Hypertension

ORIGINAL ARTICLE

Twenty-Four–Hour Central (Aortic) Systolic Blood Pressure: Reference Values and Dipping Patterns in Untreated Individuals

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ABSTRACT: Central (aortic) systolic blood pressure (cSBP) is the pressure seen by the heart, the brain, and the kidneys. If properly measured, cSBP is closer associated with hypertension-mediated organ damage and prognosis, as compared with brachial SBP (bSBP). We investigated 24-hour profiles of bSBP and cSBP, measured simultaneously using Mobilograph devices, in 2423 untreated adults (1275 women; age, 18–94 years), free from overt cardiovascular disease, aiming to develop reference values and to analyze daytime-nighttime variability. Central SBP was assessed, using brachial waveforms, calibrated with mean arterial pressure (MAP)/diastolic BP ($cSBP_{MAP/DBPcal}$), or bSBP/diastolic blood pressure ($cSBP_{SBP/DBPcal}$), and a validated transfer function, resulting in 144 509 valid brachial and 130 804 valid central measurements. Averaged 24-hour, daytime, and nighttime brachial BP across all individuals was 124/79, 126/81, and 116/72 mm Hg, respectively. Averaged 24-hour, daytime, and nighttime values for $cSBP_{MAP/DBPcal}$ were 128, 128, and 125 mm Hg and 115, 117, and 107 mm Hg for $cSBP_{SBP/DBPcal}$, respectively. We pragmatically propose as upper normal limit for 24-hour $cSBP_{MAP/DBPcal}$ 135 mm Hg and for 24-hour $cSBP_{SBP/DBPcal}$ 120 mm Hg. bSBP dipping (nighttime-daytime/daytime SBP) was −10.6 % in young participants and decreased with increasing age. Central $SBP_{SBP/DBPcal}$ dipping was less pronounced (−8.7% in young participants). In contrast, $cSBP_{MAP/DBPcal}$ dipping was completely absent in the youngest age group and less pronounced in all other participants. These data may serve for comparison in various diseases and have potential implications for refining hypertension diagnosis and management. The different dipping behavior of bSBP versus cSBP requires further investigation. **(*Hypertension*. 2022;79:00–00. DOI: 10.1161/HYPERTENSIONAHA.121.17765.)** • **Supplemental Material**

Key Words: arterial pressure ■ blood pressure ■ heart rate ■ hypertension

Whereas mean arterial pressure (MAP) and diastolic blood pressure (DBP) are relatively constant along the arterial tree, the height of the pressure pulse is amplified from the aorta toward peripheral arteries.[1] Therefore, central systolic blood pressure (cSBP), usually defined as aortic or carotid SBP, differs from brachial SBP (bSBP). When measured simultaneously and invasively at both sites, brachial systolic pressures are higher than aortic pressures to a certain amount.[1] This so-called pressure amplification is highly

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ORIGINAL ARTICLE

Novelty and Significance

What Is New?

- Reference values for 24-hour cSBP from a worldwide research consortium are now available.

What Is Relevant?

- These reference values may facilitate the clinical adoption of cSBP, particularly its 24-hour measurement. Furthermore, the different dipping behavior of central versus brachial SBP requires further study, pertaining to its physiological and pathophysiological consequences.

Summary

Derived from a research consortium (20 centers, 14 countries, and 5 continents), using 130 804 valid cSBP measurements in 2423 untreated adults, we pragmatically propose as upper normal limit for 24-hour $cSBP_{MAP/DBPcal}$ 135 mm Hg and for 24-hour $cSBP_{SBP/DBPcal}$ 120 mm Hg.

Nonstandard Abbreviations and Acronyms

bSBP	brachial systolic blood pressure
cSBP	central systolic blood pressure
DBP	diastolic blood pressure
i24abc	International 24-Hour Ambulatory Aortic Blood Pressure Consortium
MAP	mean arterial pressure

variable between individuals and is the consequence of the progressive reduction of diameter and increase in stiffness from the proximal to the distal arterial vessels and the impact of wave reflections.[2] Clinically, the amount of amplification depends on age, sex, heart rate, body height, and cardiovascular risk factors (eg, dyslipidemia, diabetes, and smoking).[3]

As vital organs such as the brain, the heart, and the kidneys are exposed to central (aortic) rather than brachial pressures, central BP is pathophysiologically more relevant.[2,4] Indeed, cSBP is more closely related to hypertension-mediated organ damage such as left ventricular hypertrophy, intima-media thickness, and pulse wave velocity.[5] In many,[6–9] but not all[10] longitudinal studies, central pressures were better predictors of cardiovascular events, as compared with brachial pressures. Finally, interventional studies have established the concept that antihypertensive drug treatment may have different effects on bSBP and cSBP.[11–14] In a randomized trial,[15] guidance of hypertension management with central BP resulted in a significantly different therapeutic pathway than conventional brachial BP and resulted in less use of medication to achieve BP control, with no adverse effects on left ventricular mass, aortic stiffness, or quality of life.

