Relationship Between 24-Hour Ambulatory Central Systolic Blood Pressure and Left Ventricular Mass

A Prospective Multicenter Study

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Abstract—We investigated the relationship between left ventricular mass and brachial office as well as brachial and central ambulatory systolic blood pressure in 7 European centers. Central systolic pressure was measured with a validated oscillometric device, using a transfer function, and mean/diastolic pressure calibration. M-mode images were obtained by echocardiography, and left ventricular mass was determined by one single reader blinded to blood pressure. We studied 289 participants (137 women) free from antihypertensive drugs (mean age: 50.8 years). Mean office blood pressure was 145/88 mm Hg and mean brachial and central ambulatory systolic pressures were 127 and 128 mm Hg, respectively. Mean left ventricular mass was 93.3 kg/m^2, and 25.6% had left ventricular hypertrophy. The correlation coefficient between left ventricular mass and brachial office, brachial ambulatory, and central ambulatory systolic pressure was 0.29, 0.41, and 0.47, respectively (P=0.003 for comparison between brachial office and central ambulatory systolic pressure and 0.32 for comparison between brachial and central ambulatory systolic pressure). The results were consistent for men and women, and young and old participants. The areas under the curve for prediction of left ventricular hypertrophy were 0.618, 0.635, and 0.666 for brachial office, brachial, and central ambulatory systolic pressure, respectively (P=0.03 for comparison between brachial and central ambulatory systolic pressure). In younger participants, central ambulatory systolic pressure was superior to both other measurements. Central ambulatory systolic pressure, measured with an oscillometric cuff, shows a strong trend toward a closer association with left ventricular mass and hypertrophy than brachial office/ambulatory systolic pressure.

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Although mean blood pressure (MBP) and diastolic blood pressure (DBP) are relatively constant in the conduit arteries, systolic blood pressure (SBP) is higher in peripheral than in central arteries.[1] This increase is the consequence of the progressive reduction of diameter and increase in stiffness from the proximal to the distal arterial vessels and the impact of wave reflections.[2] It has been suggested that central SBP (cSBP) may be pathophysiologically more relevant than brachial SBP (bSBP) for the pathogenesis of cardiovascular disease.[3] cSBP has been associated

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more closely with left ventricular hypertrophy (LVH) and carotid atherosclerosis as markers of hypertensive organ damage than bSBP in various populations.[4–6] Moreover, in a series of studies,[5,7,8] central blood pressures (BPs) were better predictors of cardiovascular outcomes than brachial BPs. Finally, antihypertensive drugs may have different effects on bSBP and cSBP.[9]

For these reasons, the estimation of cSBP in the clinic may be advantageous. However, the relationship between central and peripheral pressures depends on many variables, including age, sex, height, heart rate, and cardiovascular risk factors, together with differences in vessel stiffness and wave reflections. Thus, although highly correlated, cSBP cannot be reliably inferred from bSBP by mathematical formulae.[10] For obvious reasons, invasive measurement of cSBP is not feasible during routine care. In recent years, noninvasive methods for the estimation of cSBP have been developed.[2] Whereas initial systems relied on hand-held tonometers, recently, a novel method was introduced, based on brachial pulse waves recorded with a regular brachial oscillometric blood pressure cuff. This does not only simplify measurement of office cSBP but also facilitates ambulatory cSBP (cASBP) recordings. The latter is of particular interest in the light of earlier studies, which have documented that brachial BP-based ambulatory blood pressure monitoring (ABPM) is closer related to hypertensive organ damage (left ventricular mass [LVM] and LVH)[11] and to cardiovascular events,[12] compared with office bSBP (bOSBP).

The obvious next question is, whether cASBP is superior to brachial ambulatory systolic blood pressure (bASBP; and bOSBP) in the prediction of LVM and LVH. A single-center study has already suggested that 24-hour cASBP improves the individualized assessment of BP-associated cardiac damage (ie, LVH), compared with 24-hour bASBP.[13] We aimed to investigate this research question prospectively in a multicenter study, using standardized equipment for cASBP assessment and central Echo readings, blinded to BP results.

Methods

Participants

Participants were prospectively included, after written informed consent, in study centers listed above. All individuals were >18 years of age and free from antihypertensive medication. In general, a clinical indication for ABPM (suspected hypertension) was present. Contraindications to inclusion were LVH caused by other reasons than hypertension (hypertrophic cardiomyopathy, infiltrative cardiomyopathy, valvular heart disease, and congenital heart disease), inability to provide adequate echocardiographic readings, segmental contraction abnormalities of the left ventricle, contraindications for ABPM (lymphedema both arms), other rhythm than stable sinus rhythm, and unstable clinical conditions, including recent severe infections.

The protocol adhered to the principles outlined in the Declaration of Helsinki and was approved by institutional review boards/ethics committees in the participating centers.

Clinical Assessments

A brief history and physical examination was performed, including family history of cardiovascular disease, personal history of diabetes mellitus, cardiovascular disease, renal disease, smoking habits, anthropometric characteristics, drug history, and a physical examination. Routine laboratory investigations as recommended in recent guidelines[12] were undertaken, particularly fasting glucose, lipids, serum creatinine, serum potassium, and uric acid.

