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CLINICAL RESEARCH
Hypertension

Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors

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Aims Estimated central systolic blood pressure (cSBP) and amplification (Brachial SBP-cSBP) are non-invasive measures potentially prognostic of cardiovascular (CV) disease. No worldwide, multiple-device reference values are available. We aimed to establish reference values for a worldwide general population standardizing between the different available methods of measurement. How these values were significantly altered by cardiovascular risk factors (CVRFs) was then investigated.

Methods and results Existing data from population surveys and clinical trials were combined, whether published or not. Reference values of cSBP and amplification were calculated as percentiles for 'Normal' (no CVRFs) and 'Reference' (any CVRFs) populations. We included 45 436 subjects out of 82 930 that were gathered from 77 studies of 53 centres. Included subjects were apparently healthy, not treated for hypertension or dyslipidaemia, and free from overt CV disease and diabetes. Values of cSBP and amplification were stratified by brachial blood pressure categories and age decade in turn, both being stratified by sex. Amplification decreased with age and more so in males than in females. Sex was the most powerful factor associated with amplification with 6.6 mmHg (5.8–7.4) higher amplification in males than in females. Amplification was marginally but significantly influenced by CVRFs, with smoking and dyslipidaemia decreasing amplification, but increased with increasing levels of blood glucose.

Conclusion Typical values of cSBP and amplification in a healthy population and a population free of traditional CVRFs are now available according to age, sex, and brachial BP, providing values included from different devices with a wide geographical representation. Amplification is significantly influenced by CVRFs, but differently in men and women.

Keywords Adult • Aged • Aorta • Arteries • Arteriosclerosis • Blood pressure • Central pressure • Humans • Pulse

Introduction

The measurement of blood pressure (BP) is fundamental in the general health assessment of patients and is usually done at the brachial artery. However, systolic blood pressure (SBP) is highly dependent on the site of measurement, it is thought, due to pressure wave reflections from more distal sites. Specifically, the pressure (and flow) waves travel at finite speed within arteries, and are

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reflected at bifurcations and caliber disparities (e.g. small artery vasoconstriction).[1] Central BP (i.e. pressure at the aortic root) can be estimated non-invasively via a variety of validated techniques and is gaining popularity as potentially be useful as of 'true' pressure affecting target organs damaged by high BP such as the heart, kidney, and brain.[2–4] Central BP has been shown to be significantly associated with adverse outcome such as mortality in a recent meta-analysis[5] and associated with adverse outcome in several individual trials.[2,3,6–9] Evidence that antihypertensive treatment may have differential effects on brachial BP compared with central BP is more established.[8,10–13] Drugs such as renin–angiotensin antagonists and/or calcium antagonists were more potent than β-blockers and/or diuretics for lowering central systolic blood pressure (cSBP) even after adjusting for brachial systolic blood pressure (bSBP) level. European cohort-based values for the SphygmoCor device[14–16] or carotid tonometry[17] exist, although wider use of central BP measurements is still hampered by the heterogeneity of devices and lack of reference values available worldwide.

Here we aimed to create a large, worldwide database of central BP and the related value, amplification (bSBP − cSBP) measured with validated methods. We also aimed to standardize these data according to these differing techniques as well as disease and risk factor (RF) definitions so as to establish reference values in 'normal' healthy people without known cardiovascular risk factors (CVRFs), and separately for those with graded levels of CVRFs. Reference values for cSBP and amplification could ultimately be used as guides for assessing patient status and to provide additional effective criteria for assessing cardiovascular (CV) risk to that from bSBP and pulse wave velocity. They would also be useful for assessing cSBP targets in clinical trials testing the effect of cardiovascular drugs either as a surrogate outcome or in longitudinal trials targeting the lowering of cSBP.

Methods

Data collection

Cardiovascular centres and research teams' data were searched and selected from November 2010 to June 2011. This came from extensive networking and a literature search [bibliographic databases within our unit and a search of PubMed with keywords (central OR aortic) and (pressure) and (tonometry) NOT (eye* OR retina OR cornea OR intraocular)', filtered by 'Humans' and 'English')]. This query was followed by 'snowballing', that is, using the reference lists via already made contacts and papers found from the literature search, to be repeated iteratively until no new relevant papers appeared. After contact and agreement signature by the investigators, data were collected between January and August 2011. Essential variables for inclusion were identified as: cSBP, bSBP, brachial diastolic BP (bDBP), age, sex, smoking status, total, low and high-density cholesterol (LDL and HDL, respectively) values, triglycerides (TG); treatment status for hypertension, dyslipidaemia, diabetes, chronic kidney disease, and CV disease, to allow categorization by CV risk. Other variables such as glucose and creatinine were declared desirable if easily available. Data management was carried out such that the original data were never altered, and variables were imported into a pre-established database where they were re-coded and transformed for homogenization. At every stage of data processing, subjects were only identified through a unique code internal to the present study. Personal identities of subjects and patients were not transferred by centres.

Inclusion criteria

Centres were eligible for data inclusion if they could provide the list of essential variables, for people aged >14 years, using a validated tonometry or calibrated distension wave technique for measuring central BP, according to either British Hypertension Society (BHS) or American Association of Medical Instruments (AAMI) criteria. In addition, techniques used for assessing central BP needed to be cross-validated with the SphygmoCor system (AtCor Medical, Sydney, Australia), for which a large number of validation papers are available and so could be used to calibrate indirectly with invasive measures,[18–21] when papers validating techniques directly with invasive measures were not available.

