Abnormal Pulsatile Hemodynamics in Hypertensive Patients With Normalized 24-Hour Ambulatory Blood Pressure by Combination Therapy of Three or More Antihypertensive Agents

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It remains uncertain whether intensive antihypertensive therapy can normalize pulsatile hemodynamics resulting in minimized residual cardiovascular risks. In this study, office and 24-hour ambulatory systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure, carotid-femoral pulse wave velocity (PWV), and forward (Pf) and reflected (Pb) pressure wave from a decomposed carotid pressure wave were measured in hypertensive participants. Among them, 57 patients whose 24-hour SBP and DBP were normalized by three or more classes of antihypertensive medications were included. Another 57 age- and sex-matched normotensive participants were randomly selected from a community survey. The well-treated hypertensive patients had similar 24-hour SBP, lower DBP, and higher PP values. The treated patients had higher PWV (11.7±0.3 vs 8.3±0.2 m/s, $P<.001$), Pf, Pb, Pb/Pf, and left ventricular mass index values. After adjustment for age, sex, body mass index, and office SBP, the differences for PWV, Pb, and Pb/Pf remained significant. Hypertensive patients whose 24-hour SBP and DBP are normalized may still have markedly increased arterial stiffness and wave reflection. *J Clin Hypertens (Greenwich).* 2016; 18:281–289. © 2015 Wiley Periodicals, Inc.

Despite many decades of hypertension control, the contribution of hypertension to incident cardiovascular disease remains high.[1] Current hypertension guidelines suggest a treatment goal of office systolic blood pressure (SBP) <140 mm Hg and diastolic blood pressure (DBP) <90 mm Hg for most patients.[2] Antihypertensive treatment results in the regression of end-organ damage[3] and substantial absolute risk reductions for stroke, heart failure, coronary heart disease, and mortality.[4] However, it has well been recognized that even if blood pressure (BP) is achieved to the current treatment goal, treated hypertensive patients still have a higher risk of cardiovascular disease compared with normotensive individuals,[5–7] and the residual cardiovascular risk increases in patients with a higher baseline risk level.[8] Paradoxically, treated hypertensive patients may even have a higher cardiovascular risk compared with individuals not on treatment.[9] Thus, the preexisting high risk in hypertensive patients may set a ceiling effect to the benefits of treatment and underline the importance of early interventions.[10]

Alternatively, the high residual cardiovascular risks in high-risk hypertensive patients, such as the elderly, patients with diabetes, and patients with previous cardiovascular disease, may partly result from suboptimal antihypertensive treatment to the suboptimal office BP treatment goal. Previous pharmacologic studies have shown that only an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) may significantly improve arterial stiffness,[11–13] which is a manifestation of cumulative functional and structural changes associated with vascular aging and a major risk factor for cardiovascular disease.[14] Many epidemiological studies and clinical trials were performed in an era when only diuretics and β-blockers were available,[9] with both classes of antihypertensive medications relatively ineffective in improving arterial stiffness.[12] On the other hand, the hypertension treatment goal based on office BP criteria will inevitably encounter confounders known as white-coat hypertension or masked hypertension and introduce problems of overtreatment and undertreatment that may diminish the benefits of antihypertensive treatment.[15] Application of ambulatory BP monitoring (ABPM) has been adopted for the diagnosis and treatment of hypertension because of its superior prognostic values over office BP monitoring.[16] However, it remains to be established that a hypertension treatment goal of 24-hour ambulatory SBP <130 mm Hg and DBP <80 mm Hg improves prognosis as compared with the current office BP goal.[16]

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In the present observational study, we therefore assessed the pulsatile hemodynamics in hypertensive patients who had achieved the 24-hour ambulatory BP goal with a combination therapy of three or more antihypertensive agents including a renin-angiotensin-aldosterone system (RAAS) inhibitor. The aim of this study was to investigate whether normalization of BP with a combination of antihypertensive medications that are effective in improving arterial stiffness can be associated with normalization of pulsatile hemodynamics.

METHODS

Study population

Ambulatory patients (≥18 years) from our outpatient clinic who had been diagnosed as having hypertension (office SBP ≥140 mm Hg or SBP ≥90 mm Hg) for more than 1 year were invited to participate in a hypertension registry program started in 2013. Patients with previous stroke, coronary artery disease documented by coronary angiogram, reduced left ventricular (LV) ejection fraction (<50%), or chronic kidney disease (estimated glomerular filtration rate [eGFR] <60 mL/min/m^2) or those who were recently hospitalized for any acute disease were not enrolled. Participants underwent a series of BP measurements, including office BP and 24-hour ambulatory BP monitoring (ABPM), and studies of pulsatile hemodynamics, echocardiography, blood biochemistry, and urine analysis. Duration of treatment for hypertension, prescribed medications, and major medical comorbidities were recorded. The investigation conformed to the principles outlined in the Declaration of Helsinki. Informed consent approved by our institutional review board was obtained from every participant before enrollment.

