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ORIGINAL ARTICLE

Mean arterial pressure values calculated using seven different methods and their associations with target organ deterioration in a single-center study of 1878 individuals

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To assess the differences among seven different methods for the calculation of mean arterial pressure (MAP) and to identify the formula that provides MAP values that are more closely associated with target organ deterioration as expressed by the carotid cross-sectional area (CSA), carotid-to-femoral pulse-wave velocity (cf-PWV) and left ventricular mass (LVM). The study population consisted of 1878 subjects who underwent noninvasive cardiovascular risk assessment. Blood pressure (BP) was assessed in all subjects, and MAP was calculated by direct oscillometry and six different formulas. Carotid artery ultrasound imaging was performed in 1628 subjects. The CSA of the right and left common carotid artery (CCA) were calculated and used as surrogates of arterial wall mass and hypertrophy. Aortic stiffness was evaluated in 1763 subjects by measuring the cf-PWV. Finally, 218 subjects underwent echocardiographic examination for the assessment of LVM. Among the examined methods of MAP calculation, the formula $MAP_1 = [\text{diastolic BP}] + 0.412 \times [\text{pulse pressure}]$ yielded the strongest correlations with the LVM, cf-PWV and CSA of the right and left CCA, even after adjusting for age and gender. The MAP calculation using the 0.412 was superior compared with the traditional formula that uses the 0.33 for the discrimination of subjects with left ventricular and carotid wall hypertrophy, as well as subjects with increased aortic stiffness. MAP estimated with the 0.412 is better correlated with target organ deterioration compared with other formulas. Future studies are needed to explore the accuracy of these formulas for MAP estimation compared with direct intra-arterial BP measurement.
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INTRODUCTION

Mean arterial blood pressure (MAP) is the major hemodynamic determinant of tissue perfusion regardless of pulse pressure, and it is also a key parameter that influences cardiac function and the wall properties of central arteries. Higher MAP levels are related to cardiovascular (CV) disease and target organ damage, whereas low levels may be detrimental in hemodynamically unstable, critically ill patients. Beyond the pathophysiological and clinical relevance of MAP, there are many circumstances in which a MAP calculation is required, such as the determination of peripheral vascular resistance, fractional pulse pressure, calibration of devices that estimate central blood pressure (BP) and others.[1–4]

Undoubtedly, it is essential to estimate MAP values accurately. The gold-standard method for the measurement of the 'actual' value of MAP is the calculation of the area under the BP waveform, as determined by the time-averaged BP values over the cardiac cycle, which is recorded invasively by catheter-manometer systems. However, in routine clinical practice, MAP is estimated non-invasively either by using the internal proprietary algorithms of automated oscillometric sphygmomanometers or by mathematical formulas. The accuracy of MAP estimation using oscillometric devices is rarely reported in the literature, and most importantly, several commercial devices do not report MAP, but use it to calculate the systolic and diastolic BP via proprietary algorithms.

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Table 1 Formulas and methods for MAP estimation that were used in the present study

Abbreviation	*Method*	*Reference*
MAP_1	$MAP = 0.42 \times SBP + 0.58 \times DBP$	Wezler and Bögerr[6]
	or	
	$MAP = DBP + 0.412 \times PP$	Meaney *et al.*[7]
MAP_2	$MAP = DBP + 0.33 \times PP$	Gauer[8]
MAP_3	$MAP = DBP + 0.33 \times PP + 5$	Chemla *et al.*[9]
MAP_4	$MAP = DBP + [0.33 + (0.0012 \times HR)] \times PP$	Razminia *et al.*[10]
MAP_5	$MAP = (SBP \times DBP)^{1/2}$	Chemla *et al.*[11]
MAP_6	Integration of pressure waveforms recorded non-invasively (that is, by oscillometry or applanation tonometry) and calibrated by brachial SBP and DBP values	O'Rourke *et al.*[12]
MAP_7	Internal proprietary algorithms of validated automated oscillometric device	

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure.

