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Determinants of orthostatic cerebral oxygenation assessed using near-infrared spectroscopy

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A R T I C L E I N F O

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A B S T R A C T

Background: To understand the relationship between blood pressure changes during standing up and clinical outcome, cerebral oxygenation needs to be measured, which may be performed using near-infrared spectroscopy (NIRS). However, the role of potential determinants of NIRS-derived orthostatic cerebral oxygenation, i.e., age, sex, type of postural change (i.e., standing up from sitting versus supine position), blood pressure (BP) and baroreflex sensitivity (BRS) is still unknown and needed to better interpret findings from studies using orthostatic NIRS measurements.
Methods: 34 younger (median age 25 years, inter quartile range (IQR) 22–45) and 31 older adults (median age 77 years, IQR 72–81) underwent BP, BRS and NIRS measurements during standing up from sitting and supine position. Linear regression models were used to assess the potential determinant role of age, sex, type of postural change, BP and BRS in orthostatic cerebral oxygenation drop and recovery. Orthostatic cerebral oxygenation test-retest reliability was assessed using intra class correlations.
Results: Younger age, male sex and standing up from supine compared to sitting position were positively associated with cerebral oxygenation drop; older age and standing up from sitting compared to supine position were associated with higher cerebral oxygenation recovery. Test-retest reliability was highest (ICC > 0.83) during standing up from supine position.
Conclusion: Based on the findings of this study, age, sex and type of postural change are significant determinants of NIRS-derived orthostatic cerebral oxygenation and should be taken into account in the interpretation of NIRS measurements. In the design of new studies, standing up from supine position is preferable (higher reliability) over standing up from sitting position.

1. Introduction

Orthostatic hypotension, defined as a sustained systolic/diastolic blood pressure (BP) drop of more than 20/10 mmHg within 3 min after standing up (Freeman et al., 2011), is associated with poor clinical outcome, such as cognitive impairment, cardiovascular disease, falls and mortality (Iseli et al., 2019; Angelousi et al., 2014; Finucane et al., 2014; Mol et al., 2018a). Cerebral perfusion may explain this relationship (van Wijnen et al., 2018; van Lieshout et al., 2001). Cerebral perfusion is influenced by cerebral autoregulation (aiming to attenuate cerebral blood flow and cerebral oxygenation fluctuations during orthostatic BP drops) and may for clinical purposes be derived from near-infrared

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spectroscopy (NIRS) measurements. NIRS measurements reflect changes of cerebral oxygenated and deoxygenated hemoglobin concentrations in the brain, and are less dependent on operator training and temporal bone anatomy compared to transcranial Doppler measurements (Mol et al., 2020b; Mol et al., 2019a; Kainerstorfer et al., 2015; Mol et al., 2021). Orthostatic cerebral oxygenation changes measured with NIRS may depend on age, sex, type of postural change (i.e., standing up from sitting versus supine position), BP and baroreflex sensitivity (BRS, defined as change in inter beat interval divided by change in BP) (Mol et al., 2020b; Mol et al., 2018b; Mol et al., 2020a; Tzeng et al., 2010). However, the role of these potential determinants still needs to be addressed. These data are necessary to enable proper interpretation of NIRS-derived cerebral oxygenation results.

Previous studies were inconclusive on the association between age and orthostatic cerebral oxygenation changes measured with NIRS. Smaller (Kim et al., 2011), similar (Gatto et al., 2007) and larger (Mehagnoul-Schipper et al., 2000; Krakow et al., 2000) orthostatic cerebral oxygenation drops in older adults compared to younger adults have been reported. Though previous studies reported the association between type of postural change (Mol et al., 2019a) and BRS (Tzeng et al., 2010) and cerebral oxygenation drop in young adults, this has not been assessed in older adults in whom clinical consequences of orthostatic cerebral oxygenation drops most often occur (Goswami et al., 2017).

This study assessed role of age, sex, type of postural change, BP and BRS as potential determinants of orthostatic cerebral oxygenation changes measured with NIRS. It was hypothesized a) that age is positively associated with the size of orthostatic cerebral oxygenation drop due to impaired cerebral autoregulation function; b) no role of sex as a determinant of orthostatic cerebral oxygenation changes is anticipated; c) that cerebral oxygenation drop is larger during larger orthostatic challenges, i.e., after standing up from supine position compared to sitting position; d) that higher orthostatic BP drops are associated with higher cerebral oxygenation drops and lower recovery e) that a higher BRS is associated with lower orthostatic cerebral oxygenation changes as the baroreflex aims to warrant organ perfusion. Test-retest reliability was computed as an indication of the robustness of the cerebral oxygenation measurements to enable the assessment of the applicability of these measurements for research and clinical purposes.

2. Methods

2.1. Participants

Thirty-four younger adults aged below 62 years (median age 25 years, inter quartile range (IQR) 22–45 years) and 31 older adults aged above 70 years (median age 77 years, IQR 72–81) were recruited using oral and written advertisements. Younger adults were recruited within the Radboud University, the Netherlands, and included if they had no history of cardiovascular, respiratory or neurological disorders. Part of their orthostatic cerebral oxygenation data were also used in previous publications (Mol et al., 2020b; Mol et al., 2019 Feb). The older adults were recruited from the Nijmegen sport centers, tennis and swimming clubs, education programs for older adults, and by advertisements in a local newspaper. Older adults were included if they were community-dwelling, able to walk at least 250 m without the use of walking aids, independent for activities of daily living and not using antihypertensive medication. All participants signed informed consent and the study was performed in accordance with the Declaration of Helsinki and approved by the Ethics committee of the Faculty of Science of the Radboud University, Nijmegen.

2.2. Participant characteristics

Information about age, height, weight, handedness, alcohol use, smoking habits, morbidity and medication use was obtained from all participants. In the group of older adults, the short physical performance battery and the Montreal Cognitive Assessment were assessed as an indication of physical and cognitive performance.

2.3. Instrumentation

Beat-to-beat blood pressure and a 6-lead electrocardiogram was continuously measured (Finapres NOVA, Finapres Medical Systems, Amsterdam, The Netherlands; sampling frequency of 200 Hz). The participant's arm was kept in a sling in such a way that the blood pressure measurement cuff was kept at heart level. Any remaining hydrostatic pressure differences between finger and heart were corrected for using a height correction unit.

