Journal of the American Heart Association

CONTEMPORARY REVIEW

Cerebral Blood Flow in Orthostatic Intolerance

Muhammad Shahzeb Khan, MD, MSc;* Amanda J. Miller, PhD;* Arooba Ejaz, MBBS; Jeroen Molinger, MS; Parag Goyal, MD, MSc; David B. MacLeod, MD; Ashley Swavely, MS; Elyse Wilson, MS; Meghan Pergola, MPH; Harikrishna Tandri, MD; Camille Frazier Mills, MD; Satish R Raj, MD, MSCI; Marat Fudim, MD

ABSTRACT: Cerebral blood flow (CBF) is vital for delivering oxygen and nutrients to the brain. Many forms of orthostatic intolerance (OI) involve impaired regulation of CBF in the upright posture, which results in disabling symptoms that decrease quality of life. Because CBF is not easy to measure, rises in heart rate or drops in blood pressure are used as proxies for abnormal CBF. These result in diagnoses such as postural orthostatic tachycardia syndrome and orthostatic hypotension. However, in many other OI syndromes such as myalgic encephalomyelitis/chronic fatigue syndrome and long COVID, heart rate and blood pressure are frequently normal despite significant drops in CBF. This often leads to the incorrect conclusion that there is nothing hemodynamically abnormal in these patients and thus no explanation or treatment is needed. There is a need to measure CBF, as orthostatic hypoperfusion is the shared pathophysiology for all forms of OI. In this review, we examine the literature studying CBF dysfunction in various syndromes with OI and evaluate methods of measuring CBF including transcranial Doppler ultrasound, extracranial cerebral blood flow ultrasound, near infrared spectroscopy, and wearable devices.

Key Words: cerebral blood flow ■ long COVID ■ ME/CFS ■ orthostatic intolerance ■ POTS

Orthostatic intolerance (OI) is a set of chronic syndromes linked to dysfunction of the autonomic nervous system or dysautonomia. OI includes several syndromes such as postural orthostatic tachycardia syndrome (POTS), syncope, and orthostatic hypotension (OH).[1] There is a large overlap between OI and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).[2] While the pathophysiology is not well understood, all these syndromes experience excessive drops in cerebral blood flow (CBF) leading to symptoms including lightheadedness, fatigue, brain fog, and syncope.[3] Because of the debilitating nature of the symptoms, OI puts financial strain on economies by decreasing the workforce and increasing health care costs.[4] For example, the quality of life for people with OI is similar to that of people with congestive heart failure and chronic obstructive pulmonary disease.[5]

Most people with OI develop symptoms after an acute viral illness or injury.[1,4] Since viral illnesses are the leading trigger of OI, it is unsurprising to the autonomic field that the COVID-19 pandemic has caused an increase in cases of OI.[6,7] Long COVID, or the postacute sequelae of SARS-CoV-2 infection, describes people with chronic symptoms that persist following an acute infection of SARS-CoV-2.[8] Symptoms of long COVID that overlap with OI include fatigue, dyspnea, headache, palpitations, and brain fog.[9] According to the National Center for Health Statistics, the US Census Bureau, and the CDC, 6.8% of American adults are currently experiencing long COVID as of February 2024.[10]

Correspondence to: Marat Fudim, MD, MHS, Duke University Medical Center, 2301 Erwin Road, Durham, North Carolina 27710. Email: marat.fudim@duke.edu

*M. Shahzeb Khan and A. Miller are co-first authors.

For Sources of Funding and Disclosures, see page 11 and 12.

This manuscript was sent to Tochukwu M. Okwuosa, DO, Associate Editor, for review by expert referees, editorial decision, and final disposition.

JAHA is available at: www.ahajournals.org/journal/jaha

Nonstandard Abbreviations and Acronyms

CBF	cerebral blood flow
CBv	cerebral blood velocity
CO	cardiac output
CPP	cerebral perfusion pressure
MCA	middle cerebral artery
ME/CFS	myalgic encephalomyelitis/chronic fatigue syndrome
NIRS	near-infrared spectroscopy
OCHOS	orthostatic cerebral hypoperfusion syndrome
OH	orthostatic hypotension
OI	orthostatic intolerance
POTS	postural orthostatic tachycardia syndrome
TCD	transcranial Doppler

Two thirds of people with long COVID have symptoms of OI and moderate to severe autonomic dysfunction.[11,12] OI has been labeled an epidemic since the mid-1990s and yet is still not well understood.[13] Given the burden long COVID places on economies as a mass-disabling event with high health care usage well beyond the acute illness phase,[14] it is pressing now more than ever to understand physiological mechanisms that contribute to OI. Long COVID is a multisystem disorder with various manifestations in the immune, cardiopulmonary, and nervous systems.[7] One finding is that OI and long COVID share similar dysregulation in CBF, which may point to a shared pathogenesis.[15]

In this review, we evaluate the use of CBF and its surrogates as a diagnostic metric for the evaluation of symptoms in OI and explore available measurement techniques. We focus on techniques that have been evaluated during orthostatic testing, including transcranial Doppler (TCD) ultrasound, extracranial carotid ultrasound, near-infrared spectroscopy (NIRS), and new wearable devices.

IMPORTANCE OF CBF REGULATION

Despite weighing <2% of an individual's total body weight, the human brain uses 20% of the body's oxygen due to remarkably active cerebral metabolism.[16,17] Energy production in the brain, which is primarily driven by ATP, relies on the oxidative metabolism of glucose in resting states.[18] Since the brain cannot significantly increase oxygen extraction from blood, oxygen delivery via CBF must be maintained to meet these high oxygen demands and ensure normal brain function.[16,18]

PHYSIOLOGY OF CBF REGULATION

CBF regulation is primarily mediated by the autonomic nervous system, which is responsible for maintaining stable cardiac output (CO), by means of baroreceptors

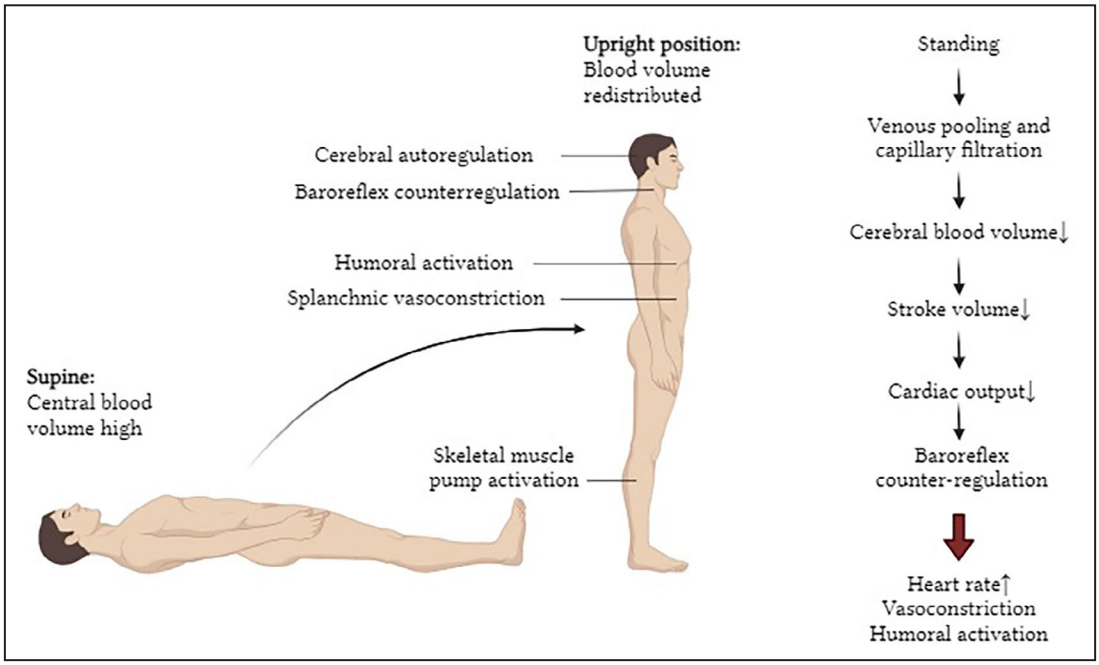

Figure 1. Physiological mechanisms involved in regulating blood flow with orthostasis (left) and order of activation of physiological changes that occur with standing (right).

located in the aortic arch and carotid sinuses.[17] Changes in blood flow regulation with orthostasis are summarized in Figure 1. In healthy humans, upon orthostasis, gravity pulls blood into the lower body, causing an instantaneous drop in preload, which then drops CO and thus CBF.[17] This causes the brief dizziness many people feel immediately upon standing. The drops in CO and CBF are detected by the baroreceptors, which respond by activating the sympathetic nervous system to trigger vasoconstriction and an increase in heart rate to bring CO back to supine values in healthy humans.[17,19] Dysfunction of various parts of the autonomic nervous system is the disease process that causes the symptomology of OI.[20] More specifically, in OI, venous pooling increases due to impairment of the skeletal muscle pump[21] and decreased splanchnic vasoconstriction.[22] Central blood volume, CO, and stroke volume decrease when upright in OI, which increases sympathetic nervous system activation and manifests as tachycardia and increased catecholamine release.[22,23]

