King's Research Portal

Link to publication record in King's Research Portal

REPRODUCIBILITY OF SEQUENTIAL AMBULATORY BLOOD PRESSURE AND PULSE WAVE VELOCITY MEASUREMENTS IN NORMOTENSIVE AND HYPERTENSIVE INDIVIDUALS

Short title: Reproducibility of ABPM and PWV

Louise KEEHN [a]

Wendy L HALL [b]

Sarah E BERRY [b]

Thomas AB SANDERS [b]

Phil CHOWIENCZYK [a*]

Christopher N FLOYD [a*]

[a] King's College London British Heart Foundation Centre, Department of Clinical Pharmacology, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH.

[b] Department of Nutritional Sciences, Franklin-Wilkins Building, King's College London, Stamford Street, London, SE1 9NH.

[*] Equal contribution

This work has not been published in its current form or a substantially similar form, has not been accepted for publication elsewhere and is not under consideration by another publication.

Corresponding author, & requests for reprints to: Professor Phil Chowienczyk,

Department of Clinical Pharmacology, St Thomas' Hospital, Westminster Bridge Road,

London, SE1 7EH. Tel: 020 7188 4771, Fax: 020 7188 5116.

Email:phil.chowienczyk@kcl.ac.uk.

Conflicts of Interest and Source of Funding

Data Availability

Data supporting this article is not openly available due to ethical restrictions. A descriptive record can be found in the Kings College London research data repository at http://doi.org/doi:10.18742/20348892. Data may be shared on reasonable request by application to Professor Tom Sanders, tom.sanders@kcl.ac.uk.

Word count: 6010

Number of Tables: 3

Number of Figures: 3

Number of Supplemental Digital Content Files: 1

ABSTRACT AND KEYWORDS

Objective: Errors in blood pressure (BP) measurement account for a large proportion of misclassified hypertension diagnoses. Ambulatory blood pressure monitoring (ABPM) is often considered to be the gold standard for measurement of BP, but uncertainty remains regarding the degree of measurement error. The aim of this study was to determine reproducibility of sequential ABPM in a population of normotensive and well-controlled hypertensive subjects.

Methods: Individual participant data from three randomised controlled trials which had recorded ABPM and carotid-femoral pulse wave velocity (PWV) at least twice was combined (*n*=501). We calculated within-subject variability of daytime and night-time BP and compared the variability between normotensive (*n*=324) and hypertensive (*n*=177) subjects. As a secondary analysis, variability of PWV measurements was also calculated, and multivariable linear regression was used to assess characteristics associated with blood pressure variability (BPV).

Results: Within-subject coefficient of variation (CoV) for systolic blood pressure was 5.4% (day) and 7.0% (night). Equivalent values for diastolic blood pressures were 6.1% and 8.4% respectively. Although variability appeared correlated to mean pressures, no statistically significant difference in CoV was demonstrated between measurements for normotensive and hypertensive individuals. Within-subject CoV for PWV exceeded that of BP measurements (10.7%). BPV was associated with mean pressures, and body mass index for night-time measurements. PWV was not independently associated with BPV.

Conclusions: The variability of single ABPM measurements will still yield considerable uncertainty regarding true average pressures, potentially resulting in misclassification of hypertensive status and incorrect treatment regimes. Repeated ABPM may be necessary to refine antihypertensive therapy.

INTRODUCTION

Ambulatory BP measurement (ABPM) has been shown to be the most cost-effective option to confirm a diagnosis of hypertension [1]. The reproducibility of average blood pressure (BP) taken by 24-hr ABPM has been previously shown to be superior to the reproducibility of clinic BP [2–4]. However, the majority of studies examining ABPM reproducibility have been performed with time intervals of 12 weeks or less, or in subjects with long term hypertension or history of cardiovascular disease.

There are fewer studies comparing techniques for long term monitoring and clinic BP remains a first-line tool despite well-known risks from white-coat or masked hypertension [5–7]. Long-term monitoring using ABPM could facilitate improved BP control, but the degree of variability between sequential ABPM in normotensive and stable hypertensive individuals otherwise free from overt cardiovascular disease is poorly characterised.

Retrospective analysis of individual patient data (IPD) from randomised controlled trial (RCTs) provides an opportunity to investigate ABPM measurement variability. Here we present analyses of measurement variability from three studies which investigated possible benefits of dietary modification on ambulatory blood pressure and arterial stiffness in subjects who were normotensive or with well-controlled hypertension [8–10]. The concurrent measurement of pulse wave velocity (PWV) in these subjects presented an ideal opportunity to directly compare the reproducibility of PWV against that of ABPM, as superior reproducibility may support the alternate use of PWV as a long-term monitoring tool for cardiovascular health.

Even in a healthy population, reproducibility of BP measurements will be affected by blood pressure variability (BPV). Some degree of BPV is a normative property but high

variability has been shown to be associated with an increased risk of cardiovascular outcomes, independent of the mean systolic pressure [11–13]. Determinants of increased BPV may include general cardiovascular risk factors such as increasing age, arterial stiffness and adverse lipid profiles [14,15] amongst others. Elucidation of factors associated with BPV in this cohort may provide clues to modifiable risk factors for high BPV in cohorts at higher risk of cardiovascular morbidities.

Therefore, the primary aim of the present study was to calculate reproducibility associated with sequential ABPM in this relatively healthy population of normotensive and well-controlled hypertensive individuals. Secondary aims were to estimate BPV and its potential determinants and to compare the reproducibility of arterial stiffness to that of ABPM for evaluation of its use as a surrogate technique for long-term measurement of vascular health.

METHODS

Subjects and Inclusion Criteria

We analysed IPD from three RCTs investigating the impact of dietary modifications on cardiovascular outcomes. Firstly, the Fruit & Veg study (ISRCTN50011192) tested whether a potassium-rich diet was beneficial for treatment-naive pre-hypertensive individuals (n=48)[8]. Secondly, the MARINA study (ISRCTN666664610, n=312) examined if increasing intake of oily fish favourably affected endothelial function and arterial stiffness [9]. Finally, the CRESSIDA study (ISRCTN9282106, n=162) considered how following UK dietary guidelines instead of a traditional British diet might affect vascular function [10]. All study and trial procedures were performed at Guy's and St. Thomas' NHS Foundation Trust. Each study was approved by a local research ethics committee.

Data were eligible for inclusion and analysis if they fulfilled the following criteria: (i) subjects must have had at least two ABPM and two PWV measurements, (ii) individual arms of each study did not show a significant change in BP measurements from baseline (statistical method detailed below) and (iii) no change in antihypertensive medications during the study. The second criterion ensured that any discrepancy between repeat measurements were secondary to measurement technique and physiological variability, rather than changes in an individual's true average BP (defined as a hypothetical estimate without measurement error and physiological variation [16]) resulting from dietary or other interventions. From the 522 available subject cases, 501 were retained in this analysis, as summarised in **Figure 1**.