Cerebral oxygenation was measured bilaterally on the forehead using two Portalite NIRS systems (Artinis Medical Systems B.V., Elst, The Netherlands; sampling frequency of 50 Hz). The differential pathway factor (DPF) for the NIRS measurements expresses the ratio of the real distance light has to travel through the tissue relative to the shortest distance. The DPF was used to compute oxygenated and deoxygenated hemoglobin concentration changes (ΔO_2Hb and ΔHHb) (Scholkmann and Wolf, 2013), and computed according to the Scholkmann formula (Scholkmann and Wolf, 2013). DPF was set to 6.61 in the older group, as this value corresponds to the highest age (i.e., 50 years) for which the Scholkmann formula is validated (Scholkmann and Wolf, 2013). Tissue saturation index (TSI) was computed as: O_2Hb / (O_2Hb + HHb) using spatially resolved spectroscopy (Suzuki et al., 1999).

2.4. Protocol

Participants were asked to void urine before start of the experiment (9.30 am or 1.30 pm). A comfortable environment with a temperature of 20–22 degrees Celsius was pursued.

The protocol consisted of two types of postural changes: 1) sit to stand, i.e., sitting quietly for 5 min, standing up and stay in standing position for 3 min; 2) supine to stand, i.e., lying in supine position for 5 min, standing up and stay in standing position for 3 min. The sequence of the types of postural changes was randomized. For each type of postural change, two subsequent repeats were performed to enable the assessment of test-retest reliability.

2.5. Data quality assessment

The duration of standing up was computed based on tilt meter data. Repeats were discarded if standing up lasted longer than 10 s.

BP, electrocardiogram and NIRS signal quality was assessed based on the visibility of a heartbeat. Signals not showing a heartbeat for more than 10 s during baseline (i.e. the 60 s before testing), more than 10 s in the first minute after the start of the test or more than 20 s in minute two and three after the start of the test, were discarded.

2.6. Data analysis

Data analysis was performed using MATLAB R2019b (MathWorks, Natick, United States). The BP and cerebral oxygenation signals were resampled at a uniform sampling frequency of 10 Hz and filtered using a 5-s moving average filter. Left and right NIRS signals were averaged. In each signal, baseline was defined as the mean of the 60 s before standing up.

2.6.1. Blood pressure and cerebral oxygenation

For mean arterial BP, O_2Hb and TSI, the following parameters were computed: initial drop amplitude, initial recovery amplitude and time, and late recovery amplitude (illustrated in Fig. 1). Initial drop amplitude was defined as baseline minus the lowest value within 30 s after standing up; initial recovery amplitude as the value of the first peak after the initial drop minus baseline; initial recovery time as the time from the

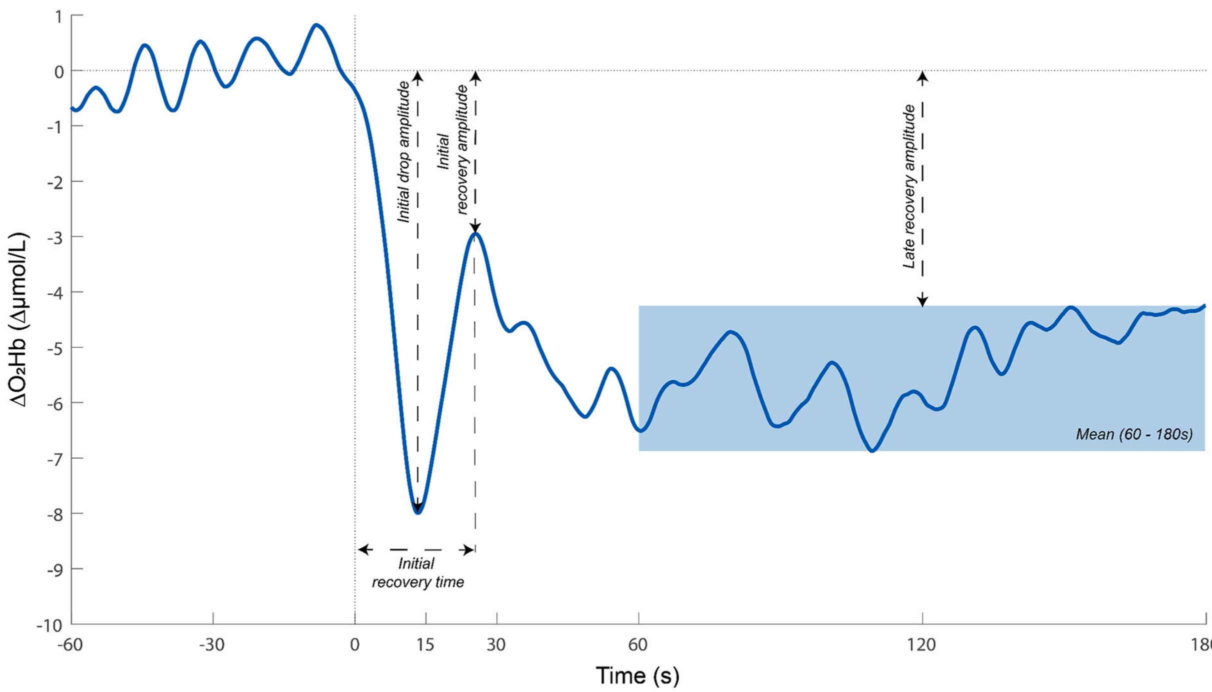

Fig. 1. Illustration of the computed parameters: initial drop amplitude, initial recovery amplitude and time, and late recovery amplitude using oxygenated hemoglobin (O_2Hb) signal. The same parameters were computed for blood pressure and tissue saturation index.

start of standing up to the first peak after the initial drop; Late recovery amplitude as the mean in the interval between 60 and 180 s after standing up minus baseline.

Initial orthostatic hypotension was defined as a SBP drop >40 mmHg and/or a DBP drop >20 mmHg within 15 s after both repeats of supine to stand. Orthostatic hypotension was defined as a mean SBP drop >20 mmHg and/or a DBP drop >10 mmHg between 15 and 60 s after both repeats of supine to stand.

