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Research Article

Impaired Stabilization of Orthostatic Cerebral Oxygenation Is Associated With Slower Gait Speed: Evidence From The Irish Longitudinal Study on Ageing

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Abstract

Background: Cerebral autoregulation (CAR) systems maintain blood flow to the brain across a wide range of blood pressures. Deficits in CAR have been linked to gait speed (GS) but previous studies had small sample sizes and used specialized equipment which impede clinical translation. The purpose of this work was to assess the association between GS and orthostatic cerebral oxygenation in a large, community-dwelling sample of older adults.

Method: Data for this study came from the Irish Longitudinal Study on Ageing. A near-infrared spectroscopy (NIRS) device attached to the forehead of each participant (n = 2 708) was used to track tissue saturation index (TSI; the ratio of oxygenated to total hemoglobin) during standing. GS was assessed using a portable walkway.

Results: Recovery was impaired in slower GS participants with a TSI value at 20 seconds (after standing) of −0.55% (95% CI: −0.67, −0.42) below baseline in the slowest GS quartile versus −0.14% (95% CI: −0.25, −0.04) in the fastest quartile. Slower GS predicted a lower TSI throughout the 3-minute monitoring period. Results were not substantially altered by adjusting for orthostatic hypotension. Adjustment for clinical and demographic covariates attenuated the association between but differences remained between GS quartiles from 20 seconds to 3 minutes after standing.

Conclusion: This study reported evidence for impaired recovery of orthostatic cerebral oxygenation depending on GS in community-dwelling older adults. Future work assessing NIRS as a clinical tool for monitoring the relationship between GS and cerebral regulation is warranted.

Keywords: Cardiovascular, Gait, Neuroimaging

Background

Gait speed (GS) is a sensitive clinical indicator of general health that has been proposed as an additional vital sign (1). Walking requires the coordination of multiple physiological systems, both central and peripheral. In particular, the integrity of the cardiovascular system is important for maintaining GS through the life course (2). Orthostatic hypotension (OH) is a cardiovascular condition characterized by impaired recovery of blood pressure after standing from a supine position. The consensus definition of OH is a systolic blood pressure (SBP) decrease of 20 mm Hg or diastolic blood pressure (DBP) drop of 10 mm Hg or greater within 3 minutes of standing (3). However, research studies using continuous monitoring have described an impaired stabilization of BP variant (eg, recovery at 30 seconds after stand), given that normative data suggest much of the hemodynamic response occurs in the first 30 seconds, especially in middle-aged adults (ie, 50–59 years old) (4). An increasing number

of negative outcomes in the older population are linked to OH including slower GS, falls, and frailty (5–9).

Orthostatic blood pressure and GS may be associated because of common risk factors, a causal link, or a mixture of both. Factors that are known to be associated with both OH and slower GS include aging, hypertension, antihypertensive use, stiffening arteries, cardiac disease, and cognitive decline (4,10–16). Along with common risk factors, there exists several plausible causal mechanisms for the association. Chronic exposure to inadequate cerebral blood flow (CBF) leading to brain atrophy is a proposed path by which impaired orthostatic recovery may influence GS (5,17–19). Although cerebral autoregulation systems have evolved to maintain CBF in the face of changing systemic pressure, their efficiency is heterogeneous and is altered by common conditions in the older population such as chronic hypertension, ischemic stroke, and arterial stenosis (20–23). Sorond et al. have reported cross-sectional differences in cerebrovascular reactivity and longitudinal alterations in cerebral autoregulation in individuals with slower GS and falls (24,25). Data from the MOBILIZE Boston Study have also shown impaired neurovascular coupling in older adults with lower GS (26).

Previous works describing the relationship between CBF after standing and GS had small sample sizes and used specialized equipment (eg, transcranial Doppler [TCD] ultrasound) which impede clinical translation. Near-infrared spectroscopy (NIRS) is a noninvasive, optical method which relies on the absorption of infrared light to measure oxygenated and deoxygenated hemoglobin concentrations. Cerebral oxygenation measurements using NIRS are a proxy for CBF and can be gathered cheaply, with minimal training, by attaching a probe to the forehead. The method has shown high reliability for the assessment of cerebral autoregulation during supine-to-stand movements and good agreement with TCD ultrasound (27,28). The aim of this work was to determine if there was a relationship between GS and cerebral oxygenation (measured using NIRS) during a supine-to-stand test.