Pressure waveforms differ along the arterial tree due to wave propagation and reflection phenomena. The change in the shape of pressure waves can be quantified via the so-called 'form factor,' which characterizes the ratio of the difference between its mean and minimum values over the amplitude of a wave.[5] Therefore, the form factor not only quantifies the shape of the wave, but it also expresses the percentage of pulse pressure to add to diastolic blood pressure (DBP) to estimate MAP.

On the basis of the concept of 'form factor,' several equations have been proposed for the calculation of MAP, as reported in Table 1. In 1939, Wezler and Bögerr[6] proposed the formula $MAP = 0.42 \times SBP + 0.58 \times DBP$, where SBP is the systolic and DBP is the diastolic BP. Meaney *et al.*[7] proposed an alternative expression of the above formula as follows: $MAP_1 = DBP + 0.412 \times PP$, where PP is the pulse pressure. The most common and widely used formula for MAP calculation is that proposed by Gauer in 1960:[8] $MAP_2 = DBP + 0.33 \times PP$. In 1999, Chemla *et al.*[9] proposed an improvement for the traditional formula, with $MAP_3 = DBP + 0.33 \times PP + 5$ mm Hg. Razminia *et al.*[10] in 2004 included the heart rate in the equation for MAP calculation as follows: $MAP_4 = DBP + [0.33 + (0.0012 \times HR)] \times PP$. In essence, these formulas differ in the coefficient used to integrate PP in the algorithm, which actually represents the form factor of the pressure waveform.[2] Chemla *et al.*,[11] in 2005, proposed a different mathematical equation based on the product of SBP by DBP: $MAP_5 = (SBP \times DBP)^{1/2}$. MAP can also be calculated by the integration of pressure waveforms recorded non-invasively (that is, applanation tonometry) and calibrated by brachial SBP and DBP values (MAP_6).[12] Finally, in the present analysis, the 'original' MAP (MAP_7), as provided by the proprietary algorithm of a commercially available automated oscillometric device, was also examined.

Currently, there is no consensus regarding which formula yields the most accurate MAP estimation, although MAP_2 is the most popular and widely used equation. In addition, there is a lack of evidence regarding which of these different MAP estimates is better associated with target organ damage. The objective of this study was to assess the differences among the original MAP values provided by a commercially available automated oscillometric device and the various MAP levels calculated using different formulas (Table 1). We also determined which method provides MAP values that are more closely associated with target organ characteristics and deterioration as expressed by the left ventricular mass, carotid wall thickness and stiffness of the aorta. Because aging and gender significantly modulate the form factor of the pressure waveform, these two parameters were taken into particular consideration in the present analysis.

Table 2 Descriptive, clinical, hemodynamic and cardiovascular characteristics of the study population

Parameter	*Total N*	*Mean ± s.d.*
Age (years)	1878	52.4 ± 14.1
Height (cm)	1878	169 ± 10
Weight (kg)	1878	78.1 ± 17.3
Body mass index (kg m^{-2})	1878	27.2 ± 5.2
Gender (males, %)	1878	49.3
Smoking (yes, %)	1878	33.8
Hypertension (yes, %)	1866	54.3
Dyslipidemia (yes, %)	1865	31
Diabetes (Type I, %)	1866	4
Diabetes (Type II, %)	1866	13.1
History of CAD (yes, %)	1878	9.1
Hemodynamic and cardiovascular parameters		
Systolic BP (mm Hg)	1878	128.2 ± 17.5
Diastolic BP (mm Hg)	1878	77.4 ± 10.4
Pulse pressure (mm Hg)	1878	50.8 ± 12.8
Heart rate (b.p.m.)	1878	66.3 ± 10.0
cf-PWV (m s^{-1})	1763	8.5 ± 2.3
Cross sectional area LCCA (mm^2)	1631	14.7 ± 4.8
Cross sectional area RCCA (mm^2)	1628	13.8 ± 4.4
Left ventricular mass (g m^{-2})	218	83.5 ± 19.4

Abbreviations: BP, blood pressure; cf-PWV, carotid-to-femoral pulse-wave velocity; LCCA, left common carotid artery; RCCA, right common carotid artery.

