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Novel Description of the 24-Hour Circadian Rhythms of Brachial Versus Central Aortic Blood Pressure and the Impact of Blood Pressure Treatment in a Randomized Controlled Clinical Trial

The Ambulatory Central Aortic Pressure (AmCAP) Study

Bryan Williams, Peter S. Lacy, Fabio Baschiera, Patrick Brunel, Rainer Düsing

Abstract—Elevated brachial blood pressure (BP) is associated with increased cardiovascular risk and predicts morbidity and mortality in humans. Recently, 24-hour ambulatory BP monitoring and assessment of central aortic BP have been introduced to improve BP phenotyping. The Ambulatory Central Aortic Pressure (AmCAP) study combines these approaches and describes, for the first time, the diurnal patterns of simultaneously measured 24-hour ambulatory brachial and central pressures in a prespecified substudy embedded within a clinical trial of BP lowering in patients with hypertension. Twenty-four-hour ambulatory brachial and central pressure measurements were acquired using a tonometer mounted into the articulating strap of a wristwatch-like device (BPro) in 171 participants with hypertension recruited into the ASSERTIVE (AliSkiren Study of profound antihypertensive efficacy in hyperTensive patients) trial. Participants were randomly assigned to BP lowering with either aliskiren 300 mg QD or telmisartan 80 mg QD for 12 weeks. Ambulatory brachial and central BP was measured in all participants both at baseline and at study end. Brachial and central BP both demonstrated typical diurnal patterns with lower pressures at night. However, night time was associated with smaller reductions in central relative to brachial pressure and decreased pulse pressure amplification ($P<0.0001$ for both). These effects were not modulated after BP lowering and were maintained after adjustment for day and night-time BP and heart rate ($P=0.02$). This study demonstrates that brachial and central pressure show different diurnal patterns, which are not modulated by BP-lowering therapy, with relatively higher night-time central pressures. These novel data indicate that night-time central BP may provide prognostic importance and warrants further investigation.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00865020. (*Hypertension*. 2013;61:00-00.) • [Online Data Supplement](#)

Key Words: ambulatory blood pressure monitoring ■ blood pressure ■ central aortic pressure ■ hypertension

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Data from ambulatory blood pressure monitoring (ABPM) have been shown to be better correlated with target-organ damage and cardiovascular outcomes in people with hypertension when compared with conventional clinic blood pressure (BP) measurements.¹⁻³ Conventional clinic BP and ABPM are measured over the brachial artery. In an endeavor to further improve BP phenotyping, there has been growing interest in the noninvasive measurement of central aortic pressure.⁴ The rationale for central aortic pressure measurement is that it more accurately represents the pressure experienced by perfused target organs. To this end, recent data suggest that central pressures may be a better predictor of target-organ damage and clinical outcomes than the corresponding brachial pressure.⁵⁻⁷

To date, noninvasive measurement of central aortic pressure has been restricted to seated measurements because of the complexity of the technology. However, BP has a natural circadian rhythm, characterized by a nocturnal dip in pressure and a morning surge in pressure that precedes waking.⁸ Disturbances to these circadian rhythms, for example, an isolated elevation of nocturnal pressure, a reduced nocturnal pressure dip, and an exaggerated morning surge in pressure, are associated with increased cardiovascular disease risk.^{3,9,10} In contrast, the circadian pattern of central aortic pressure and its temporal relationship with the circadian change in brachial pressure remain unknown.

To facilitate ambulatory central aortic pressure measurement, we have recently used a device in which a tonometer

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is embedded into the strap of a wristwatch-like device (BPro, HealthStats, Singapore), which, when worn by a patient, samples radial artery waveforms at regular time intervals, over a 24-hour period.¹¹ This device was originally designed to provide ambulatory measurement of brachial BP, because when calibrated to the patient's brachial BP, the variation in radial waveform amplitude is directly representative of variation in brachial BP.¹¹⁻¹³ We have since used waveform data acquired by this device to generate central aortic pressure measurements using an n-point moving average method. This method has subsequently been validated as providing an accurate assessment of invasively measured central aortic pressure.^{14,15} Together, these developments provided the opportunity to use the BPro device, to simultaneously measure 24-hour ambulatory brachial and central aortic pressure and to evaluate the impact of BP lowering. We thus embedded a study of the Ambulatory Brachial and Central Aortic Pressure measurement (the AmCAP study) into a randomized, controlled clinical trial.¹⁶ Here, we report a novel description of the relationship between the circadian rhythms of brachial and central aortic pressure in patients with hypertension, within the rigorous setting of a randomized clinical trial (RCT) of a BP-lowering treatment.

Methods

The AmCAP study was a prespecified analysis of data from a cohort of patients recruited into the ASSERTIVE (AliSkiren Study of profound antihypERTensive efficacy in hyperTensive patients) study, a multicentre RCT (ClinicalTrials.gov NCT00865020, EudraCT number 2008-007831-41) comparing the BP-lowering efficacy of 12 weeks treatment with an angiotensin receptor blocker versus a direct renin inhibitor in patients with stage I/II hypertension.