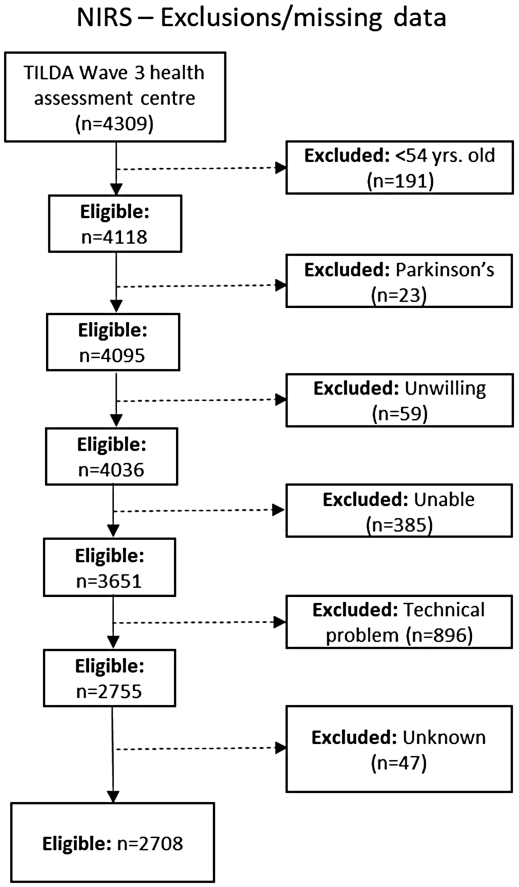

Figure 1. Exclusions and missing participants for NIRS data. NIRS = near-infrared spectroscopy; TILDA = The Irish Longitudinal Study on Ageing.

Method

Sample

Data for this work came from the wave 3 health assessment and computer-assisted personal interview (2014–2015) of The Irish Longitudinal Study on Ageing. The study has been collecting data from community-dwelling adults aged 50 and older in Ireland on a broad range of topics related to aging since 2009. Participants provided written, informed consent adhering to the guidelines set out in the Declaration of Helsinki and ethical approval was provided by the Trinity College Dublin. Participants who attended the health center assessment (n = 4 309) were included in the analysis; exclusions were applied for those with a doctor's diagnosis of Parkinson's or who were younger than 50 years at baseline (wave 1). Further exclusions were applied for technical problems with the collection of cerebral oxygenation data or the participant being unable/unwilling to perform the active stand; these exclusions are illustrated in Figure 1. Participants with valid NIRS data (n = 2 708) and a valid GS were included in analysis. Missing data on covariates were low (0%–8%).

Measurements

Orthostatic SBP and DBP were measured using a digital photoplethysmography (Finometer MIDI device, Finapres Medical Systems BV, Amsterdam, the Netherlands) attached to the finger of the participant. Impaired BP stabilization (denoted by OH30) was defined if the participant had not recovered to within 20 mm Hg SBP or 10 mm Hg DBP of baseline at 30 seconds after standing (based on normative data suggesting most older adults recover by this time) (4). This measure of impaired BP stabilization was chosen given previous work linking OH30 to outcomes such as late life depression and GS (5,29). To monitor cerebral oxygenation during the stand, a NIRS device (Portalite; Artinis Medical Systems, Zetten, the Netherlands) was fixed to the forehead above the left eyebrow in approximately the FP1 position of the ten-twenty electrode system (30). This placement was selected as the frontal lobe is known to be involved in cognitive and functional decline as well as allowing for comparison to previous works in this area (31). The device uses 3 transmitters located at 30, 35, and 40 mm from the detector and the wavelengths were 760 and 850 nm. Concentrations of oxygenated (O_2Hb) and deoxygenated hemoglobin (HHb) were monitored by the NIRS system. Tissue saturation index (TSI), a ratio of oxygenated to total hemoglobin (ie, $O_2Hb*100/[O_2Hb + HHb]$), was then calculated and used to track cerebral oxygenation. The use of multiple transmitters allowed for spatially resolved spectroscopy to be used for the calculation of TSI, meaning it was not dependent on a differential pathway factor, while also minimizing extracerebral influences (32). The mean penetration depth of the NIR light is about half of the transmitter-detector distance allowing for sufficient depth to capture cerebral tissue but limited to <2 cm by potential for tissue damage at higher powers (33). Participants rested for at least 10

