Blood pressure measurement modalities and indexed left ventricular mass in men with low-risk hypertension confirmed by ambulatory monitoring

Short Title: BP Measurement Modality and Target Organ Damage

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ABSTRACT

Background. Blood pressure (BP) measurement modalities such as ambulatory monitoring (ABPM) and non-invasive central aortic systolic pressure (CASP), have been reported to improve prediction of hypertension-mediated organ damage (HMOD) compared with conventional clinic BP. However, clinic BP is often confounded by poor measurement technique and "white coat hypertension" (WCH). We compared prediction of cardiac magnetic resonance imaging (cMRI)-derived left ventricular mass index (LVMI) by differing BP measurement modalities in young men with elevated BP, confirmed by ABPM.

Methods. 143 treatment-naïve men (< 55 years) with hypertension confirmed by ABPM and no clinical evidence of HMOD or cardiovascular disease (37% with masked hypertension) were enrolled. Relationships between BP modalities and cMRI-LVMI were evaluated.

Results. Men with higher LVMI (upper quintile) had higher clinic, central and ambulatory systolic BP (SBP) compared to men with lower LVMI. Regression coefficients for SBP with LVMI did not differ across BP modalities (r = 0.32; 0.3; 0.31, for clinic SBP, CASP and 24-hour ABPM respectively, *P* <0.01 all). Prediction for high LVMI using receiver operated curve analyses was similar between measurement modalities. No relationship between diastolic BP and LVMI was seen across measurement modalities.

Conclusion. In younger men with hypertension confirmed by ABPM and low CV risk, clinic SBP and CASP, measured under research conditions i.e. with strict adherence to guideline recommendations, performs as well as ABPM in predicting LVMI. Prior reports of inferiority for clinic BP in predicting HMOD and potentially, clinical outcomes, may be due to poor measurement technique and/or failure to exclude WCH.

Abstract 250 words.

Keywords: Blood pressure, Central aortic pressure, Blood Pressure Monitoring, Ambulatory, Pressure wave, Pulse wave, Left Ventricle, Calibration.

Introduction

Elevated blood pressure (BP) predicts risk for future cardiovascular events (CVE) with increased risk frequently developing early in life and at BP levels lower than conventionally recommended for treatment.[1,2] Accordingly, approximately 50% of global attributable cardiovascular disease (CVD) burden occurs within a systolic BP range of 130-150 mmHg.[3] Furthermore, modest BP elevation in early adulthood translates into increased incidence of CVEs in later life, preceded by cardiac structural change in people with prehypertension or high-normal BP.[4,5]

The estimation of future CVD risk is enhanced using surrogate or intermediate markers such as elevated left ventricular mass index (LVMI), which is particularly relevant in younger people where overt CVD is less likely. Furthermore, in people with hypertension, development of left ventricular hypertrophy (LVH) depends on the level of SBP and LVH regression with treatment is associated with reduced risk.[6] However, stringency of the relationship between LVMI and BP is poor and may depend upon BP measurement modality with superior relationships reported using ambulatory blood pressure monitoring (ABPM) in comparison to clinic BP measurement.[7,8] This may be because ABPM allows identification of people with white-coat hypertension (WCH) who may be at lower risk of developing LVH. Furthermore, routine clinic BP measurement is frequently performed poorly, with insufficient consideration given to measurement quality and reproducibility.[9] Nevertheless, superiority with ABPM has not been demonstrated in all studies. Thus, studies using 'research clinic' BP measurements, where emphasis is placed on good technique and averaging repeated high-quality measurements, as recommended in National guidelines, have demonstrated similar relationships to those seen with ABPM.[10-12]

Others have suggested assessment of non-invasive central aortic systolic BP (CASP) provides more relevant BP estimates. CASP is claimed to provide improved prediction of hypertension-mediated organ damage (HMOD) and CVEs, because it may better represent the pressure to which the vital organs are directly exposed.[13] Furthermore, guidelines[14] have discussed the possibility that

CASP measurement provides specific benefit in younger men, because pressure amplification (difference between brachial BP and CASP) is frequently prominent and variable in this group. Nevertheless, whilst some studies claim superiority in predicting CVEs using CASP[15], others show no or only marginal superiority[16] with meta-analyses providing essentially equivocal data.[17,18]

Whether BP measurement modalities demonstrate differing relationships with surrogate outcomes such as LVMI in younger, low risk men with hypertension is not clear. The present study compared relationships between BP measurement modalities (seated office BP, ABPM, seated CASP) and cardiac magnetic resonance imaging (cMRI) evaluated LVMI, in a cohort of treatment naïve younger men with predominantly grade 1 hypertension and no clinical evidence of CVD.