2.6.2. Baroreflex sensitivity

BRS was defined as the orthostatic drop of the interval between subsequent R-peaks in the electrocardiogram (inter beat interval) divided by systolic BP drop (Mol et al., 2020b) (illustrated in Supplementary Fig. S1). BRS was assessed separately during both types of postural changes as supine to stand typically induces a larger BP drop compared to sit to stand, and previous studies reported BRS to behave non-linearly to different degrees of BP drop (Moslehpour et al., 2016; Kawada et al., 2019; Verma et al., 2017).

Furthermore, BRS was assessed during supine rest as a baseline measurement and computed as the gain of the transfer function between BP and inter beat interval in the frequency range between 0.05 and 0.15 Hz (Lagro et al., 2013; Robbe et al., 1987).

Apart from BRS, heart rate increase in the first 30 s after standing up was computed as an indication of baroreflex activity.

2.7. Statistical analysis

All statistical analysis was performed using the statistics toolbox of MATLAB R2019b (MathWorks, Natick, United States). Normally distributed variables were reported using mean and standard deviation (SD); non-normally distributed variables using median and inter quartile range (IQR).

Linear multiple regression models were used with ΔO_2Hb and ΔTSI drop and recovery parameters as dependent variables. Independent variables used were: mean arterial BP, BRS, age (dichotomous, younger vs older adults), sex, type of postural change. The effect of mean arterial BP and BRS without age, sex and type of postural change was assessed in separate models. A detailed description of the used models is provided in Supplementary file S1. Models were constructed using both normalized and non-normalized independent variables, to assess the determinant strengths relative to each other as well as their absolute strengths. A separate analysis using heart rate increase instead of BRS was performed to discover baroreflex activity effects on cerebral oxygenation independent of BP drop.

Calculation of the required sample size was performed using the G*Power software (Universität Kiel, Germany, Version 3.1.9.7) for Linear multiple regression (settings: effect size $f^2 = 0.2$ (medium), $\alpha = 0.05$, $1\text{-}\beta = 0.95$, number of predictors = 5), resulting in a required minimum of 68 observations. As we included 65 participants and used two observations per participant (one for each type of postural change), we collected a number of observations approximately twice the minimum required sample size.

The test-retest reliability of the aforementioned NIRS-derived cerebral oxygenation parameters (O_2Hb and TSI) during two different repeats of the same postural change was expressed using two-way mixed intra class correlations (ICC). ICC scores between 0 and 0.40, 0.40–0.59, 0.60–0.74 and 0.75–1 were regarded as poor, fair, good and excellent, respectively (Cicchetti, 1994). Statistical significance was set at 0.05.

3. Results

Table 1 lists the participant characteristics. The median age of the participants was 25 years (IQR = 22–45) in the younger group (29.4% female) and 77 years (IQR = 72–81) in the older group (54.9% female). The prevalence of initial orthostatic hypotension was 32.4% and 32.3% in younger and older adults, respectively. Prevalence of orthostatic hypotension was 2.9% and 12.9%, respectively.

After data quality assessment, cerebral oxygenation data during sit to stand was available in 31/34 younger adults and 30/31 older adults; and during supine to stand in 28/34 younger adults and 28/31 older adults. BP and heart rate (HR) data during sit to stand was available in 31/34 younger adults and 30/31 older adults; during supine to stand in 28/34 younger adults and 29/31 older adults.

Table 1
Participant characteristics, stratified by age groups.

Characteristic	Younger adults ($n = 34$)	Older adults ($n = 31$)
Age, years, median [IQR]	25 [22–45]	77 [72–81]
Female, n (%)	10 (29.4)	17 (54.9)
Height, m, median [IQR]	1.80 [1.72–1.85]	1.69 [1.64–1.77]
Weight, kg, median [IQR]	70.5 [65.8–75.0]	74.0 [65.0–83.0]
Current smoking, n (%)	1 (2.9)	0 (0.0)
Medication use, yes, n (%)	8 (23.5)	7 (22.5)
Cardiovascular, yes, n (%)	2 (5.9)	0 (0)
Psychotropic, yes, n (%)	3 (8.8)	1 (3.2)
SPPB score, median [IQR]	NA	11 [11–12]
MOCA score, median [IQR]	NA	26 [25–28]
Resting HR, bpm, mean (SD)	63.1 (10.4)	69.5 (9.3)
Resting SBP, mmHg, median [IQR] (Finapres)	122 [116–130]	152 [142–174]
Resting SBP, mmHg, median [IQR] (smm)	128 [122–130]	139 [126–155]
Resting DBP, mmHg, median [IQR] (Finapres)	72 [64–82]	83 [75–92]
Resting DBP, mmHg, median [IQR] (smm)	79 [74–84]	82 [74–88]
Resting PP, mmHg, median [IQR] (Finapres)	50 [45–58]	72 [60–80]
Resting PP, mmHg, median [IQR] (smm)	49 [44–52]	56 [52–67]
Initial orthostatic hypotension, n (%)[a]	11 (32.4)	10 (32.3)
Orthostatic hypotension, n (%)[b]	1 (2.9)	4 (12.9)

Resting HR, SBP, DBP and PP were measured using a sphygmomanometer in sitting position. IQR: interquartile range; SD: standard deviation; SPPB: Short Physical Performance Battery; HR: Heart rate; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP pulse pressure; smm: sphygmomanometer; NA: not available.

[a] Defined as a SBP drop >40 mmHg and/or a DBP drop >20 mmHg within 15 s after both repeats of supine to stand.

[b] Defined as a mean SBP drop >20 mmHg and/or a DBP drop >10 mmHg between 15 and 60 s after both repeats of supine to stand.

