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Original Article

Comparsion of central aortic pressure to brachial artery pressure in hypertensive patients on drug treatment: An observational study

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ABSTRACT

Background: High brachial blood pressure (BP) is an important cardiovascular risk factor. However major differences in central systolic BP can occur among people with similar brachial systolic BP. It is known that central aortic pressure responses to antihypertensive therapy can differ substantially from brachial BP responses, such that true treatment effects cannot be gauged from conventional brachial BP.
Objective: The purpose of this study was to examine if adequate control of brachial BP was concordant with central BP control in treated hypertensive subjects.
Methods: Non-invasive acquisition of brachial and central pressures and wave forms was obtained from 100 subjects with systemic arterial hypertension on drug therapy and 50 healthy individuals. After all necessary precautions according to the guidelines, brachial and central pressures and wave forms were measured 3 times at 5 min intervals using an upper arm cuff (AGEDIO K900 HDP Stolberg, Germany). The mean of the last two measurements of each was recorded as representative of brachial and central aortic pressures and wave forms.
Results: In 45 of 50 healthy subjects with normotension (41 male, 9 female, mean age 38 years), central systolic BP was <120 mmHg. Five healthy subjects (10%) had falsely normal brachial systolic BP, but raised central systolic BP. Out of 100 patients with known hypertension and on various anti-hypertensive drug combinations, 9 had uncontrolled hypertension (defined as brachial BP of >140/90 mmHg and central systolic BP > 120 mmHg). Ninety-one patients had controlled hypertension as estimated by brachial BP of whom, 37 patients had uncontrolled central BP (systolic BP > 120 mmHg). Thus, brachial BP estimation over-estimated control of hypertension in 41% patients ($p < 0.01$). Central systolic BP control was inadequate in 9 out of 41 patients (22%) on angiotensin receptor blocking therapy versus 27 out of 31 (87%) patients on beta-blocking therapy ($p < 0.05$). Thus, there was a marked mismatch with regard to control of hypertension between central and peripheral measurements.
Conclusion: Central BP measurement provides important information on true prevalence of uncontrolled hypertension in the outpatient setting which is higher than current estimates from brachial BP measurement. Optimal BP control by central BP is far less than observed from peripheral pressure measurement. Residual cardiovascular risk despite adequate control of brachial BP can also be explained by the substantial frequency of uncontrolled hypertension as determined by the central BP in patients with apparently controlled hypertension. Both these conclusions have significant impact on prevalence of uncontrolled hypertension and its proper management. Further studies are required to confirm the current data and to provide evidence that treatment decisions based on measurements of central BP result in better outcomes.

Arterial pressure measured with a cuff in the brachial artery is recognized as an important predictor of future cardiovascular risk.[1–3] Systolic blood pressure (SBP) varies throughout the arterial tree and aortic (central) SBP (cSBP) is usually lower than corresponding brachial values, although this difference is variable between individuals.[4–6] Disparity between central and peripheral BP is mainly determined by differences in arterial tree stiffness and waveform reflection from peripheral impedance mismatch points. Central (aortic) BP, is the pressure exerted on the heart and brain and may be different from the pressure that is measured at the arm.

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There are data to suggest that surrogates of cardiovascular risk like left ventricular mass and carotid intimo-medial thickness correlate better with central rather than peripheral SBP.[6,7] Central pressure may be better predictive of outcome in specific populations[8–12] and is differentially affected by antihypertensive and other drugs.[13–15] Clinical studies have indicated that central BP may have predictive value independent of the corresponding peripheral BP.[9–12] It has also been shown that for a similar level of brachial BP, conventional cardiovascular risk factors determine the variability of central BP.[8] Despite these data, It is still not universally agreed whether central BP provides a worthwhile treatment target. A paradigm shift of this type will require direct evidence that selectively targeting central pressure, brings incremental benefit, over and above that is already provided by targeting the brachial artery pressure. The present study was designed to examine the relationship between brachial versus central BP control in treated hypertensive subjects, the influence of anti-hypertensive drugs on this relationship and how well brachial BP tracks central BP in healthy volunteers.

1. Material & methods

This was an observational cross-sectional study of cohorts with established essential arterial hypertension. The study was conducted over a six-month period (July through December 2017) in a tertiary care center having a dedicated Hypertension Clinic. All subjects above age 18 years being treated for hypertension with preferably one drug class were invited to participate in this study. The patients with heart failure, renal failure requiring maintenance dialysis, atrial fibrillation or frequent ventricular ectopy, recent myocardial infarction or stroke, unstable angina, malignancy, pregnancy and awaiting any type of surgery were excluded. The first consecutive 100 patients who fulfilled these criteria, were on regular follow-up for at least six months before the onset of study and those who consented to participate in this study, were enrolled. A group of 50 healthy volunteers from the hospital staff served as control. Of the 100 patients with hypertension, diabetes was recorded in 26, prior myocardial infarction in 18, chronic kidney disease (eGFR <60 ml/min/1.73 m^2) in 4 and hypothyroidism in 3 patients.