Methods

Study design

The present analysis uses baseline data from participants recruited into the TREAT CASP study – the study report is available.[19] The TREAT CASP study was in two parts. The first was designed to evaluate whether central aortic systolic pressure (CASP) versus other BP measurement modalities better predicted LVMI, and this is reported here. The second part evaluated the potential for BP-lowering treatment to regress elevated LVMI in these young people with low-risk early-stage hypertension and incorporated a randomised clinical trial (not reported here) in participants stratified by their central systolic BP value. The study recruited men from the community aged < 55 years with elevated BP (predominantly grade 1 hypertension), who were not taking BP lowering medication, had no prior or concurrent CVD and in whom WCH was excluded by ABPM. WCH was excluded as directed by the study protocol, to avoid potentially exposing men with WCH to BP-lowering treatment if they were randomised into the subsequent RCT part of the study.

Recruitment into the TREAT CASP study occurred between August 2015 and February 2018. TREAT CASP study participants with hypertension confirmed by ABPM were included in the present analysis.

Data acquisition and analysis

Clinic Blood pressure measurement

Brachial clinic BP was evaluated over the upper arm using a clinically validated oscillometric monitor (OMRON 705CP-II; Omron Corporation, Kyoto, Japan) with a suitably sized cuff.[20,21] Measurements were taken under research conditions with the study participant relaxed and seated comfortably in a quiet environment (minimum 5 minutes rest prior to measurement), with their back and arm supported, middle of the upper arm positioned at heart level, legs uncrossed and feet flat on the floor. BP measurements were initiated manually by the researcher with a minimum of three (up to a maximum of six) measurements being taken 1 minute apart, until three consecutive SBP and DBP readings within 10 mmHg had been achieved. BP was measured over both arms with the mean of the last two readings from the higher arm used to define the brachial BP (BrBP). In addition, where specified, we calculated clinic BP using the average of differing individual values across the sequence of measurements (minimum three, maximum six) as specified in various clinical guidelines or as commonly used in epidemiological studies.[14,22] This was done to compare whether the number of individual measurements taken before averaging, impacts average values and relationships with LVMI (see online data supplement, supplemental methods for details).

Central aortic systolic pressure measurement

Non-invasive CASP was assessed using the BPro® device (Healthstats International Pte Ltd, Singapore). This device uses applanation tonometry with a tonometer (sampling frequency 60Hz) to capture high-fidelity radial artery pulse waves accurately and with good reproducibility.[23] Pulse waves were sampled for 10 seconds immediately following complete cuff deflation after each individual BP measurement. The resulting ensemble-averaged pressure waves were calibrated to the corresponding brachial SBP and DBP. CASP was derived using a n-point moving average (n = ¼ of the sampling frequency) as previously described.[24]

In additional analyses, radial artery pulse waves were recalibrated to mean (MAP) and diastolic pressure for comparison with data from conventionally calibrated (SBP/DBP) waveforms (see online data supplement, supplemental methods for details).

Ambulatory blood pressure monitoring

Twenty-four-hour ambulatory brachial BP (ABPM) was recorded using a validated oscillometric device (90207-30/90207-1Q/90217-1Q; Spacelabs Healthcare, Hertford, UK). Measurements were taken over the participant's non-dominant arm every 30 minutes during waking hours and every 60 minutes during sleep. 24-hour, daytime and night-time averages were calculated based on information acquired using a patient diary. 70% successful measurements were required for 24-hour measurements to be valid.

Cardiac magnetic resonance imaging

All participants underwent a cMRI scan at the UCL Institute of Cardiovascular Science Imaging Centre at Great Ormond Street Hospital in London. A five-element phased-array coil set up on a 1.5-T magnetic resonance imager (MAGNETOM® Avanto; Siemens Healthineers AG, Erlangen, Germany) was used, as previously described.[19] A vector electrocardiographic system was used for cardiac gating.

Following acquisition of scout images and ventricular volumetric assessment (using cardiac-gated breath-hold cine imaging of the ventricular short axis), ventricular volume and mass were assessed using real-time, radial k-t sensitivity-encoding imaging. High-resolution imaging of aortic flow and diameter was performed during breath-hold together with phase-contrast imaging.

Images were analyzed using a DICOM imaging platform (Osirix, version 8.5.1; Pixmeo Sàrl, Bernex, Switzerland). For analysis of ventricular volumes and mass, epicardial and endocardial contours were manually drawn across a short-axis stack of 10mm sections. Volumes and mass at end-diastole were calculated using a custom-written plug-in. Trabeculae and papillary muscle were not excluded. Ventricular mass was indexed to body surface area.[25] Averaged data between two observers was used in all analyses. Intraclass correlation coefficient for LVMI was 0.90.

Height, weight and anthropometric data

Height and weight were measured using a stadiometer and weighing scales with waist and hip circumference determined using measuring tape. Segmented bioelectrical impedance was used to evaluate total body and truncal fat mass (BC-418 Body Composition Analyser; Tanita Europe BV, Amsterdam, Netherlands).

