Impact of Standing Speed on the Peripheral and Central Hemodynamic Response to Orthostasis

Evidence From the Irish Longitudinal Study on Ageing

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Abstract—Assessment of the cerebrovascular and cardiovascular response to standing has prognostic value for a range of outcomes in the older adult population. Studies generally attempt to control for standing speed differences by asking participants to stand in a specified time but little is known about the range of transition times observed. This study aimed to characterize how standing speed associates with cardiovascular and cerebrovascular measures following transition from supine to standing. Continuous cerebral oxygenation, heart rate, systolic and diastolic blood pressure were monitored for 3 minutes after transitioning from supine to standing. An algorithm was used to calculate the time taken to transition from existing Finometer data (from the height correction unit). Linear mixed-effects models were used to assess the influence of transition time on each of the signals while adjusting for covariates. Transition time ranged from 2 to 27 s with 17% of participants taking >10 s to stand. Faster transition was associated with a more extreme decrease 10 s after standing but improved recovery at 20 s for cerebral oxygenation and blood pressure. Standing faster was associated with an elevated heart rate on initiation of stand and a quicker recovery 10 to 20 s after standing. The speed of transitioning from supine to standing position is associated with cardiovascular and cerebrovascular response in the early period after standing (<40 s). Care should be taken in the interpretation of findings which may be confounded by standing speed and statistical adjustment for standing time should be applied where appropriate. **(*Hypertension*. 2020;75:524-531. DOI: 10.1161/HYPERTENSIONAHA.119.14040.)** ● **Online Data Supplement**

Key Words: blood pressure ■ heart rate ■ hemodynamics ■ orthostatic hypotension

Assessment of the cerebrovascular and cardiovascular response to standing has prognostic value for a range of outcomes in the older adult population. In particular, orthostatic hypotension (OH; ie, drop in systolic blood pressure [SBP] of ≥20 mm Hg or a drop of ≥10 mm Hg in diastolic blood pressure [DBP] within 3 minutes of standing) is predictive of a wide variety of negative outcomes such as falls,[1,2] stroke,[3] cardiovascular disease,[4] physical health/frailty,[5–9] depression[10] as well as cardiovascular morbidity and mortality.[11] Heart rate (HR) recovery (10–20 s after standing) has also been identified as a strong marker of mortality risk.[12] A potential causal pathway for these associations implicates cerebral hypoperfusion; chronic exposure to which may lead to structural changes in the brain while acute, transient deficits may contribute to increased risk of syncope and falls.[13,14] Hypoperfusion can occur when cerebral autoregulation mechanisms, evolved to protect the brain from extreme pressures, fail to maintain cerebral tissue perfusion in the presence of low systemic pressure.[13] Direct quantification of cerebral hemodynamics, therefore, provides insights into the mechanisms underpinning these associations and is being increasingly adopted in research studies.[15–19] The cerebrovascular response to supine to standing transition has been examined using transcranial Doppler[20,21] and near-infrared spectroscopy (NIRS).[16,18] These techniques have shown cerebral blood flow or oxygenation differences in research participants with depression,[18] multiple system atrophy,[21] and between older and younger cohorts.[16]

Physiological studies in healthy young adults and older OH patients have shown blunted responses to sit-to-stand and active stand following controlled slow stand compared with a more rapid stand.[15,22] The range of standing speeds encountered when performing these tests under typical conditions is unclear. This is crucially important as mobility function is highly variable in older adults and strongly associated with future health outcomes,[23] and so may confound apparent physiological relationships between these outcomes and active stand responses. Additionally, quantification of speed of transition from supine to standing is important as it can directly support clinical decision-making given evidence that slower standing shows a relatively attenuated deficit in BP.[22] Studies generally attempt to control for standing speed by asking participants to stand in a specified time.[2,12,16–18,21,24]

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However, these instructions vary across studies and little is reported on adherence to protocol or the experimental range in transition time.

This work aimed to develop an automated process for measuring transition time using widely available continuous BP monitoring equipment and to characterize how standing speed associates with cardiovascular and cerebrovascular measures following transition from supine to standing. The hypothesis was that the speed of postural transition would influence the magnitude and timing of the blood pressure, HR, and cerebral oxygenation response to standing.