3.1. Signal and BRS characteristics

Fig. 2 shows the mean BP, HR and cerebral oxygenation course during standing up in younger and older adults. During both types of postural changes, BP and cerebral oxygenation signals showed an initial drop and recovery (< 30 s) while HR showed an increase in this interval. The BP, HR and cerebral oxygenation signals reached steady state between 60 and 120 s. Drop and recovery of BP and cerebral oxygenation in younger and older adults (mean, IQR and individual subject data) are shown in Fig. 3 (supine to stand) and supplementary Fig. 2 (sit to stand). Median initial systolic BP drop was 31 (IQR = 23–40) mmHg and 42 (IQR 33–52) mmHg in younger and older adults respectively. Most individuals recovered to the resting baseline BP value and all individuals recovered substantially relative to the lowest BP during the initial drop. Fig. 4 shows BRS in younger and older adults. Medians and IQR are displayed as well as individual subject data. BRS assessed during sit to stand transitions was attenuated in older compared to younger adults (9.8 and 4.5 ms/mmHg, respectively, $p < 0.001$). BRS during supine to stand transitions was 12.0 and 4.2 ms/mmHg in younger and older adults, respectively ($p < 0.001$). BRS was similarly attenuated during supine rest in older compared to younger adults ($p < 0.001$).

3.2. Determinants of NIRS-derived orthostatic cerebral oxygenation changes

Fig. 5 shows the results of linear regression modeling (normalized determinants) and Table 2 lists the regression coefficients (non-normalized determinants). Older age was significantly associated with a smaller initial O_2Hb drop amplitude and a larger late O_2Hb and initial and late TSI recovery amplitude. Sex was a significant determinant of initial O_2Hb drop amplitude, female sex showing a smaller initial O_2Hb drop amplitude. However, this determinant effect of sex was not present for TSI. Type of postural change was a significant determinant for initial O_2Hb drop amplitude and initial and late recovery amplitude. Supine to stand resulted in larger oxygenation drops and lower recovery compared to sit to stand. This effect was observed for O_2Hb, not for TSI. Blood pressure was a significantly positive determinant of TSI initial recovery time, though not for the other outcomes. BRS was associated with neither cerebral oxygenation drop nor recovery. After exclusion of three participants smoking or using cardiovascular medication (all from younger age group), age became a significantly positive determinant of O_2Hb initial recovery time (Supplementary Table 1).

Supplementary Table 2 shows the results of the analysis using HR increase instead of BRS as potential determinant. Compared to BRS in the main analysis, HR increase additionally was a determinant of TSI initial recovery time.

Results from models with BP and BRS, without age, sex and type of postural change, are shown in Supplementary Fig. 3. In contrast to the full model, both BP and BRS were positive determinants of initial O_2Hb drop amplitude, but not of O_2Hb recovery.

3.3. Test-retest reliability

Table 3 lists the test-retest reliability (ICC) of NIRS-derived orthostatic cerebral oxygenation parameters. ICCs ranged between 0.14 and 0.99 (initial drop amplitude), −0.04–0.91 (initial recovery amplitude), −0.07–0.49 (initial recovery time) and 0.14–0.99 (late recovery amplitude). Test-retest reliability was overall higher for supine to stand compared to sit to stand and O_2Hb compared to TSI.

4. Discussion

In this study in 34 younger and 31 older adults assessing potential determinants of orthostatic cerebral oxygenation measured with near-infrared spectroscopy (NIRS), younger age, male sex and supine to stand rather than sit to stand were found to be significantly posivitve determinants of oxygenated hemoglobin concentration (O_2Hb) drop amplitude and negative determinants of O_2Hb recovery amplitude. Blood pressure (BP) and baroreflex sensitivity (BRS) were not significant determinants of O_2Hb drop or recovery. Older age and BP were significantly positive determinants of tissue saturation index (TSI) late recovery amplitude and initial recovery time, respectively, but the other determinants were not significant for TSI drop or recovery. Test-retest reliability of orthostatic cerebral oxygenation parameters expressed through intra class correlations (ICCs) were found to be excellent for O_2Hb drop and recovery amplitude parameters assessed during supine to stand, but lower for initial recovery time, for TSI parameters and drop and recovery parameters assessed during sit to stand.

4.1. Determinants of orthostatic cerebral oxygenation

Age was a negative and positive determinant of orthostatic cerebral oxygenation drop and recovery amplitude, respectively, which was not in line with the hypothesis. The present finding may indicate that younger adult brains tolerate larger drops in cerebral oxygenation compared to older adult brains as they typically have a higher baseline cerebral blood flow and cerebral oxygenation (Oudegeest-Sander et al., 2014; Stefanidis et al., 2019). Older adults may consequently be more vulnerable for drops in cerebral blood flow and cerebral oxygenation, requiring a larger compensating role of cerebral autoregulation. The results of the present study suggest that cerebral autoregulation in older adults is able to limit the magnitude of cerebral oxygenation drop, which is in line with a recent study reporting that cerebral autoregulation function in older adults is not lower compared to younger adults (Claassen et al., 2021). Alternatively, the relatively high arterial and venous compliance in younger adults may partly explain the results as this facilitates the pooling of blood in the legs, orthostatic BP drop and