Measurements

ABPM measurements were performed with the A&D TM-2430 device (ScanMed, Moreton-in-Marsh, Gloucestershire, UK) in all studies. CRESSIDA and the Fruit & Veg study took five measurements of ABPM, whilst MARINA recorded three. The first baseline measurement for CRESSIDA was followed by a second baseline measurement approximately 3 weeks later, then further measurements at 4, 8 and 12 weeks after the second baseline measurement. In Fruit & Veg, the first two measurements were approximately six weeks apart, then subsequent measurements every 11 weeks. MARINA measured ABPM at baseline, then 6 months and 12 months later. A full schedule of events can be found in **Table S1** (in Supplemental Digital Content). ABPM devices were programmed to take measurements every 30 minutes from 07:00 to 22:00 and hourly between 22:00 and 07:00, but daytime and night-time periods were defined by each participant according to a sleep diary.

PWV was measured by applanation tonometry of the carotid and femoral arteries using the SphygmoCor device (Atcor Medical, Sydney, Australia) after at least 15 minutes of rest. Further details of study procedures and study outcomes can be found in the published papers [8–10].

Nocturnal Dipping

Nocturnal dip category was estimated for each ABPM session firstly according to a simple dichotomous outcome of dipper (night-time SBP fall $\geq$ 10% of daytime SBP) or non-dipper (night-time SBP fall < 10% daytime SBP). Dipping status was then further defined according to the four classic dipping patterns (dipper: nocturnal SBP fall <10% of daytime SBP), reduced dipping (nocturnal BP fall 1-10% of daytime SBP), reverse

dipping (increase in nocturnal SBP) and extreme dipping (nocturnal SBP fall >20% of daytime SBP) [17].

Data Analysis

To verify whether individual arms of studies were eligible to be included in this analysis, repeated measures ANOVA was used to assess if there were significant differences in BP across each study timeframe. If ANOVA demonstrated significance <0.05, post-hoc pairwise comparisons were performed using the Bonferroni method between the initial and last ABPM measurement. Study arms were eligible to be included if the overall ANOVA significance was >0.05, or if $P<0.05$ but with no significant difference between the first and last measurement, (see **Table S2**, Supplemental Digital Content, which details the sequential blood pressures for each study arm, and the significance of any differences). As such, all arms of the studies were considered eligible to be included in this analysis.

Correlations were tested with Pearson's correlation coefficient unless stated otherwise. Comparison of subject characteristics at baseline and study endpoint were compared with paired t-tests. Logarithmic transformation was used to calculate the within-subject coefficient of variation (CoV) and corresponding 95% confidence interval (CI) as described by Bland and Altman [18,19] for daytime, night-time and 24-hour BP and HR, and PWV. CoV was compared between normotensive and hypertensive subjects. Normotension was defined as baseline daytime systolic blood pressure (SBP_{day}) < 135 mmHg, whereas hypertension was defined as baseline $SBP_{day} \geq 135$ mmHg.

Each subject had 2-5 measurements of SBP_{day}, night-time systolic blood pressure (SBP_{night}), daytime diastolic blood pressure (DBP_{day}) and night-time diastolic blood

pressure (DBP$_{night}$). The mean and standard deviation (SD) of these measurements was calculated for each subject. This intra-individual SD was used as an estimate of blood pressure variability (BPV) for each subject. Multivariable linear regression models were used to analyse associations between patient characteristics and BPV, using an enter method.

Effect of regression to the mean (or adaptation to the ABPM device) was analysed using repeated measures ANOVA in a subset of 199 subjects who had five ABPM measurements. Fleiss' Kappa was calculated to determine agreement above chance in dipping categories.

Statistical tests were performed in SPSS version 25 (IBM, Chicago, USA), and significance defined as $P<0.05$. One author (LK) had access to all the data and takes responsibility for its integrity and the data analysis.

RESULTS

Baseline characteristics

Participant characteristics at baseline are shown in **Table 1** (n=501). The cohort was predominantly female (61%), with mean (±SD) age 53.4 ± 8.0 years. Most subjects were of Caucasian ethnicity (80%). Mean clinic (seated) SBP and DBP were 124 ± 16 mmHg and 80 ± 10 mmHg respectively. A small proportion of subjects in the MARINA trial were on stable antihypertensive medication (4%). No subjects from CRESSIDA or Fruit & Veg were on antihypertensive therapy. Mean baseline PWV was 8.4 ± 1.6 m/s and mean baseline ambulatory SBP was 130 ± 13 mmHg during the day, 110 ± 14 mmHg at night and 125 ± 13 mmHg over 24 hours. Mean baseline ambulatory DBP was 79 ± 8 mmHg for day, 65 ± 8 mmHg at night and 76 ± 7 mmHg over 24 hours. Mean body mass index (BMI) at baseline was 26.0 ± 3.9 kg/m^2. There was no significant change in mean BMI over the duration of the studies (P=0.938).

Baseline SBP_{day} and SBP_{night} were significantly correlated with age (r=0.15, P=0.001 and r=0.14, P=0.001 respectively), but DBP_{day} and DBP_{night} were not (r=0.02, P=0.70 and r=0.85, P=0.06). Baseline BMI was significantly correlated with all baseline pressure measurements (r=0.26, P<0.001 for SBP_{day}, r=0.29, P<0.001 for SBP_{night}, r=0.16, P<0.001 for DBP_{day} and r=0.23, P<0.001 for DBP_{night}).

Associations between blood pressure variability and mean pressures

Significant associations were observed between mean ambulatory BP values and the variability of those measurements (**Figure 2**). For SBP, both day and night measurements demonstrated a significant association between mean values and the SD of those

measurements (SBP$_{day}$ r=0.21, P<0.001; SBP$_{night}$ r=0.27, P<0.001) (**Figures 2A and 2C**). When the relationship was investigated using the ratio of variability and mean SBP (individual CoV), the strength of the relationship was no longer significant for day measurements (r=0.03, P=0.449) and reduced for night (r=0.15, P=0.001; **Figures 2B and 2D**).

For ambulatory DBP measurements, a significant positive relationship was observed between mean values and the SD of those measurements (DBP$_{day}$ r=0.17, P<0.001 and DBP$_{night}$ r=0.29, P<0.001; **Figures 2E** and **2G**). Conducting the analyses with CoV removed the significant association for both DBP$_{day}$ and DBP$_{night}$ (r=0.02, P=0.696 and r=0.10, P=0.496, respectively; **Figures 2F** and **2H**).

Within-subject coefficient of variation for repeated ambulatory blood pressure measurements

Measures of within-subject CoV for each study and for the entire cohort are shown in **Table 2**. Qualitative analysis shows that measures of CoV for each BP measurement are similar for each study. In the entire cohort, the CoV for daytime measurements is significantly lower than that compared to night-time measurements: 5.4% (95% CI 5.2%-5.6%) for SBP$_{day}$ compared to 7.0% (95% CI 6.7%-7.3%) for SBP$_{night}$, and 6.1% (95% CI 5.9% –6.4%) for DBP$_{day}$ compared to 8.4% (95% CI 8.0%–8.7%) for DBP$_{night}$. CoV is significantly lower for 24-hour ABPM measurements: 4.8% (95% CI 4.6-5.0%) for SBP, and 5.3% (95% CI 5.1-5.5%) for DBP.

