Monitoring for Emboli Detection (Without and With Microbubbles)

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Monitoring for Emboli Detection (Without Micro-Bubbles Injection)

Cardioembolic stroke accounts for 14–30% of ischemic strokes [1, 2]; patients with cardioembolic infarction are prone to early and long-term stroke recurrence, although recurrences may be preventable by appropriate treatment during the acute phase and strict control at follow-up [3, 4]. Cardioembolic stroke occurs when the heart pumps unwanted materials into the brain circulation, resulting in occlusion of brain vessels and brain tissue infarction. TCD ultrasonography is the only available modality for detecting microembolic material in gaseous and solid states in real-time, within the intracranial cerebral arteries. These microembolic signals (MES) or high-intensity transient signals (HITS) have distinct acoustic impedance properties when compared to erythrocytes that flow simultaneously and early experimental studies demonstrated the high sensitivity of Doppler ultrasound in detecting arterial emboli [5, 6]. The ultrasound signals reflect off emboli prior to flowing erythrocytes in blood and due to this

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phenomenon, the reflected Doppler signal has a higher intensity signal visible within the Doppler spectrum [7]. Emboli have been detected in a number of clinical conditions: carotid artery stenosis, aortic arch plaques, atrial fibrillation, myocardial infarction, prosthetic heart valves, patent foramen ovale, valvular stenosis, during carotid surgery, open-heart surgery, stent implantation, percutaneous transluminal angioplasty, angiography and other procedures (Table 1). The 1995 Consensus Committee of the Ninth International Cerebral Hemodynamics Symposium identified embolic signals according to their defined features: short duration (lasting 0.01–0.1 second), unidirectional, high-intensity signals visible in the Doppler spectrum, occurring randomly within the cardiac cycle, accompanied by a characteristic "chirping" or "clicking" sound, and without any possible source of artifact at the same time [8] (Fig. 1). It should be noted, however, that embolic signals may occasionally produce bidirectional signals, particularly if gaseous in composition or with inadequate instrumentation settings [9]. In 1998 the International Consensus Group on microembolus detection suggested guidelines for the most important technical parameters for proper use of TCD identification of emboli in clinical practice, as well as in scientific investigations [9]. These parameters are the following:

(i) The relative intensity increase: the ratio of the acoustic power backscattered from the embolus to that of the moving blood surrounding the embolus (measured in dB).
(ii) Detection threshold: decibel thresholds ranging from 3 to 9 dB have been recommended for discriminating MES from the background noise and from spontaneous fluctuations of physiological Doppler flow signals.
(iii) The axial length of the sample volume affects the relative intensity increase and can be manipulated. Most investigators use a sample volume length $\geq$3 and $\leq$10 mm.
(iv) Frequency and temporal resolution: The data length analyzed should usually not exceed 5–10 ms to achieve a spectral resolution of the FFT of 100–200 Hz (lower FFT frequency resolution is preferred).

Table 1 Conditions in which Microembolic signals can be detected

Asymptomatic high-grade internal carotid stenosis (ACS)
Symptomatic high-grade internal carotid stenosis
Prosthetic cardiac valves
Myocardial infarction
Atrial fibrillation
Aortic arch atheroma
Fat embolization syndrome
Cerebral vascular disease
Coronary artery catheterization
Coronary angioplasty
Direct current cardioversion
Cerebral angiography
Carotid endarterectomy (CEA)
Carotid angioplasty
Cardiopulmonary bypass
Brain aneurysm
Hughes-Stovin syndrome
Marantic endocarditis
Deep vein thrombosis
Mitral valve prolapse
Polyarteritis nodosa
Pelvic vein thrombosis
IV catheter infection
Renal vein thrombosis
Idiopathic dilated cardiomyopathy
Renal vein thrombosis
Dilated cardiomyopathy
Aortic aneurysm, abdominal
Endocarditis
Atrial myxoma
Ventricular aneurysm
Surgery complication
Cholesterol embolism