To be eligible for the present study, participants of the hypertension registry should have received three or more classes of antihypertensive medications including a RAAS inhibitor at the recommended dosage for at least half a year and achieved the treatment goal defined as 24-hour ambulatory SBP <130 mm Hg and DBP <80 mm Hg.[17,18] Among 141 participants in the registry, 57 patients were included in the present analysis. A control group of 57 age- and sex-matched healthy participants was randomly drawn from 624 normotensive patients in a previous community-based survey conducted in 1992–1993.[19]

Measurement of BP

For participants of the hypertension registry, office SBP, DBP, and heart rate (HR) measurements were taken after the patient had been seated for 5 minutes using an automated digital BP recorder (WatchBP-CBP-UI, Microlife Corporation, Taipei, Taiwan). Pulse pressure (PP) was calculated as the difference between SBP and DBP, and mean arterial pressure (MAP) as DBP + 1/3 PP. Twenty-four-hour ABPM was performed using a lightweight and compact device (WatchBP O3, Microlife Corporation) on a usual working day. Patients were instructed to work normally and to rest or sleep before midnight. Nighttime was defined as 11 PM to 6 AM, with a measurement interval of 30 minutes, and daytime was defined as 7 AM to 10 PM, with a measurement interval of 15 minutes.

For participants of the community survey, office SBP, DBP, and HR were taken after the patient had been seated for 5 minutes using a mercury sphygmomanometer. Twenty-four-hour ABPM (Model 90217, Spacelabs Inc, Redmond, WA) was performed on a usual working day. Nighttime was defined as 11 PM to 6 AM with a measurement interval of 60 minutes, and daytime was defined as 7 AM to 10 PM, with a measurement interval of 20 minutes.[20]

Hemodynamics study

For participants from the hypertension registry, individuals were asked to refrain from smoking, caffeine, or alcohol consumption for at least 24 hours before examination. Patients were studied under supine resting conditions in a quiet, temperature-controlled room.[21] After resting for 10 minutes, simultaneous supine brachial SBP, DBP, HR, pulse volume recording waveforms of the arms and ankles, and pressure waveforms of the right common carotid and right femoral arteries by applanation tonometry were recorded with a commercially available device (VP-2000; Colin, Konami, Japan) incorporated with four pressure cuffs and two tonometric probes.[22,23] Subsequent echocardiography was performed using an ultrasound unit (Artida; Toshiba Medical Systems, Tokyo, Japan) with a 2.5-MHz transducer in accordance with published recommendations.[24]

For participants from the community survey, flow signals over the right common carotid artery and right femoral artery were recorded using a nondirectional Doppler device (Parks model 802; Aloha, OR).[19] Carotid pressure waveforms were registered by applanation tonometry with a pencil-type tonometer incorporating a high-fidelity strain-gauge transducer in a 7-mm diameter flat tip (SPC-350, Millar Instruments Inc, Houston, TX).[19] Echocardiography was performed by an experienced sonographer using an ultrasound unit (Sonos 500, Hewlett-Packard, Palo Alto, CA) with a 2.5-MHz transducer.[19]

Data analysis

All physiological signals were digitized and analyzed using custom-designed software on a commercial software package (Matlab, version 4.2, The MathWorks, Inc, Natick, MA). Automatic batch analysis was performed on the processed signals to avoid interobserver and intraobserver variations.

The carotid-to-femoral artery distance was the difference between the distance from the ascending aorta to common femoral pulsation and the distance from the ascending aorta to the ipsilateral carotid bulb measured with a soft tape ruler. Carotid-femoral pulse wave velocity (cf-PWV) was calculated from the above

traveling distance and the foot-to-foot pulse transit time between carotid and femoral arteries using the digitized pressure waveforms.[25] The derived pulse wave velocity (PWV) value was then divided by 0.8, a coefficient of correction based on consensus' suggestion.[26]

Carotid pressure waveforms were averaged and then calibrated to the brachial MAP and DBP taken in the seated position. Central augmentation index and carotid augmented pressure (AP) were calculated with the automated identification of the inflection point from the wave reflection on the upstroke or downstroke of the carotid pressure by finding the zero-crossing timings of the fourth derivative of the pressure waveform.[27] The forward and backward components of the carotid pressure waveform were separated using the validated triangulation method.[27,28] Pf and Pb were the amplitudes of forward and backward pressure wave, respectively.[27]

LV mass was calculated from measures of the two-dimensional–guided M-mode echocardiogram and was indexed to the body surface area as the LV mass index (LVMI).[29]

Statistical analysis

The analyses were performed using the statistical package SPSS version 18.0 (SPSS Inc, Chicago, IL). Quantitative variables are expressed as mean±standard deviation. Dichotomous variables are presented as percentages. Student *t* test and chi-square test were used for univariable comparisons between the normotension and the treated hypertension groups where appropriate. Least squares means with adjustment for age, sex, body mass index, and office SBP or MAP were compared using the Tukey-Kramer method. Determinants of the pulsatile hemodynamics were examined using the multiple stepwise analyses. A P value <.05 was considered statistically significant.