Reproducibility of ambulatory measurements were compared between subjects defined as normotensive on their baseline visit compared to those defined as hypertensive (**Table**

2 and Figure 3). The mean baseline SBP for the normotensive group was 122 ± 8 mmHg compared to 144 ± 9 mmHg for the hypertensive group. When considering all normotensives versus all hypertensives, there was no clear evidence of any difference in the reproducibility of SBP_{day}, SBP_{night}, DBP_{day} or DBP_{night}. However, both the CRESSIDA and Fruit & Veg studies showed significantly less variability in hypertensive subjects than normotensive subjects for measurements of DBP_{day}: 4.4% (95% CI 3.9%–4.9%) in hypertensive subjects compared to 5.3% (95% CI 5.0%–5.7%) in normotensive subjects in CRESSIDA, and 5.5% (95% CI 4.8%–6.2%) in hypertensive subjects compared to 7.7% (95% CI 6.4%–9.1%) in normotensive subjects in Fruit & Veg.

Association of subject risk factors to individual blood pressure variability

Average estimates of individual BPV as assessed by the SD were as follows; SBP_{day} SD 6.1 ± 3.3 mmHg, SBP_{night} SD 6.6 ± 3.8 mmHg, DBP_{day} SD 4.1 ± 2.3 mmHg and DBP_{night} SD 4.4 ± 2.5 mmHg. BPV was not correlated with age for SBP_{day}, SBP_{night}, DBP_{day} or DBP_{night} (all $P>0.05$). BMI at baseline was significantly correlated with SBP_{day} SD ($r=0.09$, $P=0.04$), SBP_{night} SD ($r=0.20$, $P<0.001$) and DBP_{night} SD ($r=0.19$, $P<0.001$), and had a borderline significant correlation with DBP_{day} SD ($r=0.09$, $P=0.054$).

Table 3 shows multivariable linear regression investigating the associations between BPV to subject demographics and mean BP. No significant associations were demonstrated for age, sex or PWV with SD for SBP_{day}, SBP_{night}, DBP_{day} or DBP_{night}. SBP_{day} SD was independently associated with non-white ethnicity, use of antihypertensive medication and mean SBP_{day}. SBP_{night} SD was independently associated with baseline BMI and mean SBP_{night}. DBP_{day} SD was only associated with mean DBP_{day}.

DBP_{night} SD was independently associated with baseline BMI and mean DBP_{night}. Further analyses were performed examining the effect of mean sleep duration on night-time variability, in a subset of 207 subjects in whom this data was available (the CRESSIDA and Fruit & Veg participants). Mean sleep duration was not independently associated with SBP_{night} SD ($P = 0.482$) or DBP_{night} SD ($P = 0.160$), as shown in Supplemental Digital Content, **Table S3**, which details the full linear regression models.

Adaptation to the ABPM device

Adaptation to the ABPM device was tested in a subset of 199 subjects who had the full five measures of each BP. Repeated measures ANOVA shows no evidence of adaptation to the device in terms of SBP_{day}, SBP_{night} or DBP_{day}, (all $P>0.05$). However, DBP_{night} changed significantly over the course of sequential measurements, being at its lowest on the baseline visit, highest on second assessment, then decreasing sequentially ($P=0.001$).

Variability of arterial stiffness measurements

Baseline PWV was 8.4 ± 1.6 m/s, compared to 8.3 ± 1.6 m/s at study endpoint ($P=0.016$). Mean PWV was positively correlated with mean ABPM values: SBP_{day} ($r=0.40$, $P<0.001$), SBP_{night} ($r=0.41$, $P<0.001$), DBP_{day} ($r=0.25$, $P<0.001$) and DBP_{night} ($r=0.30$, $P<0.001$).

Reproducibility of PWV measurements differed between studies (**Table 2**). There was a significantly lower CoV for PWV measured in the CRESSIDA study: 7.6% (95% CI 6.7%–8.4%) compared to the Fruit & Veg and MARINA studies: 10.4% (95% CI 9.3%-11.5%) and 12.1% (95% CI 11.1%–13.1%) respectively. In the total cohort, CoV of repeated PWV measurements was 10.7% (95% CI 9.0%–10.9%), with no statistical

difference demonstrated between the PWV reproducibility between normotensive and hypertensive subjects: 10.2% (95% CI 9.4%–10.9%) versus 11.5% (95% CI 10.5%–12.6%.

The mean PWV and its variability were significantly and positively correlated (*r*=0.28, *P*<0.001). However, there were no significant correlations between mean PWV and BPV of SBP$_{day}$, SBP$_{night}$, DBP$_{day}$ or DBP$_{night}$.

Variability of heart rate measurements

Baseline HR measured in clinic was 68 ± 9, compared to 75 ± 7 for the baseline HR measured by ABPM ($P < 0.001$). CoV of HR measurements was 6.3% (95% CI 6.1% - 6.5%) during the day, 7.9% (95% CI 7.6% – 8.2%) during the night and 5.9% (95% CI 5.7-6.1%) over 24 hours, as shown in Table 2.

Nocturnal dipping

Using the binary definition of dipper vs non-dipper, 385 subjects (77%) were classed as normal dippers on their first ABPM measurement, with 100 (20%) classed as non-dippers. Using the four standard categories of dipping, 243 subjects (49%) showed a normal dipping pattern, whilst 88 (18%) had reduced dipping, 142 (28%) showed extreme dipping and 12 (2%) showed reverse dipping on their baseline measurement.

The majority of normotensives and hypertensives were classified as normal dippers on the binary classification at study baseline. Dippers accounted for 240 (74%) of normotensives compared to 145 (82%) of hypertensives. When considering dipping status over all available measurements, 1% of normotensives were non-dippers throughout, 45% were dippers throughout and 53% were changeable over their measurements, compared to 3% of hypertensives being non-dippers throughout, 54% remaining a dipper throughout

and 41% changing their status. There was weak but significant agreement in dipping status for both normotensive and hypertensive subjects ($\kappa = 0.132$, $P < 0.001$ and $\kappa = 0.187$, $P < 0.001$ respectively) when analysed over five ABPM measurements ($n = 194$).

Using the four categories of dipping (reverse, reduced, normal and extreme), the majority of normotensives and hypertensives were again classed as normal dippers (51% and 44% respectively). Both groups also showed a tendency to change category over the course of their measurements. In the normotensive group, 271 (84%) changed their dipping category, and in the hypertensive group, 141 (80%) changed their dipping category. In subjects with the full 5 measurements, only 11% of normotensives maintained their original dipping category ($\kappa = 0.107$, $P < 0.001$). Similarly, only 11% of hypertensives maintained their original dipping category over 5 ABPM measurements ($\kappa = 0.160$, $P < 0.001$).

