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Hemodynamic causes of deterioration in acute ischemic stroke

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Summary Neurological deterioration can occur in 13—38% of patients with acute ischemic stroke due to hemodynamic and non-hemodynamic causes. Several non-hemodynamic mechanisms can lead to ischemic lesion extension and subsequent neurological worsening, including infections, cerebral edema, hemorrhagic conversion of infarction and metabolic disorders. The most common hemodynamic causes related to infarct expansion, leading to neurologic deterioration in the setting of acute cerebral ischemia are the following: (i) cardiac complications, (ii) arterial reocclusion, (iii) intracranial arterial steal phenomenon, and (iv) cerebral microembolization. The present review aims to address the underlying mechanisms and potential clinical implications of the hemodynamic causes of neurological deterioration in patients with acute cerebral ischemia. The contribution of neurosonology in detection of changes in cerebral hemodynamics in real-time are also going to be discussed. Finally, potential treatment strategies for specific causes of hemodynamic deterioration in acute ischemic stroke patients are reported.
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Early neurological deterioration: prevalence and definitions

Early neurological deterioration (END) has been described as worsening in neurological function during the first days of acute cerebral ischemia (ACI) [1]. The prevalence of END varies in different studies according to the definition used for END detection [1]. An Italian study reported that END occurred in 20—26% of non-thrombolysed patients presenting with acute ischemic stroke (AIS) [2]. END was defined as a decrease of 1 or more points, in the Canadian Neurological Scale (CNS) score from hospital admission to 48 h after stroke onset. The investigators of European Cooperative Acute Stroke Study (ECASS) I identified factors that potentially predicted or were associated with progression of stroke and evaluated the influence of stroke progression on neurologic worsening. Early progressing stroke (EPS) was defined as a decrease of $\geq$2 points in consciousness or motor power or a decrease of $\geq$3 points in speech scores in the Scandinavian Neurological Stroke Scale from hospital admission to the 24-h evaluation. END was documented in 37.5% of all patients during the first 24 h after inclusion in the study (37% in the placebo group and 38% in the recombinant tissue plasminogen activator group) [3]. Grotta et al. used the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trial database to document the

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prevalence of clinical deterioration following improvement (DFI) and of any significant clinical deterioration (CD) even if not preceded by improvement. DFI was defined as any 2-point deterioration on the NIH Stroke Scale (NIHSS) score after an initial 2-point improvement after treatment. CD was defined as any 4-point worsening after treatment compared with baseline. DFI and CD identified in 13% and 16% of all patients, respectively [4]. END was also detected in 19% and 13% of patients hospitalized in general medical wards and acute stroke units, respectively, according to the findings of an Australian [5] and German [6] study, respectively. END was defined as 1-point and 2-point increase in NIHSS (during the first three and five days of ictus respectively) in the Australian and German study, respectively.

Recent studies have shown that END is an independent predictor of poor outcomes in the setting of AIS. More specifically, the investigators of SORCan (Stroke Outcomes Research Canada) registry have reported that END (defined as 1-point decrease in CNS) was an independent predictor of 7-day, 30-day and 1-year case fatality rate in a cohort of 3631 patients [7]. Similarly, END was associated with higher rates of death during hospitalization, longer duration of hospitalization and lower rates of functional independence in an Australian study [5].

Causes of early neurological deterioration

The causes of END can be classified into two major groups: hemodynamic and non hemodynamic [1]. Several non-hemodynamic mechanisms can lead to ischemic lesion extension and subsequent neurological worsening, including infections, cerebral edema/increased intracranial pressure, hemorrhagic conversion of infarction and metabolic disorders (hypoxia, hyperglycemia and fever) [1]. The most common hemodynamic causes related to infarct expansion, leading to END in the setting of ACI are the following: (i) cardiac complications, (ii) arterial reocclusion, (iii) intracranial arterial steal phenomenon and (iv) cerebral microembolization.