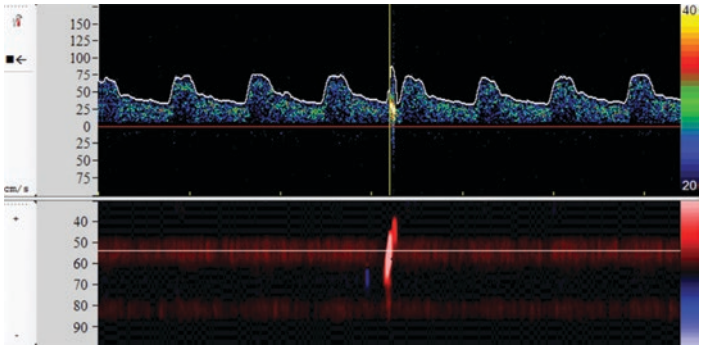

Fig. 1 Single MES reflection in regular Doppler spectrum (upper part of display) and in M-Mode (lower part of display). (This illustration is courtesy of DWL, Germany)

(v) Temporal overlap: An FFT overlap of at least 50% is important to avoid missing individual microembolic signals.
(vi) Minimizing the background signal by using a low power and low gain is recommended to allow strong embolic signals to be completely displayed within the dynamic range of the instrument.
(vii) Ultrasound frequency: The most frequently used frequency is 2 MHz because sensitivity is lower with higher frequencies.
(viii) High and low pass filter settings should be kept constant.
(ix) A recording time of at least 1 hour is recommended for patients with carotid stenosis or atrial fibrillation, but shorter times (30-minutes) may suffice in patients with mechanical heart valves.

Carotid stenosis is an important cause of ischemic stroke, with artery-to-artery embolism being the most common mechanism. In 1991, the European Carotid Surgery Trial [10] and North American Symptomatic Carotid Endarterectomy Trial [11] reported a beneficial effect in favor of CEA in recently symptomatic patients with high-grade carotid artery stenosis. In these clinical trials, the reduction in stroke risk is attributed to removal of the cerebral embolic source, carotid plaque in most cases.

Stork et al. confirmed that MES are more likely to be detected among symptomatic patients with high grade carotid stenosis compared with asymptomatic patients and that higher numbers of MES are more common among symptomatic vs. asymptomatic patients [12]. Most MES are asymptomatic, but are still believed to be a marker of risk for cerebral ischemia [13]. To define patients with ACS who will benefit from medical, surgical or endovascular intervention TCD emboli monitoring can be helpful. Molloy and Markus observed that TCD based identification of asymptomatic embolization in patients with >60% carotid artery stenosis was an independent predictor of future stroke risk in both symptomatic and asymptomatic patients [14]. Another prospective study suggested that cerebral microembolism detected with TCD sonography may define a high-risk subgroup among patients with high-grade ACS [15]. The Asymptomatic Carotid Emboli Study was a prospective observational study in patients with ACS of at least 70% from 26 centers worldwide. To detect the presence of embolic signals, patients had 1-hour TCD recordings from the ipsilateral middle cerebral artery (MCA) at baseline and at 6, 12, and 18 months. This study reported an absolute annual risk of ipsilateral stroke or TIA at 2 years of 7.13% in patients with embolic signals and 3.04% in those without, and for ipsilateral stroke, 3.62% in patients with embolic signals and 0.70% in those without [16]. Thus, the presence of emboli on TCD distal to a high-grade asymptomatic ICA stenosis identifies patients at higher risk of first-ever stroke [16]. Sometimes the presence of emboli can be the only sign of a proximal or distal arterial dissection, partially occlusive thrombus, artery-to-artery embolism or unrecognized cardiac source of embolism. Patients with ACS should not be offered surgical or endovascular intervention without first being identified as high risk as percent stenosis itself can be misleading. One way to improve the risk to benefit ratio for intervention is with TCD emboli monitoring [17]. Finally, a systematic review and meta-analysis found that TCD emboli monitoring provides clinically useful information about stroke risk for patients with carotid disease and is technically feasible in most patients [18].

