ORIGINAL ARTICLE

ECG Voltage in Relation to Peripheral and Central Ambulatory Blood Pressure

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BACKGROUND
The heart ejects in the central elastic arteries. No previous study in workers described the diurnal profile of central blood pressure (BP) or addressed the question whether electrocardiogram (ECG) indexes are more closely associated with central than peripheral BP.

METHODS
In 177 men (mean age, 29.1 years), we compared the associations of ECG indexes with brachial and central ambulatory BP, measured over 24 hours by the validated oscillometric Mobil-O-Graph 24h PWA monitor.

RESULTS
From wakefulness to sleep, as documented by diaries, systolic/diastolic BP decreased by 11.7/13.1 mm Hg peripherally and 9.3/13.6 mm Hg centrally, whereas central pulse pressure (PP) increased by 4.3 mm Hg ($P < 0.0001$). Over 24 hours and the awake and asleep periods, the peripheral-minus-central differences in systolic/diastolic BPs averaged 11.8/−1.6, 12.7/−1.8, and 10.3/−1.2 mm Hg, respectively ($P < 0.0001$).

Cornell voltage and index averaged 1.18 mV and 114.8 mV·ms. Per 1-SD increment in systolic/diastolic BP, the Cornell voltages were 0.104/0.086 mV and 0.082/0.105 mV higher in relation to brachial 24-hour and asleep BP and 0.088/0.90 mV and 0.087/0.107 mV higher in relation to central BP. The corresponding estimates for the Cornell indexes were 9.6/8.6 and 8.2/10.5 mV·ms peripherally and 8.6/8.9 and 8.8/10.7 mV·ms centrally. The regression slopes ($P \geq 0.067$) and correlation coefficients ($P \geq 0.088$) were similar for brachial and central BP. Associations of ECG measurements with awake BP and PP were not significant.

CONCLUSIONS
Peripheral and central BPs run in parallel throughout the day and are similarly associated with the Cornell voltage and index.

Keywords: ambulatory blood pressure; blood pressure; blood pressure monitoring; central blood pressure; clinical science; ECG voltage; hypertension.

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Ambulatory blood pressure (BP) monitoring provides information not only on the BP level but on the diurnal BP profile as well. The Mobil-O-Graph 24h PWA Monitor (I.E.M. GmbH, Stolberg, Germany) is a portable monitor validated for the recording of brachial BP.[1] It includes the ARCSolver software,[2] which allows estimating central BP. We[3] and other researchers[4] validated the central hemodynamic measurements in resting conditions against a tonometric[3] or invasive standard.[4]

The heart ejects blood directly into the central elastic arteries. Compared with conventional brachial pressure, several[5] but not all[6] studies suggest that central pressure is more strongly related to target organ damage and the incidence of cardiovascular complications.[7,8] In view of the close anatomical proximity of central arteries to the heart and the strong association of electrocardiogram (ECG) voltages with BP,[9] we considered that relating ECG

voltages to peripheral and central BP might generate new insights. In fact, no previous study in workers described the diurnal profile of central BP or addressed the question whether ECG voltages are more closely associated with central than peripheral ambulatory BP. We addressed these issues in male workers enrolled in the Study for Promotion of Health in Recycling Lead (SPHERL [NCT02243904]).[10]

METHODS

Study population

SPHERL complies with the Helsinki declaration.[11] The Ethics Committee of the University Hospitals Leuven approved the study. A detailed protocol has been published elsewhere.[10] In short, the nursing staff at lead acid battery manufacturing and recycling plants in the United States enrolled new hires for detailed health evaluations prior to blood lead elevations associated with occupational exposure to lead. Of 490 men joining the work force and invited to participate, 336 provided informed written consent (participation rate, 68.6%). Of those, 284 had both their ECG and 24-hour ambulatory BP recorded. We excluded 107 participants, because the central 24-hour ambulatory BP did not meet quality criteria (see below; $n = 100$), because their ECG did not include the precordial leads ($n = 4$), or because they had incomplete or complete right or left bundle branch block ($n = 3$). Thus, the number of men statistically analyzed totaled 177.

Electrocardiography

We used the Cardiax device (RDSM Medical Devices, Hasselt, Belgium) to record 12-lead ECGs at a speed of 25 mm/s with the calibration set at 1 mV/cm. Voltages and QRS duration were measured to the nearest 0.1 mV and 1 ms, respectively. Low-frequency noise originating from movement, baseline wander, and respiration and high-frequency noise emanating from power-lines or radiated electromagnetic influence were filtered before the final signal acquisition. In accordance with the recommendations of the American Heart Association,[12] cutoff values were set at 0.05 Hz and 150 Hz for the low- and high-frequency filters, respectively. The Cornell voltage was the sum of the S wave in precordial lead V_3 and the R wave in limb aVL.[13] The Cornell index was Cornell voltage multiplied by the QRS duration from its earliest onset to its latest ending across the 12 ECG leads.[14] Cornell voltage and index have high reproducibility and specificity to detect left ventricular hypertrophy[15,16] and are therefore recommended to be used in studies of BP.[17] The Cardiax software allows exporting all ECG measurements into an Excel workbook, which was subsequently imported into SAS, using standardized programming statements, thereby excluding observer-introduced bias. Two certified cardiologists (W.-Y.Y. and Z.-Y.Z.) checked the performance of the programming against a visual read of 20 Cornell indexes below the 5th or above the 95th percentile of their distributions.

