Clin Auton Res (2018) 28:187–202
https://doi.org/10.1007/s10286-017-0454-2

REVIEW

Transcranial Doppler in autonomic testing: standards and clinical applications

Lucy Norcliffe-Kaufmann[1] · Brahyan Galindo-Mendez[2] · Ana-Lucia Garcia-Guarniz[2] · Estibaliz Villarreal-Vitorica[3] · Vera Novak[2]

Received: 3 March 2017 / Accepted: 13 July 2017 / Published online: 18 August 2017

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

L. Norcliffe-Kaufmann and B. Galindo-Mendez contributed equally to the manuscript.

✉ Lucy Norcliffe-Kaufmann
Lucy.Norcliffe-Kaufmann@nyumc.org

[1] Department of Neurology, New York University School of Medicine, New York, NY, USA

[2] Department of Neurology, Beth Israel Deaconess Medical Center, 185 Pilgrim Road, Palmer 127, Boston, MA 02215, USA

[3] Department of Neurology, Hospital Universitario Son Espases, Illes Balears, Spain

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.

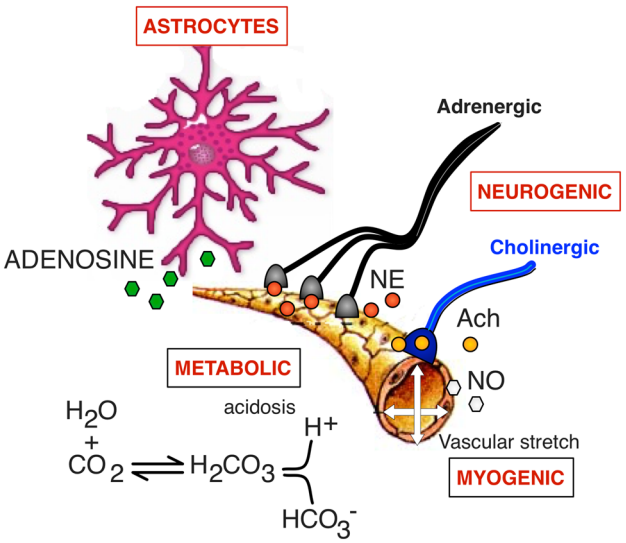

Fig. 1 Mechanisms involved the autoregulation of blood flow within cerebral arterioles. The resistance within small arterioles in the cerebral circulation is controlled by the interplay between metabolic factors (i.e., local changes in acid basis balance), the intrinsic myogenic ability of the smooth 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

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:

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

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 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 Xenon^{133} 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]:

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

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

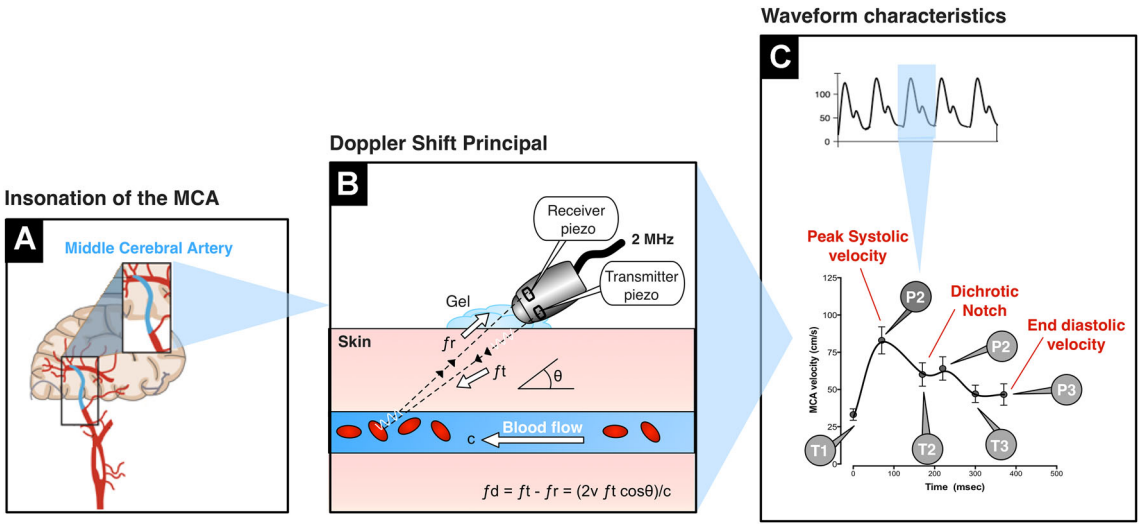

Fig. 2 Principles of transcranial Doppler ultrasonography. The middle cerebral artery (*MCA*) is usually insonated through the temporal window with a Doppler probe (**a**). The transmitting piezotransducer sends a pulsed ultrasound beam at a frequency of 2 MHz, which is reflected back from the moving 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 CO_2). 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 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-variates 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 CO_2 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