Cardiac complications and END

Patients with severe disabling strokes are particularly vulnerable to cardiac complications because stroke can provoke disturbances in autonomic and neurohormonal control and predispose patients to severe cardiac adverse events (SCAEs). It is well-known that acute stroke may lead to a variety of cardiac abnormalities such as myocardial infarction, electrocardiographic changes, cardiac arrhythmias, cardiac arrest, stress cardiomyopathy (tako-tsubo syndrome) and intracardiac thrombus [8]. SCAEs can hinder functional recovery and contribute to cardiac morbidity and mortality [8]. They are common in the acute period after stroke onset (19.0% of all patients experience at least one SCAE) and are responsible for 2—6% of the total mortality three months after acute ischemic stroke [9]. The main predictors of SCAE are outlined below: history of heart failure, diabetes mellitus, baseline creatinine >115 μmol/L, severe stroke, and a long QTc (>450 ms in men and >470 ms in women) or ventricular extrasystoles on ECG, low admission systolic blood pressure (<110 mmHg) and right insular stroke [8,9]. Right insular region has been shown to moderate the autonomic control of the heart and this may partly explain the potential relationship of right insular stroke with SCAEs. Moreover insular infarction is associated with abnormal cardiac repolarization and increased risk of vascular mortality [9].

The main mechanisms linking SCAEs with END are outlined below: (i) hemodynamic instability/hypotension (which may in turn worsen the impaired cerebral autoregulation and further reduce perfusion in the infracted brain tissue), (ii) increased risk of sudden cardiac death, and (iii) increased risk of recurrent stroke and systemic embolism. There is mounting evidence linking extremely low admission BP levels with adverse early and late functional outcomes in patients presenting with ACI [10,11]. In addition the results of a recent randomized phase III trial showed that acute antihypertensive therapy causing mild BP reductions (3—6 mmHg) during the first 7 days of AIS was not related to better functional outcome or lower rates of cardiovascular events when compared to placebo. In contrast, stroke progression was increased by almost 50% in patients treated with antihypertensive therapy in comparison to the placebo group [12].

Potential therapeutic strategies of END caused by cardiac complications

The following therapeutic measures may be considered in patients with END caused by SCAEs:

1. Avoiding antihypertensive medications during the first 48 h of ACI (unless systolic blood pressure/diastolic blood pressure > 220/120 mmHg).
2. Prolonging cardiac monitoring in patients at high risk for cardiac arrhythmias in order to increase the yield of timely detection of cardiac arrhythmias and early initiation of appropriate medications (e.g. beta-blockers).
3. Avoiding fluid overload in patients with congestive heart failure.
4. Using early anticoagulation (unfractioned heparin) in patients with intracardiac thrombus.
5. Using pressors in patients wih Tako-tsubo syndrome in order to increase the cardiac output.

Arterial reocclusion and END

Early reocclusion may be the most common mechanism of early clinical fluctuation and worsening after thrombolytic therapy and intra-arterial procedures for acute ischemic stroke, leading to poor clinic outcome and higher in-hospital mortality [13,14]. Thrombolytic therapy has been demonstrated to be effective in acute stroke by dissolving the arterial occlusion and reestablishing tissue perfusion. However, the beneficial effect of tissue plasminogen activator (tPA)-induced recanalization may be eventually hampered by the occurrence of reocclusion [13,14].

Early reocclusion occurs in 15—34% of AIS patients treated with iv-tPA achieving any initial recanalization, accounting for up 2/3 of deterioration following improvement [13,14]. Reocclusion can be detected in real-time using transcranial Doppler (TCD) monitoring [13—16]. Reocclusion is observed in 17% of patients, who undergo intra-arterial

thrombolysis based on catheter angiographic surveillance [17]. Reocclusion can also occur during or after catheter-based interventions [18]. In particular, the prevalence of reocclusion occurring during and within an hour after intra-arterial reperfusion procedures (mechanical thrombectomy, thromboaspiration, intra-arterial thrombolysis) is 19% and 8%, respectively [18].