Study Design

Details of the ASSERTIVE study have been published.¹⁶ Briefly, this was a double blind, double dummy, parallel group study conducted at 111 centres in 15 countries: Canada, Ecuador, Germany, Hungary, Malaysia, Mexico, Panama, Philippines, Republic of Korea, Singapore, Slovakia, Spain, Turkey, United Kingdom, and Venezuela. Of the 111 centers, 33 centers collected data using the BPro device and provided data for the AmCAP substudy analysis. A 2-week washout of BP-lowering medications for those previously treated was followed by a 1- to 2-week placebo run-in period for all patients. Participants were then randomized to receive either a direct renin inhibitor (aliskiren, 150 mg QD) or an angiotensin receptor blocker (telmisartan, 40 mg QD), with a forced doubling of the starting doses at 2 weeks and a total active treatment period of 12 weeks (Figure 1).

Patients

The ASSERTIVE study included men and women aged 18 years and older (n=822; mean age, 54 years) with a diagnosis of essential hypertension (stages I and II). Patients were either treatment naive or had their existing treatment withdrawn for 2 weeks before a further 2 weeks of placebo run in. To be included, participants at the randomization visit had a seated clinic brachial systolic BP (BrSBP) ≥140 mm Hg and <180 mm Hg and a 24-hour mean ambulatory systolic BP of ≥135 mmHg. The major exclusion criteria included severe hypertension, secondary hypertension, type I diabetes mellitus, poorly controlled type 2 diabetes mellitus, pregnancy, and persistent atrial fibrillation.

The AmCAP Study Cohort

All patients in the ASSERTIVE study were planned to undergo 24 hours oscillometric brachial cuff-based ABPM (Spacelabs 90207) at baseline and at the end of 12 weeks treatment. The AmCAP study cohort was defined as those patients (n=171) who also underwent simultaneous 24-hour radial tonometric ABPM (BPro) to measure both brachial and central aortic pressure, at baseline and after 12

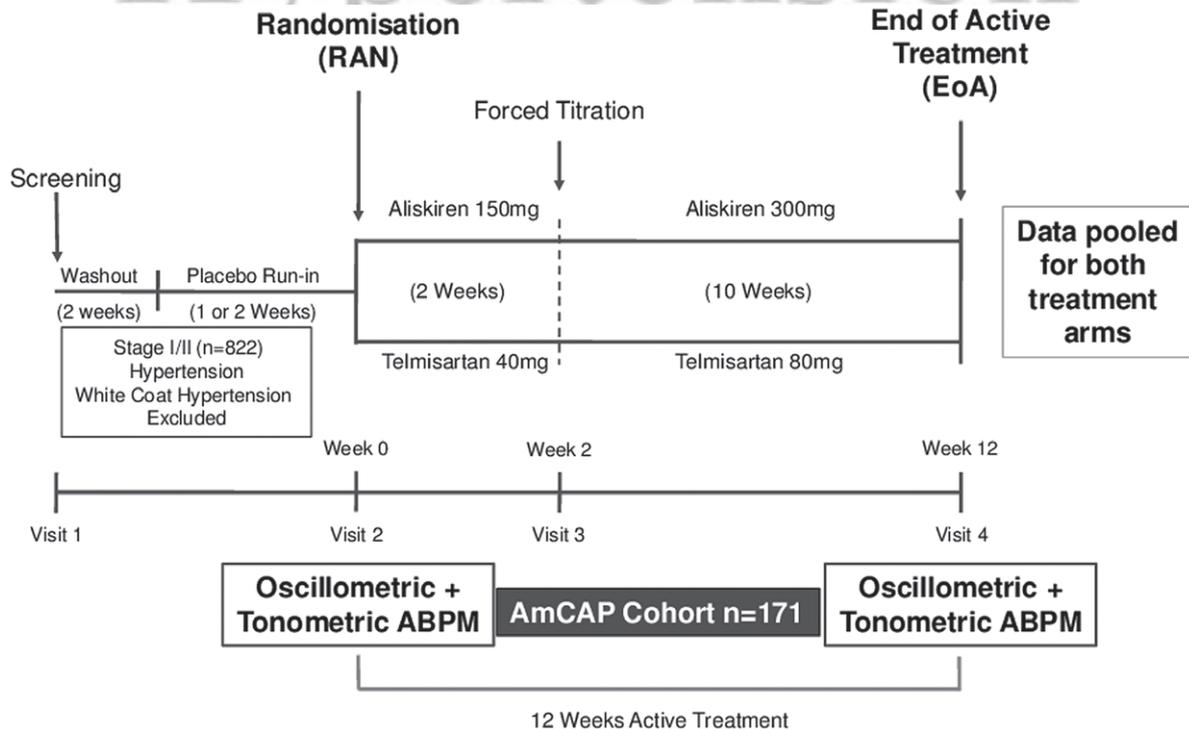


Figure 1. The Ambulatory Central Aortic Pressure (AmCAP) Study design incorporating both oscillometric (Spacelabs 90207) and tonometric (BPro) 24-hour ambulatory blood pressure monitoring (ABPM) at baseline and at study end in 154 patients. The BPro device was used to simultaneously derive ambulatory brachial and central aortic pressures in 171 patients at baseline and at study end.

weeks of study treatments; that is, 2 devices were worn at the same time (Figure 1).