Blood Pressure Measurements

Brachial office BP was measured with validated devices (Table S2 in the online-only Data Supplement) in the morning (08.30–12.30) after 5-minute rest in the supine position under controlled room temperature (22–25°C) on both arms using validated oscillometric devices. The mean of 2 consecutive measurements on the arm with the higher BP was recorded for analysis. ABPM for measurement of brachial blood pressure was performed in all patients during regular daily life, using a validated,[14,15] commercially available oscillometric brachial cuff–based sphygmomanometer (Mobil-O-Graph NG; I.E.M., Stolberg, Germany), following recent recommendations.[16] cSBP was determined from brachial waveforms, as recorded with the cuff, calibrated with MBP/DBP or SBP/DBP, and processed with the ARCSolver transfer function. The system has been validated against a common tonometric method[17,18] and against invasive pressures, recorded with fluid-filled or gold-standard solid-state pressure sensor-tipped catheters (Millar Instruments, Houston, TX).[19,20] In the validation studies, MBP/DBP calibration resulted in values for cSBP, which were closer to invasive cSBP, compared with SBP/DBP calibration.

Echocardiography

Echocardiography was performed by experienced cardiologists, according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[21] Detailed recommendations on standard operating procedures were distributed across study centers (online-only Data Supplement). Whereas recordings were performed locally, all measurements were analyzed at the echocardiographic core laboratory, located at Basel university, using a computerized review station (EZ Desk, Fukuda Denshi, Tokyo, Japan). In addition to the verification of exclusion criteria (assessed locally), echocardiography included determination of ejection fraction (2D, Simpson rule), E-wave, A-wave, left atrial diameter (m-mode, parasternal long-axis view), and LVM. For measurement of LVM, chamber dimensions and wall thicknesses were acquired from the parasternal long- and short-axis views using targeted m-mode echocardiography at the level of the mitral valve leaflet tips at end diastole, with the m-mode cursor positioned perpendicular to the septum and the left ventricular posterior wall. More than 10 consecutive beats were recorded. LVM was calculated according to the formula: LVM=0.8×{1.04 [(left ventricular wall thicknesses+internal dimension)3−(internal dimension)3]}+0.6 g. This formula correlates closely with left ventricular mass at autopsy (r=0.90; P<0.001).[22] We assessed reproducibility of LVM determination in our central laboratory in 202 patients: intraclass correlation coefficient between 2 consecutive measurements was excellent (r=0.98); coefficient of variation was 4.4%. According to the method of Bland–Altman, mean difference between 2 consecutive measurements was 3 g, without any visible bias in the corresponding plot (Figure S1). These results compare favorably with previous studies.[23] LVH was defined according to recent guidelines,[12] with LVM normalized to body surface area, as >115 g/m^2 in men and >95 g/m^2 in women. Relative wall thickness was calculated as (2×posterior wall thickness)/(left ventricular [LV] internal diameter at end diastole). Values were categorized as concentric (relative wall thickness >0.42) or eccentric (relative wall thickness ≤0.42) hypertrophy, when LVM was increased, or as concentric remodeling (normal LV mass with increased relative wall thickness).

Statistics

Normally distributed values are shown as mean (SD), non-normally distributed values are shown as median (interquartile range). Correlations between LVM and BPs were assessed, using Pearson correlation coefficient. Differences in the strengths of association between BPs and LVM were compared by z statistics for comparison of correlations within a single sample. Receiver-operating curve analysis was used to test the ability of BPs to discriminate between

LVH and normal LVM. A 2-sided $P<0.05$ was considered to indicate statistical significance.

The primary end point of the study was the difference in the relationship between LVM and 24-hour bASBP versus cASBP. Assuming a correlation coefficient of 0.40 between LVM and 24-hour bASBP, a correlation coefficient of 0.46 between LVM and 24-hour cASBP, and a coefficient of 0.90 between both BPs, we estimated a sample size of 296 subjects to have 85% power to detect a significant difference in correlation coefficients at a significance level of 0.05.

The full description of the rationale, design, and methods has already been published.[24]

Results

Overall, we included 289 individuals. Baseline values are shown in Table 1. Mean age was 51 years (range: 17–85 years). There were 137 women; 135 had a positive family history of hypertension. Only a minority had diabetes mellitus (n=4), renal disease (n=2), or coronary artery disease (n=7). Average brachial office BP was 145/88 mm Hg, average 24-hour ambulatory brachial BP was 127/83 mm Hg. Average 24-hour ambulatory central BP was 128/84 mm Hg (MBP/DBP calibration) and 119/84 mm Hg (SBP/DBP calibration), respectively. Median LVM was 93.3 g/m^2, and 68 participants (24.4%) had LVH.

Correlations Between Systolic Blood Pressures

All systolic BPs were highly correlated (Table S3). The proportion of variance (R^2) of 24-hour cASBP explained by 24-hour bASBP was 0.88 for cASBP (MBP/DBP calibration) and 0.96 for cASBP (SBP/DBP calibration).

Correlations Between Blood Pressures and LVM

The correlation between bOSBP (r=0.29), 24-hour bASBP (r=0.41), 24-hour cASBP (MBP/DBP calibration; r=0.47), 24-hour cASBP (SBP/DBP calibration; r=0.40), and LVM was statistically significant with $P<0.0001$ for all comparisons. Based on z statistics, the correlation between 24-hour bASBP and LVM tended to be stronger than that between bOSBP and LVM (P=0.06). The correlation between 24-hour cASBP (MBP/DBP calibration) and LVM was significantly stronger than that between bOSBP and LVM (P=0.003). The correlation between 24-hour cASBP (MBP/DBP calibration) and LVM was numerically, but not statistically, stronger than that between 24-hour bASBP and LVM (P=0.32; Table 2).

The results were consistent across all relevant subgroups (men–women, age above and below the median, and body mass index above and below the median; Figure).

The correlations between LVM and pulse pressures (office, ambulatory brachial, and ambulatory central) were weaker than that with systolic pressures (Table S4).

Exploratory analysis in the subgroup with office BP measurements in the sitting position did not substantially change the results (Table S5).