Ambulatory measurements

We programmed oscillometric Mobil-O-Graph 24h PWA monitors (I.E.M. GmbH)[1] fitted with the appropriate cuff size to obtain readings at intervals of 15 and 30 minutes during the awake and asleep periods of the day. These intervals were determined from the diary completed by the workers during ambulatory monitoring, which was carried out on normal working days. If the ambulatory monitoring lasted over 1 day, only the recordings during the first 24 hours were analyzed. Intraindividual means of the ambulatory measurements were weighted by the time interval between successive readings.[18]

The ARCSolver algorithm, as implemented in Mobil-O-Graph 24h PWA monitor reconstructs the central pulse wave by applying a transfer function.[2] Recordings of the central hemodynamics are carried out at the diastolic BP level (±5 mm Hg) for approximately 10 seconds, using a high-fidelity pressure sensor (MPX5050, Freescale, Tempe, AZ). The transfer function implemented in the ARCSolver software includes an algorithm for checking quality of the signal on a scale from 1 to 4. Results of excellent or good quality are labelled 1 and 2 and respectively include over 80% or over 50% of the cardiac cycles during signal acquisition. Grade 3 results are estimated from less than 50% of the recorded cycles and are of poor quality. Grade 4 indicates missing results, because of insufficient signal quality. We included central hemodynamic measurements in the analyses only if graded 1 or 2. In addition, the ARCSolver software excludes central hemodynamic measurements obtained at a cuff pressure that is not within 5 mm Hg of diastolic BP. As mentioned before, the aforementioned quality standards for central BP eliminated 100 participants from analysis.

Other measurements

Trained nurses measured the participants' anthropometric characteristics and office BP. They administered a questionnaire to collect information about each worker's medical history, smoking and drinking habits, and intake of medications. Office BP was the average of 5 consecutive readings measured after participants had rested in the sitting position for at least 5 minutes.[19] Standard cuffs had a 12 × 24 cm inflatable bladder, but, if upper arm girth exceeded 31 cm, larger cuffs with a 15 × 35 cm bladder were used. Office hypertension was a BP of at least 140 mm Hg systolic or 90 mm Hg diastolic. The corresponding thresholds for the 24-hour brachial BP were 130 mm Hg and 80 mm Hg. Patients on antihypertensive drug treatment were categorized as hypertensive irrespective of type of BP measurement. Skinfold thickness was the average of measurements obtained at 3 sites, the triceps, subscapular, and supra-iliac area by means of the Harpenden Skinfold Caliper (Bedfordshire, UK) providing a constant pressure of 0.01 kg per mm^2 (0.098 N/mm^2) at all openings of the 90 mm^2 anvils.

Plasma glucose and serum total and high-density lipoprotein were measured on venous blood samples obtained after 8 hours of fasting. Diabetes mellitus was a self-reported diagnosis, a fasting plasma glucose of 7.0 mmol/l (126 mg/dl) or higher,[20] or use of antidiabetic drugs. We estimated glomerular filtration rate from serum cystatin C, using the Chronic Kidney Disease Epidemiology Collaboration cystatin C equation.[21]

Statistical analysis

For statistical analysis and database management, we used SAS software, version 9.4 (SAS Institute, Cary, NC). We

compared means and proportions, using a *t*-test for paired or unpaired observations, as appropriate, and the χ2-statistic, respectively. Statistical significance was an *α*-level of 0.05.

From the workers' diaries, we identified the awake and sleeping periods. Next, we plotted 2-hourly averages of the ambulatory measurements of central BP level and the heart rate over 24 hours. Two criteria were applied to differentiate a significant diurnal rhythm from random variability. First, in all participants combined, we compared mean awake and asleep BP levels and heart rate. Second, in individual participants, we used the runs test with a one-sided probability of 5%.[22] We used linear regression to assess the relation of the ECG variables with peripheral and central BPs. We compared the regression slopes relating the ECG indexes to peripheral and central BP, using the TEST statement, as implemented in the PROC REG procedure of the SAS package. To check that collinearity between peripheral and central BPs did not bias our results, we applied two approaches. First, we calculated the residual of central BP removing the contribution to its variance of peripheral BP, or *vice versa*, and we introduced the residual along with the alternative BP in the regression models. Second, we pairwise compared the correlations of the ECG indexes with peripheral and central BP, using the Hotelling–William test.[23] Finally, we checked the consistency

of our observations in sensitivity analyses adjusted for body mass index and skinfolds.

RESULTS

Characteristics of participants

The 177 participants were on average (±SD) 29.1 ± 10.4 years old (5th to 95th percentile interval, 19.1–52.2). The Cornell voltage averaged 1.18 ± 0.60 mV (5th to 95th percentile interval, 0.29–2.34) and the Cornell index 114.8 ± 60.8 mV·ms (5th to 95th percentile interval, 25.5–230.4). Height averaged 1.75 ± 0.07 m, weight 86.1 ± 19.7 kg, office systolic/diastolic BP 119.9 ± 9.8/80.5 ± 8.5 mm Hg, the 24-hour brachial BP 124.7 ± 9.7/73.8 ± 8.1 mm Hg, and total and high-density lipoprotein cholesterol 4.47 ± 0.96 mmol/l and 1.21 ± 0.28 mmol/l, respectively. No participant had a history of cardiovascular disease, while 75 (32.2%) were smokers, 88 (49.7%) reported regular alcohol intake, 2 (1.1%) had diabetes mellitus, and 35 (19.8%) had office hypertension, of whom 11 (31.4%) were on antihypertensive drug treatment. Table 1 lists the main characteristics of the participants by the median (107.5 mV·ms) of the Cornell index. The workers with higher index had greater body mass index (*P* =