Standardizing definitions

Systolic blood pressure amplification was defined as bSBP − cSBP.[12] Current values of brachial BP and laboratory data (glucose, TG, etc.) were used to code hypertension, dyslipidaemia and diabetes according to 2007 ESH (European Society of Hypertension–European Society of Cardiology guidelines.[22] Where such biological data were missing (8%), patients were classified by their reported dyslipidaemic or diabetic status. Because the definition of dyslipidaemia has markedly changed with time and recent guidelines do not offer a clear, context-independent definition of dyslipidaemia, strict application of the thresholds proposed in the ESH guidelines lead to >85% of subjects with no other RFs to be classified as dyslipidaemic. For this reason, we used alternative definition of dyslipidaemia, i.e. values which are considered as necessitating intervention in primary prevention, even if the sole RF. Cut-off values used were CT ≥ 240 mg/dL or LDL ≥ 160 mg/dL or HDL ≤ 50 mg/dL (female)/40 mg/dL (male), TG ≥ 250 mg/dL, diabetes: plasma fasting glucose ≥126 mg/dL. Smoking was coded as current, past, or never. Mean blood pressure (MBP) was DBP + 0.4(SBP − DBP).[23] Overt CV disease was defined as the presence of cerebrovascular, coronary heart, valvular, or peripheral artery disease, impaired cardiac ejection fraction, left ventricular hypertrophy, or atherosclerotic plaque, as reported by centres. Obesity was defined as BMI > 30 kg/m^2. Waist circumference was abnormal if >102 cm in men and >88 cm in female.

Standardizing methodologies

Data were included that had been measured via the SphygmoCor device (AtCor Medical, Australia), the Omron HEM-9000AI (Omron, Japan), Walltrack & Artlab systems (both Esaote, Italy), the PulsePen device (PulsePen, Italy), and direct carotid tonometry. The SphygmoCor device uses radial tonometry via a high-fidelity probe to derive aortic BP from a validated transfer function after calibration.[24,25]

The Omron HEM 9000-AI also uses radial tonometry with a multi-element probe that selects the best quality pressure wave. Here, cSBP is derived from the radial late systolic peak (SP2). The software provides one reading for SP2 and one which takes this value and transforms it via a proprietary algorithm. During this study, we took the SP2 reading as it is shown to be more in accordance with algorithm independent techniques.[26,27]

Carotid tonometry was carried out using either PulsePen or direct tonometry, both validated against either invasive pressure or SphygmoCor, respectively.[28,29]

Calibrated carotid distension waveforms were obtained with echo-tracking techniques (the Walltrack and Artlab System). These provide high quality, with minimal compression distension waveforms which parallel pressure. Central BP values derived from distension waveforms were previously validated against invasive measurements and applanation tonometry.[28] All devices included in the present study showed good agreement (grade A of BHS or equivalent) with reference techniques according to the priorities for fidelity of recorded tonometric waves

and likeness to the reference central pressure, qualities independent of the calibration. The different devices used to measure and calibrate brachial BP were all validated according to BHS and/or AAMI standards (Supplementary material online, *Table S1*).[30]

Only cSBP measures needed to be standardized as DBP and MBP are assumed to be consistent throughout the body,[31] and therefore appropriately accommodate SBP and amplification calibration. Central pulse pressure (cPP) is simply calculated as cSBP − DBP. Existing publications validating measurement techniques were used to standardize cSBP values. 265 publications were found in PubMed in June 2011 via the terms '(validation OR comparison OR accuracy) and (central OR aortic) and (sphygmocor OR omron OR tonometry OR walltrack OR artlab OR distension OR pulsepen)' and selecting the filter 'Humans' and date range June 1996–2011, of which four compared crude agreement between the device estimation and invasive or SphygmoCor estimations on the same subjects.[26,28,29,32] Several other papers were provided by participating centers.[18–21,33–36]

To estimate correction factors, we first calculated the weighted mean difference for each technique between invasive aortic and estimated values and cantered those values on the weighted mean of SphygmoCor-estimated cSBP and Omron SP2 which represent >90% of data (Supplementary material online, *Table S2*; *Figure 1*). When cPP was provided alone and cSBP was not, brachial DBP was assumed to be equivalent to carotid or aortic DBP to convert cPP to cSBP values. Invasive brachial pressures are higher than non-invasive ones,[37,38] and non-invasively estimated central pressure calibrated with non-invasive cuff brachial BP is the overwhelming reference. Therefore, we chose to standardize values using cuff brachial pressure. As a consequence, non-invasive cSBP is lower than invasive intra-aortic SBP[38]; however, the gradient between invasive brachial and invasive aortic SBP is likely to be accurately estimated (*Figure 1*).

Sample sizes and estimating precision

Based on an assumed typical SD of estimated cSBP of 12 mmHg in a healthy population,[15] at least 576 subjects per group (either for populations or RF groups) would be expected to give confidence intervals (CIs) no >1 mmHg either side of the median when approximating its CI to that of the mean. For patients with CVRFs, it was assumed that the typical SD of estimated cSBP was 17 mmHg,[39] requiring at least 1156 subjects per group for a 1 mmHg precision. Checks were made after reference values had been calculated, to establish that a relevant number of different populations contributed to each reference category. For subcategories where the number of observations was <50, statistics were not calculated.

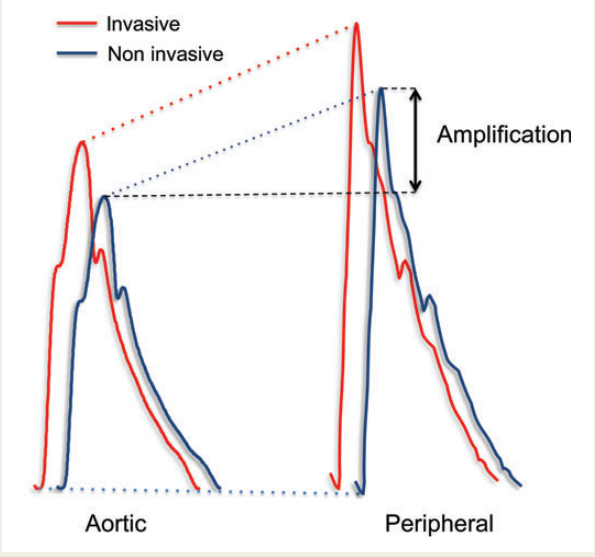

Figure 1 Illustration of the difference between central and peripheral blood pressure, either invasive (red waveform) or non-invasive (blue waveform).

Definition of populations and cardiovascular risk factors

Subjects were considered as having data valid for analysis if they had provided all essential variables (see Data collection), were untreated (hypertension and dyslipidaemia), and were devoid of CV disease and diabetes, as was done previously.[40,41] The 'Normal Population' was defined as those subjects who had no established *relevant* CVRFs (see Supplementary material online, *Table S3* for CVRF definitions), and as having *Optimal* or *Normal* BP. The 'Reference Population' was any subjects who were valid for analysis who had any *relevant* CVRFs (*Figure 2*).