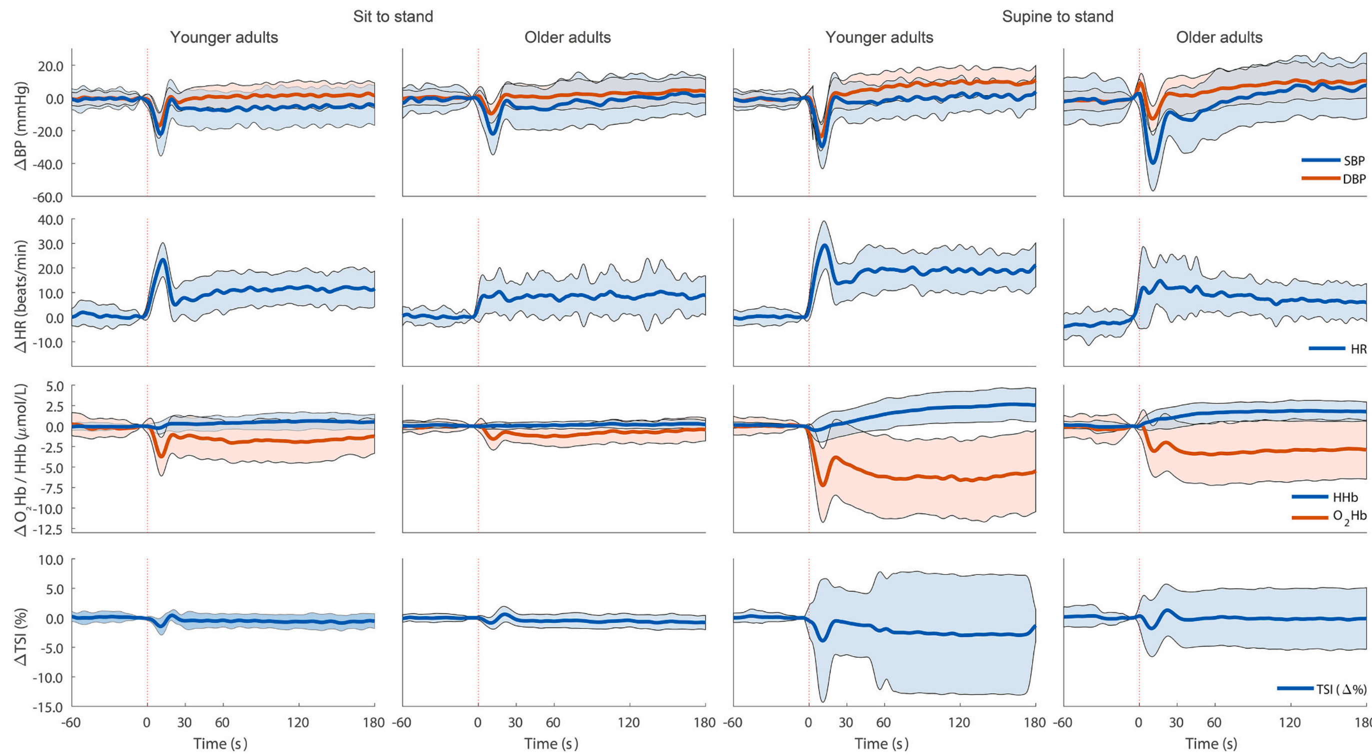

Fig. 2. Blood pressure (BP), heart rate (HR) and cerebral oxygenation measured using near infrared spectroscopy (NIRS) during sit to stand and supine to stand maneuvers in younger and older adults. All signals are unfiltered and baseline (mean of 60 s before standing up) is subtracted. The red vertical line indicates the onset of standing up. The shaded areas indicate the standard deviation. SBP: systolic blood pressure; DBP: diastolic blood pressure; O_2Hb: oxygenated hemoglobin; HHb: deoxygenated hemoglobin; TSI: tissue saturation index. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

potentially cerebral oxygenation (Gardner and Parker, 2010; Zachrisson et al., 2011; Olsen and Länne, 1998). Thirdly, differences in orthostatic expiratory CO_2 concentration between the age groups cannot be excluded, which may have affected cerebral autoregualtion and oxygenation (Hughson et al., 2001; Elting et al., 2018).

In contrast to our hypothesis, female sex was a negative determinant of initial O_2Hb drop amplitude. Sex was not significantly associated with any of the other O_2Hb and TSI drop and recovery parameters. A previous study also did not find sex differences between TSI drop during lower body negative pressure, which is in line with the present results, but did not assess O_2Hb differences (Rosenberg et al., 2021). The significant role of sex in O_2Hb initial drop amplitude found in the present study may suggest a higher cerebral autoregulation activity immediately after standing up in females, attenuating the initial orthostatic cerebral oxygenation drop. However, this is hypothetical and remains to be proven. The finding that sex was not a significant determinant of O_2Hb or TSI initial and late recovery is in line with a previous report of similar cerebral dynamic autoregulation activity in lower frequencies (i.e., during slower BP changes) in males and females (Burma et al., 2020).

The finding that type of postural change is an important determinant of cerebral oxygenation drop and recovery amplitude after standing up (larger drop and lower recovery after supine to stand compared to sit to stand) is in line with our hypothesis and seems to reflect the magnitude of the orthostatic challenge and the consequent pooling of blood in the legs. This is also suggested by the larger BP drop after supine to stand in both younger and older adults.

Apart from initial TSI recovery time, BP played no significant role in any of the O_2Hb or TSI drop or recovery parameters. However, removal of age, sex and postural change from the models showed that BP is a positive determinant of initial O_2Hb drop amplitude. Age, sex and postural change may hence have similar explanatory value as BP and BP may be an intermediate in the determinant role of age, sex and postural change in initial O_2Hb drop amplitude. Cerebral autoregulation activity may explain the absence of significant role of BP in cerebral oxygention recovery (except for TSI initial recovery time), as cerebral autoregulation aims to attenuate any BP effects on the cerebral circulation.

In contrast to our hypothesis, BRS was a significantly positive determinant of initial O_2Hb drop amplitude in the model without age, sex and type of postural change, and was not significantly associated with any cerebral oxygenation outcome when these factors were included. This may be due to the BRS parameter used in this study, which quantifies the decrease in inter beat interval, but not the increase in peripheral resistance, both of which are part of the physiological baroreflex. In the studied population, the peripheral resistance increase may have prevailed over decrease of inter beat interval, causing a decrease rather than an increase in cardiac output and cerebral perfusion (Skytioti et al., 2019; Skytioti et al., 2016). Further studies should therefore aim to measure both components of the baroreflex, e.g., by measuring peripheral resistance and/or muscle sympathetic nerve activity (Hart et al., 2010).

Factors significantly determining orthostatic O_2Hb and TSI drop and recovery were not identical. This may be partly due to the fact that O_2Hb and TSI represent a different physiological quantity, i.e., change in oxygenated hemoglobin concentration and oxygenated hemoglobin concentration relative to total hemoglobin concentration, respectively. TSI is therefore also dependent on deoxygenated hemoglobin. Further explanations can be sought in the additional assumptions needed to compute TSI compared to O_2Hb, such as the assumption of homogeneity of brain tissue (Murkin and Arango, 2009a; Yoshitani et al., 2007), which may be incorrect in some cases. Larger skull thickness was also reported to have relatively large negative impact on the fidelity of TSI measurements (Murkin and Arango, 2009b), which in the present study may be reflected by the low test-retest reliability of TSI compared to O_2Hb (discussed below).