Ambulatory BP Measurement Procedures

Conventional oscillometric brachial ABPM was undertaken using a cuff-based device (Spacelabs 90207, SpaceLabs Medical Inc, Washington) applied to the patients' nondominant arm. The minimum monitoring duration was 24 hours with measurement programmed for every 15 minutes during the daytime (06.00–22.00 hours) and every 30 minutes during the sleep period (22.00–06.00 hours). Quality control criteria had been prespecified for the ASSERTIVE study and included the following: 24 hours duration of monitoring with $\geq 70\%$ of the maximum number of possible measurements completed over a 24-hour period, and with not > 2 nonconsecutive hours with missing data and not > 1 hour without a valid BP reading.

Tonometric ambulatory BP monitoring of derived brachial and central aortic pressure was undertaken using the BPro device (HealthStats, Singapore). The device was applied to the opposite wrist from the limb to which the Spacelabs cuff-based ABPM device was applied. The BPro device was programmed to sample radial artery pulse waves for 10 seconds, at 15-minute intervals throughout the 24-hour period, and the day and night periods used were defined as described above for the Spacelabs device. When initially applied, the radial pulse wave was calibrated to seated clinic BP, measured after 5 minutes rest using a validated automated device (Omron HEM-705, J Hewitt, LLC, CA). Simultaneously, the captured calibrated radial artery pulse waves were used to derive central aortic pressures as previously validated and described.^{14,15} The BPro device takes more measurements over the 24-hour period than the conventional oscillometric ABPM device, and the quality control criteria for the BPro measurements were prespecified for the AmCAP study as a minimum of 14 daytime and 7 night-time measurements in accordance with criteria for the minimum standard for ABPM recording suggested by the European Society of Hypertension and NICE (the National Institute for health and Clinical Excellence), United Kingdom guidelines.^{17,18}

The protocol specified that at the initiation of 24 hours ABPM, the oscillometric (Spacelabs) and tonometric (BPro) ABPM devices should be synchronized to record BP as closely together in time as possible. This was designed to allow comparison of these 2 approaches in the measurement of 24-hour ambulatory brachial BP.

Additional Ambulatory Hemodynamic Parameters

In addition to BrSBP, diastolic and pulse pressures (PP), the AmCAP study analysis included the following: central aortic systolic pressure (CASP), central aortic PP (CAPP), that is, CASP–diastolic pressure, the difference between brachial and central aortic pressure (BrSBP–CASP), PP amplification (PPA), that is, the brachial:central PP ratio, and the % nocturnal dip in brachial and central aortic pressures, that is, $1 - (\text{night/day BP}) \times 100\%$.

AmCAP Study Primary Objective and Statistical Analysis Plan

The primary objective of the AmCAP study was to compare, for the first time, the circadian patterns of ambulatory brachial and central aortic pressures in man. The secondary objective was to evaluate the impact of BP-lowering treatment on these circadian patterns.

To maximize statistical power for the purposes of this analysis, before analyzing data for the AmCAP study, we prespecified that data for both treatment arms would be pooled because the ASSERTIVE study had shown no significant difference in BP lowering between treatment arms based on ABPM measurement in the entire ASSERTIVE study population.¹⁶

ABPM data were separated into daytime (06:00–22:00 hours) and night-time (22:00–06:00 hours) periods and analyzed as 24-hour data. Comparisons between daytime and night-time periods used either paired Student *t* tests or repeated measures ANOVA.

For analysis of the relationship between hemodynamic parameters with time across the 24-hour period, ABPM data from individual

participants at each time point (baseline, study end) were time-aligned into corresponding 15-minute time intervals. Data for each 15-minute time interval across the 24-hour period were averaged and plotted as shown in Figures 2 and 3.

To assess the influence of covariates on daytime and night-time BPs, a univariate ANCOVA model was applied for multivariate adjustment when comparing daytime and night-time variables. The ANCOVA models were used to analyze data at baseline or at study end and incorporated daytime/night-time period as fixed factor with adjustment for daytime and night-time BrSBP, diastolic BP, and heart rate as covariates.

Normally distributed variables are presented as mean \pm SD. Non-normally distributed data are presented as median \pm interquartile range. In all tests, a 2-tailed $P \leq 0.05$ was considered statistically significant. Database management and statistical analysis were performed using IBM SPSS for Windows version 20 (IBM corporation, Armonk, NY).

These studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and the US Code of Federal Regulation (part 46, protection of human subjects) and in accordance with the principles outlined by the International Conference on Harmonisation Guidelines for Good Clinical Practice. The trial protocol was reviewed and approved by the relevant independent ethics committees for each participating center, and written informed consent was obtained from each patient before participating in any trial procedure.

Results

AmCAP Study Patient Demographics

The mean age for patients in the AmCAP study was ≈ 54 years, with a balanced sex distribution. Approximately 56% of patients were white, and 44% of patients were Asian. Only 9% of patients were hypertension treatment naive, with median treatment duration of ≈ 5 years for those previously treated. Fourteen percent of patients had type 2 diabetes mellitus, and 20% of patients were current smokers. The mean seated BP at baseline was 156/90 mmHg (Table 1). The characteristics of the AmCAP study cohort were similar to those of the ASSERTIVE study, of which the AmCAP study subset of patients was derived.¹⁶

Comparison of 24-Hour Ambulatory Brachial BP Data Using Oscillometric (Spacelabs) and Tonometric (BPro) Devices

The BPro device, although approved for clinical ABPM measurements,¹³ is a new ABPM technology. Therefore, it was necessary to confirm that the data generated from tonometric ambulatory brachial BP were similar to conventional cuff-based ABPM data, when both devices were worn together and synchronized in time. Not all patients in the AmCAP study ended up with valid paired measurements using the Spacelabs and BPro devices, mainly because participants declined repeating ABPM with the cuff-based device, or failure to meet quality control parameters for that device. Therefore, the number of participants with paired ABPMs for comparison was 154.