Reocclusion in stroke patients appears to occur most in those with partial initial recanalization. These patients may be prone to repeated thrombosis and artery-to-artery reembolization particularly in the setting of a large vessel atherosclerosis [14,19]. Another potential independent predictor of reocclusion is severe stroke given the fact that increased stroke severity as reflected by higher NIHSS-scores represents larger thrombus burden [20]. Interestingly, Rubiera et al. have documented that admission NIHSS-scores higher than 16 points and severe ipsilateral carotid disease were independently associated with reocclusion in multivariate logistic regression models adjusting for potential confounders [14]. Finally, arterial reocclusion was related to lesser neurological improvement during hospitalization and lower rates of three-month functional independence in two stroke registries of systemic thrombolysis [14,19].

Early reocclusion can be detected in real-time with continuous 1-h TCD-monitoring during iv-tPA infusion [13,14] and our pilot study demonstrated that TCD can detect arterial reocclusion during or within an hour after completion of intra-arterial procedures [18]. There is also small anecdotal data indicating that continuous ultrasound surveillance may provide rapid detection of reocclusion (Fig. 1) as well as persistent occlusion and assist in subsequent management decisions including GPIIb-IIIa antagonist administration [21] or direct thrombin inhibitor administration (such as argatroban) [22] in patients with END due to reocclusion.

Potential therapeutic strategies of END caused by arterial reocclusion

The following therapeutic measures may be considered in patients with END caused by arterial reocclusion:

- TCD-monitoring of intracranial vessel patency during the first hours following reperfusion procedures (especially during the first 2 h following tPA-bolus).
- Emergent intra-arterial reperfusion procedures (thrombectomy/thromboaspiration) if reocclusion is detected.
- Continuous 2-h argatroban infusion following standard intravenous thrombolysis may be a future therapeutic option for reducing reocclusion.

Intracranial arterial steal phenomenon and END

The Starling resistor model defines cerebral perfusion pressure as the difference between arterial pressure and venous, intracranial, or tissue pressure (whichever is highest) [23]. Blood flow occurs due to pressure gradient with blood following the path of least resistance and flow diversion being caused by effective outflow differences for the Starling resistors [23]. The concept of blood flow steal in the cerebral circulation is well established [24]. In brain, hemodynamic steal and shunts were documented with angiomas and hypervascularized brain tumors [24,25]. Neurological symptoms were linked to cerebral blood flow reduction with