RESULTS

The baseline characteristics and biochemistry profiles of the well-treated hypertensives and the age- and sex-matched normotensive controls are shown in Table I. The 57 treated hypertensive patients had a mean age of 70.7 years and 49% of them were men. The mean duration of hypertension was 15.4 years, and they currently used an average of 3.7 types of antihypertensive agents. Compared with the normotensive controls, the treated hypertensive patients had significantly higher values of body mass index, triglycerides, and fasting glucose; lower levels of eGFR, uric acid, total cholesterol, and low-density lipoprotein cholesterol levels; and more comorbid conditions, including diabetes and stroke (Table I).

The mean 24-hour, daytime, and nighttime SBP values were similar between the treated hypertensive patients and the normotensive controls (Table II). The treated hypertensive patients had significantly lower mean 24-hour, daytime, and nighttime DBP than the

TABLE I. Baseline Characteristics in Patients With Well-Treated Hypertension vs Normotensive Controls

	Overall (N=114)	Well-Treated Hypertensive Patients (n=57)	Normotensive Controls (n=57)	*P* Value
Age, y	70.1±11.8	70.7±12.3	69.5±11.2	.840
Male sex, No. (%)	56 (49)	28 (49)	28 (49)	1
Body mass index, kg/m^2	24.9±4.3	27.2±4.2	22.7±3.0	<.001
Smoking, No. (%)	18 (15.8)	6 (10.5)	12 (21.0)	.302
Hypertension duration, y	–	15.4±8.2	–	–
Classes of antihypertensive drugs	–	3.7±0.8	–	–
Diabetes, No. (%)	18 (15.8)	18 (31.6)	0 (0)	<.001
Previous stroke, No. (%)	3 (2.6)	3 (5.3)	0 (0)	.047
eGFR, mL/min	71.5±28.4	62.4±29.4	81.3±23.9	<.001
Cr, mg/dL	1.1±0.4	1.1±0.5	1.0±0.3	.370
UA, mg/dL	6.0±1.7	5.8±2.0	6.0±1.5	.030
TC, mg/dL	189.7±36.8	179.5±32.7	199.4±38.1	.022
HDL-C, mg/dL	51.9±16.4	49.8±18.4	53.3±14.8	.440
LDL-C, mg/dL	112.5±39.0	98.4±37.0	123.5±37.3	.002
TG, mg/dL	124.8±79.4	146.6±98.3	103.4±47.2	.039
Glucose, mg/dL	101.4±18.4	108.8±21.4	94.8±12.1	.003
Medications, No. (%)				
ACE inhibitor/ARB	–	57 (100)	–	–
CCB	–	55 (96.4)	–	–
Diuretic	–	39 (68.4)	–	–
BB	–	41 (71.9)	–	–
Statin	–	23 (40.4)	–	–
Antiplatelet	–	23 (40.4)	–	–

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, β-blocker; BMI, body mass index; CCB, calcium channel blocker; Cr, creatinine; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVMI, left ventricular mass index; TC, total cholesterol; TG, triglycerides; UA, uric acid.

normotensive controls, therefore they had significantly higher mean 24-hour, daytime, and nighttime PP. On the other hand, the treated hypertensive patients had significantly higher office SBP, DBP, and MAP than the normotensive controls. The treated hypertensive patients had significantly lower office and ambulatory HR than the normotensive controls.

In univariable analysis, the treated hypertensive patients had significantly greater LVMI, PWV, AI, AP, Pf, Pb, and Pb/Pf than the normotensive controls (Table II). The between-group differences remained significant for PWV, AI, AP, Pb, and Pb/Pf with adjustment for age, sex, body mass index, and office SBP or MAP (Table III).

Correlation coefficients and partial correlation coefficients (accounting for age, sex, and body mass index) for PWV, AI, Pf, Pb, Pb/Pf, and LVMI are provided in Supplementary Tables S1–S6. The relative importance of ambulatory SBP vs PP in the determination of PWV was examined by the multiple stepwise regression analysis with adjustment for age, sex, body mass index, and HR (Table IV). In both treated hypertensive patients and normotensive controls, ambulatory PP but not SBP entered the final models. Similar analysis was performed for Pb (Table V). In both groups, ambulatory PP but not SBP entered the final models, except that daytime SBP instead of daytime PP entered the final model for the normotensive controls. Results for AI, Pf, Pb/Pf, and LVMI are shown in the Supplementary Tables S7–S10.

DISCUSSION

This observational study provides three major findings. First, the 24-hour ambulatory BP goal of 24-hour SBP <130 mm Hg and 24-hour DBP <80 mm Hg can be achieved by current antihypertensive medications, but the treated hypertensive individuals may still have high 24-hour PP due to their lower 24-hour DBP. Second, the treated hypertensive patients who achieved the 24-hour ambulatory BP goal may still have increased arterial stiffness and wave reflection but similar LVMI as compared with the normotensives, even though they received a combination therapy of three or more antihypertensive agents including a RAAS inhibitor.