Table 2 shows that the average daytime and night-time brachial pressures recorded at baseline and at study end were similar for both devices. Aggregate data (baseline and study end) for each device showed that the average difference in ambulatory BP for the 24 hours, daytime and night-time periods, was < 2 mmHg (ranging from 1.6 to -4.3 mmHg) and thus was within a 5-mmHg threshold, the standard level

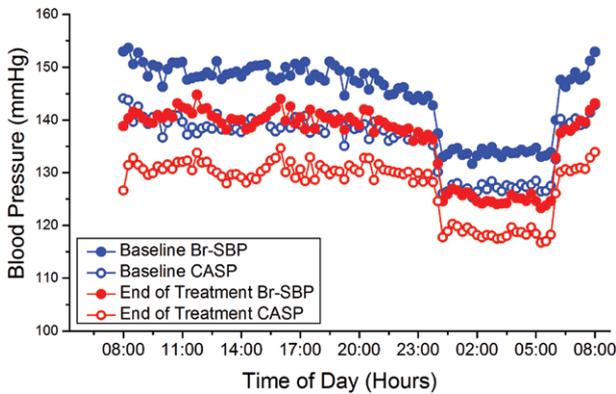


Figure 2. Twenty-four-hour patterns of brachial systolic blood pressure (BrSBP, closed symbols) and central aortic systolic pressure (CASP, open symbols) at baseline (blue) and at 12 weeks after blood pressure (BP) lowering (red). Data from 24-hour ambulatory blood pressure monitoring were time aligned, and each data point represents the mean of all valid recorded measurements from study participants ($n=171$) in contemporaneous 15-minute time intervals.

of agreement in BP monitor comparison protocols,^{19,20} for equivalent time periods. This confirmed the suitability of using the BPro device for the simultaneous measurement of 24-hour ambulatory brachial and central aortic pressures.

Diurnal Variation in Brachial and Central Aortic Systolic and Pulse Pressure for 24-Hour Period

Consistent with the usual diurnal variation in BP, at baseline there was a nocturnal fall in BrSBP of ≈ 10 mmHg (Figure 2 and Tables 3 and 4 and online-only Data Supplement). As expected, simultaneously measured 24-hour ambulatory CASP was lower than BrSBP throughout the 24-hour period and also demonstrated a diurnal variation with a nocturnal fall (Figure 2). Importantly, however, the nocturnal fall in CASP was significantly smaller than the corresponding fall in BrSBP when expressed either as an absolute nocturnal fall (9.7 ± 6.1 mmHg versus 12.3 ± 6.7 mmHg; $P < 0.001$), or as a percentage dip from the daytime pressure average ($6.9 \pm 4.3\%$ versus $8.2 \pm 4.4\%$; $P < 0.001$). This difference in the nocturnal relationship between CASP and BrSBP is further illustrated by reference to the diurnal variation for the difference between these 2 pressures, that is, BrSBP–CASP, which clearly showed a lesser difference at night (day, 9.5 ± 2.6 mmHg; night, 6.9 ± 2.1 mmHg; $P < 0.001$). This indicates that relative to BrSBP, CASP is disproportionately higher at night than during the day (Figure 3 and Tables 3 and 4 and Figure S1 in the online-only Data Supplement). PPA, that is, the ratio of brachial PP:CAPP, similarly showed a diurnal variation with a nocturnal decline (PPA day, 1.20 ± 0.05 ; PPA night, 1.15 ± 0.04 ; $P < 0.001$; Table 3). Thus, 24-hour ambulatory CASP and CAPP exhibit a diurnal variation that is similar to the corresponding brachial BP parameters but with a disproportionately higher CASP and CAPP relative to BrSBP and PP at night.

Temporal Patterns of Relative Change in Brachial Versus Central Aortic Pressures

An intriguing finding was that ambulatory measurement of PPA and BrSBP–CASP began to decline from early evening, with a