Methods

Availability of Data

The data collected for this study is of a sensitive nature, requests for access should be directed to The Irish Longitudinal study on Ageing, Lincoln Gate, Trinity College Dublin, Dublin 2, Ireland (Email: tilda@tcd.ie).

Sample

The TILDA (The Irish Longitudinal Study on Ageing) follows a sample of Irish adults aged 50 and over.[25] The project was granted ethical approval by Trinity College Dublin in 2009 to assess financial, social, and health circumstances of the cohort longitudinally.[25] Participants provided written, informed consent, and the study was designed to be compliant with the principles set out in the Declaration of Helsinki.[25] This work will focus on data collected from participants (n=4309) who completed TILDA's health center assessment during the third wave of data collection (2014–2015). A research nurse recorded instances where a participant was unwilling or unable to perform the active stand. In addition, technical problems with equipment and signal processing were recorded. Overall numbers for technical problems, unable and unwilling are presented in Appendix (Figures S1 and S2 in the online-only Data Supplement). Additional exclusions included those participants reporting a doctor's diagnosis of Parkinsons (n=23) along with those who were under 50 years old at baseline (Wave 1).

Active Stand Protocol

Participants began the active stand test with the affixing of a digital photoplethysmograph to the middle finger of the left hand (Finometer MIDI device, Finapres Medical Systems BV, Amsterdam, the Netherlands), this arm was then placed in a sling (to discourage its use during transition). This resulted in the measurement site on the finger being roughly at heart level throughout. As previously described elsewhere, the height correction unit of the Finometer was used to correct for hydrostatic pressure difference (HPD) between the level of measurement (the finger) and the heart level.[26] The unit consists of 2 sensors, one of which is placed on the finger cuff while the other is attached to the arm cuff at the level of the heart. The sensors were held at the same height and calibrated (set to zero) before each participant performed the test. The pressure correction is not crucial here since the sling kept the finger at heart level; however, the vertical difference between the 2 sensors may still be used to detect movement. The Finometer outputted measures of SBP, DBP, HR, and HPD.

Cerebral oxygenation was tracked during the challenge using a NIRS device (Portalite; Artinis Medical Systems, Zetten, the Netherlands) which was fixed to the forehead (3 cm lateral and 3.5 cm superior to the nasion) in approximately the FP1 position of the 10 to 20 electrode system.[27] Each participant spent 10 minutes in a supine position before transitioning to a standing position and remaining still for 3 minutes while recording took place. The instruction given by the nurse was to stand as quick as possible and participants were verbally counted down from 5 s before the stand. Measurements were collected by a research nurse in a quiet room with temperature controlled between 21°C and 23°C. The NIRS device outputted tissue saturation index (TSI) at a rate of 50 Hz. The TSI measure is a ratio of oxygenated hemoglobin to the sum of oxygenated hemoglobin and deoxygenated hemoglobin.

Prevalence of sustained OH (a decrease of ≥20 mm Hg systolic or ≥10 mm Hg diastolic at all of 60, 70, 80, 90, 100, and 110 s timepoints after standing) and initial OH (a decrease of ≥40 mm Hg systolic or ≥20 mm Hg diastolic within the first 15 s after standing) were calculated. Definitions are in line with previous publications of normative data.[2,24]

Signal Processing

Signals for SBP, DBP, HR, TSI, and HPD were extracted using MATLAB (R2018a, TheMathWorks, Inc, MA). The signals were downsampled to 1 Hz and smoothed using an 11th order median filter followed by a 10-point moving average filter (with the exception of the hydrostatic pressure data which was downsampled but not filtered).

Covariate Measurements

Timed-up-and-go (time taken to rise from a seated position, walk 3 m, turn and resume the seated position) was measured using a stopwatch and an armless chair with seat height of 46 cm. Gait speed was assessed using a 4.88 m walkway (GAITRite; CIR Systems Inc, New York, NY) with a 2.5 m section before (to allow for acceleration) and a 2.5 m section after (to allow for deceleration).[28] Grip strength was assessed using a hand-held hydraulic dynamometer (Fabrication Enterprises Inc White Plains, NY) with the elbow against the torso at a 90-degree angle. A Montreal cognitive assessment was also administered for each participant.

