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Pulse transit time as a proxy for vasoconstriction in younger and older adults

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ABSTRACT

Objectives: Changes of vasoconstriction may be measured non-invasively using pulse transit time. This study assessed the sensitivity, test-retest reliability and validity of pulse transit time during vasoconstriction provocation and active standing, and the predictive value of pulse transit time for blood pressure drop.

Methods: Fifty-five younger (age < 65 years) and 31 older adults (age > 70 years) underwent electrocardiography, wrist and finger photoplethysmography and continuous blood pressure and total peripheral resistance measurements during vasoconstriction provocation using a cold pressor test (21 younger adults), or active stand tests (all other participants). Pulse transit time was defined as the time lag between the electrocardiography R-peak and the peak in the photoplethysmography first derivative; sensitivity as a significant decrease relative to baseline; test-retest reliability as the intra class correlation between different repeats of the same test; validity as the association between peripheral resistance and pulse transit time; predictive value as the association between supine resting pulse transit time and mean arterial pressure drop during active standing.

Results: Finger pulse transit time was sensitive and reliable (ICC 0.2–0.8) during vasoconstriction provocation, but wrist pulse transit time was poorly reliable (ICC 0–0.5); only finger pulse transit time was sensitive to and reliable (ICC 0.4–0.8) during active standing in both younger and older adults. Finger pulse transit time was not associated with total peripheral resistance. Supine resting pulse transit time had predictive value for blood pressure drop during active standing in older adults (β −0.16; p 0.025).

Conclusions: Pulse transit time was sensitive to and reliable during vasoconstriction provocation and active standing, but did not significantly differ between younger and older adults. Pulse transit time could not be demonstrated to particularly reflect vasoconstriction, but it had predictive value for blood pressure drop during active standing.

1. Introduction

Arterial vasoconstriction may play a key role in orthostatic hypotension, a disorder of blood pressure regulation after active standing up, which is associated with negative health outcomes in older adults (Iseli et al., 2019; Mol et al., 2018a; Mol et al., 2018b; Mol et al., 2018c). Arterial vasoconstriction leads to an increase in arterial stiffness, which is considered to be reflected by pulse transit time (PTT, i.e., the time it takes the blood pressure wave to travel along an arterial trajectory (Fok et al., 2012; Kortekaas et al., 2012; van Velzen et al., 2015; Mol et al., 2020). Decreased PTT was found to be associated with atherosclerosis and blood pressure dysregulation (Ohyama et al., 2017; Abdullah Said et al., 2018; Kim and Kim, 2019; Ziegler, 2018). PTT can be measured non-invasively by a combination of electrocardiography and photoplethysmography ($PTT_{ECG\text{-}PPG}$), making it suitable for continuous and ambulatory monitoring during active maneuvers (Sun et al., 2016; Pereira et al., 2015). These $PTT_{ECG\text{-}PPG}$ measurements however, may apart from vasoconstriction also be determined by blood pressure, inter

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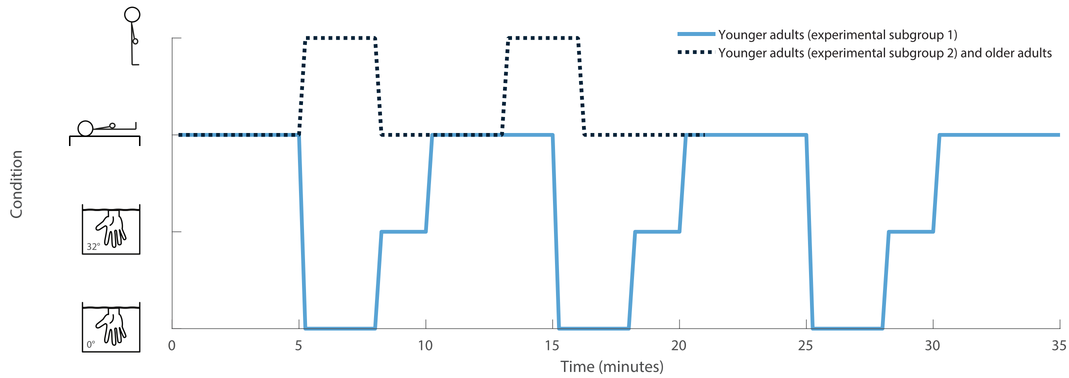

Fig. 1. Protocol for both experimental subgroups of younger adults and for older adults. Symbols along the y-axis signify (from top to bottom): standing, supine rest, thermoneutral water immersion and the cold pressor test. °Degrees Celsius.

beat interval, left ventricular ejection time and cardiac contractility (Weissler et al., 1961; Weissler et al., 1968). To determine the potential use of $PTT_{ECG\text{-}PPG}$ as an ambulatory monitor of vasoconstriction and arterial stiffness, the following need to be assessed: $PTT_{ECG\text{-}PPG}$ sensitivity and test-retest reliability after vasoconstriction provocation and active standing; $PTT_{ECG\text{-}PPG}$ validity assessed as its association with total peripheral resistance (i.e., a reflection of vasoconstriction) compared to the other aforementioned physiological quantities; $PTT_{ECG\text{-}PPG}$ predictive value for blood pressure drop after standing up.