From a technical point of view, noninvasive determination of cSBP is most commonly achieved by the acquisition of peripheral (radial or brachial) waveforms, calibration of the waveforms using brachial BP, and application of dedicated mathematics (mostly, so-called transfer formulae) to derive the central BP curve.[16] Waveform calibration is the critical aspect here, due to the well-established systematic underestimation of true (ie, invasive) bSBP by noninvasive cuff-based measurement,[17] which seems to be based on the inability of the first Korotkoff sound to determine bSBP correctly.[18] Consequently, waveform calibration with noninvasive cuff-based SBP (and DBP) will most often result in underestimation of cSBP, as compared with true (ie, actual as measured invasively) cSBP, albeit with preservation of SBP amplification. On the other hand, waveform calibration with MAP (and DBP) can result in a better estimate of true (=invasive) cSBP,[16,19,20] albeit with apparent distortion (ie, negative/inverse) of SBP amplification (apparent relates to the fact that a noninvasive gold standard is used for bSBP and an invasive gold standard is used for $cSBP_{MAP/DBP-cal}$). With respect to the Mobilograph device, one invasive study, using high-fidelity pressure-sensor dipped catheters as reference, in 30 patients has shown that calibration with MAP/DBP provides better estimation of cSBP compared with SBP/DBP calibration.[21] On the contrary, another recent study, which used fluid-filled catheters as reference, but adhered to the Association for Research into Arterial Structure and Physiology Society guidelines, reported wider limits of agreement with MAP/DBP calibration.[22] In any case, clinical superiority of noninvasive MAP/DBP calibrated cSBP has been demonstrated in terms of relationship with coronary atherosclerosis,[23] cardiac structural abnormalities,[24] and prognosis.[25]

In all the aforementioned studies, office-based BP measurements were used. As far as brachial BP is concerned, 24-hour ambulatory BP is a stronger predictor of cardiovascular events,[26] all-cause mortality, and cardiovascular mortality than office BP.[26] Nighttime BP and nighttime/daytime difference (dipping) have been of particular value[26] in aiding cardiovascular risk prediction. With technological progress, measurement of cSBP during 24-hour ambulatory monitoring is now possible, using brachial cuff-based devices.[21,27,28] Accordingly, 24-hour cSBP was closer associated with left ventricular mass/hypertrophy[29,30] and diastolic dysfunction,[31] as compared

with 24-hour bSBP. Again, the advantage of cSBP over bSBP was dependent on technical aspects, favoring the MAP/DBP calibration method.

So far, despite the growing clinical evidence, reference values for 24-hour cSBP, based on large, multinational samples, are currently missing. Moreover, the circadian variability of BP amplification[32] and, closely related, the nighttime/daytime variability of cSBP versus bSBP have been poorly studied. To address these issues, we established a global academic research network (i24abc [International 24-Hour Ambulatory Aortic Blood Pressure Consortium]), aiming to derive reference standards for 24-hour ambulatory cSBP, using a widely available validated oscillometric device.

METHODS

Study Organization and Participants

Researchers were invited through personal contact, announcements at conferences, and the project website (www.i24abc.org) to contribute to the consortium with existing study data, local ethics committee approval, and local written informed consent complying with the Declaration of Helsinki being a prerequisite. A list of contributors is shown in the Supplemental Material. The consortium itself obtained approval from the Tasmanian Health and Medical Human Research Ethics Committee Tasmania (H0015062). The i24abc consortium is an exclusively academic research undertaking, without any influence or financial support from the device manufacturer. For the current analysis, participants without overt cardiovascular disease or diabetes and free from antihypertensive drugs were selected, originating from 21 centers in 14 countries and 5 continents.

Variables used for analysis as well as the inclusion and exclusion criteria were collected systematically at each center and were drawn from medical records or from standardized measurement according to international guidelines of cardiovascular prevention, as appropriate.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Measurements

Twenty-four–hour ambulatory BP monitoring was performed in all study participants with an identical automated brachial oscillometric device (Mobilograph PWA; IEM, Stolberg, Germany), following published recommendations.[33] The device has been validated in adults for 24-hour heart rate,[34] for brachial BP measurement according to recommendations of the British Hypertension Society[35] and the European Society of Hypertension,[36] for 24-hour brachial BP monitoring[37] against a widely used device, and has received clearance from the US Food and Drug Administration and bears the Conformité Européenne mark. The algorithm for assessment of cSBP with the device has been published and validated invasively against high-fidelity pressure measurements[21] and fluid-filled catheter-based measurements.[38,39] Noninvasive comparisons have been performed in European,[21,39,40] Asian,[38,41] and Latin American[42] populations. Briefly, immediately after the conventional brachial oscillometric BP measurement, pulse waves are recorded, using the brachial cuff, at DBP level for ≈10 seconds. After digitalization, a 3-step quality control algorithm is applied.[21] Next, the recorded brachial pulse wave is calibrated with measured brachial BP. With this device, either bSBP/DBP or MAP/DBP can be used for waveform calibration, and the calibration method can be switched post hoc from the raw data. With the device used, MAP/DBP calibration provides cSBP shown to be (1) closer to invasive pressures[16,21,38] in several studies and (2) closer to hypertension-mediated organ damage[29–31] because oscillometric MAP can be measured using this device.[21,43] Thereafter, an aortic pulse waveform is generated by means of a generalized transfer function, and cSBP can be directly read as the maximum of the pulse wave. Their modulus and phase characteristics have been published.[40] Regarding ambulatory measurements with the device, the reproducibility and the feasibility have been confirmed.[27,28]