Receiver-Operating Curve Analysis for Prediction of LVH

In receiver-operating curve analysis, all SBPs were significant predictors of LVH. Areas under the curve were 0.618, 0.635, 0.666, and 0.631 for bOSBP, 24-hour bASBP, cASBP (MBP/DBP calibration), and cASBP (SBP/DBP calibration),

Table 1. Baseline Characteristics

Variable	
Demographic parameters	
Age, y	50.8 (40.0–58.2)
Men/women	152 (52.6)/137 (47.4)
Height, cm	170.0 (162.0–178.0)
Weight, kg	75.0 (64–85.2)
Body surface area, m^2	1.89 (0.23)
BMI, kg/m^2	25.7 (23.5–29.0)
Family history of hypertension	135 (46.7)
Family history of premature CV disease	32 (11.1)
Diabetes mellitus	4 (1.4)
Renal disease	2 (0.7)
Coronary artery disease	7 (2.4)
Currently smoking	77 (26.6)
Laboratory parameters	
HbA1c, %	5.4 (5.3–5.6)
Total cholesterol, mmol/L	5.4 (1.0)
LDL cholesterol, mmol/L	3.3 (0.8)
HDL cholesterol, mmol/L	1.4 (1.2–1.6)
Triglycerides, mmol/L	1.2 (0.9–1.5)
Creatinine, µmol/L	79.6 (70.8–88.5)
Potassium, mmol/L	4.3 (4.0–4.5)
Uric acid, µmol/L	321.3 (83.3)
Blood pressures and heart rates	
Brachial office SBP, mm Hg	145 (132–159)
Brachial office DBP, mm Hg	88 (14)
Brachial office PP, mm Hg	55 (46–67)
No. of brachial ABPM readings per patient	71 (62–84)
No. of successful brachial ABPM readings per patient	62 (47–70)
Percentage of successful brachial ABPM readings	88 (74–94)
Brachial ambulatory SBP 24 h, mm Hg	127 (13)
Brachial ambulatory DBP 24 h, mm Hg	83 (11)
Brachial ambulatory PP 24 h, mm Hg	43 (39–48)
No. of central ABPM readings per patient	61 (47–69)
No. of successful central ABPM readings per patient	49 (33–59)
Percentage of successful central ABPM readings	82 (69–92)
Central ambulatory SBP 24 h MBP/DBP cal, mm Hg	128 (120–135)
Central ambulatory DBP 24 h MBP/DBP cal, mm Hg	84 (11)
Central ambulatory PP 24 h MBP/DBP cal, mm Hg	43 (38–49)
Central ambulatory SBP 24 h SBP/DBP cal, mm Hg	119 (12)
Central ambulatory DBP 24 h SBP/DBP cal, mm Hg	84 (11)
Central ambulatory PP 24 h SBP/DBP cal, mm Hg	34 (30–38)
Heart rate ambulatory 24 h	73 (9)

(*Continued*)

Table 1. Continued

Variable	
Brachial ambulatory SBP day, mm Hg	130 (13)
Brachial ambulatory DBP day, mm Hg	86 (11)
Brachial ambulatory PP day, mm Hg	43 (39–49)
Central ambulatory SBP day MBP/DBP cal, mm Hg	130 (13)
Central ambulatory DBP day MBP/DBP cal, mm Hg	88 (11)
Central ambulatory PP day MBP/DBP cal, mm Hg	40 (36–47)
Central ambulatory SBP day SBP/DBP cal, mm Hg	121 (13)
Central ambulatory DBP day SBP/DBP cal, mm Hg	88 (11)
Central ambulatory PP day SBP/DBP cal, mm Hg	32 (29–37)
Heart rate ambulatory day	76 (10)
Brachial ambulatory SBP night, mm Hg	114 (105–124)
Brachial ambulatory DBP night, mm Hg	73 (11)
Brachial ambulatory PP night, mm Hg	42 (37–47)
Central ambulatory SBP night MBP/DBP cal, mm Hg	122 (112–132)
Central ambulatory DBP night MBP/DBP cal, mm Hg	74 (11)
Central ambulatory PP night MBP/DBP cal, mm Hg	48 (42–56)
Central ambulatory SBP night SBP/DBP cal, mm Hg	111 (100–120)
Central ambulatory DBP night SBP/DBP cal, mm Hg	74 (11)
Central ambulatory PP night SBP/DBP cal, mm Hg	36 (32–41)
Heart rate ambulatory night	62 (9)
Echocardiographic measurements	
Ejection fraction, %	62 (9)
Left atrial diameter, mm	42 (39–47)
Septum thickness, mm	10 (9–12)
Posterior wall thickness, mm	10 (9–11)
Left ventricular mass, g	177.5 (145.5–212.6)
Left ventricular mass/BSA, g/m^2	93.3 (82.6–108.0)
Left ventricular hypertrophy present, %	68 (24.4)
Relative wall thickness	0.41 (0.36–0.49)
Relative wall thickness increased	133 (46.0)
E/A	1.11 (0.87–1.40)

Values are represented as n (%), mean±SD, or median (25th percentile–75th percentile). ABPM indicates ambulatory blood pressure monitoring; BMI, body mass index; BSA, body surface area; cal, calibrated; CV, cardiovascular; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PP, pulse pressure; and SBP, systolic blood pressure.

respectively. On the basis of C statistics, the difference in areas under the curve between bOSBP and all ambulatory systolic pressures was not different. This may be because of the higher scatter (larger SE and wider confidence intervals), when office SBP was the comparator. However, the difference in AUCs between 24-hour bASBP and 24-hour cASBP (MBP/DBP calibration) was statistically significant (P=0.03; Table 3). Results were consistent across all relevant subgroups (men–women, age above and below the median, and body mass index above and below the median; Table S6).