Previous studies showed significant PTT decreases in response to vasoconstriction provoking tests such as the cold pressor test (CPT) (Bock et al., 2019; Moriyama and Ifuku, 2010) and isometric hand grip test (Moriyama and Ifuku, 2010; Hartog et al., 2018; Mäki-Petäjä et al., 2016), but these studies used PTT assessed at carotid and femoral artery or brachial artery and ankle, which is less suitable for ambulatory monitoring. Other studies reported a correlation between PTT and blood pressure during exercise tests, but did not address PTT during vasoconstriction provocation or active standing, and not in older adults (Sun et al., 2016; Gesche et al., 2012). One study assessed $PTT_{ECG\text{-}PPG}$ during CPT, but only during a short period of 30 s (Budidha and Kyriacou, 2019) and another study used $PTT_{ECG\text{-}PPG}$ during active standing and sustained handgrip for blood pressure estimation, but did not measure $PTT_{ECG\text{-}PPG}$ in older adults and only reported on the predictive value of $PTT_{ECG\text{-}PPG}$ for BP (Ding et al., 2017).

This study aims to assess the sensitivity, test-retest reliability and validity of $PTT_{ECG\text{-}PPG}$ during CPT induced vasoconstriction provocation and active standing in both younger and older adults. This study also addresses the predictive value of $PTT_{ECG\text{-}PPG}$ for BP drop after standing up. It is hypothesized a) that $PTT_{ECG\text{-}PPG}$ decreases significantly during CPT and after active standing in younger and older adults; b) that $PTT_{ECG\text{-}PPG}$ after active standing shows a smaller decrease or larger increase in older adults compared to younger adults, as vasoconstriction is reported to become impaired with ageing (Dinenno et al., 2001; Holowatz et al., 2010); c) that $PTT_{ECG\text{-}PPG}$ is valid, i.e., associated with total peripheral resistance rather than the other aforementioned physiological quantities; d) that supine resting $PTT_{ECG\text{-}PPG}$ has predictive value for blood pressure drop after active standing, as higher arterial stiffness is associated with impaired blood pressure restoration after standing up (Ziegler, 2018).

2. Methods

2.1. Participants

Fifty-five adults aged below 65 years were recruited from students and employees of the Radboud University and 31 older adults aged above 70 years were recruited from Nijmegen sports centers and education centers for older adults. All participants signed informed consent and the study was approved by the ethical committee of the Radboud University (ECS17022 and REC18021).

Age, height, weight and smoking habits were obtained using questionnaires. Arm span was measured as the distance between the tips of both middle fingers when the arms are spread.

2.2. Instrumentation

Two custom made photoplethysmography (PPG) sensors were applied to the wrist (radial artery) and distal phalanx of the index finger (digital artery). The sampling frequency was set at 1000 Hz.

To enable $PTT_{ECG\text{-}PPG}$ calculations, ECG was measured using a 5-lead ECG monitoring system (Finapres NOVA, Finapres Medical Systems, Amsterdam, The Netherlands; sampling frequency of 200 Hz).

Beat-to-beat blood pressure (i.e., mean arterial pressure (MAP) and pulse pressure (PP)) and inter beat interval (IBI) were monitored continuously (Finapres NOVA, Finapres Medical Systems, Amsterdam, The Netherlands) on the same arm. The modelflow algorithm employed by this device estimates total peripheral resistance (TPR), and left ventricular ejection time (LVET) (Truijen et al., 2012). Cardiac contractility was estimated by the steepness of the blood pressure increase during systole (dPdt).

During the active stand test, the posture was measured using a tilt meter, which was attached to the participants' trunk.

2.3. Protocol

The room was kept at a temperature between 21 and 23 °C. Participants were discouraged from talking during the experiment.

Fig. 1 shows the protocol for all participants. Three trials of the cold pressor test were performed by a subgroup of younger adults (experimental subgroup 1, $n = 21$), consisting of a 5-minute resting period, followed by a 3-minute immersion of the hand in ice water and a 2-minute recovery through immersion of the same hand in a bath of water of 32 degrees Celsius. The hand that was used for the cold pressor test was randomized across participants. PPG and blood pressure measurements were acquired at the contralateral hand.

