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

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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.

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

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 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.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...
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. 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. 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. 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.

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 of treatment with an angiotensin receptor blocker versus a direct renin inhibitor in patients with stage I/II hypertension.

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 mm Hg.

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 weeks of active treatment.

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.

Study Design

Details of the ASSERTIVE study have been published. 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).
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 ≥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
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 (Ommrom HEM-705,
J H 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 oscil-
llometric 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 cri-
teria 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.13,18

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 approach-
es 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, CAPP–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–(night/day BP)×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, be-
fore 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 treat-
ment arms based on ABPM measurement in the entire ASSERTIVE
study population.15

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 ei-
ther 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
BP, a univariate ANCOVA model was applied for multivariate ad-
justment 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 means±SD. Non-
normally distributed data are presented as median±interquartile
range. In all tests, a 2-tailed P≤0.05 was considered statistically
significant. Database management and statistical analysis were
performed using IBM SPSS for Windows version 20 (IBM corpo-
ration, Armonk, NY).

These studies were conducted in accordance with the ethical prin-
ciples of the Declaration of Helsinki and the US Code of Federal
Regulation (part 46, protection of human subjects) and in accord-
ance 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 mm Hg (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 mea-
urements,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 mm Hg (ranging from 1.6 to −4.3 mm Hg)
and thus was within a 5-mm Hg threshold, the standard level
of agreement in BP monitor comparison protocols,\textsuperscript{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 mm Hg (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 mm Hg versus 12.3±6.7 mm Hg; \(P<0.001\)), or as a percentage dip from the daytime pressure average (6.9±4.3% versus 8.2±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 mm Hg; night, 6.9±2.1 mm Hg; \(P<0.001\)). 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 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±21.2/-4.1±13.2\ mm Hg (\(P=0.012/P<0.001\)). Despite these significant improvements in BP control, the diurnal
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±5.8%; \( P = 0.96 \)), brachial diastolic BP (mean difference, −0.03±5.8%; \( P = 0.95 \)), brachial PP (mean difference, −0.01±6.1%; \( P = 0.98 \)), CASP (mean difference, −0.01±5.9%; \( P = 0.98 \)), central PP (mean difference, 0.19±6.9%; \( P = 0.72 \)), and PPA (mean difference, −0.28±4.3%; Table 1.

### Table 1. Demographic Parameters for the AmCAP Study Population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>All Participants (n=171)</th>
<th>Aliskiren (n=87)</th>
<th>Telmisartan (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.6±12.6</td>
<td>54.2±11.8</td>
<td>53.0±13.4</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>80 (46.8)</td>
<td>40 (46.0)</td>
<td>40 (47.6)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>95 (55.6)</td>
<td>50 (57.5)</td>
<td>45 (53.6)</td>
</tr>
<tr>
<td>Asian, n (%)</td>
<td>76 (44.4)</td>
<td>37 (42.5)</td>
<td>39 (46.4)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>163.7±11.4</td>
<td>163.3±12.4</td>
<td>164.0±10.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76.7±17.5</td>
<td>76.5±20.0</td>
<td>77.0±14.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.5±5.0</td>
<td>28.4±5.4</td>
<td>28.5±4.4</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²</td>
<td>88.7±18.7</td>
<td>86.9±19.5</td>
<td>90.6±17.7</td>
</tr>
<tr>
<td>Previous treatment naive, n (%)</td>
<td>16 (9.4)</td>
<td>10 (11.5)</td>
<td>6 (7.1)</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>5±8*</td>
<td>6±8*</td>
<td>4±7*</td>
</tr>
<tr>
<td>Previous history of diabetes mellitus, n (%)</td>
<td>24 (14.0)</td>
<td>13 (13.9)</td>
<td>11 (1.3)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>35 (20.5)</td>
<td>16 (18.4)</td>
<td>19 (22.6)</td>
</tr>
<tr>
<td>Pack years</td>
<td>15.3±12.8</td>
<td>18.1±15.7</td>
<td>13.1±9.7</td>
</tr>
<tr>
<td>Seated SBP, mm Hg</td>
<td>155.9±10.7</td>
<td>155.7±10.2</td>
<td>156.1±11.2</td>
</tr>
<tr>
<td>Seated DBP, mm Hg</td>
<td>89.8±9.3</td>
<td>89.4±10.2</td>
<td>90.1±8.4</td>
</tr>
<tr>
<td>Pulse rate, bpm</td>
<td>74.9±10.1</td>
<td>76.2±9.8</td>
<td>73.6±10.4</td>
</tr>
<tr>
<td>Twenty-four-hour ambulatory SBP (Spacelabs), mm Hg</td>
<td>147.3±9.8</td>
<td>146.4±9.7</td>
<td>148.3±9.9</td>
</tr>
<tr>
<td>Twenty-four-hour ambulatory SBP (BPro), mm Hg</td>
<td>88.6±9.3</td>
<td>88.2±9.2</td>
<td>89.0±9.6</td>
</tr>
<tr>
<td>Twenty-four-hour ambulatory DBP (Spacelabs), mm Hg</td>
<td>144.2±15.9</td>
<td>142.9±16.2</td>
<td>145.5±15.5</td>
</tr>
<tr>
<td>Twenty-four-hour ambulatory DBP (BPro), mm Hg</td>
<td>87.9±12.8</td>
<td>86.9±12.9</td>
<td>88.8±12.7</td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>Time Points</th>
<th>24-Hour Average, mm Hg</th>
<th>Daytime Average, mm Hg</th>
<th>Night-time Average, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spacelabs</td>
<td>BPro</td>
<td>Spacelabs</td>
</tr>
<tr>
<td>Baseline</td>
<td>147.5/88.5</td>
<td>143.3/87.2</td>
<td>150.4/91.0</td>
</tr>
<tr>
<td>Mean difference</td>
<td>4.2/1.3</td>
<td>2.5/1.1</td>
<td>−3.0/−3.3</td>
</tr>
<tr>
<td>n</td>
<td>154</td>
<td>154</td>
<td>154</td>
</tr>
<tr>
<td>End of treatment</td>
<td>134.5/80.1</td>
<td>135.4/83.0</td>
<td>137.1/82.4</td>
</tr>
<tr>
<td>Mean difference</td>
<td>−1.0/−2.9</td>
<td>−3.0/−3.3</td>
<td>−2.2/−5.7</td>
</tr>
<tr>
<td>n</td>
<td>154</td>
<td>154</td>
<td>154</td>
</tr>
<tr>
<td>Mean difference (all time points)</td>
<td>1.6/−0.8</td>
<td>−0.2/−1.1</td>
<td>−0.2/−4.3</td>
</tr>
<tr>
<td>n</td>
<td>308</td>
<td>308</td>
<td>308</td>
</tr>
</tbody>
</table>

