

Transcranial Doppler in autonomic testing: standards and clinical applications

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Abstract When cerebral blood flow falls below a critical limit, syncope occurs and, if prolonged, ischemia leads to neuronal death. The cerebral circulation has its own complex finely tuned autoregulatory mechanisms to ensure blood supply to the brain can meet the high metabolic demands of the underlying neuronal tissue. This involves the interplay between myogenic and metabolic mechanisms, input from noradrenergic and cholinergic neurons, and the release of vasoactive substrates, including adenosine from astrocytes and nitric oxide from the endothelium. Transcranial Doppler (TCD) is a non-invasive technique that provides real-time measurements of cerebral blood flow velocity. TCD can be very useful in the work-up of a patient with recurrent syncope. Cerebral autoregulatory mechanisms help defend the brain against hypoperfusion when perfusion pressure falls on standing. Syncope occurs when hypotension is severe, and susceptibility increases with hyperventilation, hypocapnia, and cerebral vasoconstriction. Here we review clinical standards for the acquisition and analysis of TCD signals in the autonomic laboratory and the multiple methods available to assess cerebral autoregulation. We also describe the control of

cerebral blood flow in autonomic disorders and functional syndromes.

Keywords Transcranial Doppler · Cerebral blood flow velocity · Syncope · Orthostatic hypotension · Autonomic testing · Autonomic failure · Dysautonomia

Introduction

Cerebral blood flow (CBF) is normally 50–60 ml/min per 100 g of brain tissue [52]. Despite the human brain weighing only 2% of the total body mass, it receives 15% of the cardiac output at rest and consumes 20% of the body's oxygen [94]. Brain tissue has high metabolic demands and, in order to maintain consciousness, it must receive an adequate supply of blood flow to ensure that energy and oxygen demands are met. When cerebral blood flow falls below a critical limit, even for a few seconds, syncope occurs (i.e., reversible loss of consciousness with no neurological sequelae [46, 94]). The inbuilt capacity of the cerebral circulation to regulate its own flow to remain constant in the face of changes in perfusion pressure is known as cerebrovascular autoregulation.

CBF autoregulation involves integrative interactions between brain tissue metabolism, systemic blood pressure (BP), and arterial blood gases, as well as neurogenic input from the central autonomic network. This interplay occurs at the level of the arterioles in the cerebrovasculature and at the neurovascular unit, and over multiple time scales from seconds to hours [40]. This adaptability ensures that the delivery of oxygen and nutrients can meet the high metabolic demands of the underlying neuronal tissue in different regions of the brain [52, 75, 94]. The failure of cerebral autoregulation can occur at any age. The elderly

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population, in particular those with autonomic or cardiovascular disorders, are at a greater risk for dementia, stroke, long-term disability, and death [13, 15, 69].

In this review we focus on transcranial Doppler ultrasound (TCD) as a non-invasive method to evaluate cerebral hemodynamics and its usefulness in the outpatient autonomic clinic. We review the available literature, searching the PubMed database with the following keywords: cerebral blood flow, transcranial Doppler, syncope, orthostatic hypotension, autonomic testing, and autonomic failure. Emphasis was given to articles published within the last 10 years.

The current state-of-the-art assessment of cerebral autoregulation using TCD lacks validated tools and methodologies to reliably detect impaired blood flow regulation. Clinical validation will require a collaborative effort to organize a randomized well-powered controlled trial in a large population. International consensus guidelines exist to standardize TCD measures for best clinical practice [13], and these should enable the international standardization of methodological approaches and validation of the tools necessary to assess cerebral autoregulation in the autonomic laboratory.

The physiology of CBF autoregulation

Autoregulation of CBF buffers variations in cerebral perfusion pressure to provide a constant supply of blood to the underlying brain tissue. Maintaining this steady-state requires balancing intracranial pressure (ICP), arterial BP (ABP), and cerebrovascular resistance (CVR) in a limited intracranial space [31]. This relationship is depicted in the following formula:

$$\text{CBF} = \frac{\text{ABP} - \text{ICP}}{\text{CVR}}$$

The mechanisms involved in this process are illustrated in Fig. 1. Myogenic and endothelial vascular responses play an important role in regulating CBF. The small arteries and arterioles within cerebral circulation have intrinsic mechanisms and contract when stretched to raise resistance [82]. The downstream resistance arterioles in the cerebral circulation are exquisitely sensitive to variations in arterial CO_2 (PaCO_2). They respond to small shifts in pH, with hypercapnia inducing regional acidosis, dilatation of the smooth muscle, and an increase in blood flow to the underlying region, which flushes out the CO_2 and restores acid base balance.

The Small vessels in the cerebral circulation respond less sensitively to hypoxia, particularly when chronic, as in patients with lung disease or congestive heart failure [61]. The changes in brain metabolism in response to an

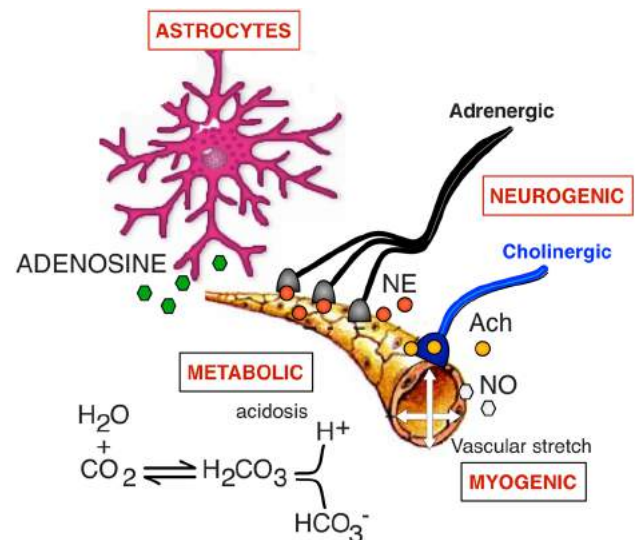


Fig. 1 Mechanisms involved the autoregulation of blood flow within cerebral arterioles. The resistance within small arterioles in the cerebral circulation is controlled by the interplay between metabolic factors (i.e., local changes in acid base balance), the intrinsic myogenic ability of the smooth muscle to constrict when stretched, input from noradrenergic and cholinergic neurons, and the release of vasoactive substrates, including adenosine from glia, nitric oxide from the epithelium, among others. See text for details. *NE* Norepinephrine, *ACh* acetylcholine, *NO* nitric oxide

increase in neuronal activity trigger the release of vasoactive compounds, such as arachidonic acid, lactate, adenosine, and nitric oxide, within the neurovascular unit to address the increased energy demands. Glial cells, neurons, and the vascular endothelium within the neurovascular unit can also re-direct local blood flow [20]. Astrocytes regulate the release of adenosine and can elicit the vasoconstriction (through changes in intracellular calcium concentration) or vasodilation of arterioles [27]. Similarly, an increase in glucose results in an increase in blood flow and oxygen supply. The cerebral arterioles are dually innervated by both parasympathetic and sympathetic fibers [32, 42], which are thought to play a role in buffering changes in perfusion. Activation of the sympathetic nerves presumably increases cerebrovascular tone, although there is uncertainty as to when these nerves are activated [26].