Table 1. Characteristics of participants by median ECG Cornell index

Characteristic	Cornell < 107.5 (*n* = 88)	Cornell ≥ 107.5 (*n* = 89)	All (*n* = 177)
Number (%) of participants			
Current smoking	28 (31.8)	29 (32.6)	57 (32.2)
Drinking alcohol	46 (52.3)	42 (47.7)	88 (49.7)
Office hypertension	13 (14.8)	22 (24.8)	35 (19.8)
24-Hour ambulatory hypertension	24 (27.3)	42 (47.2)[†]	66 (37.3)
On antihypertensive treatment	1 (1.1)	10 (11.2)[†]	11 (6.2)
Diabetes mellitus	0 (0.0)	2 (2.3)	2 (1.1)
Mean (SD) characteristic			
Age (year)	27.4 ± 8.8	30.9 ± 11.7	29.1 ± 10.4
Body mass index (kg/m^2)	27.0 ± 4.9	29.2 ± 6.0*	28.1 ± 5.6
Skinfolds (cm)	2.26 ± 0.89	2.42 ± 0.95	2.34 ± 0.92
Waist-to-hip ratio	0.96 ± 0.08	0.98 ± 0.08	0.97 ± 0.08
Office blood pressure			
Systolic (mm Hg)	117.9 ± 8.5	121.9 ± 10.6[†]	119.9 ± 9.8
Diastolic (mm Hg)	78.9 ± 8.4	82.1 ± 8.5*	80.5 ± 8.5
Office heart rate (bpm)	73.9 ± 10.5	73.9 ± 11.7	73.9 ± 11.1
Laboratory examination			
Total/HDL cholesterol ratio	3.80 ± 1.05	3.97 ± 1.31	3.88 ± 1.19
Cystatin C (mg/l)	0.66 ± 0.10	0.68 ± 0.11	0.67 ± 0.11
eGFR (ml/min/1.73 m^2)	131.9 ± 12.4	127.3 ± 15.2*	129.6 ± 14.0

Office hypertension was a blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic; the corresponding thresholds for the 24-hour brachial blood pressure were ≥130 mm Hg and ≥80 mm Hg. Patients on antihypertensive drug treatment were categorized as hypertensive irrespective of type of blood pressure measurement. Diabetes mellitus was a self-reported diagnosis, a fasting plasma glucose of ≥7.0 mmol/l or use of antidiabetic drugs. eGFR was derived from serum cystatin C, using the Chronic Kidney Disease Epidemiology Collaboration Cystatin C equation. Significance of the difference between categories: *$P \le 0.05$; †$P \le 0.01$. Abbreviations: ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

0.011) and higher BP ($P \leq 0.020$), but lower estimated glomerular filtration rate ($P = 0.028$). The other characteristics were similar between the two groups ($P \geq 0.10$).

Peripheral and central ambulatory measurements

Number of measurements. For brachial BP, the median number of readings averaged to estimate mean 24-hour awake and asleep BP was 35 (interquartile range, 30–43; 5th–95th percentile interval, 21–54), 22 (17–29 and 12–40), and 11 (7–17 and 5–23). For central BP, the corresponding numbers were 27 (20–33 and 14–44), 16 (12–24 and 7–35), and 8 (5–11 and 3–20), respectively.

Levels of central vs. peripheral BP. Over 24 hours (Table 2 and Figure 1), central systolic and pulse pressure (PP) were

11.8 mm Hg (95% confidence interval [CI], 11.3–12.4) and 13.4 mm Hg (CI, 12.9–14.0) ($P < 0.0001$) lower than the brachial levels. The same was true during the awake and asleep periods of the recordings with BP differences amounting to 12.7 mm Hg (CI, 12.0–13.3) systolic and 14.4 mm Hg (CI, 13.8–15.1) for PP during waking hours and 10.3 mm Hg (CI, 9.71–10.9) and 11.5 mm Hg (CI, 10.9–12.1), respectively, during sleep. The average differences of peripheral-minus-central diastolic BP ($P < 0.0001$; Table 2) amounted to –1.58 mm Hg (CI, –1.64 to –1.53) over 24 hours, –1.78 mm Hg (CI, –1.84 to –1.72) awake and –1.23 (CI, –1.32 to –1.13) asleep.

Levels of awake vs. asleep BP. Peripheral BP (Table 2) decreased from wakefulness to sleep by 11.7 mm Hg systolic (CI, 10.0–13.4; $P < 0.0001$) and 13.1 mm Hg diastolic