Data Handling and Statistics

Raw data from all measurements from all sites were anonymized and sent to the Austrian Institute of Technology, Vienna, Austria, to construct the database. Raw pulse waveforms underwent a 3-step quality control as published previously.[21] Homogenous spreadsheets were returned to study sites to enter available clinical characteristics and finally added to the database.

Participants were divided into 6 age groups (18–29, 30–39, 40–49, 50–59, 60–69, and 70–94 years). Results stratified per sex are shown as 24-hour, daytime, and nighttime means (SD) after testing normal distribution with the Kolmogorov-Smirnov test. Values between sexes were compared with the *t* test, values across age groups were compared using the Kruskal-Wallis ANOVA. Twenty-four–hour profiles were constructed, according to the age groups.

We calculated the threshold values for cSBP following to the approach of Head et al[44]: a least product regression between bSBP and cSBP values was performed to obtain a linear regression equation. Subsequently, the central thresholds were obtained by inserting the brachial thresholds into this equation (and rounding the result to the nearest multiple of 5). The thresholds for bSBP were based on the most recent version of the ESC/ESH guidelines,[45] that is, 130, 135, and 120 mm Hg for 24-hour, daytime, and nighttime bSBP, respectively.

In the absence of patient's diaries for the entire cohort, and based on previous recommendations,[46] nighttime/daytime difference (dipping) was defined as nighttime (01:00–06:00) minus daytime (09:00–21:00) values, either in absolute values or as a percentage of daytime SBP. Determinants of percentage nighttime/daytime difference were calculated with multiple linear regression, including as independent variables those that were clinically relevant a priori: age, sex, BMI, daytime values, and heart rate dipping. SBP amplification was defined as bSBP minus cSBP with either calibration method, keeping in mind that this will result in true amplification with SBP/DBP calibration and in apparent amplification with MAP/DBP calibration.[19] Statistical testing was performed with the MedCalc software, version 13.02 (MariaKerke, Belgium).

RESULTS

We included 2423 participants (1275 women) without overt cardiovascular disease or diabetes and free from antihypertensive drugs, from 21 centers worldwide (Table

S1 in the Supplemental Material). Mean age was 51.9 (SD, 15.3; range, 18–94) years. Mean body mass index was 26.5 (SD, 4.4) kg/m^2. Of 168 512 BP measurements performed, 144 509 bSBP measurements and 130 804 cSBP measurements were valid and used for the analysis.

Brachial and Central (Aortic) Blood Pressure

In the entire group, average 24-hour bSBP was 124 mm Hg, average 24-hour $cSBP_{MAP/DBPcal}$ was 128 mm Hg, and average 24-hour $cSBP_{SBP/DBPcal}$ was 115 mm Hg. Percentiles of average 24-hour, daytime, and nighttime cSBP with both calibration methods are shown in Figure 1 and Figure S1 in the Supplemental Material. Average 24-hour DBP was 79 mm Hg, average MAP was 99 mm Hg, and average 24-hour heart rate was 72 bpm. Across all age groups, the average value of 24-hour bSBP was in the normotensive range. As expected, 24-hour $cSBP_{MAP/DBPcal}$ was slightly higher and 24-hour $cSBP_{SBP/DBPcal}$ was lower than bSBP (Table 1; Table S2). Age- and sex-stratified values for MAP, DBP, and heart rate are shown in Table S3.

In a subgroup of 871 participants, average 24-hour bSBP/DBP was below 130/80 mm Hg, average daytime bSBP/DBP was below 135/85 mm Hg, and average nighttime bSBP/DBP was below 120/70 mm Hg, respectively (Table 2). In this true normotensive group, average 24-hour/daytime/nighttime bSBP was 115/118/104 mm Hg, respectively, and the 90th percentile of 24-hour/daytime/nighttime bSBP was 124/128/114 mm Hg. In this subgroup, the 90th percentile of average 24-hour/daytime/nighttime $cSBP_{MAP/DBPcal}$ was 132/133/130 mm Hg, respectively, and the 90th percentile of average 24-hour/daytime/nighttime $cSBP_{SBP/DBPcal}$ was 114/118/106 mm Hg, respectively.