The assessment of cerebrovascular autoregulation evaluates how well the cerebral vessels respond to changes in ABP to regulate a constant blood supply. These changes can be evaluated by physical maneuvers that reduce venous return to the heart and lower perfusion pressure within the cerebral circulation (e.g., orthostatic stress or Valsalva straining). These challenges require an effective cerebral autoregulatory response to prevent CBF from falling below critical limits [74]. Age and gender may also influence cerebral autoregulatory responses [10, 21].

Static versus dynamic cerebral autoregulation

Static autoregulation refers to the ability of the cerebral circulation to maintain a constant flow over time in response to changes in BP. The evaluation of static autoregulation requires measurements of CBF velocity (CBFv) and BP under steady-state conditions. Typically, measurements are first obtained in the supine position to establish a baseline. BP is then manipulated, usually by infusion of systemically active vasoconstrictors (phenylephrine) and/or vasodilators (sodium nitroprusside) that respectively increase or decrease the BP. Once the BP is held constant and at a different level, other steady-state measurements are acquired over several minutes [75, 88]. If during the changes in BP the CBF is maintained near to baseline levels, cerebral autoregulation is assumed to be intact [82].

Dynamic autoregulation is used to describe the responses of the CBFv to spontaneous fluctuations in BP at rest or by inducing small transient changes in BP. Common scenarios include:

1. Transient changes in BP while resting (not provoked, so-called spontaneous oscillations).
2. Transient increases or decreases in BP induced pharmacologically by the systemic infusion of active pressor agents or vasodilators, respectively, that do not cross the blood–brain barrier (e.g., intravenous administration of noradrenaline or sodium nitroprusside).
3. Transient increases in BP induced by physical maneuvers (e.g., standing, squat to stand, periodic breathing, lower body negative pressure, or thigh cuff release) [87].

The feasibility of these techniques depends upon the expertise of the local laboratory, available experimental facilities, subject mobility, and clinical risk. While lower body negative pressure has the advantage of providing a physiological rather than pharmacological hemodynamic stress, the application of suction below the level of the iliac crest may trigger other responses, such as hyperventilation [65]. The topic of dynamic cerebral autoregulation is covered in detail in the recent white paper from the International Cerebral Autoregulation Research Network (CARNet) [13] and the concepts are covered extensively in excellent review articles [14].

The transcranial Doppler method

Basic concepts

Transcranial Doppler ultrasonography provides real-time measurements of blood flow velocity in cerebral vessels.

The technique can be used to measure changes in velocity within the large diameter arteries. Sonographers usually aim for the middle cerebral artery (MCA), which is easy to locate at depths of around 50–56 mm. The MCA arises from the internal carotid artery and supplies the cerebral cortex and anterior temporal lobes with oxygenated blood.

By way of validation, measurements of blood flow velocity in the MCA correlate closely with the “gold standard” intravenous Xenon¹³³ washout technique [6, 89], magnetic resonance (MR) angiography [37], and perfusion computed tomography [96].

The Doppler probe has two piezotransducers, one to transmit a pulsed ultrasound beam and a second to receive back the scattered echoes from the moving red blood cells (Fig. 2). The difference in the frequency of the transmitted beam and the frequency received from the back-scattered beam (known as the Doppler shift; Fig. 2b) is dependent on the motion of the red blood cells traveling within the vessel. Velocity is computed as follows [19]:

$$f_d = f_t - f_r = (2v f_t \cos \theta) / c$$

where, f_d = Doppler frequency shift; f_t = transmitted frequency; f_r = received frequency; v = velocity of the blood; θ = angle of insonation; c = speed of sound in tissue.

Because flow within the vessel is laminar, the Doppler shift obtained contains a range of frequencies due to the range on velocities within the lumen. Mean flow velocity takes into account these variations, computing an average based on timing of the different frequencies and the proportion of red blood cells moving at that velocity [19]. Flow towards the probe appears as an upward deflection, and flow away from the probe appears as a downward deflection. Transient periods of partial retrograde flow in diastole can occur when intracranial pressure rises, such as with cough syncope [56].

Technical standards for measurement

Transcranial Doppler uses a pulsed probe transmitting at a frequency of 2 MHz. The ultrasound beam penetrates through the thinner skull areas, known as “windows” above the zygomatic arch or other areas, including via the transorbital or transoccipital approaches. Because autonomic testing requires TCD measurements with the patient in both the supine and upright positions, the temporal window provides the best location. The fingers can be used to feel for a thinning of the bone, above the zygomatic arch, between the ear and the orbit [19]. Ultrasound gel is used to facilitate conductivity. The angle of the probe has to be adjusted to find the strongest signal towards the probe. The MCA can usually be found at an insonation depth of between 45 and 56 mm. Alternatively, the anterior

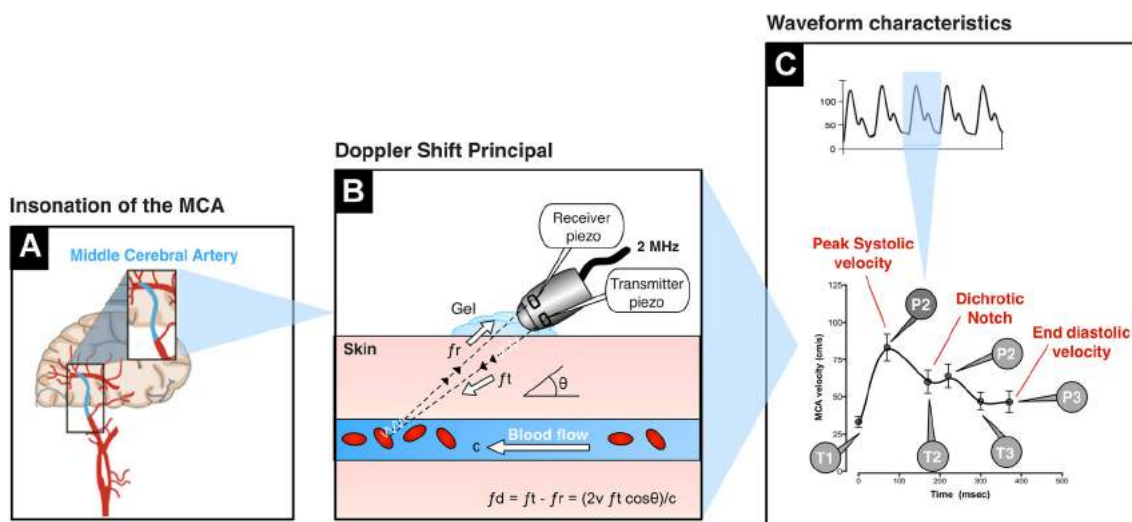


Fig. 2 Principles of transcranial Doppler ultrasonography. The middle cerebral artery (MCA) is usually insonated through the temporal window with a Doppler probe (a). The transmitting piezotransducer sends a pulsed ultrasound beam at a frequency of 2 MHz, which is reflected back from the moving red blood cells and detected by the receiving piezotransducer. The difference in frequency (known as the Doppler shift) is used to calculate the average