Statistical analyses

All statistical analyses were carried out in Stata IC/10 (StataCorp LP). Values of cSBP and amplification are presented as medians, less sensitive to the effects of skewed data and outliers, together with 10th, 25th, 75th, and 90th percentiles. As reference values should represent typical values for particular age and brachial BP groups of interest, the results were presented by age decade and ESH-defined brachial BP groups in turn, both stratified by sex. The influence of relevant CVRFs and sex was investigated via multivariable robust linear regressions with cSBP, bSBP, and amplification as the dependent variable and relevant CVRFs, age, BMI, and sex as independent variables, adjusted for heart rate (HR). Age, MBP, glucose, height, and HR were inserted as continuous variables. β-Coefficients and their CIs were calculated for convenient units of RFs. We used multiple imputation chained equations to impute those values rather than perform complete case analyses in order to decrease bias due to missing confounding variables and in order to increase the power of the analyses.[41]

Results

Database characteristics

In total, data on 82 930 subjects in 77 studies were collected from 53 centres worldwide (Supplementary material online, *Table S4*). Two centres who refused to share their data (4476 subjects), and one centre responded too late (479 subjects). *Figure 2* shows numbers with essential variables, treatment and disease status. Data for all essential variables were available on 45 436 untreated subjects without diabetes or CV disease. Other patients were not studied here. Of the 45 436 individuals, 18 183 subjects made up the 'Normal Population' (no CVRFs), and 27 253 subjects having at least one CVRF, made up the 'Reference population'.

Most data came from the SphygmoCor device ($n = 42\,050$), followed by the Omron HEM 9000-AI device ($n = 30\,541$), then calibrated carotid distension waveforms ($n = 8120$) and finally 2219 subjects in which another type of measurement was used (PulsePen or direct carotid tonometry), with the percentages of different devices in the 45 436 subjects analysed having a similar distribution. Data presented in this manuscript are cSBP and amplification.

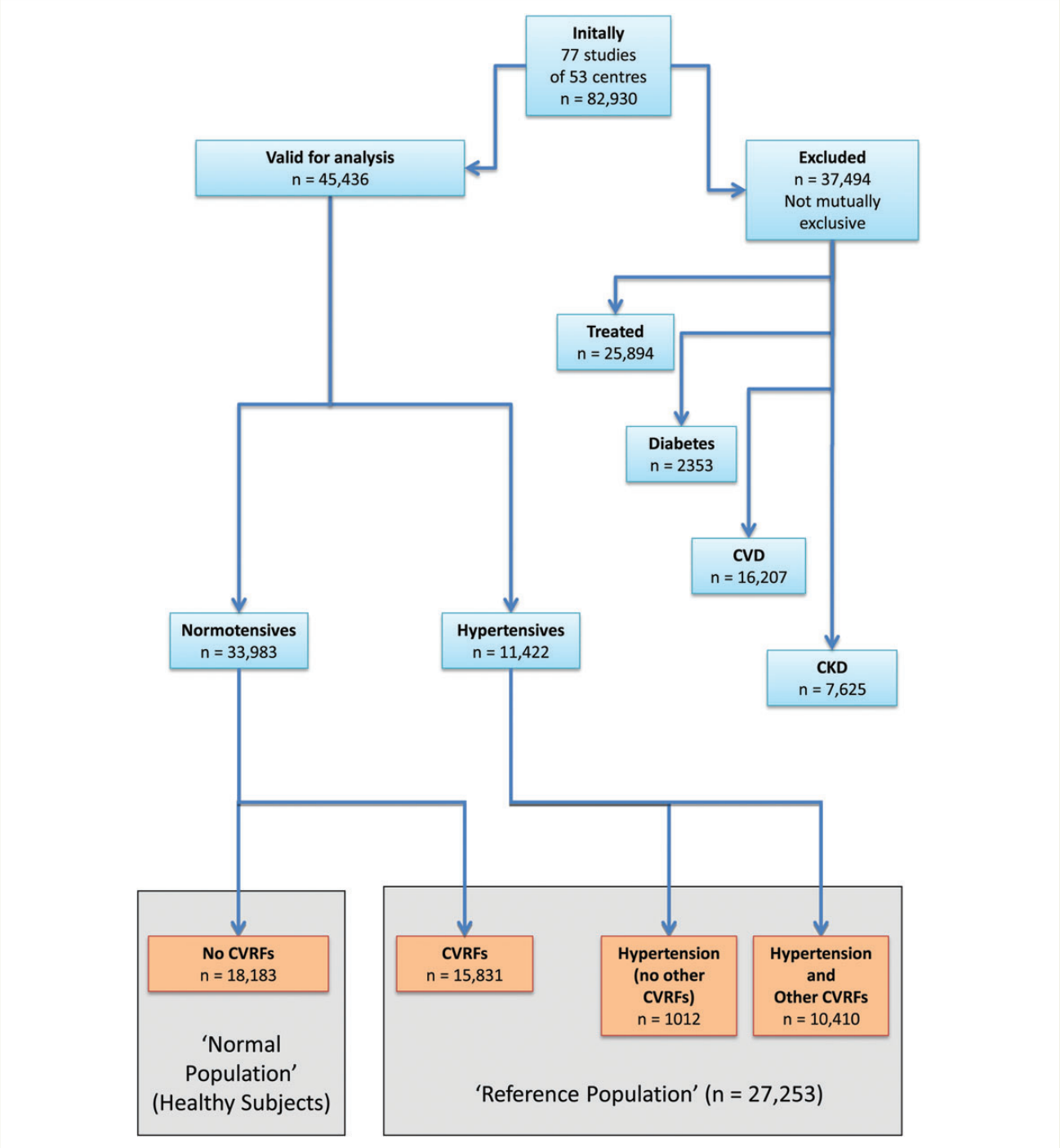

Figure 2 Dendrogram for patient selection. CVD, cardiovascular diseases; CKD, chronic kidney disease; CVRFs, cardiovascular risk factors.

Similar data are presented as Supplementary material online, tables and figures for cPP.

