Cardiac-neurovascular crosstalk: Cardiac rhythms reveal maladaptive cerebral autoregulation and constrained ventilatory status

Diego Candia-Rivera, Pierre Pouget, Mario Chavez

Sorbonne Université, Paris Brain Institute (ICM), CNRS UMR7225, INSERM U1127, Hôpital de la Pitié Salpêtrière AP-HP, INRIA Paris, 75013, Paris, France.

** Correspondence to Diego Candia-Rivera, diego.candia.r@ug.uchile.cl*

Abstract

In the context of brain-heart interactions, several pathways have been proposed to mediate feedback loops between neurophysiological oscillations. However, the role of cerebrovascular dynamics in shaping this interplay remains poorly understood. In particular, the interaction between cardiac autonomic control, ventilation mechanisms, and cerebral autoregulation is not well characterized, especially in ageing and post-stroke conditions, where cerebral perfusion is often compromised. In a cohort of 57 elderly participants, including 30 stroke survivors, we investigated the relationship between cardiac sympathetic activity and both, cerebral blood flow regulation and ventilatory status. Sympathetic reflexes, assessed via cardiac sympathetic index (CSI) during sit-to-stand transitions, were preserved across all participants, with no significant group differences between stroke and non-stroke populations. However, among individuals with constrained ventilation, indexed by reduced end-tidal CO_2 ($EtCO_2$) at baseline, we identified a more elevated CSI following postural change, scaling with the degree of CO_2 dysregulation. Furthermore, transcranial Doppler measurements revealed exaggerated changes in mean flow velocity (MFV) within the right middle cerebral artery in most participants. These MFV shifts significantly correlated with the magnitude of cardiac sympathetic change under orthostatic stress, suggesting that CSI can capture maladaptive neurovascular responses. Together, these findings highlight a distinct cardiac-neurovascular crosstalk in elderly individuals, revealing a potential mechanism of compensatory overactivation under impaired cerebrovascular control.

Keywords

Brain-heart interaction, cardiac-neurovascular crosstalk, ageing, stroke, orthostatic stress

Introduction

Understanding the interplay between cardiac and neurovascular regulation is essential for grasping how the brain and bodily systems adapt to physiological stressors. While traditionally considered as distinct systems, recent research into brain-heart interactions increasingly supports a view of bidirectional communication between neural and cardiovascular systems [1], where neurovascular dynamics appear at the inface [2]. This cardiac-neurovascular crosstalk becomes particularly relevant in dynamic conditions such as postural changes, where both autonomic cardiovascular responses and neurovascular adjustments must occur in concert [3]. Despite growing recognition of this integrative physiology, how neurovascular coupling interfaces with cardiac autonomic output remains comparatively poorly understood [4].

Cerebral autoregulation is the brain's intrinsic mechanism to maintain stable cerebral blood flow in the face of systemic blood pressure fluctuations. This complex control system involves myogenic, metabolic, and neurogenic inputs and is essential for maintaining optimal perfusion during physiological challenges [3]. A key modulator of cerebral autoregulation and neurovascular coupling is arterial CO_2 [5–7], with end-tidal CO_2 ($EtCO_2$) serving as a non-invasive proxy [8]. Impairments in CO_2 reactivity, typically indexed as low $EtCO_2$ levels, can indicate disrupted respiratory drive or inefficient gas exchange, both of which are increasingly recognized as contributing to cerebrovascular vulnerability in ageing and disease. In this context, cardiac autonomic dynamics have been explored to understand maladaptive cerebral autoregulation, particularly in populations with dysautonomia or related conditions such as orthostatic intolerance or hypertension [9–12]. These studies have often interpreted cardiac responses as isolated markers of autonomic dysfunction. While cardiac rhythms are typically associated as an epiphenomenon or the result of brain-centred effects [13], growing evidence support the presence of bidirectional brain-heart communication [14,15] supporting the informative role of cardiac dynamics about cerebral complications. Here, we hypothesized that cardiac-neurovascular crosstalk may provide a more integrated signal of maladaptive cerebral autoregulation, particularly observable in the dynamic modulation of cardiac rhythms.

The autonomic nervous system plays a crucial role in cardiovascular adaptation. Sympathetic responses ensure adequate cerebral perfusion during postural shifts by modulating heart rate, vascular tone, and cardiac output [16]. While intact autonomic state is acknowledged as necessary for optimal cerebral autoregulation [4], mixed results appear with respect to what heart rate variability analyses capture [17,18]. We recently developed a method that accurately captures sympathetic activations through time-resolved estimations of heart rate and rhythm [19]. From this, the cardiac sympathetic index (CSI) is derived. We hypothesized that CSI

changes under orthostatic stress can reflect the responsiveness and integrity of the cerebrovascular system. These autonomic adjustments are typically fast and robust in healthy individuals but may be altered in patients with cerebrovascular complications.

Despite the parallel importance of cerebral autoregulation and cardiac autonomic control, relatively little work has integrated these domains in the context of ageing and stroke. Stroke may disrupt central autonomic pathways, damage cerebrovascular networks, and create asymmetries in neurovascular control, especially when affecting key cortical or subcortical regions involved in motor and autonomic integration [20]. It remains unclear whether impaired neurovascular coupling in stroke is met with compensatory changes in sympathetic outflow, or whether the systems become uncoupled altogether, leading to maladaptive physiological patterns.

In this study, we investigated how cardiac sympathetic activity, cerebral autoregulation, and ventilatory status interrelate in a cohort of 57 elderly individuals, including 30 stroke survivors. Using a sit-to-stand test, we quantified sympathetic responsiveness through CSI and examined its relationship to both resting $EtCO_2$ levels and cerebral blood flow velocity changes, assessed via transcranial Doppler ultrasound of the middle cerebral arteries. We expected distinct cardiac sympathetic reflexes to orthostatic stress in patients with constrained CO_2 profiles (low $EtCO_2$), as well as abnormal cerebral blood flow velocity changes to postural shifts. Signatures that would highlight the relevance of tracking the cardiac-neurovascular crosstalk in ageing and stroke. We also explore whether these relationships differed between stroke and non-stroke participants. This work contributes to the emerging view that integrated brain-heart physiology is essential for understanding vulnerability and resilience in ageing and disease.

