scientific reports

OPEN

Reliability of beat-to-beat blood pressure variability in older adults

Trevor Lohman[1], Isabel J. Sible[2], Fatemah Shenasa[3], Allison C. Engstrom[3], Arunima Kapoor[3], John Paul M. Alitin[1], Aimee Gaubert[1], Julian F. Thayer[3], Farrah Ferrer[1] & Daniel A. Nation[1,4✉]

Blood pressure variability (BPV) is emerging as an important risk factor across numerous disease states, including cerebrovascular and neurodegenerative disease in older adults. However, there is no current consensus regarding specific use cases for the numerous available BPV metrics. There is also little published data supporting the ability to reliably measure BPV across metrics in older adults. The present study derived BPV metrics from continuous beat-to-beat blood pressure monitoring data. Two sequential 7 min waveforms were analyzed. Absolute and relative reliability testing was performed. Differences between antihypertensive medication users and non-users on BPV metric reliability was also assessed. All sequence and dispersion based BPV metrics displayed good test–retest reliability. A measure of BP instability displayed only moderate reliability. Systolic and diastolic average real variability displayed the highest levels of reliability at ICC = 0.87 and 0.82 respectively. Additionally, systolic average real variability was the most reliable metric in both the antihypertensive use group, and the no antihypertensive use group. In conclusion, beat-to-beat dispersion and sequence-based metrics of BPV can be reliably obtained in older adults using noninvasive continuous blood pressure monitoring. Average real variability may be the most reliable and specific beat-to-beat blood pressure variability metric due to its decreased susceptibility to outliers and low frequency blood pressure oscillations.

Blood pressure variability (BPV) has emerged as a hemodynamic marker of interest with widespread clinical and research utility. BPV is associated with increased mortality[1], and is a risk factor for cardiovascular disease[2–9], stroke[10–12], cerebral small vessel disease (CSVD)[13,14], neurodegenerative disease[15] and dementia[16,17], independent of average blood pressure (BP). BPV appears to be of particular importance in older adults while mean BP might be more important in middle aged adults[18]. The regulatory mechanisms which underlie BPV modulation are complex and multifactorial, potentially involving arterial baroreflex sensitivity[19], arterial stiffness[20], endothelial dysfunction[21], and kidney function[21] among other factors[22,23]. BPV has been assessed in multiple ways, but little is known about the reliability of any one type of assessment or the differences in reliability between assessments.

Methodologies for BPV calculation fall into four main categories including very short-term (beat-to-beat) BPV, short-term BPV (< 24 h), medium-term BPV (day-to-day), and long-term BPV (visit-to-visit over months or years)[2]. Each category offers unique advantages and disadvantages. Long-term and medium-term BPV are influenced primarily by environmental and behavioral factors such as season, altitude, and antihypertensive medication adherence[24–26]. Short-term BPV is reflective of circadian BP rhythms like nocturnal BP dipping and morning BP surge[26,27] and is influenced by central and peripheral autonomic modulation and arterial elasticity[25,28–30]. Very short-term beat-to-beat BPV dynamics yield detailed insights into autonomic and cardiovascular function[24,31,32], but have previously required invasive arterial catheterization. The validation of noninvasive continuous arterial BP measurement technology[33–37] now enables an accessible and noninvasive methodology for generating validated continuous BP waveforms without arterial catheterization. Numerous hemodynamic markers of interest can be derived from the raw arterial pressure waveforms generated, including standard deviation (SD), coefficient of variation (CV), variability independent of the mean (VIM), and average real variability (ARV) (*see methods*). The availability of MRI-compatible devices allows for the study of beat-to-beat BP dynamics during neuroimaging, which may be relevant to cerebrovascular and neurodegenerative conditions associated with increased BPV[38–41].

[1]Leonard Davis School of Gerontology, University of Southern California, Los Angeles, CA, USA. [2]Department of Psychology, University of Southern California, Los Angeles, CA, USA. [3]Department of Psychological Science, University of California, Irvine, CA, USA. [4]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA. ✉email: danation@usc.edu

Numerous studies have identified relationships between BPV metrics and clinically relevant markers of pathophysiology, but no systematic investigation has yet been performed assessing reliability and delineating specific use cases for each metric. Reporting of specific BPV metrics is therefore largely driven by outcomes or convenience. A first step towards elucidating the specific utility and rationale for using a particular BPV metric is to establish its test–retest reliability. However, despite the demonstrated utility of noninvasive continuous BP monitoring, little is known about the reliability of beat-to-beat BPV metrics. The ability to measure BPV accurately and reliably has also been questioned by some[42]. Few studies have assessed BPV test–retest reliability, of those that have, most investigations focusing on visit-to-visit BPV[43,44]. To the authors' knowledge, only one study has assessed the test–retest reliability of any beat-to-beat BPV metric, but this was performed in the context of orthostatic beat-to-beat blood pressure response[45].

The present study addresses this knowledge gap by examining the intrasession test–retest reliability of beat-to-beat BPV metrics in a sample of community dwelling older adults recruited as part of the vascular senescence and cognition (VaSC) cohort. As part of the VaSC study, beat-to-beat BPV was monitored during brain MRI using an MRI-compatible noninvasive continuous BP device. These data are leveraged in the present study to examine reliability of BPV metrics, including beat-to-beat systolic and diastolic SD, CV, VIM, and ARV, as well as SBP_{range} (maximum SBP minus minimum SBP). The test–retest reliability of noninvasive continuous average systolic BP (SBP), diastolic BP (DBP), and heart rate (HR) are also assessed.

Results

121 participant visits with continuous BP monitoring were available. Of these, 10 visits were excluded due to poor data quality and excessive motion artifacts. After exclusion, 111 participant visits were included for analysis. Participant characteristics and demographics for this sample are displayed in (Table 1). The correlation between all BPV metrics and average blood pressure with and without demographic adjustment, as well as the correlation between all BPV metrics and age is shown in (Supplementary File 1).

Blood pressure variability intrasession test–retest reliability

One Table 2 shows the sample mean for each analyzed cardiovascular parameter as well as the paired t-test p-value associated with each test–retest comparison. No significant differences between waveform 1 (test) and waveform 2 (re-test) were observed for any measure. Violin plots display waveform 1 and waveform 2 data distributions for selected measures in (Fig. 1).

All noninvasive BP waveform-derived cardiovascular parameters displayed excellent absolute test–retest reliability (SEM < 5%, SRD < 10%). HR, SBP, and DBP means displayed excellent relative test–retest reliability (ICC > 0.90), all dispersion (SD, CV, VIM) and sequence (ARV) BPV metrics displayed good relative test–retest reliability (ICC = 0.70–0.89), while SBP_{range} displayed moderate relative test–retest reliability (ICC = 0.50–0.69). These results are shown in (Table 3). Correlation and Bland–Altman[46] plots are displayed in (Fig. 1).

Antihypertensive treatment and BPV test–retest reliability

SBP ARV displayed excellent test–retest reliability in the group taking no antihypertensive medications, and good test–retest reliability in the group taking antihypertensive medications. All systolic BPV dispersion measures displayed good reliability in the no hypertensives group, but only moderate reliability in the antihypertensive group. Similar observations were seen for the diastolic BPV metrics, except for DBP VIM, which showed improved reliability in the antihypertensive group. Results displayed in (Table 4).