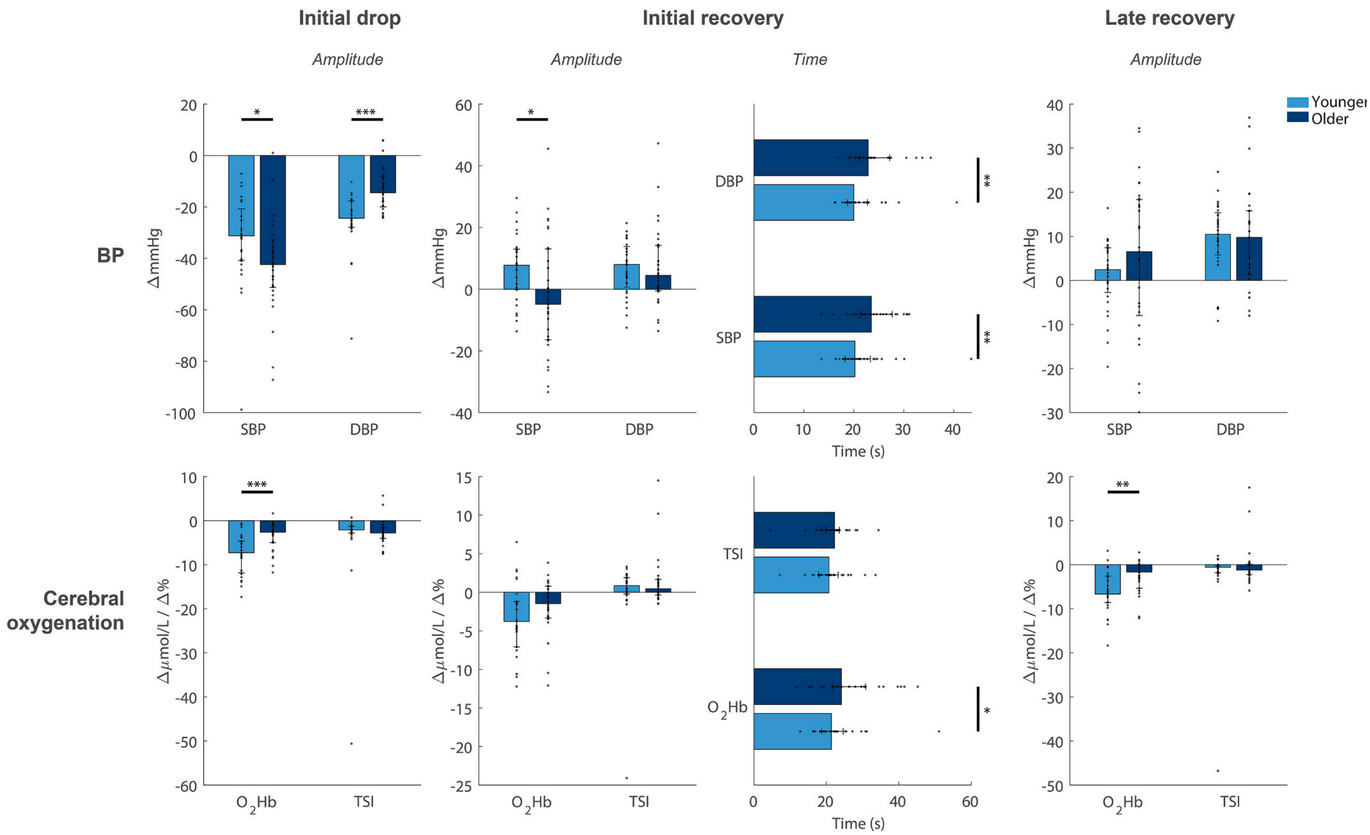

Fig. 3. Initial drop and initial and late recovery of blood pressure (top panels) and cerebral oxygenation (bottom panels) after supine to stand in younger and older adults. The error bars indicate the inter quartile range and dots the separate data points. The stars indicate statistically significant differences between younger and older adults as tested with the Mann Whitney U test (one, two and three stars indicating $p < 0.05$, < 0.01, and < 0.001, respectively). Initial BP and cerebral oxygenation drop below baseline is displayed negative. SBP: systolic blood pressure; DBP: diastolic blood pressure; O_2Hb: oxygenated hemoglobin; TSI: tissue saturation index.

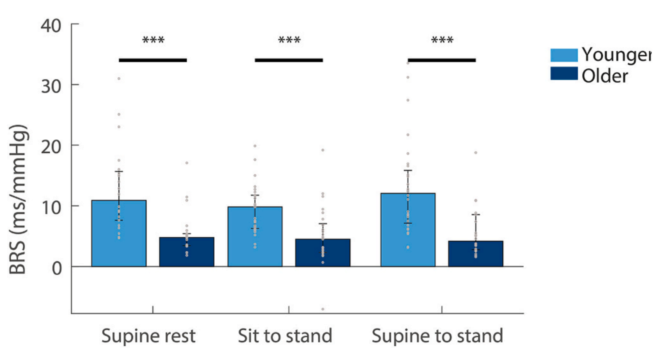

Fig. 4. Baroreflex sensitivity (BRS) after standing up and during supine rest in younger and older adults. Error bars indicate the inter quartile range. Dots indicate data points corresponding to individual participants. BRS was attenuated in older compared to younger adults during both types of postural change as well as during supine rest.

BP drop and consequent cerebral oxygenation drop in some individuals was considerable, which is in line with a large previous population study (Finucane et al., 2014). However, the BP drops may have been overestimated by the continuous BP monitor in some individuals as resting baseline BP measured using continuous BP monitoring was also higher compared to sphygmomanometer BP measurements (Table 1). The short duration of these low BP and cerebral oxygenation values (Fig. 1) may explain the absence of clinical symptoms in most individuals. Most individuals recovered to the resting baseline BP value and all individuals recovered substantially relative to the lowest BP during the initial drop.

4.2. Test-retest reliability

The test-retest reliability results indicate that robust orthostatic cerebral oxygenation measurements can be obtained after postural change using NIRS. To increase test-retest reliability, supine to stand is to be preferred over sit to stand. Amplitude parameters were found to be more reliable than the investigated time parameter, indicating that assessment of amplitude parameters is preferable in further studies and that results of the present study on the time parameter should be interpreted cautiously.

Overall, the test-retest reliability of the TSI parameters were lower compared to the O_2Hb parameters, suggesting O_2Hb to be the preferred signal when measuring orthostatic cerebral oxygenation drop and recovery. The results on determinants for orthostatic TSI drop and recovery should also be interpreted with caution due to the relatively low test-retest reliability of TSI parameters.