CO is then reflected in cerebral perfusion pressure (CPP). CPP is the pressure gradient present at the hydrostatic level of the head that propels blood flow into the brain.[24] CPP is traditionally thought of as the difference between mean arterial pressure and intracranial pressure (CPP=mean arterial pressure−intracranial pressure).[24] However, the CPP=mean arterial pressure−intracranial pressure equation only holds true in the supine posture when the head is not higher than the heart. The blood pressure (BP) that reaches the level of the head declines in an upright posture because hydrostatic pressure increases intracranial pressure and in turn lowers CPP.[25] If a person is upright, the brain is materially higher than the heart, and the hydrostatic effects of gravity on intracranial CPP must be considered as well.[25] The Bernoulli equation is key to understanding vascular physiology by connecting a loss of kinetic energy to a reduction in BP measured at the level of the brain compared with BP at the level of the heart.[25,26] Assuming the average distance between the brain and heart is 29 cm, the decrease in BP at the head in the upright posture can be calculated as Δpressure=density of blood×force of gravity (as a constant)×Δheight of column=(1000 kg/m^3) (9.81 m/s^2) (0.29 m)=11 960 Pa=21.4 mm Hg.[26] This is a material pressure difference that is often incorrectly unaccounted for on the basis of posture.[25]

Assuming stable CO and central perfusion pressure, an additional factor affecting CBF is cerebrovascular resistance, which describes the degree of resistance by the blood vessels in the brain through modulating vessel diameters. An increase in cerebrovascular resistance results in a decrease in CBF, and a decrease in cerebrovascular resistance leads to an increase in CBF. To maintain a normal CBF despite vastly varying CO and central perfusion pressure, the body adjusts cerebrovascular resistance as necessary.[19] The precise interplay between these mechanisms is critical for ensuring adequate blood supply to the brain, which is essential for normal brain function. The relationship between these variables can be expressed using the following equation:[19]

$$\text{CBF} = (\text{central perfusion pressure} - \Delta\text{pressure}) / \text{cerebrovascular resistance}.$$

Secondarily, the brain's own homeostatic mechanism of local cerebral autoregulation ensures that an increase or decrease in mean arterial pressure is directly met with consequential vasoconstriction or vasodilation of small cerebral arteries, respectively.[17] Through the regulation of cerebrovascular resistance, constant CBF is maintained. Dysfunction in autonomic control of central blood flow leads to many symptoms of orthostatic intolerance.[27]

Cerebral Autoregulation

Cerebral autoregulation is the brain's ability to maintain constant CBF despite fluctuations in BP. Cerebral autoregulation occurs over a range of CPPs through adjustments in cerebrovascular resistance.[28] Factors influencing autoregulation include BP fluctuations, CO_2 levels, cerebrovascular tone, and metabolic demands of the brain.[17]

Cerebral autoregulation can be divided into 2 subtypes: static and dynamic. Static cerebral autoregulation defines the ability of the cerebral vasculature to maintain CBF within the normal range of 60 and 160 mm Hg mean BP, regardless of steady-state changes in BP.[29] Cerebral autoregulation is typically assessed by measuring the relationship between changes in TCD-derived cerebral blood velocity (CBv) and changes in arterial BP during steady-state conditions. For evaluation of static cerebral autoregulation, baseline measurements of CBv and BP are recorded in the supine position over at least 10-minute-long time intervals. Next, sustained alterations in BP are achieved through the administration of vasoconstrictors or vasodilators, and the subsequent effect on CBv is monitored. Despite steady changes in BP, if CBF remains stable, then static cerebral autoregulation is deemed intact.

Dynamic autoregulation describes the CBv changes with rapid fluctuations in BP that occur with physiological changes such as posture or breathing manipulation or pharmacological intervention.[17] The latency of autoregulatory action, or how quickly the brain responds to changes in BP, can then be measured, in addition to its efficiency.[29] The cerebral autoregulation index, the slope of the linear regression between CBv and BP changes over time can be used to calculate the efficiency of cerebral autoregulation.[29] This factor

is particularly relevant in clinical conditions like OI, in which static cerebral autoregulation is intact, but they are unable to compensate for dynamic mean BP changes within the 60 to 160 mm Hg range (eg, drop from 100 mm Hg to 80 mm Hg) leading to presyncope or syncope.[30]

Recent analyses indicate that autoregulation is effective over a narrow range of BP changes (≈10%), with a more effective buffering of BP increases compared with decreases.[17] This autoregulatory process is often seen as static, but it is actually dynamic, with CBF rapidly adjusting to changes in central perfusion pressure.[29,31] This dynamic response is evident when CBF returns to baseline before BP does. If dynamic autoregulation is impaired, CBF changes align closely with BP changes.[17] This is particularly relevant for OI when BP and central blood volume are unstable and most commonly drop with orthostasis.[23] If autoregulation is impaired, as evidenced in OI, CBF can change rapidly with changes in BP, which leads to neurological symptoms.[32]

CBF IN OI

CBF in Syncope

CBF dysregulation can cause syncope, a transient loss of consciousness when there is significantly decreased blood flow to the brain.[33] OH is a diagnosis that commonly experiences CBF dysregulation resulting in syncope. Possible causes of OH include dehydration, medications, or health conditions with secondary dysfunction of the autonomic nervous system.[1] As the autonomic nervous system regulates the subconscious process of vasoconstriction, autonomic dysfunction hampers the body's ability to vasoconstrict to prevent venous pooling in the lower extremities in the upright position, resulting in low BP and CBF drops.[34]

A head-up tilt table test is often used by electrophysiologists to test a patient's likelihood of syncope. The test induces orthostatic stress with passive upright posture during which vital signs such as BP and heart rate are monitored, ideally continuously, throughout the test. Since all types of syncope are essentially caused by a rapid drop in CBF, it is clinically relevant to measure CBv in syncope to reach an accurate diagnosis.[1] Figure 2 shows the BP and CBv patterns of a 20-year-old woman with mixed syncope.[3] The onset of syncope coincides with a drop in CBF, followed by a delayed decline in BP.[3] Evidence suggests that CBF drops before the fall in BP in syncope contributing to a syncopal event.[34] Cerebral autoregulation, however, does not appear to be affected in syncope during head-up tilt.[17,35] Some people with syncope have a paradoxical increase in cerebrovascular resistance that proceeds the drop in BP.[34,36] There are surprisingly limited studies addressing CBF in syncope and CBF regulation may differ depending on the pathogenesis and pathophysiology of the disorder.[36] For instance, people with neurally mediated syncope or hypotension may develop an altered BP range for autoregulation and baroreflex buffering compared with otherwise healthy people with the occasional vasovagal episodes.[17,35,36]

CBF in POTS

Several studies have evaluated cardiovascular and CBv patterns in POTS. Novak et al[3] studied diagnostic

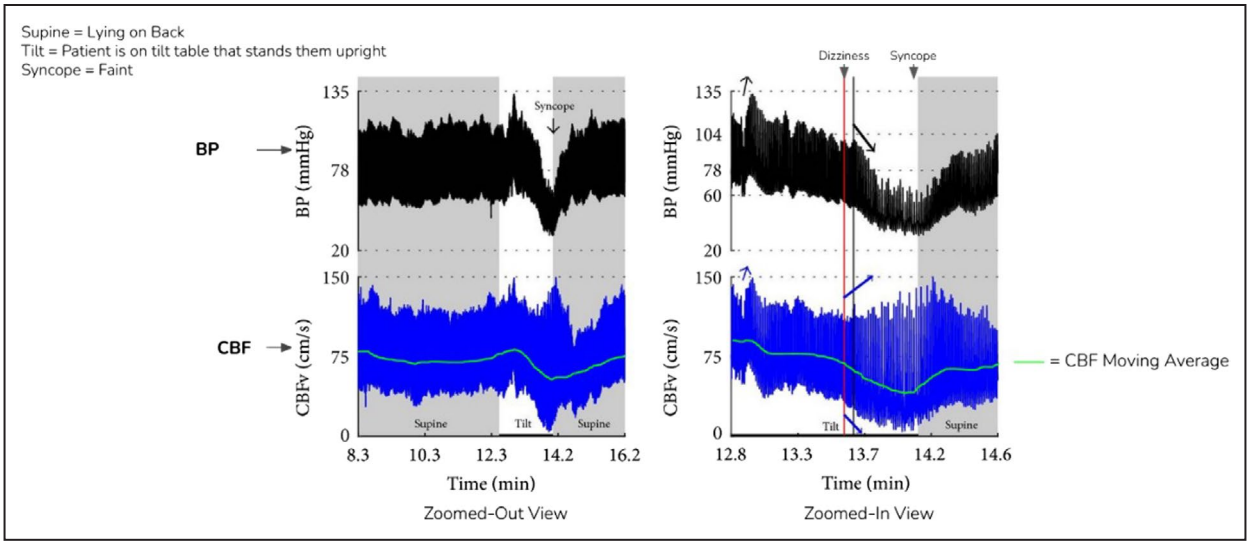

Figure 2. BP and CBF patterns in mixed syncope.
The figure depicts CBF drops being consistent with syncope, whereas BP drops only correlate in some cases (eg, orthostatic hypotension). Charts reproduced from Novak under the terms and conditions of the Creative Commons Attribution Non-Commercial-NoDerivatives license (https://creativecommons.org/licenses/by-nc-nd/4.0/). BP indicates blood pressure; and CBF, cerebral blood flow.