Based on the mean values of the entire group and the 90th percentiles of the truly normotensive group, the results of our regressions, and taking an upper normal limit of average 24-hour bSBP of 130 mm Hg into account,[45] we propose an upper normal limit for average 24-hour $cSBP_{MAP/DBPcal}$ to be 135 mm Hg and an upper normal limit for average 24-hour $cSBP_{SBP/DBPcal}$ to be 120 mm Hg. Based on similar considerations, the upper normal limit for daytime and nighttime $cSBP_{MAP/DBPcal}$ is proposed to be 140 and 135 mm Hg, respectively, and the upper normal limit for daytime and nighttime $cSBP_{SBP/DBPcal}$ is proposed to be 125 and 115 mm Hg, respectively (Table 2).

Twenty-Four–Hour Profiles of Brachial and cSBP

bSBP was lower during nighttime than during daytime in all age groups (Figure 2; Table 3), and bSBP dipping decreased with increasing age (Table 3; Figure S2). Both effects were also seen for $cSBP_{SBP/DBPcal}$, although absolute values of dipping were slightly lower in younger and middle age and approached those from bSBP in older age groups. In strong contrast, for $cSBP_{MAP/DBPcal}$, there was virtually no dipping in the youngest age and an increasing albeit small amount of nocturnal BP fall toward middle age groups that was attenuated again in the elderly (Figure S2).

Determinants of Nighttime/Daytime Difference (Dipping) of bSBP and cSBP

In multivariable models, the dipping of bSBP was mainly and directly related to heart rate dipping, which alone explained one-quarter of the variability of bSBP dipping (partial r, 0.504). Other contributors were daytime bSBP (inversely related) and age (Table S4). The degree of dipping of $cSBP_{SBP/DBPcal}$ was also mainly related to heart rate dipping and daytime $cSBP_{SBP/DBPcal}$. The dipping of

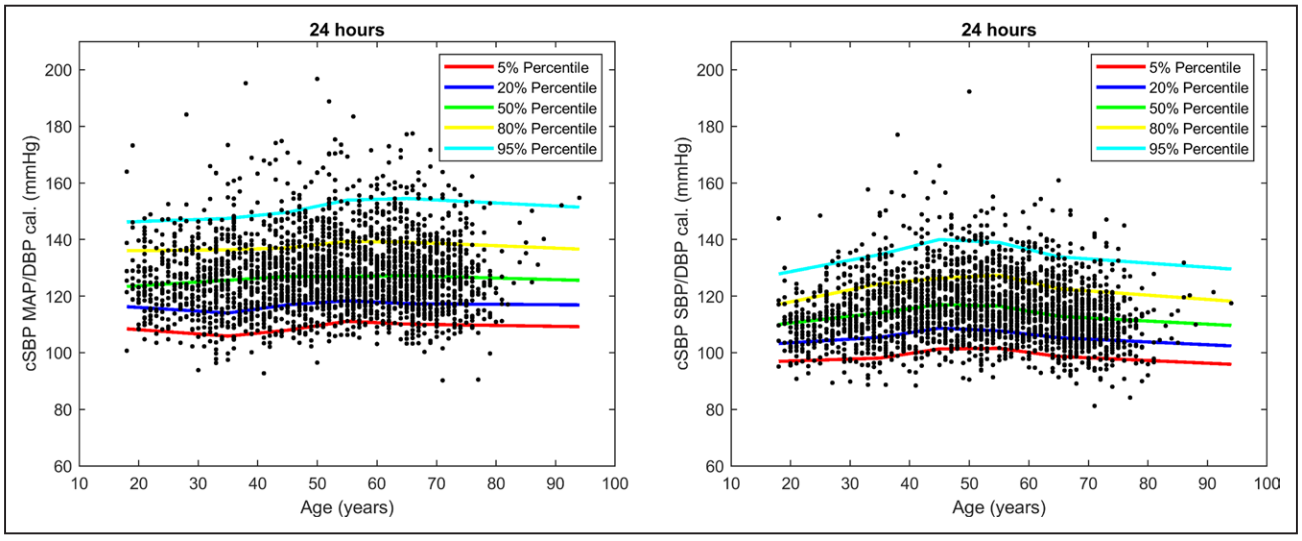

Figure 1. Percentiles of central systolic blood pressure (cSBP; 24-h average values) with 2 calibration methods from age 18 to 94 y.
DBP indicates diastolic blood pressure; MAP, mean arterial pressure; and SBP, systolic blood pressure.