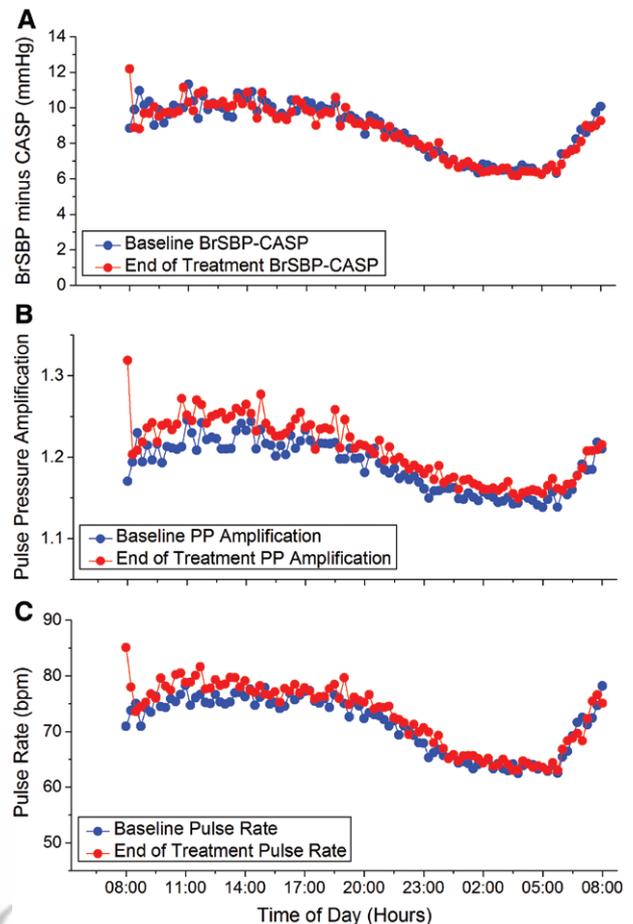


Figure 3. The circadian patterns of brachial systolic blood pressure minus central aortic systolic pressure (BrSBP–CASP; **A**), pulse pressure amplification (PP Amplification) (**B**), and heart rate (**C**); before (blue symbols) and after (red symbols) treatment of blood pressure (BP) for 12 weeks. Data were averaged from 24-hour time-aligned ambulatory blood pressure monitoring, where each data point represents the mean of all valid recorded measurements from study participants ($n=171$) in contemporaneous 15-minute time intervals.

relatively shallow change in both parameters, each reaching a nadir that coincided with the onset of the night-time BP plateau (Figure 3A and 3B). This pattern was in marked contrast to the sharp decline in both BrSBP and CASP at the presumed time of sleep onset. Furthermore, the relatively gentle decline in PPA and BrSBP–CASP toward the sleep period is in stark contrast to the much steeper early morning rise for these parameters, suggesting that a sharp increase in pressure amplification immediately precedes and coincides with waking. Remarkably, these patterns paralleled the diurnal change in heart rate (Figure 3C).

Diurnal Patterns of Brachial and Central Aortic Systolic and Pulse Pressure For 24-Hour Period—Impact of BP-Lowering Therapy

Treatment with either telmisartan ($n=84$) or aliskiren ($n=87$) similarly reduced the ambulatory brachial BP mean from baseline; thus, data from both treatment arms were pooled for analysis in the AmCAP study cohort. The mean change in 24-hour ambulatory BP for the AmCAP cohort (BPro device) was $-8.1 \pm 21.2 / -4.1 \pm 13.2$ mmHg ($P=0.012/P < 0.001$). Despite these significant improvements in BP control, the diurnal

Table 1. Demographic Parameters for the AmCAP Study Population

Parameters	All Participants (n=171)	Aliskiren (n=87)	Telmisartan (n=84)
Age, y	53.6±12.6	54.2±11.8	53.0±13.4
Male, n (%)	80 (46.8)	40 (46.0)	40 (47.6)
White, n (%)	95 (55.6)	50 (57.5)	45 (53.6)
Asian, n (%)	76 (44.4)	37 (42.5)	39 (46.4)
Height, cm	163.7±11.4	163.3±12.4	164.0±10.2
Weight, kg	76.7±17.5	76.5±20.0	77.0±14.6
BMI, kg/m ²	28.5±5.0	28.4±5.4	28.5±4.4
eGFR, mL/min per 1.73 m ²	88.7±18.7	86.9±19.5	90.6±17.7
Previous treatment naive, n (%)	16 (9.4)	10 (11.5)	6 (7.1)
Duration of hypertension, y	5±8*	6±8.0*	4±7*
Previous history of diabetes mellitus, n (%)	24 (14.0)	13 (14.9)	11 (13.1)
Current smoker	35 (20.5)	16 (18.4)	19 (22.6)
Pack years	15.3±12.8	18.1±15.7	13.1±9.7
Seated SBP, mm Hg	155.9±10.7	155.7±10.2	156.1±11.2
Seated DBP, mm Hg	89.8±9.3	89.4±10.2	90.1±8.4
Pulse rate, bpm	74.9±10.1	76.2±9.8	73.6±10.4
Twenty-four-hour ambulatory SBP (Spacelabs), mm Hg	147.3±9.8	146.4±9.7	148.3±9.9
Twenty-four-hour ambulatory DBP (Spacelabs), mm Hg	88.6±9.3	88.2±9.2	89.0±9.6
Twenty-four-hour ambulatory SBP (BPro), mm Hg	144.2±15.9	142.9±16.2	145.5±15.5
Twenty-four-hour ambulatory DBP (BPro), mm Hg	87.9±12.8	86.9±12.9	88.8±12.7

AmCAP indicates Ambulatory Central Aortic Pressure; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; and SBP, systolic blood pressure.