metrics for assessing multiple forms of OI during head-up tilt and outlined the crucial importance of measuring TCD in conditions with OI. CBv, measured in the middle cerebral artery (MCA), served as a more accurate tool in differentiating POTS from other forms of tachycardia.[37] While heart rate was significantly elevated in all conditions, CBv was considerably low in POTS, and either normal or transiently increased in supraventricular tachycardias.[3] More than 50% of POTS participants presented with central hypovolemia, resulting primarily from blood sequestration within the splanchnic vasculature, leading to reduced upright cerebral blood volume.[38] A series of intricate physiology studies by Stewart and colleagues demonstrated CBv abnormalities with head-up tilt in small samples (9–25 participants per study) of adolescent participants with POTS.[32,38–41] First, they showed that POTS participants had twice the drop in CBv on head-up tilt compared with controls even though BP remained stable.[38] In addition, CBv oscillated significantly more in POTS compared with controls during head-up tilt.[32,40] Together these data suggest impaired cerebral autoregulation in POTS. Furthermore, Stewart et al demonstrated that the drop in CBv with head-up tilt in POTS occurs before orthostatic tachycardia and hyperpnea, which suggests that CBv may be driving POTS pathophysiology.[39] In addition, this group has found associations between CBv drops on tilt and difficulty with working memory, which may account for brain fog experienced by people with POTS.[38,41]

There is also evidence that the drop in CBv with orthostasis drives other POTS symptoms, including postural tachycardia and hyperventilation.[42] Stewart et al[39] investigated the time course of physiological changes in POTS. They demonstrated that CBv drops before the rise in HR or end-tidal CO_2 in POTS.[39] A recent study by Baker et al confirmed that reduced stroke volume and CBv drive postural hyperventilation.[43] Regardless of POTS subtype (hyperadrenergic, neuropathic, hypovolemic, etc), an excessive decrease in orthostatic CBv is a consistent pathophysiological mechanism.[3,41] Whether the CBF also drops excessively in POTS with orthostatic hypertension has not been studied except for 1 case study[3] but deserves further investigation.

CBF in ME/CFS

ME/CFS is a challenging diagnosis due to a lack of specific biomarkers or diagnostic tests.[44] Clinical presentations include persistent fatigue for ≥6 months, postexertional malaise, and related deterioration in physical and mental health.[44] People with ME/CFS report symptoms that overlap with several other syndromes including fibromyalgia and POTS.[45] Two thirds of people with ME/CFS experience symptoms of autonomic dysfunction with 20% to 30% meeting POTS criteria.[3,45]

Using an extracranial CBv ultrasound technique of the carotid and vertebral arteries, van Campen et al. observed CBF changes during head-up tilt in participants with ME/CFS.[46–48] The authors found a 26% reduction in CBF at end-tilt in participants with ME/CFS, compared with a 7% decrease in healthy controls.[46] Notably, 90% of participants with ME/CFS exhibited a >13% reduction in CBv, a threshold set 2 SDs below the average drop in CBF in healthy subjects.[46] Under these definitions, an abnormal CBF drop at the end of head-up tilt was seen in 82% of participants with ME/CFS and normal heart rate and BP, in 98% of ME/CFS with delayed OH, and in 100% of ME/CFS with POTS.[46] Even more surprising was that 247 of 429 (58%) of the participants with ME/CFS who experienced orthostatic symptoms, had normal heart rate and BP.[46] Without measuring CBF, traditional vital signs appear normal in a majority of people with ME/CFS. Linear regression analysis demonstrated that the extent of CBF reduction was directly correlated with orthostatic symptoms during head-up tilt ($P<0.0005$).[46] Furthermore, CBF remained reduced in ME/CFS following head-up tilt, suggesting slower recovery of blood flow to the brain in this population.[47] Another analysis by this group revealed that participants with ME/CFS who were previously mislabeled as having psychogenic pseudosyncope to explain their frequent syncopal episodes had a more significant decline in CBv compared with participants with ME/CFS without a psychogenic pseudosyncope diagnosis.[48] This suggests that syncope in ME/CFS may be neurally mediated rather than psychogenic.

Novak and colleagues observed the same phenomenon in which many patients with ME/CFS experienced significant CBv reductions despite normal heart rate and BP when evaluating patients complaining of OI on head-up tilt.[49] Instead of using the ME/CFS diagnostic framework, they referred to this group of people as having orthostatic cerebral hypoperfusion syndrome (OCHOS). People with OCHOS have lower-than-normal orthostatic CBv despite normal changes in heart rate and BP.[3,50] Mechanisms behind cerebral hypoperfusion in OCHOS include cerebral autoregulation failure and poor central blood volume compensation to orthostatic provocation.[42,50] Both OCHOS and POTS experience an orthostatic drop of CBv without OH. However, unlike people with POTS, people with OCHOS do not experience excessive tachycardia.[3,50] A study conducted in 2016 investigated the hemodynamic mechanisms leading to orthostatic dizziness in OCHOS and found that participants with OCHOS experienced stable orthostatic BP, normal heart rate, and reduced CBv during head-up tilt. Mean CBv was significantly reduced (>20%) in the OCHOS group as compared with the control group. Both groups

reported no difference in heart rate, BP, and end-tidal CO_2 during head-up tilt. Subjects with hypocapnic cerebral hypoperfusion also had normal heart rate and BP responses, but alarmingly low end-tidal CO_2.[51] Reduction in end-tidal CO_2 is directly correlated with a consequential decrease in CBF velocity due to cerebral vasoconstriction.[51] These results further reinforce the importance of CBF velocity as a crucial biomarker for more accurate evaluation of orthostatic symptoms. Both OCHOS and ME/CFS have very similar hemodynamic patterns.[46] Therefore, we hypothesize that they have been diagnosed with different conditions only because that is what their physicians were familiar with.[3,52]

Given the insensitivity of current biomarkers including heart rate and BP for evaluating OI in ME/CFS, many with orthostatic symptoms are misdiagnosed as healthy. CBF monitoring is vital for proper and compassionate care. In addition, the pathophysiology of ME/CFS appears nearly identical to that of the OCHOS population on which Novak et al reported.[46,50] Both populations experience drops in CBF despite normal BP and heart rate, which can finally explain their significant orthostatic symptom complaints. It can be argued that the ME/CFS and OCHOS populations are effectively the same population and that they are both severely misdiagnosed as being "objectively normal" if CBF is not monitored.

CBF in Long COVID

People with long COVID also have abnormalities in CBsF. Novak et al demonstrated that long COVID symptomology may be primarily explained by CBF dysregulation and neuropathic changes.[9,53] A small study comparing 9 participants with long COVID, 10 participants with POTS, and 15 healthy controls demonstrated a 20% CBF drop in participants with long COVID during head-up tilt compasred with a 3% drop in healthy controls.[9] Moreover, 89% of participants with long COVID had small-fiber neuropathy, which compromises vasoconstriction, resulting in reduced preload, CO, and ultimately impaired CBF.[9,53] Of note is that 67% of patients with symptomatic long COVID did not exhibit orthostatic tachycardia or hypotension, again demonstrating the need to measure CBF or risk misdiagnosis.[9]

Van Campen et al reported similar findings when comparing 10 patients with long COVID against 20 patients with ME/CFS and 10 healthy controls using the extracranial ultrasound.[54] Participants with long COVID experienced a 33% decrease in CBF on head-up tilt, compared with a 4% CBF drop in healthy controls. However, unlike the study by Novak et al,[53] in which a majority of participants with long COVID did not have orthostatic tachycardia, in the study by van Campen et al,[54] all participants with long COVID experienced orthostatic tachycardia on head-up tilt. The symptoms experienced by individuals with long COVID closely resembled those reported in ME/CFS, as observed in their response to head-up tilt. The impairments of CBF and cardiac index during tilt were more severe in many participants with long COVID compared with other ME/CFS participants.[54] These findings show that the orthostatic physiology of long COVID strongly overlaps with those of POTS and ME/CFS. Moreover, these findings are in close concordance with a Swedish case series by Johansson et al in which patients with long COVID presented with clinical symptoms consistent with POTS.[6] In all these cases, monitoring CBF was the most sensitive and specific biomarker of disease. Table 1 describes major studies of clinical conditions reporting orthostatic symptoms. Despite different diagnostic criteria, all of the syndromes in Table 1 are associated with abnormal CBF or CBF regulation when upright. However, CBF is inconsistently assessed and not clinically recognized as a biomarker in OI.