Materials and methods

Participants

The data used in this study belongs to the Physionet dataset "Cerebral Vasoregulation in Elderly with Stroke" [21,22]. Participants were recruited in Boston, USA, from community advertisement. The inclusion criteria aimed at recruiting participants aged 60-80 years, both stroke and non-stroke (control) groups.

The control group inclusion required no clinical history of stroke and no focal deficit on neurological exam. The stroke group inclusion consisted in patients with at least 6 months from the stroke and clinically stable condition (defined by neurological scales Modified Rankin Scale, MRS<4; National Institute of Health Stroke Scale, NIHSS <5). Inclusion also requested patients with first ever hemispheric ischemic stroke with documented neurological deficit persisting >24 hours, confirmed by radiological findings (CT and MRI), and infarct affecting less than one third of the middle cerebral artery territory.

Exclusion criteria for the control group included individuals with carotid stenosis greater than 50%, based on clinical history, ultrasound, or magnetic resonance angiography (MRA). For the stroke group, subjects were excluded if they had carotid stenosis greater than 50% that was contralateral to the stroke or not related to the infarct, as well as those with evidence of intracranial or subarachnoid haemorrhage on MRI or CT. Additional exclusions for the stroke group included the presence of any acute or unstable medical condition; vertebrobasilar or carotid artery disease identified by MRA during initial evaluation; a history of dementia or cognitive impairment that limited compliance with the study protocol; diabetes mellitus; hemodynamically significant valvular disease; clinically significant arrhythmias such as atrial fibrillation; severe hypertension, defined as systolic blood pressure > 200 mmHg and/or diastolic blood pressure >110 mmHg, or the use of three or more antihypertensive medications. Participants were also excluded if they had current alcohol or recreational drug abuse, morbid obesity defined as a body mass index >35, or if it was not possible to obtain permission for participation from their primary care physician.

In this study, a total of 57 participants were analysed (61 participants were available, from which 4 were excluded because their corrupted ECG during the analysed protocol due to artifacts).

Protocol

The protocol was performed at the Clinical Research Center from the Beth Israel Deaconess Medical Center, Boston, USA. All participants signed an informed consent and completed symptom checklist and medical history questionnaires. ECG and vital signs, height and weight were measured by a trained nurse. The protocol encompassed several tasks. In this study, we focused in three conditions: supine position (hereafter referred as baseline), sitting and standing. Antihypertensive medications, if any, were tapered during the 5 days prior to the study using home blood pressure monitoring.

Active standing is a standard method for the diagnosing orthostatic hypotension. In elderly people, the normal response to standing up is a transient systolic blood pressure decline with recovery within the first minute [23], which is compensated primarily by increased peripheral resistance. Orthostatic hypotension (hereafter referred as dysautonomia) will be diagnosed using standard criteria accepted by The Consensus Committee of the American Autonomic Society and American Academy of Neurology, as a systolic blood pressure decline of ≥20 mm Hg or diastolic blood pressure decline of ≥10 mm Hg within 3 minutes of standing [24]. Subjects sat on the chair for 5 minutes with their legs elevated at 90 degrees in front of them on a stool to reduce venous pooling. The moment when both feet touched the ground was recorded to mark the onset of standing. The subjects were asked to breathe according to a metronome at their normal breathing rate.

Data acquisition and processing

Heartbeats were recorded using a 3-lead electrocardiogram. Beat-to-beat arterial pressure was acquired from a cuff placed on the finger on the unaffected side in the stroke group or on the nondominant arm in the control group using a Portapress-2 device (Finapres Medical Systems, Enschede, The Netherlands). Beat-to-beat blood pressure measurements were corroborated by standard Dinamap measurements of arterial pressure on the upper arm (Johnson and Johnson, New Brunswick, NJ, USA). End-tidal CO2 values were recorded using an infrared end-tidal volume gas monitor (Capnomac Ultima, Datex Ohmeda, Chicago, IL, USA) attached to a face mask. A transcranial Doppler ultrasonography system (MultiDop X4, DWL Neuroscan, Sterling, VA, USA) was be used to monitor blood flow velocity in both middle cerebral arteries. The middle cerebral arteries were insonated from the temporal windows, by placing the 2 MHz probe in the temporal area above the zygomatic arch. Each probe was positioned to record the maximal blood flow velocity and fixed at the desired angle using a

three-dimensional positioning system attached to the light-metal probe holder. Special attention is always given to stabilize the probes, since their steady position is crucial for continuous blood flow velocity recordings. Fourier transform of the Doppler shift, a difference between the frequency of the emitted signal and its echo (frequency of reflected signal), was used to calculate blood flow velocity. Mean blood flow velocity was detected from the envelope of the arterial flow waveforms. Signals were recorded at either 500 or 1000 Hz. Analog signals were recorded using Labview NIDAQ (National Instruments Data Acquisition System 64 Channel/100 Ks/s, Labview 6i, Austin, TX, USA).

Cardiac sympathetic activity estimation

ECG time series were bandpass filtered between 0.5 and 45 Hz using a fourth-order Butterworth filter. R-peaks were automatically detected using the Pan-Tompkins algorithm [25]. To identify potential misdetections, an automated procedure flagged sudden changes in inter-beat intervals, which were then reviewed through visual inspection. All detected peaks were subsequently examined manually against the raw ECG signal and the inter-beat interval histogram. Manual corrections were applied when necessary, although these were minimal and limited to a few instances.

Cardiac sympathetic activity was assessed using a method based on the time-varying geometry of the inter-beat interval Poincaré plot [19]. This approach integrates dynamic changes in heart rate and heart rate variability to derive the Cardiac Sympathetic Index (CSI). This marker has been validated under standard autonomic challenges, confirming their reliability for capturing time-resolved cardiac autonomic dynamics. For a comprehensive description of the cardiac autonomic estimation procedure, refer to the original method article [19].

Exposure and outcome measures

The primary exposure variable was the cardiac sympathetic activity, quantified using the CSI, across different physiological and participants' groups. The primary outcome was the CSI response to an orthostatic challenge (sit-to-stand task), assessed by comparing CSI values during the sitting and standing phases. Group comparisons were performed between controls and stroke patients to evaluate whether the CSI response differed by clinical status. Additional comparisons assessed the influence of dysautonomia, stroke hemisphere, and baseline physiological states.