Table 2. Ambulatory heart rate and blood pressure by median ECG Cornell index

Characteristic	Cornell < 107.5 (*n* = 88)	Cornell ≥ 107.5 (*n* = 89)	All (*n* = 177)	*P*
Heart rate (bpm)				
24-Hour	71.5 ± 7.8	73.3 ± 8.9	72.4 ± 8.4	0.16
Awake	77.4 ± 8.9	79.0 ± 11.1	78.3 ± 10.0	0.29
Asleep	60.2 ± 9.3	62.5 ± 9.8	61.4 ± 9.6	0.11
Blood pressure				
Peripheral systolic				
24-Hour	123.0 ± 8.8	126.4 ± 10.3	124.7 ± 9.7	0.020
Awake	127.5 ± 10.2	130.2 ± 10.8	128.9 ± 10.5	0.078
Asleep	115.0 ± 11.7	119.3 ± 12.9	117.2 ± 12.5	0.021
Peripheral diastolic				
24-Hour	72.4 ± 7.7	75.3 ± 8.3	73.8 ± 8.1	0.016
Awake	77.3 ± 8.5	79.5 ± 8.7	78.4 ± 8.7	0.098
Asleep	63.1 ± 8.7	67.6 ± 10.6	65.4 ± 9.9	0.0026
Peripheral pulse pressure				
24-Hour	50.7 ± 7.3	51.1 ± 8.5	50.9 ± 7.9	0.69
Awake	50.1 ± 8.6	50.8 ± 9.2	50.4 ± 8.9	0.64
Asleep	51.9 ± 8.7	51.8 ± 8.9	51.8 ± 8.8	0.92
Central systolic				
24-Hour	111.3 ± 8.5	114.5 ± 9.8	112.9 ± 9.3	0.023
Awake	115.1 ± 9.4	117.3 ± 9.9	116.2 ± 9.7	0.13
Asleep	104.6 ± 11.4	109.2 ± 12.9	106.9 ± 12.4	0.012
Central diastolic				
24-Hour	73.9 ± 7.6	76.9 ± 8.3	75.4 ± 8.1	0.012
Awake	79.1 ± 8.6	81.3 ± 8.8	80.2 ± 8.7	0.087
Asleep	64.3 ± 8.7	68.9 ± 10.6	66.6 ± 10.0	0.0019
Central pulse pressure				
24-Hour	37.4 ± 5.1	37.5 ± 6.2	37.5 ± 5.7	0.87
Awake	36.0 ± 6.1	36.0 ± 6.7	36.0 ± 6.4	0.96
Asleep	40.3 ± 7.8	40.3 ± 7.8	40.3 ± 7.8	0.97

Values are mean ± SD. *P* indicates the significance of the difference between the participants with Cornell voltage <107.5 and ≥107.5mV·ms (median). Abbreviation: ECG, electrocardiogram.
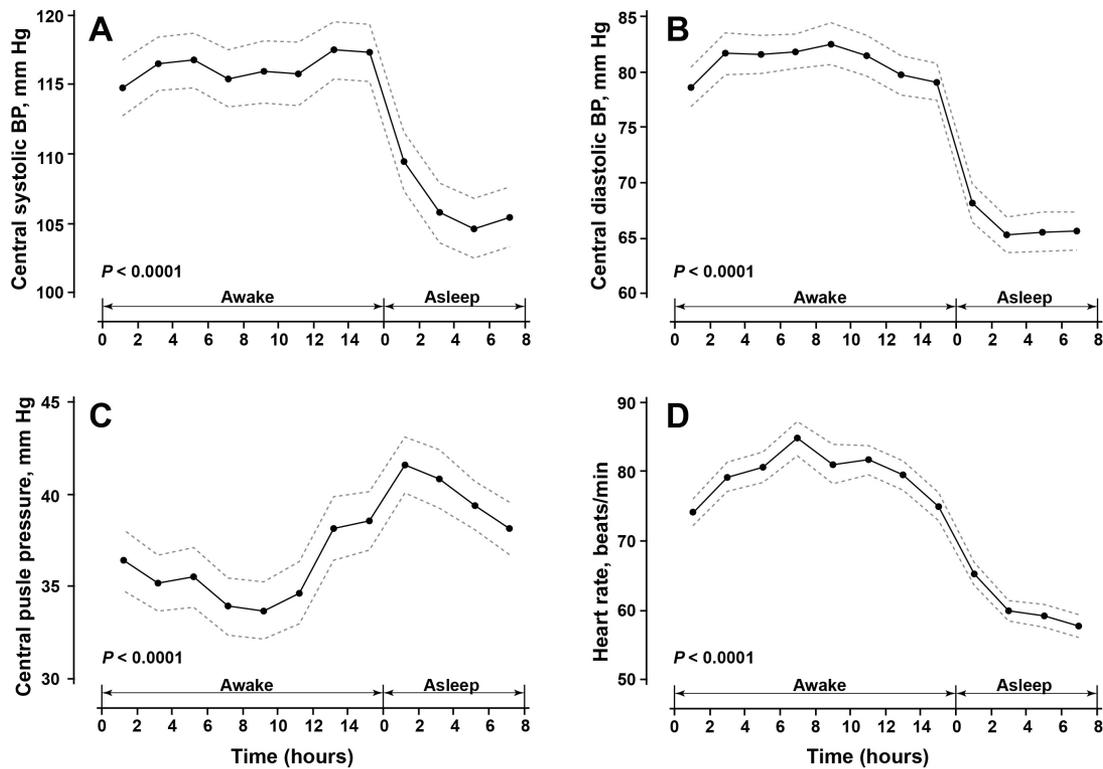
Figure 1. Diurnal profiles in 177 study participants of central systolic pressure (**a**), central diastolic pressure (**b**), central pulse pressure (**c**), and heart rate (**d**). Plotted values are 2 hourly mean with 95% confidence interval. *P* values are for the comparison between awake and asleep averages.