METHODS

Study population

The study population consisted of 1878 subjects (Caucasians) who were referred to the Cardiovascular Research Laboratory of the First Deptartment of Propaedeutic and Internal Medicine, Laiko University Hospital for CV risk assessment due to the presence of either classical and/or novel chronic inflammatory diseases. The population characteristics are shown in Table 2. All subjects had a normal sinus rhythm. Subjects with arrhythmia and severe obesity (body mass index >40 kg m^{-2}) were excluded from the study because applanation arterial tonometry and pulse-wave analysis were not feasible or had an unacceptable quality. All subjects were examined in a quiet, temperature-controlled environment (22–25 °C). According to laboratory routine practice, patients under pharmaceutical treatment were advised to abstain from their medication for at least 10 h prior to the examination, as well as to abstain from alcohol, caffeinated beverages or any other vasoactive substances for at least 3 h. The study protocol complied with the declarations of Helsinki and was approved by the institutional scientific committee. All subjects gave informed consent before entering the study.

Blood pressure measurement at the brachial artery

Brachial BP was assessed at the supine position after at least 10 min of rest. Triple brachial BP recording was performed (with 1-min interval between readings) in the right arm with a validated automated oscillometric device (Microlife WatchBP Office, Microlife AG, Widnau, Switzerland).[13] The average value of the three BP readings (for SBP and DBP) was used for the calculation of MAP values using the examined methods (Table 1).

Non-invasive recording of continuous blood pressure waves

MAP was also determined by the integration of calibrated radial pressure waves recorded by applanation tonometry, which was performed immediately after the BP triple measurement. In particular, continuous pressure waves were recorded by a high-fidelity tonometer (Millar Instruments, Houston, TX, USA),

and an averaged single pressure wave was determined using the Sphygmocor Software (Atcor Medical, West Ryde, Australia). In addition, the average value for the heart rate was determined by the system based on the cardiac periods of the recorded pressure waves, and this value was used for the calculation of MAP_4. The acquired tonometric waves were calibrated using the respective SBP and DBP levels measured at the brachial artery. The calibration of radial pressure waves using brachial SBP and DBP measured by cuff oscillometry assumes that the brachial BP is equal to the radial BP. However, this assumption may not be accurate because it is possible to have an amplification of the SBP between the brachial and radial artery.[5]

Left ventricular mass assessment

Left ventricular mass (LVM) and hypertrophy (LVH) were assessed as previously described.[14] In brief, transthoracic echocardiography was performed in all patients by the same operator using a high-end ultrasound system (Vivid 7 Pro, General Electric, Fairfield, CT, USA) in accordance with the American Society of Echocardiography (ASE) and European Association of Echocardiography guidelines and recommendations.[15] Measurements for the M-mode-guided calculation of LVM were recorded in the parasternal short-axis view. LVM was further standardized to body size, providing the LVM index (LVMI). LVMI was calculated by the ratio of LVM to body surface area (BSA), where $BSA = [(\text{weight} \times \text{height})/3600]^{0.5}$.

Carotid wall hypertrophy

Carotid wall CSA, instead of intima-medial thickness, was used as a more comprehensive index of the arterial wall volume or mass because it is closer to arterial hypertrophy[16] using a previously applied formula.[17] Briefly, the common carotid artery was scanned for the presence of plaques. The average intimal-medial thickness of a plaque-free segment of the common carotid artery (1 cm proximally to the bifurcation) was measured by a dedicated inbuilt software (Vivid 7 Pro). Two sequential CSA of the same common carotid segment were analyzed, and their mean value was used in the analysis.