Population characteristics

The demographic and clinical characteristics of the Normal and Reference populations are shown in *Table 1*. The Normal population included more women than men (52% vs. 48%) and younger subjects, than the Reference population (mean (SD) = 46 (15) and 52 (15) years, respectively). Weight, waist, percentage of current smokers, brachial BP, total and LDL cholesterol and TG were unsurprisingly higher in the Reference population than the Normal population as they form part of the definition of CVRFs. Heart rate and HDL cholesterol were not relevantly different between the two populations. Ex-smokers were in equal proportion in the two populations.

Table 1 Descriptive data of the normal and reference population

Parameter	Normal population	Reference population
Mean (SD) or *n* (percentage)	(*n* = 18 183)	(*n* = 27 253)
Age (years)	46 (15)	52 (15)
Females	9531 (52%)	13 211 (48%)
Weight (kg)	61 (10)	71 (16)
Height (cm)	165 (10)	166 (10)
Waist (cm)	80 (10)	90 (12)
BMI	22 (3)	26 (5)
bSBP (mmHg)	116 (12)	133 (20)
bDBP (mmHg)	70 (9)	79 (12)
MBP (mmHg)	88 (9)	101 (14)
PP (mmHg)	46 (9)	53 (14)
HR (beats/min)	67 (11)	68 (11)
Optimal BP	10 450 (57%)	7228 (27%)
Normal BP	4571 (25%)	4742 (17%)
High normal BP	3159 (17%)	3989 (15%)
Grade I BP		3288 (12%)
Grade II BP		1930 (7%)
Grade III BP		701 (3%)
Isolated systolic hypertension		5255 (19%)
Obesity		11 560 (43%)
Total cholesterol (mg/dL)	191 (29)	213 (43)
HDL cholesterol (mg/dL)	63 (16)	57 (18)
LDL cholesterol (mg/dL)	108 (26)	132 (39)
Triglycerides (mg/dL)	92 (53)	129 (94)
Glucose (mg/dL)	89 (11)	92 (12)
Current smokers		8470 (33%)
Number of relevant CVRFs		1.5 (0.8)

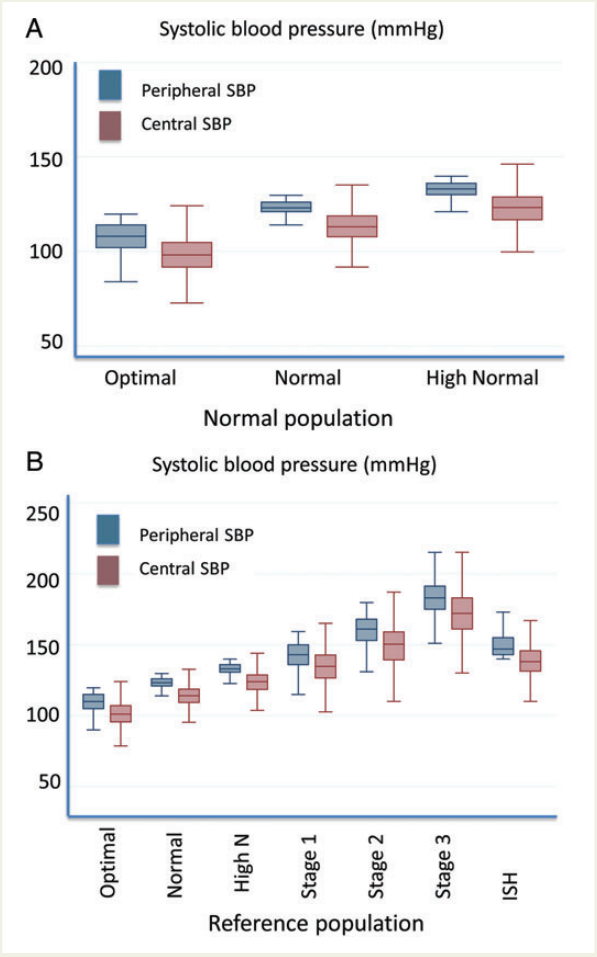

Figure 3 Box plot for peripheral systolic blood pressure (blue) and central systolic blood pressure (red) according to blood pressure categories, within the normal population (top, *A*) and the reference population (bottom, *B*). The box contains 50% of the data [25–75 percentile, interquartile range (IQR)], the line in the box is the median, the whiskers represent 25th percentile −1.5IQR, and 75th percentile +1.5IQR.

Reference values for central systolic blood pressure

The median cSBP progressively increased with bSBP category in both populations (*Figure 3A* and *B*). There was no clinically meaningful difference in cSBP between the Normal and Reference population for the *Optimal* to *High Normal* BP categories, except that values in the Reference population were more dispersed. The dispersion of cSBP values was marked within each category of brachial BP, with boxes clearly overlapping between brachial BP categories. This dispersion increased with increasing levels of BP.

Reference values for cSBP are provided for each population, stratified on sex, and further stratified on age (*Table 2*) or BP categories (*Table 3*). Tables are combined in Supplementary material online, *Table S5*. According to age, cSBP was higher in men than in women until age 50–59, after which the tendency was reversed. According to BP categories (*Table 3*), cSBP was lower in men than in women within each peripheral BP category, except 'optimal' (*Table 3*).

Amplification according to age (*Table 4*) and BP categories (*Table 5*) is given separately for males and females. *Tables 4* and *5* are combined in Supplementary material online, *Table S6*. Amplification was larger for males than females at any given age or BP value (*Tables 4* and *5*), the difference between sexes getting smaller with increasing age and values of BP. Amplification was very little influenced by BP categories (not exceeding 3 mmHg, *Table 5*). The interaction between sex, age, and BP category can be better seen on 3D bar graphs (*Figure 4*; Supplementary material online, *Table S6*). In younger females, amplification reached a maximum with lower BP (12–15 mmHg), and then it decreased with aging in each BP category and decreased with increasing levels of BP at a given age until age 40. In middle-aged women, amplification reached a plateau and tended to increase with increasing levels of BP after age 40. The pattern was quite different for males. Amplification increased with increasing levels of BP in each age category. Amplification was maximum and extreme in younger male hypertensives (up to 25 mmHg), particularly in those with isolated systolic hypertension (ISH). Amplification decreased gradually with aging without