Discussion

The present study finds that sequence and dispersion-based measures of beat-to-beat systolic and diastolic BPV can be reliably derived from a continuous BP monitoring device. Sequence-based metrics, including systolic and diastolic ARV, displayed the highest test–retest reliability in the overall sample. This is likely due to their decreased susceptibility to outliers and low-frequency oscillations in beat-to-beat BP compared to dispersion and instability

Variable name	Mean (SD) or n (%)
Age (years)	69.89 (6.92) range 55–89
Female (%)	69 (62.2)
VRFs ≥ 2	47 (42.3)
Hypertension	39 (35.1)
High cholesterol	53 (47.7)
Diabetes	11 (9.9)
History of smoking	34 (30.6)
History of cardiovascular disease	11 (9.9)
History of atrial fibrilation	5 (4.5)
History of TIA	2 (1.8)
Using antihypertensive medications	39 (35.1)

Table 1. Participant characteristics and demographics (N = 111).

Variable name	7 min BP waveform 1 mean ± SD	7 min BP waveform 2 mean ± SD	P
Heart rate	60.65 ± 10.58	60.19 ± 10.04	0.25
Systolic blood pressure	132.65 ± 16.90	131.91 ± 20.75	0.39
SBP SD	5.28 ± 2.50	5.43 ± 2.30	0.34
SBP CV	4.01 ± 1.88	4.11 ± 1.74	0.37
SBP VIM	2.02 ± .44	2.02 ± .35	0.95
SBP ARV	1.69 ± .99	1.77 ± 1.02	0.10
SBP$_{range}$	33.32 ± 12.15	34.07 ± 12.23	0.42
Diastolic blood pressure	77.42 ± 10.36	77.55 ± 10.50	0.44
DBP SD	2.93 ± 1.97	3.08 ± 2.15	0.20
DBP CV	3.92 ± 2.93	4.14 ± 3.35	0.20
DBP VIM	2.30 ± 1.26	2.30 ± 1.77	0.96
DBP ARV	1.90 ± 1.39	1.99 ± 1.35	0.20

Table 2. Cardiovascular parameters derived from two sequential 7 min continuous blood pressure waveforms. *SBP* systolic blood pressure, *SD* standard deviation, *CV* coefficient of variation, *VIM* variability independent of the mean, *ARV* average real variability, *DBP* diastolic blood pressure. P-values obtained from paired *t*-tests.
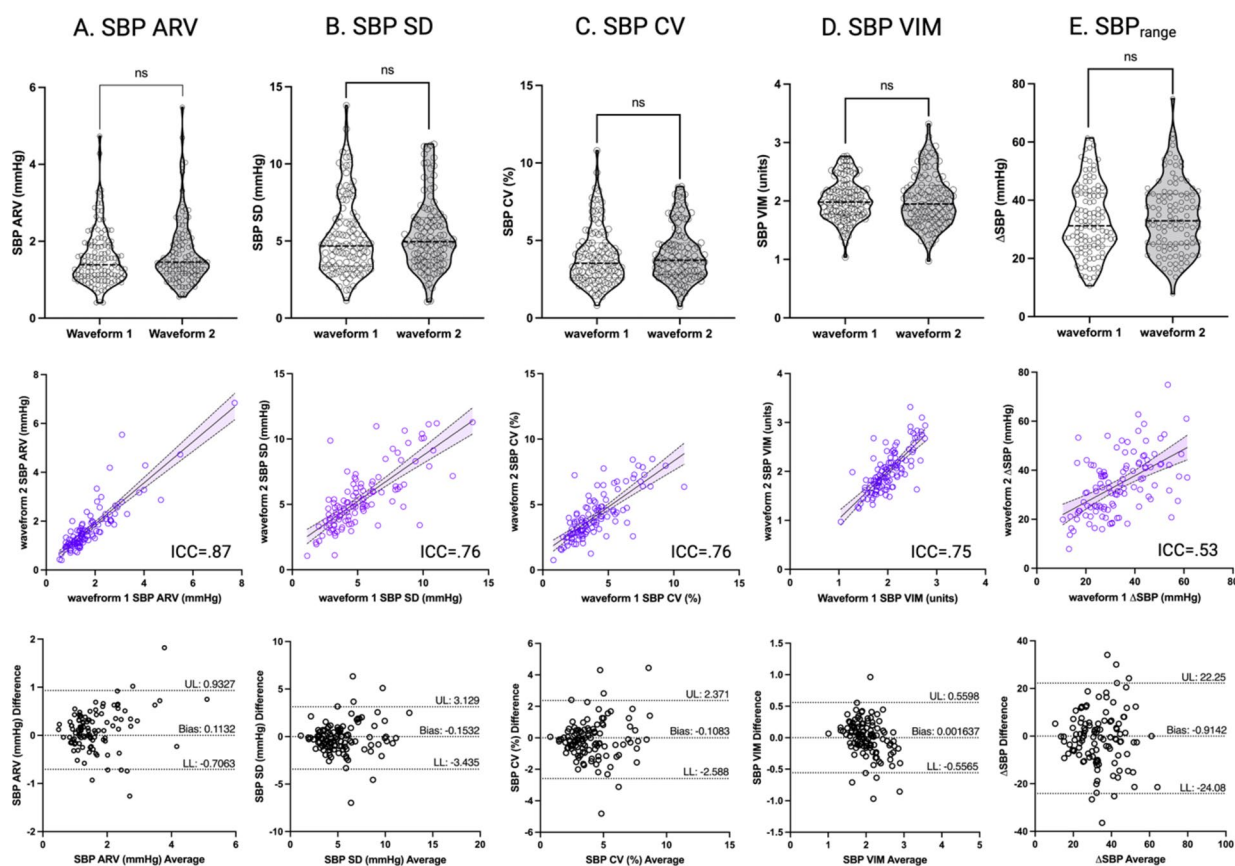

Fig. 1. Test–retest reliability of beat-to-beat blood pressure variability metrics. Test–retest violin plots with paired t-test comparison (row 1), test–retest correlation plots with intraclass correlation coefficients (ICC) (row 2) and Bland–Altman plots with bias and 95% limits of agreement indicated by horizontal dashed lines shown for five measures of systolic blood pressure variability: (**A**) Systolic blood pressure average real variability (SBP ARV), (**B**) Systolic blood pressure standard deviation (SBP SD), (**C**) Systolic blood pressure coefficient of variation (SBP CV, (**D**) Systolic blood pressure variability independent of the mean (SBP VIM), and (**E**) maximum minus minimum systolic blood pressure (SBP$_{range}$).

3

Variable name	ICC (95% CI)	SEM	SEM%	SRD	SRD%
Heart rate	0.98 (0.95–1.00)	0.19	0.31	0.27	0.43
Systolic blood pressure	0.96 (0.92–0.995)	0.48	0.36	0.67	0.50
SBP SD	0.76 (0.67–0.83)	0.16	2.98	0.23	4.21
SBP CV	0.76 (0.67–0.83)	0.12	2.97	0.17	4.20
SBP VIM	0.75 (0.65–0.82)	0.03	1.34	0.04	1.90
SBP ARV	0.87 (0.82–0.91)	0.05	2.82	0.07	3.99
SBP$_{range}$	0.53 (0.38–0.65)	1.13	3.35	1.59	4.74
Diastolic blood pressure	0.97 (0.94–1.00)	0.24	0.31	0.34	0.43
DBP SD	0.77 (0.69–0.84)	0.13	4.42	0.19	6.25
DBP CV	0.79 (0.71–0.85)	0.19	4.78	0.27	6.76
DBP VIM	0.73 (0.63–0.81)	0.11	4.71	0.15	6.67
DBP ARV	0.82 (0.75–0.87)	0.08	4.06	0.11	5.75

Table 3. Test–retest reliability of cardiovascular parameters obtained from continuous noninvasive blood pressure monitor. *ICC* intraclass correlation coefficient, *SEM, SRD* smallest real difference, *SBP* systolic blood pressure, *SD* standard deviation, *CV* coefficient of variation, *VIM* variability independent of the mean, *ARV* average real variability, *DBP* diastolic blood pressure. N = 111.