TABLE II. Comparison of Blood Pressure and Hemodynamics Parameters in Patients With Well-Treated Hypertension vs Normotensive Controls

	Overall (N=114)	Well-Treated Hypertensive Patients (n=57)	Normotensive Controls (n=57)	*P* Value
Office blood pressure				
SBP, mm Hg	128.8±14.9	137.2±13.7	120.6±10.9	<.001
DBP, mm Hg	72.5±8.2	74.7±8.1	70.3±7.8	.004
PP, mm Hg	56.3±13.2	62.5±11.7	50.3±11.9	<.001
MAP, mm Hg	91.3±9.0	95.5±8.7	87.0±7.0	<.001
HR, mm Hg	68.8±11.0	63.5±8.6	74.1±10.7	<.001
24-h ambulatory blood pressure				
24-h SBP, mm Hg	116.2±10.3	115.3±10.1	117.1±10.5	.350
Daytime SBP, mm Hg	116.6±10.0	115.4±9.6	117.8±10.3	.190
Nighttime SBP, mm Hg	114.6±12.9	115.2±11.9	114.1±13.8	.620
24-h DBP, mm Hg	67.6±7.9	63.6±7.2	71.6±6.6	<.001
Daytime DBP, mm Hg	68.4±7.9	64.4±7.2	72.4±6.4	<.001
Nighttime DBP, mm Hg	65.4±8.9	62.4±7.9	68.3±9.0	<.001
24-h PP, mm Hg	48.6±9.0	51.7±8.8	45.5±8.1	<.001
Daytime PP, mm Hg	48.2±8.5	50.9±8.2	45.5±8.0	<.001
Nighttime PP, mm Hg	49.3±10.3	52.8±9.9	45.8±9.4	<.001
24-h MAP, mm Hg	83.77±7.72	80.81±7.16	86.74±7.15	<.001
Daytime MAP, mm Hg	84.5±7.7	81.4±7.1	87.5±7.0	<.001
Nighttime MAP, mm Hg	81.8±9.2	80.0±8.2	83.5±9.9	.041
24-h HR, beats per min	70.8±9.3	66.1±8.5	75.4±7.7	<.001
Daytime HR, beats per min	72.8±10.2	67.6±9.2	78.1±8.2	<.001
Nighttime HR, beats per min	64.8±7.8	63.6±8.2	66.1±7.3	.096
LVMI, g/m^2	106.8±30.7	116.4±36.8	97.4±19.3	<.001
PWV, m/s	10.0±0.3	11.7±0.3	8.3±0.2	<.001
AIx, %	21±15	27±16	14±11	<.001
AP, mm Hg	10.4±10.9	13.7±12.8	6.0±4.9	<.001
Pf, mm Hg	35.9±10.2	38.9±9.7	31.9±9.6	<.001
Pb, mm Hg	19.1±6.5	22.8±5.4	14.3±4.3	<.001
Pb/Pf	0.54±0.14	0.60±0.14	0.46±0.11	<.001

Abbreviations: AIx, augmentation index; AP, augmented pressure; BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; LVMI, left ventricular mass index; MAP, mean arterial pressure; Pb, amplitude of the reflected pressure wave from a decomposed carotid pressure waveform; Pf, amplitude of the forward pressure wave from a decomposed carotid pressure waveform; PP, pulse pressure; PWV, carotid-femoral pulse wave velocity; SBP, systolic blood pressure.

TABLE III. Multivariable Comparison of the Pulsatile Hemodynamics Parameters and LVMI in Patients With Well-Treated Hypertension vs Normotensive Controls

	Well-Treated Hypertensive Patients (n=57)	Normotensive Controls (n=57)	*P* Value[a]
Adjusted for age, sex, BMI, and office SBP			
LVMI, g/m^2	108.6 (99.6–117.7)	104.6 (95.7–113.4)	.576
PWV, m/s	1375.4 (1269.3–1481.5)	1122.2 (1021.0–1223.4)	.003
AIx, %	27.4 (23.9–30.9)	14.2 (10.0–18.4)	<.001
AP, mm Hg	13.3 (11.3–15.4)	7.9 (5.4–10.3)	.003
Pf, mm Hg	35.6 (33.0–38.2)	36.0 (32.8–39.1)	.871
Pb, mm Hg	21.7 (20.4–22.9)	16.0 (14.5–17.4)	<.001
Pb/Pf	0.62 (0.59–0.66)	0.45 (0.41–0.49)	<.001
Adjusted for age, sex, BMI, and office MAP			
LVMI, g/m^2	110.3 (101.4–119.1)	103.0 (94.4–111.6)	.293
PWV, m/s	1405.8 (1299.4–1512.1)	1094.0 (992.3–1195.6)	<.001
AIx, %	27.4 (24.0–30.9)	14.2 (10.1–18.3)	<.001
AP, mm Hg	14.0 (11.9–16.2)	6.9 (4.4–9.5)	<.001
Pf, mm Hg	37.5 (34.7–40.4)	33.4 (30.0–36.8)	.098
Pb, mm Hg	22.6 (21.2–24.6)	14.7 (13.0–16.4)	<.001
Pb/Pf	0.62 (0.59–0.65)	0.45 (0.41–0.49)	<.001

Abbreviations: AIx, augmentation index; AP, augmented pressure; BMI, body mass index; HR, heart rate; LVMI, left ventricular mass index; MAP, mean arterial pressure; PP, pulse pressure; Pb, amplitude of the reflected pressure wave from a decomposed carotid pressure waveform; Pf, amplitude of the forward pressure wave from a decomposed carotid pressure waveform; PWV, carotid-femoral pulse wave velocity; SBP, systolic blood pressure. Values are expressed as least squares means (95% confidence limits). A significant difference between pairs of least squares means (ie, adjusted *P* value <.05) occurs when the adjusted lower and upper endpoints of the confidence intervals are both positive or both negative. [a]*P* values for differences were adjusted with the Tukey-Kramer method.

