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EDITORIAL

Imaging in autonomic failure: a window into real-time physiological mechanisms and other updates on recent autonomic research

Mitchell G. Miglis[1] · Nicholas Larsen[1] · Srikanth Muppidi[1]

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Orthostatic intolerance is one of the characteristic features of orthostatic hypotension (OH), postural tachycardia syndrome (POTS), and neurally mediated syncope. Mechanisms of orthostatic intolerance may include decreased cerebral or systemic perfusion, increased sympathetic activity, hypocapnia, and abnormal peripheral vascular resistance; however, these mechanisms are still being defined and may differ for each patient. In their article, "Real-Time Magnetic Resonance Imaging (MRI) to Study Orthostatic Intolerance Mechanisms in Human Beings: Proof of Concept," [1] the authors aimed to further investigate these mechanisms utilizing 3 T cardiac MRI in a 46-year-old male with pure autonomic failure.

The study protocol included supine cardiac imaging with an adapted lower body negative pressure (LBNP) device to stimulate orthostatic challenge and a beat-to-beat blood pressure monitor (modified for MR compatibility) to measure cardiovascular changes. Cerebral blood flow velocity (CBFv) and middle cerebral artery (MCA) diameter were estimated via real-time MRI flow velocities. Measurements were obtained after 20 min of supine rest (patient BP 118/74 mmHg, HR 67) and again during − 30 mmHg LBNP stress (patient BP 58/35 mmHg, HR 72), resulting in moderate symptoms of orthostatic intolerance for the patient. The patient's left ventricular stroke volume decreased from 74 ± 6 to 41 ± 6 mL and cardiac output decreased from 4.96 to 2.95 L/min, with no change in systemic vascular resistance. Left MCA blood flow decreased from 0.17 ± 0.01 to 0.11 ± 0.01 L/min (37.6% change). The respiration rate increased minimally, from 15.5 ± 3.9 to 16.4 ± 2.2 bpm. End-tidal carbon dioxide (CO2) was not measured, a mild limitation, and an important addition to the protocol for future analyses.

These findings presented recently at the 33rd annual meeting of the American Autonomic Society highlight a novel imaging protocol to demonstrate that in this patient with PAF, orthostatic intolerance was driven by a reduction in cardiac output and baroreflex impairment, resulting in reduced cerebral hypoperfusion. The authors emphasize the importance of estimating vessel diameter when evaluating cerebral hypoperfusion. Absolute MCA flow, calculated from MR sequenced flow velocity and vessel diameter, revealed a total blood flow reduction of 37.6% with LBNP challenge, compared to a slightly greater estimate of 42.5% reduction without taking vessel diameter into account.

In addition to the lack of CO2 measurements, and the fact that this was only a single patient, a major limitation is the fact that the protocol was performed in the supine position. Despite LBNP-induced orthostatic stress, there may be other physiologic mechanisms at play that may not be induced by supine orthostatic stress. It would have been interesting if the authors had attempted to correlate other measures of cerebral and systemic blood flow (transcranial Doppler with beat-to-beat BP measurements, for example) during both MR imaging and during traditional head-up tilt, further validating the MR-estimated cardiovascular and cerebrovascular changes observed. We look forward to the results of the authors' future studies utilizing this protocol and would be particularly interested in seeing the results in patients with other forms of orthostatic intolerance such as POTS.

✉ Srikanth Muppidi
muppidis@stanford.edu

[1] Stanford Medical Center, 213 Quarry Road, 2Nd Floor, Palo Alto, CA 94304, USA

Orthostatic hypotension in long-COVID: POTS first, then OH

Symptoms of orthostatic intolerance including OH and POTS have been commonly reported in patients with post-acute sequelae of SARS-CoV-2, colloquially known as long-COVID [2]. In a recent study, Campen and Visser [3] attempted to determine how hemodynamic abnormalities and cerebral blood flow during tilt table testing differ based on PASC duration.

The study included 29 participants with PASC who were referred to the authors' clinic between December 2020 and March 2022 for clinical evaluation of autonomic dysfunction. Eighteen of the patients had serologic testing for COVID, while the other 11 participants were diagnosed based on clinical suspicion alone by a healthcare professional. All participants underwent a tilt table test with cerebral blood flow measurement. Any medication that could affect heart rate or blood pressure was held for testing.

All 29 patients were able to complete the study. The mean age of participants was 39 years. The median time from COVID onset to tilt table testing was 18 months with a range between 3 and 28 months. Thirteen (45%) patients were diagnosed with POTS, 5 (26%) with OH and 11 (38%) had normal heart rate and blood pressure (normHRBP) during the tilt. Of participants who had a disease duration of less than 12 months, 71% had POTS and 29% had normal norm HRBP. Of participants who had had a disease duration between 12 and 18 months, 43% had POTS, 14% OH, and 43% normHRBP. Of participants who had had a disease duration between 18 and 24 months, 46% had POTS, 27% OH, and 27% normHRBP. Lastly, of participants who had had a disease duration longer than 24 months, no participants had POTS, 25% OH, and 75% normHRBP.