Two trials of the active stand test were performed by a subgroup of younger adults (experimental subgroup 2, $n = 34$) and by all older adults ($n = 31$). Participants were asked to stand up after a supine resting period of 5 min and keep standing for 3 min. During this test, the arm on which the PPG and BP measurements were performed was kept at heart height using a sling to eliminate hydrostatic pressure differences between heart and the left lower arm.

2.4. Data quality assessment and PTT computation

$PTT_{ECG\text{-}PPG}$ signals were computed from the wrist and finger PPG signals, hence referred to as wrist PTT and finger PTT.

PPG signals were filtered using a third order Butterworth bandpass filter with a passband from 0.1 to 5 Hz, after which the first derivative was computed. The first derivative was automatically assessed for signal quality based on the cross correlation of subsequent normalized 1-s data segments, assuming that a high-quality signal has high cross-correlation between subsequent segments due to the recurrent heartbeat. Segments with a cross-correlation lower than 0.5 with at least one adjacent segment were considered low quality and not used for PTT computation. A trial was discarded from further analysis if > 20% of the segments were of low quality.

An automatic peak detection algorithm was built to detect the R-peaks in the ECG and the peaks in the first derivative in the PPG signals using MATLAB R2017b (MathWorks, Natick, United States) and its signal analysis toolbox.

Wrist and finger PTT were computed as the time between the R-peak in the ECG and the peak in the first derivative of the PPG signal. Furthermore, the difference between wrist and finger PTT was computed (PTT difference).

The quality of the resulting PTT signal was automatically assessed by computing the signal standard deviation per PPG signal (wrist and finger) and trial. PTT samples were discarded if they differed > 3 standard deviations from the participant's mean.

2.5. Signal analysis

Baseline PTT, total peripheral resistance, blood pressure, inter beat interval, left ventricular ejection time and cardiac contractility were computed as the mean of the signal in the 60 s before start of the test condition. Means of twelve subsequent intervals of 15 s after the test start were computed for both the cold pressor test and the active stand test.

2.6. Statistical analysis

Continuous variables were reported as mean and standard deviation if normally distributed and as median and interquartile range in case of a non-normal distribution. Differences of the PTT signals with their baseline (i.e., sensitivity) were computed using the Wilcoxon signed rank test and differences between experimental subgroups were tested using the Mann–Whitney *U* test. Two-way mixed absolute single measure intra class correlations (ICC) were computed to express test-retest reliability. To assess validity, separate linear mixed models were developed with PTT as dependent variable and normalized (i.e., z-scored) TPR, MAP, PP, IBI, LVET and dPdt as fixed effect independent variables, allowing for random intercepts and random slopes across participants. PTT predictive value for MAP drop after standing up was assessed using linear mixed models with MAP drop as dependent variable and baseline PTT as fixed effect independent variable, allowing for random intercepts across participants.

3. Results

Table 1 lists the participant characteristics. The median age was 21, 25 and 77 years and the percentage of female participants was 28.5, 29.4 and 54.9 in younger adult experimental subgroups 1 and 2 and the group of older adults, respectively. BMI in the respective groups was 21.6, 21.9 and 24.7 kg/m^2 and the only two participants currently smoking were in experimental subgroup 2 of younger adults. Wrist PTT was available for 20/21 younger (experimental subgroup 1), 31/34 younger (experimental subgroup 2) and 24/31 older adults after data quality assessment. Finger PTT was available for 20/21 younger (experimental subgroup 1) 32/34 younger (experimental subgroup 2) and 18/31 older adults.

3.1. Sensitivity and reliability during the cold pressor test

Fig. 2 shows the results of the cold pressor test in younger subjects. Both wrist PTT and finger PTT decreased significantly relative to baseline, but finger PTT decrease was larger and longer. The difference between wrist and finger PTT also decreased significantly relative to baseline. Test-retest ICCs were lower than 0.5 for wrist PTT. For finger PTT, ICCs were only lower than 0.5 in intervals between 15 and 60 s after start of the cold pressor test. The difference between wrist and finger PTT had a low test-retest reliability (ICC $<$ 0.5). TPR showed an inverse pattern to PTT, as well as MAP, PP and cardiac contractility. IBI and LVET showed a similar pattern as PTT.