Transition Time Identification

The HPD value between the cuff on the finger and the heart remains relatively stable when supine and when standing still (Figure 1, left). There is, however, a rapid change in this value when the participant is transitioning as it is directly proportional to the height difference between the finger cuff and the sensor on the arm cuff. To identify the time to transition from supine to standing, the signal was differentiated with respect to time (Figure 1, right) and a change of 2 mm Hg/s was identified as the cut off for having started and stopped the transition (equivalent to ≈3 cm/s height change speed). The start of the transition was identified if the HPD signal crossed the threshold of 2 mm Hg/s having not done so for the previous 4 s. Similarly, the end of the transition was identified when HPD in the subsequent 4 s did not exceed the threshold. The time between start and end was defined as transition time in seconds.

Statistical Analysis

Baselines for SBP, DBP, HR, and TSI were defined as each participant's average value between 60 to 30 s before standing. Signals were then expressed as the absolute change from the baseline. Similar to previous work on SBP and HR, analysis of the effect of transition time on each of the 4 signals (SBP, DBP, HR, and TSI) was performed by fitting linear splines to the signals with knots located at 10, 20, 30, and 40 s.[7,29] This process produced parameters representing the slope of a straight line between 0 to 10, 10 to 20, 20 to 30, 30 to 40, and 40 to 180 s. These slopes were then interpreted as recovery or decline (per second) of the signal on standing. The spline parameters were incorporated into a mixed-effects model as explanatory variables using Stata (v15.1, StataCorp, TX). In each case, the terms were part of an interaction with all covariates (ie, the covariate effect was expected to differ for each time phase). The models allowed for a random intercept term for each participant. To account for values at adjacent timepoints being more correlated, residual errors were assumed to follow an autoregressive process of order 1. For each signal, 2 models were fitted: one adjusting for age and sex effects only and another adjusting for age, sex, weight, height, grip strength, timed-up-and-go, self-reported cardiac conditions, medications, Montreal cognitive assessment score, and depression. The purpose of including the covariates in model 2 was to adjust for potential confounding

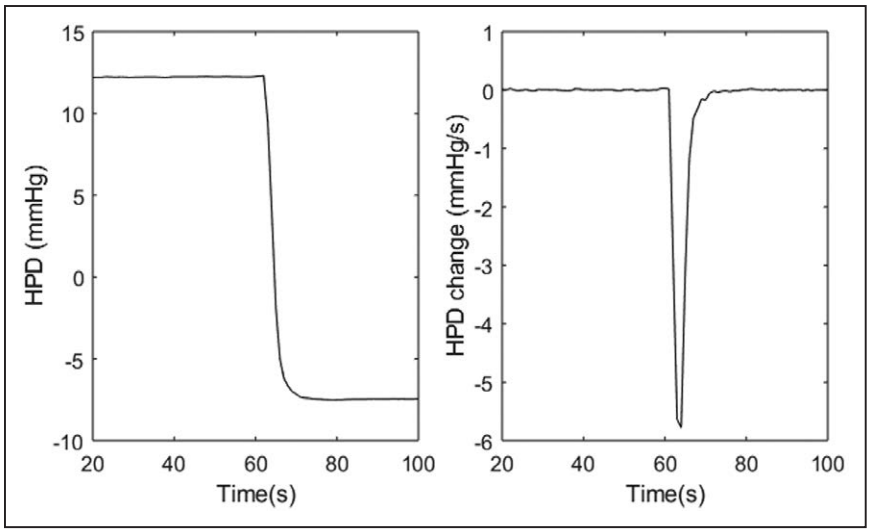

Figure 1. Mean (across participants) of hydrostatic pressure difference (HPD) signal (**left**) showing rapid change during transition from supine to standing. Mean rate of change of the HPD (mm Hg/s) signal showing a spike during transition flanked by stable regions with little movement (**right**).

(particularly in the later recovery from 40 to 180 s) due to a relationship between transition time and general health measures (which may be related to recovery). Cardiac conditions was a categorical variable, given a value of 1 if the participant reported a doctor's diagnosis of at least one of following cardiac conditions: heart attack, heart failure, angina, hypertension, stroke, diabetes mellitus, transient ischemic attack, or heart murmur. Medications were adjusted for based on the Anatomical Therapeutic Chemical classification for antidepressants (Anatomical Therapeutic Chemical N06A) and antihypertensives (Anatomical Therapeutic Chemical C02 C03 C07 C08 C09). Depression was assessed using the 8-item Centre of Epidemiological Studies-Depression scale.[18] These models were used to produce estimates from the fixed portion for transition times of 5, 10, 15, and 20 s adjusting for covariates.