Assessment of aortic stiffness

Aortic stiffness was assessed by measuring the carotid-to-femoral pulse-wave velocity (cf-PWV) as previously described.[18] In brief, cf-PWV is calculated by the ratio of the estimated pulse transit time and the distance travelled by the pressure wave between the two recording sites. Several methods exist for pulse transit time estimation, which may often yield divergent results.[19] In this study, we used the tangential (or intersecting tangents) method, which was implemented at the SphygmoCor system (AtCor Medical, Sydney, Australia). At first, the travel distance of the pressure wave was determined as the distance from the suprasternic notch to the femoral artery minus the distance from the carotid artery to the suprasternic notch. Then, arterial pressure waves were recorded by applanation tonometry using a high-fidelity hand-held tonometer (SPT-301, Millar Instruments). Pressure waves were first recorded at the carotid artery and then, within a few seconds, at the femoral artery. The time delay between the two waves (transit time) was determined using registration with a simultaneously recorded ECG. All recordings were made at the supine position. At least two repeated measurements of PWV were performed, and their average value was used in the analysis as previously recommended.[20]

Assessment of target organ deterioration

The following indices were considered as indicators of target organ deterioration:

- LVH defined as LVMI values >95 g m^{-2} in women or >115 g m^{-2} in men using the ASE formula.[15]
- Increased aortic stiffness, defined as cf-PWV >10 m s^{-1}.[21]
- Carotid wall hypertrophy, defined arbitrarily by the 4th upper quartile of CSA-RCCA or CSA-LCCA values.

All vascular studies were performed by the same experienced operator using the same device for each examination.

Statistical analysis

The agreement between different MAP estimations was assessed using the Bland and Altman analysis.[22] According to this method, the differences between the two measurements (bias) $= (MAP_i - MAP_j)$ are plotted against their mean value, $(MAP_i+MAP_j)/2$. The s.d. of the differences between the two different MAP estimates was also determined. Furthermore, we used the Pearson correlation coefficient (r), intraclass correlation coefficient (ICC) and coefficient of variation (CVar) to assess the agreement, consistency and variation between different MAP estimates. These statistical methods and parameters were described thoroughly elsewhere.[23,24] The bivariate association of each MAP estimate with parameters assessing the target organs (LV and carotid wall mass as well as cf-PWV) was evaluated using the Pearson correlation coefficient. Further multivariate regression models were used to adjust the relationship of MAP with each parameter of target organ deterioration for age and gender. Williams' statistic, which is often noted as Steiger's Z-test, was used to compare the correlation coefficients of cardiovascular parameters with MAP values. Receiver operating characteristic (ROC) curve analysis was used to determine the comparative ability of different MAP estimates to discriminate subjects with target organ damage. Areas under the ROC curves were compared based on the methodology proposed by DeLong, DeLong and Clarke-Pearson.[25] All tests were two-tailed, and statistical significance was indicated by P-values <0.05. Statistical analysis was performed using SPSS 20 (IBM Corp., Armonk, NY, USA).

RESULTS

The demographic, clinical and hemodynamic characteristics of the study population are reported in Table 2. The MAP values estimated using the seven different formulas/methods were compared with each

Table 3 Variation and agreement between different estimates of mean arterial blood pressure (MAP) values

MAP pairs	*Coefficient of variation (%)*	*Pearson (r)*	*Intraclass correlation coefficient*
MAP_1 *vs.* MAP_2	3.06	0.997	0.939
MAP_1 *vs.* MAP_3	0.85	0.997	0.994
MAP_1 *vs.* MAP_4	0.36	0.999	0.999
MAP_1 *vs.* MAP_5	0.86	0.999	0.995
MAP_1 *vs.* MAP_6	2.02	0.981	0.963
MAP_1 *vs.* MAP_7[a]	15.29	0.831	0.702
MAP_2 *vs.* MAP_3[b]	3.71	1.000	0.917
MAP_2 *vs.* MAP_4	2.96	0.997	0.942
MAP_2 *vs.* MAP_5	3.88	0.999	0.909
MAP_2 *vs.* MAP_6	1.79	0.983	0.970
MAP_2 *vs.* MAP_7[a]	12.95	0.835	0.800
MAP_3 *vs.* MAP_4	0.98	0.997	0.992
MAP_3 *vs.* MAP_5	0.43	0.999	0.998
MAP_3 *vs.* MAP_6	2.60	0.983	0.947
MAP_3 *vs.* MAP_7[a]	15.48	0.835	0.669
MAP_4 *vs.* MAP_5	0.98	0.998	0.993
MAP_4 *vs.* MAP_6	1.93	0.981	0.965
MAP_4 *vs.* MAP_7[a]	15.27	0.827	0.704
MAP_5 *vs.* MAP_6	2.71	0.983	0.945
MAP_5 *vs.* MAP_7[a]	15.94	0.833	0.670
MAP_6 *vs.* MAP_7[a]	14.26	0.826	0.761