Emboli detection can also be used to assess the effect of antithrombotic drugs. Antithrombotic therapy is usually prescribed to patients after initial presentation with stroke. MES are affected by antithrombotic agents [19]. Goertler et al. utilized TCD emboli monitoring to localize an embolic source and to monitor the effects of antithrombotic treatment in 81 patients with atherosclerotic CVD [20]. The CARESS trial was the first multicenter study to use MES detection with TCD monitoring as a surrogate end point to evaluate antiplatelet efficacy and showed that using MES as an outcome parameter with appropriate quality control measures is feasible [21]. Spence et al. showed that cardiovascular events and MES on TCD significantly declined with more intensive medical therapy [22]. They concluded that fewer than 5% of patients with ACS likely benefit from revascularization, and that ACS patients should receive intensive medical therapy with consideration of revascularization only if MES are observed on TCD [22]. A subsequent review of the role of TCD emboli monitoring in patients with multi-territory acute embolic strokes showed that presence of MES, especially in multiple intracranial arteries, is associated with increased risk of symptomatic, recurrent embolization [23]. This finding may justify a more aggressive treatment approach (clopidogrel load followed by dual antiplatelet therapy or alternatively therapeutic dose of low-molecular-weight heparin).

Several technical issues associated with TCD emboli monitoring warrant discussion, including validity of automatic software for emboli detection, total time for MES monitoring, and best time for MES monitoring during the natural day (24 hours). Kouame et al. suggested an approach for detection of small MES, called the neuro-fuzzy technique. In the field of artificial intelligence, neuro-fuzzy refers to combinations of artificial neural networks and fuzzy logic in which MES detection is performed using only one gate instead of multiple-gate TCD instruments [24]. Another study suggests that using only single-channel, single-frequency Doppler ultrasound, the HITS detection and character-

ization method using a weighted-frequency Fourier linear combiner that estimates baseline Doppler signal power allows more accurate and sensitive detection and segmentation of embolic signatures compared to commercial TCD emboli-detection software [25]. Abbott et al. demonstrated that embolism associated with ACS shows circadian variation with highest rates 4–6 hours before midday [26]. This corresponds with peak circadian incidence of stroke and other vascular complications. Accurate and reliable characterization of embolus size and composition is still not possible with current technology. An optimum recording protocol is not defined. One hour probably is required [27–29] but this finding has not been validated by a prospective study. In patients with mechanical heart valves, a 30-minute recording time may be sufficient.

Patients with acute and sub-acute ischemic strokes and TIAs can also undergo TCD emboli monitoring to detect, localize, and quantify cerebral embolization [30]. This information is helpful to establish the mechanism of stroke and potentially change management strategy, especially if emboli are found suggesting artery-to-artery embolization or continuing embolization despite treatment both in patients with symptomatic and asymptomatic extracranial or intracranial large artery disease [31].

TCD emboli monitoring may also be useful during surgeries, like CEA and cardiothoracic surgeries due to relatively high frequency of stroke as a complication. One study of 500 patients who underwent CEA with TCD monitoring of the ipsilateral MCA during various phases of CEA concluded that embolism (54%) is the primary cause of cerebrovascular complications from CEA [32]. TCD monitoring during CEA provides clinically useful information about embolic phenomena and flow patterns in the cerebral vasculature that may prompt appropriate measures at several stages of CEA to reduce the risk of perioperative stroke [32–34]. TCD emboli monitoring is therefore considered possibly useful during cardiac surgery, but remains investigational [35–39].

Monitoring for Emboli with Micro-Bubble Injection

Patent foramen ovale (PFO) has been associated with cryptogenic stroke allowing paradoxical embolism from the veins to the brain through an RLS [40]. PFO is a permanent opening through the interatrial septum or a hole between the upper chambers of the heart that fails to close after birth and often persists into adulthood. Blood flows back and forth through the defect depending on the pressure gradient between the atria. For the vast majority a PFO is well-tolerated. PFO is found in 34% of adults in the first three decades of life declining to 20% in the ninth and tenth decades and ranging from 1 to 19 mm in diameter [41].

Problems arise when a blood clot crosses the PFO and enters the cerebral circulation causing an ischemic stroke. This paradoxical embolism may occur more often than suspected.