Results

Data were available from 2593 participants for NIRS and 3164 participants for Finometer. Details for exclusions based on the categories of unable, unwilling, and technical problems are reported in the Appendix (Figures S1 and S2). Almost all participants (all but 2) with valid NIRS data also had Finometer data, the sample characteristics were, therefore, very similar (Table). Prevalence of initial OH was 34.7% while a sustained deficit was less common; sustained OH had a prevalence of 3.8%.

The time to transition from a supine to standing position had a range of 2 to 27 s with a considerable portion (17%) taking >10 s to complete the transition (Figure 2). The median standing time was 7 s. Appendix, Table S1 shows correlations between the sample characteristics and transition speed. Model parameters related to transition time are presented in Appendix, Table S2. Conditional means from the mixed-effects models adjusting for age and sex only showed considerable differences associated with the time taken to transition from supine to standing (Figure 3).

The largest differences (change from baseline) in the TSI signal (Figure 3) were at the 10 s time point (where increasing transition time from 5 to 20 s was associated with increased TSI from −1.82% [95% CI=−1.91 to −1.74] to −1.07% [95% CI=−1.38 to −0.76]) and at the 20 s time point (where increasing stand time from 5 to 20 s was linked to a decrease in TSI from −0.21% [95% CI=−0.30 to −0.13] to −0.77% [95% CI=−1.07 to −0.46]).

The major SBP and DBP differences associated with transition speed were also shortly after standing; 10 s after standing, the predicted changes in SBP and DBP for standing in 5 s were −26.43 mm Hg (95% CI=−27.08 to −25.79) and −16.42 mm Hg (95% CI=−16.75 to −16.10), respectively whereas a 20 s transition time predicted a change of −15.65 mm Hg (95% CI=−17.92 to −13.38) for SBP and −7.73 mm Hg (95% CI=−8.87 to −6.58) for DBP. Similar to TSI, this was reversed at 20 s after standing where a transition time of 5 s predicted a SBP change of −3.05 mm Hg (95% CI=−3.69 to −2.41) and a DBP change of −1.65 mm Hg (95% CI=−1.97 to −1.32) while the slower transition time of 20 s predicted values of −6.68 mm Hg (95% CI=−8.94 to −4.43) for SBP and −8.24 mm Hg (95% CI=−9.38 to −7.10) for DBP.

There was a difference in the 0 s (stand initiation) HR depending on transition time with a 5 s and 20 s stand time predicting a HR of 4.18 bpm (95% CI=3.91 to 4.45) and 1.04

Table. Sample Characteristics for NIRS and Finometer Measurements

Participant Characteristic	Finometer Group (n=3164)	NIRS Group (n=2593)
Age, y, mean (95% CI)	65.0 (64.7–65.2)	64.9 (64.6–65.2)
Females, % (n)	53.2 (1684/3164)	52.7 (1367/2593)
Weight, kg, mean±SD	78.4±15.4	78.5±15.5
Height, cm, mean±SD	166.1±9.2	166.2±9.2
One or more cardiac condition, % (n)	39.6 (1252/3164)	39.0 (1012/2593)
Antidepressant use, % (n)	7.2 (229/3164)	7.3 (188/2593)
Antihypertensive use % (n)	38.5 (1218/3164)	37.5 (972/2593)
Timed-up-and-go, s, mean±SD	8.5±2.1	8.5±2.1
Grip strength, kg, mean±SD	27.4±9.4	27.6±9.5
CES-D score, mean±SD	2.9±3.5	2.9±3.5
Transition time, s, mean±SD	7.3±3.0	7.3±2.9
MOCA score, mean±SD	26.0±3.1	26.0±3.0

The vast majority (all but 2 participants) in the NIRS group had Finometer data. CES-D indicates Centre of Epidemiological Studies-Depression; MOCA, Montreal cognitive assessment; and NIRS, near-infrared spectroscopy.