Abbreviation: MAP, mean arterial blood pressure.
$MAP_1 = DBP+0.412 \times PP$.
$MAP_2 = DBP+0.33 \times PP$.
$MAP_3 = DBP+0.33 \times PP+5$ (this formula provides identical correlations with MAP_2).
$MAP_4 = DBP+[0.33+(0.0012 \times HR)] \times PP$.
$MAP_5 = (SBP \times DBP)^{1/2}$.
MAP_6 = integration of pressure wave.
MAP7 = internal proprietary algorithm of oscillometric device.
[a]MAP_7 was measured only in a subgroup of 872 subjects, while $MAP_{1,2,3,4,5,6}$ were estimated for the total population.
[b]Correlation between MAP_2 and MAP_3 is redundant since these two estimates are linearly related by definition.

other. The statistical parameters indicating variation and agreement between different MAP estimates are shown in Table 3. The mean ± s.d. value of the MAP values determined by each formula is depicted in Figure 1. The mean differences and s.d. of differences between each pair of different estimates for MAP are presented in Figure 2.

Association of each MAP estimate with cardiovascular parameters

The bivariate correlations of each MAP estimate with LVMI, carotid wall mass and aortic stiffness are reported in Table 4. All MAP estimates are correlated with all of the examined cardiac and vascular parameters ($P<0.01$). Among the seven different MAP estimates, MAP_1 yielded the strongest correlation with all three cardiovascular parameters. MAP_7 provided the lowest correlation coefficient. We compared the correlation coefficient of LVMI with MAP_1 ($r=0.212$) with the respective correlation coefficient of LVMI with the traditional MAP_2 estimate ($r=0.202$). The two correlation coefficients were marginally not significantly different ($P=0.052$). The correlation coefficients of MAP_1 with CSA-LCCA ($r=0.35$) and CSA-RCCA ($r=0.365$) were higher ($P<0.001$) than the respective coefficients of MAP_2 ($r=0.332$ and $r=0.344$). Finally, the correlation of MAP_1 with cf-PWV ($r=0.441$) was significantly stronger than the respective correlation ($r=0.415$) with MAP_2 ($P<0.001$). MAP_1 yielded significantly higher correlation coefficients with LVMI, the CSA of the right and left common carotid artery, as well as with cf-PWV compared with the MAP_7 value estimated by the internal algorithm of the automated oscillometric device used in this study. The correlation coefficients of MAP_1 with cardiovascular parameters were compared only with those of MAP_2 because the latter provided the closest results to the former compared with the remaining $MAP_{3,4,5,6,7}$ values.

The relationship of each MAP estimate with the parameters of target organ damage was further assessed after adjusting for age and gender (Table 5). MAP_1 was, still, better associated with LVMI, CSA-LCCA, CSA-RCCA and cf-PWV compared with the traditional formula (MAP_2).

Association of MAP_1 and MAP_2 estimates with target organ deterioration

Assessment of the comparative ability of MAP_1 and MAP_2 to discriminate target organ deterioration was performed by ROC curve analysis. MAP_1 had a greater ability than MAP_2 to discriminate LV hypertrophy and carotid wall hypertrophy (cross-sectional area at the fourth quartile of the studied population) as well as aortic stiffness