DISCUSSION

To our knowledge, this is the largest study to examine reproducibility of serial ABPM measurements in a cohort of adult subjects with minimal cardiovascular comorbidities. Reproducibility estimates are not dissimilar to those calculated by others. Our CoV estimates of 5.4% and 6.1% for daytime SBP and DBP respectively are close to the 5.5% and 4.9% calculated by Warren *et al* [20] in a cohort of 163 subjects of similar age (although with a higher proportion of antihypertensive use) and lower than 7.4% and 6.3% calculated by Mansoor *et al*, in their cohort of hypertensive patients (n=25). Our night-time CoVs were slightly higher than those obtained by Mansoor: 7.0% compared to 6.3% for night-time SBP, and 8.4% compared to their 7.1% for night-time DBP [3]. Despite

the large difference in baseline SBP_{day} between the normotensive and hypertensive group, we did not demonstrate any marked differences in ABPM measurement reproducibility in normotensive versus hypertensive individuals. By using CoV as a measure of reproducibility (rather than SD, which is correlated to mean BP), we show that in our cohort, ABPM measurements were no more variable in stable hypertensive subjects than in normotensive subjects when the mean BP was accounted for.

Variability of our night-time measurements generally exceeded that of daytime measurements, as also found by Bo *et al*[21]. This could be attributable to inconsistency of nocturnal dipping patterns [22] or direct interruption of sleep due to the operation of the ABPM device. Poor sleep quality is associated with increased BPV [23] and with increased BP [24] but it is contentious whether ABPM devices impair sleep quality enough to produce a significant increase in nocturnal pressures [25,26]. We were not able to analyse the effect of sleep quality in this study, but sleep duration did not appear to have a significant effect on night-time variability. When we analysed patterns of nocturnal dipping, we found little agreement above chance in categorisation of dipping status. This trend persisted whether we used four categories of classification, or a simplified dichotomous classification, and with little difference seen between normotensive and hypertensive subject groups. Although abnormal nocturnal dipping has been shown to be associated with adverse cardiovascular outcomes [27], its poor reproducibility shown by ourselves and others [21,22,28] may limit its use for stratifying risk. As many studies on nocturnal dip variability examine only two measurements, further large studies are needed to examine reproducibility of nocturnal dip over multiple measurements with emphasis on determining subgroups particularly prone to high variation.

We have shown that blood pressure variability, an important predictor of cardiovascular risk, is positively associated with mean BP but were unable to demonstrate any significant associations with age, sex or concurrent arterial stiffness when the mean BP was accounted for. Arterial stiffening may be a long-term consequence rather than a cause of blood pressure variability [15], hence the lack of association seen in cross-sectional regression. Increased BMI was associated with higher baseline BP and increased variability of night-time measurements, but not daytime pressures, which may reflect findings by others that higher BMI is associated with increased BPV, and disruption of normal nocturnal dipping patterns [29,30]. Caucasian participants appeared to have less variability in their SBP_{day} measurements compared to non-white ethnicity subjects, in agreement with other studies showing that African-Americans have higher BPV than white subjects, as well as higher mean ambulatory pressures [31], for which several physical and socioeconomic reasons have been suggested [32].

A secondary aim of this study was to examine if the variability of arterial stiffness, as measured by PWV, was superior to that of ABPM. Overall, PWV was found to have a CoV of 10.7% for the whole cohort, which is similar to that found by others in short-term studies [33], but higher than the CoV for the BP measures which ranged from 5.4% to 8.4%. Coupled with the fact that PWV requires specialist equipment and user training this suggests that, unless it is more strongly related to risk of clinical outcomes, it is not preferable as a surrogate measurement for long-term BP monitoring. PWV measurements appeared more variable in hypertensive compared to normotensive subjects, but this is to be expected given that mean and SD values of PWV were correlated, and PWV is itself highly correlated with concurrent BP.

Use of ABPM is becoming more widespread as current guidelines recommend its use to confirm a new diagnosis of hypertension [34,35]. However, for long-term monitoring of blood pressure, NICE still advises use of clinic BP measurement, with ABPM suggested as an confirmatory tool for subjects who could have white coat or masked hypertension [35]. Reproducibility of repeated ABPM has been studied, but often in small cohorts and a wide range of reproducibility indices used across the literature. Our cohort was comprised of subjects with minimal cardiovascular morbidities and who did not require initiation or alteration of antihypertensive medication during the study period. In such subjects, it could be hypothesized that variability of blood pressure measurements should be minimal. However, we have shown that the within-subject variability of ABPM measurements is still large when considered in clinical context. A borderline hypertensive clinic subject may be given ABPM to confirm or refute the presence of true hypertension. If their true daytime SBP was 140mmHg, however, a CoV of 5.4% for SBP_{day} by ABPM implies that 95% of readings will normally occur within a range of 125–155 mmHg, making diagnosis uncertain. Similarly, for a true daytime diastolic pressure of 90 mmHg, 95% of measurements would occur within a range of 78–102 mmHg (based on a CoV of 6.1%). Night-time estimates may be subject to even greater variability, as we have noted that the CoV of night-time measurements is significantly higher than those found during the day. Currently, NICE only recommends use of daytime ABPM to guide diagnosis [35] but future work could explore the use of night-time and 24-hour BP to guide antihypertensive therapy, as nocturnal BP is correlated with cardiovascular outcomes [36,37], and variability of 24-hour BP is less than daytime BP, as shown in this work and others [4,38–40].

Clinicians should note that SD of measurements is proportional to mean pressure and precise assessment of BP in a hypertensive subject may therefore be subject to additional complexity. An additional consideration in the use of single ABPM measurements to guide treatment is the possibility of an adaptive response to the device, whereby the first use elicits an additional pressor response with subsequent values showing regression to the mean. Whilst we were unable to show evidence of adaptation in terms of SBP_{day}, SBP_{night} or DBP_{day}, we did note some changes in DBP_{night} over the course of sequential measurements and nocturnal ABPs have been shown to be susceptible to adaptation as well as daytime measurements [38,41].

Our recent work using Monte Carlo simulations of BP treatments showed that measurement error is the main cause for misclassification of BP target when undertaking step-wise titration of antihypertensive therapy [16,42]. Readings of low error are likely to improve BP control; a conclusion supported by general consensus [43,44]. It is interesting to note that the measurement margins calculated here are in excess of the likely response to antihypertensive monotherapy (~ 9.1 mmHg SBP, ~5.5 mmHg DBP), and may even exceed that expected for dual therapy in some instances [45], highlighting the limitations of single ABPM measurements.