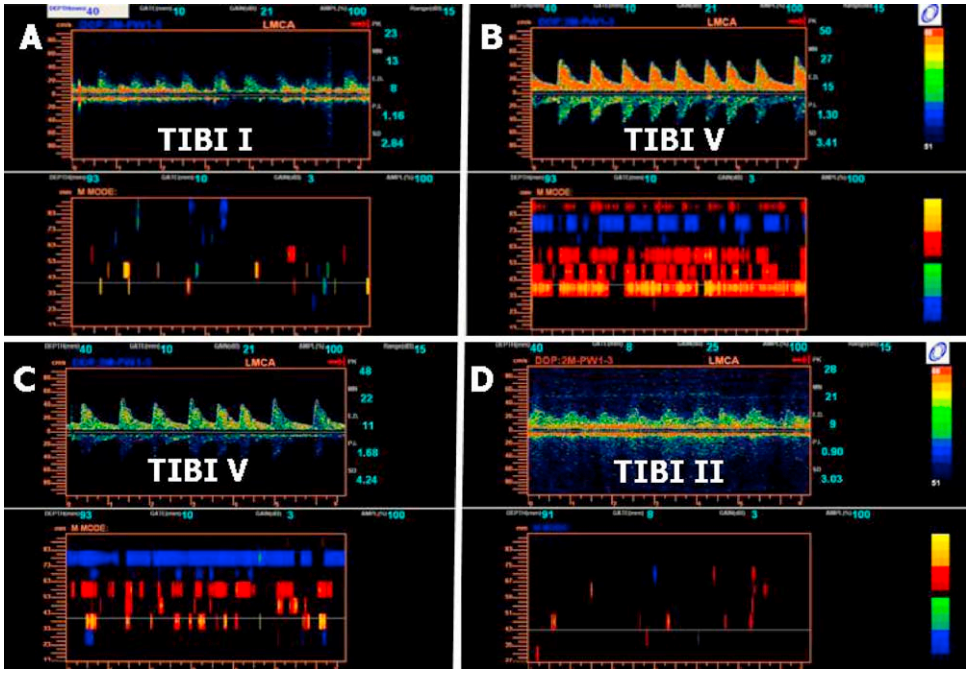

Figure 1 (A) Left M2MCA (middle cerebral artery) occlusion (thrombolysis in brain ischemia TIBI II) before the onset of intravenous thrombolysis (MFV = 13 cm/s, high-resistance flow on M-Mode spectrum). (B) Complete recanalization was achieved 28 min after tPA bolus (TIBI V; MFV = 27 cm/s, low-resistance flow on M-Mode spectrum), (C) Complete recanalization is sustained at 42 min following tPA-bolus (TIBI V) but high-resistance flow signatures appear on M-Mode spectrum, while spectral interrogation reveals an increase in Pulsatility Index (from 1.3 in (B) to 1.7), and (D) re-occlusion occurred at 56 min following tPA-bolus (TIBI II).