Third, the increased arterial stiffness and wave reflection in the treated hypertensives was associated with high PP. These findings have important implications in refining the BP treatment goal and designing an optimal antihypertensive treatment strategy to reduce the residual cardiovascular risk possibly resulting from the persistent abnormal pulsatile hemodynamics in the treated hypertensive patients.

Residual cardiovascular risk in treated hypertensive patients

The increased cardiovascular mortality in treated hypertensive patients as compared with untreated individuals may be due to high SBP levels under treatment,[7] consistent with our findings that treated hypertensives had elevated pulsatile hemodynamics. Among those with BP levels <140/90 mm Hg, cardiovascular disease mortality was slightly but significantly higher in treated patients.[7] Therefore, there was still some residual cardiovascular risk in the treated hypertensive patients with controlled BP. Moreover, the actual residual cardiovascular risk may have been underestimated due to the limitations of a single-visit office BP measurement in classifying high or controlled BP.[7] One major strength of the present study is that we were able to identify a group of treated hypertensive patients with normalized BP defined by ambulatory BP.

Arterial stiffness and hypertension control

In the Framingham Heart Study, 89.7% of hypertensive patients achieved DBP goal, 49.0% achieved SBP goal, and only 47.8% achieved both SBP and DBP goals.[30] Poor SBP control was overwhelmingly responsible for the poor overall hypertension control rate.[30] Baseline PWV may be a significant predictor of BP response to antihypertensive treatment, independent of age, increase in drug dosage, and presence of cardiovascular risk factors.[31] In the presence of increased arterial stiffness, SBP is more difficult to control than DBP.[31]

Elevated arterial stiffness in hypertensive individuals relates to structural change in the arterial wall, because acute reduction of BP by nitroglycerin does not normalize large artery stiffness.[32] On the other hand, antihypertensive medications can improve arterial stiffness beyond the effect on BP reduction in hypertensive patients.[12,14] A large and sustained decrease in arterial stiffness can be obtained in treated hypertensive patients over a long follow-up period (>5 years), likely representing a delayed response to long-term arterial remodeling.[33] In a recent meta-analysis, compared with placebo, there was a significant reduction in PWV with short-term (<4 weeks) and long-term (4 weeks and more) treatment of four different classes of antihypertensive drugs, including ACE inhibitors, calcium channel blockers, β-blockers, and diuretics, after adjustment for BP, HR, sex, and risk factors.[34]

RAAS blockers have specific BP-independent effects on arterial stiffness via reducing endothelial dysfunction,[35] smooth muscle proliferation,[36,37] and collagen synthesis,[38] which are activated by tissue and circulating angiotensin II. However, the destiffening effect of RAAS blockers, ie, ACE inhibitors or ARBs, is dose-dependent.

TABLE IV. Determinants of PWV: SBP vs PP by Multiple Stepwise Analysis

	Well-Treated Hypertensive Patients (n=57)		Normotensive Controls (n=57)	
	Partial R^2	Beta	Partial R^2	Beta
Model 1: 24-h SBP and 24-h PP				
	Model R^2=0.370		Model R^2=0.305	
Age, y	0.279	0.395[b]	0.158	0.227
Male sex		0.129		0.187
BMI, kg/m^2		−0.017		0.051
24-h HR, beats per min		0.360[b]		0.139
24-h SBP, mm Hg				
24-h PP, mm Hg	**0.091**	**0.330[a]**	**0.147**	**0.438[b]**
Model 2: daytime SBP and daytime PP				
	Model R^2=0.348		Model R^2=0.309	
Age, y	0.264	0.395[b]	0.161	0.246
Male sex		0.097		0.188
BMI, kg/m^2		−0.013		0.048
Daytime HR, beats per min		0.347[b]		0.132
Daytime SBP, mm Hg				
Daytime PP, mm Hg	**0.084**	**0.322[a]**	**0.148**	**0.430[b]**
Model 3: nighttime SBP and nighttime PP				
	Model R^2=0.357		Model R^2=0.255	
Age, y	0.297	0.399[b]	0.156	0.222
Male sex		0.167		0.148
BMI, kg/m^2		−0.016		0.069
Nighttime HR, beats per min		0.342[b]		0.111
Nighttime SBP, mm Hg				
Nighttime PP, mm Hg	**0.06**	**0.263[a]**	**0.099**	**0.374[a]**

Abbreviations: BMI, body mass index; HR, heart rate; PP, pulse pressure; PWV, carotid-femoral pulse wave velocity; SBP, systolic blood pressure. All models were adjusted for age, sex, BMI, and HR. Bold values indicates significance. [a]P<.05. [b]P<.01. [c]P<.001.