	No antihypertensives n = 60	Antihypertensives n = 39
Variable name	ICC (95% CI)	ICC (95% CI)
Systolic blood pressure	0.96 (0.93–0.98)	0.98 (0.95–0.99)
SBP SD	0.77 (0.64–0.86)	0.63 (0.40–0.79)
SBP CV	0.75 (.61–0.84)	0.63 (0.39–0.78)
SBP VIM	0.75 (0.61–0.84)	0.64 (0.41–0.80)
SBP ARV	0.93 (0.88–0.96)	0.81 (0.67–0.90)
SBP$_{range}$	0.53 (0.31–0.69)	0.49 (0.21–0.70)
Diastolic blood pressure	0.97 (0.96–0.98)	0.98 (0.96–0.99)
DBP SD	0.83 (0.73–0.90)	0.66 (0.44–0.81)
DBP CV	0.86 (0.77–0.91)	0.68 (0.46–0.82)
DBP VIM	0.70 (0.54–0.81)	0.83 (0.70–0.91)
DBP ARV	0.90 (0.83–0.94)	0.70 (0.50–0.83)

Table 4. Test–retest reliability of blood pressure variability metrics obtained from continuous noninvasive blood pressure monitor stratified by antihypertensive medication use. *ICC* intraclass correlation coefficient, *SBP* systolic blood pressure, *SD* standard deviation, *CV* coefficient of variation, *VIM* variability independent of the mean, *ARV* average real variability, *DBP* diastolic blood pressure. N = 99.

BPV metrics[47–49]. This concept is illustrated in (Fig. 2A,B), where we can see BP dispersion metrics, such as SD, are more heavily influenced by low-frequency oscillations in BP, while BP ARV is more directly influenced by beat-to-beat changes in blood pressure.

Low-frequency oscillations may be modulated in part by changes to peripheral vascular resistance[50], transient oscillatory responses to hemodynamic perturbations[51], and intrinsic vasomotor rhythmicity[50] while beat-to-beat changes in BP are mediated by central sympathetic drive, arterial and cardiopulmonary reflexes, and arterial stiffness[26,52]. Additionally, ARV considers the temporal order of BP measurements, adding a time series variability component to the measurement[53] since it reflects the variation in successive differences in beat-to-beat BP. These features of ARV potentially add prognostic value[54] and overcome some pitfalls of the SD-based measures which only measure dispersion around mean BP and may be more influenced by outliers[55], while also ignoring the temporal order of BP measurements[2,54,56–58]. Additionally, two individuals with different BP profiles may have similar BPV dispersion measures but different ARVs[59]. The fact that ARV entails measurement of consecutive beat-to-beat differences rather than dispersion from the mean make ARV particularly well-suited for assessing beat-to-beat variation in BP[2]. A parallel can be drawn here to a heart rate variability (HRV) metric, root mean square of successive differences (RMSSD)[60], which acts as a high pass filter thus reflecting the high frequency variability in heart rate and is calculated similarly to ARV[60]. RMSSD has been shown to offer certain advantages over other HRV metrics, and it's possible that ARV may share some of these same advantages such as shorter required sampling durations for reliable measurements[61], and unique insights into parasympathetic tone[62], but further research is needed.

Conversely, SBP$_{range}$, a measure of systolic BP instability, displayed the lowest test–retest reliability, likely due to increased susceptibility to outliers and swings in BP over time[47]. All six systolic and diastolic BP dispersion
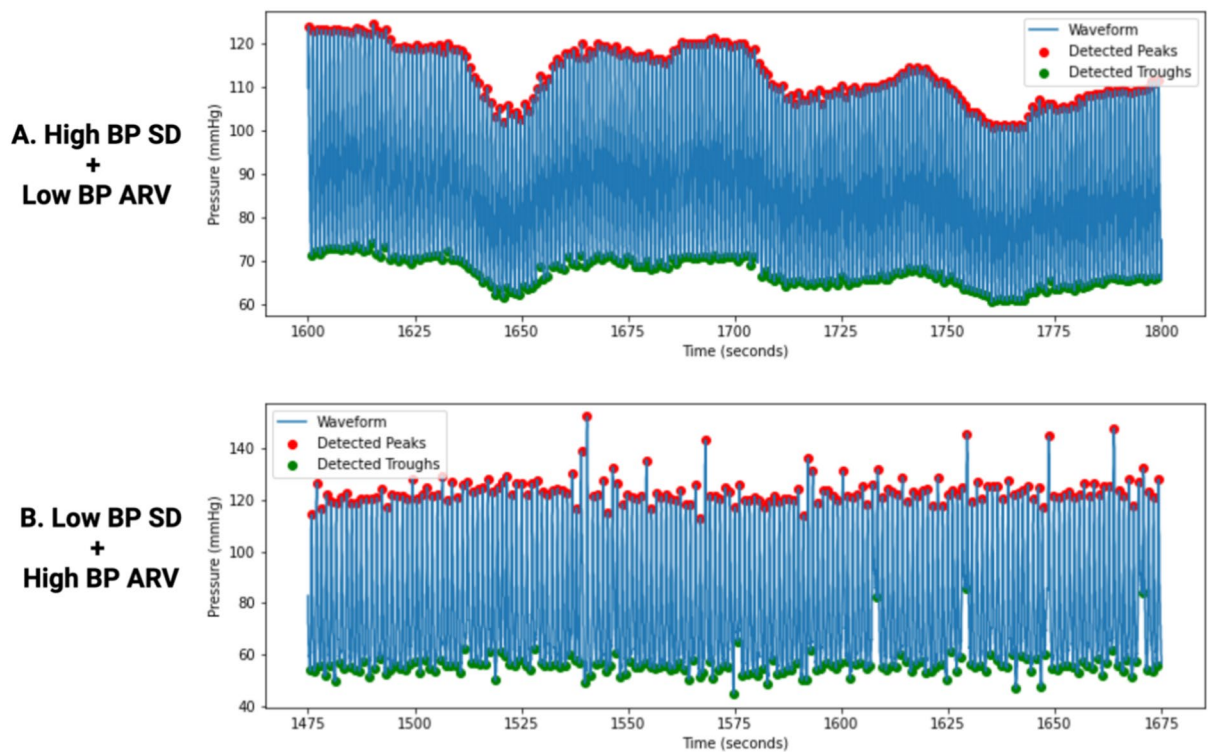
Fig. 2. Visualization of two distinct blood pressure variability profiles (**A**) An example waveform from an individual with high blood pressure standard deviation (BP SD) but low average real variability (ARV). (**B**) An example waveform from an individual with high ARV but low BP SD.

metrics displayed good test–retest reliability. The similar reliability between dispersion measures means that metric choice should be based on context and the individual characteristics of each measure.

