statement of the 2013 American Heart Association/American Stroke Association (AHA/ASA) guideline "the effectiveness of sonothrombolysis for treatment of patients with acute stroke is not well established *(Class IIb; Level of Evidence B)*" [5]

Arterial recanalization can be enhanced by combining rtPA with ultrasound, and even further with gaseous microbubbles, which increase the surface area for the thrombolytic action of rtPA, but further investigations are necessary.

Vasomotor reactivity

Vasomotor reactivity or cerebrovascular reactivity (CVR) describes the ability of the cerebral circulation to respond to vasomotor stimuli; the changes in cerebral blood flow (velocity in TCD studies) in response to such stimuli can be studied by TCD. CO_2 is a widely used agent to measure cerebral vasomotor reactivity. Another widely used agent is i.v. acetazolamide (0.15 mg/kg).

CO_2 results in vasodilatation and increased cerebral blood flow velocity. Measuring vasomotor reactivity requires standard experimental conditions. Markus *et al.* [42] described a simple measurement of the MCA velocity in response to 30 seconds breath-holding and termed it the breath-holding index (BHI):

$$\mathrm{BHI} = \frac{\mathrm{MFV_{end}} - \mathrm{MFV_{baseline}}}{\mathrm{MFV_{baseline}}} \times \frac{100}{\text{seconds of breath-holding}}$$

(MFV: mean flow velocity).

Others [43] evaluated BHI in different studies and showed that impaired vasomotor reactivity can help to identify patients at higher risk of stroke. Decreased vasomotor reactivity suggests failure of collateral flow to adapt to the stenosis. Various studies using different provocative measures for assessing cerebral vasomotor reactivity have demonstrated a remarkable ipsilateral event rate of approx. 30% risk of stroke over 2 years.

A recent international multicenter study did not find any association between impaired CVR and recurrent vascular events. Meta-analysis of available data suggested an association between impaired CVR and future risk. However, currently there are insufficient data to justify the routine clinical use of CVR [44].

The changes in cerebral blood flow in response to vasomotor stimuli can be studied by TCD.

Right-to-left shunt detection

Right-to-left shunts, particularly a patent foramen ovale (PFO), are common in the general population, with a prevalence of 10–35% in various echocardiography and autopsy studies for PFO. The prevalence is even higher in cryptogenic stroke or TIA and especially in younger patients without an apparent etiology. Contrast-enhanced TCD can be used for detecting the high-intensity transient signals (HITS) passing through the MCA, thus indicating the presence of a right-to-left shunt. The results of contrast-enhanced TCD have been compared with those of contrast-transesophageal echo and found to have a sensitivity and specificity of 68–100% and 67–100%, respectively [45]. Other studies with TCD and transesophageal echocardiography (TEE) proved the strength of TCD in PFO detection and right-to-left (RLS) quantification [46, 47]. Advantages of TCD include calibrated Valsalva maneuver and the ability to change body positioning during the test. The TCD "bubble" test for right-to-left shunt is superior to transthoracic echocardiography, and possibly TEE.

Contrast-enhanced TCD can also be used to identify patients with a patent foramen ovale.

Sickle-cell disease (SCD)

Children with SCD have a significant risk of stroke before the age of 20 years from a stenosis or occlusion of the distal ICAs and proximal MCAs. Several studies have demonstrated that children with this disease should be monitored with serial TCD evaluations as TCD can be used to identify children with SCD at an increased risk of stroke. The Stroke Prevention in Sickle Cell Disease (STOP) trial evaluated children who had velocities of >200 cm/s in one or both of the MCAs or terminal ICAs at baseline TCD. They were randomized to either blood transfusion or standard care. Greater than 90% relative risk

reduction in stroke incidence could be seen in the treated population [48]. The recent American guideline dealing with the primary stroke prevention recommends the use of TCD for selecting SCD children for transfusion therapy. Children with SCD should be screened with TCD starting at age 2 years (Class I; Level of Evidence B) [49].

Chapter summary

Doppler ultrasonography is the primary non-invasive test for evaluating carotid stenosis.

The sonographic characteristics of symptomatic and asymptomatic carotid plaques are different: symptomatic plaques are more likely to be hypoechoic and highly stenotic, while asymptomatic plaques are hyperechoic and moderately stenotic. The degree of stenosis is better measured on the basis of the waveform and spectral analysis. When no stenosis is present, blood flow is laminar. With greater stenosis, the flow becomes turbulent. An important general rule for ultrasound is the greater the degree of stenosis, the higher the velocity.

Most studies consider carotid stenosis of 60% or greater to be clinically important.

Commonly used methods to estimate stenosis with ultrasonography are:

- Peak systolic velocities:
  - Normal: ICA PSV $<$125 cm/s, no plaque or intimal thickening.
  - $<$50% stenosis: ICA PSV $<$125 cm/s and plaque or intimal thickening.
  - 50–69% stenosis: ICA PSV is 125–230 cm/s and plaque is visible.
  - $>$70% stenosis to near occlusion: ICA PSV $>$230 cm/s and visible lumen narrowing.
  - Near occlusion: a markedly narrowed lumen on color Doppler ultrasound.
  - Total occlusion: no detectable patent lumen is seen on grayscale ultrasound, and no flow is seen on spectral, power, and color Doppler ultrasound.
- Ratios of the maximal systolic flow velocity within the ICA stenosis to the maximal systolic flow velocity within the non-affected CCA:
  - $<$50% stenoses ICA/CCA: $<$2.0.
  - 50–69% stenoses ICA/CCA: 2.0–4.0.
  - $\geq$70% stenoses ICA/CCA: $>$4.0.