Blood flow for bilateral internal and vertebral arteries was calculated by multiplying the mean blood flow rate by the blood vessel surface (expressed in mL/min). Blood flow in each artery was calculated in 3–6 heartbeats and the results were averaged. The total cerebral blood flow was calculated by adding the blood flow of the four arteries together. Participants with post-COVID POTS had a 36% reduction in cerebral blood flow, which was significantly higher than the cerebral blood flow reduction seen in OH (30%) and normHRBP (30%) (ANOVA: $p = 0.035$). A linear regression of all participants showed that cerebral blood flow reduction diminishes over time from the onset of COVID infection (linear regression: $p = 0.024$).

The results of this study indicate that the incidence of post-COVID POTS decreases over time and is replaced with participants who had normHRBP or OH. The authors hypothesize that the reduction in the frequency of POTS over time could be due to a decrease in catecholamine production by cytokine-producing immune cells [4]. OH was not present in participants with a disease duration of less than 12 months but was seen in about 1/4 of participants with a disease duration greater than 18 months. To our knowledge, this is the first study to report that OH becomes more frequent when PASC duration exceeds 12 months. The reduction in CBF during tilt in participants with post-COVID POTS (36%) was greater than previously reported in healthy volunteers (7%) [5]. Cerebral blood flow reduction may cause some of the orthostatic symptom burden seen in post-COVID POST including brain fog.

The main limitation of this study, aside from the lack of a control population, is that hemodynamic change over time was inferred from individual patients with variable PASC disease intervals rather than following individual patients over time. The prevalence of POTS and OH in PASC could not be assessed, because many of the patients in this study had asked for a referral to the authors' clinic based on information on social media (selection bias). This study included participants whose COVID had not been confirmed by serologic testing, which is also a significant limitation. Lastly, the authors note that none of the PASC participants had alternative explanations for their symptoms, but the authors did not report what work-up was done to exclude COVID-independent causes of autonomic dysfunction. In addition, the authors report having limited information on comorbid diseases and other organ-specific abnormalities so alternative causes of orthostatic tachycardia and OH were not fully excluded. Prospective studies are needed to confirm these findings and investigate possible etiologies for the delayed appearance of OH in PASC.

Autonomic fibers replace somatic nerve fibers

Somatic nerve injury or nerve transection leads to muscle denervation with an unclear prognosis and the extent of recovery depends on the type and nature of the injury. Neuromuscular plasticity/recovery after somatic nerve injury is superior if there is early reinnervation of the muscle; however, it is unclear if the innervation must be with somatic fibers or if other sensory/autonomic fibers may also improve muscle function.

Recently, Tereshenko et al., published their work on the role of autonomic nerve fibers in the reinnervation of selected muscles the in the *Journal of Neurosciences* titled " Autonomic Nerve Fibers Aberrantly Reinnervate Denervated Facial Muscles and Alter Muscle Fiber Population," expanding the understanding of the role of autonomic fibers

in muscle function recovery [6]. In this study, researchers used 40 Sprague Dawley rats and all had ipsilateral resection of the facial nerve with appropriate surgical protocols. Over the next 16 weeks, an assessment of the whisker movement was performed at regular intervals. Muscle fibers were harvested from the denervated and healthy sides to perform immunofluorescence staining, and appropriate labeling with injection into the intramuscular space used to understand new neural pathways. Finally, physiological and quantitative assessment of neural pathways was performed by stimulating the infraorbital nerve.

Post-facial nerve transection, the motor function of the whisker spontaneously improved but was less than the normal contralateral side. Whole mount staining of the denervated muscles revealed thin nerve fibers suggestive of ingrown axons. Using anti-choline acetyltransferase staining, a specific marker for cholinergic axons, the authors found that the denervated fibers were primarily parasympathetic. Muscle fiber composition in the denervating muscle changed from a mix of IIa, and IIb fibers to purely IIa fibers. Intramuscular injection with an appropriate tracer into the denervated muscle revealed no fluorescent signal in the brainstem, excluding the possibility of apparent somatic reinnervation, however, signal was noted in the pterygopalatine ganglion, confirming the parasympathetic fiber innervation. Finally, parasympathetic innervation was also studied by electrophysiological stimulation. Stimulation of the infraorbital nerve revealed whisker movement on the affected side.

These thorough experiments shed further light on the role of autonomic fibers. Readers of this editorial might notice that some of the methodologies used including retrograde tracing have been used in multiple recent studies covered in this section to further elucidate the role of autonomic fibers [7]. While this elegant but limited study may not translate to a significant change in clinical practice, it provides new insights into autonomic physiology.

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Declarations

Conflict of interest None.

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