Blood Pressures and Left Ventricular Remodeling

Fifty-three percent of the participants had LVs with normal configuration, 23% had concentric remodeling, 12.9% eccentric, and 11.1% concentric hypertrophy, respectively. All BPs showed a clear increase with more pathological forms of LV geometry (Figure S2). In receiver-operating curve analysis, only 24-hour cASBP (MBP/DBP calibration) was superior to bOSBP in discriminating concentric hypertrophy from all other forms of LV configuration (Table 4).

Discussion

We have shown—for the first time in a prospective multicenter setting with blinded echocardiographic readings in an independent center—that 24-hour cASBP, measured with regular brachial cuffs and dedicated software, tends to be superior to 24-hour bASBP in predicting the most widely accepted hypertensive organ damage related to the heart, which is LVH. This result depends on a particular technical aspect, namely, on the way how brachial waveforms are calibrated.

A recent report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography[25] stated that the main contribution of echocardiography to the management of hypertension is the assessment of LVM (and LVH). LVH is an important end-organ consequence of high blood pressure. LVH has been linked with cardiovascular events,[26] and its regression is associated with improved outcomes.[27] Therefore, we selected LVM/LVH as intermediate end point for our study.

Compared with brachial BP, central BP is located closer to the heart and may be a closer estimate of cardiac loading conditions.[6] Indeed, as recently reviewed,[6] the relationship between BPs (SBP and pulse pressure) and LVM/LVH was closer for central compared with brachial pressures in most of the studies.[4,28–31] In consequence, central BPs have been closer associated with cardiovascular outcomes in some,[5] but not all,[32] longitudinal studies.

These findings, however, are limited to office measurements of BP. Compared with office BPs, ABPM-derived brachial BPs are closer associated with markers of hypertensive organ damage (including LVM and LVH) and cardiovascular events.[12] Recently, advances in technology enabled researchers to use brachial cuffs to measure central BPs, not only in the office but also in the ambulatory setting over 24 hours. The obvious question, if cASBP is superior to bASBP, has been preliminary answered in a single-center study from Greece. In 229 middle-aged individuals (93 of them treated for hypertension), 24-hour cASBP was significantly better associated with LVM and LVH than 24-hour bASBP, as well as office SBP.[13] In addition, the same group of authors observed that cASBP is superior to all other blood pressures in predicting left ventricular diastolic dysfunction.[33] We confirm these findings in a larger group of untreated individuals, which is important, because antihypertensive drugs can have a different impact on brachial and central BPs.[9] Interestingly, the estimates were similar in both studies: in untreated individuals, the correlation coefficients between LVM and bOSBP, bASBP, and cASBP were 0.299, 0.38, and 0.49 in the Greece study, and 0.29, 0.41, and 0.47 in our study, respectively. The prospective

Table 2. Associations Between Blood Pressure Components and LVM (Indexed to Body Surface Area)

Blood Pressure Component	Correlation Coefficient	95% CI	*P* vs 24-h bASBP	*P* vs 24-h cASBP (MBP/DBP cal)
Office blood pressure				
bOSBP	0.29*	0.18–0.40	0.06	0.003
Ambulatory bSBP				
24-h bASBP	0.41*	0.31–0.51	…	0.32
Daytime bASBP	0.41*	0.31–0.50	…	…
Night-time bASBP	0.36*	0.25–0.46	…	…
Ambulatory cSBP (MBP/DBP cal)				
24-h cASBP (MBP/DBP cal)	0.47*	0.38–0.56	0.32	…
Daytime cASBP (MBP/DBP cal)	0.47*	0.37–0.56	…	…
Night-time cASBP (MBP/DBP cal)	0.41*	0.31–0.51	…	…
Ambulatory cSBP (SBP/DBP cal)				
24-h cASBP (SBP/DBP cal)	0.40*	0.29–0.49	0.87	0.23
Daytime cASBP (SBP/DBP cal)	0.39*	0.28–0.48	…	…
Night-time cASBP (SBP/DBP cal)	0.34*	0.23–0.44	…	…

bASBP indicates brachial ambulatory systolic blood pressure; bOSBP, brachial office systolic blood pressure; cal, calibrated; cASBP, central ambulatory systolic blood pressure; CI, confidence interval; DBP, diastolic blood pressure; LVM, left ventricular mass; MBP, mean blood pressure; and SBP, systolic blood pressure.

*$P<0.0001$ for correlation with LVM.

multicenter design and the blinded independent echo readings are advantages of our trial. In particular, results from multicenter studies can be easier generalized. On the contrary, even with standardized procedures and central end point assessment, the multicenter design may introduce an element of variability (noise), which may explain that initial reports from single-center studies often have more pronounced findings.

We observed that the superiority of 24-hour cASBP over 24-hour bASBP depended on an often overlooked methodological aspect, which was the calibration method. To understand this particular aspect, we need to briefly review the most common noninvasive methods to measure cSBP.[34] First, pressure waveforms are acquired, typically at the brachial or radial artery. Next, these waveforms are calibrated with brachial BP, measured by the auscultatory method or—in case of ABPM—by oscillometry, which allows MBP/DBP or SBP/DBP scaling of the waveforms. Mathematical formulae (most often transfer functions) may then be used to derive central BPs. Each step may give rise to inaccuracies, but the most important source of error is measurement of brachial BP for calibration.[35] Invasive data