minutes in a supine position before being asked to stand as quickly as possible at the end of a 5-second countdown. TSI was tracked for 3 minutes at 50 Hz from the moment standing was initiated by the participant. Resting blood pressure was also evaluated twice in a seated position using an automated digital sphygmomanometer (Omron, Kyoto, Japan); the mean of the 2 measures was used in analysis.

Pulse wave velocity was assessed using the Vicorder (SMT Medical GmbH & Co. KG, Germany) which measures the time taken for a pressure pulse to propagate from the carotid artery to the femoral artery. The distance between the sternal notch and the center of the femoral cuff is then divided by the time to give a speed in meters per second. This value is a surrogate measure for arterial stiffness, given that the pulse will propagate faster in stiffer vessels.

GS was measured using a 4.88-m sensored walkway (GAITRite, CIR Systems Inc., New York, NY). Participants were asked to walk at their usual pace starting from 2.5 m before the mat and ending 2.5 m after the walkway to allow for exclusion of acceleration and deceleration phases, respectively. This was repeated twice for each respondent and the 2 trials were averaged.

Signal Processing

The TSI and BP data were processed using Matlab (R2018a, TheMathWorks, Inc., Natick, MA). The signals were downsampled to 1 Hz and smoothed using an 11th order median filter followed by a 10-point moving average filter. Baselines were defined as the mean of the data between 60 and 30 seconds before standing. Signals were then expressed as a change from baseline value. The initiation of standing (ie, point when movement started) and end of transition were identified using the height correction sensor on the Finometer and a previously described algorithm (34); this process yielded a transition time variable (the time difference between start and end). Data cleaning followed previously published rationale for exclusions (35). NIRS data could not be used if height sensor data or nurse recorded markers were missing as the stand initiation could not be identified. After visual inspection of the signals, exclusions were applied for data suspected to be a measurement error—TSI falling below 10%, absolute O_2Hb or HHb of less than 0.1 μM in over a quarter of data points, TSI change of over 45% overall, TSI change of less than 0.1% over first 30 seconds of stand, and participants with a variation of more than 10% in the TSI baseline. A measure of agreement between sensors (fit factor) was also used to identify and exclude unreliable data, an average greater than 98% was required (according to the manufacturer's guidance) (35).

Statistical Analysis

In order to assess the influence of GS on TSI while adjusting for relevant covariates, mixed-effects models were fitted to the data using Stata (v15.1, StataCorp LP, College Station, TX). The data had 19 TSI measures for each participant at 10-second intervals after standing and was therefore unsuitable for linear regression which does not account for correlation between measures from the same person. Mixed-effects regression allowed for modeling of all timepoints by using a participant-level random intercept and can also handle missing timepoints which occur in the data. This approach has been used previously and has the benefit of including all timepoints which would not be possible with simpler methods. Linear piecewise splines were also implemented (to reduce the number of parameters from 19 to 5) with each parameter representing a straight line between the following timepoints after stand: 0–10, 10–20, 20–30, 30–40, and 40–180 seconds (8,34,36). These ranges were selected based on the large variation in the first 40 seconds and more stable signal from 40 to 180 seconds. The spline parameters were included as independent variables in the mixed-effects model along with each covariate as part of an interaction term (ie, the effect of covariates on TSI changes was expected to differ between time phases). Residuals were assumed to follow a first-order autoregressive process to account for more correlation between adjacent timepoints. The relationship between the GS and TSI was assessed using 3 models for TSI: a base model adjusting for age and sex only (model 1), a model adjusting for age, sex and OH30 (model 2) as well as a more comprehensive model (model 3), adjusting for age, sex, transition time, depressive symptoms (measured by the Centre for Epidemiological Studies Depression scale), seated SBP, seated DBP, OH30, one or more cardiac conditions (including heart attack, heart failure, angina, hypertension, stroke, diabetes mellitus, transient ischemic attack, heart rhythm problem or heart murmur), medication use (antihypertensives: Anatomical Therapeutic Chemical codes C02, C03, C07, C08, and C09 or antidepressants: Anatomical Therapeutic Chemical code N06A), weight, height, and pulse wave velocity. These adjustments were made according to relationships with TSI from previous works, showing links with orthostatic hemodynamics and theory (4,12,15,34). Full model outputs from the models are available in Supplementary Data. Although GS is continuous in the model, to simplify the presentation of the mixed-effects models (which contain splines and interaction terms), marginal effects (holding covariates at their mean) plots were produced for mean GS in the slowest quartile (GS = 108 cm/s), the median (GS = 137 cm/s), and mean GS in the fastest quartile (GS = 159 cm/s). TSI was used for the primary analyses as normalization of oxygenated to total hemoglobin within participants accounts for the noise in the measurements across participants and the scaling to percentage change from baseline provides more interpretable units for analysis. Models were repeated treating O_2Hb and HHb as outcome and results are presented in Supplementary Data.