Table 2 Central systolic blood pressure values according to age categories, for males and females, in the normal and reference populations

	Normal population		Reference population	
	Female	Male	Female	Male
Age category				
<20 ($n = 1104$)	97 (86, 91, 102, 109) $n = 350$	105 (95, 99, 109, 113) $n = 290$	99 (88, 93, 105, 120) $n = 182$	109 (96, 102, 117, 127) $n = 282$
20–29 ($n = 4157$)	95 (80, 88, 102, 110) $n = 1411$	103 (92, 97, 109, 115) $n = 880$	101 (88, 94, 110, 124) $n = 888$	110 (95, 102, 120, 130) $n = 974$
30–39 ($n = 6386$)	98 (84, 90, 108, 119) $n = 1860$	103 (88, 95, 112, 120) $n = 1259$	111 (92, 100, 127, 141) $n = 1373$	114 (95, 103, 129, 144) $n = 1889$
40–49 ($n = 9595$)	102 (87, 93, 113, 123) $n = 2318$	106 (90, 97, 114, 123) $n = 2068$	116 (95, 104, 133, 146) $n = 2196$	118 (97, 106, 132, 144) $n = 2995$
50–59 ($n = 11950$)	110 (93, 100, 119, 127) $n = 2002$	110 (96, 102, 118, 126) $n = 1997$	120 (100, 109, 134, 148) $n = 4251$	123 (102, 111, 137, 150) $n = 3646$
60–69 ($n = 7779$)	114 (97, 105, 122, 129) $n = 1057$	114 (97, 105, 122, 128) $n = 1410$	128 (105, 115, 141, 154) $n = 2656$	128 (105, 115, 142, 155) $n = 2629$
70+ ($n = 4445$)	118 (100, 109, 126, 131) $n = 530$	116 (99, 107, 124, 130) $n = 747$	138 (113, 126, 152, 164) $n = 1567$	135 (113, 124, 147, 160) $n = 1592$

Values given here are 50th (10th, 25th, 75th, and 90th) percentiles.

Table 3 Central systolic blood pressure values according to blood pressure categories, for males and females, in the normal and reference populations

	Normal population		Reference population	
	Female	Male	Female	Male
Blood pressure category				
Optimal ($n = 17\,678$) 108 (96, 102, 114, 117)	97 (84, 90, 104, 110) $n = 6415$	100 (88, 94, 106, 111) $n = 4035$	102 (89, 95, 108, 112) $n = 4082$	101 (90, 96, 107, 112) $n = 3146$
Normal (= 9313) 123 (120, 121, 126, 128)	116 (104, 110, 121, 125) $n = 1902$	112 (102, 106, 117, 122) $n = 2669$	116 (107, 111, 120, 123) $n = 2281$	113 (103, 108, 118, 122) $n = 2461$
High normal ($n = 7148$) 133 (128, 130, 136, 138)	126 (115, 120, 131, 135) $n = 1212$	122 (110, 115, 128, 132) $n = 1947$	125 (116, 120, 130, 133) $n = 1861$	123 (111, 116, 128, 132) $n = 2128$
Stage 1 ($n = 3288$) 143 (130, 137, 150, 155)			137 (122, 129, 144, 150) $n = 1276$	133 (119, 126, 142, 148) $n = 2012$
Stage 2 (= 1930) 161 (146, 154, 168, 174)			154 (128, 142, 161, 168) $n = 798$	148 (128, 138, 158, 165) $n = 1132$
Stage 3 ($n = 701$) 183 (162, 178, 193, 206)			173 (153, 164, 183, 194) $n = 312$	171 (143, 158, 183, 192) $n = 389$
ISH ($n = 5255$) 147 (141, 143, 155, 163)			140 (128, 134, 148, 156) $n = 2507$	137 (122, 129, 144, 152) $n = 2748$

Values given here are 50th (10th, 25th, 75th, and 90th) percentiles. Values given below blood pressure categories are for brachial blood pressure.

clearly reaching a plateau, except in those with optimal brachial BP (*Figure 4*; Supplementary material online, *Table S6*).

Determinants of central systolic blood pressure

Multivariable regressions of CVRFs on cSBP and peripheral SBP are given separately for normotensives and hypertensives (*Table 6A*). All CVRFs were positively and significantly related to peripheral BP, if only accounting for 20% of its variance in normotensives, and only 5% of the variance in hypertensives. However, for central cSBP, RFs affected differently normotensives and hypertensives. All RFs except glucose had a statistically significant impact on cSBP in normotensives ($R^2 = 0.21$), whereas only smoking, male sex, and HR were significantly related to cSBP in hypertensives ($R^2 = 0.13$). Male sex was associated with lower cSBP in hypertensives, whereas

Table 4 Amplification of systolic blood pressure values (peripheral SBP − central SBP) according to age categories, for males and females, in the normal and reference populations

	Normal population		Reference population	
	Female	Male	Female	Male
Age category				
<20 ($n = 1104$)	14 (9, 11, 16, 20) $n = 350$	19 (11, 15, 22, 24) $n = 290$	14 (6, 10, 17, 20) $n = 182$	21 (12, 16, 25, 30) $n = 282$
20–29 ($n = 4157$)	12 (5, 8, 16, 19) $n = 1411$	15 (6, 11, 20, 24) $n = 880$	11 (4, 8, 15, 19) $n = 888$	17 (7, 12, 23, 30) $n = 974$
30–39 ($n = 6386$)	8 (0, 4, 12, 17) $n = 1860$	13 (4, 8, 18, 23) $n = 1259$	7 (−2, 3, 12, 17) $n = 1373$	11 (1, 7, 17, 22) $n = 1889$
40–49 ($n = 9595$)	6 (0, 3, 11, 15) $n = 2318$	11 (2, 6, 16, 21) $n = 2068$	6 (0, 3, 10, 16) $n = 2196$	9 (2, 5, 15, 21) $n = 2995$
50–59 ($n = 11950$)	5 (0, 2, 10, 13) $n = 2002$	9 (2, 5, 13, 18) $n = 1997$	8 (1, 4, 11, 15) $n = 4251$	8 (1, 4, 12, 18) $n = 3646$
60–69 ($n = 7779$)	6 (1, 3, 9, 12) $n = 1057$	8 (2, 5, 12, 17) $n = 1410$	7 (1, 4, 11, 15) $n = 2656$	8 (2, 5, 13, 18) $n = 2629$
70+ ($n = 4445$)	6 (1, 3, 9, 13) $n = 530$	8 (1, 4, 12, 17) $n = 747$	7 (2, 4, 10, 15) $n = 1567$	8 (2, 4, 12, 17) $n = 1592$

Values given here are 50th (10th, 25th, 75th, and 90th) percentiles.