Limitations

The present study is subject to several important limitations. Firstly, this study uses retrospective data from interventional studies which were designed to detect differences from baseline in ABPM and PWV, rather than assess variability within a stable population

over time. Furthermore, the three studies differ in design and so the extent to which their data are directly comparable must be considered. The analyses presented here were designed to mitigate against these potential issues. Firstly, each study arm was only included if there was no significant change in parameters from baseline. This is a different approach to that used within each study which generally compared interventions and so may have reported a difference between arms despite no significant within arm change from baseline. Our approach was defined *a priori* and was designed to maximise the data available albeit with a recognition that various interventions may have an unknown impact on measures of interest. For example, we note that subsequent analysis from the MARINA study has identified that genotype may have dictated an individual's response to the fish oils given [46]. However, even with a potential post-intervention increase up to 5mmHg on endpoint SBP, our CoV estimates for SBP would not be significantly altered (calculation not shown). Secondly, we used IPD rather than summary data to provide more reliable results [47]. Thirdly, the limited number of repeat measurements for each participant may have inflated true values for individual variability but does approximate better to clinical practice than a high number of repeated ABPMs. The consistency of results between the three different studies provides some reassurance for our approach and the comparability of the datasets.

Conclusion

This study highlights that whilst ABPM is the gold-standard for BP measurement and monitoring, variability between measurements may result in misclassification and incorrect treatment decisions. Within our analysis population, PWV measurement was

not a more reproducible technique than ABPM when assessed as coefficient of variation.

Repeated ABPM may be necessary to refine antihypertensive therapy.

SUPPLEMENTAL DIGITAL CONTENT

Table S1

Table S2

Table S3

REFERENCES

1   Constanti M, Boffa R, Floyd CN, Wierzbicki AS, McManus RJ, Glover M. Options for the diagnosis of high blood pressure in primary care: a systematic review and economic model. *J Hum Hypertens* 2021; 35:455–461.

2   James GD, Pickering TG, Yee LS, Harshfield GA, Riva S, Laragh JH. The reproducibility of average ambulatory, home, and clinic pressures. *Hypertension* 1988; 11:545–549.

3   Mansoor G, McCable E, White W. Long-term reproducibility of ambulatory blood pressure. *J Hypertens* 1994; 12:703–708.

4   Palatini P, Mormino P, Canali C, Santonastaso M, De Venuto G, Zanata G, *et al.* Factors affecting ambulatory blood pressure reproducibility: Results of the HARVEST trial. *Hypertension* 1994; 23:211–216.

5   Boffa RJ, Constanti M, Floyd CN, Wierzbicki AS. Hypertension in adults: Summary of updated NICE guidance. *BMJ* 2019; 367:1–6.

6   Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. *Hypertension* 2002; 40:795–796.

7   Mancia, Guiseppe; Grassi, Guido, Pomidossi, Guido, Gregorini, Luisa, Bertinieri, Giovanni, Parati, Gianfranco, Ferrari, Alberto, Zanchetti A. Effects of blood-pressure measurement by the doctor on patient's blood pressure and heart rate. *Lancet* 1983; 2:695–8.

8   Berry SE, Mulla UZ, Chowienczyk PJ, Sanders TAB. Increased potassium intake

from fruit and vegetables or supplements does not lower blood pressure or improve vascular function in UK men and women with early hypertension: A randomised controlled trial. *Br J Nutr* 2010; 104:1839–1847.

9   Sanders TAB, Hall WL, Maniou Z, Lewis F, Seed PT, Chowienczyk PJ. Effect of low doses of long-chain n-3 PUFAs on endothelial function and arterial stiffness: A randomized controlled trial. *Am J Clin Nutr* 2011; 94:973–980.

10   Reidlinger DP, Darzi J, Hall WL, Seed PT, Chowienczyk PJ, Sanders TAB, *et al.* How effective are current dietary guidelines for cardiovascular disease prevention in healthy middle-aged and older men and women? A randomized controlled trial. *Am J Clin Nutr* 2015; 101:922–930.

11   Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, *et al.* Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010; 375:895–905.

12   Diaz KM, Tanner RM, Falzon L, Levitan EB, Reynolds K, Shimbo D, *et al.* Visit-to-visit variability of blood pressure and cardiovascular disease and all-cause mortality a systematic review and meta-analysis. *Hypertension* 2014; 64:965–982.

13   Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Stevens RJ, *et al.* Blood pressure variability and cardiovascular disease: Systematic review and meta-analysis. *BMJ* 2016; 354:14–16.

14   Li W, Yu Y, Liang D, Jia EZ. Factors Associated with Blood Pressure Variability Based on Ambulatory Blood Pressure Monitoring in Subjects with Hypertension in China. *Kidney Blood Press Res* 2017; 42:267–275.

15   Zhou TL, Henry RMA, Stehouwer CDA, Van Sloten TT, Reesink KD, Kroon
      AA. Blood pressure variability, arterial stiffness, and arterial remodeling the
      Maastricht study. *Hypertension* 2018; 72:1002–1010.

16   Zanisi L, Floyd CN, Barrett JE, Bunce C, Frohmaier C, Shankar F, *et al.* Monte
      Carlo simulation of uncertainty to identify barriers to optimizing blood pressure
      control. *J Hypertens* 2020; 38:2318–2324.

17   O'Brien E, Parati G, Stergiou G, Asmar R, Beilin L, Bilo G, *et al.* European
      society of hypertension position paper on ambulatory blood pressure monitoring.
      J Hypertens 2013; 31:1731–1768.

18   Bland JM, Altman DG. Measurement error proportional to the mean. *Br Med J*
      1996; 313:106.

19   Bland M. How should I calculate a within-subject coefficient of variation?
      2006.https://www-users.york.ac.uk/~mb55/meas/cv.htm

20   Warren RE, Marshall T, Padfield PL, Chrubasik S. Variability of office, 24-hour
      ambulatory, and self-monitored blood pressure measurements. *Br J Gen Pract*
      2010; 60:675–680.

21   Bo Y, Kwok KO, Chung VCH, Yu CP, Tsoi KKF, Wong SYS, *et al.* Short-term
      reproducibility of ambulatory blood pressure measurements: a systematic review
      and meta-analysis of 35 observational studies. *J Hypertens* 2020; 38:2095–2109.

22   Cuspidi C, Meani S, Salerno M, Valerio C, Fusi V, Severgnini B, *et al.*
      Reproducibility of nocturnal blood pressure fall in early phases of untreated
      essential hypertension: A prospective observational study. *J Hum Hypertens*

2004; 18:503–509.

23   Liu X, Yan G, Bullock L, Barksdale DJ, Logan JG. Sleep moderates the
association between arterial stiffness and 24-hour blood pressure variability.
Sleep Med 2021; 83:222–229.

24   Oume M, Obayashi K, Asai Y, Ogura M, Takeuchi K, Tai Y, *et al.* Objective
sleep quality and night-Time blood pressure in the general elderly population: A
cross-sectional study of the HEIJO-KYO cohort. *J Hypertens* 2018; 36:601–607.

25   Schwan ??ke, Eriksson G. Effect on sleep but not on blood pressure of nocturnal
non-invasive blood pressure monitoring. *J Hypertens* 1992; 10:189–194.