When stratified by antihypertensive medication use, SBP ARV displayed excellent reliability in the group not using antihypertensive medications and was the only systolic BPV metric that displayed good reliability in the group using antihypertensive medications. All other measures of systolic BPV displayed moderate or poor test–retest reliability. This is a clinically relevant finding given the widespread use of antihypertensive medication in older adults[63], and supports the use of SBP ARV regardless of antihypertensive treatment status.

The mechanisms responsible for increased systolic BPV are more clearly understood than those associated with increased diastolic BPV. For example, visit-to-visit systolic BPV has been shown to correlate with arterial stiffness[64] and worsening renal function[65], while visit-to-visit DBP variability has not. A key difference between visit-to-visit BPV and beat-to-beat BPV is that visit-to-visit BPV could be influenced by antihypertensive medication adherence[66]. For this reason, beat-to-beat BPV may be a more accurate assessment of the underlying physiology which modulates BPV. Regarding this underlying physiology, although not fully understood[55], most studies place central importance on the central sympathetic drive[24,26], neuronal reflexes[22,24,67,68], and arterial stiffness[64,69,70].

The variety of available BPV metrics and relative lack of understanding pertaining to causal mechanisms has resulted in metric choice being largely based on convenience up to this point, and most studies have used less granular and likely less reliable visit-to-visit measures. More investigations should be conducted to differentiate the underlying mechanisms that modulate beat-to-beat BPV metrics and continued assessment of reliability is needed. Limitations of the current study include a relatively small sample size and a restricted age range potentially limiting generalizability.

The present study supports the use of continuous noninvasive BP derived metrics of BPV in older adults. Of those metrics tested, ARV displayed the highest level of test–retest reliability, perhaps due to its decreased susceptibility to outliers and low frequency oscillations in BP. While these low frequency oscillations reduced the reliability of beat-to-beat dispersion BPV measures, they may not be entirely extraneous, and should therefore continue to be studied to fully capture the multi-dimensional nature of BPV. All BPV metrics displayed good or excellent test–retest reliability in the present investigation, except for maximum minus minimum systolic BP. Future studies investigating the effects of beat-to-beat BPV should include ARV due to its increased reliability regardless of antihypertensive treatment status, and sensitivity to consecutive beat-to-beat differences in BP.

Methods
Participants
Participants were recruited from Los Angeles County and Orange County communities, and all procedures were conducted as part of the VaSC Study at the University of Southern California (USC) and University of California Irvine (UCI). Older adults aged 55 to 89 years who were living independently were included. Exclusion criteria

were history of clinical stroke, dementia, major neurological or psychiatric disorder or medications impairing the central nervous system, current organ failure or other uncontrolled systemic illness, or contraindication for brain MRI. Study inclusions and exclusions were verified by a structured clinical health interview and review of current medications with the participant and, when available, an informed study partner. This study was approved by the University of Southern California (HS-14-00784) and University of California, Irvine (HS-2019-5324) Institutional Review Boards, all participants gave informed consent, and the study was performed in accordance with all relevant guidelines and regulations.

Continuous BP data processing and analysis

Participants were asked to take medications as normally prescribed and abstain from caffeine the morning of data collection. Beat-to-beat BP measurements were obtained continuously during supine rest in a 3 T Siemens MRI scanner, using an MRI compatible non-invasive continuous BP finger cuff device (Biopac®). First, the participant rests for 3 min in the supine position prior to the calibration period. During calibration, BP waveforms are acquired by the continuous monitoring device and 2 static pressures are simultaneously acquired using a calibrated, MRI compatible automatic BP device with an inflatable brachial artery cuff (TeslaDUO). These static pressures are used to calibrate the continuous BP monitor using the Caretaker® system (Biopac®). After calibration, continuous BP was monitored during 2 sequential, 7 min MRI scans.

The Calib upsample utility (Biopac®) was used to extract continuous arterial pressure data obtained during the 2 sequential, 7 min MRI scans at a sample rate of 100 Hz. Data segments free from obvious motion artifacts were selected from each 7-min continuous BP data segment for further processing. Waveforms were excluded if more than 10% of the data needed to be excluded to remove obvious motion artifacts. Two 420 s waveform segment examples, one with an obvious motion artifact and one without, are shown in (Fig. 3) for illustration purposes.

A peak detection algorithm was used to identify SBP peaks which served as the basis for further cardiovascular parameter calculation. Peaks were detected using the find_peaks function from the scipy.signal library[71], with default parameters set to a minimum detection height of 80 mmHg, and a minimum peak separation of 400 ms by default. Diastolic troughs were identified as the lowest BP reading between two systolic peaks. Each waveform was then visually inspected using the VaSC BP Signal Toolbox application for erroneous or missing peaks and troughs by TL. Occasionally, default data filtering parameters were adjusted as needed to ensure accurate peak and trough detection. A visual illustration of this process is shown in (Fig. 4A,B).
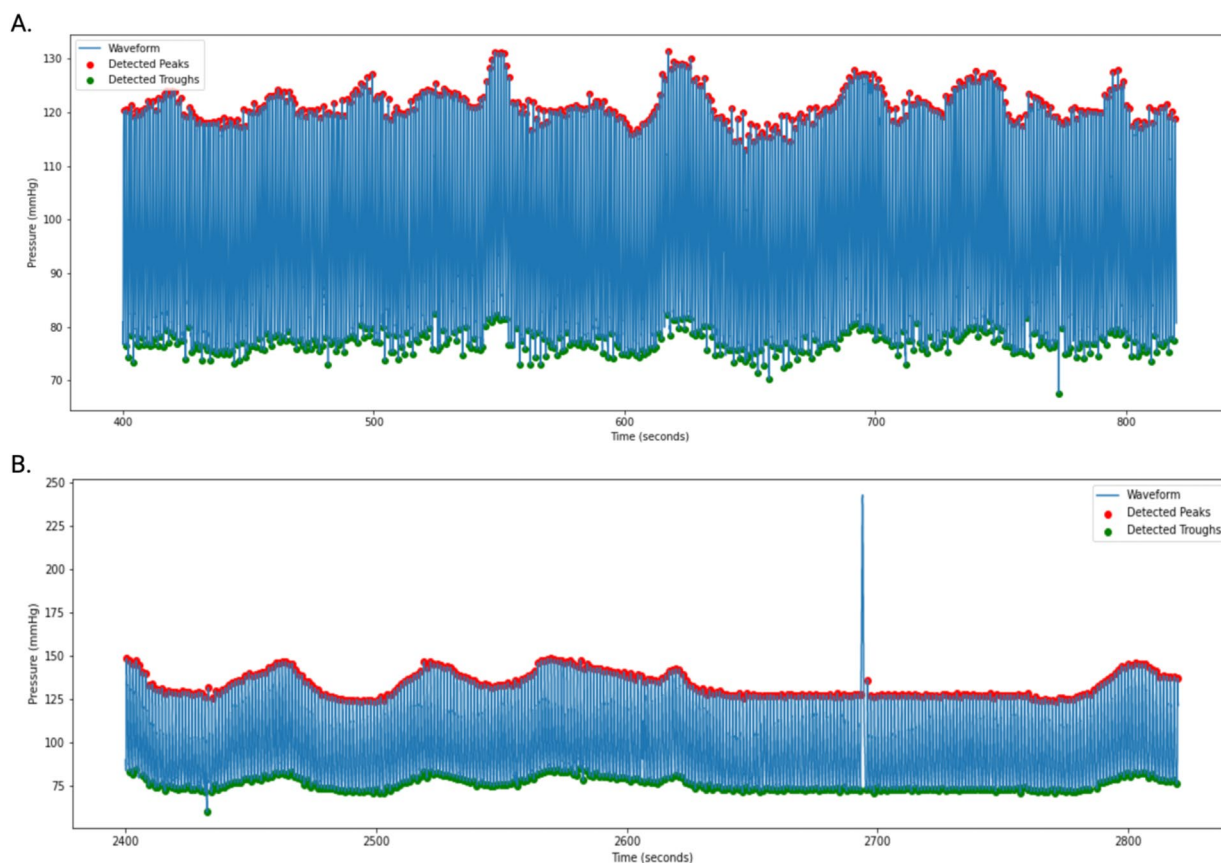

