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Baseline Predictors of Central Aortic Blood Pressure: A PEAR Substudy

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Abstract

Background—Elevated central systolic blood pressure (BP) increases the risk of cardiovascular events and appears superior to peripheral BP for long term risk prediction. The objective of this study was to identify demographic and clinical factors associated with central pressures in patients with uncomplicated hypertension.

Methods and Results—We prospectively examined peripheral BP, central aortic BP, and arterial wall properties and wave reflection in 57 subjects with uncomplicated essential hypertension in the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) Study. Significant predictors of central SBP included height, smoking status, HR, and peripheral SBP, while central DBP was explained by peripheral DBP and HR. These variables accounted for nearly all of the variability in central SBP and central DBP (R^2 = 0.94 and R^2 = 0.98, respectively). Central pulse pressure variability was largely explained by gender, ex-smoking status, HR, peripheral SBP, and peripheral DBP (R^2 =0.94). Central augmented pressure had a direct relationship with smoking status, peripheral SBP, and duration of hypertension, whereas it was indirectly related to height, HR, peripheral DBP.

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Conclusions—Easily obtainable demographic and clinical factors are associated with central pressures in essential hypertensive persons. These relationships should be considered in future studies to improve assessment of BP to reduce cardiovascular risk and mortality.

Keywords

Hypertension; arterial pressure; blood pressure; pulse wave analysis; vascular stiffness; applanation tonometry; cardiovascular disease

Introduction

The degree to which patient demographics, heart rate (HR), and peripheral blood pressure (BP) affect central arterial properties is not well established. Differences in BP occur between the brachial artery (peripheral) and the ascending aorta (central) with the latter being a better surrogate marker of cardiovascular risk, left ventricular afterload, and circumferential arterial shear stress.¹

Although clinical practice is almost exclusively guided by pressures at the brachial artery, systolic BP (SBP) varies widely throughout the arterial tree. Pressure waves generated during systole traverse the arterial tree and are reflected back to the aorta at varying velocities depending on the stiffness of the arterial tree. Pressure waves are prematurely reflected in hypertensive patients, such that their return to the aorta is simultaneous with the generation of the next pressure wave, increasing the pressure in the aorta or the central BP.

With the knowledge that increased central SBP increases the risk of cardiovascular events, emerging data suggest that central pressure might be superior to its peripheral counterpart for forecasting risk.^{2,3} These observations highlight the importance of understanding the relationships between patient demographic variables, arterial properties and arterial pressure. A more comprehensive appreciation for these relationships might afford clinicians an opportunity to estimate a patient's central BP. This practice could improve the use of antihypertensive therapy and allow a greater chance of preventing cardiovascular events, rather than simply achieving a goal BP measured in the brachial artery.

Multiple factors have the potential to influence central aortic function and hemodynamics. A better awareness of these relationships would be useful for clinicians to tailor therapy for each patient in order to improve control of peripheral BP and central BP. Numerous published studies established that age, gender, ethnicity, height, HR, smoking, and exercise all affect various parameters of central pressure. 4,5,6,7,8,9,10,11,12 Although these studies provide the knowledge that demographic elements do indeed affect central pressure, they do not examine the relationship of the demographic variables on central pressure in relation to peripheral blood pressure, nor explain which variables could be utilized in estimating patients' central BP. The objective of the present study was to examine baseline predictors of central pressure by identifying demographic and clinical factors associated with central pressures in uncomplicated hypertensive persons.