26   Petersen EH, Theilade S, Hansen TW, Lindhardt MK, Rossing P. Cuff inflations
do not affect night-time blood pressure: Comparison of 24 h ambulatory blood
pressure measured by a cuff and a tonometric device in type 2 diabetes. *Blood
Press Monit* 2015; 20:369–372.

27   Fagard RH, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer
DA. Night-day blood pressure ratio and dipping pattern as predictors of death and
cardiovascular events in hypertension. *J Hum Hypertens* 2009; 23:645–653.

28   Burgos-Alonso N, Ruiz Arzalluz MV, Garcia-Alvarez A, Fernandez-Fernandez
de Quincoces D, Grandes G. Reproducibility study of nocturnal blood pressure
dipping in patients with high cardiovascular risk. *J Clin Hypertens* 2021;
23:1041–1050.

29   Chen H, Zhang R, Zheng Q, Yan X, Wu S, Chen Y. Impact of body mass index
on long-term blood pressure variability : a cross-sectional study in a cohort of

Chinese adults. *BMC Public Health* 2018; 18:1193.

30   Kotsis V, Stabouli S, Bouldin M, Low A, Toumanidis S, Zakopoulos N. Impact

of Obesity on 24-Hour Ambulatory Blood Pressure and Hypertension.

Hypertension 2005; 45:602–607.

31   Li Z, Snieder H, Su S, Harshfield GA, Treiber FA, Wang X. A longitudinal study

of blood pressure variability in African-American and European American youth.

J Hypertens 2010; 28:715–722.

32   Muntner P, Lewis CE, Diaz KM, Carson AP, Kim Y, Calhoun D, *et al.* Racial

differences in abnormal ambulatory blood pressure monitoring measures: Results

from the coronary artery risk development in young adults (CARDIA) study. *Am

J Hypertens* 2015; 28:640–648.

33   Grillo A, Parati G, Rovina M, Moretti F, Salvi L, Gao L, *et al.* Short-Term

Repeatability of Noninvasive Aortic Pulse Wave Velocity Assessment:

Comparison between Methods and Devices. *Am J Hypertens* 2018; 31:80–88.

34   Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, *et al.* 2018

ESC/ESH Guidelines for themanagement of arterial hypertension. *Eur Heart J*

2018; 39:3021–3104.

35   National Institute for Health and Care Excellence. Hypertension in adults:

Diagnosis and management. 2019.https://www.nice.org.uk/guidance/ng136

36   Roush GC, Fagard RH, Salles GF, Pierdomenico SD, Reboldi G, Verdecchiaf P,

et al. Prognostic impact from clinic, daytime, and nighttime systolic blood

pressure in nine cohorts of 13844 patients with hypertension. *J Hypertens* 2014;

32:2332–2340.

37   Cardoso CRL, Salles GF. Associations of the nocturnal blood pressure fall and morning surge with cardiovascular events and mortality in individuals with resistant hypertension. *J Hypertens* 2021; 39:1177–1187.

38   Musso NR, Vergassola C, Barone C, Lotti G. Ambulatory blood pressure monitoring: How reproducible is it? *Am J Hypertens* 1997; 10:936–939.

39   Stergiou GS, Baibas NM, Gantzarou AP, Skeva II, Kalkana CB, Roussias LG, *et al.* Reproducibility of home, ambulatory, and clinic blood pressure: Implications for the design of trials for the assessment of antihypertensive drug efficacy. *Am J Hypertens* 2002; 15:101–104.

40   Campbell P, Ghuman N, Wakefield D, Wolfson L, White WB. Long-term reproducibility of ambulatory blood pressure is superior to office blood pressure in the very elderly. *J Hum Hypertens* 2010; 24:749–754.

41   Moore MN, Atkins ER, Salam A, Callisaya ML, Hare JL, Marwick TH, *et al.* Regression to the mean of repeated ambulatory blood pressure monitoring in five studies. *J Hypertens* 2019; 37:24–29.

42   Augustin A, Coutts L, Zanisi L, Wierzbicki AS, Shankar F, Chowienczyk PJ, *et al.* Impact of Therapeutic Inertia on Long-Term Blood Pressure Control: A Monte Carlo Simulation Study. *Hypertension* 2021; :1350–1359.

43   Muntner P, Shimbo D, Carey RM, Charleston JB, Gaillard T, Misra S, *et al.* Measurement of Blood Pressure in Humans: A Scientific Statement from the American Heart Association. *Hypertension* 2019; 73:E35–E66.

44   Stergiou GS, Parati G, Vlachopoulos C, Achimastos A, Andreadis E, Asmar R, *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 a. *J Hypertens* 2016; 34:1665–1677.

45   Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: Analysis of 354 randomised trials. *Br Med J* 2003; 326:1427–1431.

46   AlSaleh A, Maniou Z, Lewis FJ, Hall WL, Sanders TAB, O'Dell SD. Interaction between a CSK gene variant and fish oil intake influences blood pressure in healthy adults. *J Nutr* 2014; 144:267–272.

47   Tierney JF, Vale C, Riley R, Smith CT, Stewart L, Clarke M, *et al.* Individual participant data (IPD) meta-analyses of randomised controlled trials: Guidance on their use. *PLoS Med* 2015; 12:1–16.

TABLES

Table 1: Subject characteristics at baseline

	CRESSIDA (*n*=159)	Fruit & Veg (*n*=48)	MARINA (*n*=294)	All (*n*=501)
Age (years)	52.9 ± 8.0	45.2 ± 9.4	55.1 ± 6.6	53.4 ± 8.0
Female [*n* (%)]	96 (60)	25 (52)	184 (63)	305 (61)
Ethnicity				
White [*n* (%)]	133 (84)	29 (60)	239 (81)	401 (80)
Black [*n* (%)]	14 (9)	10 (21)	15 (5)	39 (8)
Asian [*n* (%)]	10 (6)	9 (19)	27 (9)	46 (9)
Other / Mixed [*n* (%)]	2 (1)	0	13 (4)	15 (3)
BMI (kg/m^2)	26.0 ± 3.8	28.4 ± 3.8	25.5 ± 3.9	26.0 ± 3.9
Antihypertensive use [*n* (%)]	0	0	11 (4)	11 (2)
PWV (m/s)	7.5 ± 1.2	7.9 ± 1.0	8.9 ± 1.7	8.4 ± 1.6
Clinic seated measurements:				
SBP (mmHg)	120 ± 16	129 ± 12	126 ± 16	124 ± 16
DBP (mmHg)	79 ± 10	87 ± 8	80 ± 10	80 ± 10
HR (bpm)	66 ± 9	73 ± 9	68 ± 9	68 ± 9
Ambulatory measurements:				
SBP_{day} (mmHg)	126 ± 13	139 ± 14	131 ± 13	130 ± 13
SBP_{night} (mmHg)	107 ± 14	116 ± 14	110 ± 13	110 ± 14
24-hour SBP (mmHg)	122 ± 12	135 ± 13	126 ± 12	125 ± 13
DBP_{day} (mmHg)	77 ± 8	88 ± 7	79 ± 7	79 ± 8

DBP$_{night}$ (mmHg)	64 ± 9	71 ± 8	65 ± 7	65 ± 8
24-hour DBP (mmHg)	74 ± 7	85 ± 7	76 ± 7	76 ± 7
HR$_{day}$ (bpm)	72 ± 9	76 ± 7	76 ± 8	75 ± 8
HR$_{night}$ (bpm)	62 ± 9	65 ± 9	64 ± 8	63 ± 9
24-hour HR (bpm)	70 ± 8	74 ± 7	73 ± 7	72 ± 8

Values represent means ± standard deviation, or number [percentage].