Fig. 3. Illustration of visual inspection for motion artifacts. (**A**) 420 s continuous blood pressure (BP) waveform with accurate peak (systolic blood pressure) and trough (diastolic blood pressure) detection free from obvious motion artifacts. (**B**) 420 s continuous BP waveform with motion artifact visible at approximately 2693 s.
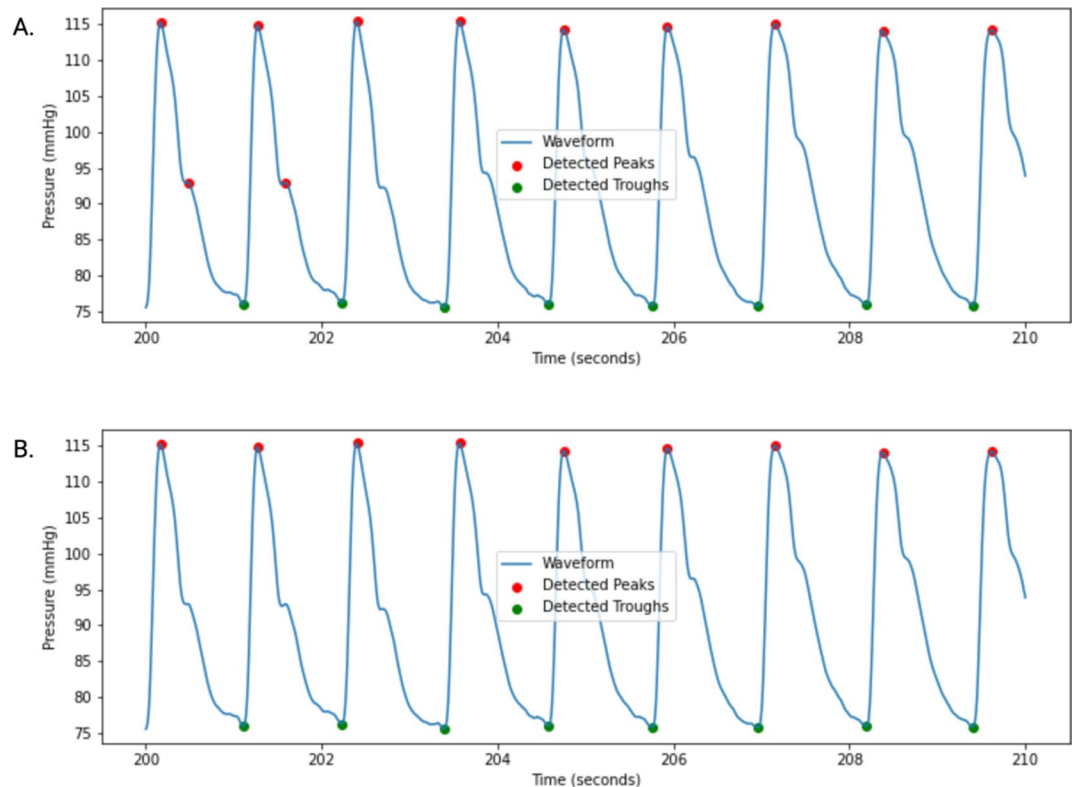
Fig. 4. Illustration of peak detection parameter adjustment. (**A**) A 10 s continuous blood pressure waveform with systolic peak and diastolic trough detection applied. Two pronounced dicrotic notches are erroneously detected as peaks by the peak detection algorithm at the 200.5 and 201.6 s marks when using the default minimum detection height and distance parameters (80 mmHg and 400 ms). (**B**) The same waveform displayed in (Fig. 2A) is now displayed with a modified minimum distance peak detection parameter of 450 ms. This modification results in accurate peak detection across the waveform.

Calculation of blood pressure variability metrics

In addition to measurement time, BPV metrics can also be categorized by index type (frequency, dispersion, sequence, or instability)[55,72]. Three measures of BP dispersion (SD, CV, and VIM), 1 measure of BP instability (SBP$_{range}$), and 1 measure of BP sequence (ARV) were calculated for test–retest comparison in the present study.

The standard deviation of SBP and DBP amplitude measurements (Fig. 5A) was obtained across the waveform's duration as shown in (Fig. 5B,C). BP SD was then further processed into CV and VIM[3]. Similar processes were repeated for diastolic BP metrics. Of these metrics, BP SD is used most often due to its straightforward calculation and interpretation, however, it may be correlated with sample mean BP[26,73]. BP CV and BP VIM measures may compliment BP SD because they are generally reported as less strongly correlated with mean BP[11,25,42,74], allowing for comparison of samples with different means in the case of CV[75] without average BP adjustment. BP CV is calculated as (BP SD/BP mean)*100 (Fig. 5B), while BP VIM is calculated by taking BP SD readings divided by mean BP raised to the power of x (SBP VIM x = 0.46), where x was derived from a non-linear curve fitting of BP standard deviation (SD) against average BP using the nls package in R[76] (Fig. 5B).

The difference between the maximum SBP reading and minimum SBP reading (SBP$_{range}$) was included as a measure of BP instability. SBP$_{range}$ is the difference between the maximum and minimum systolic BP readings in a specified window, 7 min for the present study.

Systolic and diastolic ARV measures were calculated by taking the absolute differences between consecutive peaks and troughs respectively, and then averaging them across the 7 min continuous BP waveform[26,56] (Fig. 5B). To further confirm the reliability of the continuous BP monitoring methodology the intrasession test–retest reliability of HR and BP were also assessed by comparing the mean HR, mean SBP, and mean DBP across each selected 7 min waveform.