(CI, 11.8–14.3; *P* < 0.0001), whereas peripheral PP slightly increased (1.4, CI, 0.1–2.6; *P* = 0.029). Compared with BP during waking hours (Table 2 and Figure 1), central BP during sleep decreased by 9.3 mm Hg systolic (CI, 7.7–10.9; *P* < 0.0001) and 13.6 mm Hg diastolic (CI, 12.3–14.9; *P* < 0.0001), whereas central PP increased by 4.3 mm Hg (CI, 3.1–5.5; *P* < 0.0001). The awake–asleep decrease in systolic BP (11.7 vs. 9.3 mm Hg) was 2.4 mm Hg (CI, 1.7–3.1; *P* < 0.0001) greater peripherally than centrally. In contrast, the awake–asleep decrease in diastolic BP (13.1 vs. 13.6 mm Hg) was 0.6 mm Hg (CI, 0.4–0.7; *P* < 0.0001) less peripherally than centrally. Consequently, the awake–asleep change in PP (1.4 vs. 4.3 mm Hg) was 2.9 mm Hg (CI, 2.2–3.7 mm Hg; *P* < 0.0001) less peripherally than centrally. Based on comparison of the awake and asleep BP levels, there was in all participants combined significant diurnal BP rhythmicity. When we applied the runs test to individual 24-hour BP recording, among 177 workers, there was a significant (*P* < 0.05) diurnal rhythm in 96 (54.2%) for systolic pressure, in 104 (58.8%) for diastolic pressure, in 69 (39.0%) for PP, and in 129 (72.9%) for heart rate.

Associations of ECG indexes with peripheral vs. central BP

The ECG indexes showed formally significant (*P* ≤ 0.05) or borderline significant (*P* ≤ 0.07) positive associations with 24-hour and asleep systolic and diastolic BP (Table 3). In contrast, the ECG indexes were unrelated to central and peripheral PP (*P* ≥ 0.29). Per 1-SD increment in systolic pressure, the Cornell voltages were 0.104/0.086 mV and

0.082/0.105 mV higher in relation to brachial 24-hour and asleep BP and 0.088/0.90 mV and 0.087/0.107 mV higher in relation to central BP (Table 3). The corresponding estimates for the Cornell index were 9.6/8.6 and 8.2/10.5 mV·ms peripherally and 8.6/8.9 and 8.8/10.7 mV·ms centrally. The regression slopes were similar for brachial and central BP (*P* ≥ 0.067). These findings remained unchanged if in the regression models we substituted peripheral pressure by its residual that removed the variance explained by central pressure or *vice versa*. Figure 2 graphically displays the regression slopes of the ECG indexes plotted against 24-hour peripheral and central systolic pressure. For clarity, the data markers in Figure 2 are averaged peripheral and central systolic pressure by sixths of the distributions of ECG indexes. Finally, Figure 3 shows the correlations of the ECG indexes with 24-hour and asleep systolic and diastolic pressures. *P* values derived by the Hotelling–William test indicate that none of the pairwise differences in the correlations of ECG indexes with peripheral and central BP reached significance (*P* ≥ 0.088). Sensitivity analyses adjusted for body mass index and skinfolds were confirmatory.

DISCUSSION

The key findings of our current study can be summarized as follows: (i) central systolic and diastolic BP and PP follow the same diurnal rhythm as brachial BP; (ii) the Cornell voltage and Cornell index were positively and significantly or borderline significantly associated with peripheral and

Table 3. Association of Cornell voltage and index with peripheral and central blood pressure

Blood pressure (mm Hg)	Cornell voltage (mV)			Cornell index (mV·ms)		
	Association size			Association size		
	Peripheral pressure	Central pressure	P	Peripheral pressure	Central pressure	P
Systolic pressure						
24-Hour	0.104 (0.016 to 0.191)†	0.088 (0.0003 to 0.177)†	0.36	9.6 (0.65 to 18.6)†	8.6 (–0.40 to 17.6)*	0.54
Awake	0.086 (–0.001 to 0.175)*	0.062 (–0.026 to 0.151)	0.19	7.7 (–1.30 to 16.7)	5.8 (–3.2 to 14.8)	0.32
Asleep	0.082 (–0.006 to 0.170)*	0.087 (–0.001 to 0.175)*	0.74	8.2 (–0.82 to 17.2)*	8.8 (–0.22 to 17.7)*	0.68
Diastolic pressure						
24-Hour	0.086 (–0.002 to 0.174)*	0.090 (0.002 to 0.178)†	0.076	8.6 (–0.41 to 17.6)*	8.9 (–0.04 to 17.9)*	0.087
Awake	0.056 (–0.032 to 0.145)	0.060 (–0.029 to 0.149)	0.067	5.6 (–3.42 to 14.6)	6.0 (–3.1 to 15.0)	0.10
Asleep	0.105 (0.017 to 0.192)†	0.107 (0.019 to 0.194)†	0.45	10.5 (1.6 to 19.5)†	10.7 (1.8 to 19.6)†	0.55
Pulse pressure						
24-Hour	0.040 (–0.049 to 0.129)	0.016 (–0.073 to 0.105)	0.24	3.2 (–6.0 to 12.1)	1.3 (–7.8 to 10.4)	0.38
Awake	0.048 (–0.041 to 0.137)	0.012 (–0.077 to 0.101)	0.12	3.6 (–5.4 to 12.7)	0.68 (–8.4 to 9.7)	0.20
Asleep	0.001 (–0.091 to 0.088)	0.001 (–0.087 to 0.090)	0.90	–0.29 (–9.4 to 8.8)	0.21 (–8.9 to 9.3)	0.82