NEED FOR CBF MONITORING IN OI

For conditions associated with OI, monitoring a validated proxy of CBF is essential. TCD-derived CBF velocity has been the primary method used in specialty autonomic centers. However, TCD equipment and training are not widely available. Currently, BP and heart rate are used as surrogates of CBF to assess OI; however, the accuracy of diagnosing conditions with CBF dysregulation using BP and heart rate alone has been shown to have poor sensitivity.[3,9]

Approximately half (22%–58%) of patients who meet the symptomatic criteria for OI do not meet heart rate and BP criteria for POTS or OH during head-up tilt.[3,46] Without monitoring a proxy for CBF, many of these patients would be labeled as objectively normal, and their symptoms could be incorrectly attributed to psychological causes. In OCHOS, BP remains normal, heart rate shows normal increments (≥10 and <30 beats/min), and CBF drops (Figure 3). In the absence of CBF velocity monitoring, people with OCHOS would pass as having normal head-up tilt results, and hence run the risk of being misdiagnosed with psychogenic or vestibular disorders on the basis of orthostatic symptoms. In addition, patients with primary cerebral autoregulatory failure who have characteristically low supine and upright CBv will remain undiagnosed if CBv is not used.[3] People with ME/CFS can have normal heart rate and BP but reduced CBF.[46] Similarly, in participants with long COVID, a decline in orthostatic CBF velocity was observed, while heart rate and BP remained stable.[54] The lack of proper diagnosis of OI stems from the unmet need to provide bedside CBF evaluation.

Table 1. Large Studies Reporting CBv in Orthostatic Intolerance

Study	Year	Design	Diagnosis	No.	Age, y, mean (SD)	Tilt					Outcome
						HR	MAP	Systolic MCA Velocity	Diastolic MCA Velocity	Mean MCA Velocity/ CBF	
Albina et al[55]	2004	Prospective OS	History of Syncope or Presyncope	206	40 (22)	↓	↓	↓	↓	↓	Drop in CBF during neurocardiogenic syncope
Novak et. al[56]	1998	Prospective OS	OI	30	31.3 (1.2)	↑	↔	↓	↓	↓	In OI, orthostatic stress triggers hyperventilation, leading to hypocapnia and cerebral hypoperfusion
Del Pozzi et al[39]	2014	Prospective OS	POTS	11	19 (3)	↑	↓	NA	NA	↓	Initial orthostatic hypotension in POTS results in reduced cerebral blood flow velocity, and postural hypocapnic hyperpnea, which exacerbates cerebral ischemia
Novak, et al[50]	2016	Retrospective OS	OCHOS	102	51.1 (14.9)	↔	↔	↓	↓	↓	Orthostatic cerebral hypoperfusion exists without orthostatic hypotension in patients with orthostatic symptoms
Novak[3]	2016	Retrospective OS	OH, OCHOS, POTS, Syncope, Pseudosyncope	744	NA	↔↕	↔↕	NA	NA	↔↕	Orthostatic syndromes have variable changes in cerebral blood flow and cardiovascular patterns upon TCD monitoring
Novak[42]	2018	Retrospective OS	OI	16	38.6 (8.1)	↔	↔	NA	NA	↓	Cerebral hypoperfusion due to hypocapnia can be an objective biomarker of OI patients without tachycardia
Van Campen et al[46]	2020	Prospective OS	ME/CFS	429	39.0 (12)	↔↑	↔↓	NA	NA	↓	CBF is reduced in ME/CFS patients
Van Campen et al[47]	2021	Case–control OS	ME/CFS	60	39.0 (12)	↔↑	↔↓	NA	NA	↓	ME/CFS patients show a large decline in CBF following head-up tilt
Novak et al[9]	2022	Retrospective OS	PASC	34	35.8 (7.3)	↑↔	↔	NA	NA	↓	Long-COVID is associated with cerebrovascular dysregulation with cerebral arteriolar vasoconstriction

CBF indicates cerebral blood flow; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; OI, orthostatic intolerance; OS, observational study; POTS, postural orthostatic tachycardia syndrome; and TCD, transcranial Doppler. ↑, increased; ↓, decreased; ↔, normal; ↔↑, normal or increased; and ↕, any.

Since measuring CBF is time and labor consuming and technically complex to measure, BP and heart rate are routinely measured instead, resulting in misdiagnoses. Therefore, it is critical to start measuring CBF more directly, instead of relying on inferences from secondary metrics.

METHODS FOR CBF MEASUREMENT

An overview of common methods for orthostatic CBF measurement is shown in Figure 4. Comparison of the advantages and disadvantages of these systems for measuring CBF is summarized in Table 2.

Transcranial Doppler

TCD is one method of measuring a proxy of CBF that can be used for noninvasive in-clinic monitoring both at the bedside or during head-up tilt.[49] TCD does not measure total CBF but looks at changes in CBF velocity in the MCA. Sonographers insonate the MCA using a low-frequency transducer probe at a depth of 45 to 56 mm. The Doppler probe transmits ultrasound beams at a frequency of ≤2 MHz through thin cranial bone windows. The beams are reflected and Doppler shifted as they encounter moving red blood cells. Spectral analysis of the TCD signal at a given time

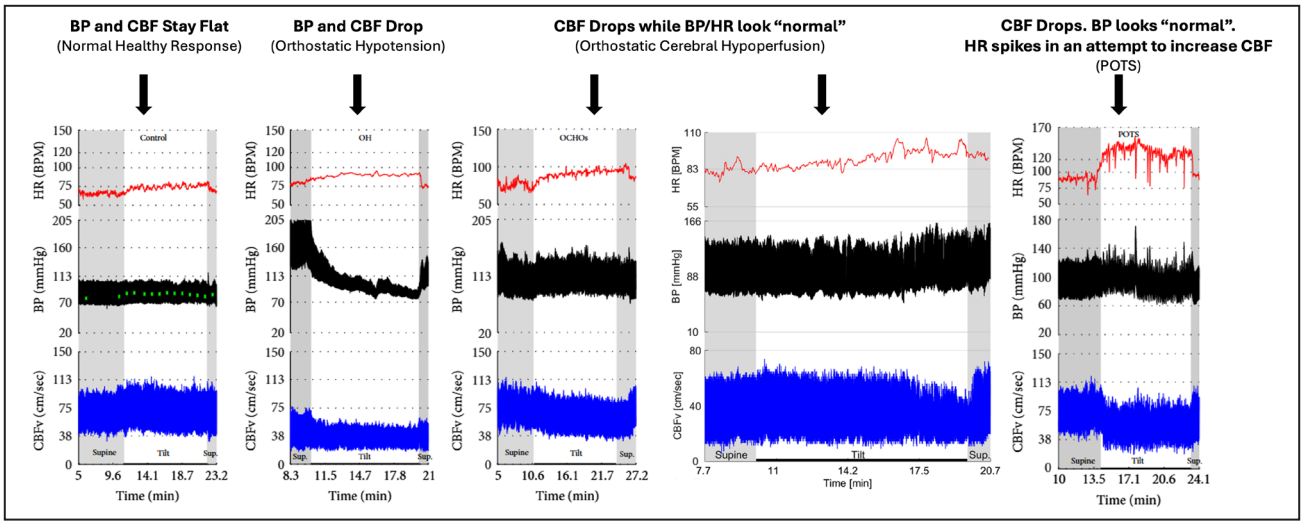

Figure 3. HR, BP, and CBF velocity patterns in example participants with orthostatic hypotension, orthostatic cerebral hypoperfusion syndrome, and POTS during supine (gray) and head-up tilt (white) compared with a healthy control on the left.

Despite different changes or no change in BP and HR during head-up tilt, participants with orthostatic intolerance experience a similar and excessive decline in cerebral blood velocity. Charts reproduced from Novak[3] under the terms and conditions of the Creative Commons Attribution Non-Commercial-NoDerivatives license (https://creativecommons.org/licenses/by-nc-nd/4.0/). BP indicates blood pressure; CBF, cerebral blood flow; HR, heart rate; and POTS, postural orthostatic tachycardia syndrome.

point reveals a wide spread of frequencies due to variable blood flow velocities through the arterial cross-section. This frequency spread can be calculated at each time point as a peak velocity value representing the fastest-moving red blood cells at the center of the sampled cross-section, or an intensity-weighted mean that represents an average velocity of the blood cells in the sampled cross-section.

The transtemporal window is used to insonate the MCA. However, it can be difficult to acquire an adequate signal in some individuals, as ≈10% to 20% of participants do not have a thin enough transtemporal acoustic window to get a reliable TCD signal.[60] To assume that TCD-derived CBF velocity represents total CBF, there are 3 primary assumptions: (1) the diameter of the insonated vessel remains unchanged; (2) the angle of insonation remains fixed in position; (3) flow through a single MCA is representative of all 4 cerebral arteries. Despite these major assumptions, TCD has been demonstrated to still be able to differentiate between normal perfusion and hypoperfusion in multiple patient populations.

A unique advantage to TCD is the ability to measure CBF velocity with high time resolution, due to the existence of mounting headgear that can continually hold the ultrasound probe against the transtemporal window. This headgear can help ensure that the angle of insonation remains fixed. This also allows monitoring of a patient through a postural change, allowing the ability to see a continuous drop in flow leading to a syncopal event.