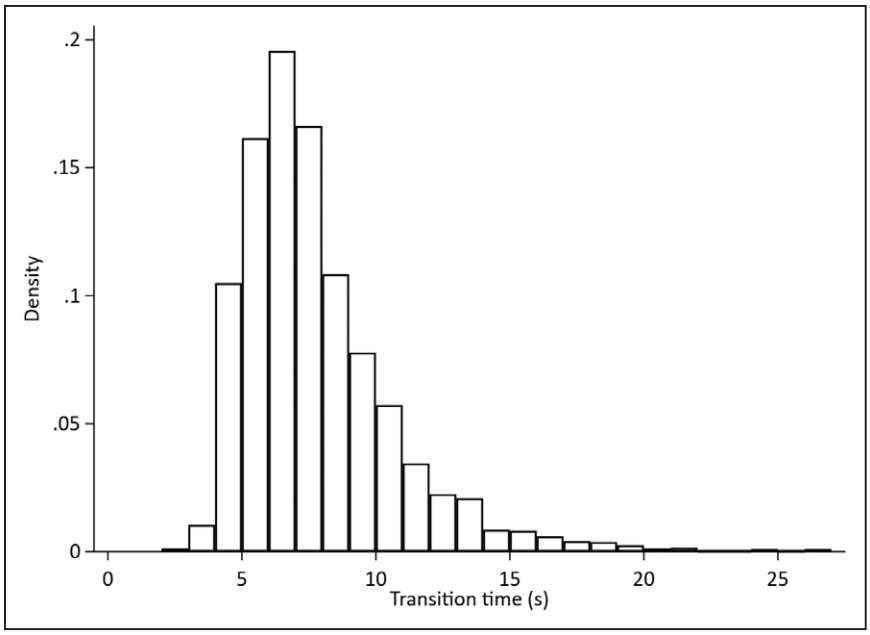

Figure 2. Histogram of transition times showing a variation between participants with the majority (83%) standing in under 10 s.

bpm (95% CI=0.09 to 2.00), respectively. There was also a transition time association with HR at the 20 s after standing with slower standers remaining elevated; the predicted value for a 20 s stand time was 12.34 bpm (95% CI=11.40 to 13.28) whereas a 5 s stand resulted in a value of 8.03 bpm (95% CI=7.76 to 8.30).

In general, the largest differences in cardiovascular and cerebrovascular response occurred in the early period after standing (<40 s). The trough for SBP and DBP was lower with a faster transition time, this was also reflected in TSI where the drop was less extreme for slower standers (Figure 3). In addition, the DBP trough occurred later for slow standers and was less pronounced (Figure 3). Distinct features of the HR response were present at the initiation of standing with faster standing increasing initial HR (Figure 3). Increased speed of standing was also associated with faster HR recovery in the 10 to 20 s phase. When other covariates were adjusted for (model 2), early stand differences were somewhat attenuated for TSI, SBP, and HR suggesting some of the effect is explained by the covariates whereas