*Median±IQR.

patterns of peripheral and central pressure measurement relative to each other remained unchanged. This is best illustrated by reference to the 24-hour profile for BrSBP-CASP (Figure 3A). This is further underscored by the fact that the average value for BrSBP-CASP, for either daytime or night-time, did not differ before or after treatment (daytime BrSBP-CASP change [baseline to study end] -0.09 ± 2.6 mm Hg; $P=0.64$; night-time BrSBP-CASP change [baseline to study end] 0.004 ± 2.3 mm Hg; $P=0.99$; Figure 3). For other hemodynamic

parameters, there was also no difference in the relationships between day and night values before and after treatment. Thus, comparison of the day-night change (% dip) between baseline and study end showed no difference for the following: BrSBP (mean difference, $-0.02\pm 5.8\%$; $P=0.96$), brachial diastolic BP (mean difference, $-0.03\pm 5.8\%$; $P=0.95$), brachial PP (mean difference, $-0.01\pm 6.1\%$; $P=0.98$), CASP (mean difference, $-0.01\pm 5.9\%$; $P=0.98$), central PP (mean difference, $0.19\pm 6.9\%$; $P=0.72$), and PPA (mean difference, $-0.28\pm 4.3\%$;

Table 2. Comparison of Data Using Oscillometric Cuff-Based 24-Hour ABPM (Spacelabs) With Radial Artery Tonometric 24-Hour ABPM (BPro)

Time Points	24-Hour Average, mm Hg		Daytime Average, mm Hg		Night-time Average, mm Hg	
	Spacelabs	BPro	Spacelabs	BPro	Spacelabs	BPro
Baseline	147.5/88.5	143.3/87.2	150.4/91.0	147.9/89.9	137.4/79.9	135.7/82.7
Mean difference	4.2/1.3		2.5/1.1		1.7/-2.8	
n	154	154	154	154	154	154
End of treatment	134.5/80.1	135.4/83.0	137.1/82.4	140.0/85.7	125.9/72.9	128.1/78.6
Mean difference	-1.0/-2.9		-3.0/-3.3		-2.2/-5.7	
n	154	154	154	154	154	154
Mean difference (all time points)	1.6/-0.8		-0.2/-1.1		-0.2/-4.3	
n	308		308		308	

Data show ambulatory BP values for each time point together with an average of all measurements using each device. ABPM indicates ambulatory blood pressure monitoring; and BP, blood pressure.

Table 3. Average Brachial and Central Aortic Pressure and Derived Hemodynamic Parameters at Baseline and After 12-Weeks BP-Lowering Treatment for the AmCAP Study Population (n=171)

Parameters	Baseline (Day)	Baseline (Night)	End of Treatment (Day)	End of Treatment (Night)
BrSBP, mm Hg	148.8±16.5	136.5±15.8*	140.6±17.9‡	129.0±17.2*‡
CASP, mm Hg	139.3±15.3	129.6±15.1*	131.2±17.1‡	122.1±16.6*‡
BrDBP, mm Hg	90.6±13.2	83.3±12.6*	86.5±12.7‡	79.5±12.3*‡
BrPP, mm Hg	58.2±10.6	53.2±9.8*	54.1±10.3‡	49.4±9.4*‡
CAPP, mm Hg	48.7±9.0	46.3±8.7*	44.7±9.0‡	42.5±8.5*‡
Heart rate, bpm	74.3±7.5	64.8±8.2*	76.1±8.9‡	66.0±8.3*
Brachial–central pressure, mm Hg	9.5±2.6	6.9±2.1*	9.4±2.5	6.9±2.1*
Pulse pressure amplification	1.20±0.05	1.15±0.04*	1.23±0.06‡	1.17±0.05*‡

AmCAP indicates Ambulatory Central Aortic Pressure; BP, blood pressure; BrDBP, brachial diastolic blood pressure; BrPP, brachial pulse pressure; BrSBP, brachial systolic blood pressure; CAPP, central aortic pulse pressure; and CASP, central aortic systolic pressure.

* $P<0.0001$ day vs night.

‡ $P<0.05$ baseline vs end of treatment.

‡ $P<0.001$ baseline vs end of treatment, repeated measures ANOVA.

$P=0.38$). These data further suggest that the relative pattern of BP change between day and night for BrSBP and CASP is not modulated by BP lowering. A caveat is that BP lowering increased PPA across the 24-hour period (24-hour PPA change [baseline to study end] 0.02 ± 0.05 ; $P<0.001$) but without altering the pattern of the relationship between daytime and night-time (Figure 3B).

Adjusting for Potential Confounding Factors

The relationship between brachial and central BP can be influenced by a number of factors, including age, sex, BP treatment, smoking status, height, weight, and heart rate. The majority of these parameters were controlled for by the paired design of this study, that is, the same participants were studied both at baseline and at study end with both daytime and night-time measurements. However, variation in BP and heart rate across the 24-hour period between individuals may have influenced the circadian change in the relationship between brachial and central pressures. To control for this variation, we used an ANCOVA model that included both daytime and night-time BrSBP and diastolic pressures together with heart rate as covariates. In this model, the relationship between brachial and central pressure was described using the parameters PPA and BrSBP–CASP, which were included as dependent variables.

Although adjustment for BP and heart rate largely attenuated the differences in PPA and BrSBP–CASP between daytime and night-time values, statistically significant differences remained (BrSBP–CASP; mean day–night difference at baseline, 0.41 mm Hg [95% confidence interval, 0.05–0.76]; $P=0.02$; mean difference at end of treatment, 0.43 mm Hg [95% confidence interval, 0.06–0.81]; $P=0.02$; PPA; mean day–night difference at baseline, 0.014 mm Hg [95% confidence

interval, 0.005–0.023]; $P=0.002$; mean difference end of treatment, 0.016 mm Hg [95% confidence interval, 0.005–0.027]; $P=0.005$; Tables 5 and 6). Moreover, the parameter day versus night remained a significant determinant in the model ($P<0.001$). These data suggest that residual differences in the day–night patterns of brachial and central pressure remain in spite of adjusting for the influence of BP and heart rate.