velocity of blood moving within the lamina of the MCA (b). Transcranial Doppler provides continuous measures of blood flow velocity. As depicted, (c) the TCD waveform has a characteristic profile, with three peaks ($P1$, $P2$, $P3$) and three troughs ($T1$, $T2$, $T3$). f_d Doppler shift, f_t Transmitted frequency, f_r received frequency, v velocity of the blood, θ angle of insonation, c speed of sound in tissue

cerebral artery can be insonated at depths of 70–75 mm [75] and the posterior cerebral artery can be insonated at depths of 55–75 mm [43]. The direction of the blood flow and sound can be used to locate the insonated artery. When insonating from the middle/anterior insonation window (above the zygomatic arch), velocity in the MCA flows toward the transducer, while both anterior cerebral artery velocity and posterior cerebral artery velocity flow away from the transducer. The occipital window is needed to insonate the vertebral arteries, and the transorbital window is used to insonate the ophthalmic artery. Sonographers must understand how to scan safely and adopt the practice of ALARA (as low as reasonably achievable power [1]) when optimizing the signal for recording. The gain should be reduced until all background noise is removed without compromise of the signal envelope, which traces the waveform.

Flow velocity depends on two assumptions; first, that the diameter of the insonated vessel does not change [91] and, second, that the angle of insonation (at which the beam hits the vessel) remains at a constant. This is achieved by having the 2-MHz Doppler probes mounted on an adjustable headband holder to lock the angle in place at the optimal signal position. With meticulous care, it can be assumed that the angle of insonation remains constant. The subjects should be instructed to keep their head still as movement can cause the probe to shift and the signal to deteriorate. Artifacts/noise must be removed from the analysis.

TCD in autonomic testing

The autonomic laboratory provides a controlled environment to study cerebral autoregulation. The recent CARNET white paper provides detailed consensus guidelines [13]. The laboratory should be temperature controlled, and there should be minimal distractions for the patient. Medications known to cross the blood–brain barrier and modulate autonomic activity should be tapered and withdrawn, if safe to do so. Concomitant recordings of CO_2 (end-tidal) and beat-to-beat BP are needed for clinical interpretation. Simultaneous video recordings can be very useful to correlate symptoms/behaviors [83]. Transcutaneous measures of CO_2 have poor temporal resolution and cannot provide the information needed to interpret parallel measurements of CBFv and BP. End-tidal CO_2 measurements during a full tidal breath when gas-exchange equilibrium is achieved in the alveolar space are superior.

With the finger plethysmography technique, the hand must always be supported at heart level or a height corrector must be used to accurately correct for the distance between the transducer and the heart. Changes in body position should be captured along with the TCD signals. The sampling rate for analog–digital conversion of the CBFv envelope signal should be at least 50 Hz with a low pass frequency cut-off at 20 Hz, based on the Nyquist theorem (the sampling frequency should be at least double the largest frequency in the signal) [13]. A higher sampling frequency (e.g., 250, 500 Hz or higher) may be needed

when the CBFv is recorded together with other signals, such as electrocardiogram (ECG) or electromyogram, as the latter have faster frequency components and require a higher sampling rate. A faster sampling rate also provides higher resolution for time–frequency, waveform analyses and the time-shift between different waveforms. All signals should be synchronized, and the delay in timing of other signal outputs should be accounted for (e.g., ECG, BP, end-tidal CO₂). Due to the hydrostatic pressure difference between the head and the heart when the patient is supine and upright, head-up tilt or standing from a supine position require the use of a correction factor to estimate perfusion pressure at brain level. The distance between the heart and TCD probe should be measured in centimeters and can be used to estimate cerebral perfusion pressure in the upright position with the following equation:

$$\text{estBPbrain} = \text{BPheart} - (\text{HD}/1.36)$$

where estBPbrain = estimated BP at brain level; BPheart = BP at heart level, which must be corrected for the position of the transducer if placed on the finger; HD = height difference between height of the transducer (on the arm, finger, etc.) and the TCD probe in centimeters.

It is recommended that the subject be given at least 20 min in the supine position to allow for a steady-state. Steady-state values with good-quality signals should be acquired for at least 5 min (300 s) for analysis. The subject should then be tilted to a 60° (or similar) angle with footplate support [48]. If a tilt table is not available, the subject should be instructed to stand immobile. All signals should be acquired in the upright position and symptoms documented in the recording file. The subject should remain upright for a minimum of 10 min or until syncope/near syncope develop. Prolonged tilt of 40 min or longer may be required to trigger an impending vasovagal episode. Lower body negative pressure can be applied while the subject is in the tilted position to increase orthostatic stress by exaggerating venous pooling [22].

Waveform analysis

The Doppler signal has a characteristic waveform with peak velocity in systole and lowest velocities in diastole (Fig. 2c). The small downwards deflection midway in the waveform is known as the dichotic notch and occurs on closure of the aortic valve during the cardiac cycle. The characteristics of the waveform can be analyzed by measuring flow velocity at six key inflection points, identifiable as three distinctive peaks (P1, P2 and P3) and three troughs (T1, T2 and T3) [2, 25]. Waveform analysis should be performed only when there is an artifact-free signal, and values should be averaged over a several beats.

Derived indices

Area under the curve is a descriptive parameter that can be used to estimate overall changes in CBFv. Changes in the waveform are thought to reflect the overall tone of the vasculature. As the cerebral arterioles dilate, vascular resistance falls, allowing more flow pass through the vessels in diastole. This principle underlies many of the derived indices used to estimate cerebral hemodynamics. One common method is pulsatility index, calculated by subtracting end diastolic velocity from peak systolic velocity and dividing the product by the mean velocity. When systolic flow remains stable, a high pulsatility index suggests cerebral vasoconstriction, and a low index suggests vasodilatation. High intracranial pressure results in a decrease in diastolic flow and an increase in pulsatility index [60]. Similarly, flow acceleration can be calculated by subtracting the peak systolic velocity from the end systolic velocity and then dividing the product by the systolic upstroke time. When the cerebral arterioles are constricted or there is underlying stenosis, the flow moves slower in systole and acceleration time is reduced [98].