Estimates (95% confidence interval) reflect the association size per 1-SD increment in blood pressure (mm Hg). Significance of the association sizes: *$P \leq 0.07$ and †$P \leq 0.05$; P values are for the differences in association sizes between peripheral and central blood pressure measurements.
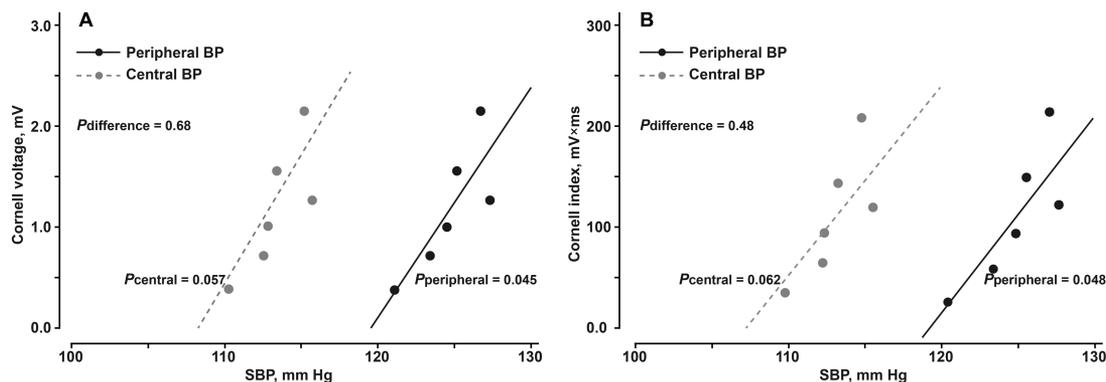

Figure 2. The Cornell voltage (**a**) and index (**b**) plotted against peripheral and central systolic 24-hour blood pressure (SBP). The data markers are averages by sixths of the distributions of ECG indexes. The lines are the slopes of the ECG indexes on peripheral and central SBP averaged by sixths of the distributions of the ECG indexes. $P_{peripheral}$ and $P_{central}$ indicate the corresponding significance levels. $P_{difference}$ is the significance of the difference between the slopes for peripheral and central SBP. Abbreviation: BP, blood pressure; ECG, electrocardiogram; SBP, systolic blood pressure.

central BP over the whole day and during sleep; (iii) associations of Cornell voltage and Cornell index with BP were not tighter for central compared with peripheral BP. The association of the ECG indexes with the asleep, but not with the awake BP, can be explained by the higher level of standardization of the nighttime recordings, when participants were sleeping in the supine position and not exposed to the physical and psychological stressors of work during daytime. In our current study, brachial systolic pressure was 9.0 mm Hg higher on awake ambulatory than office measurement, because office BP was measured in a quiet environment in the sitting position, whereas ambulatory monitoring was performed on working days when the laborers were standing and physically active along the production lines. The small 2.1-mm Hg differences in brachial office and awake diastolic BP, which is well within validation criteria of ambulatory

devices,[24] can probably be explained by using the auscultatory vs. oscillometric approach.

To our knowledge, few previous studies[25,26] assessed the central BP in ambulatory conditions. In the population-based Genotipo, Fenotipo y Ambiente de la Hipertensión Arterial en Uruguay Study (GEFA-HT-UY),[26] investigators applied the same technology as in our current study. This population sample included 167 participants (mean age, 56.1 years; 63.5% women).[26] The Ambulatory Central Aortic Pressure (AmCAP) study described the diurnal patterns of simultaneously measured 24-hour ambulatory brachial and central BPs in 171 hypertensive patients (mean age, 53.6 years; 53.2% women) enrolled into the ASSERTIVE trial.[25] The brachial and central pressures were measured by an oscillometric and tonometric approach, using the SpaceLabs monitor (Spacelabs Healthcare, Snoqualmie, WA) and the
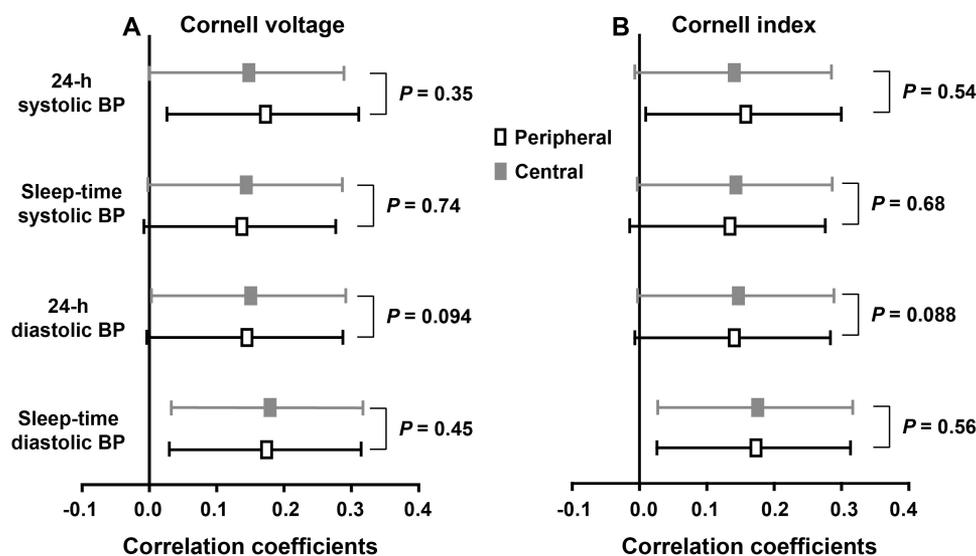
Figure 3. Correlations of Cornell voltage (**a**) and index (**b**) with 24-hour and asleep systolic and diastolic pressures. Data markers and whiskers represent the point estimates of the correlation coefficients and their 95% confidence interval, respectively. *P* values derived by the Hotelling–William test denote the significance of the pairwise comparison of peripheral (open symbols) vs. central (closed symbols) blood pressure. Abbreviation: BP, blood pressure.