Table 1. Average Values of 24-h, Daytime, and Nighttime Brachial and Aortic Blood Pressures (MAP/DBP and SBP/DBP Calibrations, Stratified by Sex and Age)

Age group		n	bSBP, mm Hg						$cSBP_{MAP/DBPcal}$, mm Hg						$cSBP_{SBP/DBPcal}$, mm Hg					
Years			24 h		Day		Night		24 h		Day		Night		24 h		Day		Night	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Overall	Total	2423	124	12	126	13	116	15	128	13	128	14	125	16	115	12	117	12	109	14
	Men	1148	126	12	129	13	117	14	130	13	131	14	128	15	117	11	119	12	110	14
	Women	1275	122	12	124	13	115	15	125	13	126	13	122	16	114	11	116	12	108	15
18–29	Total	225	121	10	125	11	111	11	126	12	125	13	126	15	111	9	113	10	103	11
	Men	146	123	9	127	10	112	10	129	12	128	12	129	14	112	8	115	9	104	10
	Women	79	118	11	121	12	109	11	119	11	118	11	120	13	108	11	110	11	102	11
30–39	Total	356	124	13	128	14	115	14	126	14	127	14	123	15	115	12	118	13	108	14
	Men	202	128	12	132	13	118	13	131	13	132	13	129	13	118	11	121	12	110	13
	Women	154	119	13	122	13	111	14	119	12	120	13	117	13	112	12	114	13	105	14
40–49	Total	446	126	13	130	13	117	15	128	13	129	13	124	15	118	12	121	12	111	14
	Men	229	127	12	131	12	117	14	130	12	131	12	126	14	119	11	122	11	111	14
	Women	217	125	13	128	14	116	16	125	13	127	14	121	16	117	13	120	13	110	15
50–59	Total	522	126	13	128	14	119	16	129	14	130	14	125	17	118	12	120	12	111	15
	Men	235	128	13	131	14	120	16	133	15	133	15	129	17	120	12	122	13	113	15
	Women	287	124	12	126	13	117	15	127	12	128	12	123	16	116	11	118	12	110	14
60–69	Total	549	123	12	125	12	118	16	129	13	129	14	126	16	114	11	116	11	109	15
	Men	218	124	13	126	13	119	16	130	14	131	15	128	17	115	12	117	12	110	15
	Women	331	122	11	124	12	117	16	128	13	128	13	125	16	113	11	115	11	108	15
70–94	Total	325	120	11	122	11	114	14	127	12	127	12	124	15	111	10	112	10	105	14
	Men	118	119	11	121	11	114	13	128	13	128	13	125	15	109	10	111	10	104	13
	Women	207	121	11	122	11	114	15	127	12	127	12	124	15	111	10	113	10	105	14

Differences between age categories were statistically significant ($P<0.001$ for all tests; Kruskal-Wallis ANOVA) for all parameters shown. bSBP indicates brachial systolic blood pressure; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; and MAP, mean arterial pressure.

$cSBP_{MAP/DBPcal}$ was mainly and inversely related to daytime $cSBP_{MAP/DBPcal}$, and the relationship with heart rate dipping was weak (Figure 3).

Systolic Blood Pressure Amplification During 24 Hours, Daytime, and Nighttime

With SBP/DBP calibration, 24-hour SBP amplification was relatively stable across all age groups (Table S5; Figure S3). Furthermore, SBP amplification was higher during daytime as compared with nighttime, in particular in younger age, whereas this difference tended to disappear in old age. With MAP/DBP calibration, we observed an apparently inverse amplification, which was particularly pronounced during nighttime (due to the lack of nighttime dipping of $cSBP_{MAP/DBPcal}$ in the presence of nighttime dipping of bSBP). This apparently inverse amplification was more pronounced in younger age (up to 14.6 mm Hg) and decreased in middle and older age (to a minimum of 4.1 mm Hg; Figure S3).

The nighttime/daytime difference (dipping) of SBP amplification was closely related to the dipping of heart rate: r=0.76 with MAP/DBP calibration and r=0.42 with SBP/DBP calibration and thus the main driver of the different dipping patterns of bSBP and cSBP, in particular, $cSBP_{MAP/DBPcal}$.

Table 2. Proposed Upper Normal Limits for Ambulatory cSBP in 2021*

	bSBP ESC/ESH GL	bSBP average value all participants current study	bSBP 90th percentile true normotensives* current study	Proposal $cSBP_{MAP/DBPcal}$	$cSBP_{MAP/DBPcal}$ average value all participants current study	$cSBP_{MAP/DBPcal}$ 90th percentile true normotensives* current study	Proposal $cSBP_{SBP/DBPcal}$	$cSBP_{SBP/DBPcal}$ average value all participants current study	$cSBP_{SBP/DBPcal}$ 90th percentile true normotensives* current study
24 h	130	124	124	135	128	132	120	115	114
Daytime	135	126	128	140	128	133	125	117	118
Nighttime	120	116	114	130	125	130	115	109	106

True normotensives were defined as average 24-h BP <130/80 mm Hg, average daytime BP <135/85 mm Hg, and average nighttime BP <120/70 mm Hg. BP indicates blood pressure; bSBP, brachial systolic blood pressure; cSBP, central systolic blood pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension; and GL, guideline.