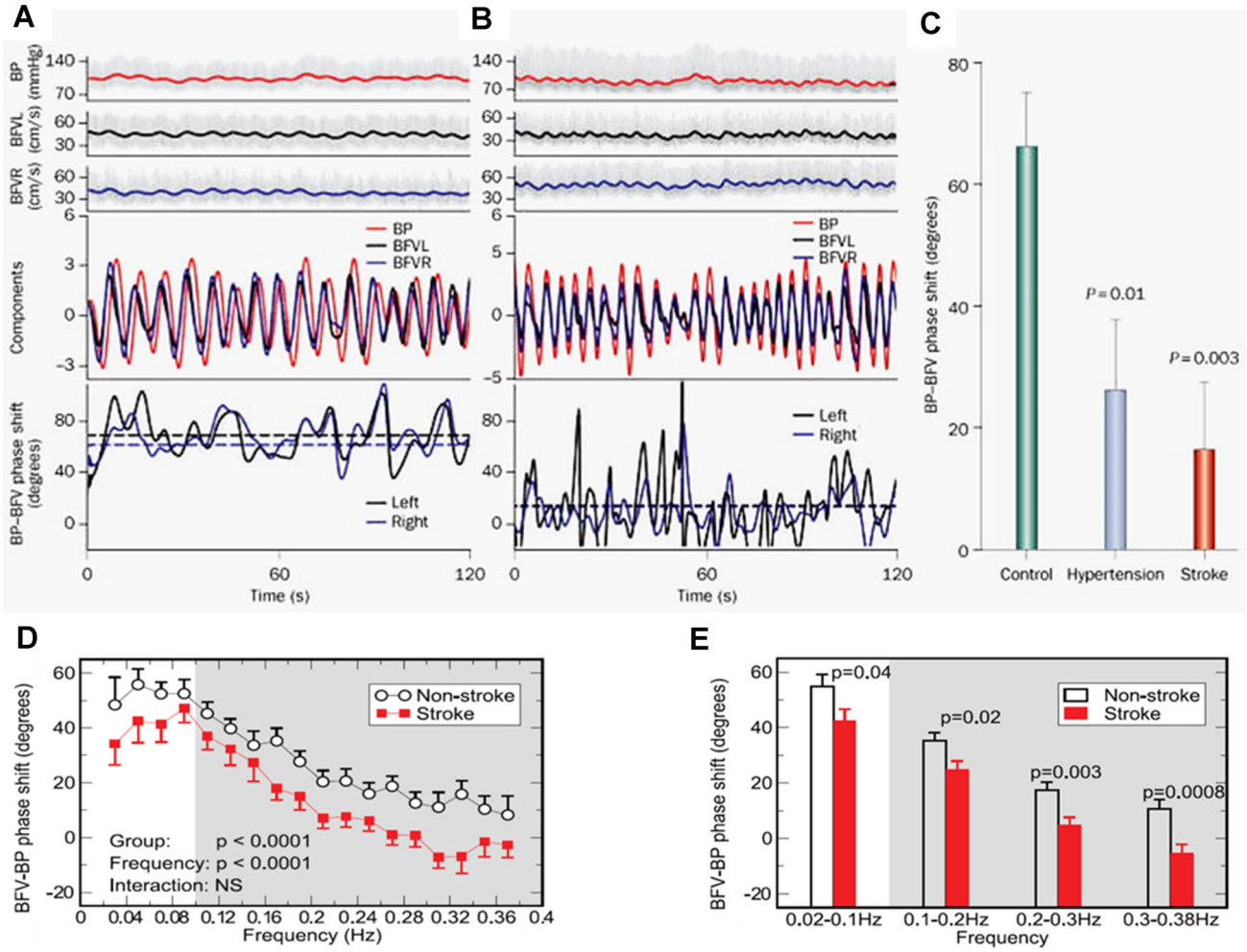

Fig. 3 Dynamic cerebral autoregulation measure based on shifts in the pressure–flow phase. **a**, **b** Spontaneous oscillations in blood pressure (*BP*) and blood flow velocity (*BFV*) and dominant decomposed signals from older (**a**) and healthy (**b**) diabetic subjects and instantaneous phases of 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 CO_2 [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		Respiratory		
						HR	MAP	Systolic MCA velocity	Diastolic MCA velocity	Pet CO_2	Resp. rate	
Murrel [59]	27–65	*Exercise trained young and elderly vs. controls* Young healthy and trained, $n = 9$ Young healthy and untrained, $n = 12$ Older healthy and trained, $n = 9$ Older healthy and untrained, $n = 9$	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	*Healthy controls* Group 1: (+) alpha blockade, $n = 6$ Group 2: (−) alpha blockade, $n = 6$	Supine to standing	Dynamic CA TFA analysis	Effect of alpha-2 blockade on CBF	↓	↓	↓	↓	↓	NR	Sympathetic response contributes to CBF regulation
Lewis [54]	25	*Healthy controls* Group 1a: hypocapnia(−) and LBNP(+), $n = 7$ Group 2a: hypocapnia(+) & LBNP(+), $n = 5$ Group 1b: acetazolamide(−) & LBNP(+), $n = 6$ Group 2b: acetazolamide(+) & LBNP(+), $n = 4$	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	*Healthy controls* Group 1: young women, $n = 7$ Group 2: post-menopausal women, $n = 11$ Group 3: young men, $n = 10$ Group 4: older men, $n = 9$	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	*Healthy controls* Volunteers, $n = 9$	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	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		