Results

The mean age of the sample with valid measurements (Table 1) was 64.8 years (range: 54–93 years). There were slightly more females (53.1%) than males and the mean weight and height in the sample

Table 1. Sample Characteristics for NIRS Measurements

Participant Characteristic	NIRS Sample (n = 2 708)
Age (years), mean ± *SD*	64.8 ± 7.4
Females, % (n)	53.1 (1 437/2 708)
Weight (kg), mean ± *SD*	78.4 ± 15.4
Height (cm), mean ± *SD*	166.2 ± 9.2
Seated systolic blood pressure (mm Hg), mean ± *SD*	132.8 ± 18.2
One or more cardiac condition, % (n)	38.9 (1 053/2 708)
Pulse wave velocity (m/s), mean ± *SD*	10.4 ± 2.0
Antidepressant use, % (n)	7.3 (197/2 708)
Antihypertensive use % (n)	37.0 (1 002/2 708)
CES-D score, mean ± *SD*	2.9 ± 3.5
Transition time (s), mean ± *SD*	7.3 ± 2.8
Gait speed (cm/s), mean ± *SD*	137.3 ± 19.1
≥1 ADL limitation, % (n)	2.8 (77/2 708)

Note: ADL = activities of daily living; CES-D = Centre for Epidemiological Studies Depression; NIRS = near-infrared spectroscopy.

were 78.4 ± 15.4 kg and 166.2 ± 9.2 cm, respectively. Cardiac conditions were prevalent with 38.9% of the sample experiencing at least one while 37.0% were using antihypertensives and 7.3% antidepressants. The mean transition time from supine to standing was 7.3 (range: 2–27) seconds. Mean GS was 137.3 cm/s with a *SD* of 19.1 cm/s. Data from 2 708 participants were available for analysis (Figure 1). Participants (n = 444) unable/unwilling to perform the active stand often complained of musculoskeletal issues such as back pain. Data from 896 participants could not be used due to technical problems related to equipment and data cleaning as described in the "Signal Processing" section.

On average, TSI showed a sharp decline from 0 to 10 seconds after standing, followed by a relatively rapid recovery from 10 to 20 seconds, a smaller decrease from 20–40 seconds, and finally a gradual increase from 40 seconds to the end of the monitoring period at 180 seconds (Figure 2). There was evidence for this trend being dependent on GS. In model 1 (adjusting for age and sex only), the TSI value 20 seconds after standing was predicted at −0.14% (95% CI: −0.25, −0.04) below baseline for the fastest quartile of GS, whereas the slowest quartile of GS had a TSI of −0.55% (95% CI: −0.67, −0.42) (Figure 2). These separate profiles of recovery were observed despite similar minimum value at 10 seconds: −1.64% (95% CI: −1.77, −1.51) for the lowest GS quartile versus −1.76% (95% CI: −1.86, −1.65) for the highest GS quartile. Differences in TSI remained throughout. At the end of the 3-minute standing period, faster GS suggested better recovery to prestand levels at −0.39% (95% CI: −0.49, −0.28) versus −0.72% (95% CI: −0.84, −0.59) for the slowest quartile (Figure 2)." Adding OH30 to the model as a covariate did not substantially change the TSI values for the fastest and slowest GS (Figure 2).