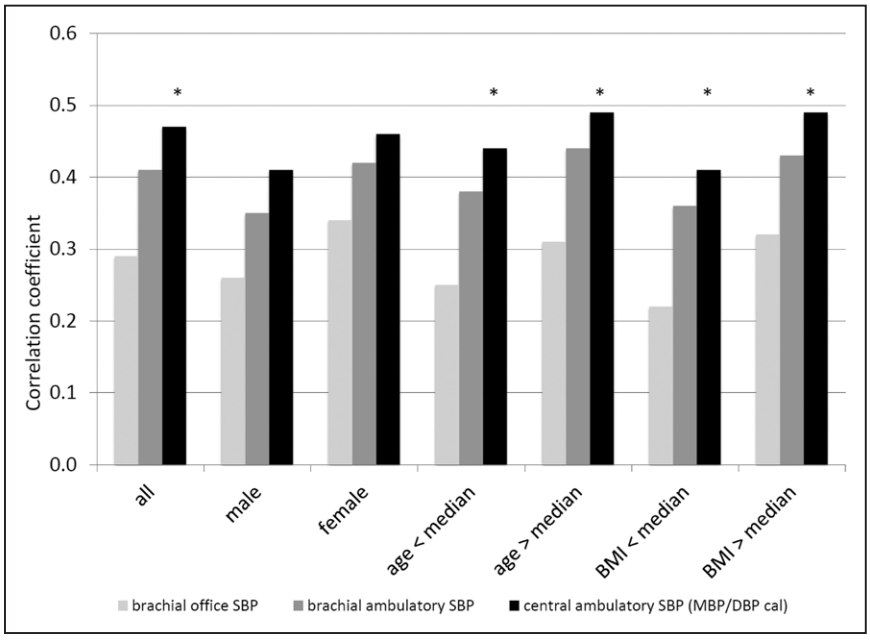

Figure. Correlation coefficients between left ventricular mass and blood pressure components. BMI indicates body mass index; DBP, diastolic blood pressure; MBP, mean blood pressure; and SBP, systolic blood pressure. *$P<0.05$ for difference with brachial office SBP.

Table 3. ROC Characteristics Analysis for Prediction of Left Ventricular Hypertrophy With Different Blood Pressure Components

Blood Pressure Component	AUC	95% CI	SE	*P* for AUC
bOSBP	0.618	0.558 to 0.675	0.0406	0.004
24-h bASBP	0.635	0.576 to 0.692	0.0409	0.0006
24-h cASBP (MBP/DBP cal)	0.666	0.607 to 0.721	0.0387	<0.0001
24-h cASBP (SBP/DBP cal)	0.631	0.572 to 0.688	0.0401	0.0007
Comparison of ROC				
bOSBP vs 24-h bASBP	0.0169	–0.056 to 0.0898	0.0372	0.65
bOSBP vs 24-h cASBP (MBP/DBP cal)	0.0475	–0.02 to 0.115	0.0344	0.17
24-h bASBP vs 24-h cASBP (MBP/DBP cal)	0.0306	0.0023 to 0.0589	0.0144	0.03
24-h cASBP (SBP/DBP cal) vs 24-h cASBP (MBP/DBP cal)	0.0343	0.0061 to 0.0624	0.0144	0.017

Please note that *P* values for comparisons of AUCs depend on the difference between AUCs and on the SE of the difference. AUC indicates area under the curve; bASBP, brachial ambulatory systolic blood pressure; bOSBP, brachial office systolic blood pressure; cal, calibrated; cASBP, central ambulatory systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; ROC, receiver-operating curve; and SBP, systolic blood pressure.

from our institution[19] and others,[20,36] summarized recently in a meta-analysis,[34] suggest that MBP/DBP calibration of waveforms results in cSBP values that are much closer to the invasively determined reference, compared with SBP/DBP calibration. This is physiologically plausible, if the working principle of oscillometry is considered: first, MBP is assessed as the point of maximum oscillations during cuff deflation.[37] Compared with the invasive gold standard, this is usually achieved with high accuracy.[19,38] In a second step, each manufacturer of oscillometric sphgymomanometers has his own (proprietary) algorithm to determine SBP and DBP.[37] Thus, using MBP (determined directly during the first step as outlined above) for waveform calibration instead of SBP (which is assessed in a second step) avoids one potential source of error. Moreover, when directly measured MBP is used for calibration, the correlation between 24-hour bASBP and cASBP is still strong but not as tight as with SBP/DBP calibration (the coefficient of variation is lowered from 0.96 to 0.88), giving the resulting cSBP more chances for superiority. Indeed, the method of MBP/DBP calibration was not only superior in predicting LVH in our study and the single-center study mentioned above[13] but also in a study comparing office BPs.[39] In addition, only office cSBP, assessed with MBP/DBP calibration, independently predicted mortality and provided additional prognostic value on top of office bSBP readings.[40]

The device we used in our study has the ability to use both methods for calibration (MBP/DBP and SBP/DBP), and both methods can be performed post hoc from stored raw data, making clinical comparisons possible.

Limitations

The correlation between 24-hour cASBP (MBP/DBP calibration) and LVM was numerically, but not statistically, stronger than that between 24-hour bASBP and LVM. The main reason may be the high proportion of individuals with normal BP and normal LVM, in whom BP per se (brachial and central) is not the main determinant of LVM. In this condition, sample size calculation was too optimistic. However, based on (1) the numeric superiority of 24-hour cASBP (MBP/DBP calibration), which is consistent in all subgroups; (2) the fact that only 24-hour cASBP (MBP/DBP calibration), but not 24-hour bASBP, was statistically superior to office systolic blood pressure in continuous analysis; and (3) the statistical superiority of 24-hour cASBP (MBP/DBP calibration) in categorical analysis (prediction of LVH and prediction of concentric LVH), we think that our data provide some indication for a clinical superiority of 24-hour cASBP (MBP/DBP calibration) over 24-hour bASBP. Pooling of larger data sets will overcome the problem of limited statistical power in future studies. Another limitation was the fact that we did not measure office central SBP.