Ratios may be particularly helpful in situations in which cardiovascular factors (e.g. poor ejection fraction) limit the increase in velocity.

Velocity measurements in a stenosis (PSV and carotid ratio) alone are not sufficient to differentiate a moderate from a severe ($\geq$70% NASCET) stenosis.

Additional criteria refer to the effect of a stenosis on pre-stenotic flow (common carotid artery), the extent of post-stenotic flow disturbances, and derived velocity criteria (diastolic peak velocity and the carotid ratio).

With ultrasound, the intimal-medial thickness (TMT) of the carotid artery can be measured. Increases in the IMT of the carotid artery are associated with an increased risk of myocardial infarction and stroke.

In case of hemodynamically significant ICA stenosis or occlusion (proximal to the origin of the ophthalmic artery) a reversed (extra $\rightarrow$ intracranial) flow can be detected in the ophthalmic artery. Occlusion results in a complete absence of color-flow signal in ICA, and the diagnosis can be confirmed by ultrasound contrast agents (UCAs).

Intracranial stenosis and occlusion corresponds to approximately 8–10% of acute ischemic stroke.

Transcranial color-coded duplex sonography (TCCD) combines the imaging of intracranial vessels and parenchymal structures. To penetrate the skull, TCCD uses low frequencies (1.75–3.5 MHz), which limit the spatial resolution. Some patients cannot be examined because of an insufficient acoustic window. The duplex mode of TCCD enables sampling of vessels and Doppler measurements of angle-corrected blood-flow velocities. Mean velocity analysis is not enough to identify intracranial vessel abnormalities. It must be combined with other parameters such as asymmetry, segmental elevations, spectral analysis, and knowledge of extracranial circulation. The use of echo-contrast enhancing agents (ECE) increases the sensitivity and specificity and with ECE the diagnostic confidence of TCCD for intracranial vessel occlusion is similar to that of magnetic resonance angiography.

Recently, a practical algorithm has been published for urgent bedside neurovascular ultrasound examination.

Sonography in acute stroke of the anterior cerebral circulation.

- Technical requirements: extracranial and transcranial duplex, supplemented by Doppler if necessary (e.g.supratrochlear artery)
- Course of examination: color-coded visualization of the ipsilateral internal carotid artery and middle cerebral artery (MCA) with Doppler spectrum, supported by signal enhancers if necessary. In case of a suspected proximal

occlusion of the MCA, color-coded visualization of the other ipsilateral and contralateral arteries of the cerebral circle in the same acoustic window. In case of a suspected distal occlusion of the MCA or its branches, angle-oriented determination of the blood flow velocity in the proximal MCA. In case of unclear situations, also sonographic detection of the supratrochlear artery and the common carotid artery comparing the two sides.

With a completely normal spectral TCD, there is less than 5% chance that an urgent angiogram will show any acute obstruction.

TCD identifies microembolic signs (MES) in the intracranial circulation. Detection of MES can identify patients with stroke or TIA likely to be due to embolism and, in addition, acts as a predictor for new cerebral ischemic event recurrence. TCD monitoring may help to discriminate between different potential sources of embolism (i.e. artery-to-artery or cardioembolic strokes). Different types of emboli (i.e. cardiac or carotid) have different acoustic properties and ultrasonic characteristics, based on composition and size, which could permit differentiation. MES detection by TCD in carotid endarterectomy (CEA) candidates may allow identification of a particularly high-risk group of patients who merit an early intervention or, if this is not possible, more aggressive antithrombotic therapy.

New UCAs that can pass through the microcirculation and the development of contrast-specific imaging modalities make it possible to use ultrasound for the visualization of brain perfusion deficits. But perfusion imaging in acute stroke is still in the experimental phase.

Ultrasound has an important prognostic role in acute stroke and can be used to monitor thrombus dissolution during thrombolysis. The waveform changes correlate well with clinical improvement and a rapid arterial recanalization is associated with better short-term improvement, whereas slow flow improvement and dampened flow signals are less favorable prognostic signs.

TCD can be used not only for diagnostic and prognostic purposes, but also for therapy. The ultrasound enhances enzymatic thrombolysis, increasing the transport of rtPA into the thrombus and improving the binding affinity, and provides a unique opportunity to detect recanalization during and after rtPA administration. Arterial recanalization can be further enhanced by combining rtPA, ultrasound, and gaseous microbubbles. Newer-generation bubbles permeate through the thrombus and erode the thrombus surface, which increases the surface area for the thrombolytic action of rtPA.

The changes in cerebral blood flow in response to vasomotor stimuli can be studied by TCD. Decreased vasomotor reactivity suggests failure of collateral flow to adapt to a stenosis and can help identify patients at higher risk of stroke.

Contrast-enhanced TCD can also be used to identify patients with a patent foramen ovale.

TCD can further help in clinical decision-making by

- monitoring during CEA and thus reducing perioperative complications due to cerebral hypoperfusion– if flow velocity in the MCA velocity decreases by more than 30% on carotid cross-clamping
- detecting microembolism during release of carotid cross-clamps
- identifying the possibility of cerebral hyperperfusion syndrome if MCA velocities increase by more than 1.5 times pre-cross-clamp values and last more than 30 seconds after release of carotid cross-clamps
- monitoring sickle-cell disease children to determine those suitable for receiving for transfusion therapy.

Acknowledgement

The author is very grateful for the help and advice of Professor Manfred Kaps by preparing the manuscript.

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