3.2. Sensitivity and reliability during the active stand test

Fig. 3 shows the results of the active stand test in younger and older adults. Wrist PTT significantly increased in young adults and only showed an initial significant decrease in older adults. Finger PTT significantly decreased in both younger and older adults. PTT difference significantly decreased only in young adults. Patterns of wrist PTT, finger PTT and their difference did not significantly differ between the young and older participants. TPR, MAP, PP and contractility showed an initial decrease followed by recovery, while a persistent decrease was shown by IBI and LVET. Test retest reliability ranged between 0.4 and 0.7 (wrist PTT, young adults), −0.2–0.6 (wrist PTT, older adults), 0.4–0.7 (finger PTT, young adults), 0.4–0.8 (finger PTT, older adults), −0.2–0.5 (PTT difference, young adults) and 0.1–0.5 (PTT difference, older adults).

3.3. PTT validity

Fig. 4 shows the regression betas from the models explaining PTT from the physiological quantities (TPR, MAP, PP, IBI, LVET, contractility) both during the cold pressor test and the active stand test. None of the physiological quantities was found to significantly associate with changes in wrist PTT and PTT difference during the cold pressor test. MAP, PP and contractility were significantly negatively associated with finger PTT. TPR was not associated with finger PTT during the cold pressor test.

During the active stand test, TPR was positively associated with wrist PTT, only in older adults. IBI and contractility were significantly associated with finger PTT and PTT difference only in young adults. PP was associated with PTT difference in young adults. TPR was not associated with finger PTT and PTT difference in either young or older adults.

3.4. Supine resting PTT predictive value

Fig. 5 shows the supine resting PTT of the younger and older adults who performed the active stand test and its predictive value for MAP drop after standing up. Neither wrist nor finger supine resting PTT nor PTT difference significantly differed between younger and older adults. Supine resting finger PTT was negatively associated with MAP drop after standing up ($\beta = -0.16$; 95% confidence interval $= -0.30$ to -0.02; $p = .025$).

4. Discussion

Wrist and finger pulse transit time determined using ECG and PPG ($PTT_{ECG\text{-}PPG}$) as well as their difference were sensitive (i.e., decreased significantly) during vasoconstriction provocation using a cold pressor test in young adults. Only finger PTT was sensitive to active standing in both young and older adults. PTT showed no statistically significant differences between age groups after active standing. Overall, test-retest reliability was highest for finger PTT, both during the cold pressor test active standing. PTT validity could not be demonstrated as neither wrist and finger PTT, nor PTT difference, was associated with total peripheral resistance as a reflection of vasoconstriction. Supine resting finger PTT had predictive value as it was negatively associated

Table 1
Participant characteristics, stratified by subgroups.

Characteristic	N	Younger adults Experimental subgroup 1 (n = 21)	N	Younger adults Experimental subgroup 2 (n = 34)	N	Older adults (*n* = 31)
Age, years, median [IQR]	21	21 [20–21.5]	34	25 [22–45]	31	77 [72–81]
Female, n (%)	21	6 (28.5)	34	10 (29.4)	31	17 (54.9)
Height, m, median [IQR]	21	1.79 [1.74–1.84]	34	1.80 [1.72–1.85]	31	1.69 [1.64–1.77]
Weight, kg, median [IQR]	21	70 [64.5–76]	34	70.5 [65.8–75.0]	31	74.0 [65.0–83.0]
BMI, kg/m^2, median, [IQR]	21	21.6 [21.6–23.6]	34	21.9 [20.9–23.2]	31	24.7 [23.4–27.0]
Current smoking, n (%)	21	0 (0)	34	2 (5.9)	31	0 (0)
Resting HR, bpm, median [IQR]	19	68 [66–71]	34	60 [55–71]	30	67 [63–77]
Resting SBP, mm Hg, median [IQR]	19	121 [115–135]	34	124 [114–132]	30	153 [145–172]
Resting DBP, mm Hg, median [IQR]	19	96 [88–108]	34	71 [64–84]	30	83 [77–94]
Resting pulse pressure, mmHg, median [IQR]	19	26 [21 – 30]	34	50 [44–60]	30	71 [64–78]
Resting wrist PTT, ms, median [IQR]	20	200 [188–219]	31	213 [200–228]	24	198 [180–229]
Resting finger PTT, ms, median [IQR]	20	230 [218–245]	32	252 [236–276]	18	261 [219–285]

Resting HR, SBP and DBP were computed as the baseline mean. IQR: interquartile range; SD: standard deviation; BMI: Body Mass Index; HR: Heart rate; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure.

with mean arterial pressure (MAP) drop after standing up in older adults.

4.1. Sensitivity

4.1.1. Wrist and finger PTT during the cold pressor test

The significant decrease of both wrist and finger PTT relative to baseline during CPT confirmed the hypothesis and suggests the potential value of PTT measured using ECG and wrist and finger photoplethysmography as a proxy for vasoconstriction.