Table 5 Amplification of systolic blood pressure values (peripheral SBP − central SBP) according to blood pressure categories, for males and females, in the normal and reference populations

	Normal population		Reference population	
	Female	Male	Female	Male
Blood pressure category				
Optimal ($n = 17\,678$) 108 (96, 102, 114, 117)	8 (1, 4, 12, 16) $n = 6415$	10 (2, 6, 15, 20) $n = 4035$	7 (1, 3, 11, 14) $n = 4082$	9 (2, 5, 13, 17) $n = 3146$
Normal (= 9313) 123 (120, 121, 126, 128)	7 (0, 3, 11, 16) $n = 1902$	11 (3, 7, 17, 22) $n = 2669$	8 (1, 4, 11, 15) $n = 2281$	10 (3, 6, 15, 20) $n = 2461$
High normal ($n = 7148$) 133 (128, 130, 136, 138)	6 (0, 3, 11, 16) $n = 1212$	11 (2, 6, 17, 22) $n = 1947$	8 (1, 4, 12, 15) $n = 1861$	10 (2, 5, 15, 21) $n = 2128$
Stage 1 ($n = 3288$) 143 (130, 137, 150, 155)			6 (0, 2, 10, 15) $n = 1276$	8 (1, 4, 13, 20) $n = 2012$
Stage 2 (= 1930) 161 (146, 154, 168, 174)			8 (1, 4, 14, 26) $n = 798$	10 (1, 5, 17, 26) $n = 1132$
Stage 3 ($n = 701$) 183 (162, 178, 193, 206)			9 (2, 4, 16, 25) $n = 312$	10 (1, 5, 16, 25) $n = 389$
ISH ($n = 5255$) 147 (141, 143, 155, 163)			8 (1, 4, 13, 18) $n = 2507$	11 (2, 6, 17, 25) $n = 2748$

Values given here are 50th (10th, 25th, 75th, and 90th) percentiles. Values given below blood pressure categories are for brachial blood pressure.

it was the opposite in normotensives. This result suggests a strong interaction between age, sex, and BP value for cSBP.

Determinants of amplification

Multivariable regressions of CVRFs on amplification are given separately for males and females because of the strong interaction between sex and all other variables (*Figure 4* and *Table 6B*). The global R^2 is 0.2 in males and 0.1 in females. Variables associated with amplification were quite similar between sexes, with β-coefficients in the same direction and range. Associated variables were age, smoking, and dyslipidaemia (men only), with negative coefficients, showing that these RFs had adverse effect on amplification (i.e. had a stronger detrimental effect on central compared with brachial pressure). As observed in *Figure 4*, relation to age was steeper for men than women (for 10 years, −2.4 mmHg (−2.5 to −2.3) and −1.8 mmHg (−1.9 to −1.7), respectively). On the contrary, blood glucose had a strong, positive influence in both sexes, meaning that central pressure was disproportionately lower than