4.3. Methodological considerations

4.3.1. Experimental protocol

The duration of supine rest before standing up was relatively short (i.e, 5 min). However, cardiovascular stabilization may be assumed to complete within this period as reported by a previous study (Finucane et al., 2019).

4.3.2. Included population

In this study, we selected patients based on function level rather than

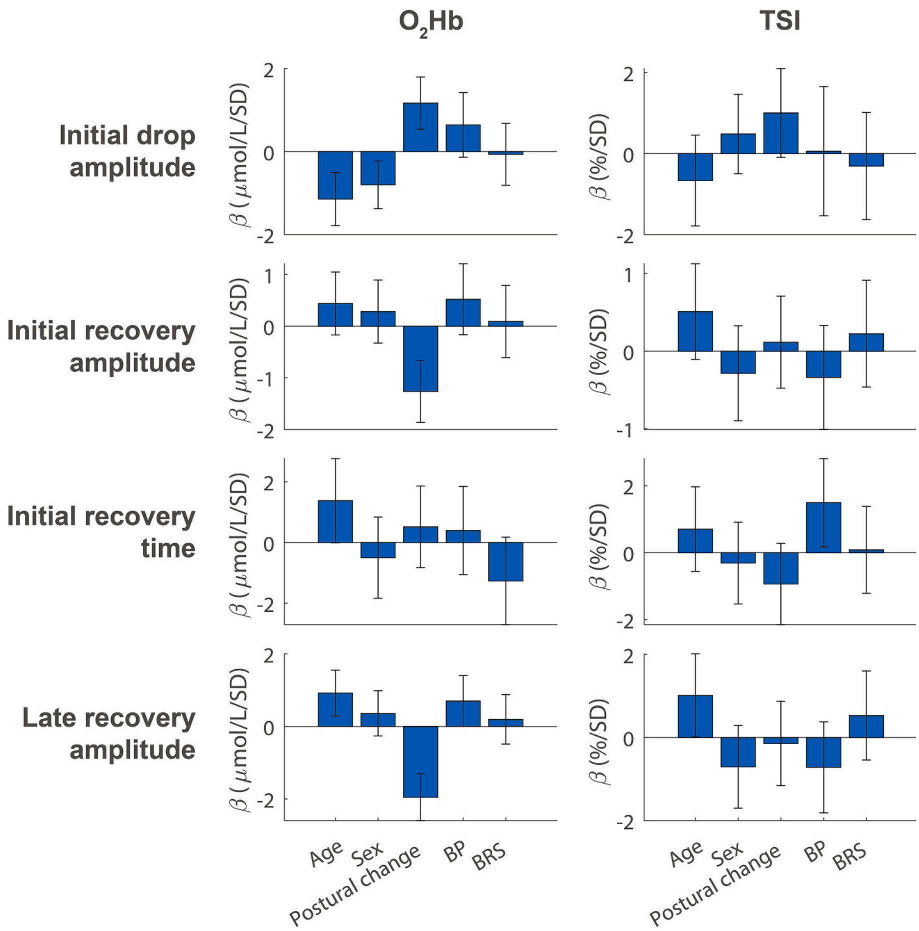

Fig. 5. Determinants of orthostatic cerebral oxygenation. The regression betas (β) of the linear regression models with normalized determinants (x-axis) are shown. The error bars indicate the 95% confidence intervals. Age, sex, postural change and blood pressure (BP) were determinants of oxygenated hemoglobin (O_2Hb) drop and recovery amplitude. Baroreflex sensitivity (BRS) was not significantly associated with any of the drop or recovery parameters. TSI: tissue saturation index.

a set of health criteria as we aimed to test the determinants of orthostatic cerebral oxygenation drop in a real life population with good function levels. We therefore did not exclude patients based on resting blood pressure or the presence of orthostatic hypotension. The finding that approximately half of the older adults were hypertensive may be partly due to measurement situation (in the lab, not at home).

The included older adults were relatively fit as they were recruited in sports centers, swimming pools and education centers. The results of the present study therefore cannot merely be extrapolated to older adults with multi-morbidity, polypharmacy and low function levels, without further study.

4.3.3. *Measurement of cerebral oxygenation using NIRS*

NIRS measurements may be influenced by scalp perfusion. A previous study reported that oxygenation signals derived from NIRS correlated with jugular vein perfusion, but not with facial vein perfusion, suggesting that NIRS signals primarily reflect cerebral oxygenation (Murkin and Arango, 2009a). However, inducing scalp ischemia affected NIRS signals in another study (Germon et al., 1994). Further studies using short distance optodes should further quantify this effect (Sato et al., 2016).

Cerebral oxygenation measured by NIRS may apart from global cerebral perfusion also be determined by local neurovascular coupling, which is associated with age and may hence act as a confounder. However, these effects are probably minor as the effects of neurovascular coupling were reported to be several orders of magnitude smaller than the effects observed in the present study (Csipo et al., 2021).

In this study, measurements from left and right NIRS measurements were averaged to obtain a proxy for global cerebral oxygenation. A previous study showed good agreement between NIRS measurements from both sides during orthostatic challenges (Mol et al., 2019 Feb). Adding NIRS measurements to other cortical areas may increase precision.

The estimation of differential pathway factor (DPF) for NIRS measurements is important as it is used to compute changes in cerebral oxygenation levels in individuals (Bhatt et al., 2016). Assumptions for this estimation in the present study may explain part of the found orthostatic cerebral oxygenation differences between younger and older adults. However, inaccurate estimation of DPF based on the Scholkmann formula is unlikely to fully explain the differences between the groups as demonstrated in Supplementary file S2.

4.3.4. *Statistical analysis*

In this study, age was analyzed as a dichotomous variable instead of a continuous variable due to it non-linear nature by study design and as reflected by median ages of 25 and 77 years of the younger and older group respectively. This may have negatively impacted statistical power.

4.4. *Strength and limitations*

The strength of this study is that it assessed clinically relevant determinants of orthostatic cerebral oxygenation drop and recovery in a generally healthy population of a wide age range (18–88 years). Inclusion of cerebral blood flow, expiratory CO_2, peripheral ressitance and

Table 2
Determinants of orthostatic cerebral oxygenation.