Associations between CSI and other physiological parameters were examined to identify potential modulators of the sympathetic response. Specifically, we analysed the relationship between CSI and: (1) baseline blood pressure and heart rate; (2) changes in blood pressure and heart rate during the sit-to-stand task; (3) baseline end-tidal CO_2 ($EtCO_2$); and (4) percentage changes in cerebral blood flow velocity from baseline to both sitting and standing phases. We focus in the right middle central artery because of its known dominance in autonomic control [26] and postural balance [27–29]. We also focus on the percentual changes in blood flow velocity (baseline with respect to the postural change), to reduce potential confounds associated with individual anatomical differences. Each of these variables was tested for their correlation with CSI within and across groups. These analyses aimed to determine the extent to which cardiac sympathetic modulation is influenced by cardiovascular, respiratory, and cerebrovascular dynamics.

Patients were stratified, based on the available information and the range of the measurements of $EtCO_2$ and blood flow velocity (Table 1). CO_2 constrained patients were identified as $EtCO_2$ <35 mmHg, as these values are typically associated with overall higher health risk [30–32]. Typical change in blood flow velocity in healthy individuals is within 10-15% [33,34]. Therefore, we focused on the "abnormal" range 10-100%, to test whether the degree of change in blood flow velocity relates to CSI.

Table 1. Participants inclusion in each analysis

Condition/measure	Groups' count*
Dysautonomia	Control=9, stroke=14
No dysautonomia	Control=22, stroke=16
Blood pressure/heart rate	Control=27, stroke=30
CO2 constrained	Control=7, left stroke=5, right stroke=4, stroke no hemisphere information = 1
CO2 unconstrained	Control=20, left stroke=7, right stroke=10, stroke no hemisphere information = 3
Blood flow velocity (right MCA)	Control=9, left stroke=8, right stroke=8, stroke no hemisphere information = 1
Blood flow velocity (left MCA)	Control=18, left stroke=8, right stroke=8, stroke no hemisphere information = 2

** Additional exclusion of patients because of corrupted or missing information on the specific measurement*

Statistical analysis

Continuous variables were expressed as medians and median absolute deviations. Paired and unpaired comparisons were performed using Wilcoxon-Mann-Whitney tests. Spearman correlations were used to test relationships between physiological variables. Statistical significance was set to α=0.05.

Code and data availability statement

All physiological data used in this study are publicly available in Physionet [21,22]. Codes implementing the methods of this study are available at https://github.com/diegocandiar/robust_hrv.

Results

To investigate the dynamics of cardiac sympathetic activity in response to orthostatic stress, we analysed the CSI derived from ECG recordings during a sit-to-stand task in aged controls and stroke patients. We examined the magnitude and consistency of the CSI response across groups, assessed its relationship with standard cardiovascular markers (blood pressure and heart rate), and explored how individual differences in CO_2 regulation and cerebral blood flow modulation may influence sympathetic reflexes. The results provide insight into the integrity and modulators of cardiac autonomic function, even in the presence of cerebrovascular pathology.

Cardiac sympathetic reflex to orthostatic challenge

Figure 1A illustrates the changes in the CSI during a sit-to-stand test in both controls and stroke patients. In both groups, CSI significantly increased during the standing phase compared to the sitting baseline (Figure 1B; Wilcoxon paired test, controls $p<0.0001$, $Z=4.5407$, stroke $p<0.0001$, $Z=4.7832$). This confirms that stroke patients have intact cardiac sympathetic reflex to orthostatic stress, with no apparent delays with respect to controls. The magnitude of this increase (CSI stand-CSI sit) did not differ significantly between groups (Wilcoxon unpaired test, $p=0.9173$, $Z=0.1039$). This trend was also observed in individuals exhibiting orthostatic dysautonomia, indicating that the CSI increase is preserved even in those with impaired blood pressure regulation (Figure 1C; Wilcoxon paired test, controls $p=0.0077$, $Z=2.6656$, stroke $p=0.001$, $Z=3.2974$; Wilcoxon unpaired test, control vs stroke $p = 0.0725$, $Z=1.7962$).

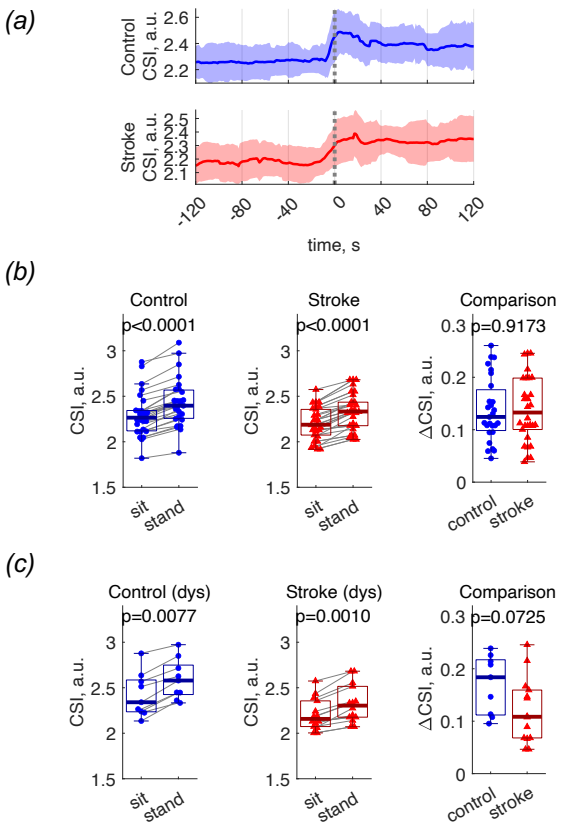

Figure 1. Cardiac sympathetic response to orthostatic stress. (A) Group median CSI continuous values during the sit-to-stand test in controls (n=27) and stroke patients (n=30). (B) Both groups show a significant increase in CSI from sit to stand, with no significant difference in the CSI change (ΔCSI) between groups. (C) The pattern of increased CSI during standing is maintained in individuals with dysautonomia (dys) in both controls (n=9) and stroke patients (n=14).