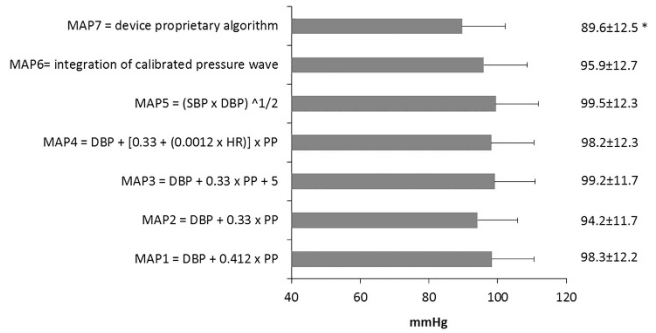

Figure 1 Mean value ± s.d. of mean arterial pressure (MAP) estimated by each different method. *MAP values by using the Microlife WatchBP device was recorded in 872 subjects. A full color version of this figure is available at *Hypertension Research* journal online.

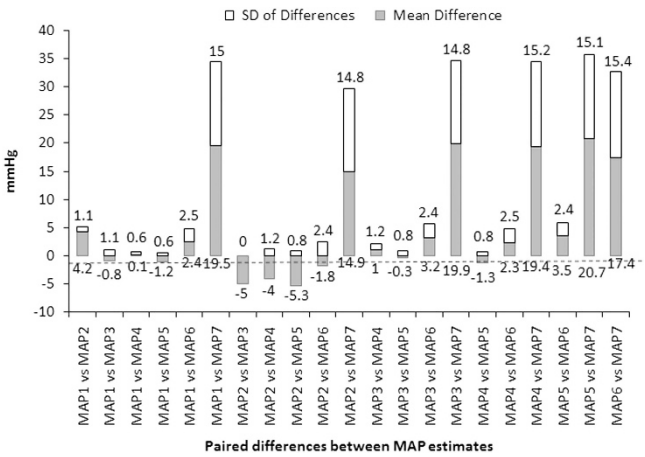

Figure 2 Mean differences and s.d. of differences from paired comparisons between MAP estimates derived by different methods/formulas as defined in Table 1. A full color version of this figure is available at *Hypertension Research* journal online.

Table 4 Bivariate linear correlations between different estimates of MAP and parameters of target organs deterioration

Parameter	*MAP_1 (mm Hg)*	*MAP_2 (mm Hg)*	*MAP_3[a] (mm Hg)*	*MAP_4 (mm Hg)*	*MAP_5 (mm Hg)*	*MAP_6 (mm Hg)*	*MAP_7 (mm Hg)*
Mean arterial pressure calculations by different formulas							
LVMI (g m^{-2})	0.212 (0.002)	0.202 (0.003)	0.202 (0.003)	0.199 (0.003)	0.207 (0.002)	0.191 (0.005)	N/A
	$N=218$	$N=218$	$N=218$	$N=218$	$N=218$	$N=218$	
CSA-LCCA	0.350 (<0.001)	0.332 (<0.001)	0.332 (<0.001)	0.343 (<0.001)	0.341 (<0.001)	0.339 (<0.001)	0.302 (<0.001)
	$N=1631$	$N=1631$	$N=1631$	$N=1631$	$N=1631$	$N=1631$	$N=727$
CSA-RCCA	0.365 (<0.001)	0.344 (<0.001)	0.344 (<0.001)	0.357 (<0.001)	0.354 (<0.001)	0.349 (<0.001)	0.318 (<0.001)
	$N=1628$	$N=1628$	$N=1628$	$N=1628$	$N=1628$	$N=1628$	$N=728$
cf-PWV	0.441 (<0.001)	0.415 (<0.001)	0.415 (<0.001)	0.439 (<0.001)	0.427 (<0.001)	0.427 (<0.001)	0.374 (<0.001)
	$N=1763$	$N=1763$	$N=1763$	$N=1763$	$N=1763$	$N=1763$	$N=784$

Abbreviations: cf-PWV, carotid-to-femoral pulse-wave velocity; CSA-LCCA, cross-sectional area of left common carotid artery; CSA-RCCA, cross-sectional area of right common carotid artery; DBP, diastolic blood pressure; HR, heart rate; LVMI, left ventricular mass index; MAP, mean arterial pressure; PP, pulse pressure.
$MAP_1 = DBP + 0.412 \times PP$.
$MAP_2 = DBP + 0.33 \times PP$.
$MAP_4 = DBP + [0.33 + (0.0012 \times HR)] \times PP$.
$MAP_5 = (SBP \times DBP)^{1/2}$.
MAP_6 = integration of pressure wave.
MAP_7 = internal proprietary algorithm of oscillometric device.
[a]$MAP_3 = DBP + 0.33 \times PP + 5$ (this formula provides identical correlations with MAP_2).