4.1.2. Wrist and finger PTT during the active stand test

Wrist PTT did not significantly decrease in young adults and only showed a short initial decrease in older adults, which might be explained by a relatively large contribution of the pre-ejection period to wrist PPG. The significant decrease of finger PTT confirmed the hypothesis.

4.1.3. PTT difference during cold pressor test and active stand test

PTT difference decreased both during the cold pressor test and the active stand test only in young adults, suggesting that PTT difference may reflect vasoconstriction. The finding that PTT difference did not significantly decrease during the active stand test in older adults might indicate that vasoconstriction is impaired in older adults, but may also be caused by the large variance within the group of older participants. This variance should be further investigated in further studies as it may reflect the compensatory capacity of the peripheral arteries.

The PTT difference measure has the advantage of particularly reflecting the arterial trajectory between wrist and finger, which is mainly of the muscular artery type that is able to constrict and therefore a suitable trajectory to assess vasoconstriction (Johnson, 2008). Furthermore, unlike wrist and finger PTT, PTT difference eliminates the pre-ejection period, i.e. the time between electrical and mechanical activation of the heart, which may vary within and between individuals and is not a reflection of vasoconstriction (Krohova et al., 2017; Wong et al., 2011; Kortekaas et al., 2018). However, no linear relationship

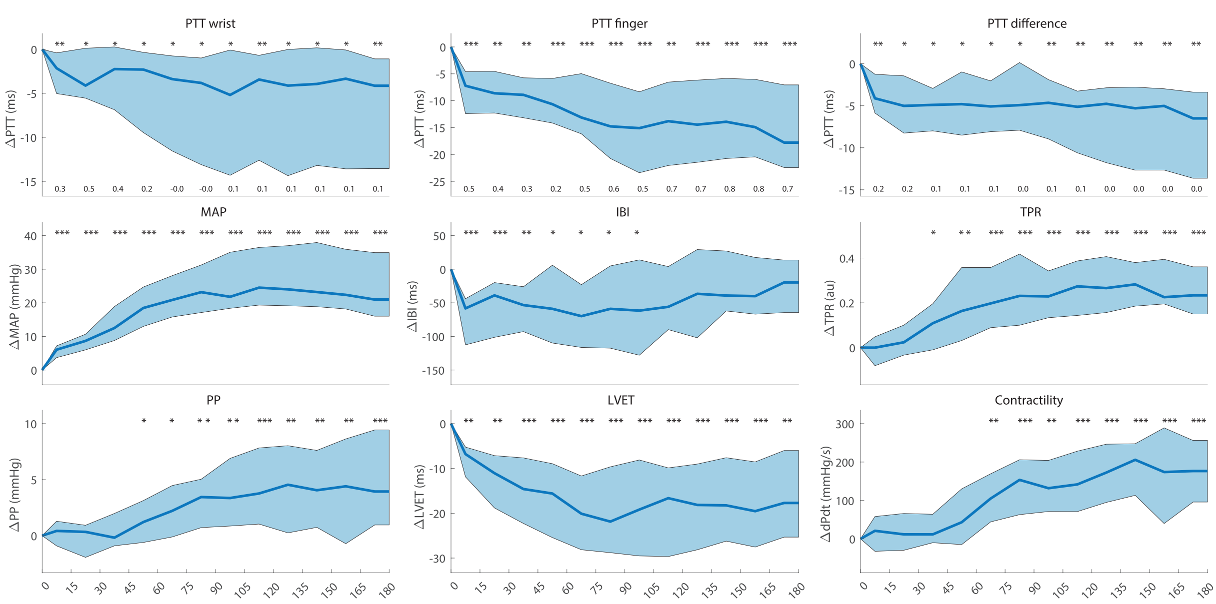

Fig. 2. Pulse transit time (PTT), total peripheral resistance (TPR), mean arterial pressure (MAP), pulse pressure (PP), inter beat interval (IBI), left ventricular ejection time (LVET) and cardiac contractility during the cold pressor test in younger adults. The graphs show the median difference with baseline for each interval of 15 s. The shaded areas indicate the inter quartile ranges and one–three stars indicate statistically significant differences with baseline ($p < .05$, $p < .01$ and $p < .001$, respectively). Time = 0 indicates the start of the cold pressor test. Test-retest reliability is expressed as intraclass correlation (ICC) and shown for each time interval at the base of the top panels.