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 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)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (Day)</th>
<th>Baseline (Night)</th>
<th>End of Treatment (Day)</th>
<th>End of Treatment (Night)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night-time dip, %</td>
<td>8.2 ± 4.4</td>
<td>6.9 ± 4.3*</td>
<td>8.2 ± 4.9</td>
<td>6.9 ± 4.7*</td>
</tr>
</tbody>
</table>

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

*P<0.0001 day vs night.
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 waking6,10 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 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

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

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.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Brachial SBP (Adjusted*)</th>
<th>Baseline CASP (Adjusted*)</th>
<th>P Value</th>
<th>End of Treatment Brachial SBP (Adjusted*)</th>
<th>End of Treatment CASP (Adjusted*)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night-time dip, %</td>
<td>8.5 (7.8–9.2)</td>
<td>6.6 (5.8–7.3)</td>
<td>&lt;0.001</td>
<td>8.5 (7.7–9.3)</td>
<td>6.6 (5.8–7.4)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

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.\textsuperscript{36} 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,\textsuperscript{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.

**Acknowledgments**

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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.

**References**


**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.
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 and Rainer Düsing

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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 Randomised Controlled Clinical Trial – The Ambulatory Central Aortic Pressure Study (The AmCAP Study).

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Short title: 24-hour ambulatory brachial and central pressure in hypertension

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**Methods.**

Instruction to study staff and participants with regard to applying and wearing 24-hour ambulatory blood pressure monitoring devices:

Only clinical staff who had received specialist training (verbal and written) undertook ambulatory BP measurements. With regard to tonometric measurement of ambulatory blood pressure (BPro), staff were trained in the theory and practice of applanation tonometry as seated measurements of central aortic pressure were also collected in a separate sub-study. Clinical staff were also trained to provide instruction to study participant with regard to undergoing ambulatory blood pressure monitoring and participants were provided written information and contact telephone numbers, to address any issues arising during ambulatory monitoring. Data quality for ABPM measurements was monitored independently at a central data management facility.
Results.

Figure S1.
**Figure S1.** Day and night time hemodynamic parameters at baseline and end of treatment. Data shows, brachial SBP (panel A), CASP (panel B), brachial DBP (panel C), brachial pulse pressure (panel D), central pulse pressure (panel E), pulse rate (panel F), brachial minus central pressure (panel G), pulse pressure amplification (panel H), brachial and central systolic night-time dip (panel I). Data shows mean values ± SD.)