We then assessed whether the cardiac sympathetic reflex related to other cardiovascular variables. At rest, CSI values showed no significant association with baseline blood pressure (Figure 2A; Spearman Correlation, stroke p=0.3889, r=-0.1626, control p=0.0701, r=-0.3547) or with changes in blood pressure during the sit-to-stand manoeuvre (Figure 2B; Spearman Correlation, stroke p=0.4379, r=-0.1522, control p=0.5607, r=0.1275). A negative correlation was observed between CSI and baseline heart rate in the control group, but not in the stroke group (Figure 2C; Spearman Correlation, stroke p=0.1889, r=-0.2463, control p=0.0099, r=-0.4921). Moreover, CSI changes during the sit-to-stand test were significantly correlated with heart rate changes in both groups (Figure 2D; Spearman Correlation, stroke p=0.0003,

r=0.6426, control p<0.0001, r=0.7747), suggesting that although CSI is influenced by heart rate modulation, it also reflects additional autonomic components.

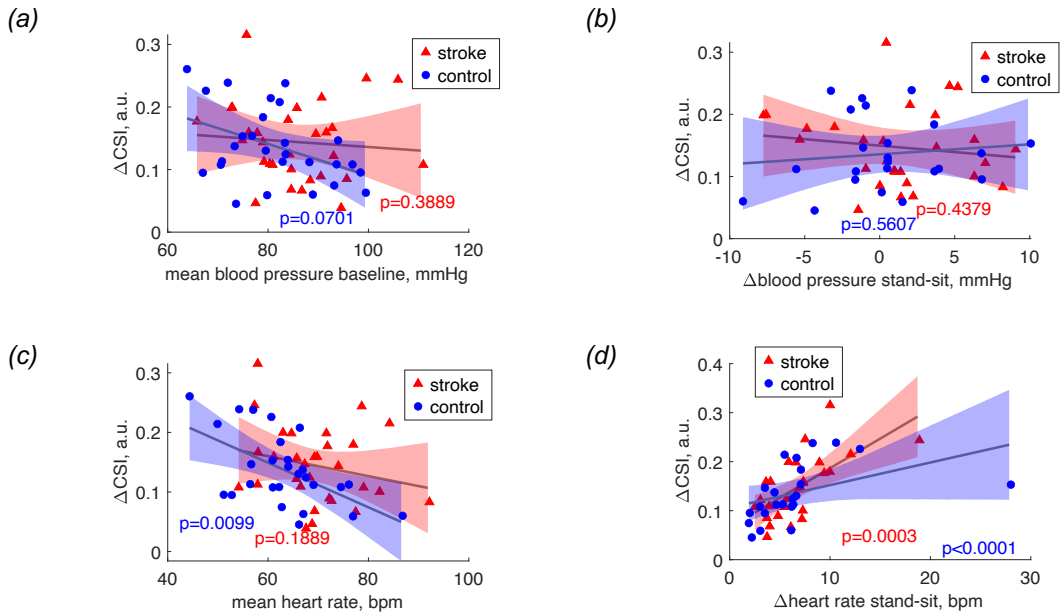

Figure 2. Relationship between cardiac sympathetic reflex and cardiovascular parameters in controls (n=27) and stroke patients (n=30). (A) Sympathetic reflex (ΔCSI) does not correlate with baseline blood pressure. (B) ΔCSI during the sit-to-stand test do not relate to concurrent changes in blood pressure during the protocol. (C) A significant negative correlation is found between resting CSI and baseline heart rate in controls, but not in stroke patients. (D) ΔCSI is significantly correlated with changes in heart rate during the protocol in both groups.

CO_2 regulation and sympathetic responsiveness

In participants with altered CO_2 regulation, a strong negative association was found between baseline $EtCO_2$ and the amplitude of the CSI response to standing, in both controls and stroke patients (Figure 3A; Spearman Correlation, $EtCO_2$ constrained p=0.0081, r=-0.6299, $EtCO_2$ unconstrained p=0.3467, r=-0.1523). This relationship was not driven by a specific stroke hemisphere (Figures 3B and 3C), indicating that the link between CO_2 regulation and sympathetic reflex is preserved regardless of lesion and its laterality.

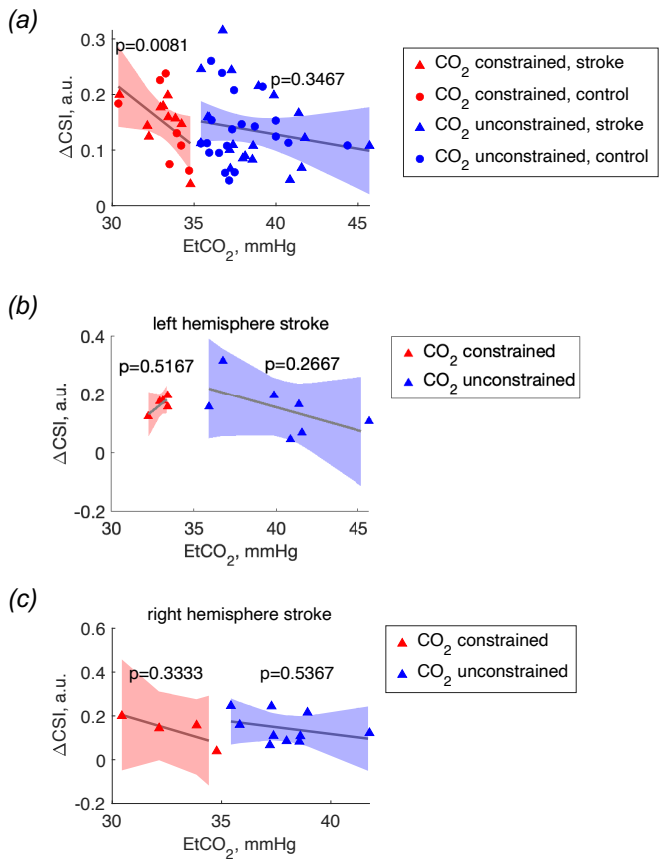

Figure 3. Influence of CO_2 regulation on the cardiac sympathetic reflex. (A) A negative correlation is observed between baseline end-tidal CO_2 ($EtCO_2$) levels and the magnitude of the CSI response to orthostatic stress in participants with constrained $EtCO_2$, in both controls (n=7) and stroke patients (n=10). Relationship not found in unconstrained $EtCO_2$ (controls, n=20; stroke patients, n=20). (B, C) This relationship is not driven by stroke hemisphere, indicating that CO_2-related modulation of sympathetic activity is preserved regardless of lesion laterality (constrained $EtCO_2$, left stroke, n=5, right stroke, n=4; unconstrained $EtCO_2$, left stroke, n=7, right stroke, n=10).