The effect of GS on the profiles of TSI in the fully adjusted model 3 was attenuated compared to model 1 and model 2 although differences remained in all but the 0- and 10-second timepoints (Figure 2). Despite both fast and slow quartiles of GS predicting a similar minimum value at 10 seconds, recovery at 20s was improved in the faster quartile at −0.17% (95% CI: −0.29, −0.06) below baseline versus −0.48% (95% CI: −0.62, −0.34) in the slowest quartile. Differences between the quartiles remained throughout (although attenuated) with the values for the slowest quartile of −0.69 (95% CI: −0.83, −0.55) at 3 minutes after standing while the fastest quartile had a value of −0.32 (95% CI: −0.44, −0.21). Analysis using O_2Hb as outcome showed broadly similar gradients to TSI across GS (Supplementary Figure S1). Differences in HHb were generally less clear throughout the stand across the different models (Supplementary Figure S2).

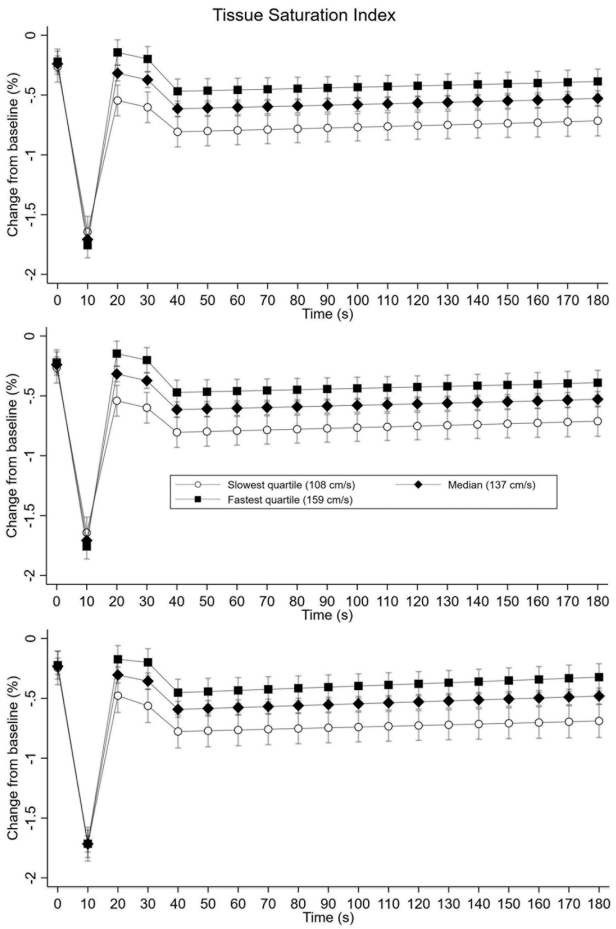

Figure 2. Predictions for tissue saturation index change after standing at the median, slowest and fastest gait speed quartiles. Model 1 (top) was adjusted for age and sex only; model 2 (middle) adjusted for age, sex, and OH30, whereas model 3 (bottom) adjusted for age, sex, OH30, transition time, seated systolic blood pressure, seated diastolic blood pressure, depressive symptoms, cardiac conditions, medication use, weight, height, and pulse wave velocity.

Discussion

The aim of this work was to assess the association between GS and TSI after standing from a supine position. The results showed a marked difference in orthostatic TSI recovery between GS quartiles despite a similar minimum value 10 seconds after standing. Initial recovery was attenuated for the slowest GS compared to the fastest GS and TSI remained lower for the duration of the 3-minute monitoring period. The presence of OH at 30 seconds did not substantially change the results, suggesting that the association between GS and TSI may be independent of peripheral recovery of SBP. A fully adjusted model with a range of covariates (eg, medications and standing speed) suggested that some of the GS effect was explained by clinical and demographic factors; however, differences remained between GS quartiles after adjustment.