Methods

This prospective substudy was designed as part of the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study (NCT00246519), a prospective, multicenter, randomized, open-label, parallelgroup study with a primary focus on identifying the genetic determinants of antihypertensive and adverse metabolic responses to a thiazide diuretic (hydrochlorothiazide), a β -blocker (atenolol), and their combination; full details of PEAR study methodology have been reported elsewhere. ¹³ Concisely, the study population of

PEAR included males and females, of any race and ethnicity, aged 17 to 65 at enrollment who had newly diagnosed, untreated, or known mild-to-moderate essential hypertension (average home diastolic BP [DBP] >85 mmHg and office DBP >90 mmHg) treated with two or fewer antihypertensive medications at enrollment. Patients on treatment with antihypertensive medications at enrollment tapered their medications (as necessary) and discontinued therapy, with a minimum antihypertensive-free period of 18 days, and a preferred washout period of 4–6 weeks. Patients were excluded if they had an office or average home SBP >180 mmHg or DBP >110 mmHg, secondary forms of hypertension (including sleep apnea), isolated systolic hypertension, known cardiovascular disease, HR <55 beats per minute (bpm) in the absence of β -blocker therapy, diabetes mellitus (type 1 or 2) or screening fasting blood glucose >126 mg/dL, primary renal disease, concomitant diseases treated with BP-lowering medications, or chronic treatment with BP-elevating drugs. 13

Patient Recruitment

Patients already recruited into the parent PEAR study from one PEAR study center (University of Florida, Gainesville, FL) were eligible for recruitment into the present study. Recruitment began in 2007 and a total of 88 participants were recruited. Institutional Review Board approved the parent and substudy protocols and all patients provided written informed consent prior to initiating the substudy.

Procedures

All measurements of BP were performed in a quiet, temperature-controlled room after a brief rest period of at least five minutes. Peripheral BP was measured prior to central BP assessment according to the parent PEAR study protocol, using a home BP monitor (Microlife model 3AC1-PC Home BP Monitor) assigned to the patient. All BP measurements were performed in triplicate after the patient had been seated for at least 5 minutes. ¹³

Central aortic BP and assessment of arterial wall properties and wave reflection characteristics were performed noninvasively, whereas radial artery BP waveforms were recorded at the wrist, using applanation tonometry with a high-fidelity micromanometer (Millar Instruments, Houston, Texas). After 20 sequential waveforms were acquired and averaged, a validated generalized mathematical transfer function was used to synthesize the corresponding central aortic BP waveform. The radial waveforms were processed with the SphygmoCor device (AtCor Medical, Sydney, Australia) to yield estimates of central SBP, central DBP, ejection duration, central pulse pressure, pulse pressure amplification ratio (PPamp) defined as brachial pulse pressure divided by central pulse pressure, central augmented pressure defined as the pressure difference between the 1st peak/shoulder and 2nd peak/shoulder of the aortic pressure waves, and heart rate-corrected central augmented pressure. Central pulse pressure was calculated as the difference of central SBP and central DBP. To minimize the risk of variations in operator use, an operator index, which is an indicator of overall reproducibility of the captured signal from the radial artery, was calculated to determine if a measurement was of sufficient quality and only those values greater than or equal to 90% were reserved.

Statistical Analysis

Descriptive statistics were used to report demographic information, peripheral BP measurements, HR, and central hemodynamic parameters at baseline. We summarized continuous variables using mean \pm standard deviation since all were approximately normally distributed; categorical variables were summarized using n (%).

We developed multiple linear regression models to analyze statistically predictors of each of the dependent variables under study, including central SBP, central DBP, central pulse pressure, PPamp, ejection duration, central augmented pressure, and heart rate corrected central augmented pressure. In each model, we used forward stepwise selection to add independent variables including, age, gender, self-identified race, height (in cm), waist circumference (in cm), smoking status (current smoker, ex-smoker, or never-smoker), alcohol consumption (drinks per week), duration of hypertension (years), previous use of antihypertensive drug (yes/no), baseline peripheral SBP, baseline peripheral diastolic BP, baseline HR, and weekly exercise (minutes/week). Variables entered each model stepwise with criteria of p<0.2 for entry and p>0.05 for staying in the model.

Statistical significance was defined *a priori* by a p-value < 0.05. All statistical analyses were performed with SAS 9.3 (SAS Institute, Cary, NC) statistical software.