Dynamic cerebral autoregulation analysis

Dynamic cerebral autoregulation is the mechanism involved in the rapid buffering of acute variations in perfusion pressure and the restoration of CBF with everyday activities through rapid adaptation of cerebrovascular resistance. In recent years, mathematical models have been used to overcome some of the limitations in assessing cerebral autoregulation. These models rely on indirect measures of critical parameters (e.g., intracranial pressure or derivation of cerebral blood flow from arterial spin labeling MR imaging of blood flow velocity [35]). For the present, these techniques remain experimental. Multiple methods exist to quantify dynamic cerebral autoregulation. While it is beyond the scope of this paper to review the methodology in great detail, several excellent review papers cover this topic [73, 92]. Techniques to measure dynamic cerebral autoregulation include correlation analysis, frequency domain analysis, and non-linear/multimodal pressure–flow analysis.

Correlation analysis

This method uses cerebral perfusion pressure and TCD-based blood flow velocity to predict the dynamics of cerebral autoregulation, and it has shown promising results in clinical studies [16]. This coefficient is known as mean velocity index. Mean arterial pressure is frequently used as a surrogate when intracranial pressure measurements are either low or not available.

Frequency domain analysis

One common method used in frequency domain analysis is the transfer function analysis (TFA) between cerebral perfusion pressure and blood flow velocity derived from the Fourier transform. Since invasive intracranial measurements of cerebral perfusion pressure are not available outside the intensive care setting, systemic BP is often used as a surrogate.

There are several potential limitations that have to be considered with TFA. First, a recent meta-analysis highlights the importance of standardizing measurements to enable the findings to be generally applicable across clinical practices [57]. Second, TFA assumes a linear association between the two signals, but it is well known that the pressure–flow relationship in cerebral autoregulation is nonlinear [77]. Finally, TFA assumes stationary oscillations with constant amplitude and period, an assumption that may be unreliable or even invalid for analysis of nonstationary BP and blood flow velocity signals [12, 55]. Standards for TFA analysis are covered by the CARNet white paper [13] and are aimed at (1) minimizing variability in the data acquisition; (2) improving the quality of recordings; (3) preprocessing and TFA parameters, and (4) interpreting data and preventing a large spread of results that makes data interpretation difficult.

There are a number of methods in the time–frequency analyses that have been used experimentally to assess dynamic autoregulation, including autoregressive moving average modeling with shifting windows, sub-component analysis, Laguerre–Volterra network, neural networks, cross-correlation, principal dynamic modes, wavelet phase synchronization, and support vector machines. Collectively, results with these techniques have shown that dynamic autoregulation is not a stationary process; therefore, a key priority for future work is the development and validation of multivariate time-varying techniques to minimize the influence of co-variables that affect dynamic autoregulation on multiple time scales. As a detailed description of these approaches exceeds the scope of this review, we direct the interested readers to the excellent review of these techniques by Panerai [76].

Non-linear/multimodal pressure–flow analysis

The nonlinear pressure–pressure flow method is a novel computational tool used to assess cerebral autoregulation based on the nonlinear dynamic theory of empirical mode decomposition [40]. The method assesses the relationship between BP and CBFv without assuming that these are stationary signals [40, 71]. Multimodal pressure–flow (MMPF) relationships based on phase shift have a greater sensitivity and specificity to detect abnormalities in

dynamic cerebral autoregulation in people with chronic infarcts and type 2 diabetes that were missed using the TFA method [40]. Figure 3 shows the frequency dependency of the BP–CBFv phase relationship at slower and faster frequencies (Fig. 3d) and a comparison of the phase shift between the stroke and nonstroke subjects at multiple time scales (Fig. 3e) [40]. A recent MMPF modification overcomes many limitations of the MMPF and TFA by examining the phase shift of intrinsic cycle-by-cycle BP–CBFv oscillations at different time scales. It also uses a spectrum to describe frequency-dependent phase interaction to better account for nonstationarities and noise in the BP and CBFv recordings by filtering out data without matched BP–CBFv cycles [18, 55].

Clinical applications of TCD in the autonomic clinic

Over one million patients are evaluated for syncope in the USA each year, thereby accounting for around 1% of emergency visits [94]. TCD measurements can be very useful in the clinical work-up of a patient with recurrent transient loss of consciousness. Symptoms of cerebral perfusion usually occur when blood flow velocity is reduced by 50% [31]. In cases of pseudo/psychogenic syncope there is unresponsiveness with no change in cerebral flow velocity [66]. Panic, hyperventilation, and presyncope produce hypocapnia and strong constriction of the cerebral vessels [65, 70]. These are normal physiological responses to stress and are reversible by CO₂ re-breathing [70]. However, orthostatic intolerance symptoms may persist despite improvement in blood flow velocity. There is substantial evidence supporting the usefulness of physical counter maneuvers that increase venous return as a technique to abort and impending vasovagal episode [49, 50, 97]. These maneuvers have been shown to increase CBFv [34].

Syncope

Syncope is defined as global cerebral hypoperfusion that results in transient loss of consciousness characterized by rapid onset, short duration, and spontaneous complete recovery [85]. Syncope occurs when CBF falls below a critical limit and consciousness can no longer be maintained [11]. Rapid loss of postural tone physically restores blood supply back to the brain, most likely due to a hardwired protective mechanism [7]. The overall goal of clinical autonomic testing is to determine whether orthostatic symptoms are a result of an autonomic abnormality and whether the autonomic nerves are transiently switched off [95], not properly activated [44], or functionally impaired [29, 45]. TCD studies in disorders of orthostatic