The destiffening effect of a maximum single dose of RAAS blocker may still be limited. A RAAS blocker in combination with a neprilysin inhibitor, which increases levels of endogenous vasodilator peptides, including natriuretic peptides, adrenomedullin, bradykinin and others, can further attenuate vasoconstriction[39] and hyperplasia of vascular smooth muscle.[40] Omapatrilat, an inhibitor of ACE and neprilysin, induced a greater reduction in arterial stiffness compared with enalapril at comparable levels of reduction in mean arterial pressure.[41] More recently, LCZ696, an inhibitor of the angiotensin II receptor and neprilysin, provided complementary and fully additive reduction of BP compared with valsartan.[42]

The superiority of the neurohormonal modulation over the neurohormonal inhibition strategy has been confirmed in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.[43] Thus, arterial stiffness may only be partially improved with long-term treatment of currently available antihypertensive medications. The dual-acting LCZ696 may become a novel antihypertensive medication that possesses a remarkable arterial destiffening effect.

The present study clearly demonstrates that markedly elevated arterial stiffness can be observed in treated hypertensive individuals whose 24-hour ambulatory BP has achieved treatment goal. The apparent dissociation between BP control and improvement in arterial stiffness in the treated hypertensive patients may partly be due to the suboptimal BP treatment target or suboptimal destiffening effects from the currently available antihypertensive medications.

Wave reflection, PP, and hypertension control

Wave reflection amplifies the original forward wave amplitude at or near the peripheral reflection site and therefore is a major determinant of PP and SBP.[44] With increasing arterial stiffening, the reflected waves will return to the central aorta earlier and augment central PP and SBP.[45] Increased wave reflection contributes to the development of hypertension[46] and increases cardiovascular risk independently of arterial stiffness.[27,47] β-Blockers are less effective than other antihypertensive drugs in reducing wave reflection and central BP.[44]

When the aorta stiffens, the amplitude of the forward pressure wave generated by ventricular contraction increases and contributes to an increase in PP. Therefore, PP is determined from several independent hemo-

TABLE V. Determinants of Reflected Pressure: SBP vs PP by Multiple Stepwise Analysis

	Well-Treated Hypertensive Patients (n=57)		Normotensive Controls (n=57)	
	Partial R^2	Beta	Partial R^2	Beta
Model 1: 24-h SBP and 24-h PP				
	Model R^2=0.303		Model R^2=0.505	
Age, y	0.14	−0.067	0.209	0.154
Male sex		−.293[a]		0.065
BMI, kg/m^2		0.067		−0.211
24-h HR, beats per min		−0.068		0.034
24-h SBP, mm Hg				
24-h PP, mm Hg	**0.163**	**0.448**[b]	**0.296**	**0.624**[c]
Model 2: daytime SBP and daytime PP				
	Model R^2=0.282		Model R^2=0.479	
Age, y	0.151	−0.058	0.201	0.313[a]
Male sex		−.290[a]		−0.061
BMI, kg/m^2		0.068		−.272[a]
Daytime HR, beats per min		−0.086		−0.05
Daytime SBP, mm Hg			**0.278**	**0.538**[c]
Daytime PP, mm Hg	**0.131**	**0.408**[b]		
Model 3: nighttime SBP and nighttime PP				
	Model R^2=0.327		Model R^2=0.502	
Age, y	0.128	−0.082	0.267	0.111
Male sex		−.296[a]		−0.039
BMI, kg/m^2		0.053		−0.202
Nighttime HR, beats per min		−0.075		−0.056
Nighttime SBP, mm Hg				
Nighttime PP, mm Hg	**0.199**	**0.484**[c]	**0.235**	**0.593**[c]

Abbreviations: BMI, body mass index; HR, heart rate; PP, pulse pressure; SBP, systolic blood pressure. All models were adjusted for age, sex, BMI, and HR. Bold values indicate significance. [a]P<.05. [b]P<.01. [c]P<.001.

dynamic mechanisms, such as the amplitude of the forward pressure wave, arterial stiffness, and the augmentation of the reflected waves. Brachial PP was independently associated with subclinical cardiovascular disease after adjustment for cardiovascular risk factors and MAP.[48] Classes of antihypertensive agents differ in their ability to reduce PP.[41,42,49] In short-term trials, ACE inhibitors but not calcium channel blockers significantly reduced PP more than placebo.[34] In long-term trials, PP decreased significantly with ACE inhibitors, calcium channel blockers, β-blockers, and diuretics compared with placebo.[40]

The present study indicates that in treated hypertensive individuals with normalized 24-hour ambulatory SBP and DBP, high wave reflection and PP remain to be expected. The association between increased arterial stiffness, wave reflection, and PP is consistent with the observation in clinical trials that changes in PWV are independently related to the changes in PP.[33,34]

STUDY LIMITATIONS

The present case-control cross-sectional study did not allow us to investigate the cause of abnormal pulsatile hemodynamics in the treated patients with hypertension. The treated hypertensive individuals were enrolled from a hypertension registry and the age- and sex-matched normotensive controls were selected from a previous community survey. The results of the present study should be interpreted as hypothesis-generating because of the potential introduction of selection bias in both groups.