Results

Baseline Characteristics

A total of 88 patients were enrolled in the study with 57 having complete, evaluable central BP data, defined as having a high quality central BP reading at the baseline clinic visit. Of the 57 patients with data, the majority were male (68%) and most were non-Hispanic Whites (61%) or Blacks (30%), with an overall average age of 47 years (Table 1). Fifty-seven percent of enrolled subjects reported a current or previous history of smoking, while 37% reported drinking alcohol on a weekly basis. The average duration of hypertension within the population was 5.95 years and 82% had taken an antihypertensive in the past. The average HR amongst the population was 73 bpm and mean peripheral BP was 151/97 mmHg.

Central Systolic and Diastolic BP

Height, smoking status, baseline HR, and baseline peripheral SBP were significant predictors of central SBP (Table 2). Central SBP had a direct relationship with current smoker status and baseline peripheral SBP, while it had an indirect relationship with height and baseline HR (Table 2 & 3). Central DBP had a direct relationship with baseline peripheral DBP and baseline HR. Central SBP was lower in those of shorter stature or presenting with a lower baseline HR and was higher among current smokers or those with an increased baseline peripheral SBP. Elevated baseline peripheral DBP and increased baseline HR significantly explained greater central DBP (Table 2 & 3). These variables accounted for nearly all of the variability in central SBP and central DBP ($R^2 = 0.94$ and $R^2 = 0.98$ respectively).

Pulse Pressure Amplification Ratio (PPamp)

Age, gender, smoking status, baseline HR, and baseline peripheral SBP were all statistically significant predictors of PPamp (Table 2). PPamp was directly related to male gender and baseline HR and indirectly related to age (Table 2 & 3). Combined, all of these variables explained the majority of the variability in PPamp (R²=0.48). Advanced age accounted for a reduced PPamp, but male gender and increased baseline HR justified a greater PPamp (Table 2 & 3).

Ejection Duration

Gender, baseline HR, baseline peripheral SBP, and baseline peripheral DBP explained a large portion of the variability in ejection duration (R^2 =0.78) (Table 2). Ejection duration had a direct relationship with baseline peripheral SBP, but an indirect relationship with male

gender, baseline HR, and baseline peripheral DBP (Table 2 & 3). Male gender, elevated HR, and increased baseline peripheral DBP explained reduced ejection duration, but greater peripheral SBP accounted for greater ejection duration (Table 2 & 3).

Central Pulse Pressure

Central pulse pressure variability was largely explained by gender, current smoker status, baseline HR, baseline peripheral SBP, and baseline peripheral DBP (R²=0.94) (Table 2). Central pulse pressure was directly related to baseline peripheral SBP and current smoker status, although it was indirectly related to male gender, baseline HR, and baseline peripheral DBP (Table 2 & 3). Male gender, elevated baseline HR, and increased baseline peripheral DBP justified a reduced central pulse pressure (Table 2 & 3). Alternatively, an increase in baseline peripheral SBP and positive current smoker status accounted for greater central pulse pressure (Table 2 & 3).

Central Augmented Pressure and Heart Rate Corrected Central Augmented Pressure

Variability in the prediction central augmented pressure was greatly explained by age, height, current smoker status, baseline HR, baseline peripheral SBP, and baseline peripheral DBP (R²= 0.77) (Table 2). Central augmented pressure had a direct relationship with age, positive current smoker status, and baseline peripheral SBP, whereas it was indirectly related to height, baseline HR, baseline peripheral DBP (Table 2 & 3). Increased height, increases in baseline HR, and elevated baseline peripheral DBP explained reduced central augmented pressure. However, increased age, current smoking status, and elevated baseline peripheral SBP justified greater central augmented pressure (Table 2 & 3).

Furthermore, variability in the prediction of heart rate corrected central augmented pressure was mainly explained by gender, current smoker status, duration of hypertension, baseline peripheral SBP, and baseline peripheral DBP (R²= 0.74). HR corrected central augmented pressure was directly related to positive smoking status, duration of hypertension, and baseline peripheral SBP, as it was indirectly related to male gender and baseline peripheral DBP (Table 2 & 3). In this case, males and increases in baseline peripheral DBP accounted for a reduced HR corrected central augmented pressure. However, HR corrected central augmented pressure was explained larger in current smokers, those with a longer duration of hypertension, and increases in baseline peripheral SBP.