Data analysis

All statistical analyses were carried out using R[76]. Paired t-tests were used to compare mean values of waveform 1 and 2 (test–retest). Intraclass correlation coefficient (ICC) with a 95% confidence interval was used to assess relative reliability using Munro's criteria[77] for interpretation while absolute reliability was assessed using the standard error of measurement (SEM), SEM%, smallest real difference (SRD), and SRD%. SEM is calculated as the SD of differences between paired measurements divided by the square root of the sample size[78,79] while SRD represents the smallest change in a measurement that likely represents a true change rather than a measurement
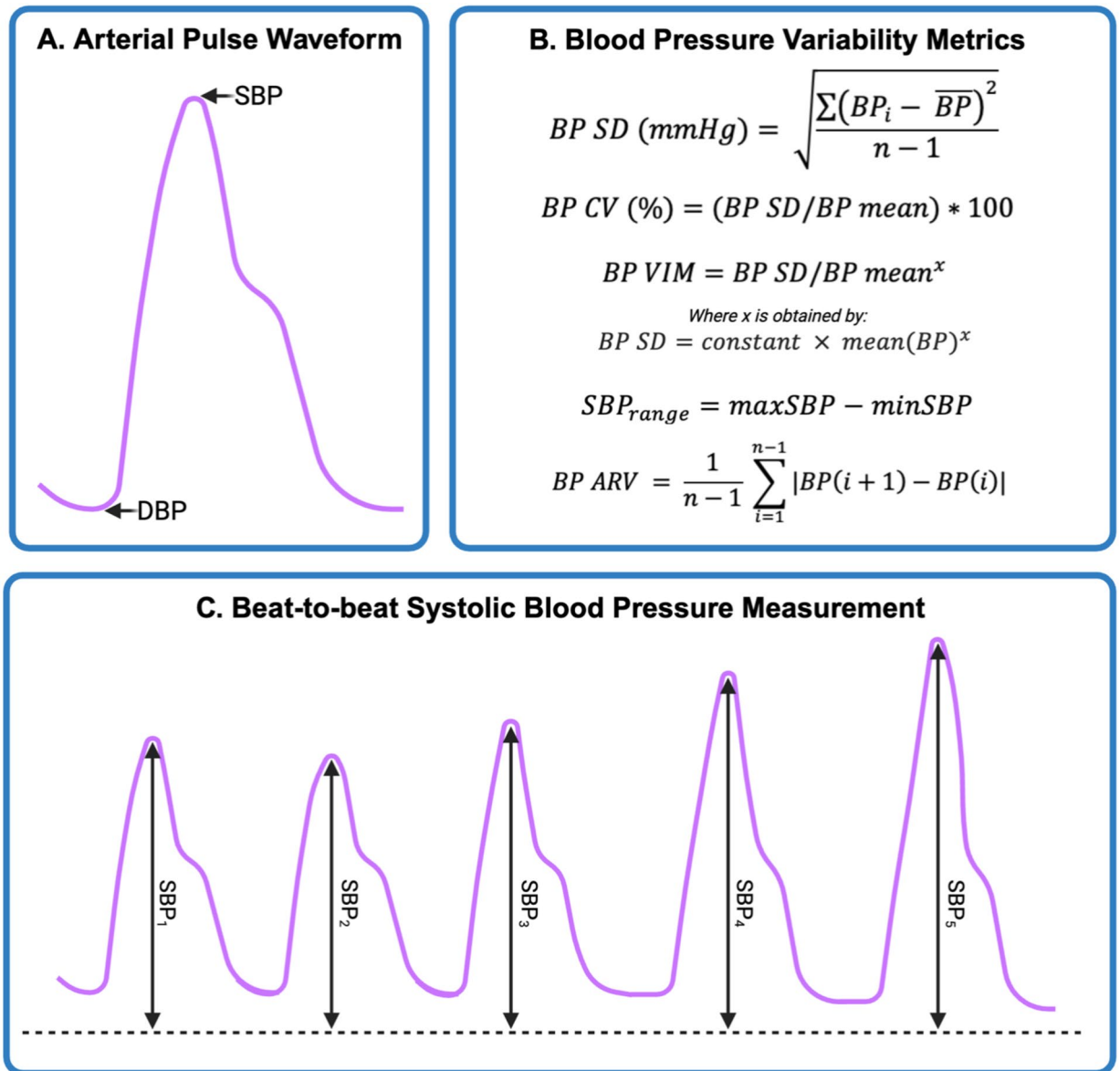
Fig. 5. Calculation of blood pressure variability metrics. (**A**) A single arterial pulse waveform with systolic blood pressure (SBP) peak and diastolic blood pressure (DBP) trough indicated. (**B**) Five blood pressure variability metric formulas used in the present analysis: Blood pressure (BP) standard deviation, coefficient of variation (CV), variability independent of the mean (VIM), SBP_{range}, and average real variability (ARV). (**C**) A visual representation of continuous BP waveform with 5 arterial pulse cycles and SBP measurements used for systolic blood pressure variability calculations.

error[78,80]. ICC, SEM, and SRD are commonly used measures of test–retest reliability and are specifically used for this purpose in literature[81–84].

Data availability
The anonymous data that support the findings of this study are available upon reasonable request from the corresponding author, DN, through appropriate data sharing protocols.

Code availability
The VaSC BP Signal Toolbox can be accessed at https://github.com/BP-Signal-Toolbox.git after requesting repository access from the corresponding author, DN.