						HR	MAP	Systolic MCA velocity	Diastolic MCA velocity	Pet CO_2	Resp. rate	
Gur [30]	69–77	*Synucleinopathies* Parkinson disease, $n = 15$ Multiple system atrophy, $n = 9$ Pure autonomic failure, $n = 5$ 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	NR	Association between syncope and decreased calculated VMR
Brooks [9]	52.8	*Autonomic failure* Multiple system atrophy, $n = 4$ Pure autonomic failure, $n = 4$ Dopamine- ß-hydroxylase deficiency, $n = 2$	45° tilt,eEphedrine, 113Xe washout technique	Static CA No BP/CBF velocity correlation	Effect of autonomic failure in CA	↑	↓	↓	NR	NR	NR	CA is preserved in autonomic failure
Horowitz [38]	72	*Autonomic failure* Multiple system atrophy, $n = 3$ Pure autonomic failure, $n = 6$	60° tilt	Static CA No BP/CBF velocity correlation	CBF in autonomic failure when hypotension occurs	NR	↓	↓	NR	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, *Pet* 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

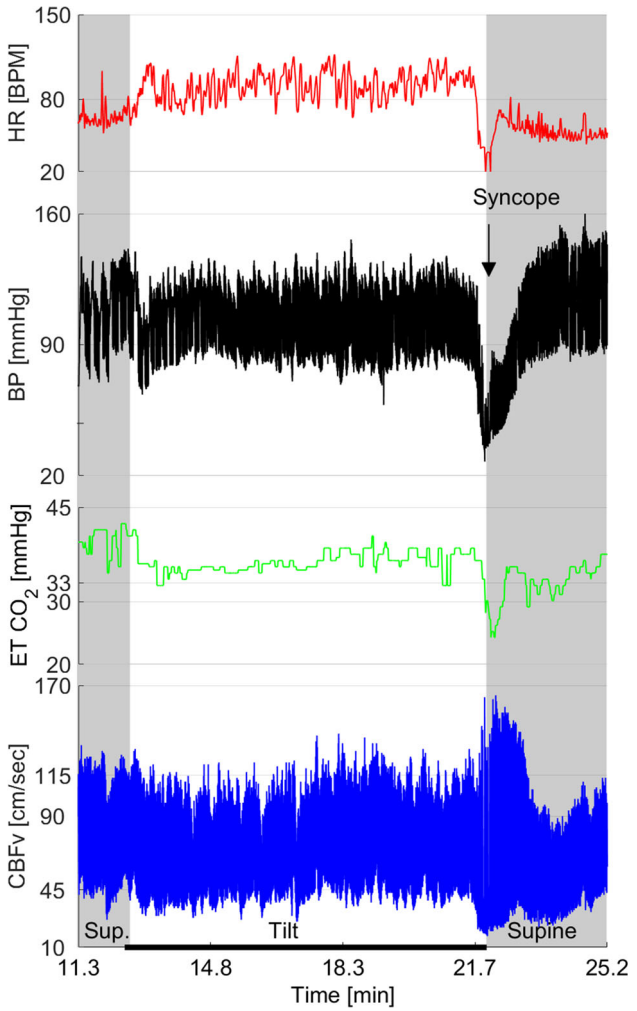

Fig. 4 Transcranial Doppler and autonomic findings on the tilt test in syncope showing the physiological responses of subjects to head-up tilt in terms of blood pressure (*BP*), heart rate [*HR* in beats per minute (*BPM*)], end-tidal (*ET*) CO_2 level, and cerebral blood flow velocity (*CBFv*) in syncope.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