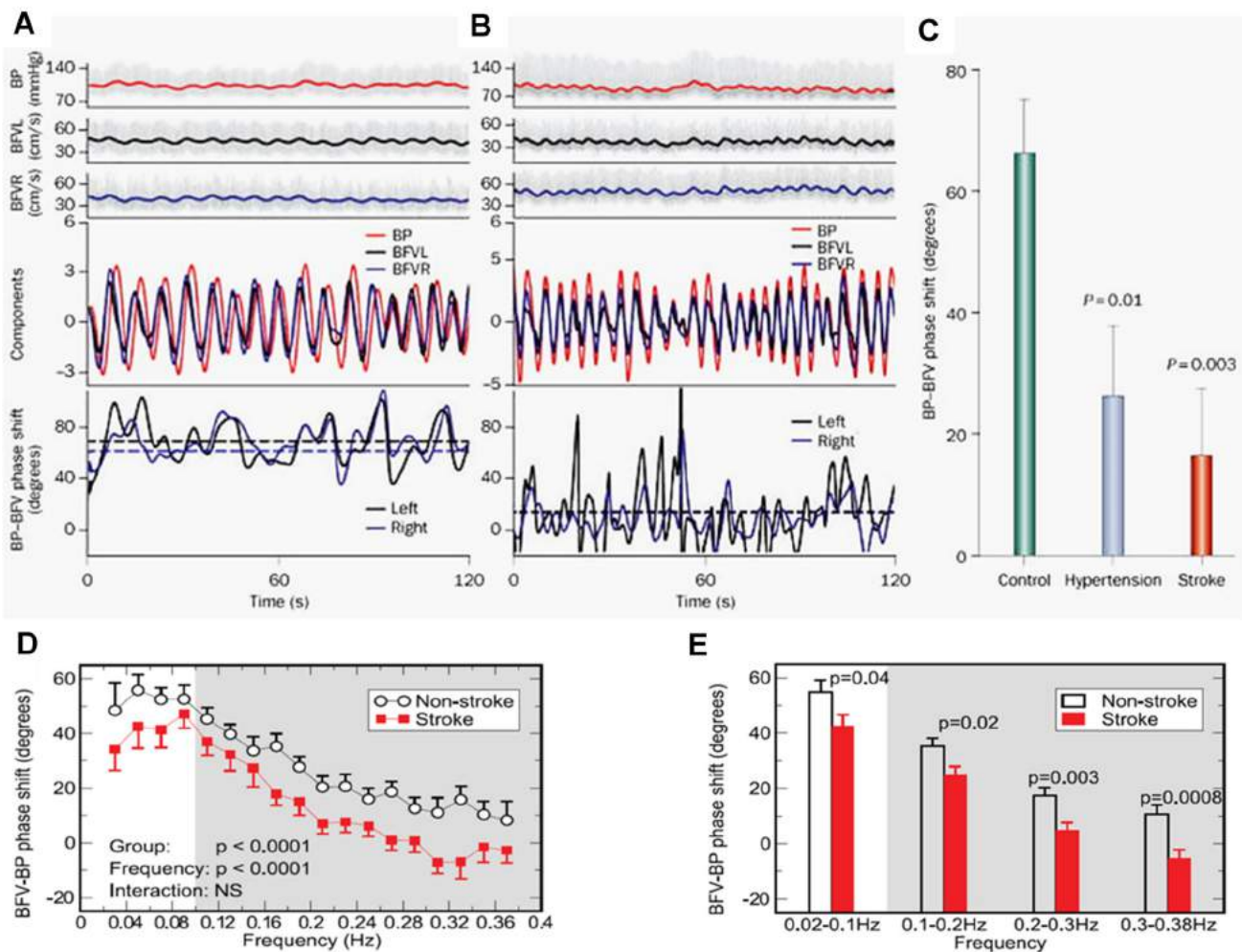


Fig. 3 Dynamic cerebral autoregulation measure based on shifts in the pressure–flow phase. **a, b** Spontaneous oscillations in blood pressure (BP) and blood flow velocity (BFV) and dominant decomposed signals from older (a) and healthy (b) diabetic subjects and instantaneous phases of BP and BFV oscillations (solid lines, bottom graphs). BFVL = BFV signal from left MCA, BFVR = BFV signal from right MCA. **c** The mean BP–BFV phase shift (dashed lines) was

reduced between controls, hypertension patients, and stroke patients. **d, e** In stroke subjects, the phase shift was reduced across multiple frequencies from 0.02 to 0.38 Hz as compared to controls. This phase shift reduction indicates impaired cerebral autoregulation among the groups and across multiple time scales Figures reprinted from [39–41, 68]

intolerance and syncope have used different methods to assess cerebral autoregulation and the results are heterogeneous. Previous reviews have covered early work describing TCD findings in the evaluation of syncope [75]. Table 1 provides a description of key studies examining the TCD in syncope. The information presented in the table does not represent an exhaustive literature review, rather it provides an update and summarize the more recent relevant studies.

Vasovagal syncope

Vasovagal syncope (also known as neurally mediated or reflex syncope) is the most common cause of transient loss of consciousness. It is characterized by the sudden

withdrawal of sympathetic activity to the systemic circulation accompanied by an increase in parasympathetic activity and slowing of the heart [84]. Emotional factors play a significant role in many vasovagal episodes [93], and hyperventilation-induced hypocapnia is common prior to loss of consciousness. A reduction in CBFv usually occurs before the fall in BP, as a physiological consequence of the hyperventilation-induced hypocapnia that occurs in habitual fainters.

Hypocapnia causes dilatation in the peripheral circulation and constriction within the cerebral circulation, and individual susceptibility to vasovagal syncope may depend on vascular sensitivity to alterations in CO₂ [65]. Dynamic cerebral autoregulation appears to be intact in patients with vasovagal syncope (Figs. 4, 5) [80]. Cerebrovascular

Table 1 List of selected studies examining the use of transcranial Doppler in syncope

First author and reference	Age (years)	Population and N	Stimuli	TCD analysis method	Primary study goal	Responses to syncope		Outcome				
						Cardio-vascular	Cerebro-vascular					
						HR	MAP	Systolic MCA velocity	Diastolic MCA velocity	Pet CO ₂ rate	Resp. rate	
Murrell [59]	27–65	<i>Exercise trained young and elderly vs. controls</i> Young healthy and trained, <i>n</i> = 9 Young healthy and untrained, <i>n</i> = 12 Older healthy and trained, <i>n</i> = 9 Older healthy and untrained, <i>n</i> = 9	60° tilt	Static CA No model to correlate BP/CBF velocity	Effect of physical fitness on orthostatic tolerance	↑	↑	↓	↓	↓	NR	Orthostatic tolerance did not differ with age or fitness
Lewis [53]	25	<i>Healthy controls</i> Group 1: (+) alpha blockade, <i>n</i> = 6 Group 2: (−) alpha blockade, <i>n</i> = 6	Supine to standing	Dynamic CA TFA analysis	Effect of alpha-2 blockade on CBF	↓	↓	↓	↓	↓	NR	Sympathetic response contributes to CBF regulation
Lewis [54]	25	<i>Healthy controls</i> Group 1a: hypocapnia(−) and LBNP(+), <i>n</i> = 7 Group 2a: hypocapnia(+)& LBNP(+), <i>n</i> = 5 Group 1b: acetazolamide(−)& LBNP(+), <i>n</i> = 6 Group 2b: acetazolamide(+)& LBNP(+), <i>n</i> = 4	LBNP + induced-hypocapnia (acetazolamide)	Static CA No model to correlate BP/CBF velocity	Effect of hypocapnia and decreased CBF on orthostatic tolerance	↓	↓	↓	↓	↑	↑	Hypocapnia does not affect orthostatic tolerance
Edgell [21]	27 vs. 57	<i>Healthy controls</i> Group 1: young women, <i>n</i> = 7 Group 2: post-menopausal women, <i>n</i> = 11 Group 3: young men, <i>n</i> = 10 Group 4: older men, <i>n</i> = 9	Supine to standing	Static CA No model to correlate BP/CBF velocity	CBF responses to orthostatic stress in younger and older women vs. men	↑	↑	↓	↓	↓	(=)	Sex differences in cerebral autoregulation
Deegan [17]	28	<i>Healthy controls</i> Volunteers, <i>n</i> = 9	70° tilt with LBNP	Static CA No model to correlate BP/CBF velocity	CBF changes in the anterior and posterior circulation	↑	↓	↓	↓	↓	NR	No differences between anterior and posterior cerebral circulation