References

1. Dasa, O. *et al.* Association of 1 year blood pressure variability with long-term mortality among adults with coronary artery disease: A post hoc analysis of a randomized clinical trial. *JAMA Netw. Open* **4**, e218418–e218418 (2021).
2. Sheikh, A. B. *et al.* Blood pressure variability in clinical practice: Past, present and the future. *J. Am. Heart Assoc.* **12**, e029297 (2023).
3. Ebinger, J. E. *et al.* Variability independent of mean blood pressure as a real-world measure of cardiovascular risk. *EClinicalMedicine* **48**, 101442 (2022).
4. Stevens, S. L. *et al.* Blood pressure variability and cardiovascular disease: Systematic review and meta-analysis. *BMJ* **354**, i4098 (2016).
5. Gosmanova, E. O. *et al.* Association of systolic blood pressure variability with mortality, coronary heart disease, stroke, and renal disease. *J. Am. Coll. Cardiol.* **68**, 1375–1386 (2016).
6. Muntner, P. *et al.* Visit-to-visit variability of blood pressure and coronary heart disease, stroke, heart failure, and mortality: A cohort study. *Ann. Intern. Med.* **163**, 329–338 (2015).
7. Ohkuma, T. *et al.* Prognostic value of variability in systolic blood pressure related to vascular events and premature death in type 2 diabetes mellitus: The advance-on study. *Hypertension* **70**, 461–468 (2017).
8. Wan, E. Y. F. *et al.* Association of visit-to-visit variability of systolic blood pressure with cardiovascular disease, chronic kidney disease and mortality in patients with hypertension. *J. Hypertens.* **38**, 943–953 (2020).
9. Mehlum, M. H. *et al.* Blood pressure variability and risk of cardiovascular events and death in patients with hypertension and different baseline risks. *Eur. Heart J.* **39**, 2243–2251 (2018).
10. Heshmatollah, A. *et al.* Visit-to-visit blood pressure variability and the risk of stroke in the Netherlands: A population-based cohort study. *PLoS Med.* **19**, e1003942 (2022).
11. Rothwell, P. M. *et al.* Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* **375**, 895–905 (2010).
12. Shimbo, D. *et al.* Association between annual visit-to-visit blood pressure variability and stroke in postmenopausal women: Data from the women's health initiative. *Hypertension* **60**, 625–630 (2012).
13. Ma, Y. *et al.* Blood pressure variability and cerebral small vessel disease. *Stroke* **51**, 82–89 (2020).
14. Sible, I. J., Bangen, K. J., Blanken, A. E., Ho, J. K. & Nation, D. A. Antemortem visit-to-visit blood pressure variability predicts cerebrovascular lesion burden in autopsy-confirmed Alzheimer's disease. *J. Alzheimers Dis.* **83**, 65–75 (2021).
15. Sible, I. J. & Nation, I. Alzheimer's disease neuroimaging, visit-to-visit blood pressure variability and csf alzheimer disease biomarkers in cognitively unimpaired and mildly impaired older adults. *Neurology* **98**, e2446–e2453 (2022).
16. Yoo, J. E. *et al.* Blood pressure variability and the risk of dementia. *Hypertension* **75**, 982–990 (2020).
17. Ebinger, J. *et al.* Blood pressure variability supersedes heart rate variability as a real-world measure of dementia risk. *Sci. Rep.* https://doi.org/10.1038/s41598-024-52406-8 (2024).
18. Gutteridge, D. S., Tully, P. J., Smith, A. E., Loetscher, T. & Keage, H. A. Cross-sectional associations between short and mid-term blood pressure variability, cognition, and vascular stiffness in older adults. *Cereb. Circ. Cogn. Behav.* **5**, 100181 (2023).
19. Hesse, C., Charkoudian, N., Liu, Z., Joyner, M. J. & Eisenach, J. H. Baroreflex sensitivity inversely correlates with ambulatory blood pressure in healthy normotensive humans. *Hypertension* **50**, 41–46 (2007).
20. Zhou, T. L. *et al.* Blood pressure variability, arterial stiffness, and arterial remodeling. *Hypertension* **72**, 1002–1010 (2018).
21. Clark, D. III. *et al.* Visit-to-visit blood pressure variability, coronary atheroma progression, and clinical outcomes. *JAMA Cardiol.* **4**, 437–443 (2019).
22. Lanfranchi, P. A. & Somers, V. K. Arterial baroreflex function and cardiovascular variability: Interactions and implications. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **283**, R815-826 (2002).
23. Ding, K. *et al.* Central autonomic network functional connectivity: Correlation with baroreflex function and cardiovascular variability in older adults. *Brain Struct. Funct.* **225**, 1575–1585 (2020).
24. Rosei, E. A., Chiarini, G. & Rizzoni, D. How important is blood pressure variability?. *Eur. Heart J. Suppl.* **22**, E1-e6 (2020).
25. Chadachan, V. M., Ye, M. T., Tay, J. C., Subramaniam, K. & Setia, S. Understanding short-term blood-pressure-variability phenotypes: From concept to clinical practice. *Int. J. Gen. Med.* **11**, 241–254 (2018).
26. Parati, G., Ochoa, J. E., Lombardi, C. & Bilo, G. Assessment and management of blood-pressure variability. *Nat. Rev. Cardiol.* **10**, 143–155 (2013).
27. Parati, G., Ochoa, J. E., Salvi, P., Lombardi, C. & Bilo, G. Prognostic value of blood pressure variability and average blood pressure levels in patients with hypertension and diabetes. *Diabetes Care* **36**(2), S312-324 (2013).
28. Parati, G., Saul, J. P., Di Rienzo, M. & Mancia, G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. *Hypertension* **25**, 1276–1286 (1995).
29. Mancia, G. *et al.* Arterial baroreflexes and blood pressure and heart rate variabilities in humans. *Hypertension* **8**, 147–153 (1986).
30. Conway, J., Boon, N., Davies, C., Jones, J. V. & Sleight, P. Neural and humoral mechanisms involved in blood pressure variability. *J. Hypertens.* **2**, 203–208 (1984).
31. Webb, A. J. S., Lawson, A., Wartolowska, K., Mazzucco, S. & Rothwell, P. M. Progression of beat-to-beat blood pressure variability despite best medical management. *Hypertension* **77**, 193–201 (2021).
32. Tian, G. *et al.* Beat-to-beat blood pressure variability and heart rate variability in relation to autonomic dysregulation in patients with acute mild-moderate ischemic stroke. *J. Clin. Neurosci.* **64**, 187–193 (2019).
33. Kwon, Y., Stafford, P. L., Enfield, K., Mazimba, S. & Baruch, M. C. Continuous noninvasive blood pressure monitoring of beat-by-beat blood pressure and heart rate using caretaker compared with invasive arterial catheter in the intensive care unit. *J. Cardiothorac. Vasc. Anesth.* **36**, 2012–2021 (2022).
34. Kwon, Y. *et al.* Tracking of the beat-to-beat blood pressure changes by the caretaker physiological monitor against invasive central aortic measurement. *Blood Press. Monit.* **27**, 70–76 (2022).
35. Gratz, I. *et al.* Continuous non-invasive finger cuff caretaker® comparable to invasive intra-arterial pressure in patients undergoing major intra-abdominal surgery. *BMC Anesthesiol.* **17**, 48 (2017).
36. Schutte, A. E., Huisman, H. W., van Rooyen, J. M., Malan, N. T. & Schutte, R. Validation of the finometer device for measurement of blood pressure in black women. *J. Hum. Hypertens.* **18**, 79–84 (2004).
37. Ameloot, K. *et al.* Validation study of Nexfin® continuous non-invasive blood pressure monitoring in critically ill adult patients. *Minerva Anestesiol.* **80**, 1294–1301 (2014).
38. Sible, I. J. *et al.* Visit-to-visit blood pressure variability and longitudinal tau accumulation in older adults. *Hypertension* **79**, 629–637 (2022).
39. Sible, I. J. *et al.* Visit-to-visit blood pressure variability and regional cerebral perfusion decline in older adults. *Neurobiol. Aging* **105**, 57–63 (2021).
40. Sible, I. J. & Nation, D. A. Blood pressure variability and medial temporal atrophy in apolipoprotein ε4 carriers. *Brain Imaging Behav.* **16**, 792–801 (2022).
41. Sible, I. J. *et al.* Short-term blood pressure variability is inversely related to regional amplitude of low frequency fluctuations in older and younger adults. *Aging Brain* **4**, 100085 (2023).

42. Stergiou, G. S. *et al.* Methodology and technology for peripheral and central blood pressure and blood pressure variability measurement: current status and future directions—Position statement of the European society of hypertension working group on blood pressure monitoring and cardiovascular variability. *J. Hypertens.* **34**, 1665–1677 (2016).

43. Muntner, P. *et al.* Reproducibility of visit-to-visit variability of blood pressure measured as part of routine clinical care. *J. Hypertens.* **29**, 2332–2338 (2011).

44. Howard, S. C. & Rothwell, P. M. Reproducibility of measures of visit-to-visit variability in blood pressure after transient ischaemic attack or minor stroke. *Cerebrovasc. Dis.* **28**, 331–340 (2009).

45. Finucane, C., Savva, G. M. & Kenny, R. A. Reliability of orthostatic beat-to-beat blood pressure tests: Implications for population and clinical studies. *Clin. Auton. Res.* **27**, 31–39 (2017).

46. Bland, J. M. & Altman, D. G. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* **1**, 307–310 (1986).

47. Levitan, E. B., Kaciroti, N., Oparil, S., Julius, S. & Muntner, P. Relationships between metrics of visit-to-visit variability of blood pressure. *J. Hum. Hypertens.* **27**, 589–593 (2013).

48. Yano, Y. Visit-to-visit blood pressure variability—What is the current challenge?. *Am. J. Hypertens.* **30**, 112–114 (2017).

49. Sun, F. The impact of blood pressure variability on cognition: Current limitations and new advances. *J. Hypertens.* **41**, 888–905 (2023).

50. Zhang, R. *et al.* Mechanism of blood pressure and R-R variability: Insights from ganglion blockade in humans. *J. Physiol.* **543**, 337–348 (2002).