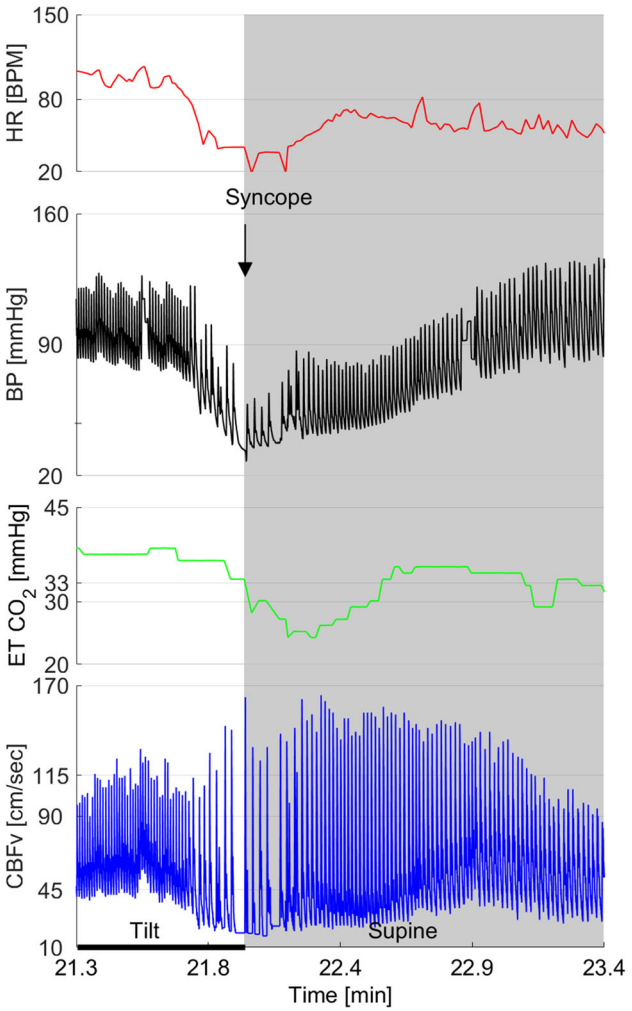

Fig. 5 Transcranial Doppler and autonomic findings on tilt test in syncope—a detailed recording when syncope occurs, showing the physiological responses of the subjects to head-up tilt in terms of BP, HR, ET CO_2, CBFv in syncope Image courtesy of Dr. Peter Novak

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 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 (*n*OH), 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]. *n*OH 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 *n*OH [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.

Funding This study was supported by grants from the National Institutes of Health NINDS (U54-NS065736 to LN-K) and by NIH-NIDDK (R01-DK13902-01A2 to VN).

References

1. Abramowicz JS, Kremkau FW, Merz E (2012) Obstetrical ultrasound: can the fetus hear the wave and feel the heat? Ultraschall Med 33:215–217
2. Aggarwal S, Brooks DM, Kang Y, Linden PK, Patzer JF 2nd (2008) Noninvasive monitoring of cerebral perfusion pressure in patients with acute liver failure using transcranial doppler ultrasonography. Liver Transpl 14:1048–1057
3. Angeli S, Marchese R, Abbruzzese G, Gandolfo C, Conti M, Gasparetto B, Del Sette M (2003) Tilt-table test during