Statistical analysis

Data are presented as mean ± standard deviation (SD) for normally distributed data or median with interquartile range (IQR, 25th to 75th percentile) for non-normally distributed data. Categorical variables are presented as n (%). High LVMI was defined as the highest quintile (LVMI ≥ 75.0 g/m^2 measured at end-diastole, n = 29). Comparisons of demographics and BP parameters, by LVMI group (i.e. high LVMI versus low LVMI) used an independent Student's t-test or a Mann-Whitney test for non-normally distributed data. Comparisons across groups used one way analysis of variance with Bonferroni adjustment for multiple comparisons in normally distributed data. The impact of number and order of clinic measurements forming the average value for clinic BP was also studied. Pearson's correlation coefficient was used to assess relationships between LVMI and brachial SBP (clinic and ambulatory) and CASP. Correlation coefficients (r) were compared using Fisher's r-to-z transformation. Where appropriate, data was adjusted for heart rate and ethnicity. Receiver Operated Curve (ROC) analysis was used to compare the discriminatory power of BP measurement modalities in detecting higher LVMI, where an area under the ROC (AUC) value of 0.50 is considered to have no discriminatory power and 1.0 has perfect discriminatory power[26]. Differences in the AUC value was compared using the method of DeLong [27], adjusted using Sidak's procedure for multiple comparisons.

All statistical analyses were performed using Stata® (version 14.2; StataCorp LP, College Station, TX, USA) or RStudio (version 3.6.0; RStudio, Inc., Boston, MA, USA). Statistical significance for all analyses was taken using $P < 0.05$.

Results

Demographics for the study population.

The present analysis included 143 participants with a daytime ABPM SBP ≥ 135 and/or daytime ABPM DBP ≥ 85 mmHg and predominantly with grade 1 hypertension without WCH. Of these 90 (62.9%) had sustained hypertension and 53 (37.1%) had masked hypertension (i.e. ambulatory BP in the hypertensive range but with normal or high-normal clinic BP; see online data supplement, table S1 and Fig S1: BP thresholds are shown in table S2). Whilst the majority of participants had grade 1 hypertension at baseline, a small proportion (n=30, 21%) had grade 2 hypertension either on ABPM or clinic BP, typically 3-5mmHg above the threshold DBP on ABPM. Importantly no study participant had grade 2 hypertension on both ABPM and clinic BP. One participant did not have an ABPM at study entry, but was subsequently confirmed to be hypertensive by ABPM.

The study population comprised predominantly white men (median age 47. 5 years) with low (5%) 10-year cardiovascular Q-Risk risk scores (table 1). Median BMI was 27.3 kg/m^2 with the majority being overweight (50.3%: BMI ≥ 25 & ≤ 29.9 kg/m^2) or obese (23.1%: BMI≥ 30kg/m^2).

Mean cMRI LVMI was 66.2 ± 8.9 g/m^2. Only two participants had LVH based on a cut-off value for mildly elevated LVMI of 86 g/m^2 (European Association for Cardiovascular imaging recommendations).[28] The population was sub-divided into the highest quintile for LVMI (high LVMI group), versus other quintiles (low LVMI group). LVMI difference between groups was 16.6 g/m^2 ($P < 0.001$).

Broadly similar demographic characteristics were seen between groups (table 1). However, men in the low LVMI group were shorter (176.8 vs. 179.7 cm, $P < 0.05$), with more current smokers (although smoking frequency was low) and men of non-white ethnicity. Blood glucose and lifetime Q-Risk scores were modestly raised in the low LVMI group (4.9 vs. 4.7 mmol/L and 44.0 vs. 40.0 %, $P < 0.05$, both). Men in the low LVMI group also had lower end-diastolic and stroke volumes ($P< 0.01$), however there were no differences in cardiac output or relative wall mass (mass: volume ratio, an index of ventricular wall remodeling) between groups.

Haemodynamics for the Study Population

By design, study participants had elevated BP (predominantly grade 1 hypertension) with average clinic BP 140.9 ± 9.0/85.8 ± 7.0 mmHg, average clinic CASP 127.6 ± 9.2 mmHg, and average 24-hour BP 135.5 ± 6.9/85.0 [82.0 – 90.0] mmHg, table 2. Comparing LVMI groups, SBP for all measurement modalities (except ambulatory night-time SBP, $P = 0.06$) was elevated in the higher LVMI group, $P < 0.05$ all (table 2). By contrast, DBP did not differ between groups. Heart rate was on average 9.5 beats/minute lower in the higher LVMI group (P < 0.01).

As cardiac loading occurs throughout the cardiac cycle, in order to evaluate whether alternative waveform calibration influences relationships with LVMI, CASP was derived from waveforms calibrated to MAP/DBP (with MAP calculated using a commonly-applied fixed form factor (FF) 0.4).

Average MAP/DBP calibrated CASP was 127.6 ± 9.0 mmHg. This did not differ from conventional, SBP/DBP calibrated CASP (127.6 ± 9.2 mmHg; $P = 0.67$). This similarity between calibrations is unsurprising, as both the FF used for MAP calculation (0.4) and the average study waveform FF were identical (0.4 ± 0.04, online data supplement table S3). Similarly, MAP/DBP calibrated SBP (i.e. the peak of the MAP/DBP calibrated waveform) did not differ from brachial BP monitor SBP (MAP/DBP calibrated SBP 141.4 ± 11.0 mmHg vs. BP monitor SBP 140.9 ± 9.0 mmHg, $P = 0.67$). MAP/DBP calibrated CASP and SBP were higher in the high LVMI group (P<0.01, online data supplement table S3).