Table 4. ROC Analysis for Discrimination Between Concentric Hypertrophy and All Other Forms of Remodeling With Different Blood Pressure Components

Blood Pressure Component	AUC	*P* for AUC	*P* vs bOSBP	*P* vs 24-h bASBP	*P* vs 24-h cASBP (MBP/DBP cal)
bOSBP	0.719 (0.662–0.771)	0.004	…	0.13	0.05
24-h bASBP	0.786 (0.734–0.832)	0.0006	0.13	…	0.07
24-h cASBP (MBP/DBP cal)	0.800 (0.749–0.845)	<0.0001	0.05	0.43	…
24-h cASBP (SBP/DBP cal)	0.793 (0.742–0.838)	0.0007	0.07	0.52	0.72

AUC indicates area under the curve; bASBP, brachial ambulatory systolic blood pressure; bOSBP, brachial office systolic blood pressure; cal, calibrated; cASBP, central ambulatory systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; ROC, receiver-operating curve; and SBP, systolic blood pressure.

Perspectives

Considering our findings together with previous studies, the concept of cASBP seems to hold some promise for hypertension. The assessment of cASBP is nowadays feasible in large trials and even in clinical routine. Before its implementation in everyday practice can be recommended, important questions (reference values, prognostic significance for clinical outcomes, and effects of BP lowering drugs) need to be addressed.

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Novelty and Significance

What Is New?

- For the first time, we prospectively observed in a multicenter study a strong trend toward superiority of 24-hour ambulatory central systolic blood pressure (BP) compared with brachial ambulatory systolic BP and brachial office systolic BP in the estimation of cardiac loading conditions, reflected by left ventricular mass and left ventricular hypertrophy.

What Is Relevant?

- When ambulatory central systolic BP is measured, technical details need to be scrutinized. Ambulatory central systolic BP is only superior with mean BP/diastolic BP calibration of the BP measurement system we used, which is a logical consequence of the findings in the validation studies. These details may be different with different systems, however.

Summary

In individuals not treated for hypertension, 24-hour ambulatory central systolic BP (with mean BP/diastolic BP calibration) was the BP component closest associated with left ventricular mass and left ventricular hypertrophy, the most widely accepted measures of BP-related organ damage, in a prospective multinational multicenter study with blinded central echo readings.

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Online supplement

Relationship between 24 hour ambulatory central blood pressure and left ventricular mass – a prospective multicenter study

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Inclusion criteria:

- ≥ 18 years of age,
- no intake of antihypertensive medications
- indication for ABPM (e.g. suspected hypertension)

Exclusion criteria:

- no written informed consent
- left ventricular hypertrophy due to other reasons than hypertension (hypertrophic cardiomyopathy, infiltrative cardiomyopathy, valvular heart disease, congenital heart disease)
- inability to provide adequate echocardiographic readings
- segmental contraction abnormalities of the left ventricle
- contraindications for ABPM (lymphedema both arms)
- other rhythm than stable sinus rhythm
- unstable clinical condition, including recent severe infections

Table S1: Inclusion and exclusion criteria

- 24 hour ABPM will be taken in all patients during regular daily life (no in-hospital measutrements)
- A validated, commercially available oscillometric brachial-cuff based sphygmomanometer (Mobil-O-Graph NG, I.E.M., Stolberg, Germany) is used for all measurements.
- Patients should engage in normal activities but refrain from strenuous exercise, and keep the arm extended and still at the time of cuff inflations.
- Provide adequate explanation to the patient concerning the measurement procedure
- Cuffs of appropriate sizes (will be provided)
- Take bilateral conventional blood pressure readings. If differences less than 20/10 mmHg systolic/diastolic are present, choose the nondominant arm for ambulatory blood pressure measurement.
- Measurement period is 24 hours
- Program 15 minutes intervals of measurement between 6:00 am and 10:00 pm
- Program 30 minutes intervals of measurement between 10:00 pm and 6:00 am
- Edit mean systolic and diastolic blood pressure and heart rate for 24 hour period
- Edit mean systolic and diastolic blood pressure and heart rate for daytime period (09:00 am – 09:00 pm)
- Edit mean systolic and diastolic blood pressure and heart rate for nighttime period (01:00 am – 06:00 am)
- Patients should use a diary to monitor 1) awaking hours, 2) sleeping hours, 3) activities
- If less than 70% of the expected number of valid values are available by the first ABPM measurement due to frequent artefacts, undertake a second attempt.

Standard operating procedure: ABPM protocol

- Acquire LV dimensions (septum thickness, LV enddiastolic diameter, posterior wall thickness) from the parasternal long and short-axis view using targeted m-mode echocardiography at the level of the mitral valve leaflet tips at enddiastole (defined as the onset of the QRS complex), with the m-mode cursor positioned perpendicular to the septum and the left ventricular posterior wall.
- Acquire LV dimensions (septum thickness, LV endsystolic diameter, posterior wall thickness) as well.
- Measure 5 consecutive beats from parasternal long axis view and 5 consecutive beats from parasternal short axis view (targeted m-mode see above)
- Save measurements as single images (no image runs) in DICOM format, label as PSLongM and PSShortM, respectively, and send them to the echocardiographic core-lab at Basel university (internet address will be provided).
- At the core-lab, all tracings will be examined by 6 expert readers to remove echocardiographic tracings of poor quality by uniform criteria, and data will be recalculated and averaged blinded to blood pressure and arterial stiffness results.
- The LVM (mean of all measurements) provided by the control analysis will be used for further calculations. Inter- and intraobserver coefficients of variation for LVM will be provided.