transcranial Doppler monitoring in Parkinson's disease. Parkinsonism Relat Disord 10:41–46
4. Benarroch EE (2012) Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. Mayo Clin Proc 87:1214–1225
5. Berman JR, Berman LA, Werbin TJ, Goldstein I (1999) Female sexual dysfunction: anatomy, physiology, evaluation and treatment options. Curr Opin Urol 9:563–568
6. Bishop CC, Powell S, Rutt D, Browse NL (1986) Transcranial Doppler measurement of middle cerebral artery blood flow velocity: a validation study. Stroke 17:913–915
7. Blanc JJ, Benditt DG (2016) Vasovagal syncope: hypothesis focusing on its being a clinical feature unique to humans. J Cardiovasc Electrophysiol 27:623–629
8. Bondar RL, Dunphy PT, Moradshahi P, Kassam MS, Blaber AP, Stein F, Freeman R (1997) Cerebrovascular and cardiovascular responses to graded tilt in patients with autonomic failure. Stroke 28:1677–1685
9. Brooks DJ, Redmond S, Mathias CJ, Bannister R, Symon L (1989) The effect of orthostatic hypotension on cerebral blood flow and middle cerebral artery velocity in autonomic failure, with observations on the action of ephedrine. J Neurol Neurosurg Psychiatry 52:962–966
10. Brouwers PJ, Vriens EM, Musbach M, Wieneke GH, van Huffelen AC (1990) Transcranial pulsed Doppler measurements of blood flow velocity in the middle cerebral artery: reference values at rest and during hyperventilation in healthy children and adolescents in relation to age and sex. Ultrasound Med Biol 16:1–8
11. Carey BJ, Eames PJ, Panerai RB, Potter JF (2001) Carbon dioxide, critical closing pressure and cerebral haemodynamics prior to vasovagal syncope in humans. Clin Sci (London) 101:351–358
12. Chen Z, Hu K, Stanley HE, Novak V, Ivanov PC (2006) Cross-correlation of instantaneous phase increments in pressure-flow fluctuations: applications to cerebral autoregulation. Phys Rev E 73:031915
13. Claassen JA, Meel-van den Abeelen AS, Simpson DM, Panerai RB, International Cerebral Autoregulation Research Network (2016) Transfer function analysis of dynamic cerebral autoregulation: a white paper from the International Cerebral Autoregulation Research Network. J Cereb Blood Flow Metab 36:665–680
14. Czosnyka M, Brady K, Reinhard M, Smielewski P, Steiner LA (2009) Monitoring of cerebrovascular autoregulation: facts, myths, and missing links. Neurocrit Care 10:373–386
15. Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD (1996) Monitoring of cerebral autoregulation in head-injured patients. Stroke 27:1829–1834
16. Czosnyka M, Smielewski P, Lavinio A, Pickard JD, Panerai R (2008) An assessment of dynamic autoregulation from spontaneous fluctuations of cerebral blood flow velocity: a comparison of two models, index of autoregulation and mean flow index. Anesth Analg 106:234–239 (table of contents)
17. Deegan BM, Cooke JP, Lyons D, Olaighin G, Serrador JM (2010) Cerebral autoregulation in the vertebral and middle cerebral arteries during combine head upright tilt and lower body negative pressure in healthy humans. Eng Med Biol Soc 2010:2505–2508
18. Devault K, Gremaud PA, Novak V, Olufsen MS, Vernieres G, Zhao P (2008) Blood flow in the circle of willis: modeling and calibration. Multiscale Model Simul 7:888–909
19. DeWitt LD, Wechsler LR (1988) Transcranial Doppler. Stroke 19:915–921
20. Donnelly J, Budohoski KP, Smielewski P, Czosnyka M (2016) Regulation of the cerebral circulation: bedside assessment and clinical implications. Crit Care 20:129
21. Edgell H, Robertson AD, Hughson RL (2012) Hemodynamics and brain blood flow during posture change in younger women and postmenopausal women compared with age-matched men. J Appl Physiol 112:1482–1493
22. El-Bedawi K, Hainsworth R (1994) Combined head-up tilt and lower body suction: a test of orthostatic tolerance. Clin Auton Res 4:41–47
23. Endo A, Fujita Y, Fuchigami T, Takahashi S, Mugishima H, Skatani K (2014) Changes in cerebral blood oxygenation induced by active standing test in children with POTS and NMS. Adv Exp Med Biol 812:253–261
24. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, Cheshire WP, Chelimsky T, Cortelli P, Gibbons CH, Goldstein DS, Hainsworth R, Hilz MJ, Jacob G, Kaufmann H, Jordan J, Lipsitz LA, Levine BD, Low PA, Mathias C, Raj SR, Robertson D, Sandroni P, Schatz I, Schondorff R, Stewart JM, van Dijk JG (2011) Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 21:69–72
25. Fuente Mora C, Palma JA, Kaufmann H, Norcliffe-Kaufmann L (2016) Cerebral autoregulation and symptoms of orthostatic hypotension in familial dysautonomia. J Cereb Blood Flow Metab 7(7):2414– 2422
26. Gierthmuhlen J, Allardt A, Sawade M, Baron R, Wasner G (2011) Dynamic cerebral autoregulation in stroke patients with a central sympathetic deficit. Acta Neurol Scand 123:332–338
27. Gordon GR, Choi HB, Rungta RL, Ellis-Davies GC, MacVicar BA (2008) Brain metabolism dictates the polarity of astrocyte control over arterioles. Nature 456:745–749
28. Greaves DK, Arbeille P, Hughson RL (2007) WISE 2005: altered cerebrovascular autoregulation after 60 day head-down bed rest. J Gravit Physiol 14:P61–P62
29. Gupta A, Harris S, Vernino S, Naina HV (2015) Rituximab-based therapy and long-term control of autoimmune autonomic ganglionopathy. Clin Auton Res 25:255–258
30. Gur AY, Auriel E, Korczyn AD, Gadoth A, Shopin L, Giladi N, Bornstein NM, Gurevich T (2012) Vasomotor reactivity as a predictor for syncope in patients with orthostatism. Acta Neurol Scand 126:32–36
31. Hainsworth R (2004) Pathophysiology of syncope. Clin Auton Res 14[Suppl 1]:18–24
32. Hamner JW, Tan CO, Tzeng YC, Taylor JA (2012) Cholinergic control of the cerebral vasculature in humans. J Physiol 590:6343–6352
33. Hanby MF, Panerai RB, Robinson TG, Haunton VJ (2017) Is cerebral vasomotor reactivity impaired in Parkinson disease? Clin Auton Res 27:107–111
34. Harms MP, Wieling W, Colier WN, Lenders JW, Secher NH, van Lieshout JJ (2010) Central and cerebrovascular effects of leg crossing in humans with sympathetic failure. Clin Sci (London) 118:573–581
35. Hart J, Novak V, Saunders C, Gremaud PA (2016) Transcranial Doppler-based surrogates for cerebral blood flow: a statistical study. PLoS One 11:e0165536
36. Haubrich C, Pies K, Dafotakis M, Block F, Kloetzsch C, Diehl RR (2010) Transcranial Doppler monitoring in Parkinson's disease: cerebrovascular compensation of orthostatic hypotension. Ultrasound Med Biol 36:1581–1587
37. Helton KJ, Adams RJ, Kesler KL, Lockhart A, Aygun B, Driscoll C, Heeney MM, Jackson SM, Krishnamurti L, Miller ST, Sarnaik SA, Schultz WH, Ware RE, Investigators SW (2014) Magnetic resonance imaging/angiography and transcranial Doppler velocities in sickle cell anemia: results from the SWiTCH trial. Blood 124:891–898