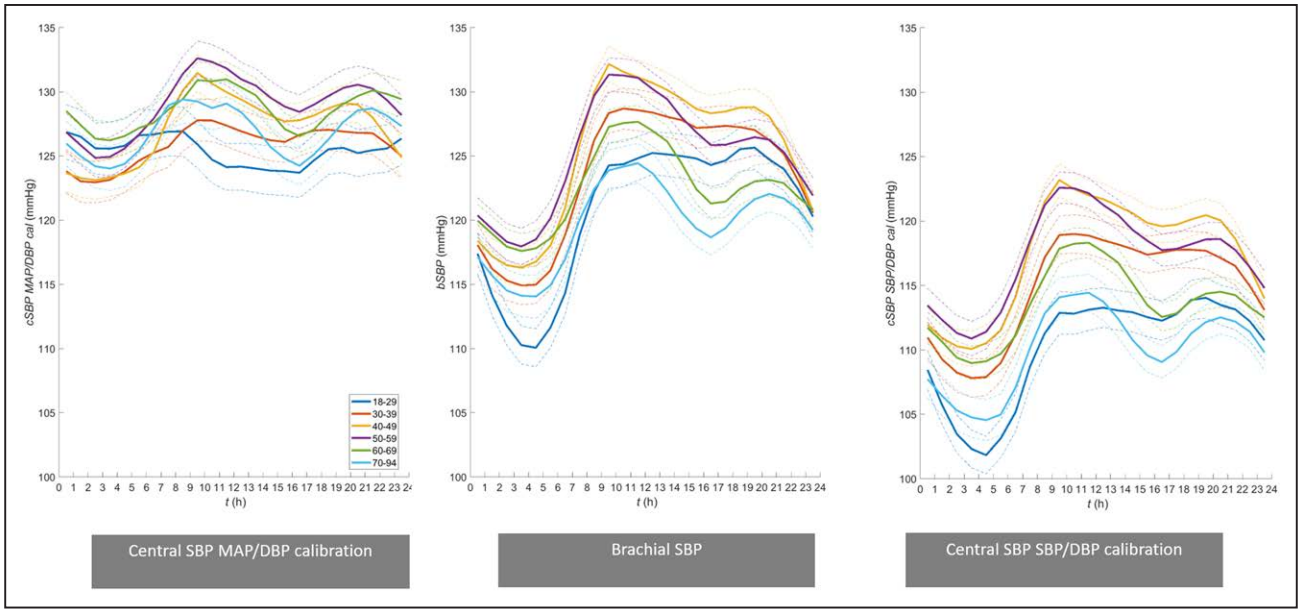

Figure 2. Twenty-four–hour profiles of brachial and central systolic blood pressure (cSBP; 2 calibration methods), stratified by age. Solid lines are mean values, dashed lines 95% CIs. DBP indicates diastolic blood pressure; MAP, mean arterial pressure; and SBP, systolic blood pressure.

Twenty-Four–Hour Profiles of bSBP and cSBP in Men and Women

In the younger age groups, men had higher BPs, as compared with women (Table 1). The difference was largest with regard to $cSBP_{MAP/DBPcal}$ and amounted a maximum of 12 mm Hg in individuals 30 to39 years old. In the older age groups, differences were smaller. Percentiles of average 24-hour, daytime, and nighttime cSBP with both calibration methods are shown in Figures S4 and S5.

DISCUSSION

In this study, we describe for the first time reference values and 24-hour profiles of cSBP, based on >140 000 individual BP measurements from a worldwide research consortium. We present results for 2 technical options of assessing cSBP, based on different waveform calibration methods. Moreover, our results shed new light on nighttime/daytime SBP variability (dipping), relating diurnal changes in SBP and heart rate.

Based on brachial 24-hour BP, average systolic values in all age groups were well below 130 mm Hg (121–126 mm Hg), which is the upper limit of normal BP according to the European Society of Cardiology/European Society of Hypertension guidelines.[45] Corresponding 24-hour average cSBP values could, therefore, be assigned as preliminary thresholds, until outcome-based values become available, and would be, rounded for simplification, 135 mm Hg for $cSBP_{MAP/DBPcal}$ and 120 mm Hg for $cSBP_{SBP/DBPcal}$ (graphic abstract). In the large Reference Value project[3] for office-based cSBP, data were standardized across different devices and techniques, yielding values roughly equivalent to our SBP/DBP calibration. In that project, the 50th percentile of cSBP of the so-called normal population with high-normal BP (bSBP, 133 mm Hg) was 126 mm Hg in women and 122 mm Hg in men. In a recent analysis, based on

Table 3. Nighttime to Daytime Difference (Dipping) of Brachial and Central Blood Pressures As Well As Heart Rate, Stratified by Age