Table 5 Multivariate linear regression between different estimates of mean arterial pressure (MAP) and parameters of target organs damage, after adjustment for age and gender (values correspond to standardized coefficient beta and *P*-value from each MAP as well as model's R^2)

MODELS	MAP_1	MAP_2	MAP_3[a]	MAP_4	MAP_5	MAP_6	MAP_7
Dependent variable: left ventricular mass (LVMI; N = *217)*							
Adjusted for age	0.193; 0.004	0.187; 0.005	[a]	0.181; 0.007	0.191; 0.004	0.168; 0.012	N/A
	$R^2=0.081$	$R^2=0.078$		$R^2=0.076$	$R^2=0.080$	$R^2=0.072$	
Adjusted for gender	0.190; 0.003	0.175; 0.007	[a]	0.178; 0.006	0.182; 0.005	0.185; 0.004	N/A
	$R^2=0.137$	$R^2=0.132$		$R^2=0.133$	$R^2=0.134$	$R^2=0.136$	
Adjusted for age and gender	0.151; 0.014	0.143; 0.019	[a]	0.141; 0.022	0.147; 0.016	0.145; 0.018	N/A
	$R^2=0.226$	$R^2=0.223$		$R^2=0.223$	$R^2=0.224$	$R^2=0.224$	
MODELS	MAP_1	MAP_2	MAP_3[a]	MAP_4	MAP_5	MAP_6	MAP_7[b]
Dependent variable: right carotid wall thickness (CSA-RCCA; N = *1628)*							
Adjusted for age	0.235; <0.001	0.223; <0.001	[a]	0.231; <0.001	0.228; <0.001	0.206; <0.001	0.212; <0.001
	$R^2=0.375$	$R^2=0.370$		$R^2=0.373$	$R^2=0.371$	$R^2=0.362$	$R^2=0.327$
Adjusted for gender	0.359; <0.001	0.338; <0.001	[a]	0.352; <0.001	0.348; <0.001	0.345; <0.001	0.309; <0.001
	$R^2=0.134$	$R^2=0.120$		$R^2=0.129$	$R^2=0.127$	$R^2=0.126$	$R^2=0.107$
Adjusted for age and gender	0.204; <0.001	0.190; <0.001	[a]	0.200; <0.001	0.196; <0.001	0.181; <0.001	0.188; <0.001
	$R^2=0.399$	$R^2=0.395$		$R^2=0.398$	$R^2=0.397$	$R^2=0.392$	$R^2=0.348$
Dependent variable: left carotid wall thickness (CSA-LCCA; N = *1627)*							
Adjusted for age	0.226; <0.001	0.217; <0.001	[a]	0.223; <0.001	0.221; <0.001	0.202; <0.001	0.194; <0.001
	$R^2=0.350$	$R^2=0.347$		$R^2=0.349$	$R^2=0.348$	$R^2=0.340$	$R^2=0.315$
Adjusted for gender	0.338; <0.001	0.320; <0.001	[a]	0.331; <0.001	0.329; <0.001	0.331; <0.001	0.286; <0.001
	$R^2=0.130$	$R^2=0.117$		$R^2=0.125$	$R^2=0.123$	$R^2=0.126$	$R^2=0.106$
Adjusted for age and gender	0.186; <0.001	0.176; <0.001	[a]	0.184; <0.001	0.181; <0.001	0.171; <0.001	0.164; <0.001
	$R^2=0.389$	$R^2=0.386$		$R^2=0.389$	$R^2=0.388$	$R^2=0.385$	$R^2=0.351$
Dependent variable: aortic stiffness (cf-PWV; N = *1762)*							
Adjusted for age	0.291; <0.001	0.275; <0.001	[a]	0.292; <0.001	0.282; <0.001	0.261; <0.001	0.262; <0.001
	$R^2=0.480$	$R^2=0.472$		$R^2=0.481$	$R^2=0.475$	$R^2=0.463$	$R^2=0.426$
Adjusted for gender	0.451; <0.001	0.426; <0.001	[a]	0.449; <0.001	0.438; <0.001	0.430; <0.001	0.373; <0.001
	$R^2=0.198$	$R^2=0.176$		$R^2=0.196$	$R^2=0.186$	$R^2=0.183$	$R^2=0.140$
Adjusted for age and gender	0.276; <0.001	0.259; <0.001	[a]	0.278; <0.001	0.267; <0.001	0.246; <0.001	0.244; <0.001
	$R^2=0.483$	$R^2=0.476$		$R^2=0.485$	$R^2=0.479$	$R^2=0.470$	$R^2=0.431$