BPro wrist device (HealthSTATS International, Singapore), respectively.[25] In GEFA-HT, daytime was the interval from 10 AM until 8 PM and nighttime ranged from midnight to 6 AM. These fixed intervals eliminate the transition periods in the morning and evening when BP changes rapidly, resulting in daytime and nighttime BP levels that are within 1–2 mm Hg of the awake and asleep levels.[27] In AmCAP,[25] these transition periods were not excluded from analysis and daytime ranged from 6 AM until 10 PM and nighttime from 10 PM until 6 AM. In spite of these methodological differences—in line with our current findings in workers—both studies[25,26] demonstrated a high degree of parallelism between the diurnal course of peripheral and central BP.

We searched PubMed for relevant publications without limitations of publication date or language using as terms "central blood pressure" OR "central BP" OR "ambulatory blood pressure" OR "ambulatory BP" OR "24-hour blood pressure" OR "24-hour BP" AND "ECG" OR "ECG voltage" OR "left ventricular hypertrophy" OR "hypertrophy" OR "electrocardiography". Our literature search revealed only two other studies with possible relevance to the issue addressed in the current manuscript.[28,29] In 728 participants (57.6% women) enrolled in the Czech post-MONICA study (Monitoring Trends and Determinants in Cardiovascular Disease), Wohlfahrt and colleagues assessed the Sokolow–Lyon index and central BP determined by a static tonometric approach (SphygmoCor, Atcor Medical Ltd, West Ryde, Australia).[28] The prevalence of electrocardiographic left ventricular hypertrophy was only 9.4% (*n* = 17) among 181 participants younger than 45 years and 9.0% (*n* = 43) in 547 older participants. In the younger participants, the standardized regression coefficients relating the Sokolow–Lyon index to BP with adjustments applied for sex and body mass index were 0.04 mV/mm Hg (*P* = 0.56) vs. 0.10 mV/mm Hg (*P* = 0.15) for peripheral vs. central systolic BP and 0.09 mV/mm Hg (*P* = 0.23) vs. 0.10 mV/mm Hg (*P* = 0.20)

for peripheral vs. central PP. The Czech authors recognized that there was a problem of collinearity but did not formally compare the estimates produced by peripheral vs. central BP in the younger participants. In the older participants, with adjustments applied for sex age, heart rate, and use of antihypertensive drugs (30.7%), the standardized odds ratios relating left ventricular hypertrophy to BP were 1.046 vs. 1.113 for peripheral vs. central systolic BP and 1.034 vs. 1.101 for peripheral vs. central PP. All odds ratios were significant (*P* < 0.001).[28] As a work-around to avoid the problem of collinearity, Wohlfahrt and coworkers reported that in older participants the area under the curve for discriminating electrocardiographic left ventricular hypertrophy was 0.90 *vs.* 0.83 for central *vs.* peripheral systolic BP (*P* < 0.05) and 0.90 vs. 0.81 for central vs. peripheral PP (*P* < 0.05).[28] They concluded that the noninvasively determined central pressure in older individuals was more strongly related to electrocardiographic left ventricular hypertrophy than brachial pressure, but that in younger subjects the voltage criteria of left ventricular hypertrophy were not independently associated with central and brachial BP.[28] The interpretation of the Czech report[28] is not straightforward, as the 45-year age threshold is arbitrary and about one third of the older participants were on antihypertensive drug treatment. Measurements of central BP in the Czech study[28] were momentary and did not cover the whole day as in our present study. Furthermore, Gómez-Marcos and colleagues enrolled 1,544 patients (mean age, 55 years; 61% women) recruited from primary care into the EVIDENT cross-sectional observational study (Physical Exercise, Fitness and Dietary Pattern and Their Relationship with Blood Pressure Circadian Pattern, Augmentation Index and Endothelial Dysfunction Biological Markers; NCT01083082).[29] Electrocardiographic left ventricular hypertrophy was associated with the 24-hour, awake, and asleep systolic BP, but the authors did not formally compare the associations with

peripheral vs. central BP.[29] In summary, what our study adds to the current literature[28,29] is (i) the recruitment of participants at a stage in life when the association between ECG voltages and BP can already be picked up, but when the prevalence of left ventricular hypertrophy in response to the BP load is still low; (ii) measurement of central BP over the whole day rather than momentary as in other studies; (iii) and the proper statistical approach to account for the collinearity between peripheral and central BP. The clinical implication is that given the timeframe over which left ventricular hypertrophy develops, early intervention with hypertension is a prerequisite to prevent cardiovascular complications.