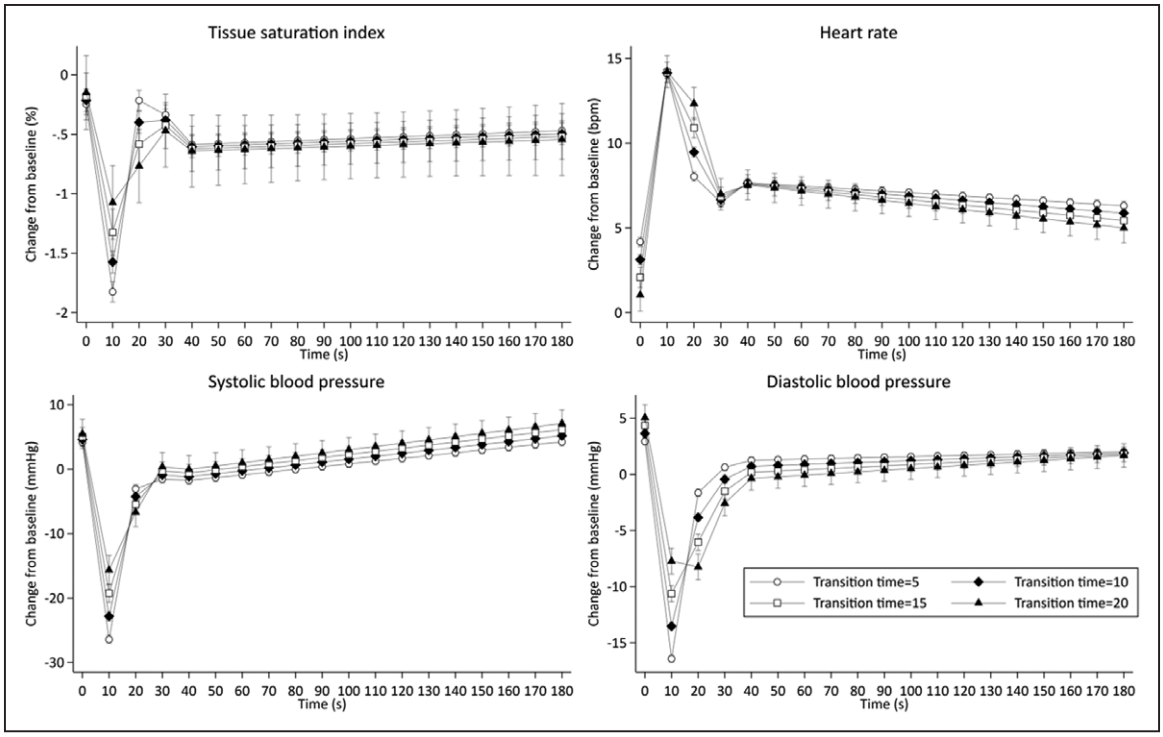

Figure 3. Conditional means and 95% CIs from the fixed portion of the mixed-effects model with transition time fixed at 5, 10, 15, and 20 s. All values are adjusted for age and sex. Since the baseline measure is calculated as the average of the signal between 60 s and 30 s before stand, the 0 s value on these graphs is often not 0%.

DBP remained relatively similar in comparison. Differences in the latter part of the stand (40–180 s) were considerably less influenced by transition time compared to changes in the early hemodynamic reaction.

Discussion

A large sample of older Irish adults was examined in this study with the purpose of assessing the effect of transition time on the cardiovascular and cerebrovascular response to orthostasis. A novel method to extract standing time from existing Finometer data was presented, and considerable variation in standing speed was observed. Transition speed was shown to be important in the early response (<40 s post standing) of both peripheral and central measures. Slower standers did not drop as much but remained low at 20 s for cerebral oxygenation and blood pressure. Standing faster was associated with an elevated HR on initiation of stand and a quicker recovery 10 to 20 s after standing.

In the older population, the active stand test has provided a useful and simple challenge to both the cardiovascular and cerebrovascular systems. Recent interest in the development of protocols for measurement of dynamic physiological resilience introduces a challenge in standardization (ie, ensuring the stressor is physiologically equivalent for all demographics).[30,31] The data herein suggest that the physiological stressor posed by the active stand differs based on the transition speed. This has implications both clinically and for research studies. The influence on the early response to standing suggests that transition time may be an important factor in initial OH, that is, a transient drop of >40 mm Hg and >20 mm Hg within the first 15 s of standing.[2] Transition time may partially explain previously reported lack of utility in predicting falls, younger age, and lower cardiovascular burden for those classified as having initial OH in TILDA.[2] Conversely, OH definitions based on later time points (eg, 40 s or 60–110 s after standing) have previously shown utility in predicting falls and are shown here to be less influenced by transition time.[2] Given the effects of transition times on each of the signals here, comparison of early recovery time points should be approached with care given that a time delay may be present. This could mean that the recovery phase for one group is compared with the lowest point for another group (eg, the DBP signal 20 s after standing; Figure 4).

This work provides a method which may be applied retrospectively if height correction sensor data has been retained. Since we would expect differences in standing speed in many research and clinical settings, adjustment is important. This data is also relevant for research studies seeking to assess connections between autonomic function and various outcome measures. Statistical adjustment for transition time may reveal important associations by controlling for the differing physiological challenge of a fast versus a slow stand. Equally, it may partially explain associations that were previously believed to reflect primary physiological mechanisms.

The data provided here is compatible with a recent study showing attenuated BP response to standing slowly, the mean measured time to transition in this study (7.3 s) was similar to the fast transition time of 7.1 s in their older group (mean age of 79.3 years).[22] The transition speed was slightly slower here than a younger cohort (mean age of 22 years; fast transition time of 6.0 s) described in a study assessing standing speed influences on cerebral oxygenation measurements.[15] Mol et al[15] did not find differences in cerebral oxygenation response based on the time taken to stand in the much younger cohort, although the sample size was relatively small and predominantly male (n=15, 12 male) and the 0 to 30 s phase was averaged for analysis. A cerebral oxygenation comparison between older and younger adults showed differences between the age groups consistent with those presented here for different transition times (ie, attenuated trough of longer duration) although the authors note that time to complete the active stand was constant at 3 s.[16] It should also be noted that the instructions given to the participant may influence the speed of stand (eg, stand as quickly as possible versus usual speed).