Standard operating procedure: Determination of left ventricular mass

Center	*Device*	*Manufacturer*
Hospital de Sagunto, Spain	Omron Intellisense 705IT	Omron Healthcare, Kyoto, Japan
Medical University Graz, Austria	medicus	boso Bosch + Sohn, Jungingen, Germany
Jagellonian University Krakow, Poland	M5-I	Omron Healthcare, Kyoto, Japan
University of Brescia, Italy	M5-I	Omron Healthcare, Kyoto, Japan
Milano-Bicocca University, Italy	M5-I	Omron Healthcare, Kyoto, Japan
University of Cambridge, UK	HEM-705 CP	Omron Healthcare, Kyoto, Japan
Klinikum Wels-Grieskirchen, Austria	M5-I	Omron Healthcare, Kyoto, Japan

Table S2: Devices used to measure brachial office blood pressure

Blood pressure component	BOSBP	24h BASBP	24h CASBP (MBP/DBP cal)	24h CASBP (SBP/DBP cal)
BOSBP	-	0.65	0.64	0.65
BASBP 24h	0.65	-	0.94	0.98
CASBP 24h (MBP/DBP cal)	0.64	0.94	-	0.92
CASBP 24h (SBP/DBP cal)	0.65	0.98	0.92	-

Table S3: Cross-correlations between blood pressures; values are Pearson´s correlation coefficients; bOSBP indicates brachial office systolic blood pressure; bASBP, brachial ambulatory systolic blood pressure; cASBP, central ambulatory systolic blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure;

Blood pressure component	correlation coefficient	95% CI	p-value
Office blood pressure			
Office brachial PP	0.21*	0.09-0.32	0.0004
Ambulatory brachial blood pressure			
24 h ambulatory brachial PP	0.23*	0.11-0.34	0.0001
Daytime ambulatory brachial PP	0.23*	0.11-0.33	0.0001
Nighttime ambulatory brachial PP	0.20*	0.09-0.32	0.0008
Ambulatory central blood pressure (MBP/DBP calibration)			
24h ambulatory central PP (MBP/DBP cal)	0.25*	0.14-0.36	<0.0001
Daytime ambulatory central PP (MBP/DBP cal)	0.25*	0.13-0.35	<0.0001
Nighttime ambulatory central PP (MBP/DBP cal)	0.23*	0.12-0.35	0.0001
Ambulatory central blood pressure (SBP/DBP calibration)			
24h ambulatory central PP (SBP/DBP cal)	0.18#	0.07-0.30	0.002
Daytime ambulatory central PP (SBP/DBP cal)	0.17#	0.06-0.29	0.003
Nighttime ambulatory central PP (SBP/DBP cal)	0.14*	0.02-0.26	0.02

Table S4: Associations between pulse pressures and left ventricular mass (LVM; indexed to body surface area). CI indicates confidence interval; PP, pulse pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; cal, calibrated;

Blood pressure component	correlation coefficient	95% CI
Office brachial SBP (supine position)	0.32*	0.21-0.43
Office brachial SBP (sitting position)	0.34*	0.23-0.45
24 h ambulatory brachial SBP	0.42*	0.32-0.52
24h ambulatory central SBP (MBP/DBP cal)	0.48*	0.38-0.57
24h ambulatory central SBP 24h (SBP/DBP cal)	0.40*	0.30-0.50

Table S5: Associations between blood pressure components and left ventricular mass (LVM; indexed to body surface area) in the subgroup of participants with measurement of office blood pressure in the sitting position (n=259). Based on z-statistics, the correlation between 24h ambulatory central SBP and LVM was significantly stronger than that between office brachial SBP (both positions) and LVM (p=0.02). The other correlations were not significantly different.
** ... p<0.0001 for correlation with LVM; CI indicates confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; cal, calibrated;*

Subgroup	bOSBP	24h bASBP	24h cASBP MBP/DBP cal
Female	0.612	0.651	0.669
Male	0.624	0.626	0.668
Age < median	0.524	0.634	0.675
Age > median	0.649	0.641	0.658
BMI below median	0.604	0.629	0.660
BMI above median	0.613	0.631	0.661

Table S6: Receiver operating curve characteristics analysis for prediction of left ventricular hypertrophy with different blood pressure components in subgroups. Values are areas under the curve; bOSBP indicates brachial office systolic blood pressure; bASBP, brachial ambulatory systolic blood pressure; cASBP, central ambulatory systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; cal, calibrated; BMI, body mass index