1.1. Non-invasive acquisition of brachial and central pressures and wave forms

The patients were seated and rested for 5 min in a quiet room after which brachial and central pressures and wave forms were measured 3 times at 5 min intervals using an upper arm cuff–based sensor equipment (AGEDIO K900 I.E.M. GmbH Cockerillstraße HDP Stolberg, Germany). This is an oscillometric device in which ordinary oscillometric pulse volume recording (diastolic oscillometry) data are fed into a certain transfer function to estimate a central aortic pressure waveform. The technology offers an (upper-arm) cuff-based BP and arterial stiffness measurement within one single procedure. This arm-cuff based method makes use of a transfer function with the ARC Solver algorithm built in the Mobil-o-graph and has been validated against invasive measurements and against radial applanation tonometry.[16,17] Arterial stiffness is quantified with the aortic pulse wave velocity (PWV), measured in m/s. In addition to arterial stiffness, the output includes the hemodynamic data such as cardiac output, total vascular resistance and central (aortic) BP. The mean of the last two measurements of each is recorded as representative of brachial and central aortic pressures and wave forms. In order to obtain pressure waveforms from the cuff, it has to be inflated to a certain pressure. Once inflated the change of volume of air in the cuff can mirror the very small change of volume of the arm created by the change in pressure in the arteries. Change in volume creates a change in pressure that can be recorded and used as the input of a brachial artery to aorta transfer function. cSBP >120 mmHg was considered hypertension based upon data obtained from a large number of healthy subjects.[8]

1.2. Statistical analysis

Descriptive statistics was performed on all demographic and clinical parameters. Baseline patient characteristics were reported as percentages for categorical variables and means and standard deviations for continuous ones. All statistical analyses were performed using SPSS, with two-sided *p*-values with statistical significance set at 0.05. Paired data were analyzed by Student's *t* test and ANOVA. PEARSON'S coefficient and correlation was used wherever appropriate. For multiple comparisons, Bonfferoni correction was utilized to assess level of significance.

2. Results

In this study, 50 healthy normotensive subjects were included as controls of which 41 were male and nine were female (mean age 38 ± 7 years, range 26–55 years). Hundred patients were included as cases of which 73 were males and 27 females (mean age 58 ± 11 years, range 29–88 years) (Table 1). Mean heart rate in healthy volunteers was 78 ± 6 beats/minute (range 66–92) while in hypertensive subjects 76 ± 7 beats/minute (range 58–82). No patient or volunteer had body height <155 cm or greater than 182 cm.

2.1. Observations on measured blood pressure

In 50 normotensive subjects, 41 were males, 37 of whom had cSBP < 120 mmHg (mean cSBP 115.16 ± 3.7 mmHg). The remaining 4 subjects had cSBP >120 mmHg (mean 129 ± 3.36 mmHg). Nine control subjects were females, 8 of whom had cSBP <120 mmHg (mean 116.62 ± 2.32 mmHg) and only one subject had cSBP >120 mmHg (Table 2).

Of 100 treated patients with established hypertension, nine had uncontrolled hypertension (defined as brachial BP of >140/90 mmHg and cSBP > 120 mmHg). Ninety-one patients had controlled hypertension by the estimation of brachial BP (<140/90 on 2 or more consecutive occasions), 37 of those with controlled brachial BP (41%) had uncontrolled cSBP (>120 mmHg, $p < 0.01$)) (Table 2).

If a cut-off of >130 mmHg cSBP was used as a definition of central hypertension, brachial BP control accurately detected simultaneous control of cSBP in 79% (vs 59% with cut-off limit of 120 mmHg cSBP, $p < 0.05$).

2.2. Effect of therapy on cSBP

Most patients were on mono-therapy (73%). However, 27 patients were on combination therapy. It is difficult to study the exclusive effect of monotherapy on cSBP control. Only an approximate guess can be made of the relative efficacy or otherwise of a component of drug combinations with regard to cSBP control. However, data do represent the pattern of BP control by class of anti-hypertensive drug used (Table 3).

In general, patients with controlled hypertension by measurement of brachial BP but with high cSBP were more likely to be on beta-adrenergic receptor blocking agents ($p < 0.05$) (Fig. 1).

Table 1
Age- and gender-distribution of the study population.