Determinant	O_2Hb ($N = 114$) β, µmol/L/det. unit (95% CI)	p	TSI ($N = 111$) β, %/L/det. unit (95% CI)	p
Initial drop amplitude				
Age < 70 years, yes/no	**−2.29 (−3.57 to −1.01)**	**<0.001**	−1.34 (−3.58–0.91)	0.242
Sex, male/female	**−1.61 (−2.78 to −0.44)**	**0.007**	0.98 (−1.00–2.96)	0.330
Postural change type, sit/supine to stand	**2.33 (1.08–3.58)**	**<0.001**	1.99 (−0.19–4.18)	0.073
Blood pressure, mmHg	0.06 (−0.01–0.13)	0.105	0.01 (−0.14–0.15)	0.942
BRS, ms/mmHg	−0.01 (−0.09–0.07)	0.860	−0.03 (−0.17–0.11)	0.644
Initial recovery amplitude				
Age < 70 years, yes/no	0.88 (−0.34–2.10)	0.156	1.02 (−0.21–2.26)	0.103
Sex, male/female	0.57 (−0.66–1.81)	0.357	−0.58 (−1.82–0.66)	0.358
Postural change type, sit/supine to stand	**−2.52 (−3.71 to −1.32)**	**<0.001**	0.23 (−0.95–1.41)	0.702
Blood pressure, mmHg	0.06 (−0.02–0.13)	0.134	−0.04 (−0.11–0.04)	0.317
BRS, ms/mmHg	0.01 (−0.06–0.08)	0.794	0.02 (−0.05–0.10)	0.520
Initial recovery time				
Age < 70 years, yes/no	2.76 (−0.02–5.54)	0.051	1.41 (−1.13–3.94)	0.273
Sex, male/female	−1.01 (−3.71–1.69)	0.461	−0.63 (−3.10–1.84)	0.615
Postural change type, sit/supine to stand	1.03 (−1.65–3.71)	0.448	−1.86 (−4.29–0.56)	0.130
Blood pressure, s	0.08 (−0.21–0.37)	0.592	**0.30 (0.04–0.56)**	**0.026**
BRS, ms/mmHg	−0.14 (−0.29–0.02)	0.084	0.01 (−0.13–0.15)	0.898
Late recovery amplitude				
Age < 70 years, yes/no	**1.85 (0.58–3.11)**	**0.005**	**2.04 (0.02–4.05)**	**0.047**
Sex, male/female	0.73 (−0.54–1.99)	0.258	−1.42 (−3.44–0.59)	0.163
Postural change type, sit/supine to stand	**−3.88 (−5.17 to −2.59)**	**<0.001**	−0.28 (−2.31–1.74)	0.783
Blood pressure, mmHg	0.07 (0.00–0.14)	0.050	−0.07 (−0.19–0.04)	0.198
BRS, ms/mmHg	0.02 (−0.05–0.09)	0.574	0.06 (−0.06–0.17)	0.329

Regression coefficients (β) from linear regression modeling with age (dichotomous, < 70: 0, ≥ 70: 1), sex (dichotomous, male: 0, female: 1), postural change (sit to stand: 0, supine to stand: 1), blood pressure and baroreflex sensitivity (BRS) as determinants. Initial drop amplitude is defined as positive if a drop is present. Recovery amplitude is positive if recovery cerebral oxygenation amplitude exceeds baseline. Significant determinants are listed in bold. O_2Hb: oxygenated hemoglobin concentration; TSI: tissue saturation index; det.unit: determinant unit; CI: confidence interval.

muscle sympathetic nerve activity measurements would have provided more insight in the physiological mechanisms underlying the found results. Limitations of the study are the relatively short duration of supine rest in the measurement protocol and the potential influence of scalp perfusion on the NIRS measurements, potentially compromising the validity of the NIRS measurements.

4.5. Conclusion and future directions

Younger age, male sex and supine to stand rather than sit to stand are associated with larger orthostatic cerebral oxygenation drop and lower recovery measured with NIRS. Age, sex and type of postural change should hence be taken into account in the interpretation of orthostatic cerebral oxygenation measured with NIRS. To optimize robustness in terms of test-retest reliability, orthostatic cerebral oxygenation measurements should be performed during supine to stand rather than sit to stand; drop and recovery amplitude should be assessed rather than recovery time. O_2Hb signals should be measured rather than TSI signals as they were more robust, which may be due to the fact that less assumptions are needed to compute O_2Hb compared to TSI.

Further studies should determine clinical relevance of the investigated cerebral oxygenation measures by addressing their association with clinical outcome in patients with orthostatic hypotension.

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Table 3
Test-retest reliability of cerebral oxygenation parameters.

	O_2Hb Sit to stand	O_2Hb Supine to stand	TSI Sit to stand	TSI Supine to stand
Initial drop amplitude				
Younger adults	0.67	**0.83**	**0.76**	**0.99**
Older adults	0.31	**0.88**	0.14	0.50
Initial recovery amplitude				
Younger adults	0.66	**0.86**	−0.04	0.11
Older adults	0.04	**0.91**	0.14	0.17
Initial recovery time				
Younger adults	0.03	0.10	0.02	−0.07
Older adults	−0.03	0.49	0.34	0.14
Late recovery amplitude				
Younger adults	0.64	**0.85**	0.62	**0.99**
Older adults	0.13	**0.94**	0.24	0.42

Intra class correlations expressing test-retest reliability between cerebral oxygenation parameters from different repeats of the same postural change in younger and older adults. Excellent test-retest reliability (see methods) is listed in bold.

Availability of data and code

The acquired data and analysis scripts are available upon reasonable request.

Declaration of competing interest

None.

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Statement of ethics

All participants signed informed consent and the study was performed in accordance with the Declaration of Helsinki and approved by the Ethics committee of the Faculty of Science of the Radboud University, Nijmegen (study approval reference number: REC18021).

CRediT authorship contribution statement

AM, JAHRC, ABM, RJAvW and CM conceived of the presented idea and designed the study. AM performed the data collection. AM performed the analysis and took the lead in writing the manuscript. All authors discussed the results and contributed to the final manuscript. All authors approved the final version of the manuscript and agree to be accountable for the study. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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