Discussion

The results of this study are the first to provide information on which demographic variables are associated with changes in central pressures in uncomplicated hypertensive persons. This data can used to for future studies aiming to better elucidate central aortic BP and arterial properties in order to better assess patients' risk of cardiovascular risks. ^{14,15,16,17}

Overall, among a diverse, essential hypertension patient population, the results of the current study support the idea that the earlier the reflected wave returns to the aorta during the cardiac cycle, the greater the central augmented pressure and the lower the PPamp will be, as seen previously in research. ¹⁸ Earlier return, resulting in increased central SBP, is associated with increased vascular stiffness, an outcome of aging and smoking, and shorter distance to travel, accompanying shorter statute. Medications known to reduce vascular stiffness such as angiotensin converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and dihydropyridine calcium channel blockers (DHP-CCBs) are beneficial in these patients with stiffer vessels because of their ability to relax the vasculature, leading to decreases in pulse wave velocity and central augmented pressure, which results in both central BP and peripheral BP reductions. ¹⁹ HR also affects central augmented pressure as

observed in this study and has been reported to be the most influential predictor of augmentation index (augmented pressure/pulse pressure), central SBP, and PPamp in previous investigations. ^{20, 21, 22} A decrease in HR leads to a prolonged ejection duration during the cardiac cycle. Therefore, the reflected wave returns during late systole rather than during diastole, which causes the central SBP to increase and central DBP to decrease. When the central SBP increases, the central pulse pressure increases and the peripheral pulse pressure remains unchanged, resulting in a decrease in the PPamp. ²³ Since central pulse pressure, not peripheral pulse pressure, determines left ventricular workload, PPamp is possibly a better predictor for cardiovascular events and mortality when compared to BP. ²⁴

We identified multiple predictors of central SBP, central DBP, ejection duration, central augmented pressure, HR corrected central augmented pressure, and central pulse pressure utilizing demographic variables and/or clinical factors listed above (Table 2). This information allows practitioners to appreciate the effects of demographic variables and clinical factors on central BP, as well as peripheral BP, which can improve pharmacologic therapy choices to target individualized baseline demographic variables and the underlying cause of mortality.

With growing knowledge of the importance of central aortic BP, studies examining the effects of various pharmacological BP agents on central BP, rather than peripheral BP, may become more significant. The earliest study in this area of research, CAFÉ, reported that the HR lowering effects of beta blockers, specifically atenolol, caused an inverse increase in central SBP and central pulse pressure, as also seen in our current study when looking at baseline HR and central SBP. This effect on HR may be an underlying reason for why betablockers have been shown to be less effective at reducing cardiovascular events when compared with other treatments regimens in hypertensive patients.²¹ This data provides literature to support physicians in selecting anti-hypertensive therapies, such as inhibitors of the renin angiotensin-aldosterone system (RAAS), over beta-blockers in essential hypertensive patients not requiring HR reductions. Inhibitors of RAAS, ACE-Is and ARBs, not only have beneficial peripheral BP lowering capabilities, but they also provide decreases in central BP and long-term cardiovascular protection. Conversely, despite beta-blockers superior effects on peripheral BP, they have negative effects on central BP and central hemodynamics, which are thought to be the reasons they are less effective at reducing cardiovascular events.

Multiple factors have the potential to influence central aortic function and hemodynamics. A better understanding of these relationships would be useful for clinicians to tailor therapy for each patient in order to improve control of both peripheral BP and central BP. For example, arterial wave reflection occurs at various times in patients of different body heights due to aortic length resulting in greater central augmented pressure.⁴ However, when matched for body height, the timing of both left ventricular ejection and arterial wave reflection are different in men compared with women, suggesting that other patient features might affect central aortic structure and function. More specifically, this finding may be due to women having smaller, stiffer blood vessels which increase the pulse wave velocity, resulting in an earlier return of the reflected arterial wave, an increased pulse pressure, and greater augmentation index. 5,6 Therefore, ACE-Is, ARBs, or DHP-CCBs may be an ideal initial treatment for women because of their ability to decrease vascular stiffness and central hemodynamics. Another study, in elderly females, reported that age, gender, heart rate, and other factors were predictive of pulse pressure in multivariate analysis.⁷ Additionally, the pulse pressure ratio (1/amplification) significantly increases with age, signifying that aortic pulse pressure rises more than brachial pulse pressure. 8 Mahmud and Feely discovered that pulse pressure amplification was significantly reduced in smokers, likely due to increased arterial stiffness which increases arterial wave reflection, leading to increased aortic systolic