38. Horowitz DR, Kaufmann H (2001) Autoregulatory cerebral vasodilation occurs during orthostatic hypotension in patients with primary autonomic failure. Clin Auton Res 11:363–367
39. Hu K, Lo M-T, Peng CK, Novak V, Schmidt EA, Kumar A, Czosnyka M (2009) Nonlinear pressure–flow relationship is able to detect asymmetry of brain blood circulation associated with midline shift. J Neurotrauma 26:227–233
40. Hu K, Lo MT, Peng CK, Liu Y, Novak V (2012) A nonlinear dynamic approach reveals a long-term stroke effect on cerebral blood flow regulation at multiple time scales. PLoS Comput Biol 8:e1002601
41. Hu K, Peng CK, Huang NE, Wu Z, Lipsitz LA, Cavallerano J, Novak V (2008) Altered phase interactions between spontaneous blood pressure and flow fluctuations in type 2 diabetes mellitus: nonlinear assessment of cerebral autoregulation. Phys A 387:2279–2292
42. Itakura T, Yamamoto K, Tohyama M, Shimizu N (1977) Central dual innervation of arterioles and capillaries in the brain. Stroke 8:360–365
43. Jatuzis D, Zachrisson H, Blomstrand C, Ekholm S, Holm J, Volkmann R (2000) Evaluation of posterior cerebral artery blood flow with transcranial Doppler sonography: value and risk of common carotid artery compression. J Clin Ultrasound 28:452–460
44. Jordan J, Shibao C, Biaggioni I (2015) Multiple system atrophy: using clinical pharmacology to reveal pathophysiology. Clin Auton Res 25:53–59
45. Kaufmann H, Hague K, Perl D (2001) Accumulation of alpha-synuclein in autonomic nerves in pure autonomic failure. Neurology 56:980–981
46. Kaufmann H, Hainsworth R (2001) Why do we faint? Muscle Nerve 24:981–983
47. Kaufmann H, Malamut R, Norcliffe-Kaufmann L, Rosa K, Freeman R (2012) The orthostatic hypotension questionnaire (OHQ): validation of a novel symptom assessment scale. Clin Auton Res 22:79–90
48. Kaufmann H, Norcliffe-Kaufmann L, Palma JA, Biaggioni I, Low PA, Singer W, Goldstein DS, Peltier AC, Shibao CA, Gibbons CH, Freeman R, Robertson D, Autonomic Disorders C (2017) Natural history of pure autonomic failure: a United States prospective cohort. Ann Neurol 81:287–297
49. Krediet CT, de Bruin IG, Ganzeboom KS, Linzer M, van Lieshout JJ, Wieling W (2005) Leg crossing, muscle tensing, squatting, and the crash position are effective against vasovagal reactions solely through increases in cardiac output. J Appl Physiol 99:1697–1703
50. Krediet CT, van Dijk N, Linzer M, van Lieshout JJ, Wieling W (2002) Management of vasovagal syncope: controlling or aborting faints by leg crossing and muscle tensing. Circulation 106:1684–1689
51. Lankford J, Numan M, Hashmi SS, Gourishankar A, Butler IJ (2015) Cerebral blood flow during HUTT in young patients with orthostatic intolerance. Clin Auton Res 25:277–284
52. Lassen NA, Christensen MS (1976) Physiology of cerebral blood flow. Br J Anaesth 48:719–734
53. Lewis NC, Ainslie PN, Atkinson G, Jones H, Grant EJ, Lucas SJ (2013) Initial orthostatic hypotension and cerebral blood flow regulation: effect of alpha1-adrenoreceptor activity. Am J Physiol 304:R147–R154
54. Lewis NC, Bain AR, MacLeod DB, Wildfong KW, Smith KJ, Willie CK, Sanders ML, Numan T, Morrison SA, Foster GE, Stewart JM, Ainslie PN (2014) Impact of hypocapnia and cerebral perfusion on orthostatic tolerance. J Physiol 592:5203–5219