51. Julien, C. The enigma of mayer waves: Facts and models. *Cardiovasc. Res.* **70**, 12–21 (2006).

52. Webb, A. J. S. *et al.* Body mass index and arterial stiffness are associated with greater beat-to-beat blood pressure variability after transient ischemic attack or minor stroke. *Stroke* **52**, 1330–1338 (2021).

53. Del Giorno, R., Balestra, L., Heiniger, P. S. & Gabutti, L. Blood pressure variability with different measurement methods: Reliability and predictors. A proof of concept cross sectional study in elderly hypertensive hospitalized patients. *Medicine (Baltimore)* **98**, e16347 (2019).

54. Mena, L. J., Felix, V. G., Melgarejo, J. D. & Maestre, G. E. 24-hour blood pressure variability assessed by average real variability: A systematic review and meta-analysis. *J.Am. Heart Assoc.* **6**, e006895 (2017).

55. Parati, G., Stergiou, G. S., Dolan, E. & Bilo, G. Blood pressure variability: Clinical relevance and application. *J. Clin. Hypertens.* **20**, 1133–1137 (2018).

56. Mena, L. *et al.* A reliable index for the prognostic significance of blood pressure variability. *J. Hypertens.* **23**, 505–511 (2005).

57. Mena, L. J. *et al.* How many measurements are needed to estimate blood pressure variability without loss of prognostic information?. *Am. J. Hypertens.* **27**, 46–55 (2014).

58. Parati, G. & Rizzoni, D. Assessing the prognostic relevance of blood pressure variability: Discrepant information from different indices. *J. Hypertens.* **23**, 483–486 (2005).

59. Hansen, T. W. *et al.* Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. *Hypertension* **55**, 1049–1057 (2010).

60. Ellis, R. J., Zhu, B., Koenig, J., Thayer, J. F. & Wang, Y. A careful look at ECG sampling frequency and R-peak interpolation on short-term measures of heart rate variability. *Physiol. Meas.* **36**, 1827 (2015).

61. Baek, H. J., Cho, C. H., Cho, J. & Woo, J. M. Reliability of ultra-short-term analysis as a surrogate of standard 5 min analysis of heart rate variability. *Telemed. E Health* **21**, 404–414 (2015).

62. Thayer, J. F. & Lane, R. D. A model of neurovisceral integration in emotion regulation and dysregulation. *J. Affect. Disord.* **61**, 201–216 (2000).

63. Bowling, C. B., Lee, A. & Williamson, J. D. Blood pressure control among older adults with hypertension: Narrative review and introduction of a framework for improving care. *Am. J. Hypertens.* **34**, 258–266 (2021).

64. Schillaci, G. *et al.* Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: findings from 2 large databases. *Hypertension* **60**, 369–377 (2012).

65. Sarafidis, P. A. *et al.* Blood pressure variability increases with advancing chronic kidney disease stage: A cross-sectional analysis of 16 546 hypertensive patients. *J. Hypertens.* **36**, 1076–1085 (2018).

66. Muntner, P. *et al.* Association between antihypertensive medication adherence and visit-to-visit variability of blood pressure. *J. Clin. Hypertens. (Greenwich)* **15**, 112–117 (2013).

67. Young, B. E. *et al.* Augmented resting beat-to-beat blood pressure variability in young, healthy, non-hispanic black men. *Exp. Physiol.* **105**, 1102–1110 (2020).

68. Fadel, P. J. Arterial baroreflex control of the peripheral vasculature in humans: Rest and exercise. *Med. Sci. Sports Exerc.* **40**, 2055–2062 (2008).

69. Kotsis, V. *et al.* Arterial stiffness and 24 h ambulatory blood pressure monitoring in young healthy volunteers: The early vascular ageing aristotle university thessaloniki study (EVA-ARIS Study). *Atherosclerosis* **219**, 194–199 (2011).

70. Stabouli, S. *et al.* Arterial stiffness and SBP variability in children and adolescents. *J. Hypertens.* **33**, 88–95 (2015).

71. Virtanen, P. *et al.* SciPy 1.0: Fundamental algorithms for scientific computing in python. *Nat. Methods* **17**, 261–272 (2020).

72. Stergiou, G. S. & Parati, G. How to best assess blood pressure?. *Hypertension* **57**, 1041–1042 (2011).

73. Parati, G., Torlasco, C., Pengo, M., Bilo, G. & Ochoa, J. E. Blood pressure variability: Its relevance for cardiovascular homeostasis and cardiovascular diseases. *Hypertens. Res.* **43**, 609–620 (2020).

74. Bilo, G., Grillo, A., Guida, V. & Parati, G. Morning blood pressure surge: Pathophysiology, clinical relevance and therapeutic aspects. *Integr. Blood Press. Contr.* **11**, 47–56 (2018).

75. Schutte, A. E., Kollias, A. & Stergiou, G. S. Blood pressure and its variability: Classic and novel measurement techniques. *Nat. Rev. Cardiol.* **19**, 643–654 (2022).

76. R Core Team. R: A language and environment for statistical computing. (Foundation for Statistical Computing, Vienna, Austria, 2022).

77. Plichta, S. B., Kelvin, E. A. Munro's statistical methods for health care research: Sixth edition. pp. 1–567 (2011).

78. Mokkink, L. B., Eekhout, I., Boers, M., van der Vleuten, C. P. M. & de Vet, H. C. W. Studies on reliability and measurement error of measurements in medicine—From design to statistics explained for medical researchers. *Patient Relat. Outcome Meas.* **14**, 193–212 (2023).

79. Harvill, L. M. Standard error of measurement. *Educ. Meas. Issues Pract.* **10**, 33–41 (1991).

80. Beckerman, H. *et al.* Smallest real difference, a link between reproducibility and responsiveness. *Qual. Life Res.* **10**, 571–578 (2001).

81. Barrios-Fernandez, S. *et al.* Intrasession reliability analysis for oscillometric blood pressure method using a digital blood pressure monitor in peruvian population. *Healthcare (Basel)* **10**, 209 (2022).

82. Brody, S., Veit, R. & Rau, H. Four-year test-retest reliability of self-measured blood pressure. *Arch. Intern. Med.* **159**, 1007–1008 (1999).

83. Koh, Y. L. E. *et al.* Using a web-based approach to assess test-retest reliability of the "hypertension self-care profile" tool in an Asian population: A validation study. *Medicine* **95**, e2955 (2016).

84. Schuck, P. & Zwingmann, C. The 'smallest real difference' as a measure of sensitivity to change: A critical analysis. *Int. J. Rehabil. Res.* **26**, 85–91 (2003).

Acknowledgements

Author contributions

T.L. conceived, designed, and performed the analysis, wrote the main manuscript text, and prepared all figures and tables. I.J.S. contributed to study execution and manuscript preparation. F.S. contributed to study execution and manuscript preparation. A.E. contributed to study execution and manuscript preparation. A.K. contributed to study execution and manuscript preparation. J.M.A. contributed to study execution and manuscript preparation. A.G. contributed to study execution and manuscript preparation. J.F.T. contributed to study execution and manuscript preparation. F.F. contributed to study execution and manuscript preparation. D.A.N. conceived and designed the analysis and contributed to study execution manuscript preparation. All authors reviewed the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-71183-y.

Correspondence and requests for materials should be addressed to D.A.N.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.