Initially, PFO is considered when stroke occurs in a young person. One study reported an incidence of abnormal cardiac RLS – i.e. PFO or atrium septum defect in 40% of ischemic stroke patients compared with 10% of a control group [42]. Thus cardiac RLS is considered a risk factor in cryptogenic stroke, particularly in young patients with no additional risk factors. The frequency of PFO is even higher (55%) in patients with cerebral infarct of unknown etiology or so-called cryptogenic infarct [43], especially in the younger age group [44, 45]. Nevertheless, a recent systematic review and meta-analysis showed the association of RLS with cryptogenic events remained at older ages and overall the population burden of PFO-associated events is substantial [46]. In addition, migraine patients with aura have 3–1 odds of having a PFO compared to a non-migraine group [47]. Given that the conditions for venous thrombosis and pulmonary embolism are also common in the general population, the risk for paradoxical embolism is prevalent at all ages.

The motivation to diagnose PFO is driven by the manufacture of safe transcatheter closure devices and the popularity of contrast-TCD (c-TCD) over invasive contrast transesophageal echocardiography (c-TEE) or contrast transthoracic echocardiography

(c-TTE). Using intravenous injections of agitated saline (Fig. 2), the suspended bubbles pass through the PFO from the right to the left atrium and are easily detected by TCD as audible chirps and microembolic spectra in the cerebral arteries. A Valsalva Maneuver (VM) facilitates passage of the microbubbles through the PFO by

Fig. 2 Example of set-up for intravenous injection of agitated saline

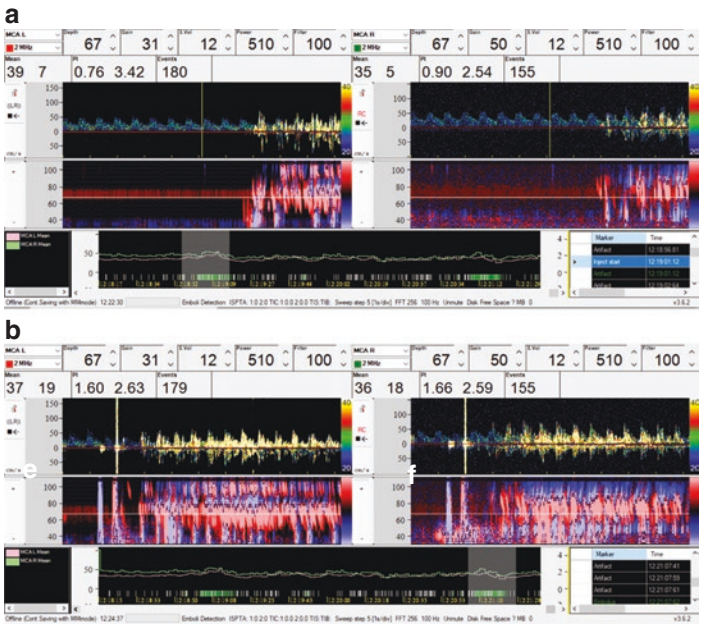

Fig. 3 C-TCD at rest (**a**) and at Valsalva maneuver demonstrating "curtain" of emboli (**b**)

raising the pressure in the right atrium over that of the left atrium (Fig. 3). Agitated saline contrast agent has been used safely for many years in echocardiography and TCD.

C-TEE until recently was considered the gold standard for PFO detection and diagnostic yield is enhanced using contrast agents. However, the c-TEE examination may lack sufficient sensitivity if sedation is required, as the sedated patient is often not capable of performing VM or forced expiratory effort adequately, which is frequently an indispensable prerequisite to elicit a RLS. Although c-TTE allows the diagnosis of RLS by means of color Doppler, the flow that is inverted intermittently may not be detected, and thus c-TTE may not be sensitive enough to diagnose RLS [48]. TCD monitoring with contrast injection has turned out to be a reliable method to diagnose PFO [49, 50] and has

demonstrated high accuracy in ruling in and ruling out PFO when compared to the gold standard c-TEE [47, 51–54]. Belvis et al. [53] showed almost perfect concordance between simultaneous c-TCD and c-TEE in the quantification of RLS. Moreover, c-TCD appears to be more sensitive and specific for PFO detection than c-TEE or c-TTE [55, 56]. c-TCD is sensitive to detect RLS, even in patients with negative TTE or TTE [58].