There are several mechanisms by which a faster stand could lead to differences in early cardiovascular and cerebrovascular response. Muscular effort when assuming a standing position (presumably increased in faster standers) causes an initial increase in HR due to an exercise reflex (due to motor signals from the brain and feedback from contracting muscles).[32,33] This may be the cause of the 0 s difference between transition times (Figure 4), suggesting some muscle activation before the stand was initiated. The largest difference in HR for slower standers at 20 s may be caused by decreased arterial baroreflex activation due to BP remaining low for slow standers at this point. Increased muscle activation during standing also compresses the vasculature in the lower limbs, increasing venous return, and cardiac output which would be expected to maintain BP were it not coupled with a large deficit in systemic vascular resistance. The drop in systemic vascular resistance can be attributed to several factors which may be mediated by the extent of muscle contraction in the lower limbs during standing, including rapid vasodilation of muscles in the lower limbs, pressure differential between arterial and venous systems, stimulation of cardiopulmonary receptors, and arterial baroreflex activation.[32] The association between cerebral oxygenation and supine-to-stand speed (ie, less pronounced drop in slower standers) is expected given the influence on SBP and DBP presents a lesser challenge to cerebral autoregulation. The shallower slope in recovery is likely caused by the postural transition lasting longer for slower standers and hence delaying recovery but may be caused by an association between transition time and poor cerebral autoregulation, particularly given that the fully adjusted model showed a comparatively improved recovery.

There are several strengths to this analysis. The sample size is very large and well characterized compared with other works in this area. Cerebral oxygenation, HR, and BP were assessed simultaneously, and standing time was estimated objectively using data which is available with commonly used BP monitoring equipment. There are also several relevant limitations to this work. Although the transition time is based on movement which can be detected by the height correction unit and magnitudes are in line with previous studies, the algorithm was not compared with other techniques for measuring