Extracranial CBF Ultrasound

Extracranial CBF ultrasound is another method of measuring CBF with significantly fewer assumptions compared with TCD.[52] Unlike TCD's approach of trying to measure a single cerebral artery through the cranium, extracranial CBF ultrasound measures all 4 cerebral arteries before they enter the skull, thus avoiding the difficulty of measuring through the skull.[52] This allows sonographers to take a carotid duplex scan using simultaneous B-mode and pulsed-wave Doppler to capture flow velocities and artery diameters for all the internal carotid and vertebral arteries.[61] Flow velocities are multiplied against their respective artery diameter to get a volume flow (mL/min) measurement. Then, volume flow of all 4 cerebral arteries is added together to get total CBF. This method arguably measures true CBF without requiring any of the significant assumptions needed for TCD ultrasound measurements.

In exchange for the higher-quality CBF measurement, the extracranial CBF technique loses the continuous monitoring nature of TCD ultrasound. Extracranial CBF ultrasound takes snapshots of CBF where the sampling rate is limited to the time it takes to make duplex measurements of all 4 cerebral arteries, which typically takes 1 to 2 minutes for a trained sonographer. It also requires a nontrivial amount of post-processing including diameter measurements, losing some of the real-time nature. However, the sampling frequency trade-off does support a more sensitive, specific, and theoretically sound measurement of true

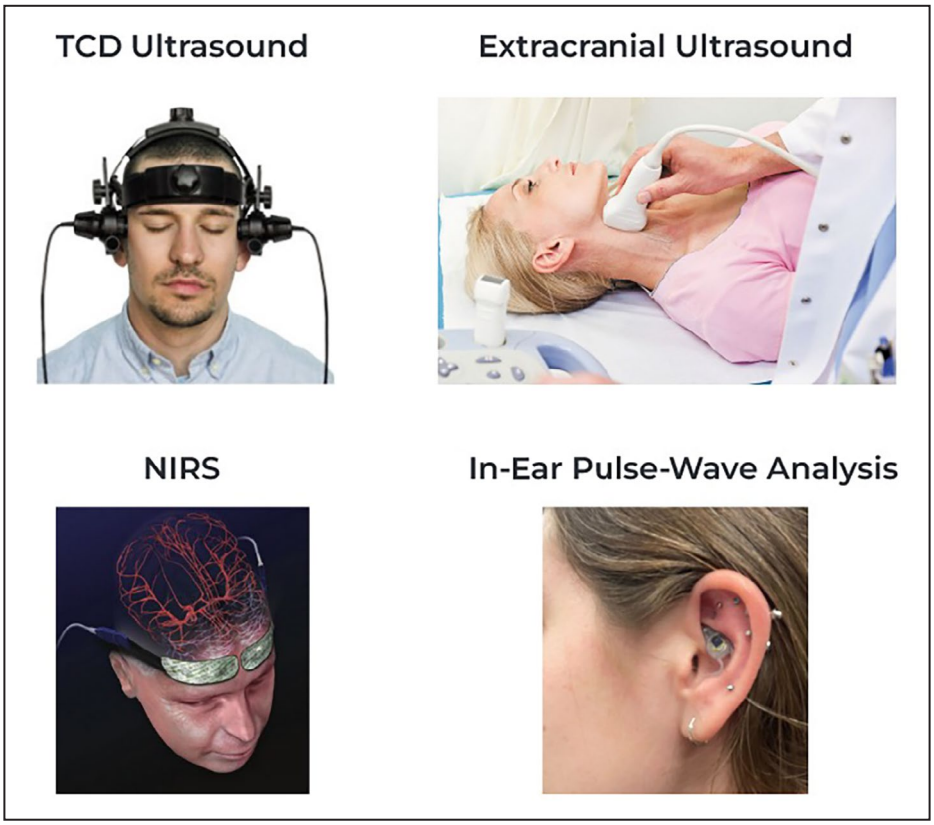

Figure 4. Methods for CBF measurement.
Ultrasound is used to assess blood flow velocity to the head either at the middle cerebral artery using TCD ultrasound or at the external carotid artery via extracranial ultrasound. NIRS supplies an index of oxygen saturation of the frontal lobe with oximetry by shining near-infrared light at the forehead. In-ear pulse-wave analysis is an emerging technique to remotely measure blood flow to the head using infrared light to the posterior auricular branch of the external carotid artery. CBF indicates cerebral blood flow; NIRS, near-infrared spectroscopy; and TCD, transcranial Doppler.

CBF. Extracranial ultrasound has not been studied as frequently and across as many different clinics and laboratories as TCD has in orthostatic populations. However, in the studies in which extracranial CBF ultrasound has been used, it has thus far had more consistently repeatable measurements compared

Table 2. Comparison of Methods for Detecting Orthostatic CBF Changes

Cerebral blood flow measurement method	Advantages	Disadvantages	Access	Cost
Transcranial ultrasound	Able to use at bedside and during head-up tilt Headgear allows hands-free continuous monitoring High temporal resolution can catch transient events like syncope	Only a velocity measurement, not true cerebral flow. Relying on assumptions that were proven to be problematic Variability in data quality based on sonographer skill ≈10% of skulls are impenetrable	Need TCD ultrasound machine and specially trained sonographer, headband holder	$20k–$50k device cost + highly specialized technician time
Extracranial ultrasound	True CBF measurement without significant assumptions. Most sensitive way to measure CBF drops in OI	Low temporal resolution (2+ min per sample) misses transient events	Need ultrasound machine and specially trained sonographer	$20k–$50k device cost + highly specialized technician time
NIRS	Easy to use and stick onto a patient's forehead. No trained technician required	Depends on skull thickness and spacing from frontal lobe Has failed to discriminate orthostatic hypoperfusion in patients with OI	Just need NIRS device	$5k–$20k device cost
In-ear pulse-wave analysis	Scalable, remote monitoring Tracks postural changes in real-life settings	New technology, not a direct CBF measurement. Fewer validation data available	Can be mailed to patients and supported via telehealth	≈$500 device cost

CBF indicates cerebral blood flow; NsIRS, near-infrared spectroscopy; OI, orthostatic intolerance; and TCD, transcranial Doppler.

with TCD, which has had problems with interlabratory repeatability.[35,46]

Near-Infrared Spectroscopy

NIRS, also known as cerebral oximetry, offers another proxy for CBF by using near-infrared light into the forehead to measure the oxygen saturation of the frontal lobe similar to finger pulse oximetry.[57,58] If CBF drops, cerebral oxygenation should also drop in theory. Like pulse oximetry, wavelengths of light are differentially affected by oxyhemoglobin or deoxyhemoglobin and total hemoglobin, and the amount of reflected light at each wavelength can be used to infer cerebral oxygenation.[58] NIRS has been tested in OI populations compared against healthy controls; however, both participants with OI and healthy control experience similar reductions in oxyhemoglobin.[57,59,62,63] Significant reductions in oxyhemoglobin may be related to the fact that NIRS partially samples superficial scalp blood oxygen, as well as shifting tissue within the optical sampling volume upon orthostasis. Slightly larger drops in oxyhemoglobin have been shown in patients with OI compared with healthy controls, but these differences are small, resulting in poor diagnostic specificity.[63,64] Instead of focusing on relative drops in oxyhemoglobin, NIRS research has focused more on the time it takes for cerebral oxygenation to recover from the initial drop during upright periods, where recovery takes longer in orthostatic populations.[63,65] As the discriminative ability of NIRS to differentiate people with orthostatic intolerance from healthy controls is much weaker than more direct measures of CBF, this review will not cover NIRS at length. There is also a different variant of NIRS that uses coherent hemodynamics spectroscopy, which relies on fundamentally different physics principles to attain proxies for CBF.[66] These have shown promise in measuring CBF trends in supine patients; however, these have not been tested in orthostatic populations and are thus out of scope for this review.

Wearable Pulse-Wave Analysis

New wearables that measure correlates of CBF via pulse-wave analysis have been developed in recent years. These devices will have the advantage of being more affordable and widely available to both medical providers and patients. These devices are portable and can capture real-world data and provide feedback to clinicians and patients. The goal of wearable CBF monitoring is to correlate CBF to symptoms, triggers, and treatments patients experience in their daily lives and be able to evaluate the effects of activities and treatments on their CBF. The ease of deployment of wearable CBF monitors could be similar to a Holter monitor that provides feedback to patients and clinicians.

The Lumia (Lumia Health, Boston, MA) is an in-ear wearable device that has been clinically validated and is being marketed to people with OI for them to track their own trends in blood flow to the head as a proxy for CBF.[67] The Lumia uses infrared light to interrogate the posterior auricular artery, which branches off the external carotid artery. It does not measure true flow but instead analyzes the pulse waveform's fullness to generate a relative flow index they call external carotid blood flow. It has been demonstrated to see significant blood flow drops preceding syncope during head-up tilt.[68] Fudim, an author of this paper, tested this device against TCD ultrasound during head-up tilt and has shared preliminary prepublished data demonstrating reasonable correlation.[67]

Another potentially relevant wearable is the Flosonics carotid ultrasound patch wearable (Flosonics Medical, Sudbury, Ontario, Canada), which targets monitoring the common carotid artery with continuous-wave Doppler. This also primarily targets a form of pulse-wave analysis, specifically looking at the corrected carotid artery flow time as a proxy for preload and volume status. There has been some promise of sensitivity to preload modifying maneuvers,[69] but the device has not been tested or validated in patients who are orthostatic intolerant to our knowledge.