BMI: body mass index, PWV: pulse wave velocity, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate.

Table 2: Measures of reproducibility in ambulatory blood pressure and pulse wave velocity (PWV).

	CRESSIDA		FV		MARINA		ALL	
	n	CoV,% (95% CI)	n	CoV,% (95% CI)	n	CoV,% (95% CI)	n	CoV,% (95% CI)
All subjects	159		48		294		501	
SBP_{day}		5.0 (4.8 - 5.4)		5.4 (4.9 – 6.0)		5.6 (5.3 – 5.9)		5.4 (5.2 – 5.6)
SBP_{night}		6.7 (6.3 - 7.0)		7.5 (6.7 – 8.4)		7.1 (6.7 – 7.5)		7.0 (6.7 – 7.3)
24-hour SBP		4.7 (4.4 – 4.9)		4.9 (4.4 – 5.5)		4.8 (4.5 – 5.1)		4.8 (4.6 – 5.0)
DBP_{day}		5.1 (4.8 - 5.4)		6.3 (5.7 – 7.0)		6.6 (6.2 – 7.0)		6.1 (5.9 – 6.4)
DBP_{night}		9.0 (8.5 – 9.5)		8.1 (7.2 – 8.9)		8.0 (7.5 – 8.5)		8.4 (8.0 – 8.7)
24-hour DBP		4.8 (4.5 – 5.0)		5.7 (5.1 – 6.4)		5.5 (5.1 – 5.8)		5.3 (5.1 – 5.5)
HR_{day}		6.0 (5.7 – 6.4)		6.5 (5.8 – 7.2)		6.4 (6.0 – 6.8)		6.3 (6.1 – 6.5)
HR_{night}		7.2 (6.8 – 7.7)		7.8 (7.0 – 8.7)		8.3 (7.8 – 8.8)		7.9 (7.6 – 8.2)
24-hour HR		5.8 (5.5 – 6.1)		6.0 (5.3 – 6.6)		5.9 (5.6 – 6.3)		5.9 (5.7 – 6.1)
PWV		7.6 (6.7 - 8.4)		10.4 (9.3 – 11.5)		12.1 (11.1 – 13.1)		10.7 (9.0 – 10.9)

Normotensive subjects	121	17	186	324
SBP$_{day}$	5.3 (4.9 – 5.6)	6.0 (5.0 – 7.0)	5.6 (5.2 – 6.0)	5.5 (5.2 – 5.8)
SBP$_{night}$	6.7 (6.2 – 7.1)	7.2 (5.9 – 8.5)	7.0 (6.5 – 7.5)	6.9 (6.6 – 7.2)
24-hour SBP	4.8 (4.5 – 5.1)	4.8 (3.9 – 5.6)	4.7 (4.3 – 5.1)	4.7 (4.5 – 5.0)
DBP$_{day}$	5.3 (5.0 – 5.7)	7.7 (6.4 – 9.1)	6.4 (5.9 – 6.8)	6.1 (5.8 – 6.4)
DBP$_{night}$	9.2 (8.6 – 9.8)	7.7 (6.3 – 9.1)	8.3 (7.7 – 8.9)	8.6 (8.2 – 9.0)
24-hour DBP	5.0 (4.6 – 5.3)	6.5 (5.3 – 7.6)	5.3 (4.9 – 5.7)	5.3 (5.0 – 5.5)
HR$_{day}$	6.1 (5.7 – 6.5)	6.5 (5.4 – 7.6)	6.3 (5.9 – 6.8)	6.3 (6.0 – 6.6)
HR$_{night}$	7.4 (6.9 – 7.8)	7.0 (5.7 – 8.3)	8.7 (8.0 – 9.4)	8.1 (7.7 – 8.5)
24-hour HR	6.0 (5.6 – 6.3)	5.4 (4.4 – 6.4)	5.8 (5.4 – 6.3)	5.9 (5.6 – 6.1)
PWV	7.1 (6.2 – 8.0)	11.0 (9.1 – 13.0)	11.7 (10.5 – 13.0)	10.2 (9.4 – 10.9)
Hypertensive subjects	38	31	108	177
SBP$_{day}$	4.4 (3.9 – 4.9)	5.1 (4.4 – 5.7)	5.6 (5.1 – 6.2)	5.3 (4.9 – 5.6)
SBP$_{night}$	6.6 (5.8 – 7.4)	7.8 (6.7 – 8.8)	7.3 (6.5 – 8.0)	7.2 (6.7 – 7.7)
24-hour SBP	4.1 (3.6 – 4.6)	5.0 (4.4 – 5.7)	5.1 (4.6 – 5.6)	4.9 (4.5 – 5.2)

|				
DBP$_{day}$	4.4 (3.9 – 4.9)	5.5 (4.8 – 6.2)	6.9 (6.2 – 7.6)	6.2 (5.8 – 6.6)
DBP$_{night}$	8.2 (7.3 – 9.2)	8.3 (7.2 – 9.4)	7.6 (6.8 – 8.3)	7.8 (7.3 – 8.4)
24-hour DBP	4.1 (3.6 – 4.6)	5.3 (4.6 – 6.0)	5.6 (5.1 – 6.2)	5.3 (4.9 – 5.6)
HR$_{day}$	5.6 (5.0 – 6.3)	6.5 (5.7 – 7.3)	6.6 (5.9 – 7.2)	6.4 (6.0 – 6.8)
HR$_{night}$	6.9 (6.1 – 7.7)	8.3 (7.2 – 9.3)	7.6 (6.8 – 8.4)	7.6 (7.1 – 8.1)
HR	5.3 (4.7 – 5.9)	6.2 (5.4 – 7.1)	6.1 (5.5 – 6.7)	5.9 (5.6 – 6.3)
PWV	9.0 (6.9 – 11.1)	10.0 (8.7 – 11.4)	12.7 (10.9 – 14.5)	11.5 (10.5 – 12.6)

SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, CoV: within-subject coefficient of variation, CI: confidence interval

Normotension defined as baseline ambulatory SBP$_{day}$<135mmHg. Hypertension defined as baseline ambulatory SBP$_{day}$≥135mmHg