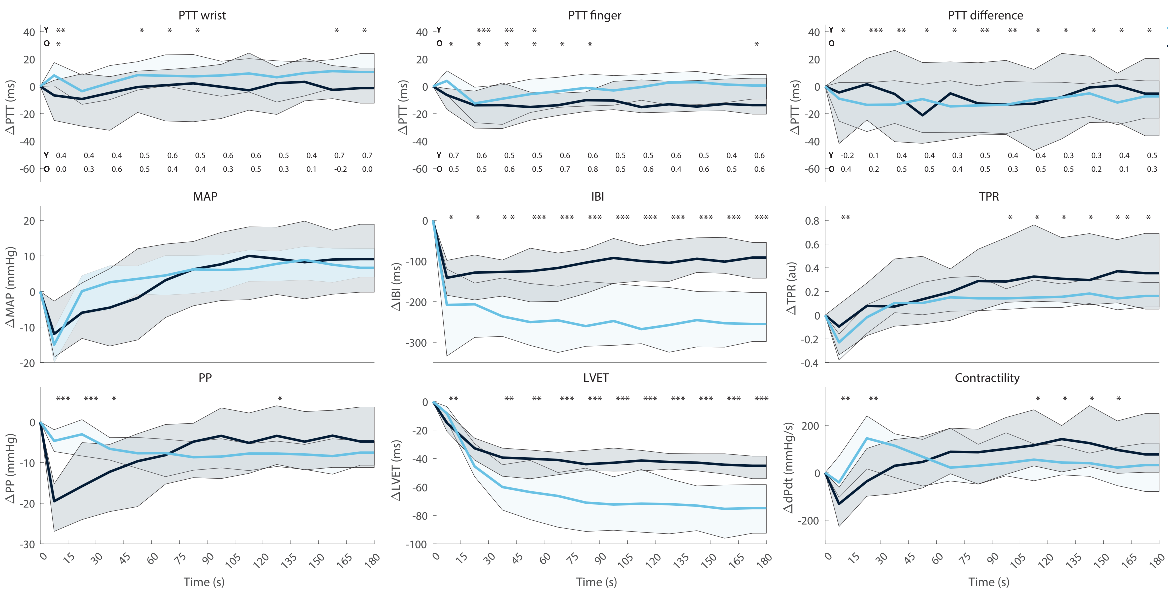

Fig. 3. Pulse transit time (PTT), total peripheral resistance (TPR), mean arterial pressure (MAP), pulse pressure (PP), inter beat interval (IBI), left ventricular ejection time (LVET) and cardiac contractility during active standing in younger and older adults. The top panels show the course of median wrist PTT, finger PTT and the PTT difference after active standing as means of the consecutive 15-second intervals. Stars in the three top panels indicate statistical differences relative to baseline for the young (Y) and older (O) participants, 1–3 stars indicating *p*-values below 0.05, 0.01 and 0.001, respectively. There were no significant differences between younger and older adults. Test-retest reliability expressed as intraclass correlations for each time interval are shown at the base of the top panels, both for the young and older participants. The lower six panels show the median course of TPR, MAP, PP, IBI, LVET and contractility. Stars in the lower six panels indicate statistically significant differences relative to baseline. Shaded areas in any panel indicate the inter quartile range.

between total peripheral resistance and PTT difference was found in the present study, either during the cold pressor test or during the active stand test.

4.1.4. Older compared to young adults

Wrist and finger PTT showed no significant differences between younger and older adults after active standing, contrary to the hypothesis. Absence of the expected differences may be due to the fact that the included population of older adults in this study used to exercise regularly, which slows down vascular ageing (Seals et al., 2009). Future studies should investigate wrist and finger PTT during active standing in individuals with more progressed vascular ageing and atherosclerosis, to investigate whether wrist and finger PPG discriminate between these patients. As the variance within the groups