Discussion

We describe, for the first time, the patterns of ambulatory brachial and simultaneously measured central aortic pressures in the setting of a multicenter, randomized, controlled, clinical trial of BP lowering in patients with hypertension. The results from this study demonstrate that despite similarities in the circadian rhythms of brachial and central aortic pressures, there was a significantly reduced night-time dip in CASP and CAPP relative to the corresponding night-time dip in brachial pressure. These novel findings suggest that nocturnal aortic pressures are disproportionately higher than brachial pressures during sleep. This is underscored by our finding of a significantly reduced PPA at night.

An important consideration in our use of the BPro device for this study was to demonstrate reasonable equivalence in the monitoring of brachial BP compared with conventional ABPM measurements. To this end, we showed that averaged ambulatory values for brachial BP acquired using the BPro device differed by not >5 mm Hg than averaged values acquired using a conventional oscillometric cuff–based device. This confirmed the suitability in using the BPro device for the measurement of 24-hour ambulatory brachial pressures, the radial waveforms from which could then be used for the simultaneous derivation of central pressure. This approach proved effective in allowing us to compare

Table 4. Average Night-Time Dip in Brachial and Central Aortic Pressure at Baseline and After 12-Weeks BP-Lowering Treatment for the AmCAP Study Population (n=171)

Parameter	Baseline (Brachial SBP)	Baseline (CASP)	End of Treatment (Brachial SBP)	End of Treatment (CASP)
Night-time dip, %	8.2±4.4	6.9±4.3*	8.2±4.9	6.9±4.7*

AmCAP indicates Ambulatory Central Aortic Pressure; BP, blood pressure; and CASP, central aortic systolic pressure.

* $P<0.0001$ day vs night.

Table 5. Average Brachial and Central Aortic Pressure and Derived Hemodynamic Parameters at Baseline and After 12-Wk BP-Lowering Treatment After Adjustment for Day and Night Blood Pressure and Heart Rate Using 1-Way ANCOVA

Parameters	Baseline Day (Adjusted*)	Baseline Night (Adjusted*)	P Value	End of Treatment Day (Adjusted*)	End of Treatment Night (Adjusted*)	P Value
Brachial SBP–CASP, mm Hg	8.39 (8.16–8.62)	7.98 (7.75–8.21)	0.024	8.36 (8.12–8.60)	7.93 (7.68–8.17)	0.022
Pulse pressure amplification	1.19 (1.181–1.192)	1.17 (1.166–1.178)	0.002	1.20 (1.198–1.212)	1.19 (1.182–1.196)	0.005

Data show mean value (95% CI). BP indicates blood pressure; CASP, central aortic systolic pressure; CI, confidence interval; and SBP, systolic blood pressure.

*Data adjusted for day/night brachial SBP, brachial diastolic blood pressure, and pulse rate.

the diurnal patterns of simultaneously derived brachial and central pressure together with other derived parameters (PPA, BrSBP–CASP) of potential prognostic significance, across the 24-hour period.

An intriguing finding from our study was the asymmetry in the patterns of PPA and BrSBP–CASP across the 24-hour period. The gradual decline in PPA and BrSBP–CASP values toward the onset of sleep contrasted markedly with the more abrupt change in PPA and BrSBP–CASP before waking. This suggests that the often reported early morning surge in BrSBP that usually precedes waking^{8,10} is at least in part a function of an abrupt enhancement of PPA around the time of waking. Further work is needed to better understand the mechanistic basis for this novel finding.

The mechanism for our finding of a lesser nocturnal reduction in CASP and CAPP relative to BrSBP and brachial PP is not known. To evaluate this, we adjusted for variables known to influence pressure amplification.^{21–23} Adjusting for heart rate, and to a lesser extent brachial BP, substantially attenuated the day–night differences in PPA and BrSBP–CASP, suggesting that heart rate reduction during sleep, in particular, accounted for much of the lesser decline in CASP relative to BrSBP at night. Nevertheless, adjusting for heart rate and brachial BP did not entirely eliminate the lesser difference between BrSBP and CASP at night. In this regard, had BP been an important factor, we might have expected to see an impact of BP lowering on this relationship, but this was not the case. Indeed, the difference between BrSBP and CASP at night and the nocturnal dips were almost identical, before and after treatment (Tables 3 and 4). Another possibility is that supine posture during sleep reduces pressure wave amplification.^{24,25} Whilst this needs further study, the fact that PPA began to decline gradually, hours before the nadir of BP was reached, which we assume was during sleep, implies that this phenomenon is unlikely to be explained by posture alone.

A key question is whether our finding of a disproportionately higher CASP relative to BrSBP at night is clinically important. The following points are noteworthy: (1) that nocturnal brachial BP has been shown to be the strongest BP parameter

as a predictor of clinical outcomes,^{3,9} (2) that data are emerging to suggest that central aortic pressure may be a better predictor of target-organ damage and clinical outcomes than its brachial counterpart,^{5–7} and (3) that data are emerging, implicating an association between reduced PPA and risk for cardiovascular events.^{22,26,27} Thus, it is conceivable that nocturnal CASP or CAPP could represent the most important hemodynamic determinant of BP-related cardiovascular disease risk.