Relationship between LVMI and SBP for the Study Population

Linear regression relationships between LVMI and SBP are shown in the Figure. Regardless of measurement modality, SBP showed similar positive relationships with LVMI (Fishers r-z transformation all P>0.05; table 3). These similarities were consistent even after accounting for heart rate, age and ethnicity. Similar findings were also seen with MAP/DBP calibrated SBP and CASP (online data supplement, figure S2).

Influence of multiple approaches to averaging clinic BP on relationship with LVMI

Mean values for SBP and CASP were seen to reduce as BP was calculated as the average of the last two (where available) of increasing numbers of prior measurements (method 1 (using the first measurement taken only) through to method 4 (average of the last two measurements once three consecutive measurements differed by ≤10mmHg);); (Data in online supplement table S4 & fig S3 shows approaches to averaging the readings). Similarly, correlation coefficients for BP with LVMI tended to improve with progression from clinic readings average methods 1 through 4, although this improvement did not achieve statistical significance (Fishers R-Z transformation all P > 0.05; online data supplement table S4 and figure S3).

Comparison of Predictive ability for Higher LVMI by BP Measurement Modality.

ROC analysis with comparison of area under the curve (AUC) was used to compare BP modalities for predicting high LVMI. In these models, clinic brachial SBP acted as reference standard. No difference was seen in predicting higher LVMI between BP measurement modalities except when MAP/DBP calibrated CASP was compared to brachial SBP, where a trend to a greater predictive value was seen (adjusted P = 0.02, table 4, Model 3). However, when the corresponding MAP/DBP calibrated brachial SBP was used as reference in place of brachial SBP from the BP monitor, no difference in predicting higher LVMI was seen (adjusted $P = 0.3$, Table 4, Model 4). Additionally, no difference in predicting high LVMI between MAP/DBP calibrated CASP and brachial SBP was seen in ROC models where data was adjusted for heart rate and ethnicity (online data supplement, Table S5).

Discussion

This study compared relationships between SBP and LVMI in younger men with hypertension confirmed by ABPM and low concurrent cardiovascular risk (average 10-year Q-Risk-score 5%). SBP recorded using different measurement modalities (brachial clinic SBP, brachial ambulatory SBP and clinic CASP) showed a continuous positive relationship with LVMI, accounting for about 10% of the variability and with similar correlations. In ROC analysis, similar predictive ability for SBP was seen across measurement modalities. Taken together, this data suggests no inherent superiority for any

BP measurement mode in the study population, when clinic brachial BP is measured carefully and after exclusion of WCH.

Characteristic of the Study Population

We aimed to recruit men with predominantly grade 1 hypertension and in doing so, the population was screened to exclude WCH using ABPM. WCH was excluded to allow for comparisons only across participants with hypertension confirmed by ABPM and because a second part of the study (not reported here) included a RCT of BP-lowering into which the study protocol precluded randomisation of participants with WCH. Whilst this strategy identified men with sustained hypertension, it also allowed for recruitment of men with masked hypertension. Study entry criterion were for elevated BP confirmed using ABPM (daytime mean ≥ 135/85 mmHg) with or without elevated clinic BP (≥ 140/90 mmHg), consequently, 37% of the study population had masked hypertension, a condition prevalent in middle aged men with high-normal clinic BP. Despite this, and even with LVMI values largely in the normal range, a significant positive relationship between BP and LVMI was seen for the overall study population. This observation is consistent with other published data in people at low CV risk, including normotensive people with no overt CVD and people with pre-hypertension.[4,29]

Relationships Between Brachial BP and LVMI

Given that increasing SBP was associated with increasing LVMI, we wanted to investigate whether different BP measurement modalities showed different relationships with LVMI. There is a large body of evidence demonstrating that 24-hour ABPM shows stronger relationships with HMOD and/or clinical outcomes compared with clinic BP.[7,8] However, these findings are not unequivocal and other studies report little difference in relationships between BP and HMOD comparing ABPM and clinic BP.[10,11] Data from the present study is consistent with the latter and may relate to either or both of the following; i) exclusion of participants exhibiting WCH, potentially strengthening the relationship between clinic BP and LVMI; ii) use of research quality measurements for clinic BP, effectively replicating what is recommended in guidelines but rarely delivered in practice.

It is recognized that clinic BP is frequently higher than corresponding out of clinic measurements. This relates in part to an alerting mechanism i.e. WCH / white coat effect, during clinical consultation, particularly in the presence of a physician.[30] This may temporarily raise clinic BP to levels inappropriate for the patient's LV mass. With sufficient cases, this could weaken the overall relationship between clinic BP and LV mass, through introducing random scatter. ABPM, by contrast, could provide more reliable BP estimates due to averaging multiple measurements, without an alerting response. Our strategy to excluded participants with WCH most likely eliminated cases where clinic BP elevation was not confirmed by ABPM, contributing to the finding of similar relationships for clinic and ambulatory BP with LVMI.