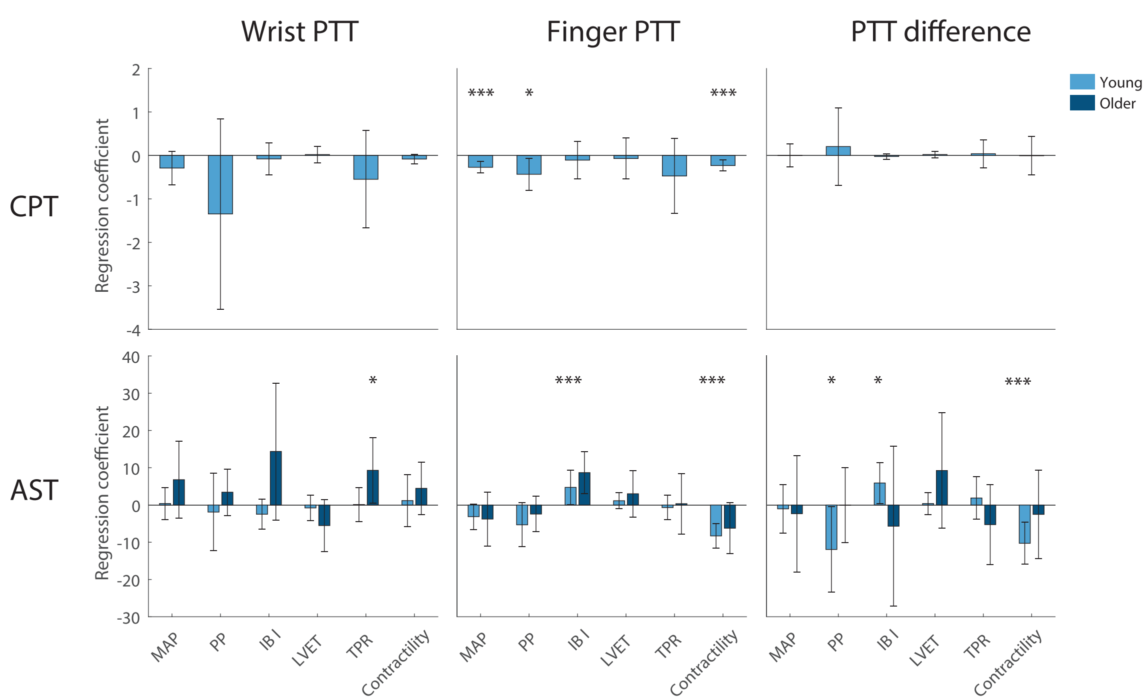

Fig. 4. Associations between physiological quantities (TPR, MAP, PP, IBI, LVET and contractility) and PTT. The bars indicate the regression betas of the mixed linear models with PTT as dependent variable and the z-scored physiological quantity as dependent variable. The error bars indicate 95% confidence intervals. Stars indicate statistical significance baseline ($p < .05$, $p < .01$ and $p < .001$, respectively). PTT: pulse transit time; CPT: cold pressor test; AST: active stand test; TPR: total peripheral resistance; MAP: mean arterial pressure; PP: pulse pressure; IBI: inter beat interval; LVET: left ventricular ejection time.