Age (Years)			
CASES	**Male**	**Female**	**Total**
N	73	27	100
Mean ± SD	58.04 ± 12.27	57.88 ± 9.9	58.00 ± 11.62
Median	56	57	56.5
Min-Max	35–88	29–76	29–88
CONTROL	**Male**	**Female**	**Total**
N	41	09	50
Mean ± SD	37.78 ± 7.6	37.55 ± 6.38	37.74 ± 7.35
Median	36	36	36
Min-Max	26–55	31–46	26–55

Table 2
Peripheral and central blood pressure in the study groups.

	Peripheral blood pressure	Central systolic blood pressure	
		Controlled[b]	Uncontrolled
Controls ($n = 50$)	Controlled[a] ($n = 50$)	45 (90%)	5 (10%)
	Uncontrolled ($n = 0$)	–	–
Patients ($n = 100$)	Controlled ($n = 91$)	54 (59%)[c]	37 (41%)[c]
	Uncontrolled ($n = 9$)	0 (0%)	9 (100%)

[a] Peripheral blood pressure-controlled <140/90 mmHg, uncontrolled ≥140/90 mmHg.
[b] Central systolic blood pressure-controlled <120 mmHg, uncontrolled ≥120 mmHg.
[c] *P*-value <0.01 for comparison with controls.

3. Discussion

In this study we derived central aortic BP and hemodynamic indices contemporaneously with brachial BP in hypertensive patients who were already on treatment and apparently normotensive individuals. It is an observational study designed to study the relevance of central BP in treated hypertensive patients to further optimize the therapy and to study the differential effect of anti-hypertensive drugs or combination of drugs on central BP In 100 hypertensive patients who were on treatment serving as case material of the study protocol, nine had uncontrolled hypertension (defined as brachial BP of >140/90 mmHg and cSBP >120 mmHg). Ninety-one patients had controlled hypertension by the estimation of brachial BP, 37 of whom (41%) had uncontrolled cSBP (>120 mmHg). Brachial BP values over-estimated control of hypertension in 41% patients. So, patients who are on treatment can have controlled brachial BP, but higher central pressures if cSBP >120 mmHg is considered a cut-off upper limit. In this study the findings that different BP–lowering drugs might differentially affect cSBP despite similar effects on brachial BP is consistent with data from previous studies.[13–15]

Central hypertension is predominantly due to wave reflection within the arterial tree. This is based on the assumption that augmentation pressure is the direct consequence of a backward travelling pressure wave, reflected from the distal circulation, adding on to a forward pressure wave. Central arterial and hemodynamic parameters can be estimated noninvasively using several techniques. These include Doppler ultrasound; applanation tonometry, oscillometry, and magnetic resonance imaging; all of which are associated with their own strengths and weaknesses.[8] Most used are tonometric techniques and oscillometric techniques for post-wave analysis. cSBP can be estimated from peripheral waveforms using a general transfer function and from the second wave of systolic blood pressure (by oscillometry) with the same accuracy as radial applanation tonometry, irrespective of the calibration method.[16,17] This means that both techniques are affected in the same way by the inaccuracy of noninvasive brachial measurements, but the peripheral to central systolic pressure increment remains relatively unaffected. Estimation of cSBP does not require complex equipment and it can potentially be obtained from a simple upper arm cuff, thus allowing its usage in routine care as was shown in our study. Oscillometric devices have been suggested to be especially useful since the methodology includes the use of a simple pressure cuff and has the advantages of being relatively fast, operator independent and require minimal cooperation of the patient.[16,17] In this study, we used a validated oscillometric technique as described in methods.

The current limitation of non-invasive cSBP estimation is that neither the age-, sex-, and ethnicity specific reference ranges nor the specific central pressure treatment targets have been well defined. Central pressure measurements by non-invasive methods are rarely described according to age and sex in healthy populations. For age- and sex-specific reference ranges, AtCor Medical applanation tonometer software (AtCor Medical, West Ryde, New South Wales, Australia) used measurements from 4001 healthy, normotensive participants in the first Anglo-Cardiff Collaboration Trial.[8] Overall, cSBP increases with age, is lower in women than in men until the sixth decade of life, and reaches a maximum of 120 ± 8 mmHg in men and 120 ± 11 mmHg in women. Central pulse pressure is higher in women after the fifth decade of life. For healthy people, initiation of BP–lowering strategies may be considered in patients older than 40 years when cSBP is >121 mmHg (both sexes) and central pulse pressure is more than 50 mmHg in women and 45 mmHg in men.[8] We defined central hypertension when cSBP was >120 mmHg in both genders. Despite similar data from other studies, this definition is arbitrary for our study.

There is growing evidence to support the importance of cSBP as a marker of cardiovascular morbidity, mortality and treatment efficacy. An individual patient data meta-analysis of prospective

Table 3
Frequency of anti-hypertensive drug use and status of central blood pressure.