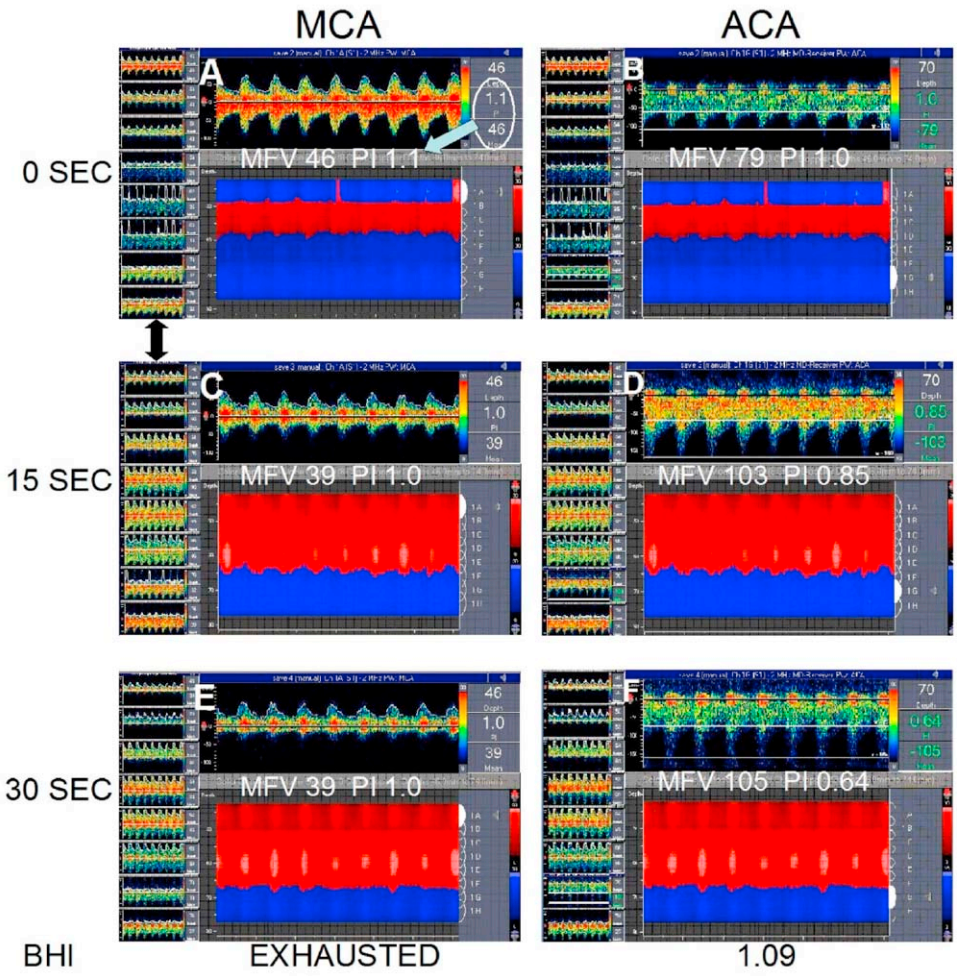

Figure 2 Intracranial arterial steal phenomenon during voluntary breath-holding in a patient with acute cerebral ischemia due to proximal M1MCA occlusion. A decrease in M1MCA MFV (mean flow velocity) is documented during voluntary breath-holding (from 46 cm/s at the beginning to 39 cm/s at the end of breath-holding). A simultaneous substantial flow diversion toward ipsilateral ACA (anterior cerebral artery) is documented during voluntary breath-holding (from 79 cm/s at the beginning to 105 cm/s at the end of breath-holding).

arterio-venous malformations [24] or rare cases of the subclavian steal syndrome [26].

The concept of arterial steal has been evaluated in real-time in the setting of ACI. Alexandrov et al. observed paradoxical decreases in flow velocity during episodes of hypercapnia in vessels supplying ischemic areas of the brain at the time of expected velocity increase in nonaffected vessels [27]. Hypercapnia triggered vasodilation more effectively in normal vessels, thus producing arterial blood flow steal toward the path of least resistance (Fig. 2) [27]. The hemodynamic steal was also documented on CT perfusion before and after challenge with acetazolamide (Diamox). The steal magnitude was linked to severity of neurological worsening in patients with acute stroke [27,28]. This intrancranial steal phenomenon when coupled with END (determined as an increase of >2 points in NIHSS-score) was termed ''Reversed Robin Hood Syndrome (RRHS)'' for an analogy with ''rob the poor to feed the rich [27].

Sharma et al. attempted to evaluate RRHS in a prospective series of patients with severe intracranial steno-occlusive disease using bilateral TCD-monitoring with voluntary breath-holding and acetazolamide-challenged ^{99m}Tc-HMPAO (hexamethylpropylene amine oxime) SPECT [29,30]. The magnitude of arterial steal was calculated using changes in mean flow velocities (MFVs) during TCD-monitoring and net deficit in metabolic perfusion after acetazolamide-challenge on HMPAO-SPECT (Fig. 3). Interestingly, identification of intracranial steal phenomenon on TCD had satisfactory agreement with detection of inadequate vasodilatory reserve leading to perfusion deficit on acetazolamide-challenged HMPAO-SPECT. Moreover, a strong linear correlation was identified between intracranial steal magnitude (%) on TCD [calculated as $[(MFVm - MFVb)/MFVb] \times 100$, where m = minimum and b = baseline MFVs during the 15- to 30-s period of a total 30 s of breath-holding] [27] and net perfusion deficit on SPECT after Diamox-challenge in patients who exhibited both steal phenomenon on TCD and failed vasodilatory reserve on SPECT (Fig. 4).

Alexandrov et al. conducted a pilot study to investigate the prevalence of RRHS in a consecutive series of patients with ACI. They showed that among 153 patients admitted

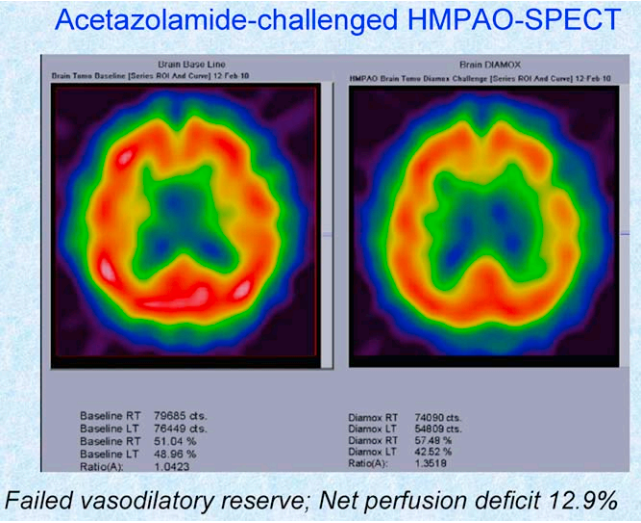

Figure 3 HMPAO SPECT (single-photon emission computed tomography) imaging after acetazolamide (Diamox) challenge shows a paradoxical reduction in the left MCA territory perfusion (net perfusion deficit 12.9%) resulting from the Reversed Robin Hood Syndrome in a patients with acute cerebral arterial ischemia due to left terminal internal carotid artery occlusion.