55. Lo MT, Hu K, Liu Y, Peng CK, Novak V (2008) Multimodal pressure flow analysis: application of Hilbert Huang transform in cerebral blood flow regulation. EURASIP J Adv Signal Process 2008:785243
56. Mattle HP, Nirkko AC, Baumgartner RW, Sturzenegger M (1995) Transient cerebral circulatory arrest coincides with fainting in cough syncope. Neurology 45:498–501
57. Meel-van den Abeelen AS, van Beek AH, Slump CH, Panerai RB, Claassen JA (2014) Transfer function analysis for the assessment of cerebral autoregulation using spontaneous oscillations in blood pressure and cerebral blood flow. Med Eng Phys 36:563–575
58. Mihci E, Dora B, Balkan S (2007) Transcranial Doppler ultrasonographic evaluation of cerebral circulation during passive tilting in patients with Parkinson's disease. J Clin Ultrasound 35:138–143
59. Murrell CJ, Cotter JD, George K, Shave R, Wilson L, Thomas K, Williams MJ, Ainslie PN (2011) Cardiorespiratory and cerebrovascular responses to head-up tilt II: influence of age, training status and acute exercise. Exp Gerontol 46:1–8
60. Nicoletto HA, Burkman MH (2009) Transcranial Doppler series part III: interpretation. Am J Electroneurodiagnostic Technol 49:244–259
61. Norcliffe LJ, Rivera-Ch M, Claydon VE, Moore JP, Leon-Velarde F, Appenzeller O, Hainsworth R (2005) Cerebrovascular responses to hypoxia and hypocapnia in high-altitude dwellers. J Physiol 566:287–294
62. Norcliffe-Kaufmann L, Axelrod F, Kaufmann H (2010) Afferent baroreflex failure in familial dysautonomia. Neurology 75:1904–1911
63. Norcliffe-Kaufmann L, Palma JA, Kaufmann H (2016) Mother-induced hypertension in familial dysautonomia. Clin Auton Res 26:79–81
64. Norcliffe-Kaufmann L, Slaugenhaupt SA, Kaufmann H (2017) Familial dysautonomia: History, genotype, phenotype and translational research. Prog Neurobiol 152:131–148
65. Norcliffe-Kaufmann LJ, Kaufmann H, Hainsworth R (2008) Enhanced vascular responses to hypocapnia in neurally mediated syncope. Ann Neurol 63:288–294
66. Novak P (2016) Cerebral blood flow, heart rate, and blood pressure patterns during the tilt test in common orthostatic syndromes. Neurosci J 2016:6127340
67. Novak P (2016) Orthostatic cerebral hypoperfusion syndrome. Front Aging Neurosci 8:22
68. Novak V, Hajjar I (2010) The relationship between blood pressure and cognitive function. Nat Rev Cardiol 7:686–698
69. Novak V, Novak P, Spies JM, Low PA (1998) Autoregulation of cerebral blood flow in orthostatic hypotension. Stroke 29:104–111
70. Novak V, Spies JM, Novak P, McPhee BR, Rummans TA, Low PA (1998) Hypocapnia and cerebral hypoperfusion in orthostatic intolerance. Stroke 29:1876–1881
71. Novak V, Yang AC, Lepicovsky L, Goldberger AL, Lipsitz LA, Peng CK (2004) Multimodal pressure-flow method to assess dynamics of cerebral autoregulation in stroke and hypertension. Biomed Eng Online 3:39
72. Palma JA, Norcliffe-Kaufmann L, Fuente-Mora C, Percival L, Mendoza-Santiesteban C, Kaufmann H (2014) Current treatments in familial dysautonomia. Expert Opin Pharmacother 15:2653–2671
73. Panerai RB (1998) Assessment of cerebral pressure autoregulation in humans—a review of measurement methods. Physiol Meas 19:305–338
74. Panerai RB (2003) The critical closing pressure of the cerebral circulation. Med Eng Phys 25:621–632
75. Panerai RB (2009) Transcranial Doppler for evaluation of cerebral autoregulation. Clin Auton Res 19:197–211