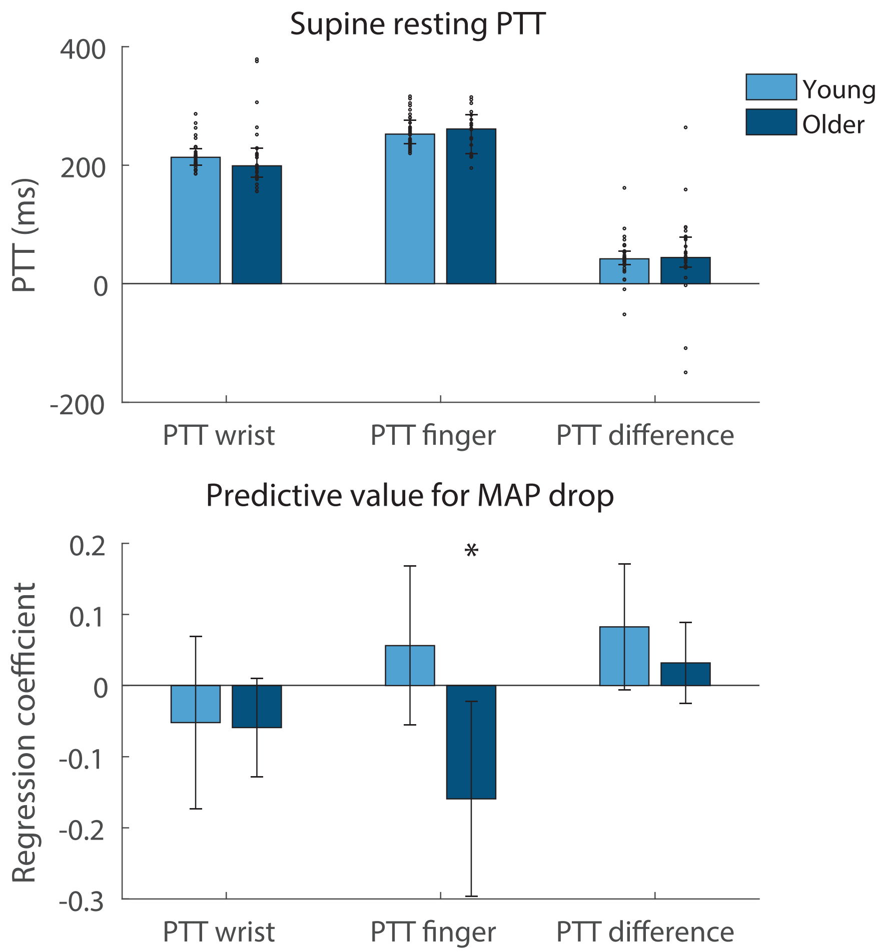

Fig. 5. Supine resting pulse transit time (PTT) in younger and older adults and the predictive value for MAP drop after standingup. The upper panel shows supine resting PTT as the median (bar height), inter quartile range (error bars) and the mean values per participant (dots) for wrist PTT, finger PTT and PTT difference. There were no significant differences between younger and older subjects. The lower panel shows the regression coefficient of the predictive value of PTT for mean arterial pressure (MAP) drop after standing up. Error bars indicate 95% confidence intervals. The star indicates statistical significance.

was high, inter-individual differences should be addressed in further research as they may reflect the efficacy of cardiovascular adaptions after active standing and hence may determine clinical outcome.

4.2. Test-retest reliability

Overall, test-retest reliability was higher for finger PTT than for wrist PTT, potentially due to the smaller distance between the finger PPG sensor and the digital artery than between the wrist PPG sensor and the radial artery. The larger arterial trajectory assessed by finger PTT compared to wrist PTT renders finger PTT susceptible to more sources of noise and is hence unlikely to explain this result.

4.3. Validity

TPR was not significantly associated with either wrist or finger PTT or PTT difference during the cold pressor test. During the active stand test, TPR was not associated with finger PTT and PTT difference. These results might be explained by the absence of any relationship between total peripheral resistance and PTT, a the presence of a non-linear relationship which was not accounted for by the linear models, or limited reliability of the total peripheral resistance estimates derived from the modelflow algorithm implemented in the used Finapres device. Changes in pre-ejection period during the cold pressor test and the active stand test may have had a large contribution to wrist and finger PTT, potentially explaining the absence of an association with TPR. However, pre-ejection period has not contributed to PTT difference, which was not associated with TPR either. Future research should measure PTT, TPR and sympathetic efferent nerve activity and pre-ejection period simultaneously to further assess the validity of PTT and TPR as a measure of vasoconstriction and eliminate the effect of pre-ejection period (Holowatz et al., 2010).

4.4. Predictive value of supine resting PTT

The observation that supine resting finger PTT was significantly associated with mean arterial pressure drop after standing up confirmed our hypothesis. The association was only present in older adults, suggesting that younger adults have not yet developed a vessel stiffness level that impairs the baroreflex as much as older adults (James and Potter, 1999). However, this was not supported by a significantly lower supine resting PTT in older compared to younger adults. To further establish the value of supine resting wrist and finger PTT as a measure of arterial stiffness, its association with established techniques such as arterial ultrasound intima-media thickness measurements and aortic pulse wave velocity measurements should be addressed.

4.5. Signal quality

Low PPG signal quality prevented PTT calculation for approximately one tenth of the PPG signals in younger adults and approximately one third of the PPG signals in older adults, indicating that it is more challenging to obtain good quality PPG signals from older adults. This may be due to a thicker layer of subcutaneous fat between PPG sensor and the artery, which reduces the detected light intensity by PPG. Combining multiple small PPG sensors in one measurement unit would potentially enable canceling out random noise by averaging over the sensors.

4.6. Strength and limitations

The strength of this study is that it systematically assessed the sensitivity, test-retest reliability and validity of $PTT_{ECG\text{-}PPG}$, which is potentially suitable for ambulatory use in the home situation, both during a strong standardized vasoconstriction provocation (i.e., the cold pressor test) and during active standing. Comparison with gold standard measurements for vasoconstriction and arterial stiffness are required to elucidate the vascular activity underlying the present results. Furthermore, the relatively large part of PPG signals in older adults that could not be used to compute PTT due to low signal quality is a limitation of the study.

4.7. Conclusion

$PTT_{PPG\text{-}ECG}$, particularly finger PTT, is sensitive to and reliable during vasoconstriction provocation and active standing. $PTT_{PPG\text{-}ECG}$ was not sensitive to discriminate between different age groups in the present study. $PTT_{PPG\text{-}ECG}$ could not be demonstrated to be valid, i.e., associated with total peripheral resistance. Supine resting finger PTT has predictive value for mean arterial pressure drop during active standing.

Data availability

All data and analysis scripts are available via the following link: http://hdl.handle.net/11633/aacthxia.

Author contribution

AM, CGMM, SPN, ABM and RJAvW conceived 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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Declaration of competing interest

None.

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