Table 1 continued

First author and reference	Age (years)	Population and N	Stimuli	TCD analysis method	Primary study goal	Responses to syncope				Outcome		
						Cardio-vascular	Cerebro-vascular	Respiratory				
						HR	MAP	Systolic MCA velocity	Diastolic MCA velocity	Pet CO ₂ rate	Resp. rate	
Gierthmuhlen [26]	42.8 ± 16.7	Central sympathetic deficit in stroke vs controls Healthy controls, n = 21 Subjects with stroke having central sympathetic deficit, n = 17	65° tilt with LBNP	Dynamic CA ARI analysis	Functional role of sympathetic innervation on CA	↑	↓	↓	NR	NR	NR	Sympathetic innervation is not involved on CA
Novak [70]	61.7 ± 2.4	Orthostatic hypotension vs controls Healthy controls, n = 14 Multiple system atrophy, n = 8 Pure autonomic failure, n = 3 Diabetic neuropathy, n = 6 Idiopathic autonomic neuropathy, n = 4	80° tilt + hyperventilation	Static CA No model to correlate BP/CBF velocity	CBF changes when BP decreases	↑	↓	↓	↓	↓	(=)	Normal or impaired CA in OH
Tugba [90]	7–17	Vasovagal vs. controls Group 1: syncopal history(+) and HUT(+), n = 31 Group 2: Syncopal history(+) and HUT(-), n = 21 Group 3: healthy children, n = 22	80° Tilt	Static CA No BP/CBF velocity correlation	Describe CBF in vasovagal syncope	NR	NR	↓	↓	NR	NR	Decreased CBF when syncope and tilt (=) occur
Thomas [86]	25 ± 5	Syncope vs. controls Healthy controls, n = 37 37 Healthy volunteers Group 1: syncope and venular dysfunction, n = 15 Group 2: syncope and arteriolar dysfunction, n = 1 Group 3: syncope + mixed dysfunction, n = 21	70° tilt with LBNP	Static CA No model to correlate BP/CBF velocity	CBF changes in syncope ± impaired systemic vascular resistance	↑	↓	↓	↓	↓	NR	No changes in CBF velocity if syncope classified based on SVR

Table 1 continued

First author and reference	Age (years)	Population and N	Stimuli	TCD analysis method	Primary study goal	Responses to syncope			Outcome
						Cardio-vascular	Cerebro-vascular	Respiratory	
Gur [30]	69–77	<i>Synucleinopathies</i> Parkinson disease, <i>n</i> = 15 Multiple system atrophy, <i>n</i> = 9 Pure autonomic failure, <i>n</i> = 5 Group 1: Syncopal history(+) Group 2: no syncopal history (-)	70° tilt with acetazolamide	Static CA No model to correlate BP/CBF velocity	Cerebral vasomotor reactivity in syncope	NR	NR	NR	Association between syncope and decreased calculated VMR
Brooks [9]	52.8	<i>Autonomic failure</i> Multiple system atrophy, <i>n</i> = 4 Pure autonomic failure, <i>n</i> = 4 Dopamine-β-hydroxylase deficiency, <i>n</i> = 2	45° tilt, eEphedrine, 113Xe washout technique	Static CA No BP/CBF velocity correlation	Effect of autonomic failure in CA	↑	↓	NR	CA is preserved in autonomic failure
Horowitz [38]	72	<i>Autonomic failure</i> Multiple system atrophy, <i>n</i> = 3 Pure autonomic failure, <i>n</i> = 6	60° tilt	Static CA No BP/CBF velocity correlation	CBF in autonomic failure when hypotension occurs	NR	↓	NR	OH induces autoregulatory cerebral vasodilation

For additional details see references [9, 17, 21, 26, 30, 38, 53, 54, 59, 70, 86, 90]

Arrows indicate the main response

ARI Autoregulation Index *TCA* Transcranial Doppler, *HR* heart rate, *MAP* median arterial pressure, *MCA* middle cerebral artery, *P_{et}* partial pressure of end tidal gases, *LBNP* lower body negative pressure, *HUT* Head up-tilt, *BP* blood pressure, *CBF* cerebral blood flow, *TFA* transfer function analysis, *CA* cerebral autoregulation, *VMR* vasomotor reactivity, *NR* not reported

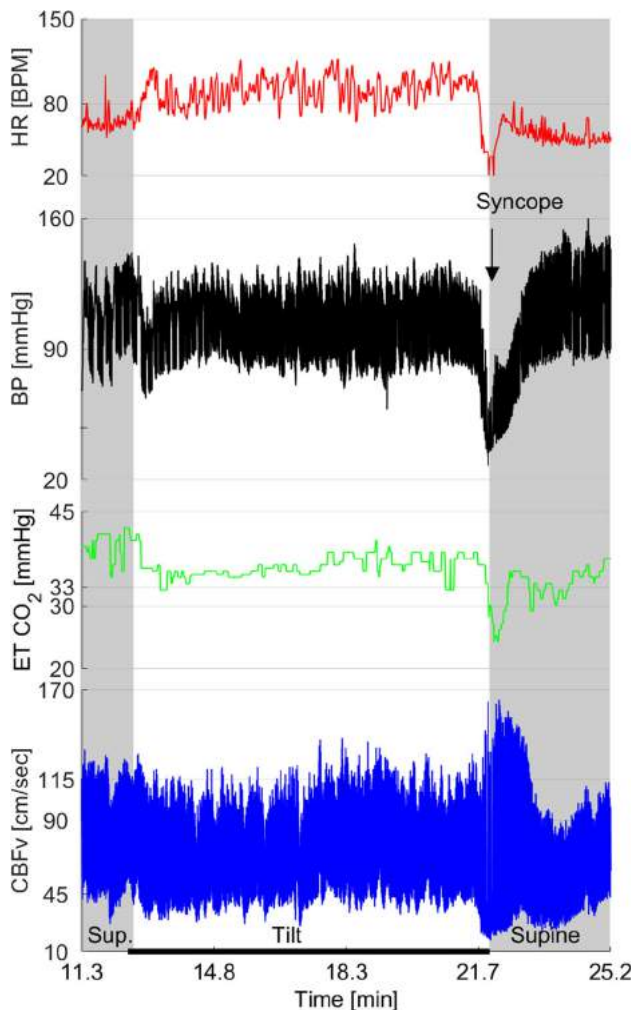


Fig. 4 Transcranial Doppler and autonomic findings on the tilt test in syncope showing the physiological responses of subjects to head-up tilt in terms of blood pressure (*BP*), heart rate [*HR* in beats per minute (*BPM*)], end-tidal (*ET*) CO_2 level, and cerebral blood flow velocity (*CBFv*) in syncope. Image courtesy of Dr. Peter Novak