With regard to quality of BP measurements, previous studies and national guidelines highlight the importance of attention to detail and repeated measurements for accuracy. Indeed, poor technique with rushed, single measurements in clinical practice has been cited as a major contributor to poor diagnostic precision and outcome prediction.[9] Thus, with rigorous application of good measurement technique, together with repeated measurements until stable values are achieved, i.e. use of so called 'research clinic' BP measurements, BP values tend to be lower compared with measurements taken under routine clinical care.[31] In this regard, we showed a significant decline in SBP values and a trend towards improved correlation with LVMI as measurement technique improved i.e. mimicking a "busy clinic" using only a single first measurement through to multiple measurements with averaging of the last two once values became stable. Good measurement technique is claimed to be exemplified using the `automated office BP' (AOBP) technique, in which multiple, automatically repeated BP measurements are taken following a fixed period of rest and with the healthcare personnel or researcher absent. Indeed, studies comparing AOBP with ABPM have reported similar relationships between SBP and LVMI whilst routine clinic BP performs less well.[32] Other studies have shown that improving clinic measurement technique reduces differences between clinic and ambulatory BP. Thus, differences of 14.5, 7.0 and 0.3 mmHg between clinic and ambulatory daytime measurements were reported in a recent meta-analysis when clinic SBP was measured using routine clinic procedures (9 studies), research clinic BP (9 studies) and

AOBP (19 studies) respectively.[33] In our study we demonstrated no significant overall difference in mean SBP between clinic and ambulatory daytime measurements (mean difference 0.9 mmHg 95% CI, -1.0 to 2.7) and this may have contributed to similarities in relationships between BP modalities and LVMI. Additionally, inclusion of men with masked hypertension, may have contributed to the small difference between clinic BP and ABPM observed in our study.

It is notable that for men with predominantly grade 1 hypertension in our study, SBP accounted for only around 10% in the variability for LVMI with no significant association for DBP. These findings were consistent across measurement modalities. This modest proportion attributable to SBP may have contributed to the similarities in correlations with LVMI. Moreover, it may also account for the absence of correlation for DBP with LVMI as previous studies report stronger associations for SBP over DBP or no association with DBP.[34-36] The other main determinant was heart rate, accounting for about 15% of variability in LVMI. Given that the study recruited relatively young men (under the age of 55) with predominantly grade 1 hypertension and low cardiovascular risk, variability in LVMI attributable to BP may be lower than reported in studies recruiting older patients with higher grade hypertension, who may have longer-established HMOD identified using echocardiography rather than MRI.[34] Nevertheless, we have previously demonstrated that BP lowering treatment regresses LVMI by about 5% in this population,[19] which is consistent with the modest proportion of variability in LVMI attributable to SBP.

Central BP, waveform calibration and LVMI

Whilst non-invasive CASP measurement has been claimed to confer advantage in predicting HMOD and CVD [13,15], we saw no clear superiority for central over brachial BP in its relationship with or its prediction of high LVMI. However, CASP in this study was routinely calibrated to brachial SBP/DBP measured using a clinically validated BP monitor. BP load may be better represented by its steady-state component (MAP) and recent reports have suggested that waveform calibration to MAP/DBP generates higher, more accurate CASP values using some devices.[37] Nevertheless, waveform re-calibration in this study generated similar CASP values to SBP/DBP calibration (127.6 ±9.0 mmHg vs.

127.6 ±9.2 mmHg). This likely resulted from identical values between the average radial waveform FF and the FF of 0.4 used for MAP calculation, and may have contributed to similarities in regression relationships between LVMI and CASP between calibration types. Nevertheless, a higher ROC AUC value was seen comparing MAP/DBP versus SBP/DBP calibrated CASP relative to brachial BP monitor SBP as reference (ROC AUC difference MAP/DBP calibrated CASP vs. clinic SBP 0.069, P = 0.02; table 4). However, any potential improvement in relationships between CASP and LVMI needs to be seen in the context of the calibration used. Thus, when MAP/DBP and SBP/DBP calibrated CASP were compared relative to MAP/DBP calibrated SBP as reference, no difference in predicting higher LVMI was seen (ROC AUC difference MAP/DBP calibrated CASP vs. MAP/DBP calibrated SBP 0.051, P = 0.3). This we believe is a novel observation implying that whilst different calibrations may confer different relationships between CASP and LVMI, the influence of calibration type on the reference standard (brachial SBP or the peak of the MAP/DBP calibrated pressure wave) must be considered.[38]

Additional Considerations

In prediction analyses, use of the upper quintile of LVMI was based on the distribution of LVH in a general population (i.e. 20%).[39] Nevertheless, data for outcomes would not have differed meaningfully had we subdivided the population based on other LVMI quantiles (online data supplement. Table S6). In comparing clinical characteristics, participants in the high LVMI group had lower heart rates. This may imply some contribution of athletic ventricular remodeling in the high LVMI group. In support of this, men in the higher LVMI group had higher end-diastolic and stroke volumes (table 2) with LVMI correlating negatively with heart rate and positively with end-diastolic and stroke volume (online data supplement fig S4). Nevertheless, any impact of athletic remodeling on the relationship between BP and LVMI (online data supplement fig S5) would likely have been consistent across all BP measurement modalities and should not have significantly influenced study comparisons. In support of this, systolic BP was higher and heart rate was lower in the high LVMI group in data from all measurement modalities and this was seen irrespective of how the population was subdivided for LVMI.