LIMITATIONS OF EXISTING TECHNIQUES

Both TCD and extracranial ultrasound methods of measuring CBF are limited by the lack of trained sonographers, varying sonography skills, likelihood of sonographer mistakes, and a limited ability to retrospectively identify sonographer mistakes, which can result in inadequate measurement quality passing as good signal.[70,71] In addition, there can be significant pulsed-wave Doppler measurement variability between different ultrasound systems, which introduces further interlaboratory repeatability challenges.[70,72,73] Having a well-trained sonographer with a validated ultrasound system are vital prerequisites for these techniques to be used successfully.

In addition to the above limitations, which are common to ultrasound in general, TCD monitoring of CBv has its own unique limitations.[37] TCD-derived CBv is an imperfect proxy for total CBF that relies on several significant aforementioned assumptions such as constant MCA diameter, which have been shown to be problematic.[70,74,75] Specifically, 10% to 20% of patients cannot be insonated due to inadequate acoustic windows in the skull, and multiple laboratories have not been able to reproduce CBv measurements likely due to the described limitations.[45,60,70,76]

The extracranial ultrasound method addresses many of the assumptions that TCD operates under and does

not have the issue of thick skulls preventing signal acquisition in 10% to 20% of subjects.[61] However, extracranial ultrasound is a more advanced technique than TCD with more steps required of sonographers, increasing the existing susceptibility to sonographer error and skill variability.[70,71] In addition, we were unable to find commercially available ultrasound systems that can automate diameter measurements and volume flow calculations, thus requiring nontrivial manual postprocessing, which may make it more difficult to increase clinician adoption. In addition, the extracranial ultrasound technique loses the continuous monitoring nature of TCD, as it only takes snapshots limited to a 1- to 2-minute sampling period for a fast sonographer.

Due to the issues of ultrasound variability mentioned above,[37] developing quality standards to ensure that sonographers have proper technique in ultrasound measurement of CBF will be key to wider adoption and repeatability. Like TCD, the in-ear optical wearable devices have similar assumptions as they measure branches of the external carotid artery. External carotid artery flow is known to deviate from internal carotid artery flow specifically when there is local intracranial vasoconstriction caused by hyperventilation.[77] External carotid flow is not a true measure of CBF, and as such the clinical implementation of such a device will be limited to situations in which total CBF reduction is caused by fluctuations in CO. In addition, notable challenges include that up to 10% of ears may not be compatible with these devices.

CONCLUSIONS

CBF is a critical biomarker for OI and related disorders. CBF is measurably and considerably reduced in a vast majority of patients with OI, often despite normal heart rate and BP. Moreover, studies have found that 22% to 58% of patients with OI can have normal heart rate and BP readings despite abnormal CBF, often resulting in misdiagnoses.[52] Because of the poor sensitivity of diagnostic criteria relying on heart rate and BP such as that of POTS and OH, we recommend the incorporation of CBF monitoring as the core diagnostic criteria of cerebral autoregulatory abnormality. However, further validation of CBF monitoring techniques must be conducted before unified diagnostic criteria can be defined and recommended.

TCD ultrasound and extracranial ultrasound offer viable ways to measure CBF that have been tested in thousands of patients undergoing orthostasis. However, scalability and interlaboratory repeatability are known problems with existing CBF monitoring methods. There are not enough testing facilities to meet the current patient demand; for example, wait time for tilt table testing even without ultrasound can be years. CBF measurements are mainly used in research and specialty centers, and methods are not standardized for OI. TCD has had multiple reports of interlaboratory repeatability issues,[76] and the extracranial CBF ultrasound method has not yet demonstrated interlaboratory repeatability.[61] Both techniques require highly skilled sonographers, which may be a barrier to wider clinical adoption. Both ultrasound techniques must define more standardized monitoring techniques, such as mandating the use of time-averaged mean instead of time-averaged maximum velocities. Both methods must also find ways to verify sonographer quality to ensure interlaboratory repeatability.

New techniques and wearable devices on the horizon plan to address these challenges and make CBF monitoring more accessible in OI. However, these have significant fundamental assumptions, similar to TCD, so further validation is required before they can be incorporated into clinical practice.

ARTICLE INFORMATION

Received June 7, 2024; accepted December 19, 2024.

Affiliations

Department of Medicine, Duke University Medical Center Durham, Durham, NC (M.S.K., J.M., A.S., E.W., M.P., C.F.M., M.F.); Department of Physical Therapy, Lebanon Valley College, Annville, PA (A.J.M.); Department of Medicine, Dow University of Health Sciences, Karachi, Pakistan (A.E.); Department of Anesthesia, Duke University Medical Center, Durham, NC (J.M., D.B.M.); Department of Medicine, Weill Cornell Medicine, New York, NY (P.G.); Department of Medicine, Vanderbilt University Medical Center, Nashville, TN (H.T.); Department of Cardiac Sciences, Libin Cardiovascular Institute, University of Calgary, Calgary, AB, Canada (S.R.R.); and Duke Clinical Research Institute, Durham, NC (M.F.).

Sources of Funding

None.

Disclosures

Dr Miller is a consultant to Lumia Health. Dr Fudim was supported by the National Institutes of Health, Reprieve, Sardocor, and Doris Duke. He is a consultant/has ownership interest in Abbott, Ajax, Alio Health, Alleviant, Artha, Audicor, AxonTherapies, Bayer, Bodyguide, Bodyport, Boston Scientific, Broadview, Cadence, Cardioflow, CVRx, Daxor, Edwards LifeSciences, Echosens, EKO, Feldschuh Foundation, Fire1, FutureCardia, Galvani, Gradient, Hatteras, HemodynamiQ, Impulse Dynamics, Intershunt, Medtronic, Merck, NovoNordisk, NucleusRx, NXT Biomedical, Orchestra, Pharmacosmos, Presidio, Procyreon, Proton Intelligence, ReCor, SCPharma, Shifamed, Splendo, Lumia Health, Summacor, SyMap, Verily, Vironix, Viscardia, and Zoll. Dr Tandri is a consultant to Lumia Health and Abbott. Dr Frazier Mills is a consultant to Medtronic, Johnson & Johnson, and Boston Scientific. Dr Raj is a consultant to Theravance Biopharma, Amneal Pharma, Servier Affaires Medicales, Regeneron, argenx BV, Antag Pharma, and Lumia Health. Jeroen Molinger has received honoraria or travel expenses for lectures from Abbott, Baxter, Danone-Nutricia, Nestlé, Corsano Health, CalibreBio, VO2Master, Rockley Photonics, Vital Impact, Train-Red, Vyaire Medical, MuscleSound. Dr Goyal received consulting fees from Agepha Pharma, Akros Pharma, Axon Therapies, Bayer HealthCare Pharmaceuticals, and Sensorum Health.

REFERENCES

1. Sheldon RS, Grubb BP 2nd, Olshansky B, Shen WK, Calkins H, Brignole M, Raj SR, Krahn AD, Morillo CA, Stewart JM, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of

postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm*. 2015;12:e41–e63. doi: 10.1016/j.hrthm.2015.03.029
2. Stiles LE. Chronic fatigue syndrome and the autonomic nervous system. *Chronic Fatigue Syndrome and the Autonomic Nervous System*. Primer on the Autonomic Nervous System: In; 2023. doi: 10.1016/B978-0-323-85492-4.00027-2
3. Novak P. Cerebral blood flow, heart rate, and blood pressure patterns during the tilt test in common orthostatic syndromes. *Neurosci J*. 2016;2016:6127340. doi: 10.1155/2016/6127340
4. Shaw BH, Stiles LE, Bourne K, Green EA, Shibao CA, Okamoto LE, Garland EM, Gamboa A, Diedrich A, Raj V, et al. The face of postural tachycardia syndrome - insights from a large cross-sectional online community-based survey. *J Intern Med*. 2019;286:438–448. doi: 10.1111/joim.12895
5. McDonald C, Koshi S, Busner L, Kavi L, Newton JL. Postural tachycardia syndrome is associated with significant symptoms and functional impairment predominantly affecting young women: a UK perspective. *BMJ Open*. 2014;4:e004127. doi: 10.1136/bmjopen-2013-004127
6. Johansson M, Stahlberg M, Runold M, Nygren-Bonnier M, Nilsson J, Olshansky B, Bruchfeld J, Fedorowski A. Long-haul post-COVID-19 symptoms presenting as a variant of postural orthostatic tachycardia syndrome: the Swedish experience. *JACC Case Rep*. 2021;3:573–580. doi: 10.1016/j.jaccas.2021.01.009
7. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21:133–146. doi: 10.1038/s41579-022-00846-2
8. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ*. 2020;370:m3026.
9. Novak P, Mukerji SS, Alabsi HS, Systrom D, Marciano SP, Felsenstein D, Mullally WJ, Pilgrim DM. Multisystem involvement in post-acute sequelae of coronavirus disease 19. *Ann Neurol*. 2022;91:367–379. doi: 10.1002/ana.26286
10. Long COVID Household Pulse Survey. Accessed August 6, 2024. https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm.
11. Larsen NW, Stiles LE, Shaik R, Schneider L, Muppidi S, Tsui CT, Geng LN, Bonilla H, Miglis MG. Characterization of autonomic symptom burden in long COVID: a global survey of 2,314 adults. *Front Neurol*. 2022;13:1012668. doi: 10.3389/fneur.2022.1012668
12. Bisaccia G, Ricci F, Recce V, Serio A, Iannetti G, Chahal AA, Stahlberg M, Khanji MY, Fedorowski A, Gallina S. Post-acute sequelae of COVID-19 and cardiovascular autonomic dysfunction: what do we know? *J Cardiovasc Dev Dis*. 2021;8:156. doi: 10.3390/jcdd8110156.
13. Robertson D. The epidemic of orthostatic tachycardia and orthostatic intolerance. *Am J Med Sci*. 1999;317:75–77. doi: 10.1016/S0002-9629(15)40480-X
14. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*. 2021;594:259–264. doi: 10.1038/s41586-021-03553-9
15. Campen C, Visser FC. Long-haul COVID patients: prevalence of POTS are reduced but cerebral blood flow abnormalities remain abnormal with longer disease duration. *Healthcare (Basel)*. 2022;10:2105. doi: 10.3390/healthcare10102105
16. Rink C, Khanna S. Significance of brain tissue oxygenation and the arachidonic acid cascade in stroke. *Antioxid Redox Signal*. 2011;14:1889–1903. doi: 10.1089/ars.2010.3474
17. Schondorf R. Cerebral circulation. In: Biaggioni I, ed *Primer on the Autonomic Nervous System*. Academic Press; 2023. doi: 10.1016/B978-0-323-85492-4.00097-1
18. Mintun MA, Lundstrom BN, Snyder AZ, Vlassenko AG, Shulman GL, Raichle ME. Blood flow and oxygen delivery to human brain during functional activity: theoretical modeling and experimental data. *Proc Natl Acad Sci USA*. 2001;98:6859–6864. doi: 10.1073/pnas.111164398
19. Silverman A, Petersen NH. Physiology, Cerebral Autoregulation. *StatPearls*. Treasure Island (FL): Ineligible Companies. Disclosure: Nils Petersen declares no relevant financial relationships with ineligible companies; 2024.
20. Mar PL, Raj SR. Postural orthostatic tachycardia syndrome: mechanisms and new therapies. *Annu Rev Med*. 2020;71:235–248. doi: 10.1146/annurev-med-041818-011630
21. Stewart JM, Medow MS, Montgomery LD, McLeod K. Decreased skeletal muscle pump activity in patients with postural tachycardia syndrome and low peripheral blood flow. *Am J Physiol Heart Circ Physiol*. 2004;286:H1216–H1222. doi: 10.1152/ajpheart.00738.2003
22. Stewart JM, Medow MS, Sutton R, Visintainer P, Jardine DL, Wieling W. Mechanisms of vasovagal syncope in the young: reduced systemic vascular resistance versus reduced cardiac output. *J Am Heart Assoc*. 2017;18:e004417. doi: 10.1161/JAHA.116.004417
23. Raj SR, Robertson D. Blood volume perturbations in the postural tachycardia syndrome. *Am J Med Sci*. 2007;334:57–60. doi: 10.1097/MAJ.0b013e318063c6c0
24. Mount CA, Das JM. *Cerebral Perfusion Pressure. In: StatPearls. Treasure Island (FL) Ineligible Companies*. Joe Das declares no relevant financial relationships with ineligible companies: Disclosure; 2024.
25. Favre ME, Lim V, Falvo MJ, Serrador JM. Cerebrovascular reactivity and cerebral autoregulation are improved in the supine posture compared to upright in healthy men and women. *PLoS One*. 2020;15:e0229049. doi: 10.1371/journal.pone.0229049
26. Lawence-Brown MMD, Liffman K, Semmens JB, Sutalo ID. Vascular Arterial Haemodynamics. In: Fitridge R, Thompson M, eds *Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists*. Adelaide (AU): Barr Smith Press; 2011. doi: 10.1017/UPO9781922064004.009
27. Stewart JM, Taneja I, Medow MS. Reduced central blood volume and cardiac output and increased vascular resistance during static handgrip exercise in postural tachycardia syndrome. *Am J Physiol Heart Circ Physiol*. 2007;293:H1908–H1917. doi: 10.1152/ajpheart.00439.2007
28. Lassen NA. Cerebral blood flow and oxygen consumption in man. *Physiol Rev*. 1959;39:183–238. doi: 10.1152/physrev.1959.39.2.183
29. Claassen J, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. *Physiol Rev*. 2021;101:1487–1559. doi: 10.1152/physrev.00022.2020
30. Low PA, Novak V, Spies JM, Novak P, Petty GW. Cerebrovascular regulation in the postural orthostatic tachycardia syndrome (POTS). *Am J Med Sci*. 1999;317:124–133. doi: 10.1097/00000441-199902000-00007
31. Doczi TP. Comparison of static and dynamic cerebral autoregulation measurements. *Stroke*. 1995;26:2372–2373.
32. Medow MS, Del Pozzi AT, Messer ZR, Terilli C, Stewart JM. Altered oscillatory cerebral blood flow velocity and autoregulation in postural tachycardia syndrome. *Front Physiol*. 2014;5:234. doi: 10.3389/fphys.2014.00234
33. Kidd SK, Doughty C, Goldhaber SZ. Syncope (fainting). *Circulation*. 2016;133:e600–e602. doi: 10.1161/CIRCULATIONAHA.115.017308
34. Dan D, Hoag JB, Ellenbogen KA, Wood MA, Eckberg DL, Gilligan DM. Cerebral blood flow velocity declines before arterial pressure in patients with orthostatic vasovagal presyncope. *J Am Coll Cardiol*. 2002;39:1039–1045. doi: 10.1016/S0735-1097(02)01719-9
35. Schondorf R, Stein R, Roberts R, Benoit J, Cupples W. Dynamic cerebral autoregulation is preserved in neurally mediated syncope. *J Appl Physiol*. 1985;2001:2493–2502. doi: 10.1152/jappl.2001.91.6.2493
36. Folino AF. Cerebral autoregulation in neurally mediated syncope: victim or executioner? *Heart*. 2006;92:724–726.
37. Skow RJ, Brothers RM, Claassen J, Day TA, Rickards CA, Smirl JD, Brassard P. On the use and misuse of cerebral hemodynamics terminology using transcranial Doppler ultrasound: a call for standardization. *Am J Physiol Heart Circ Physiol*. 2022;323:H350–H357. doi: 10.1152/ajpheart.00107.2022
38. Ocon AJ, Medow MS, Taneja I, Clarke D, Stewart JM. Decreased upright cerebral blood flow and cerebral autoregulation in normocapnic postural tachycardia syndrome. *Am J Physiol Heart Circ Physiol*. 2009;297:H664–H673. doi: 10.1152/ajpheart.00138.2009
39. Del Pozzi AT, Schwartz CE, Tewari D, Medow MS, Stewart JM. Reduced cerebral blood flow with orthostasis precedes hypocapnic hyperpnea, sympathetic activation, and postural tachycardia syndrome. *Hypertension*. 2014;63:1302–1308. doi: 10.1161/HYPERTENSIONAHA.113.02824
40. Stewart JM, Del Pozzi AT, Pandey A, Messer ZR, Terilli C, Medow MS. Oscillatory cerebral blood flow is associated with impaired neurocognition and functional hyperemia in postural tachycardia syndrome during graded tilt. *Hypertension*. 2015;65:636–643. doi: 10.1161/HYPERTENSIONAHA.114.04576
41. Stewart JM, Medow MS, Messer ZR, Baugham IL, Terilli C, Ocon AJ. Postural neurocognitive and neuronal activated cerebral blood flow deficits in young chronic fatigue syndrome patients with postural tachycardia syndrome. *Am J Physiol Heart Circ Physiol*. 2012;302:H1185–H1194. doi: 10.1152/ajpheart.00994.2011
42. Novak P. Hypocapnic cerebral hypoperfusion: a biomarker of orthostatic intolerance. *PLoS One*. 2018;13:e0204419. doi: 10.1371/journal.pone.0204419