Further analyses confirmed the specificity of this relationship. $EtCO_2$ values did not correlate with the changes in blood pressure (Figure 4A; Spearman Correlation, $EtCO_2$ constrained p=0.7241, r=0.1, $EtCO_2$ unconstrained p=0.2095, r=0.2139) or heart rate (Figure 4B; Spearman Correlation, $EtCO_2$ constrained p=0.7144, r=-0.1036, $EtCO_2$ unconstrained p=0.8007, r=-0.0435) during the orthostatic challenge, reinforcing the idea that the observed CO_2–cardiac sympathetic association is not captured by conventional cardiovascular measures.

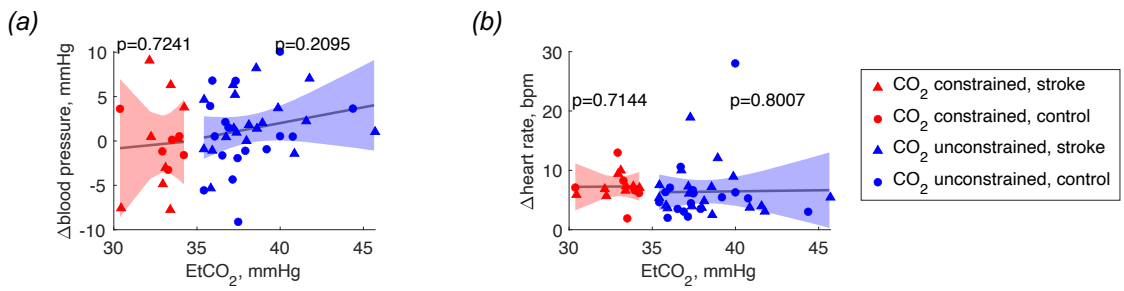

Figure 4. Specificity of the baseline end-tidal CO_2 ($EtCO_2$)–CSI relationship. No significant correlations are found between $EtCO_2$ and changes in blood pressure (A) or heart rate (B) during the sit-to-stand test (constrained $EtCO_2$, controls, n=7, stroke patients, n=10; unconstrained $EtCO_2$, controls, n=20, stroke patients, n=20).

Cerebral hemodynamics and sympathetic drive

Finally, we explored whether the CSI response to standing was associated with changes in cerebral blood flow. CSI correlated significantly with the percentage change in cerebral blood flow velocity in the right middle cerebral artery, from baseline to both sitting and standing phases (Figures 5A). A stronger correlation was found in the case of baseline vs sit (Spearman correlation, baseline vs sit p=0.0009, r=0.6239, baseline vs stand p=0.0365, r=0.4140). This effect was not observed in the case of the left middle cerebral artery. Notably, this coupling between sympathetic activity and the right middle cerebral artery hemodynamics, during the baseline to sit change, was preserved in stroke patients regardless of the affected hemisphere (Figure 5B; Spearman correlation p=0.0072, r=0.6559).

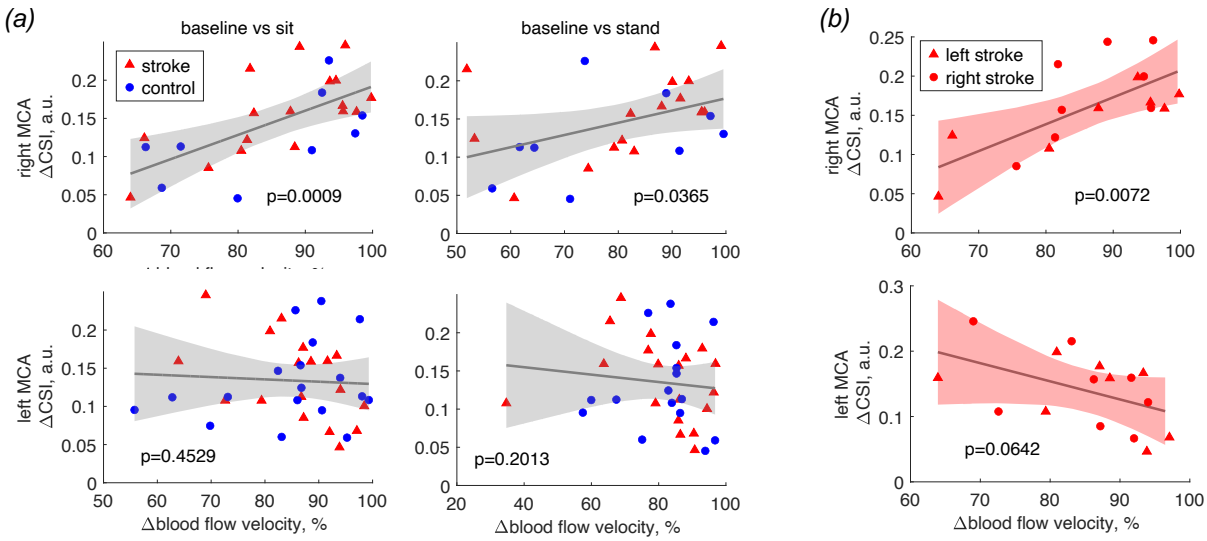

Figure 5. Association between sympathetic reflex and cerebral blood flow in the middle cerebral artery (MCA; right hemisphere, left hemisphere). (A) CSI changes during sit-to-stand correlate, only in the right MCA, with the percentage change in cerebral blood flow velocity, both from baseline to sitting and from baseline to standing. (B) This association is preserved in stroke patients regardless of the affected hemisphere. Right MCA, control, n=9, left stroke, n=8, right stroke, n=8, stroke no hemisphere information, n=1. Left MCA, control, n=18, left stroke, n=8, right stroke, n=8, stroke no hemisphere information, n=2.