BP Measurement Considerations.

We used a pre-specified protocol for measuring clinic BP, designed to average BP measurements once variability between consecutive readings was within a tolerable error (10mmHg). Whilst this may have taken longer to complete compared with protocols outlined in National Guidelines, we believe that, together with exclusion of participants with white coat hypertension, we achieved clinic BP readings comparable to, or with greater reliability than would be achieved using protocols outlined in National Guidelines for measurements collected at a single visit.[10,14,22]

Using ABPM, linear regression showed a numerically lower correlation between LVMI and nighttime BP relative to daytime BP. This is interesting given reports that nighttime BP may better predict HMOD and CVEs.[40] However, in low-risk patients with intact autonomic function, nighttime BP has been reported to contribute to HMOD only where there is nighttime hypertension and/or an absence of a nighttime BP dip.[41] The low proportion of nighttime non-dippers (<20%) together with fewer men with elevated nighttime versus daytime BP in our study may account for similar correlations between LVMI and day/nighttime BP.

Study strengths and Limitations

Strengths of the present work include the study population which was selected to identify early effects of BP on LVMI and to maximize potential effects of pressure amplification on BP measurement modalities. Moreover, exclusion of participants with WCH likely avoided inclusion of data from participants whose clinic BP was unrepresentative of their out-of-clinic measurements. Comparison against a group exclusively with confirmed WCH, might confirm this in future work. Cardiac MRI was used to provide an accurate and sensitive endpoint that enabled the study to be adequately powered with smaller numbers than would otherwise be required, e.g. for an echocardiograph-based LV mass study.

Potential limitations include the absence of a gold-standard invasive measurement of 24-hour ABPM. However it was not feasible to use this in a general, low-risk population. Similarly non-invasive ambulatory central pressure was not evaluated as this technology was only in development for the BPro device when the study was designed. As with any cross-sectional study, the potential for reverse-causality could not be ruled out. However, given the weight of evidence relating elevated BP with increased LVMI we think this an unlikely possibility. Another limitation is the use of FFs for MAP estimation as oscillometric MAP was unavailable for the device used. Nevertheless, correspondence between the average waveform FF and the FF used for MAP calculation (0.4) suggests that an appropriate fixed FF was used. We were not able to assess reproducibility of out of office BP measurement by ABPM due to the inconvenience for participants of closely repeated ABPM measurements. Such reproducibility might better be evaluated in future work using home BP monitoring. This study was performed in men under the age of 55 years. We cannot rule out the possibility that our findings may not apply to older men and women in whom WCH may be more prevalent. Finally, both correlations of LVMI with BP parameters and ROC AUC values were modest, but are consistent with those reported for other studies.[6,42]

In summary, this study indicates that clinic BP, when carefully measured according to guideline recommendations and after exclusion of WCH, is a good predictor of LVMI, relative to other BP measurement modalities. These findings suggest that prior reports of inferiority of clinic BP in predicting HMOD and outcomes, are likely due to failure to identify/exclude WCH and use of poor BP measurement technique. Finally, whilst guidelines suggest that central BP may be considered in managing BP, particularly in younger men where BP amplification may be prominent[14], the present study, conducted specifically in this population, demonstrated no advantage for central over brachial BP in predicting HMOD.

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Disclosures

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Figure Legend.

Figure. Panel A: Relationship between LVMI at end-diastole and seated clinic SBP (left) seated clinic CASP (SBP/DBP calibrated, middle) and 24-hour ambulatory SBP (right). Panel B: Relationship between LVMI at end-diastole and ambulatory daytime or night-time SBP. CASP was derived following application of a n-point moving average to the SBP and DBP calibrated waveform. For both panels, fitted regression line and grey band represents 95% confidence interval.

Table 1 Demographics for the study population and by LVMI status.