	Number of patients	% of the total population (n = 100)	Number of patients with uncontrolled central systolic blood pressure (>120 mmHg)	% of those receiving the drug
Angiotensin converting enzyme inhibitors	26	26%	5	19%
Angiotensin receptor blocking agents	41	41%	9	22%
Beta-blockers	31	31%	27	87 %[a]
Calcium channel blockers	16	16%	8	50%
Diuretics	08	08%	5	62%
Others	01	01%	1	100%

[a] $p < 0.05$ compared to angiotensin converting enzyme inhibitors.

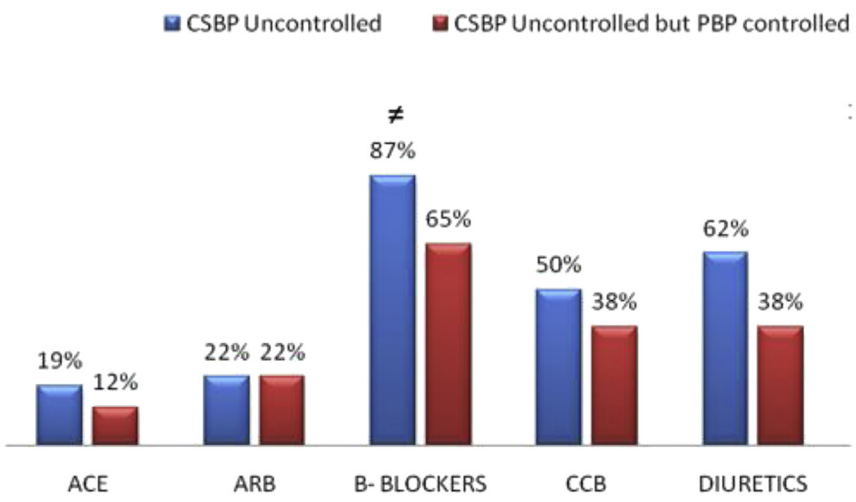

Fig. 1. Anti-hypertensive drug use and control of central blood pressure. CSBP- central systolic blood pressure; PBP- peripheral blood pressure; ACE-angiotensin converting enzyme inhibitors, ARB- angiotensin receptor blocking drugs; CCB- calcium channel blocking drugs, B-blockers- beta-adrenergic receptor antagonists. ≠ $p < 0.05$ for comparison with angiotensin converting enzyme inhibitors.

observational data from 22,433 subjects showed cSBP to be a better predictor for future stroke than brachial systolic BP, but not myocardial infarction.[18] Assessment of cSBP may improve the adverse events prediction after percutaneous coronary interventions.[19] As suggested by the CAFE and other studies, making cSBP measurements part of the routine care could improve cardiovascular outcome.[13,20] Given the potential benefits of lowering cSBP relative to brachial systolic BP as demonstrated in the CAFE study, it is also necessary to understand how drugs may lower cSBP. The literature on this aspect is progressively expanding.[21–25] However consensus over choice of age and morbidity-specific therapy to control central hypertension eludes us so far.

4. Limitations of the study

This study includes a small number of patients and hence this magnitude of lack of control of central hypertension in treated hypertensive patients may not be accurate. Validation studies on this single upper arm cuff-based oscillometric method for estimating cSBP are limited. A number of factors such as age, heart rate and height have differential effects on central and peripheral pressure. We did not analyze these differences. In addition, cardiovascular risk factors such as diabetes, hypercholesterolemia, smoking and metabolic syndromes, which accelerate aortic stiffening in the large arteries, may have greater effects on cSBP and can explain the differences between central and brachial systolic BP. Female gender on average is associated with a lower cSBP in comparison with males and hence definition of central hypertension might be gender-specific. We did not report this difference.

4.1. Conclusions

Central BP measurement provides important information on true prevalence of uncontrolled hypertension in the outpatient setting which is higher than current estimates from brachial BP measurement. Residual cardiovascular risk despite adequate control of brachial BP can partly be explained by the substantial frequency of uncontrolled hypertension as determined by the central BP in patients with apparently controlled hypertension. Both these conclusions have significant impact on prevalence of uncontrolled hypertension and its proper management. Further studies are required to confirm the current data and to provide evidence that treatment decisions based on measurements of central BP result in better outcomes.

5. Clinical perspective

Current guidelines for the diagnosis and treatment of hypertension are based solely on brachial BP. However, brachial and central BPs are not the same. The merging of forward and backward pressure waves can make central BP values different from peripherally (brachial artery) measured ones in patients with treated hypertension. The difference may vary between subjects and so can the centrally vs. the peripherally measured pressure effects of antihypertensive drugs. Central BP is the BP to which vital organs are exposed and hence its control is vital. Current study suggests that a significant number of patients with so-called controlled hypertension, have elevated central BP.

Conflicts of interest

All authors have none to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2018.10.418.

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