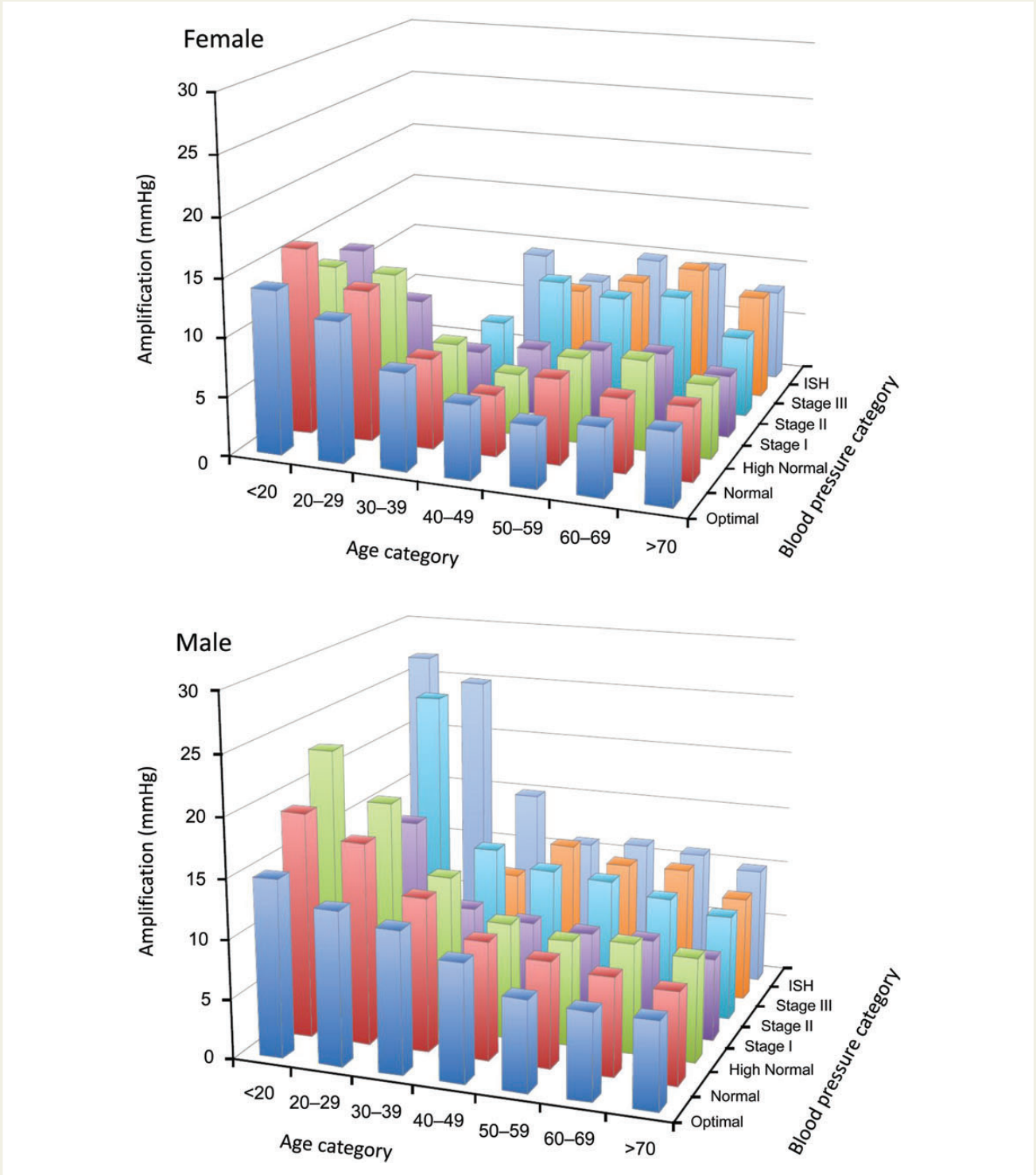

Figure 4 Tridimensional bar graphs representing amplification (peripheral–central systolic blood pressures) according to sex (females up, males bottom), age categories, and blood pressure categories. The value represented here is the median of the group. Some categories are not represented because there were less than 50 observations.

brachial pressure with higher blood glucose. As expected, body height and HR had small, positive and significant associations with amplification. Actual MBP level was borderline significant in women only, whereas obesity status was not associated with amplification. Age × hypertension interaction was significant in both sexes. Inclusion of additional interaction factors in a global model

Table 6 Multivariable robust regression for peripheral and central blood pressure (A) and amplification (B) as a function of risk factors

	Normotensives	Hypertensives	Normotensives	Hypertensives
(A)				
Total R^2	0.21	0.13	0.20	0.05
β-Coefficient (95% CI)				
Age (10 years)	7.1 (6.7–7.5)	−0.1 (−1.3 to 1.1)	5.8 (5.4–6.2)	3.0 (1.8–4.2)
Smoking (yes)	5.2 (4.6–5.8)	3.1 (1.8–4.4)	2.4 (1.8–3)	2.4 (1.2–3.6)
Dyslipidaemia (yes)	1.5 (1–2)	0.7 (−0.3 to 1.7)	1.1 (0.7–1.5)	−0.3 (−1.2 to 0.6)
Sex (male)	9.3 (8.1–10.5)	−14.8 (−18.6 to −11)	13.8 (12.6–15)	1.9 (−1.8 to 5.6)
Blood glucose (20 mmol/L)	−0.2 (−0.6 to 0.2)	0.0 (−0.9 to 0.9)	1.8 (1.5–2.1)	1.8 (1–2.6)
Height (10 cm)	2.0 (1.7–2.3)	0.0 (−0.7 to 0.7)	2.5 (2.2–2.8)	0.4 (−0.2 to 1)
HR (10 bpm)	0.5 (0.3–0.7)	−1.8 (−2.2 to −1.4)	1.3 (1.1–1.5)	0.2 (−0.2 to 0.6)
Age × sex interaction (AU)	−2.1 (−2.4 to −1.8)	2.0 (1.3–2.7)	−2.4 (−2.6 to −2.2)	−0.6 (−1.3 to 0.1)
Parameters	Females ($n = 9651$)	Males ($n = 9582$)		
(B)				
Total R^2	0.10	0.20		
Age (10 years)	−1.8 (−1.9 to −1.7)	−2.4 (−2.5 to −2.3)		
Smoking (yes)	−2.1 (−2.7 to −1.5)	−2.3 (−2.8 to −1.8)		
Dyslipidaemia (yes)	−0.2 (−0.6 to 0.2)	−0.9 (−1.3 to −0.5)		
Mean blood pressure (10 mmHg)	−0.3 (−0.5 to −0.1)	0.3 (0.1 to 0.5)		
Obesity (yes)	0.3 (−0.1 to 0.7)	−0.4 (−0.9 to 0.1)		
Blood glucose (20 mg/dL)	1.6 (1.3–1.9)	2.2 (1.9–2.5)		
Height (10 cm)	−0.1 (−0.3 to 0.1)	1 (0.7–1.3)		
HR (10 bpm)	1 (0.8–1.2)	1.2 (1–1.4)		
Age × hypertension interaction (AU)	0.3 (0.2–0.4)	0.2 (0.1–0.3)		
Constant (AU)	5.1 (0.6–9.6)	−15.1 (−20.4 to −9.8)		

β-Coefficients are given as value (95% confidence interval), given for a certain span of risk factors. For instance, 10 years of age is associated with −2.4 mmHg of amplification for males. Unit for β-coefficient is mmHg.

with both sexes (age × sex, age × hypertension × sex) did not change the pattern of association (Supplementary material online, *Table S7*). In this model, sex was by far the most powerful factor associated with amplification with 6.6 mmHg [5.8–6.4] higher amplification in males than in females.

Discussion

Reference values are now readily available for cSBP and SBP amplification for both healthy subjects devoid of and individuals with CVRFs. From this substantial worldwide dataset, these values can now be used as a solid guideline for assessing patient status and providing criteria additional to peripheral SBP and pulse wave velocity. They would also be useful as targets in clinical trials testing the effect of cardiovascular drugs in the likely event that more data become available looking into the association between central BP and amplification targeting and hard outcomes such as mortality.

Interpretations of findings

This study's large sample size allows more precise estimation than was previously available, with more degrees of freedom in which to explore CVRFs, and provides these values for a range of percentiles without losing precision. Within any combinations of categories of population, brachial BP, age and sex, sample sizes ranged from $n = 154$ to 8493. Moreover, the data for both Normal and Reference populations came from 41 of the 54 centres on four continents, using various validated devices. The criteria used to classify RFs and diseases were very stringent, matched with the ESH categories of CVRFs and any extra RFs carefully described. These features give us a strong external validity for derived reference values. This paper extends results of smaller single-site cohorts using specific devices to a wider geographical area and to several validated measurement devices.