The cardiovascular and cerebrovascular response to standing is an important biomarker in older adults, one which is elicited up to 65 times a day in the average adult (37,38). Previous studies have shown associations between OH or SBP recovery and slower GS, and the present study showed a similar relationship for central hemodynamic (9,18). It has been hypothesized that poor hemodynamic response to standing could be manifested in mobility tests by inability to quickly redistribute pooling blood in peripheral vessels (18). It is also plausible that longer-term changes to the structure and function of the brain (eg, atrophy or development of white matter hyperintensities), in response to chronic deficits in cerebral perfusion, could lead to poorer physical functioning (19,39). This is supported by the findings here (ie, impaired stabilization of TSI despite similar minimum drop) along with recent work using TCD showing impaired cerebral autoregulation, cerebrovascular reactivity, and neurovascular coupling in slower older adults (cross-sectionally) and in those with longitudinally declining GS (25,26).

The large and well-characterized sample was a strength of this study. The continuous measurement of cerebral oxygenation at relatively high resolution was also advantageous, allowing for examination of the immediate changes in TSI after standing.

This is particularly important given that the largest differences from baseline occur within 10 seconds of standing. Despite these strengths, there are some important limitations. The direction of the association was unclear from the cross-sectional analysis presented here; future longitudinal studies could help to address this by including another timepoint for NIRS and GS assessment. Several aspects of the cardiovascular and cerebrovascular reaction to standing (eg, blood hemoglobin, natremia, partial pressure of CO_2) remained unmeasured in this study due to feasibility. There was a relatively high rate of missingness in NIRS measurements due to technical problems and some participants being unable to perform the active stand. This may limit generalization of these findings to samples outside the GS range studied here. This study used a NIRS device to track cerebral oxygenation due to its ease of use, low cost, and portability. Although measurements can be influenced by the assumption of homogenous tissue, extracerebral influences are minimized by the use of spatially resolved spectroscopy and data with a lack of agreement between the 3 sensors can be excluded (32). It should also be noted that cerebral oxygenation in the frontal lobe region studied here may not be generalizable to other brain regions. Previous works in this area have used TCD ultrasound, which is a validated method to determine blood flow velocity in the middle cerebral artery as a proxy for CBF during postural transition. However, there are significant barriers to the use of TCD ultrasound clinically including a susceptibility to motion artifacts, the need for technical training, and absence of a temporal acoustic window in up to 35% of individuals (depending on sample characteristics) (40,41).

This study suggests that NIRS during active stand may be a useful clinical tool for tracking cerebral hemodynamics in older adults. Issues with the widespread use of TCD ultrasound hamper its clinical uptake and future studies directly comparing the 2 methods in the older population are warranted. Further work linking individual profiles of peripheral (eg, SBP, heart rate) and central hemodynamics (eg, TSI) may also provide clinical utility in identifying poor cerebral regulation. Future research involving interventions in older adults aimed at improving GS (eg, exercise programs) may also provide insights into the direction of causation between impaired orthostatic hemodynamics and slower GS if the methodology described here was implemented before and after intervention.

Conclusion

This study reported evidence for impairment in the recovery profile of cerebral oxygenation after standing in community-dwelling older adults with lower GS. This difference was present despite a similar magnitude of decrease after standing for faster and slower GS. Future work assessing NIRS as a clinical tool for monitoring the relationship between GS and cerebral regulation is warranted.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

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Author Contributions

Study concept and design: J.D.O.C., M.D.L.O.C., S.P.K., L.N., O.A.D., and R.A.K. Acquisition of data: L.N., O.A.D., and R.A.K. Analysis and interpretation of data: J.D.O.C., M.D.L.O.C., S.P.K., L.N., O.A.D., and R.A.K. Drafting of the manuscript: J.D.O.C. and M.D.L.O.C. Critical revision of the manuscript for important intellectual content: J.D.O.C., M.D.L.O.C., S.P.K., L.N., O.A.D., and R.A.K.

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