within 48 h from ACI onset, 21 (14%) had steal phenomenon (median steal magnitude, 20%; interquartile range, 11%; range, 6—45%), and 11 (7%) had RRHS. RRHS was most frequent in patients with proximal arterial occlusions in the anterior circulation (17% versus 1%; $p < 0.001$). Male gender, younger age, persisting arterial occlusions, and excessive sleepiness (evaluated by the Epworth Sleepiness Scale and Berlin Questionnaire) were independently associated with RRHS on multivariate logistic regression models [31].

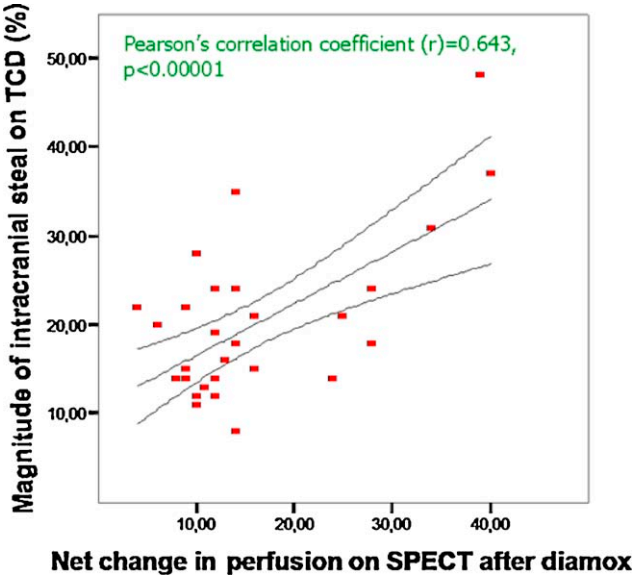

Figure 4 Linear correlation of magnitude of steal phenomenon as quantified on bilateral TCD-monitoring with net perfusion deficit as quantified on SPECT after Diamox-challenge in patients who exhibited both steal phenomenon on TCD and failed vasodilatory reserve on SPECT.

The same group also sought to determine the potential association of RRHS with risk of early recurrent stroke. Their findings indicated that patients with acute anterior circulation ischemic events and RRHS have a significantly higher risk of new ischemic stroke occurrence than acute stroke patients without this condition [32]. This longitudinal association persisted even after adjustment for demographic characteristics, vascular risk factors, and secondary prevention therapies. They also observed that all recurrent strokes in the RRHS subgroup occurred in the anterior circulation vascular territory ipsilateral to the index event [32]. Moreover the risk of recurrent stroke was front-loaded with a four-fold increase being documented during the first 30 days of ictus [30-day stroke risk in RRHS(+) and RRHS(−) patients: 12% and 3%, respectively] [32]. These findings indicate that the hemodynamic compromise caused by the vascular steal phenomenon may be an underlying mechanism linking large vessel atherosclerosis both with neurologic deterioration in the acute stroke setting as well as with recurrent cerebral ischemia during the first month after the index event.

Potential therapeutic strategies of END caused by intracranial arterial steal phenomenon

In the first documented cases of reversed Robin Hood syndrome (RRHS), neurological worsening was also more pronounced in patients with sleep apnea [27] or excessive sleepiness [31]. Hence, patients with persisting arterial occlusions and excessive sleepiness can be particularly vulnerable to the steal. In the first two reports describing RRHS no further END was observed in patients with intracranial arterial steal that were treated with non-invasive ventilatory correction. [27,31] Moreover, early noninvasive ventilatory correction in AIS patients has been shown to be safe and feasible in a recent pilot study [33]. In view of the former considerations, it has been hypothesized that:

(i) RRHS may provide a missing link between the respiratory status and END in ACI with history of obstructive sleep apnea [34]
(ii) and intracranial arterial steal phenomenon and sleep-disordered breathing may represent linked therapeutic targets [34].