76. Panerai RB (2014) Nonstationarity of dynamic cerebral autoregulation. Med Eng Phys 36:576–584
77. Panerai RB, Sammons EL, Smith SM, Rathbone WE, Bentley S, Potter JF, Samani NJ (2008) Continuous estimates of dynamic cerebral autoregulation: influence of non-invasive arterial blood pressure measurements. Physiol Meas 29:497–513
78. Pederson CL, Brook JB (2017) Health-related quality of life and suicide risk in postural tachycardia syndrome. Clin Auton Res 27:75–81
79. Purkayastha S, Sorond F (2012) Transcranial Doppler ultrasound: technique and application. Semin Neurol 32:411–420
80. Schondorf R, Stein R, Roberts R, Benoit J, Cupples W (2001) Dynamic cerebral autoregulation is preserved in neurally mediated syncope. J Appl Physiol 91:2493–2502
81. Shin KJ, Kim SE, Park KM, Park J, Ha SY, Kim SE, Kwon OY (2016) Cerebral hemodynamics in orthostatic intolerance with normal head-up tilt test. Acta Neurol Scand 134:108–115
82. Strandgaard S, Paulson OB (1992) Regulation of cerebral blood flow in health and disease. J Cardiovasc Pharmacol 19[Suppl 6]:S89–S93
83. Tannemaat MR, Thijs RD, van Dijk JG (2014) Managing psychogenic pseudosyncope: facts and experiences. Cardiol J 21:658–664
84. Tellez MJ, Norcliffe-Kaufmann LJ, Lenina S, Voustianiouk A, Kaufmann H (2009) Usefulness of tilt-induced heart rate changes in the differential diagnosis of vasovagal syncope and chronic autonomic failure. Clin Auton Res 19:375–380
85. Thijs RD, Wieling W, Kaufmann H, van Dijk G (2004) Defining and classifying syncope. Clin Auton Res 14[Suppl 1]:4–8
86. Thomas KN, Galvin SD, Williams MJ, Willie CK, Ainslie PN (2010) Identical pattern of cerebral hypoperfusion during different types of syncope. J Hum Hypertens 24:458–466
87. Tiecks FP, Douville C, Byrd S, Lam AM, Newell DW (1996) Evaluation of impaired cerebral autoregulation by the Valsalva maneuver. Stroke 27:1177–1182
88. Tiecks FP, Lam AM, Aaslid R, Newell DW (1995) Comparison of static and dynamic cerebral autoregulation measurements. Stroke 26:1014–1019
89. Trivedi UH, Patel RL, Turtle MR, Venn GE, Chambers DJ (1997) Relative changes in cerebral blood flow during cardiac operations using xenon-133 clearance versus transcranial Doppler sonography. Ann Thorac Surg 63:167–174
90. Tugba B, Zubeyir K, Nevzat U, Ali Y, Birsen U, Tevfik D (2015) Cerebral blood flow of children with vasovagal syncope. Cardiol Young 25:267–273
91. Valdueza JM, Balzer JO, Villringer A, Vogl TJ, Kutter R, Einhaupl KM (1997) Changes in blood flow velocity and diameter of the middle cerebral artery during hyperventilation: assessment with MR and transcranial Doppler sonography. AJNR Am J Neuroradiol 18:1929–1934
92. van Beek AH, Claassen JA, Rikkert MG, Jansen RW (2008) Cerebral autoregulation: an overview of current concepts and methodology with special focus on the elderly. J Cereb Blood Flow Metab 28:1071–1085
93. van Dijk JG (2003) Fainting in animals. Clin Auton Res 13:247–255
94. Van Lieshout JJ, Wieling W, Karemaker JM, Secher NH (2003) Syncope, cerebral perfusion, and oxygenation. J Appl Physiol 94:833–848
95. Wallin B, Sundlof G (1982) Sympathetic outflow to muscles during vasovagal syncope. J Auton Nerv Syst 6:287–291
96. Westermaier T, Pham M, Stetter C, Willner N, Solymosi L, Ernestus RI, Vince GH, Kunze E (2014) Value of transcranial Doppler, perfusion-CT and neurological evaluation to forecast secondary ischemia after aneurysmal SAH. Neurocrit Care 20:406–412
97. Wieling W, van Lieshout JJ, van Leeuwen AM (1993) Physical manoeuvres that reduce postural hypotension in autonomic failure. Clin Auton Res 3:57–65
98. Wilterdink JL, Feldmann E, Furie KL, Bragoni M, Benavides JG (1997) Transcranial Doppler ultrasound battery reliably identifies severe internal carotid artery stenosis. Stroke 28:133–136
99. Xu WH, Wang H, Hu YH, Wang B, Chen J, Gao S (2013) Supine-to-standing transcranial Doppler test in patients with multiple system atrophy. Parkinsonism Relat Disord 19:539–542
100. Zuj KA, Edgell H, Shoemaker JK, Custaud MA, Arbeille P, Hughson RL (2012) WISE 2005: responses of women to sublingual nitroglycerin before and after 56 days of 6° head-down bed rest. J Appl Physiol 113:434–441