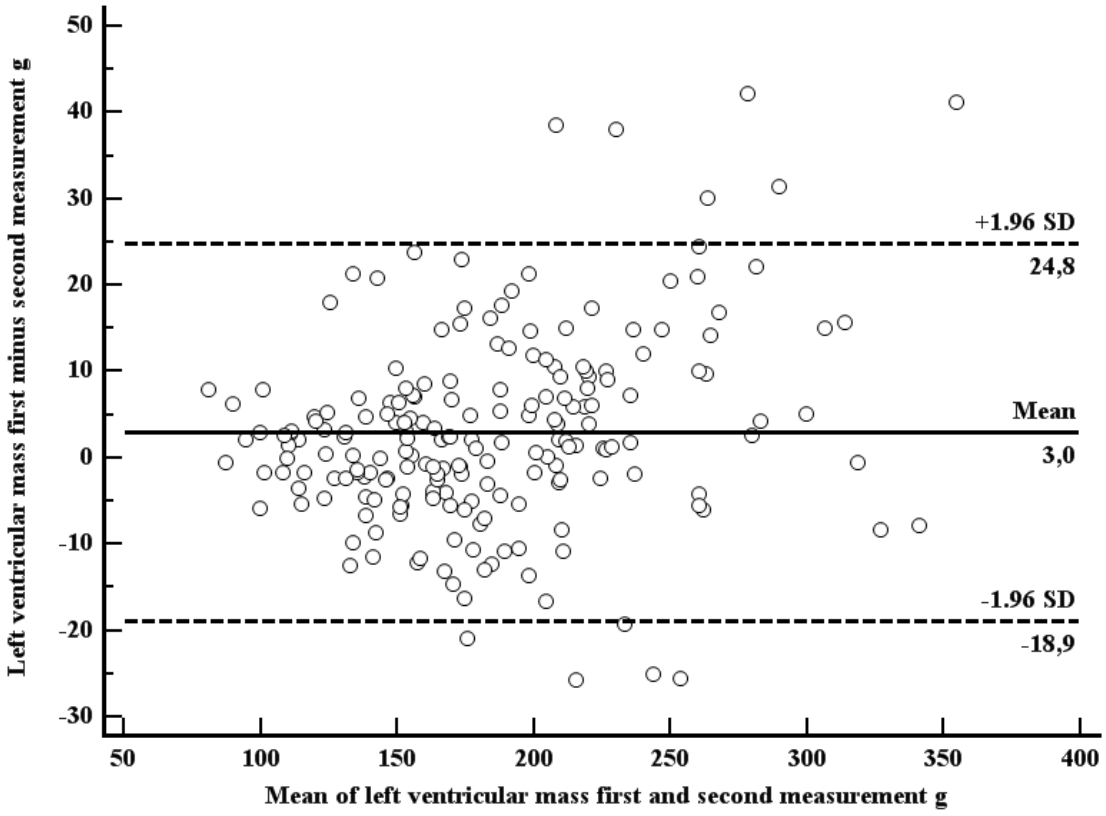

Figure S1: Reproducibility of left ventrikular mass determination

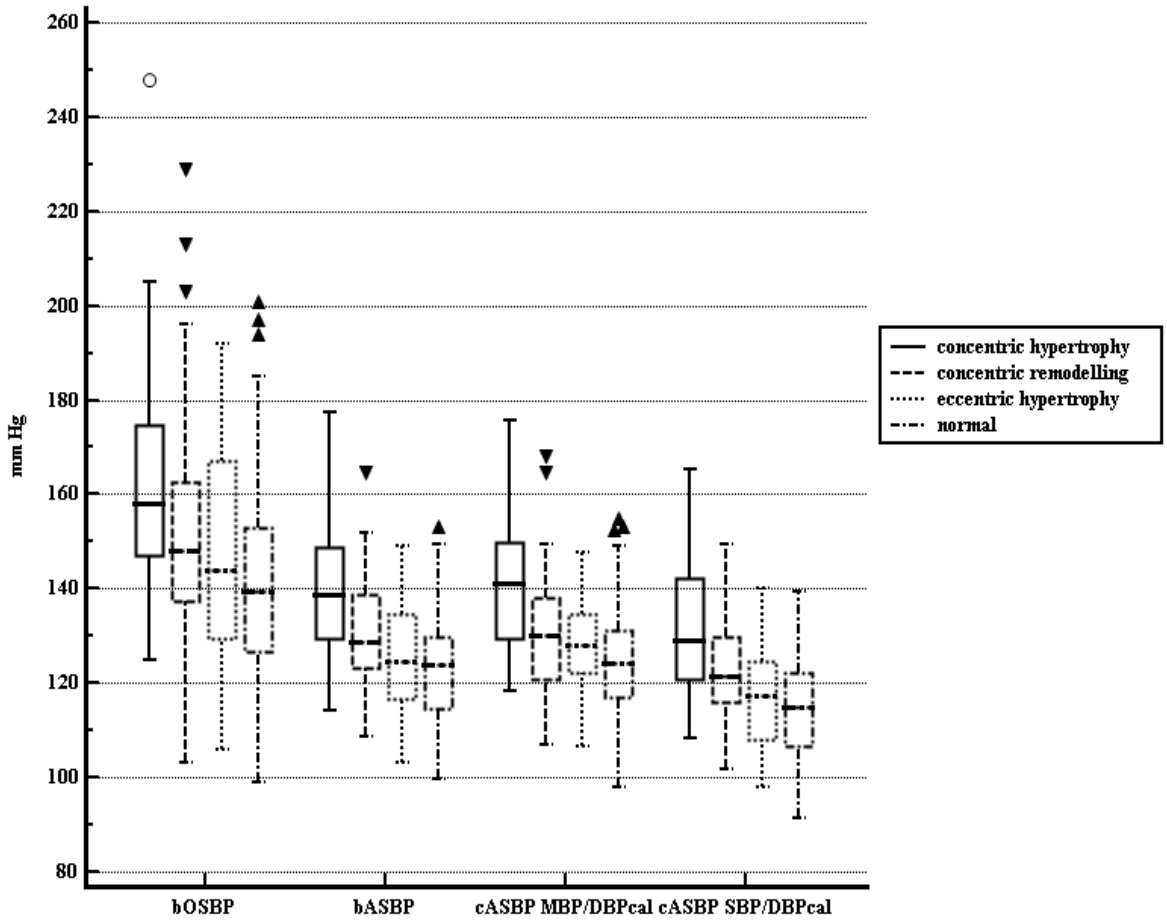

Figure S2: Left ventricular remodeling and blood pressure components. The increase in all BP categories across increasing levels of pathological left ventricular remodeling was statistically significant ($p<0.0001$, ANOVA).