Table 3: Multivariable linear regression showing associations between variability of ambulatory blood pressures to mean blood pressure and demographic risk factors.
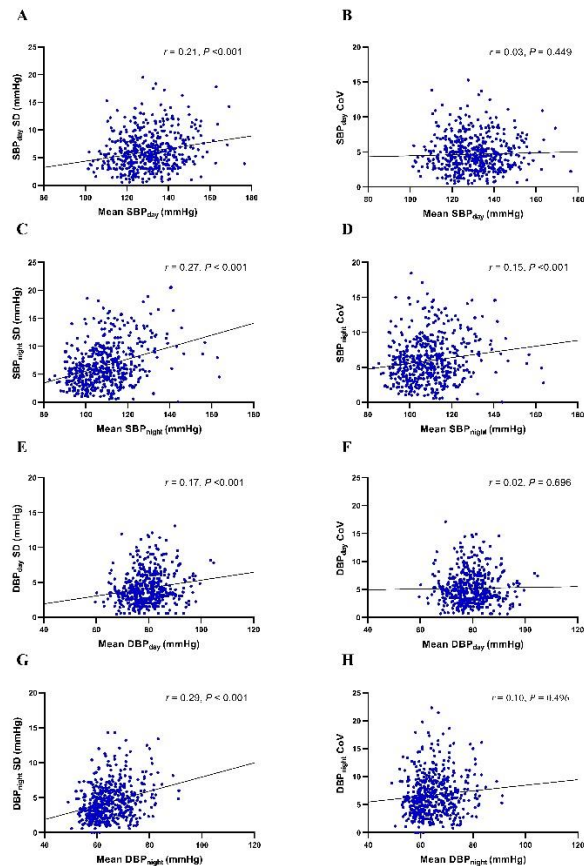
	SBP$_{day}$ SD		SBP$_{night}$ SD		DBP$_{day}$ SD		DBP$_{night}$ SD	
	β	*P*	β	*P*	β	*P*	β	*P*
Age (years)	0.030	0.578	0.020	0.705	-0.062	0.256	0.088	0.094
Sex (male/female)	0.030	0.521	-0.042	0.349	0.040	0.397	0.014	0.763
Ethnicity (white/other)	**0.090**	**0.049**	0.023	0.608	0.029	0.542	0.009	0.838
BMI (kg/m^2)	0.027	0.561	**0.097**	**0.033**	0.052	0.277	**0.136**	**0.003**
PWV (m/s)	-0.056	0.319	-0.092	0.088	-0.019	0.733	-0.106	0.055
Antihypertensives (yes/no)	**0.112**	**0.012**	-0.049	0.251	0.083	0.068	0.034	0.437
Mean SBP$_{day}$ (mmHg)	**0.271**	**0.001**	**-**	-	0.023	0.709	-	-
Mean DBP$_{day}$ (mmHg)	-0.079	0.279	-	-	**0.155**	**0.008**	-	-
Mean SBP$_{night}$ (mmHg)	-	-	**0.414**	**<0.001**	**-**	-	0.063	0.456
Mean DBP$_{night}$ (mmHg)	-	-	-0.093	0.245	-	-	**0.223**	**0.006**

B: standardised regression coefficient. SD: standard deviation (measure of blood pressure variability), BMI: body mass index, PWV: pulse wave velocity, SBP: systolic blood pressure, DBP: diastolic blood pressure. *P* <0.05 highlighted in bold.

FIGURES

**Figure 1: Consort diagram of the flow of subjects through the study**
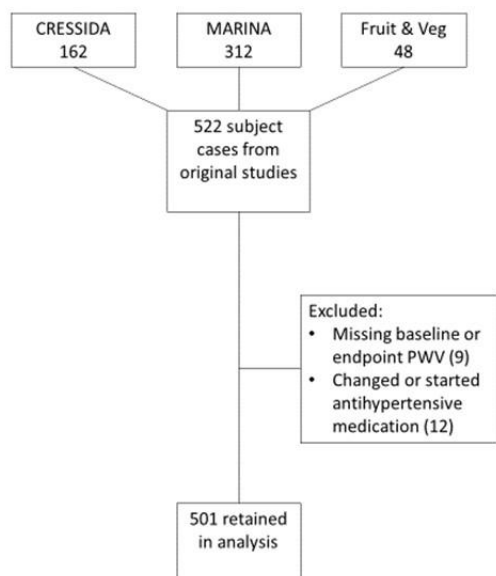
PWV:pulse wave velocity

Figure 2: Associations between individual ambulatory mean pressures and SD or CoV.

A: correlation between mean SBP$_{day}$ and SBP$_{day}$ SD. B: correlation between mean SBP$_{day}$ and SBP$_{day}$ CoV. C: correlation between mean SBP$_{night}$ and SBP$_{night}$ SD, D: correlation between mean SBP$_{night}$ and SBP$_{night}$ CoV. E: correlation between mean DBP$_{day}$ and DBP$_{day}$ SD. F: correlation between mean DBP$_{day}$ and DBP$_{day}$ CoV. G: correlation between mean DBP$_{night}$ and DBP$_{night}$ SD. H: correlation between mean DBP$_{night}$ and DBP$_{night}$ CoV. SBP: systolic blood pressure, DBP: diastolic blood pressure, SD: standard deviation, CoV: coefficient of variation.

Figure 3: Comparison of within-subject coefficient of variation between subjects defined as normotensive at study baseline (SBP<135mmHg) versus subjects defined as hypertensive at study baseline (SBP$_{day}$≥135mmHg).
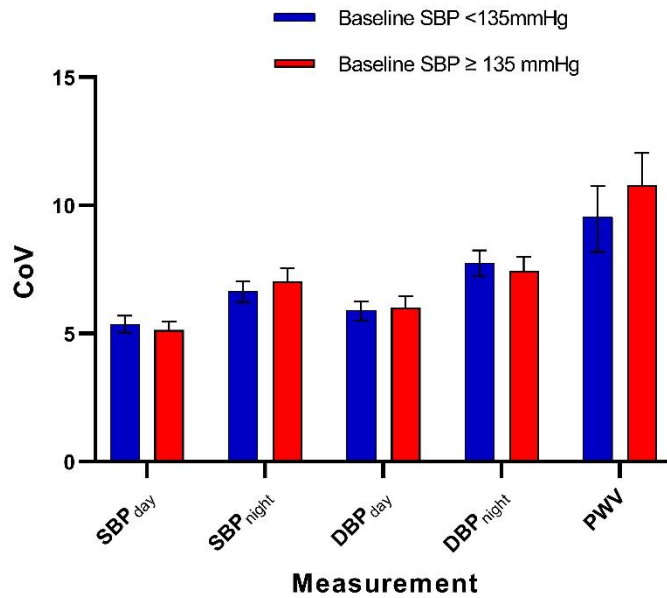
SBP: systolic blood pressure, DBP: diastolic blood pressure, PWV: pulse wave velocity.

CoV: within-subject coefficient of variation. Error bars represent 95% confidence intervals.