One major finding is the different pattern of amplification between sexes according to age and BP category. We have found that women had relatively flat amplification profiles with age, with a plateau after age 30–39 years, whereas men had a much steeper, continuous decline with age. This pattern is quite different from the previously published data,[39] where the plateau tended to occur later. The pattern of amplification in younger hypertensive men is new, even if partially discussed before.[12] It could only be detected here due to the very large number of subjects. For instance, in a multivariate model (Supplementary material online, *Table S5*), sex was by far the most powerful factor associated with amplification with

6.6 mmHg [5.8–6.4] higher amplification in males than in females. Proposed explanations for these extreme values of amplification in young men are so far only speculative. One possible explanation is spurious systolic hypertension because of systolic over-boost in brachial measurements (i.e. a high narrow systolic peak of the brachial pressure wave) for young subjects with hyperkinetic hearts.[42,43] Whether this phenomenon is more frequent in young men than women has not been reported yet. However, it may be linked to a higher reactivity to stress in young men than in young women, a finding that has been described in some studies.[44,45] A second possible explanation is the higher amount of wave reflection in women, due to their lower height and higher HR, increasing cSBP and reducing amplification. Indeed, in multivariate analysis (*Table 6A*), height accounted for a lesser increase in cSBP in men than in women, thus more amplification between central and peripheral SBP in men. However, in multivariate analysis, the sex × age × interaction remained significant independently of height (Supplementary material online, *Table S7*). Other explanations could be differences in physical activity or hormonal status, which could not be investigated here. Whether the individuals with elevated peripheral SBP and normal cSBP are at increased risk is controversial.[46–48] Isolated systolic hypertension in younger individuals increases risk of hypertension at older ages[49] so this condition might not be totally benign.

Risk factors associated with amplification are the same as those previously found. The strength ($R^2 = 0.18$) of the association is smaller than in the ACCT trial ($R^2 = 0.44$), likely because of the variety of populations selected and mixed techniques, as opposed to the general population sample of two countries. Amplification values measured with each of the main devices used (Sphygmocor, Omron, or calibrated carotid waveforms) were very similar, see Supplementary material online, *Table S8*). One striking feature is the weak association between amplification and level of BP. This may be explained by the tautological link between peripheral and central BP in the calibration process. A new finding is the association of blood glucose with amplification, within the normal range of blood glucose values. This strong association goes in opposite direction (i.e. higher blood glucose associated with higher amplification), compared with previous data on diabetes.[39] The association is both statistically and physiologically relevant. It might reflect the interaction between glucose regulation and autonomic nervous system activation.[50] Although all blood sampling was assumed to be during fasting, it is likely that incomplete fasting occurred in some participants. Amplification has been shown to be predictive for cardiovascular events in the MESA study,[51] a 10% increase conferring an HR of 0.82; 95% CI: 0.70–0.96; $P = 0.012$). Although the metrics in Chirinos and our study are different (ratio or difference, respectively), both expressions carry similar information. Wave reflection carries additional information to the amplitude of pressure in terms of prediction of events,[52] unfortunately, wave reflections indexes were not available here.

As calibration of any device assessing central BP has to be done via peripheral BP, brachial BP is tautologically associated with central BP. One major point, noted by previous investigators was the wider distribution of central BP to that of peripheral BP, within the same peripheral BP categories.[15] This is the case at lower level of BP, but was not so apparent here for higher categories of hypertension.

Limitations

The concept of the study could be criticized for combining existing databases, and therefore summing heterogeneity from the variety of populations and techniques. Although we took great precautions to adjust for it, some residual differences may remain. One advantage of the wide inclusion criteria and extended recruitment of centres was to provide as representative a sample of data as possible, greatly improving the external validity and applicability of our results. How to handle some RFs was difficult, especially as defining dyslipidaemia according to the recent guidelines[53] was not practical here, as its application results in >80% of the otherwise normal population being classified as dyslipidaemic. We thus chose a more practical definition that is the thresholds in lipid parameters above which intervention is considered even in the absence of additional RFs.[53] Several RFs such as family history of CVD were available in large numbers of subjects, but they could not be used because of heterogeneity in coding. Important information has been placed as Supplementary material online, such as age, BP, and sex distribution of cPP, cSBP, and amplification (Supplementary material online, *Tables S9* and *S10* and *Figure S1*). We could not study the influence of ethnicity on central pressure and amplification because the information was missing.

Some limitations are inherent to the methods used for central pressure measurement. As noted previously,[17] it is very unlikely that a single (linear) transfer function such as that used in Sphygmocor would adequately deal with the variability due to age, sex, or arterial properties. The advantage of the present study is that it includes alternative techniques using late systolic peak (Omron), or carotid distension waveforms. Because this paper deals mostly with amplitude of waves which mostly depend on form factors and calibration, all three techniques provided quite similar distributions of values within patient subcategories. Combining data from different techniques was possible because of cross-validation data between these and/or reference techniques. It enhanced external validity and applicability of these measurements, but was nevertheless at the cost of additional noise to the data. Brachial pressure is necessary to calibrate central pressure, and errors in measuring brachial pressure translate in central pressure. In the present dataset, we observed that errors occurred in transcribing values of brachial pressure in the software, even in previously published high-quality populations. That explained a significant proportion of outlier values, which could not be corrected *post hoc*. It is thus important to encourage manufacturers to develop devices which shortcut the manual typing of BP values in order to avoid such errors. Absolute calibration issues have been discussed widely elsewhere.[1,37,38] Since no alternative calibration is available for large populations,[54] the problem will not readily be solved. We chose to compare central BP with cuff measurement because it remains the reference. The added value of central BP cumulates to the one of brachial BP because nearly all epidemiological data are based on the latter.

Clinical implications

Several studies have clearly showed that central BP is more representative of the BP acting on target organs than brachial BP. Although central BP is used for nearly 25 years, there are still no widely sourced reference values for cSBP per se or for its comparison

with bSBP until the collection and analysis of these data. The present study provides distributions of central BP values and amplification of BP in a Normal (no RFs) and a Reference population (with RFs), according to age and sex. We show evidence for a strong interaction between sex and age of its effect on central BP. At any age or BP category, men had higher amplification than women. We further show that younger men with high BP have extreme amplification. Whether age and sex should be used in defining normal cSBP, or if amplification is interesting above cSBP itself for taking care of patients remain to be established.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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