CONCLUSIONS

Treated hypertensive individuals with normalized 24-hour ambulatory SBP and DBP may still have significantly elevated arterial stiffness, wave reflection, and PP, as compared with age- and sex-matched normotensive individuals. The abnormal pulsatile hemodynamics in the apparently well-controlled hypertensive patients may partly explain the recognized residual cardiovascular risk associated with hypertension treatment. Future interventional studies targeting pulsatile hemodynamics are required to investigate the appropriateness of the BP treatment target and the effectiveness of the antihypertensive medications in normalizing abnormal pulsatile hemodynamics in hypertensive individuals.

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Conflict of interest: None.

References

1. Cheng S, Claggett B, Correia AW, et al. Temporal trends in the population attributable risk for cardiovascular disease: the Atherosclerosis Risk in Communities Study. *Circulation*. 2014;130:820–828.
2. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311:507–520.
3. Wachtell K, Okin PM. Regression of target organ damage. *J Hypertens*. 2013;31:1535–1536.
4. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, meta-analyses, and meta-regression analyses of randomized trials. *J Hypertens*. 2014;32:2285–2295.
5. Kelly TN, Gu D, Chen J, et al. Hypertension subtype and risk of cardiovascular disease in Chinese adults. *Circulation*. 2008;118:1558–1566.
6. Lotfaliany M, Akbarpour S, Mozafary A, et al. Hypertension phenotypes and incident cardiovascular disease and mortality events in a decade follow-up of a Middle East cohort. *J Hypertens*. 2015;33:1153–1161.
7. Benetos A, Thomas F, Bean KE, Guize L. Why cardiovascular mortality is higher in treated hypertensives versus subjects of the same age, in the general population. *J Hypertens*. 2003;21:1635–1640.
8. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 3. Effects in patients at different levels of cardiovascular risk–overview and meta-analyses of randomized trials. *J Hypertens*. 2014;32:2305–2314.
9. Asayama K, Satoh M, Murakami Y, et al. Cardiovascular risk with and without antihypertensive drug treatment in the Japanese general population: participant-level meta-analysis. *Hypertension*. 2014;63:1189–1197.
10. Zanchetti A. Bottom blood pressure or bottom cardiovascular risk? How far can cardiovascular risk be reduced? *J Hypertens*. 2009;27:1509–1520.
11. Mitchell GF, Dunlap ME, Warnica W, et al. Long-term trandolapril treatment is associated with reduced aortic stiffness: the prevention of events with angiotensin-converting enzyme inhibition hemodynamic substudy. *Hypertension*. 2007;49:1271–1277.
12. Mahmud A, Feely J. Antihypertensive drugs and arterial stiffness. *Expert Rev Cardiovasc Ther*. 2003;1:65–78.
13. Laurent S, Boutouyrie P, Vascular Mechanism C. Dose-dependent arterial destiffening and inward remodeling after olmesartan in hypertensives with metabolic syndrome. *Hypertension*. 2014;64:709–716.
14. Arnett DK, Evans GW, Riley WA. Arterial stiffness: a new cardiovascular risk factor? *Am J Epidemiol*. 1994;140:669–682.
15. O'Brien E. First Thomas Pickering memorial lecture: ambulatory blood pressure measurement is essential for the management of hypertension. *J Clin Hypertens (Greenwich)*. 2012;14:836–847.
16. O'Brien E, Parati G, Stergiou G, et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens*. 2013;31:1731–1768.
17. Chiang CE, Wang TD, Ueng KC, et al. 2015 guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the Management of Hypertension. *J Chin Med Assoc*. 2015;78:1–47.
18. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2159–2219.
19. Chen CH, Ting CT, Lin SJ, et al. Which arterial and cardiac parameters best predict left ventricular mass? *Circulation*. 1998;98:422–428.
20. Chen CH, Ting CT, Lin SJ, et al. Relation between diurnal variation of blood pressure and left ventricular mass in a Chinese population. *Am J Cardiol*. 1995;75:1239–1243.
21. Sung SH, Yu WC, Cheng HM, et al. Excessive wave reflections on admission predict post-discharge events in patients hospitalized due to acute heart failure. *Eur J Heart Fail*. 2012;14:1348–1355.
22. Sung SH, Chuang SY, Sheu WH, et al. Relation of adiponectin and high-sensitivity C-reactive protein to pulse-wave velocity and N-terminal pro-B-type natriuretic peptide in the general population. *Am J Cardiol*. 2009;103:1411–1416.
23. Cortez-Cooper MY, Supak JA, Tanaka H. A new device for automatic measurements of arterial stiffness and ankle-brachial index. *Am J Cardiol*. 2003;91:1519–1522, A1519.
24. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation*. 1978;58:1072–1083.
25. Yu WC, Chuang SY, Lin YP, Chen CH. Brachial-ankle vs carotid-femoral pulse wave velocity as a determinant of cardiovascular structure and function. *J Hum Hypertens*. 2008;22:24–31.
26. Van Bortel LM, Laurent S, Boutouyrie P, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens*. 2012;30:445–448.
27. Wang KL, Cheng HM, Sung SH, et al. Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. *Hypertension*. 2010;55:799–805.
28. Westerhof BE, Guelen I, Westerhof N, et al. Quantification of wave reflection in the human aorta from pressure alone: a proof of principle. *Hypertension*. 2006;48:595–601.
29. Devereux RB, Lutas EM, Casale PN, et al. Standardization of M-mode echocardiographic left ventricular anatomic measurements. *J Am Coll Cardiol*. 1984;4:1222–1230.
30. Lloyd-Jones DM, Evans JC, Larson MG, et al. Differential control of systolic and diastolic blood pressure: factors associated with lack of blood pressure control in the community. *Hypertension*. 2000;36:594–599.
31. Protogerou A, Blacher J, Stergiou GS, et al. Blood pressure response under chronic antihypertensive drug therapy: the role of aortic stiffness in the REASON (Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind) study. *J Am Coll Cardiol*. 2009;53:445–451.
32. Stewart AD, Jiang B, Millasseau SC, et al. Acute reduction of blood pressure by nitroglycerin does not normalize large artery stiffness in essential hypertension. *Hypertension*. 2006;48:404–410.
33. Ait-Oufella H, Collin C, Bozec E, et al. Long-term reduction in aortic stiffness: a 5.3-year follow-up in routine clinical practice. *J Hypertens*. 2010;28:2336–2341.
34. Ong KT, Delerme S, Pannier B, et al. Aortic stiffness is reduced beyond blood pressure lowering by short-term and long-term antihypertensive treatment: a meta-analysis of individual data in 294 patients. *J Hypertens*. 2011;29:1034–1042.
35. Clozel M. Mechanism of action of angiotensin converting enzyme inhibitors on endothelial function in hypertension. *Hypertension*. 1991;18(4 Suppl):II37–II42.
36. Sharifi AM, Schiffrin EL. Apoptosis in vasculature of spontaneously hypertensive rats: effect of an angiotensin converting enzyme inhibitor and a calcium channel antagonist. *Am J Hypertens*. 1998;11:1108–1116.
37. Fujii K, Umemoto S, Fujii A, et al. Angiotensin II type 1 receptor antagonist downregulates nonmuscle myosin heavy chains in spontaneously hypertensive rat aorta. *Hypertension*. 1999;33:975–980.
38. Albaladejo P, Bouaziz H, Duriez M, et al. Angiotensin converting enzyme inhibition prevents the increase in aortic collagen in rats. *Hypertension*. 1994;23:74–82.
39. Garcia R, Thibault G, Cantin M, Genest J. Effect of a purified atrial natriuretic factor on rat and rabbit vascular strips and vascular beds. *Am J Physiol*. 1984;247:R34–R39.
40. Cahill PA, Hassid A. Clearance receptor-binding atrial natriuretic peptides inhibit mitogenesis and proliferation of rat aortic smooth muscle cells. *Biochem Biophys Res Commun*. 1991;179:1606–1613.
41. Mitchell GF, Izzo JL Jr, Lacourciere Y, et al. Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension: results of the conduit hemodynamics of omapatrilat international research study. *Circulation*. 2002;105:2955–2961.
42. Ruilope LM, Dukat A, Bohm M, et al. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet*. 2010;375:1255–1266.
43. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.
44. McEniery CM, Cockcroft JR, Roman MJ, et al. Central blood pressure: current evidence and clinical importance. *Eur Heart J*. 2014;35:1719–1725.
45. Mitchell GF. Does measurement of central blood pressure have treatment consequences in the clinical praxis? *Curr Hypertens Rep*. 2015;17:573.