Age group, y	n	bSBP, mm Hg	bSBP, %	$cSBP_{MAP/DBPcal}$, mm Hg	$cSBP_{MAP/DBPcal}$, %	$cSBP_{SBP/DBPcal}$, mm Hg	$cSBP_{SBP/DBPcal}$, %	MAP, mm Hg	MAP, %	DBP, mm Hg	DBP, %	Heart rate, bpm	Heart rate, %
18–29	225	−13.5	−10.6	1.0	1.1	−10.1	−8.7	−13.6	−13.5	−13.7	−17.2	−15.7	−19.8
30–39	356	−12.4	−9.5	−3.4	−2.5	−9.8	−8.2	−12.1	−11.4	−11.9	−13.9	−13.5	−16.5
40–49	446	−12.7	−9.6	−5.6	−4.3	−10.2	−8.3	−12.2	−11.2	−11.7	−13.3	−11.9	−14.7
50–59	522	−9.7	−7.2	−5.0	−3.7	−8.3	−6.6	−9.3	−8.5	−9.0	−10.1	−7.4	−9.2
60–69	549	−6.9	−5.3	−2.8	−2.0	−6.5	−5.4	−6.7	−6.6	−6.6	−8.3	−6.7	−8.8
70–94	325	−7.6	−6.1	−2.9	−2.1	−7.3	−6.4	−7.5	−7.7	−7.4	−10.1	−8.4	−11.6

Data are presented either as absolute changes (night-day) or percentage (%) of change (night-day/day). Values across age categories were statistically significant ($P<0.001$ for all tests; Kruskal-Wallis ANOVA) for all parameters shown. bSBP indicates brachial systolic blood pressure; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; and MAP, mean arterial pressure.

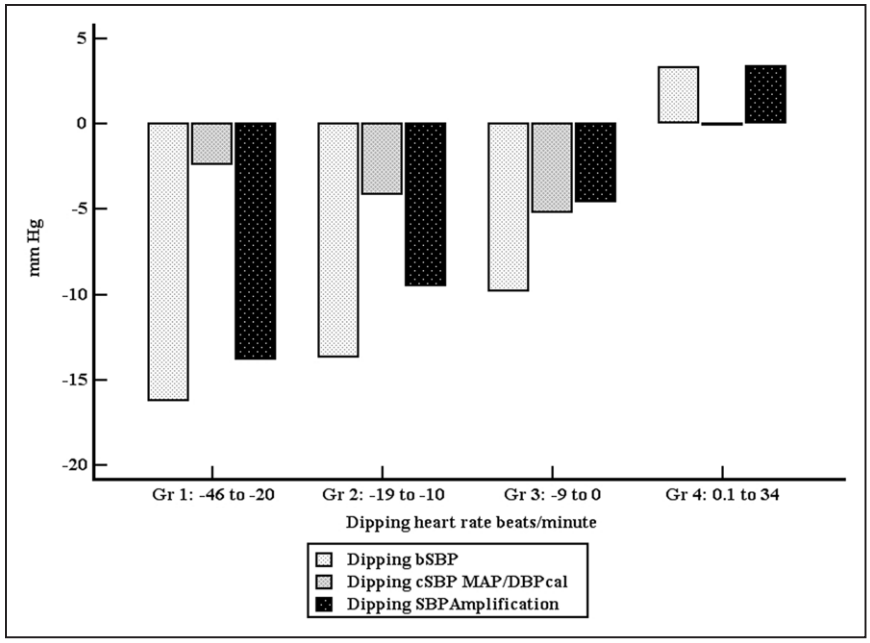

Figure 3. Relationship between dipping of heart rate, divided into 4 groups, on the one hand and dipping of brachial systolic blood pressure (bSBP) and central systolic blood pressure (cSBP)$_{\text{MAP/DBP calibration}}$, as well as apparent systolic blood pressure (SBP) amplification on the other hand.

Dipping was calculated as nighttime minus daytime values. Note that dipping of brachial SBP is strongly related to dipping of heart rate, whereas dipping of cSBP$_{\text{MAP/DBP calibration}}$ is not. DBP indicates diastolic blood pressure; and MAP, mean arterial pressure.

triplicate office-based measurements with the Mobilograph device in 5632 participants with cardiovascular risk factors, mean bSBP was 133 (men) and 135 (women) mm Hg, and the corresponding cSBP$_{\text{SBP/DBPcal}}$ was 125 (men) and 127 (women) mm Hg.[47] As 24-hour average BP values are generally lower than office blood pressures, our findings regarding cSBP$_{\text{SBP/DBPcal}}$ are in good agreement. Similarly, an outcome-based threshold for office cSBP was proposed in a study from Taiwan[48] to be 130 mm Hg. Again, in this study, calibration was close to the SBP/DBP method of our work, and given the differences in office- and 24-hour SBP, results were in accordance with our study.