Parameter	Total n = 143	Higher LVMI n = 29	Lower LVMI n = 114
Age (years)	47.5 [39.9 – 50.9]	48.1 [44.1 - 49.7]	46.8 [39.5 - 51.1]
Height (cm)	177.4 ± 7.9	179.7 ± 7.3	176.8 ± 7.9*
Weight (kg)	86.0 [77.3 - 96.0]	86.0 [79.2 - 95.5]	85.9 [77.0 - 96.0]
BMI (kg/m^2)	27.3 [25.2 - 30.1]	27.0 [25.4 - 29.3]	27.3 [25.1 - 30.1]
Waist Circumference (cm)	95.0 [87.9 - 103.5]	94.5 [86.9 - 102.4]	95.4 [89.2 - 103.5]
Total body fat (kg)	20.8 [15.8 - 24.9]	21.4 [12.7 - 23.8]	20.8 [15.9 - 25.1]
Total trunk fat (kg)	13.1 [9.9 - 15.2]	13.6 [6.7 - 14.7]	12.9 [10.0 - 15.5]
Creatinine (μmol/L)	81.8 ± 12.0	80.2 ± 12.3	82.2 ± 11.9
eGFR (mL/min/1.73m^2)	96.4 [82.5 – 108.5]	100.7 [86.7 - 109.7]	96.3 [82.4 – 108.5]
Glucose (mmol/L)	4.9 [4.6 - 5.2]	4.7 [4.4 - 4.9]	4.9 [4.6 - 5.3]*
Potassium (mmol/L)	4.3 ± 0.3	4.3 ± 0.3	4.4 ± 0.3
Sodium (mmol/L)	141 [140 - 142]	141 [139 - 141]	141 [140 - 142]
HDL cholesterol (mmol/L)	1.3 [1.0 - 1.5]	1.3 [1.1 - 1.5]	1.3 [1.0 - 1.5]
Total:HDL cholesterol ratio	4.1 [3.3 - 5.2]	4.1 [2.8 - 4.8]	4.2 [3.4 - 5.2]
LDL cholesterol (mmol/L)	3.0 ± 0.8	2.8 ± 0.9	3.1 ± 0.8
Q-RISK 10 year (%)	5 [2 - 8]	5 [3 - 7]	5 2 - 8]
Q-RISK lifetime (%)	43 [33 - 59]	40 [31 - 49]	44 [33 – 60] *
LVMI end-diastole (g/m^2)	66.2 ± 8.9	79.5 ± 3.5 **	62.9 ± 6.3

End-Diastolic Volume Index (ml/m^2)	68.8 [60.3 – 75.7]	80.5 [71.8 – 90.6]**	67.8 [58.9 – 72.8]
Stroke Volume Index (ml/m^2)	44.3 [39.9 – 50.3]	52.2 [46.6 – 56.1]**	42.5 [38.7 – 47.9]
Cardiac Output (L/min)	6.1 [5.2 – 6.9]	6.3 [5.7 – 7.3]	6.0 [5.0 – 6.9]
Relative Wall Mass (g/ml)	0.95 [0.86 – 1.06]	0.97 [0.89 – 1.06]	0.94 [0.86 – 1.04]
Ejection Fraction (%)	65.5 ± 5.9	64.5 ± 4.5	65.7 ± 6.2
White	106 (76.8)	25 (96.2)	81 (72.3)
Mixed Race	1 (0.7)	0 (0)	1 (0.9)
South Asian	20 (14.5)	0 (0)	20 (17.9)
Black	10 (7.2)	1 (3.8)	9 (8.0)
East Asian	1 (0.7)	0 (0)	1 (0.9)
Current smoker n (%)	10 (7.4)	4 (14.8)	6 (5.6)

Abbreviations: BMI: body mass index; eGRF: estimated glomerular filtration rate; HDL: high density lipoprotein; LDL: low density lipoprotein; LVMI: left ventricular mass indexed to body surface area.

Data shows mean ± SD or median [IQR] or n (%).

IQR is defined as P25-P75.

Comparison Higher LVMI versus Lower LVMI: * $P < 0.05$, ** $P < 0.01$

Table 2 Hemodynamic parameters for the study population and by LVMI status.

Parameter	Total n=143	Higher LVMI n= 29	Lower LVMI n=114
Clinic SBP (mmHg)	140.9 ± 9.0	145.3 ± 6.7 **	139.8 ± 9.2
Clinic DBP (mmHg)	85.8 ± 7.0	86.4 ± 9.8	85.7 ± 6.1
$CASP_{(SBP/DBP)}$ (mmHg)	127.6 ± 9.2	132.4 ± 7.7 **	126.4 ± 9.2
Heart rate (beats/min)	69.0 [60.5 – 75.0]	60.5 [51.5 - 64.5] **	71.0 [62.5 - 77.0]
ABPM 24-Hour SBP (mmHg)[†]	135.5 ± 6.9	138.8 ± 6.5 **	134.7 ± 6.8
ABPM 24-Hour DBP (mmHg)[†]	85.0 [82.0 – 90.0]	85.5 [79.5 – 90.0]	85.0 [82.0 – 90.0]
ABPM Daytime SBP (mmHg)[†]	140.0 ± 6.9	143.4 ± 6.5 **	139.1 ± 6.7
ABPM Daytime DBP (mmHg)[†]	89.0 [86.0 - 92.0]	90.0 [82.0 – 93.0]	89.0 [86.0 - 92.0]
ABPM Night-time SBP (mmHg)[†]	119.6 ± 9.1	122.4 ± 9.3	118.8 ± 9.0
ABPM Night-time DBP (mmHg)[†]	72.2 ± 7.8	72.7 ± 8.5	72.1 ± 7.7
ABPM Nighttime Non-Dipper (SBP)[†]	25 (17.6)	6 (21.4)	19 (16.7)
ABPM Nighttime Non-Dipper (DBP)[†]	13 (9.2)	3 (10.7)	11 (8.8)

Abbreviations: ABPM: ambulatory blood pressure monitoring; cal: calibration; $CASP_{(SBP/DBP)}$: central aortic systolic pressure (SBP/DBP calibrated); DBP: diastolic blood pressure; SBP: systolic blood pressure.