46. Kaess BM, Rong J, Larson MG, et al. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA*. 2012;308:875–881.
47. Vlachopoulos C, Aznaouridis K, O'Rourke MF, et al. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *Eur Heart J*. 2010;31:1865–1871.
48. Winston GJ, Palmas W, Lima J, et al. Pulse pressure and subclinical cardiovascular disease in the multi-ethnic study of atherosclerosis. *Am J Hypertens*. 2013;26:636–642.
49. Cushman WC, Materson BJ, Williams DW, Reda DJ. Pulse pressure changes with six classes of antihypertensive agents in a randomized, controlled trial. *Hypertension*. 2001;38:953–957.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Correlates of PWV: univariable and multivariable analysis.

Table S2. Correlates of AI: univariable and multivariable analysis.

Table S3. Correlates of Pf: univariable and multivariable analysis.

Table S4. Correlates of Pb: univariable and multivariable analysis.

Table S5. Correlates of Pb/Pf: univariable and multivariable analysis.

Table S6. Correlates of LVMI: univariable and multivariable analysis.

Table S7. Determinants of AI: SBP vs PP by multiple stepwise analysis.

Table S8. Determinants of Pf: SBP vs PP by multiple stepwise analysis.

Table S9. Determinants of Pb/Pf: SBP vs PP by multiple stepwise analysis.

Table S10. Determinants of LVMI: SBP vs PP by multiple stepwise analysis.