Our literature search revealed two other studies that focused on echocardiographic left ventricular mass index[30] or hypertrophy[6,30] in relation to the 24-hour brachial and central BP measured by the same technology as implemented in the present study. However, these 2 studies[6,30] produced contradictory results. Protogerou and coworkers showed in 229 patients (mean age, 54.3 years; 43% women), of whom 75% were hypertensive, that 24-hour central systolic BP was significantly better associated with left ventricular mass index and left ventricular hypertrophy than the 24-hour and office brachial systolic BP, independent of sex, age, obesity, and antihypertensive drug treatment.[30] As in the Czech ECG study,[28] receiver operator characteristics curves showed a higher discriminatory ability of 24-hour central than brachial systolic BP to detect the presence of left ventricular hypertrophy (area under the curve, 0.73 vs. 0.69; $P = 0.007$). de la Sierra and coworkers enrolled 208 hypertensive patients, of whom 37.0% had echocardiographic left ventricular hypertrophy.[6] With adjustments applied for sex, age, and antihypertensive drug treatment, the odds ratios expressing the risk of target organ damage per mm Hg, including left ventricular hypertrophy, were 1.056 vs. 1.053 for peripheral vs. central systolic BP and 1.076 vs. 1.081 for peripheral vs. central PP.[6] When introduced in the same logistic model only peripheral—not central—BP retained significance.[6] Two additional studies[31,32] assessed the association of left ventricular mass index[31,32] or left ventricular hypertrophy[31] with central BP measured in the supine position using a tonometric approach. Among 2,585 participants enrolled in the Strong Heart Study[31] (mean age, 40 years; 60% women), the unadjusted correlations coefficients relating left ventricular end-diastolic diameter to BP were closer for brachial than central systolic BP (0.242 vs. 0.179) and PP (0.165 vs. 0.135). The opposite was observed in relation to relative wall thickness and left ventricular mass index. For relative wall thickness, the correlation coefficients in relation to peripheral and central systolic BP and PP were 0.250 vs. 0.286 and 0.130 vs. 0.167. The corresponding estimates for left ventricular mass index were 0.374 vs. 0.396 and 0.290 vs. 0.335. In view of the large sample size,[31] these marginal but inconsistent differences reached formal statistical significance. In a study of 392 treatment-naïve hypertensive patients (mean age, 49 years; 45% women),[32] the unadjusted correlation coefficients relating left ventricular mass index to BP were similar for office and the tonometrically assessed central systolic pressure (0.21 vs. 0.19).

Strong points of our current study are that we measured central BP under ambulatory—not static—conditions, that we report on quality control of the ambulatory recordings based on the number of peripheral and central BP readings available for analysis, that participants kept a diary, the gold standard[33] to document the awake and asleep portions of the day, that all ambulatory BP readings in individual recordings were processed using the same standardized SAS macro, and that the initial participation rate was as high as 68.6%. On the other hand, our study must also be interpreted within the context of its potential limitations. First, we excluded 100 potentially eligible workers, because of the quality of the ambulatory central hemodynamic readings. However, workers analyzed and excluded had similar age (29.1 vs. 28.3 years), body mass index (28.1 vs. 29.6 kg/m²), systolic/diastolic brachial BP in office (120.0/80.5 vs. 120.3/80.9 mm Hg), and 24-hour ambulatory (124.7/73.8 vs. 124.4/74.1 mm Hg) measurement and Cornell index (114.8 vs. 121.6 mV·ms). Second, the median number of ambulatory readings was only 35 over a whole day, because participants, most of whom were production line workers doing physically strenuous labor, had the option to cancel readings interfering with their work rhythm. Third, the sample size was relatively small, but nevertheless of the same order of magnitude as in other reports.[25,26] Of note, studies with an ECG[28,29] or echocardiographic[6,30–32] outcome related to peripheral and central BP with sample size ranging from 208[6] to 2,585[31] produced contradictory results. Fourth, we conducted our study in predominantly young men enrolled in the work force of lead acid battery manufacturing and recycling plants in the United States. Our main finding that there is no difference in the associations of the ECG indexes with peripheral and central BP should therefore not be extrapolated to women, older men or the general population. Finally, the prevalence left ventricular hypertrophy among the workers was only 1 (0.6%) or 6 (3.4%) by Cornell voltage or index criteria, precluding any categorical analysis of the ECG indexes. However, the spread of the Cornell voltage (5th to 95th percentile interval, 0.29–2.34 mV) and the Cornell index (25.5–230.4 mV·ms) was wide and cannot explain absence of any difference in the associations of the ECG indexes with peripheral vs. central BP.

Perspectives

Whether or not central BP is more closely related to target organ damage or is a better predictor of adverse health outcomes remains a matter of debate. Opinions range from the view point that central BP is an independent predictors of future cardiovascular events and all-cause mortality[34–36] to that there is no compelling scientific or practical reason to replace brachial systolic BP with any of the newer hemodynamic measures in the vast majority of clinical situations.[17,34] Only clinical trials, in which patients would be randomly allocated to interventions specifically lowering central BP[37] vs. no intervention can definitely resolve the debate. Previous experience[38] shows that ECG voltages and ECG criteria for left ventricular hypertrophy might be used as study endpoints in such trials, because these intermediate

outcomes can be reached within 6 months of randomization. ECG voltage indexes[39] and left ventricular hypertrophy[40,41] are strong and independent predictors of adverse cardiovascular outcomes. From a clinical perspective, our study does not support any incremental value of central over and beyond brachial BP in risk stratification.

DISCLOSURE

The authors declared no conflict of interest.

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