In contrast, no such relationships were found when analysing changes in blood pressure (Figure 6A; Spearman correlation p=0.5123, r=-0.1369) or heart rate alone (Figure 6B; Spearman correlation p=0.0575, r=0.3862), underscoring the unique role of CSI in capturing relevant cardiac autonomic-cerebral interactions.

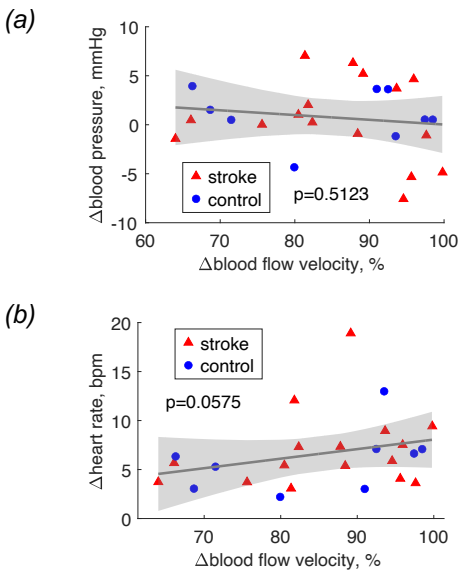

Figure 6. Lack of association between cerebral blood flow changes in the right middle cerebral artery and conventional cardiovascular markers. Changes in blood pressure (A) and heart rate (B) during the sit-to-stand test do not correlate with changes in cerebral blood flow velocity. Control, n=9, stroke, n=17.

Discussion

This study demonstrates that cardiac sympathetic reflexes under orthostatic stress provide meaningful information about potentially impaired neurovascular mechanisms at baseline. The relationships were related to cerebral autoregulation, which is affected not only by the presence of cerebrovascular or autonomic disease but also by the underlying ventilatory status, particularly CO_2 regulation. In a cohort of older adults, including stroke survivors and matched controls, we found that while cardiac sympathetic reflexes in response to orthostatic stress were broadly preserved across groups, some minimal differences were indicative of maladaptive cerebral hemodynamics (blood flow velocity) and constrained ventilatory status ($EtCO_2$).

Our results show that elevated cardiac sympathetic responsiveness during a sit-to-stand test was specifically associated with lower resting $EtCO_2$ levels, but only in patients with evidence of CO_2 constraint. This relationship was not observed in participants with normal $EtCO_2$, regardless of stroke status. Indeed, neurovascular coupling appears unconnected to CO_2 as they relate to distinct regulations [35]. We found that all patients had a percentual change in blood flow velocity in the abnormal range (>10%), and that change scaled with cardiac sympathetic responses to orthostatic stress as well. These results suggest that sympathetic reactivity (or overactivity) may reflect a compensatory, or potentially maladaptive, response to impaired cerebral hemodynamics and ventilatory inefficiency.

While ventilatory inefficiency is traditionally attributed to impaired central respiratory drive or reduced pulmonary perfusion, low $EtCO_2$ may also signify impaired cerebrovascular CO_2 responsiveness, which we found to be present in participants with stroke as well. Importantly, this cardiac autonomic-ventilatory association was paralleled by exaggerated changes in cerebral blood flow velocity in the right middle cerebral artery, in response to postural shifts, which occurred in most participants. Heightened sympathetic activation exhibited larger increases in cerebral blood flow velocity, possibly indicating overcompensation due to impaired autoregulatory buffering. This finding aligns with the expected maladaptive neurovascular crosstalk, wherein autonomic and cerebrovascular systems meant to cooperate fail to maintain homeostasis when one component is compromised [3]. That the right middle central artery was predominantly affected may point to a lateralized role in integrating motor-postural and autonomic regulation, consistent with previous reports suggesting right-hemisphere dominance in autonomic control [26] and postural balance [27–29].

While impaired cerebral autoregulation can be expected in chronic stroke patients [36], stroke history alone did not show distinct cardiac sympathetic reactivity, blood flow velocity or $EtCO_2$ profiles in this cohort, suggesting that maladaptive patterns are not exclusively a result of focal lesions but may emerge from broader network-level disintegration and systemic vulnerabilities that occur with ageing [37,38]. Still, stroke may act as a sensitizing event that unmasks or exacerbates latent cardiac, vascular and respiratory inefficiencies [39], particularly when autoregulatory control is weakened. It is also possible that the heterogeneity of lesion locations and small sample size diluted group-level effects, further highlighting the need for stratified approaches based on functional phenotypes (e.g., CO_2-constrained vs. non-constrained [40]) rather than clinical diagnosis alone.

We acknowledge limitations of our study. First, our CO_2 vasoreactivity measure was based on a single value rather than continuous reactivity curves, which may limit sensitivity. Second, although the sit-to-stand paradigm is ecologically valid, it lacks the precision of controlled tilt-table testing. Third, we did not assess dynamic baroreflex sensitivity or direct cerebral oxygenation, which could provide further granularity to the interplay between cardiovascular and cerebrovascular responses. Finally, this study did not include measurements in the posterior cerebral arteries, which have shown certain specificity in capturing reduced perfusion in elderly under orthostatic stress [41]. However, it is important to note that the posterior cerebral artery may receive collaterals from the anterior circulation via the posterior communicating arteries and may therefore be a poor surrogate for the basilar artery, which is the main supply to the brain stem [42,43]. Unfortunately, simultaneous continuous monitoring of the basilar, posterior and middle cerebral arteries during the sit-to-stand protocol was not available.

From a translational perspective, our findings emphasize the need to consider ventilatory efficiency and autonomic capacity jointly when assessing cerebrovascular risk in the elderly [40]. While autonomic testing is routine in some clinical settings, the incorporation of novel cardiac-based measures [19] under simple postural challenges could enhance our ability to detect subclinical dysregulations. Importantly, we demonstrated that cardiac sympathetic responses are better reflected in the CSI, as compared to standard measures [22], such as heart rate and blood pressure. The relevance of these findings highlight that cardiac sympathetic activity and cardiovascular coupling do not necessarily correlate [44], and may convey information about distinct mechanisms. Future research can further enlighten how brain-heart interactions are disrupted in the elderly and in stroke patients, helping to clarify the role of these dynamics in the regulatory mechanisms involved in postural control [45].