Nighttime non-dipper is defined as nighttime BP dip < 10%

Data shows mean ± SD or median [IQR] or n (%).

IQR is defined as P25-P75.

Comparison Higher LVMI versus Lower LVMI: ** P < 0.01; † n= 144, (n=28 Hi LVMI group, n=116 Low LVMI group)

Table 3 Relationship of LVMI and BP

BP Parameter (mmHg)	Univariate			Multivariate		
	r	P	P for comparison	r	P	P for comparison
Clinic SBP	0.32	< 0.001***	Reference	0.49	< 0.001***	Reference
$CASP_{(SBP/DBP)}$	0.3	< 0.001***	0.86	0.44	< 0.001***	0.64
ABPM day-time SBP	0.34	< 0.001***	0.85	0.48	< 0.001***	0.96
ABPM 24-hour SBP	0.31	< 0.001***	0.90	0.46	< 0.001***	0.80
ABPM night-time SBP	0.29	< 0.001**	0.75	0.47	< 0.001***	0.87
$SBP_{(MAP/DBP:FF\ 0.4)}$	0.34	< 0.001***	0.89	0.51	< 0.001***	0.83
$CASP_{(MAP/DBP:FF\ 0.4)}$	0.38	< 0.001***	0.60	0.48	< 0.001***	0.96

Abbreviations: ABPM: ambulatory blood pressure monitoring; CASP: central aortic systolic pressure; DBP: diastolic blood pressure; FF form factor; MAP: mean arterial pressure; SBP: systolic blood pressure.

P-values 2-tailed. Multivariate analysis adjusted for heart rate, age and ethnicity.

Table 4, ROC models for predicting high LVMI

Model 1: Predictor variables: Brachial SBP (reference), $CASP_{(SBPDBP)}$*, ABPM 24-hour SBP: Outcome variable: LVMI in diastole

	ROC Area	95% CI	Chi^2	df	$P > Chi^2$	Sidak $P > Chi^2$
Br SBP$_{(Reference)}$	0.66	0.56, 0.76				
$CASP_{(SBP/DBP)}$	0.68	0.58, 0.79	0.31	1	0.58	0.82
ABPM 24-hour SBP	0.66	0.55, 0.76	0.003	1	0.96	0.99

Ho: area (Brachial SBP) = area ($CASP_{(SBP/DBP)}$) = area (ABPM 24-hour SBP): Model Chi^2 0.31, $P = 0.86$

Model 2: Predictor variables: Brachial SBP (reference), $CASP_{(SBP/DBP)}$, $CASP_{(MAP/DBP:FF\ 0.4)}$† : Outcome variable: LVMI in diastole

	ROC Area	95% CI	Chi^2	df	$P > Chi^2$	Sidak $P > Chi^2$
Br SBP$_{(Reference)}$	0.67	0.57, 0.77				
$CASP_{(SBP/DBP)}$	0.69	0.59, 0.80	0.29	1	0.59	0.83
$CASP_{(MAP/DBP:FF\ 0.4)}$	0.74	0.65, 0.83	6.84	1	0.01	0.02

Ho: area (Brachial SBP) = area ($CASP_{(SD)}$) = area ($CASP_{(MD:FF\ 0.4)}$): Model Chi^2 9.2 $P = 0.01$

Model 3: Predictor variables: brachial $SBP_{(MAP/DBP:FF\ 0.4)}$§; (reference), $CASP_{(SBP/DBP)}$, CASP $_{(MAP/DBP:FF\ 0.4)}$† :

Outcome variable: LVMI in diastole

	ROC Area	95% CI	Chi^2	df	P > Chi^2	Sidak P > Chi^2
SBP$_{(MAP/DBP:FF\ 0.4)\ (Reference)}$	0.69	0.60, 0.78				
$CASP_{(SBP/DBP)}$	0.69	0.59, 0.80	0.01	1	0.96	0.99
$CASP_{(MAPDBP:FF\ 0.4)}$	0.74	0.65, 0.83	1.06	1	0.15	0.28

Ho: area ($SBP_{(MAP/DBP:FF\ 0.4)}$) = area (CASP $_{(SBP/DBP)}$) = area (CASP $_{(MAP/DBP:FF\ 0.4)}$): Model Chi^2 14.3, *P* = 0.001

* CASP derived from SBP/DBP calibrated waveforms, † CASP derived from MAP/DBP calibrated waveforms using fixed form factor 0.4, § SBP derived from MAP/DBP calibrated waveforms using fixed form factor 0.4.