Cerebral microembolization and END

TCD can reliably detect in real-time asymptomatic microembolic signals (MESs) in cerebral circulation that are characterized as ''High Intensity Transient Signals'' (HITS) [35—39]. Asymptomatic cerebral embolization can be detected by TCD in 7—71% of patients with ACI (Fig. 5) [35—39]. The prevalence of MES is highest in patients with large-artery atherosclerotic stroke with cardioembolic infarction being the second most common stroke subtype with concomitant asymptomatic microembolization. MES are rarely identified in patients with lacunar stroke. The number of MES detected by TCD negatively correlates to the elapsed time from symptom onset in patients with ACI [35—39]. In other words, the sooner TCD-monitoring is performed from symptom onset the higher the yield of ultrasound detection of MES.

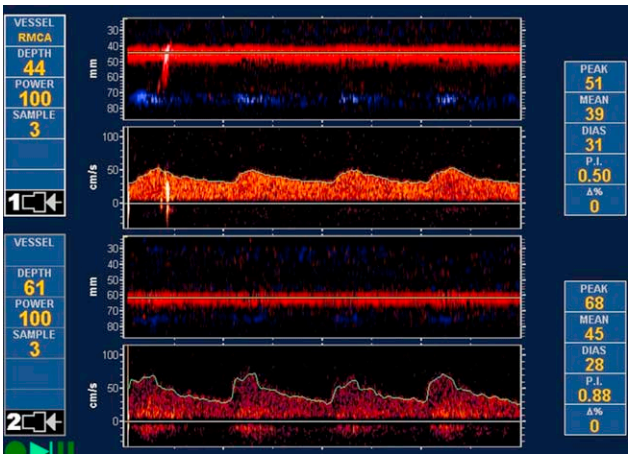

Figure 5 Detection of a microembolic signal in right MCA in a patient with severe (>70%) extracranial carotid artery stenosis during bilateral TCD-monitoring of MCAs. The flow in right MCA displays a characteristic ''blunted'' waveform appearance that is indicative of a more proximal hemodynamically significant steno-occlusive lesion.

MES have been shown to predict recurrent stroke risk in acute stroke, symptomatic carotid stenosis and postoperatively after CEA (Table 1) [35]. MES may also predict first-ever stroke risk in patients with asymptomatic carotid stenosis (Table 1) [36]. More specifically, MES detection by TCD-monitoring increases the risk of recurrent stroke by almost ten-fold (OR: 9.6; 95%CI: 1.5—59.3) in patients with symptomatic carotid artery stenosis (Table 1). Similarly, MES detection by TCD-monitoring increases the risk of ipsilateral stroke by almost seven-fold (OR: 6.6; 95%CI: 2.9—15.4) in patients with asymptomatic carotid artery stenosis (Table 1). Consequently, MES have been used for risk stratification and assessment of therapeutic efficacy in the former conditions [35—37,39]. Hao et al. have recently shown that MES have been associated with END and worsening of neurological deficit in patients with ACI due to large artery atherosclerosis [38]. Iguchi et al. have also reported that the presence of MES at 48 h after symptom onset was associated with recurrence of cerebral ischemia on diffusion weighted imaging (DWI) independent of underlying stroke subtype, [40] while MES detection on baseline TCD-monitoring has been related to the presence of multiple infarction on baseline DWI [35,38].

Potential therapeutic strategies of END caused by cerebral microembolization

Two small pilot randomized clinical trials have provided preliminary evidence that clopidogrel load (300 mg) followed by dual antiplatelet therapy (combination of clopidogrel 75 mg and aspirin 75—100 mg for up to seven days following stroke onset) may reduce substantially asymptomatic microembolization in patients with symptomatic extracranial carotid artery stenosis [CARESS (clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis) trial] [41] or symptomatic stenosis in cerebral or extracranial carotid arteries [CLAIR (clopidogrel plus aspirin versus aspirin alone for reducing embolization in patients with acute symptomatic cerebral or carotid artery stenosis) trial]. [42] Neither CARESS nor CLAIR showed a beneficial effect of dual therapy in reducing the risk of recurrent stroke, but when both studies were combined there was an absolute risk reduction of 6% (95% CI 1—11%) in recurrent stroke with use of dual therapy (combination of aspirin and clopidogrel) compared with aspirin monotherapy. [42] In view of the former considerations, it may be postulated that:

(i) Continuous TCD-monitoring to detect the presence of cerebral microembolization in real-time in patients with large-artery atherosclerotic stroke may be indicated.
(ii) Aggressive antiplatelet therapy (clopidogrel load followed by combination antiplatelet therapy) may be considered during the first days of ictus in patients with ACI due to large-artery atherosclerosis and detection of MES on TCD-monitoring [43].

Table 1 Association of microembolic signals (MESs) detected by TCD and risk of recurrent events in different clinical subgroups.

Patient subgroup	*N* (studies/patients)	Outcome event	OR (95%CI)	Heterogeneity (I^2)
ACI (AIS/TIA) [35]	8/737	Rec. stroke	2.4 (1.2—5.1)[#]	12% (NS)
ACI (AIS/TIA) [35]	8/737	Rec. stroke/TIA	3.7 (1.6—8.4)[¶]	47% (NS)
Sym. Car. Sten. [35]	4/270	Rec. stroke	9.6 (1.5—59.3)[#]	6% (NS)
Sym. Car. Sten. [35]	4/270	Rec. stroke/TIA	6.4 (2.9—13.4)[*]	0% (NS)
Asym. Car. Sten. [36]	6/1144	Ips. stroke	6.6 (2.9—15.4)[*]	13% (NS)
Asym. Car. Sten. [36]	6/1144	Ips. st./TIA	7.6 (2.3—24.7)[&]	73% ($p = 0.002$)
Post-oper. CEA [35]	6/649	Rec. stroke	2.5 (0.8—7.7)[$]	0% (NS)
Post-oper. CEA [35]	6/649	Rec. stroke/TIA	3.6 (1.4—9.2)[@]	0% (NS)

ACI, acute cerebral ischemia; AIS, acute ischemic stroke; TIA, transient ischemic attack; Asym., asymptomatic; Sym., symptomatic; Car. Sten., carotid stenosis; Post-Oper. CEA, post-operative carotid endarterectomy; Rec, recurrent; Ips., ipsilateral; St, stroke; Heter/ty, heterogeneity; and NS, non-significant.

[#] $p = 0.02$.
[¶] $p = 0.002$.
[*] $p < 0.00001$.
[&] $p < 0.001$.
[$] $p = 0.1$.
[@] $p = 0.009$.

(iii) Urgent carotid revascularization procedure (within 2 weeks from symptom onset) should be performed in patients with symptomatic extracranial carotid artery stenosis independent of the presence of MES on TCD-monitoring [44].

Conclusions

Numerous studies using different definitions have shown that END is common in ACI and is associated with adverse functional outcomes. The causes of END may be stratified in two major groups: hemodynamic and non-hemodynamic. The four main hemodynamic causes of END include: cardiac complications, arterial reocclusion, intracranial arterial steal phenomenon and cerebral microembolization. TCD can reliably detect reocclusion in real-time offering us the opportunity to pursue alternative reperfusion strategies. Intracranial arterial steal/RRHS can also be detected by TCD during voluntary breath-holding or using acetazolamide-challenged perfusion CT or HMPAO SPECT. RRHS and sleep-disordered breathing in ACI may represent linked therapeutic targets that potentially could be managed using non-invasive ventilatory correction. TCD can also reliably detect in real-time MES in cerebral circulation that have been independently associated with higher risk of recurrent stroke in patients with ACI. Aggressive antiplatelet therapy may be considered in patients with symptomatic carotid stenosis and MES on TCD, while urgent carotid revascularization procedure (within 2 weeks from symptom onset) should be performed in patients with symptomatic extracranial carotid artery stenosis independent of the presence of MES on TCD-monitoring.

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