In conclusion, our findings support a model in which impaired cerebrovascular dynamics and ventilatory status modifies the expression of cardiac autonomic responses to postural stress in aged individuals. This cardiac-neurovascular crosstalk appears most pronounced in CO_2-constrained individuals, regardless of stroke history, and may underlie a broader phenotype of age-related physiological decline. These insights contribute to the emerging framework of brain-heart interactions and underscore the importance of multidomain physiological profiling in ageing and neurovascular disease.

Acknowledgements

Diego Candia-Rivera is supported by the European Commission, Horizon MSCA Postdoctoral Fellowship Program (grant n° 101151118).

References

1. Candia-Rivera D, Faes L, Fallani FDV, Chavez M. 2025 Measures and Models of Brain-Heart Interactions. *IEEE Reviews in Biomedical Engineering* **in press**. (doi:10.1109/RBME.2025.3529363)
2. Phillips AA, Chan FH, Zheng MMZ, Krassioukov AV, Ainslie PN. 2016 Neurovascular coupling in humans: Physiology, methodological advances and clinical implications. *J Cereb Blood Flow Metab* **36**, 647–664. (doi:10.1177/0271678X15617954)
3. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. 1989 Cerebral autoregulation dynamics in humans. *Stroke* **20**, 45–52. (doi:10.1161/01.STR.20.1.45)
4. Tan CO, Taylor JA. 2014 Integrative physiological and computational approaches to understand autonomic control of cerebral autoregulation. *Experimental Physiology* **99**, 3–15. (doi:10.1113/expphysiol.2013.072355)
5. Attwell D, Buchan AM, Charpak S, Lauritzen M, MacVicar BA, Newman EA. 2010 Glial and neuronal control of brain blood flow. *Nature* **468**, 232–243. (doi:10.1038/nature09613)
6. Iadecola C. 2017 The Neurovascular Unit Coming of Age: A Journey through Neurovascular Coupling in Health and Disease. *Neuron* **96**, 17–42. (doi:10.1016/j.neuron.2017.07.030)
7. DiNuzzo M *et al.* 2024 Neurovascular coupling is optimized to compensate for the increase in proton production from nonoxidative glycolysis and glycogenolysis during brain activation and maintain homeostasis of pH, pCO2, and pO2. *J Neurochem* **168**, 632–662. (doi:10.1111/jnc.15839)
8. Panerai RB, Deverson ST, Mahony P, Hayes P, Evans DH. 1999 Effect of CO2 on dynamic cerebral autoregulation measurement. *Physiol. Meas.* **20**, 265. (doi:10.1088/0967-3334/20/3/304)
9. Wheeler C, Pacheco JM, Kim AC, Camacho-Santiago M, Kalafut MA, Ahern T, White AA, Patay B, Criado JR. 2022 Cardiovascular Autonomic Regulation, ETCO2 and the Heart Rate Response to the Tilt Table Test in Patients with Orthostatic Intolerance. *Appl Psychophysiol Biofeedback* **47**, 107–119. (doi:10.1007/s10484-022-09536-4)
10. Burzyńska M, Woźniak J, Urbański P, Kędziora J, Załuski R, Goździk W, Uryga A. 2025 Heart Rate Variability and Cerebral Autoregulation in Patients with Traumatic Brain Injury with Paroxysmal Sympathetic Hyperactivity Syndrome. *Neurocrit Care* **42**, 864–877. (doi:10.1007/s12028-024-02149-1)
11. Head GA. 1995 Baroreflexes and Cardiovascular Regulation in Hypertension. *Journal of Cardiovascular Pharmacology* **26**, S7.
12. Xing C-Y *et al.* 2017 Arterial Pressure, Heart Rate, and Cerebral Hemodynamics Across the Adult Life Span. *Hypertension* **69**, 712–720. (doi:10.1161/HYPERTENSIONAHA.116.08986)
13. Olufsen MS, Tran HT, Ottesen JT, Research Experiences for Undergraduates Program, Lipsitz LA, Novak V. 2006 Modeling baroreflex regulation of heart rate during orthostatic stress. *Am J Physiol Regul Integr Comp Physiol* **291**, R1355-1368. (doi:10.1152/ajpregu.00205.2006)
14. Wang S, Wang X, Zhao Y, Xie L, Zhang J. 2025 A feedback loop study of brain-heart interaction based on HEP and HRV. *Biocybernetics and Biomedical Engineering* **45**, 181–188. (doi:10.1016/j.bbe.2025.02.005)
15. Doehner W *et al.* 2018 Heart and brain interaction in patients with heart failure: overview and proposal for a taxonomy. A position paper from the Study Group on Heart and Brain Interaction of the Heart Failure Association. *European Journal of Heart Failure* **20**, 199–215. (doi:10.1002/ejhf.1100)
16. Cheshire WP, Goldstein DS. 2019 Autonomic uprising: the tilt table test in autonomic