responses are similar in vasodepressor, cardio-vagal, and mixed forms of vasovagal syncope [66]. Vasovagal syncope after exercise can occur due to cerebral hypoperfusion. Simple behavioral techniques that minimize hypocapnia with hypoventilation may be helpful [54], as this helps the vessels in the cerebral circulation remain dilated [11]. Studies show that although prolonged bed rest lowers CO_2 levels and increases susceptibility to vasovagal syncope, the cerebral autoregulatory capacity appears to adequately compensate [28] and cerebral responses to nitroglycerin challenge are preserved [100].

Orthostatic intolerance

Postural tachycardia syndrome (PoTS) is a common and poorly understood disorder encountered in the autonomic clinic that affects children as well as young and middle-age

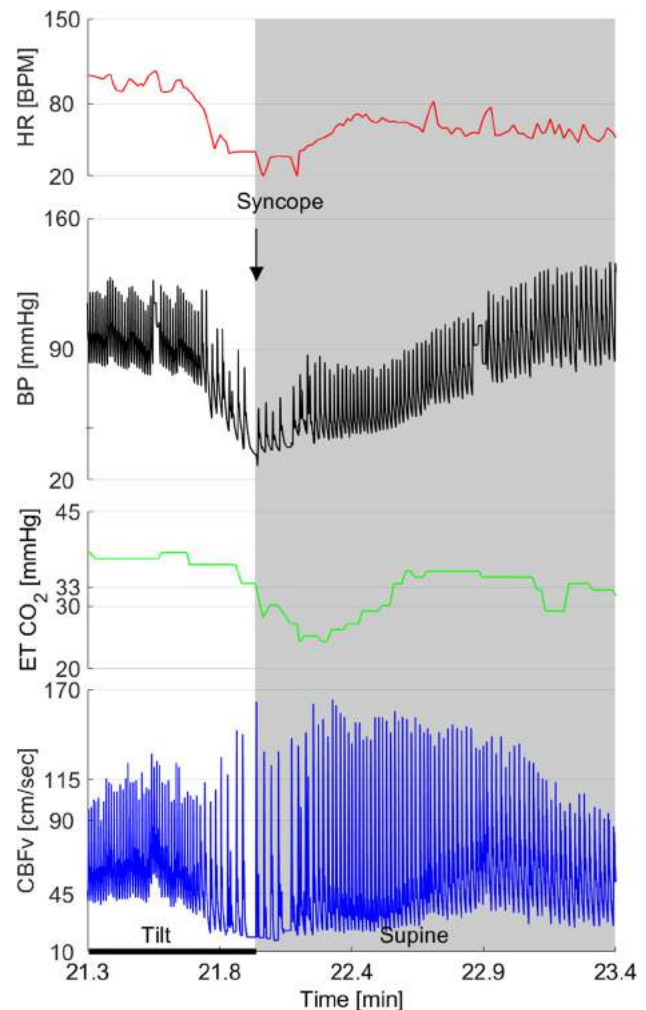


Fig. 5 Transcranial Doppler and autonomic findings on tilt test in syncope—a detailed recording when syncope occurs, showing the physiological responses of the subjects to head-up tilt in terms of *BP*, *HR*, *ET* CO_2 , *CBFv* in syncope Image courtesy of Dr. Peter Novak

adults, and is more prevalent in women. It is defined by orthostatic symptoms, including light-headedness, generalized weakness, and palpitations accompanied by a sustained increase in heart rate of >40 bpm in a child (or >30 bpm an adult) within 10 min of being in an upright position [24]. There are usually multiple mechanisms involved (including drugs that increase the heart rate, anemia, hypovolemia, hyperadrenergic states, peripheral neuropathies), and comorbid disorders are frequent (e.g., psychiatric somatic sensory disorders [78], anxiety, fibromyalgia, chronic headache, etc. [4]). Children and young adults with PoTS appear to have intact cerebral autoregulation [23]. Symptoms on standing can be triggered when cardiovascular responses are normal and cerebral vasodilatation is intact [67]. A recent study in patients with orthostatic intolerance of mixed causes suggested that simultaneous measurements of TCD and near-infrared spectroscopy maybe of additional use to monitor cerebral hypoperfusion and correlate symptoms [51].

Table 2 Transcranial Doppler and autonomic findings on Tilt test in orthostatic syndromes and synucleinopathies

Syndrome	Heart rate		Median arterial pressure		Cerebral blood flow velocity	
	Supine	Head up-tilt	Supine	Head up-tilt	Supine	Head up-tilt
Orthostatic hypotension (OH)	↔	↓	↓	↓ ^a	↔	↔ ↓
Postural tachycardia syndrome (PoTS)	↔	↑ ^a	↔ ↓	↔ ↑	↔	↔ ↓
Syncope, cardiovagal	↔	↓	↔	↓ ^a	↔	↓
Syncope, vasodepressor	↔	↔ ↑	↔	↓ ^a	↔	↓
Syncope, mixed	↔	↓	↔	↓ ^a	↔	↓
Primary cerebral autoregulatory failure (pCAF)	↔	↔	↔ ↑	↔	↓ ^a	↔ ↓
Orthostatic cerebral hypoperfusion syndrome (OCHOS)	↔	↔	↓	↔	↔	↓ ^{a, b}
Orthostatic intolerance with normal HUT (OINH) [81]	↔	↑	↔	↔	↔	↓ ^{a, b}
Pure autonomic failure (PAF) [48]	↔ ↓	~ ↑	↔	↓	↔	↔ [9] ↓ [34]
Parkinson's disease (PD) [58]	↔ ↓	~ ↑	↔	↓	↔	↔ [3] ↓ [36]
Multiple system atrophy (MSA) [5]	↔	~ ↑	↔	↓	↔	↓