BP. They also found that augmentation index was significantly higher at baseline in smokers compared with nonsmokers. In addition, young African-American men have greater central BP despite comparable peripheral BP, and greater central augmented pressure when compared with Caucasian young men. Lastly, multiple studies have shown that regular aerobic exercise lowers aortic stiffness, leading to reduced pulse pressure and central augmented pressure. 11,12

Limitations

This study has limitations that are important to consider. The sample size in the present study is relatively small and thus may have limited our ability to determine small but significant associations between demographic or clinical factors and central aortic and hemodynamic parameters. However, the maximum number of independent variables in any of our models was six and thus our sample size is within the general rule of thumb requiring approximately 10 observations per independent variable given moderate effect sizes. 25 Importantly, all of our models resulted in large effect sizes (all R^2 values >0.5) which can reduce the sample size necessary for robust results. Nevertheless, we cannot rule out that our models may lose some predictive power if applied to alternative samples. In addition, the population was not well balanced in terms of race and sex, with a majority of the subjects being white and male, respectively.

The current study identified several factors that influence central BP behavior. To our knowledge, this study is the first to specifically examine demographic and clinical factors, easily obtained during patient assessment, associated with central pressures in uncomplicated hypertensive persons. These factors should be considered carefully in subsequent studies attempting to elucidate the relationship between central and peripheral BP, drug treatment and outcomes. A working knowledge of these relationships will be important for understanding how best to customize pharmacological therapy for individualize patients if the goal is to maximize control of peripheral and central BP to reduce cardiovascular risk and mortality.

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Table 1

Baseline Characteristics

	Territ Deciment N. 57
	Total Patients, N=57
Age, years	46.88 ± 10.07
Female sex, n (%)	18 (32)
Race*, n (%)	
White – Non Hispanic	34 (61)
Black	17 (30)
White – Hispanic	1 (2)
Asian	3 (5)
Other	1 (2)
BMI, kg/m ²	31.5 ± 5.96
HR, beat/min	73 ± 11
Height, (cm)	171.65 ± 9.92
Waist circumference, (cm)	99.61 ± 12.97
Smoking Status	
Current smoker, n(%)	18 (32)
Ex-smoker, n(%)	14 (25)
Ever Take an Antihypertensive Drug	
Yes, n(%)	46 (82)
Alcohol Consumption A Week, (drink/week)	2.81 ± 5.41
Duration of Hypertension, (years)	5.95 ± 7.05
Weekly Exercise, (mins/per week)	145.09 ± 142.17
Peripheral SBP, mmHg	151 ± 13
Peripheral DBP, mmHg	97 ± 5
Daytime Ambulatory SBP, mmHg	146 ± 11
Daytime Ambulatory DBP, mmHg	93 ± 5
Central SBP, mmHg	1389 ± 14
Central DBP, mmHg	99 ± 5
Central Augmentation Pressure	11 ± 8
Central Augmented Pressure adjusted at HR=75	10 ± 7
Central Augmentation / Pulse Height %	23 ± 13

Central Augmentation / Pulse Height % adjusted at HR=75	22 ± 12
Pulse Pressure Amplification Ratio	136.79 ± 18.83
Central Pulse Pressure, absolute difference, mmHg	40 ± 14
Peripheral Pulse Pressure, absolute difference, mmHg	53 ± 13
Ejection Duration	303 ± 25

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure. HR: heart rate. Data are expressed as mean \pm SD or n (%), where applicable.