medicine. *Clin Auton Res* **29**, 215–230. (doi:10.1007/s10286-019-00598-9)
17. Nasr N, Czosnyka M, Pavy-Le Traon A, Custaud M-A, Liu X, Varsos GV, Larrue V. 2014 Baroreflex and Cerebral Autoregulation Are Inversely Correlated. *Circulation Journal* **78**, 2460–2467. (doi:10.1253/circj.CJ-14-0445)
18. Castro P, Serrador J, Sorond F, Azevedo E, Rocha I. 2022 Sympathovagal imbalance in early ischemic stroke is linked to impaired cerebral autoregulation and increased infarct volumes. *Autonomic Neuroscience* **241**, 102986. (doi:10.1016/j.autneu.2022.102986)
19. Candia-Rivera D, de Vico Fallani F, Chavez M. 2025 Robust and time-resolved estimation of cardiac sympathetic and parasympathetic indices. *Royal Society Open Science* **12**, 240750. (doi:10.1098/rsos.240750)
20. Korpelainen JT, Sotaniemi KA, Myllylä VV. 1999 Autonomic nervous system disorders in stroke. *Clinical Autonomic Research* **9**, 325–333. (doi:10.1007/BF02318379)
21. Goldberger AL *et al.* 2000 PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. *Circulation* **101**, E215-220. (doi:10.1161/01.cir.101.23.e215)
22. Novak V, Hu K, Desrochers L, Novak P, Caplan L, Lipsitz L, Selim M. 2010 Cerebral flow velocities during daily activities depend on blood pressure in patients with chronic ischemic infarctions. *Stroke* **41**, 61–66. (doi:10.1161/STROKEAHA.109.565556)
23. Low PA, Opfer-Gehrking TL, Proper CJ, Zimmerman I. 1990 The effect of aging on cardiac autonomic and postganglionic sudomotor function. *Muscle Nerve* **13**, 152–157. (doi:10.1002/mus.880130212)
24. 1996 Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology* **46**, 1470. (doi:10.1212/wnl.46.5.1470)
25. Pan J, Tompkins WJ. 1985 A Real-Time QRS Detection Algorithm. *IEEE Transactions on Biomedical Engineering* **32**, 230–236. (doi:10.1109/TBME.1985.325532)
26. Hilz MJ, Dütsch M, Perrine K, Nelson PK, Rauhut U, Devinsky O. 2001 Hemispheric influence on autonomic modulation and baroreflex sensitivity. *Annals of Neurology* **49**, 575–584. (doi:10.1002/ana.1006)
27. Manor B, Hu K, Zhao P, Selim M, Alsop D, Novak P, Lipsitz L, Novak V. 2010 Altered control of postural sway following cerebral infarction. *Neurology* **74**, 458–464. (doi:10.1212/WNL.0b013e3181cef647)
28. Pérennou D, Pélissier J, Amblard B. 1996 La posture et le contrôle postural du patient cérébrolésé vasculaire: une revue de la littérature. *Annales de Réadaptation et de Médecine Physique* **39**, 497–513. (doi:10.1016/S0168-6054(97)84233-X)
29. Spinazzola L, Cubelli R, Della Sala S. 2003 Impairments of trunk movements following left or right hemisphere lesions: dissociation between apraxic errors and postural instability. *Brain* **126**, 2656–2666. (doi:10.1093/brain/awg266)
30. Dong L, Takeda C, Kamitani T, Hamada M, Hirotsu A, Yamamoto Y, Mizota T. 2023 Association between intraoperative end-tidal carbon dioxide and postoperative organ dysfunction in major abdominal surgery: A cohort study. *PLoS One* **18**, e0268362. (doi:10.1371/journal.pone.0268362)
31. Dong L, Takeda C, Yamazaki H, Kamitani T, Kimachi M, Hamada M, Fukuhara S, Mizota T, Yamamoto Y. 2021 Intraoperative end-tidal carbon dioxide and postoperative mortality in major abdominal surgery: a historical cohort study. *Can J Anesth/J Can Anesth* **68**, 1601–1610. (doi:10.1007/s12630-021-02086-z)
32. Le Gall A, Eustache G, Coquet A, Seguin P, Launey Y. 2024 End-tidal carbon dioxide and arterial to end-tidal carbon dioxide gradient are associated with mortality in patients with neurological injuries. *Sci Rep* **14**, 19172. (doi:10.1038/s41598-024-69143-7)

33. Garrett ZK, Pearson J, Subudhi AW. 2017 Postural effects on cerebral blood flow and autoregulation. *Physiol Rep* **5**, e13150. (doi:10.14814/phy2.13150)
34. Aries MJ, Elting JW, Stewart R, De Keyser J, Kremer B, Vroomen P. 2013 Cerebral blood flow velocity changes during upright positioning in bed after acute stroke: an observational study. *BMJ Open* **3**, e002960. (doi:10.1136/bmjopen-2013-002960)
35. Tournissac M *et al.* 2024 Neurovascular coupling and CO2 interrogate distinct vascular regulations. *Nat Commun* **15**, 7635. (doi:10.1038/s41467-024-49698-9)
36. Aoi MC, Hu K, Lo M-T, Selim M, Olufsen MS, Novak V. 2012 Impaired cerebral autoregulation is associated with brain atrophy and worse functional status in chronic ischemic stroke. *PLoS One* **7**, e46794. (doi:10.1371/journal.pone.0046794)
37. Kumral D *et al.* 2019 The age-dependent relationship between resting heart rate variability and functional brain connectivity. *NeuroImage* **185**, 521–533. (doi:10.1016/j.neuroimage.2018.10.027)
38. Satoh K, Ohashi A, Kumagai M, Sato M, Kuji A, Joh S. 2015 Evaluation of Differences between PaCO2 and ETCO2 by Age as Measured during General Anesthesia with Patients in a Supine Position. *Journal of Anesthesiology* **2015**, 710537. (doi:10.1155/2015/710537)
39. Smith AC, Saunders DH, Mead G. 2012 Cardiorespiratory Fitness after Stroke: A Systematic Review. *International Journal of Stroke* **7**, 499–510. (doi:10.1111/j.1747-4949.2012.00791.x)
40. Dempsey JA, Smith CA. 2014 Pathophysiology of human ventilatory control. *European Respiratory Journal* **44**, 495–512. (doi:10.1183/09031936.00048514)
41. Sorond FA, Khavari R, Serrador JM, Lipsitz LA. 2005 Regional Cerebral Autoregulation During Orthostatic Stress: Age-Related Differences. *The Journals of Gerontology: Series A* **60**, 1484–1487. (doi:10.1093/gerona/60.11.1484)
42. Tatu L, Moulin T, Bogousslavsky J, Duvernoy H. 1996 Arterial territories of human brain. *Neurology* **47**, 1125–1135. (doi:10.1212/WNL.47.5.1125)
43. Fujii K, Heistad DD, Faraci FM. 1991 Role of the basilar artery in regulation of blood flow to the brain stem in rats. *Stroke* **22**, 763–767. (doi:10.1161/01.STR.22.6.763)
44. Xie L, Liu B, Wang X, Mei M, Li M, Yu X, Zhang J. 2017 Effects of different stresses on cardiac autonomic control and cardiovascular coupling. *Journal of Applied Physiology* **122**, 435–445. (doi:10.1152/japplphysiol.00245.2016)
45. Dohata M, Kaneko N, Takahashi R, Suzuki Y, Nakazawa K. 2025 Posture-Dependent Modulation of Interoceptive Processing in Young Male Participants: A Heartbeat-Evoked Potential Study. *European Journal of Neuroscience* **61**, e70021. (doi:10.1111/ejn.70021)