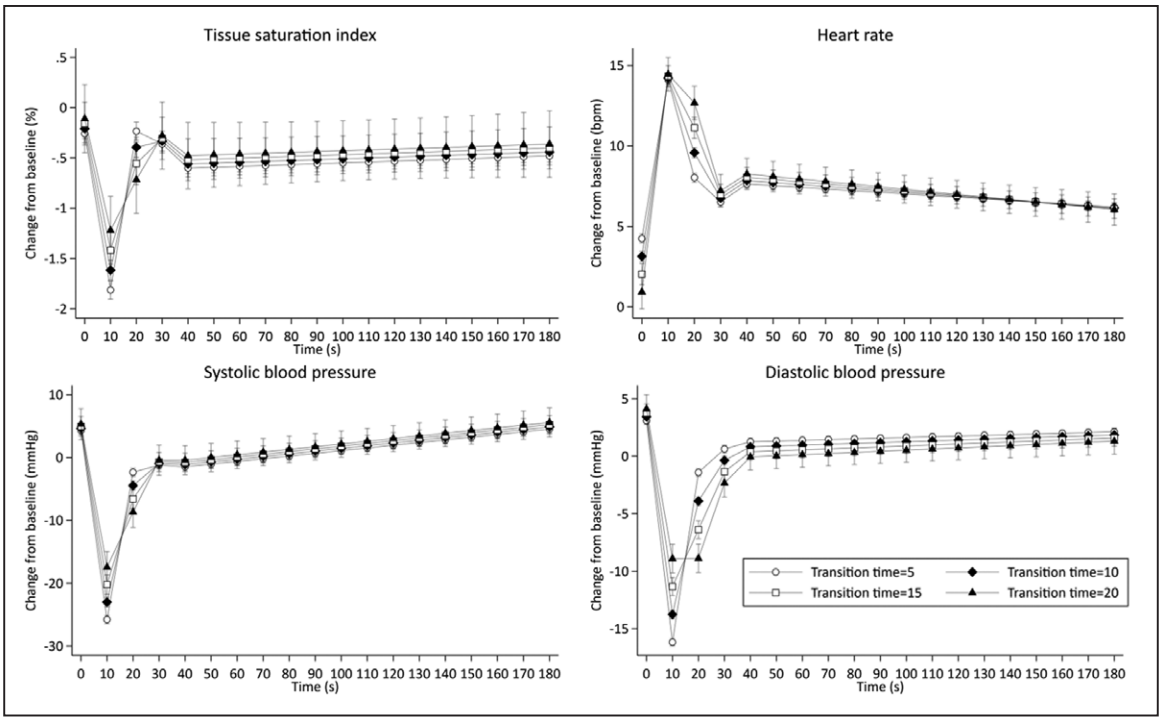

Figure 4. Conditional means and 95% CIs from the linear portion of the mixed-effects model with transition time fixed at 5, 10, 15, and 20 s. These predictions are adjusted age, sex, weight, height, grip strength, timed-up-and-go, self-reported cardiac conditions, medications, Montreal cognitive assessment score, and depression. Since the baseline measure is calculated as the average of the signal between 60 s and 30 s before stand, the 0 s value on these graphs is often not 0%.

transition time (eg, visually with a stopwatch). Additionally, the algorithm is designed to account for short pauses in the transition (ie, it checks that the threshold for movement has not been crossed for 4 consecutive seconds before identifying the end of transition), however, longer pauses could be possible in the clinic and in research studies. The sample consists of those study participants who attended the health center and may be biased towards healthier individuals with faster than average standing speed, this is particularly relevant to the application of this work in a clinical setting. Additionally, in the sample who attended the health assessment, the rate of missingness for both NIRS and Finometer data was considerable. Technical problems may be reasonably assumed to occur at random; however, those unable and unwilling to perform the active stand may be in poorer health which can bias the sample towards more mobile participants. Lastly, there are several important aspects to the orthostatic challenge including partial pressure of CO2, natriema and blood hemoglobin level which were unmeasured in the study due to feasibility.

Future work may involve application of time registration techniques and more complex analysis techniques allowing for temporal shifting. Separating the mobility aspect of the active stand test from the autonomic component may remain difficult in studies where physical function is the outcome (given that transition time is itself a measure of physical function). Future work should examine the relationship between the active stand and physical function while controlling for transition time as well as assessment with tests which do not have a mobility component such as the hypercapnic challenge administered during MRI (which necessitates as little movement as possible) or a head-up tilt test.[34,35] In addition, comparison of the algorithm presented here in conjunction with data from the height correction unit for calculating transition could be compared with other methods to assess accuracy and allow for transition time adjustment using other equipment (eg, stopwatch).

Conclusions

The speed of transitioning from supine to standing position is associated with the magnitude of both cardiovascular and cerebrovascular response to orthostasis. Specifically, slower standers did not decrease as much but remained low at 20 s for cerebral oxygenation and blood pressure. Standing faster was associated with an elevated HR on initiation of stand and a quicker recovery 10 to 20 s after standing. These results suggest that transition time may be an important aspect to the physiological response to standing, and future mechanistic studies should consider adjustment.

Perspectives

An increasing interest in measures of resilience in the older population has driven the development of protocols designed (eg, the active stand) to physiologically challenge the cardiovascular and cerebrovascular systems.[7,36] An understanding of methodological considerations can help to ensure important associations are not overlooked and improve understanding of the causal mechanisms underlying existing research findings.

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Disclosures

None.

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Novelty and Signifigance

What Is New?

- Assessment of the cerebrovascular and cardiovascular response to standing has shown prognostic value for a range of outcomes in the older adult population including falls, mortality and stroke. However, little is known about potential influence of standing speed on recovery of heart rate, blood pressure, and cerebral oxygenation on standing. In addition, this work provides a method to assess transition time with continuous blood pressure monitoring equipment, commonly used in clinic.

What Is Relevant?

- The results have important implications. Assessment of the cardiovascular and cerebrovascular response to standing should be interpreted with recourse to the speed of postural transition. In research studies, transition time differences could confound associations previously believed to be caused by direct physiological mechanisms and efforts should be made to adjust for the effect of standing speed if the study hypothesis warrants it.

Summary

This analysis of a large sample of older adults provides good evidence for effects of transition time on blood pressure and cerebral oxygenation recovery after standing. It offers potential to control for varied speed of stand in research studies as well as an important insight into the effect of transition speed on cardiovascular and cerebrovascular measures.