 $^{^{*}}$ Total percent does not equal to 1 due to rounding.

 Table 2

 Significant Independent Variables of Central Aortic BP and Central Hemodynamic Parameters.

Dependent Variables	Significant Independent Variables	Parameter Estimate (β)	Standard Error	P Value	Partial R ²	Adjusted Model R ²
Central Systolic BP	Baseline peripheral systolic BP (mmHg)	0.93	0.04	<0.0001	0.8799	0.9365
	Baseline HR (beat/min)	-0.22	0.04	< 0.0001	0.0315	
	Height (cm)	-0.22	0.05	0.0001	0.0232	
	Current Smoker (yes)	2.44	1.03	0.0222	0.0068	
Central Diastolic BP	Baseline peripheral diastolic BP (mmHg)	1.038	0.018	< 0.0001	0.9832	0.9848
	Baseline HR (beat/min)	0.019	0.007	0.0088	0.0022	
Pulse Pressure Amplification	Baseline HR (beat/min)	0.97	0.18	< 0.0001	0.2417	0.4821
Ratio	Gender (male)	17.20	4.26	0.0002	0.1572	
	Age (year)	-0.63	0.19	0.0019	0.1149	
Ejection Duration	Baseline HR (beat/min)	-1.73	0.14	< 0.0001	0.6596	0.7783
	Gender (male)	-10.86	3.42	0.0026	0.0717	
	Baseline peripheral diastolic BP (mmHg)	-1.22	0.34	0.0009	0.0397	
	Baseline peripheral systolic BP (mmHg)	0.30	0.13	0.0207	0.0244	
Central Augmented Pressure	Baseline peripheral systolic BP (mmHg)	0.30	0.04	<0.0001	0.4030	0.7745
	Height (cm)	-0.30	0.06	< 0.0001	0.1406	
	Baseline HR (beat/min)	-0.23	0.05	< 0.0001	0.1318	
	Baseline peripheral diastolic BP (mmHg)	-0.32	0.11	0.0063	0.0673	
	Current Smoker (yes)	2.86	1.14	0.0158	0.0381	
	Age (year)	0.12	0.06	0.0387	0.0196	
Heart Rate Corrected	Baseline peripheral systolic BP (mmHg)	0.32	0.04	< 0.0001	0.4601	0.7419
Central Augmented Pressure	Gender (male)	-4.79	0.96	< 0.0001	0.1584	
	Current Smoker (yes)	3.20	0.97	0.0018	0.0799	
	Baseline peripheral diastolic BP (mmHg)	-0.29	0.10	0.0035	0.0434	
	Hypertension duration (year)	0.14	0.06	0.0301	0.0248	
Central Pulse Pressure	Baseline peripheral systolic BP (mmHg)	0.93	0.04	<0.0001	0.7477	0.9360
	Baseline peripheral diastolic BP (mmHg)	-0.85	0.10	< 0.0001	0.1266	
	Baseline HR (beat/min)	-0.26	0.04	< 0.0001	0.0373	
	Gender (male)	-4.21	1.03	0.0002	0.0189	
	Current Smoker (yes)	3.20	1.03	0.0033	0.0115]

BP= blood pressure; cm=centimeters; HR=heart rate

Table 3

Significant independent variables of central aortic BP and central hemodynamic parameters (positive and negative relationship)

Dependent Variable								
	Age (years)	Height (cm)	Height Gender (cm) (male)	Current Smoker (yes)	HTN Duration (years)	Baseline HR (bpm)	Baseline Peripheral Systolic BP (mmHg)	Baseline Peripheral Diastolic BP (mmHg
Central Systolic BP		-		+		-	+	
Central Diastolic BP						+		+
Pulse Pressure Amplification Ratio	-		+			+		
Ejection Duration			_			-	+	_
Central Augmented Pressure	+	-		+		-	+	_
Heart Rate Corrected Central Augmented Pressure			_	+	+		+	_
Central Pulse Pressure			-	+		_	+	_

BP= blood pressure; bpm=beats per minute; cm=centimeters; HTN=hypertension; HR=heart rate