The strengths of the present study are the following points: (1) the rigor of the RCT setting in which the study was conducted, (2) evaluation of the BPro device for the measurement of ABPM via direct comparison of brachial ABPM data with an often used conventional cuff–based ABPM device; however, we acknowledge that this was not a formal validation study, (3) brachial and central pressure measurements were both derived via extraction of data from the same arterial waveforms, and (4) the inclusion of a BP-lowering treatment strategy to evaluate whether BP lowering impacts on the 24-hour circadian rhythms of brachial versus central aortic pressure.

We also acknowledge potential weaknesses of the present study, which include the noninvasive assessment of central aortic pressure, rather than direct measurement. The method used for measurement of central aortic pressures has been validated versus direct invasive pressure measurement and versus alternative algorithms for computing central aortic pressure from peripheral artery waveforms.^{14,15} Furthermore, all of the patients included in this study had hypertension, and it is unknown whether these novel findings of disproportionately higher nocturnal central pressures apply to other populations. The fact that neither the treatment-induced BP reduction nor the adjustment for day–night BP and heart rate altered the relationships between brachial and central BP at night suggests that a relatively higher nocturnal central pressure is a natural phenomenon associated with sleep. Finally, we acknowledge that the absolute difference between central and brachial BP between day and night, although statistically significant, is numerically small, and further work is required to evaluate its clinical impact.

Table 6. Average Night-Time Dip in Brachial and Central Aortic Pressure at Baseline and After 12-Wk BP-Lowering Treatment After Adjustment for Day and Night Blood Pressure and Heart Rate Using 1-Way ANCOVA

Parameter	Baseline Brachial SBP (Adjusted*)	Baseline CASP (Adjusted*)	P Value	End of Treatment Brachial SBP (Adjusted*)	End of Treatment CASP (Adjusted*)	P Value
Night-time dip, %	8.5 (7.8–9.2)	6.6 (5.8–7.3)	<0.001	8.5 (7.7–9.3)	6.6 (5.8–7.4)	0.002

Data show mean value (95% CI).

BP indicates blood pressure; CASP, central aortic systolic pressure; and CI, confidence interval.

*Data adjusted for day/night brachial systolic blood pressure, brachial diastolic blood pressure, and pulse rate.

In conclusion, we have shown, for the first time, that the measurement of 24-hour ambulatory central aortic pressure is feasible in the setting of a multicenter randomized controlled clinical trial.¹⁶ We have also shown that the 24-hour circadian rhythms for CASP and central PP differ significantly from the circadian rhythms for BrSBP and Brachial PP, most notably at night. Specifically, the nocturnal dips in CASP and central PP are reduced relative to the respective nocturnal dips in BrSBP and Brachial PP, because of reduced nocturnal pressure amplification. These differences were maintained after adjustment for BP and heart rate and remained despite BP lowering. Mindful of the emerging importance of nocturnal and central pressures as predictors of target-organ damage and cardiovascular outcomes,^{3,5-7,9} these findings suggest that nocturnal central aortic pressures could have previously unrecognized implications for pressure-mediated disease pathophysiology and strategies for the optimal evaluation and treatment of hypertension.

Perspectives

This study demonstrates, for the first time, the simultaneous noninvasive measurement of ambulatory brachial and central aortic pressures and reports the circadian patterns of concurrently measured 24-hour brachial and central aortic pressures together with the influence of BP lowering on these parameters. Although we observed a similar pattern for 24-hour brachial and central pressures, the extent of the night-time reduction in central relative to brachial pressure was significantly reduced. This indicates a relatively higher night-time central pressure for any given brachial pressure at night, which seemed largely dependent on heart rate. Moreover, this pattern remained even after BP-lowering therapy. Furthermore, we demonstrated a potential contribution of PPA to the morning surge in brachial BP. Given the emerging importance of night-time and potential impact of central aortic pressure on clinical outcomes, these data imply that night-time central pressure could have prognostic importance. Moreover, the study demonstrates that testing this hypothesis is now feasible in future clinical trials.

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Disclosures

B. Williams and R. Düsing have previously received research support from Novartis and have acted as consultants for Novartis. B. Williams and P.S. Lacy have also worked in nonremunerated scientific collaboration with HealthStats Singapore in developing methods for the noninvasive measurement of central aortic pressures. P. Brunel and F. Baschiera are employees of Novartis (Novartis Pharma AG, Basel, Switzerland) and eligible for Novartis stock and stock options. The other authors report no conflicts.

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Novelty and Significance

What Is New?

- The first description of the simultaneous measurement of 24-hour ambulatory central aortic pressure (CAP) and brachial blood pressure (BP).
- The first description of the circadian pattern of 24-hour ambulatory CAP relative to brachial BP.
- The first description of the effects of BP lowering on ambulatory CAP.

What Is Relevant?

- CAP may be a better predictor of clinical outcome than conventional brachial BP.

- There is increasing use of CAP measurement in clinical studies to evaluate drug actions—this can now be extended to ambulatory CAP measurements.

Summary

The Ambulatory Central Aortic Pressure (AmCAP) study demonstrates that there is reduced pressure wave amplification at night, resulting in relatively higher CAP versus brachial pressure at night; the relatively higher night-time CAP seems largely dependent on heart rate but remains significant even after adjustment; pressure wave amplification contributes to the morning surge in brachial BP; these patterns remain unchanged despite BP-lowering therapy.