43. Baker J. Reduced stroke volume and brain perfusion drive postural hyperventilation in postural orthostatic tachycardia syndrome. *JACC Basic Trans Sci*. 2024;9:939–953.
44. Sandler CX, Lloyd AR. Chronic fatigue syndrome: progress and possibilities. *Med J Aust*. 2020;212:428–433. doi: 10.5694/mja2.50553
45. Razumovsky AY, DeBusk K, Calkins H, Snader S, Lucas KE, Vyas P, Hanley DF, Rowe PC. Cerebral and systemic hemodynamics changes during upright tilt in chronic fatigue syndrome. *J Neuroimaging*. 2003;13:57–67. doi: 10.1111/j.1552-6569.2003.tb00158.x
46. van Campen C, Verheugt FWA, Rowe PC, Visser FC. Cerebral blood flow is reduced in ME/CFS during head-up tilt testing even in the absence of hypotension or tachycardia: a quantitative, controlled study using Doppler echography. *Clin Neurophysiol Pract*. 2020;5:50–58. doi: 10.1016/j.cnp.2020.01.003
47. van Campen C, Rowe PC, Visser FC. Cerebral blood flow remains reduced after tilt testing in myalgic encephalomyelitis/chronic fatigue syndrome patients. *Clin Neurophysiol Pract*. 2021;6:245–255. doi: 10.1016/j.cnp.2021.09.001
48. van Campen C, Visser FC. *Psychogenic Pseudosyncope: Real or Imaginary? Results from a Case-Control Study in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Patients*. Medicina (Kaunas); 2022;58:98. doi: 10.3390/medicina58010098
49. Norcliffe-Kaufmann L, Galindo-Mendez B, Garcia-Guarniz AL, Villarreal-Vitorica E, Novak V. Transcranial Doppler in autonomic testing: standards and clinical applications. *Clin Auton Res*. 2018;28:187–202. doi: 10.1007/s10286-017-0454-2
50. Novak P. Orthostatic cerebral Hypoperfusion syndrome. *Front Aging Neurosci*. 2016;8:22. doi: 10.3389/fnagi.2016.00022
51. Immink RV, Pott FC, Secher NH, van Lieshout JJ. Hyperventilation, cerebral perfusion, and syncope. *J Appl Physiol*. 1985;2014:844–851. doi: 10.1152/japplphysiol.00637.2013
52. van Campen C, Verheugt FWA, Visser FC. Cerebral blood flow changes during tilt table testing in healthy volunteers, as assessed by Doppler imaging of the carotid and vertebral arteries. *Clin Neurophysiol Pract*. 2018;3:91–95. doi: 10.1016/j.cnp.2018.02.004
53. Novak P. Post COVID-19 syndrome associated with orthostatic cerebral hypoperfusion syndrome, small fiber neuropathy and benefit of immunotherapy: a case report. *eNeurologicalSci*. 2020;21:100276. doi: 10.1016/j.ensci.2020.100276
54. Campen C, Rowe PC, Visser FC. *Orthostatic Symptoms and Reductions in Cerebral Blood Flow in Long-Haul COVID-19 Patients: Similarities with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome*. Medicina (Kaunas): MDPI; Medicina; 2021:58.
55. Albina G, Fernandez Cisneros L, Laino R, Nobo UL, Ortega D, Schwarz E, Barja L, Lagos R, Giniger A, Ameriso SF. Transcranial Doppler monitoring during head upright tilt table testing in patients with suspected neurocardiogenic syncope. *Europace*. 2004;6:63–69. doi: 10.1016/j.eupc.2003.09.009
56. Novak V, Spies JM, Novak P, McPhee BR, Rummans TA, Low PA. Hypocapnia and cerebral hypoperfusion in orthostatic intolerance. *Stroke*. 1998;29:1876–1881. doi: 10.1161/01.str.29.9.1876
57. Shoemaker LN, Milej D, Mistry J, St LK. Using depth-enhanced diffuse correlation spectroscopy and near-infrared spectroscopy to isolate cerebral hemodynamics during transient hypotension. *Neurophotonics*. 2023;10:025013. doi: 10.1117/1.NPh.10.2.025013
58. Sakudo A. Near-infrared spectroscopy for medical applications: current status and future perspectives. *Clin Chim Acta*. 2016;455:181–188. doi: 10.1016/j.cca.2016.02.009
59. Kharraziha I, Holm H, Bachus E, Melander O, Sutton R, Fedorowski A, Hamrefors V. Monitoring of cerebral oximetry in patients with postural orthostatic tachycardia syndrome. *Europace*. 2019;21:1575–1583. doi: 10.1093/europace/euz204
60. D'Andrea A, Conte M, Scarafile R, Riegler L, Cocchia R, Pezzullo E, Cavallaro M, Carbone A, Natale F, Russo MG, et al. Transcranial Doppler ultrasound: physical principles and principal applications in Neurocritical care unit. *J Cardiovasc Echogr*. 2016;26:28–41. doi: 10.4103/2211-4122.183746
61. Dhingra K, Salisbury BH, Chakko MN. Doppler Extra-Cranial Carotid Assessment, Protocols, and Interpretation. *StatPearls*. Treasure Island (FL): Ineligible Companies. Disclosure: Blake Salisbury Declares no Relevant Financial Relationships with Ineligible Companies. Disclosure: Mathew Chakko declares no relevant financial relationships with ineligible companies; 2024.
62. Kharraziha I, Holm H, Bachus E, Ricci F, Sutton R, Fedorowski A, Hamrefors V. Cerebral oximetry in syncope and syndromes of orthostatic intolerance. *Front Cardiovasc Med*. 2019;6:171. doi: 10.3389/fcvm.2019.00171
63. Kim JM, Choi JK, Choi M, Ji M, Hwang G, Ko SB, Bae HM. Assessment of cerebral autoregulation using continuous-wave near-infrared spectroscopy during squat-stand maneuvers in subjects with symptoms of orthostatic intolerance. *Sci Rep*. 2018;8:13257. doi: 10.1038/s41598-018-31685-y
64. Harms MP, Colier WN, Wieling W, Lenders JW, Secher NH, van Lieshout JJ. Orthostatic tolerance, cerebral oxygenation, and blood velocity in humans with sympathetic failure. *Stroke*. 2000;31:1608–1614. doi: 10.1161/01.STR.31.7.1608
65. Kim JM, Park KI, Choi SY, Park HE, Lee H, Bae HM. Dynamic alterations in cerebral hemodynamics measured by portable near-infrared spectroscopy in orthostatic hypotension and intolerance. *Am J Hypertens*. 2023;36:385–393. doi: 10.1093/ajh/hpad025
66. Pham T, Tgavalekos K, Sassaroli A, Blaney G, Fantini S. Quantitative measurements of cerebral blood flow with near-infrared spectroscopy. *Biomed Opt Express*. 2019;10:2117–2134. doi: 10.1364/BOE.10.002117
67. Lee D, Fudim M. *Using an Ear Device to to Monitor Blood Flow to the Head as a Dysautonomia Management Tool*. Dysautonomic International; 2023. https://vimeo.com/859062357.
68. Tripathi H, Gonuguntla A, Lee D, Fudim M, Brinker J, Tandri H. Monitoring carotid blood flow using in-ear wearable device during tilt-table testing. *JACC Clin Electrophysiol*. 2023;9:710–712. doi: 10.1016/j.jacep.2023.02.002
69. Kenny JS, Barjaktarevic I, Eibl AM, Parrotta M, Long BF, Eibl JK, Michard F. A carotid Doppler patch accurately tracks stroke volume changes during a preload-modifying maneuver in healthy volunteers. *Crit Care Explor*. 2020;2:e0072. doi: 10.1097/CCE.0000000000000072
70. Purkayastha S, Sorond F. Transcranial Doppler ultrasound: technique and application. *Semin Neurol*. 2012;32:411–420. doi: 10.1055/s-0032-1331812
71. Lui EYL, Steinman AH, Cobbold RSC, Johnston KW. Human factors as a source of error in peak Doppler velocity measurement. *J Vasc Surg*. 2005;42:972–979. doi: 10.1016/j.jvs.2005.07.014
72. Russ MK, Lafata NM, Robertson SH, Samei E. Pulsed wave Doppler ultrasound: accuracy, variability, and impact of acquisition parameters on flow measurements. *Med Phys*. 2023;50:6704–6713. doi: 10.1002/mp.16774
73. Walker AR, Uejima T, Prinz C, Voigt JU, Fraser AG. Inaccuracies in measuring velocities and timing of flow and tissue motion using high-end ultrasound systems. *Ultrasound Med Biol*. 2019;45:1446–1454. doi: 10.1016/j.ultrasmedbio.2019.02.010
74. Verbree J, Bronzwaer AS, Ghariq E, Versluis MJ, Daemen MJ, van Buchem MA, Dahan A, van Lieshout JJ, van Osch MJ. Assessment of middle cerebral artery diameter during hypocapnia and hypercapnia in humans using ultra-high-field MRI. *J Appl Physiol*. 1985;2014:1084–1089. doi: 10.1152/japplphysiol.00651.2014
75. Al-Khazraji BK, Shoemaker LN, Gati JS, Szekeres T, Shoemaker JK. Reactivity of larger intracranial arteries using 7 T MRI in young adults. *J Cereb Blood Flow Metab*. 2019;39:1204–1214. doi: 10.1177/0271678X18762880
76. Marinoni M, Ginanneschi A, Forleo P, Amaducci L. Technical limits in transcranial Doppler recording: inadequate acoustic windows. *Ultrasound Med Biol*. 1997;23:1275–1277. doi: 10.1016/S0301-5629(97)00077-X
77. Sato K, Sadamoto T, Hirasawa A, Oue A, Subudhi AW, Miyazawa T, Ogoh S. Differential blood flow responses to CO(2) in human internal and external carotid and vertebral arteries. *J Physiol*. 2012;590:3277–3290. doi: 10.1113/jphysiol.2012.230425