The 2000 International Consensus Meeting determined a four-level categorization according to emboli appearance in the TCD spectrum as category 1: up to 10 MES; category 2: 11–20 MES; category 3: more than 20 MES; category 4: "curtain-like" pattern, quantification is not possible because the MES signals fills the entire spectrum [57]. In addition, main advantages of contrast TCD as compared to TEE in the detection of RLS are: (1) the VM can more comfortably be applied during TCD than during TEE and (2) size and functional relevance of RLS can more easily be assessed using contrast TCD than using TEE. Spencer et al. [58] also suggested a PFO grading scale using a 6-level logarithmic scale: no MES – grade 0; 1–10 MES grade I; 11–30 MES grade II; 31–100 MES grade III; 101–300 MES grade IV; and above 300 MES – grade V (Table 2). Examples of c-TCD test at rest and with VM are shown in Fig. 3.

Power m-mode TCD (pmTCD) detects more bubble microemboli than traditional single gate conventional TCD [59]. If pmTCD testing is positive, TEE may be indicated to confirm the type and

Table 2 Spencer grading scale for reporting MES on TCD using power m-mode [58]

	Unilateral test	Bilateral test
Grade 0	0	0
Grade 1	1–5	1–10
Grade 2	6–15	11–30
Grade 3	16–50	31–100
Grade 4	51–150	101–300
Grade 5	>150	>300
Grade 5+	Uncountable, curtain	Uncountable, curtain

MES counted at rest and during Valsalva release

location of the shunt and to detect other potential cardiac abnormalities including an atrial septal aneurysm. If pmTCD is negative, there is no need to search further for a RLS as a cause of cryptogenic stroke. pmTCD provides greater sensitivity to contrast bubble emboli that does single-gate TCD and among candidates for transcatheter closure, pmTCD therefore offers an improved noninvasive method for diagnosing PFO and evaluating effect of transcatheter closure [48, 60–62].

Optimal patient setup and protocol for c-TCD are still to be perfected. Patient positioning while performing c-TCD is a matter of ongoing discussion. Some authors suggest raising the patient's position from supine to sitting to improve the sensitivity of c-TCD in the detection of PFO in the case of a first negative test [63, 64]. Some publications suggest using a small sample of the patient's own blood to obtain an agitated saline solution as a means of increasing the number of microbubbles generated [65, 66]. Other authors discuss the importance of the time interval between injection in the antecubital vein and detection of microbubbles in the MCA and concluded that observation of >10 microbubbles of agitated saline at less than 10 seconds on TCD (with VM) is highly sensitive and specific for the diagnosis of RLS [67]. They also found that use of a plasma volume expander, oxypolygelatine, caused a significantly higher number of microbubbles compared with saline as contrast media. Similarly, Droste et al. showed that c-TCD yielded 100% sensitivity to identify TEE–proven cardiac RLS [51]. Patients in this study were asked to perform VM 5 seconds after administration of contrast. Schwarze et al. suggested that 10 mL of contrast medium should be injected with the patient in the supine position and that VM be performed 5 seconds after the start of the injection [68]. A strong relationship is reported between the size of the PFO on TEE and the number of MES on c-TCD ($P < 0.0001$) [69]. A consensus statement established a standardization of the c-TCD technique protocol and its interpretation [46]. Among these recommendations: (a) Always quantify the MES at rest and during provocative maneuvers; report numbers of MES separately; (b) Perform the examination three times at rest, and afterwards three times under provocative maneuvers. Consider the examination

completed if the "curtain-like" pattern is observed at rest; (c) Explain the Valsalva maneuver to the patient and have them practice it prior to beginning the test in order to check that the provocative test has a reliable response; (d) Consider a positive result the detection of at least one MES with spectral visualization and coincident signal on M-mode, as well as the typical sound pattern. Consider it a non-significant positive result if fewer than 10 MES are detected only during the provocative maneuver; (e) Report the findings according to four categorization levels [57]; (f) For bilateral tests, use the highest number obtained in each channel and do not sum the number of MES detected in the right and left MCA; g) Document results for "at rest" and VM separately.

Conclusion

C-TCD monitoring with contract injection has established value for evaluation of patients with unknown cause of stroke and suspected RLS. Although c-TCD itself is sufficient for diagnostic screening of RLS with high sensitivity (97%) and specificity (93%) – class IIA, its use alone is not recommended [35]. The direct evaluation of RLS and anatomical observation of the atrial septum remains important, especially if PFO closure is to be considered.

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