Given the potential of new, cuff-based methods to assess cSBP, a widespread application in clinical routine is conceivable.[49] One potential concern, which has been raised repeatedly, is that cSBP is too highly correlated with bSBP to provide meaningful additional information.[50] Indeed, in a recently reported meta-analysis of cSBP derived from radial tonometry, cardiovascular end points and mortality were not more closely associated with cSBP than bSBP.[51] These findings have been confirmed in a recent, large, population-based study from Canada, where tonometry-derived cSBP was statistically superior to bSBP but with limited additional clinical value in predicting cardiovascular events.[10] Notably, in both studies, cSBP was assessed with SBP/DBP calibration, yielding a correlation between bSBP and cSBP of 0.97. We have addressed this issue earlier for office BP in a more diverse group of 7409 individuals[52] and observed that (1) correlation is close when investigated across the entire spectrum of SBP but much weaker when clinically more relevant BP categories (ie, optimal, normal, high-normal, etc) are taken into account, and (2) correlation with bSBP is closer with cSBP$_{\text{SBP/DBPcal}}$, as compared with cSBP$_{\text{MAP/DBPcal}}$. We confirmed and extended these findings to average 24-hour SBPs (Table S6), showing for instance a Pearson's correlation coefficient between mean 24-hour bSBP and mean 24-hour cSBP$_{\text{MAP/DBPcal}}$ in the group of individuals with 24-hour bSBP between 121 and 130 mm Hg as low as 0.35, which obviously should allow additive information from cSBP. From a clinical point of view, based on our proposed thresholds for 24-hour cSBP, 149 of 1780 participants would be diagnosed as hypertensive, and 179 of 643 would be diagnosed as normotensive, had cSBP$_{\text{MAP/DBPcal}}$ instead of bSBP been used for diagnosis.

Nighttime/daytime difference variability (dipping) of BP and heart rate has been long detected, using invasive[53] and noninvasive[54] recordings, and has been attributed to a reduction of responsiveness to external stimuli/change in activity, together with a diminished level of sympathetic nervous activity,[54] and changing to the supine position. Dipping of DBP (14%–17%) is somewhat more pronounced than dipping of (brachial) SBP (10%–12%),[55] as shown in our data set as well. Many, if not most body functions, exhibit clear circadian rhythms,[56] and many among them, including the sympathetic nervous system, body temperature, and kidney function, show a decrease during nighttime. However, these nocturnal changes, for instance in glomerular filtration rate and renal plasma flow, may have only weak associations[57] with systemic hemodynamics and brachial BP. Other measures, such as cerebral blood flow[58] or peripheral subcutaneous blood flow,[59] are even the highest during nighttime but again have only weak if any associations with BP. The probably most intriguing finding of the current study, that is, the absence of nocturnal dipping of cSBP$_{\text{MAP/DBPcal}}$, particularly in young individuals, should be viewed within this context.

The strongest determinant of dipping of bSBP was dipping of heart rate, followed by daytime bSBP (initial value) and age. In contrast, dipping of $cSBP_{MAP/DBPcal}$ was only weakly associated with dipping of heart rate. Therefore, we propose a new integrative model for bSBP dipping, stressing the role of heart rate dipping: whereas SBP at the aorta and central arteries exhibits no or only little decrease during nighttime, SBP dipping is exaggerated at the usual measuring site of BP, which is the brachial artery, in part, due to accompanying dipping in heart rate, because the difference between cSBP and bSBP (amplification) strongly depends on heart rate[3,60] (Figure S6). Although, when using the Mobilograph PWA device, we prefer the MAP/DBP calibration for several reasons, among them a better concordance with true invasive cSBP,[16,21] a closer relationship with hypertension-associated organ damage,[23,29–31] and a closer association with clinical end points[25]; it should be noted that a smaller dipping of SBP amplification was noted for $cSBP_{SBP/DBPcal}$ as well.

Our results have to be considered in the light of potential strengths and limitations. Among the strong points, we took advantage of the raw data of a worldwide large data set of measurements with a single device, which allows post hoc quality control, data harmonization, and recalculation of different methods for waveform calibration. Reassuring is also the fact that SBP amplification and its changes from daytime to nighttime have been observed with other devices[61,62] and calibration methods[63,64] as well, although the differences were not as pronounced as with our preferred MAP/DBP calibration method. One limitation is the fact that our results related to nighttime/daytime difference amplification are not yet based on clinical outcomes. Furthermore, based on previous recommendations,[46] we relied on fixed time intervals for definition of daytime and nighttime, rather than utilizing individual patient diaries. Although this is not expected to be a major limitation, the relevant results should be interpreted with this in mind. Finally, our findings, obtained with the Mobilograph device in all centers, cannot be necessarily generalized to other noninvasive central BP devices.

PERSPECTIVES

We present reference values for ambulatory 24-hour cSBP from a worldwide research consortium. These thresholds need to be tested prospectively in longitudinal studies with clinical outcomes. Furthermore, we challenge the widely held view on nocturnal SBP dipping and propose that the nighttime fall in SBP is largely confined to the brachial artery, mediated to an important degree by the nighttime fall in heart rate. The physiological and pathophysiological consequences should be further explored.

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