Table is modified from [66]. For further details on autonomic findings in synucleinopathies, the reader is referred to the respective references [3, 9, 34, 36, 48, 58, 81, 99]

(↔) normal, (↓) decreased, (↑) increased, (↓) not specific, (↔ ↓) normal or decreased, (↔ ↑) normal or increased, (~ ↑) very low variability

^a Arrows indicate the main autonomic abnormality found in the syndrome

^b Cerebrovascular resistance is increased in OCHOS compared to controls, but decreased in OINH

Chronic autonomic failure

Chronic failure of the autonomic nervous system results in neurogenic orthostatic hypotension (*nOH*), defined as a fall in systolic BP of ≥ 20 mmHg or in diastolic BP of ≥ 10 mmHg within 3 min of standing or tilt [24]. It occurs because of a failure to increase sympathetic activity when upright. Accompanying symptoms are the result of tissue ischemia and include lightheadedness, visual difficulties, and weakness [47]. *nOH* is the hallmark of autonomic failure. Underlying causes include neurodegenerative synucleinopathies (Parkinson disease, dementia with Lewy bodies, multiple system atrophy, pure autonomic failure), toxic/metabolic/inherited neuropathies (post-chemotherapy, diabetes, familial dysautonomia), or autoimmune conditions (ganglionopathies, paraneoplastic syndromes).

The key studies to define cerebral autoregulation in patients with chronic autonomic failure were performed almost two decades ago [8, 38, 69]. Overall, the findings show preserved autoregulatory capacity. Regression analysis shows that in order to withstand periods of low BP while standing, most patients with chronic autonomic failure have intact static autoregulation or an expanded autoregulatory range [69]. Others show marked cerebral vasodilatation on standing and syncope occurring when this adaptation is overridden by orthostatic dyspnea and ensuing hypocapnia [8]. Once BP is passively restored in the supine position, most patients with autonomic failure show a dynamic overshoot in CBFv (i.e., a hyperemic response), suggesting intact vasodilatation in response to hypotension [38]. A small minority with synucleinopathies or diabetes

may have autoregulatory failure, which impairs their tolerance to standing [69]. A study of dynamic autoregulation showed that in some patients with multiple system atrophy, CBFv may be slow to return to baseline after standing [99]. However, none of these studies took into account whether the patient had underlying vascular disease or supine hypertension, or whether he/she was being treated with fludrocortisone or other vasoactive agents. A recent large study in patients with Parkinson disease showed normal cerebrovascular responses to hypocapnia, suggesting that metabolic autoregulation was intact [33]. TCD and autonomic findings in recent studies of patients with synucleinopathies have produced mixed results and are described in Table 2.

Afferent baroreflex failure

Afferent baroreflex failure (not to be confused with efferent autonomic failure) occurs when there are acquired or genetic lesions in the nerves relaying information from the arterial baroreceptors in the peripheral circulation to the brainstem [62]. As a result, patients have unstable BP, with hypotension alternating with stress-induced hypertension [63]. Inherited congenital lesions in the ninth and tenth cranial nerves do not impair cerebral autoregulation [64]. Patients retain a remarkable ability to withstand hypotension when upright without developing cerebral hypoperfusion and do not develop hypocapnia when standing [25]. They seldom complain of orthostatic symptoms, and syncope usually only occurs in the setting of additional

stressors, including hypovolemia or hypoxia [72]. It is thought that negative pressure within the sinuses may help suction blood to the cerebral circulation. There are no TCD studies in patients with acquired afferent baroreflex lesions due to cancer, surgery, or radiotherapy of the neck.

Other disorders

A recent retrospective review of 669 patients described primary cerebral autoregulatory failure as a low CBFv in the supine position without systemic hypotension [67] and orthostatic cerebral hypoperfusion syndrome as an abnormal drop of mean blood flow velocity without orthostatic hypotension or tachycardia [67].

Patients with orthostatic cerebral hypoperfusion syndrome (OCHOS) have low CBFv with normal cardiovascular reflex responses to standing [66]. They are predominately women (59%), with comorbid hypertension (21%) and migraine (up to 35%). CBFv decreases by $\geq 20\%$ in the standing position compared to controls, presumably caused by cerebral vasoconstriction and ineffective compensation [67] (see Fig. 5). Another similar syndrome is orthostatic intolerance with normal head-up tilt defined as orthostatic symptoms in patients with normal BP and heart rate responses to tilt. These patients have a decreased cerebrovascular resistance and CBFv (mainly systolic) compared with controls, but no significant CBFv change when compared with patients diagnosed with PoTS or *nOH* [81]. Expected cardiovascular responses and TCD velocity changes in the syndromes are described in Table 2.

Recognizing different TCD profiles with autonomic testing can be useful to correlate orthostatic symptoms in patients with normal cardiovascular responses. Further studies are needed to better define the spectrum of these disorders and reach consensus.

Limitations

Acquiring TCD data requires a rigorous approach with proper insonation and good quality blood flow velocity recordings, especially during head-up tilt. TCD measurements are limited by the operator's ability to detect an optimal insonation window, to maintain the probe stable, and to properly identify and remove artifacts caused by signal loss due to improper probe positioning. Newer devices allow automatic detection and maintain maximal flow velocity and proper probe positioning. Transcranial color-coded duplex ultrasonography (TCDD) is a relatively novel instrument that can also be used to assess the cerebral circulation. The method is based upon TCD parameters and has similar limitations due to the insonation window.

However, it allows direct visualization of the insonated artery, which may be beneficial for angle correction. TCDD is not typically used for longitudinal recordings. Most of the studies that have assessed cerebral autoregulation in autonomic disorders have used TCD, hence further studies are warranted to assess the advantages of TCDD in the autonomic clinic [79].

TCD measures flow velocity within the large vessels, which is poorly correlated with tissue perfusion within the insonated territory [35]. Flow velocity measurements are also affected by underlying small vessel disease and gray and white matter abnormalities. Therefore, a decline in MCA blood flow velocity may be compensated for by redistribution of perfusion to other vascular territories, rather than representing global hypoperfusion.

Clinical studies in autonomic disorders are limited due to method variability and a small sample size. International guidelines for cerebral autoregulation measurements and analyses have been proposed, but these are still lacking validation in a large sample size [13]. Multicenter studies using unifying criteria would provide a gold standard to characterize normal and abnormal cerebral autoregulatory responses. Validated methods for cerebral autoregulatory assessment and interpretation would enhance clinical autonomic testing diagnosis and treatment options.

Conclusions and future directions

The transcranial Doppler is an excellent way to study acute changes in CBFv in the autonomic clinic. Cerebral autoregulation is a well-defined physiological mechanism essential in everyday life. Standardization of TCD recordings is essential.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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