Abbreviations: cf-PWV, carotid-to-femoral pulse-wave velocity; CSA-LCCA, cross-sectional area of left common carotid artery; CSA-RCCA, cross-sectional area of right common carotid artery; DBP, diastolic blood pressure; HR, heart rate; LVMI, left ventricular mass index; MAP, mean arterial pressure; PP, pulse pressure.
$MAP_1 = DBP+0.412\times PP$.
$MAP_2 = DBP+0.33\times PP$.
$MAP_4 = DBP+[0.33+(0.0012\times HR)]\times PP$.
$MAP_5 = (SBP\times DBP)^{1/2}$.
MAP_6 = integration of pressure wave.
MAP_7 = internal proprietary algorithm of oscillometric device.
N/A: <20 subjects underwent both LVM assessment and MAP estimation by the Microlife apparatus.
[a]$MAP_3 = DBP+0.33\times PP+5$ (this formula provides identical correlations with MAP_2).
[b]Models including MAP_7 in the independent variables were performed in a subgroup of 727 subjects with CSA measurements and in 783 subjects with PWV measurements.

(defined by cf-PWV values greater than 10 m s^{-1}), as shown by the larger areas under the ROC curves (Table 6).

DISCUSSION

The present study evaluated, for the first time, the association of 7 different MAP estimates using various methods (formulas) with LVM, carotid wall mass and aortic stiffness. The formula proposed by Meaney *et al.*, $MAP_1 = DBP+0.412\times PP$,[7] provided MAP values better related to these cardiovascular parameters than the respective MAP values estimated using the classic formula, $MAP_2 = DBP+0.33\times PP$. Furthermore, MAP_1 was a better discriminator than MAP_2 for subjects with left ventricular and carotid wall hypertrophy, as well as with increased aortic stiffness. The other MAP estimates ($MAP_{3,4,5,6,7}$) were less able to discriminate subjects with target organ deterioration.

Physiological and clinical relevance of mean arterial blood pressure

The mean arterial BP is the actual driving pressure for peripheral blood flow and is, physiologically, a better indicator of perfusion to vital organs than systolic blood pressure. MAP values together with measures of cardiac output permit the estimation of peripheral resistance. When MAP is perturbed from the regulated level, cardiac output and total peripheral resistance are adjusted to restore MAP back to the appropriate level. This regulation occurs due to the reflex of baroreceptors, which are located in the carotid sinus and also in the aortic arch and ventricles.

In some populations, MAP is a stronger determinant of LV structural features compared with other BP parameters.[26] Moreover, in specific populations, MAP may be more accurate in predicting cardiovascular prognosis than other BP parameters, such as systolic

Table 6 Assessment of the comparative ability of MAP_1 and MAP_2 to discriminate target organ deterioration by ROC curve analysis

	N	*ROC area*	*95% confidence interval*	P-*value*
Left ventricular hypertrophy				
MAP_1	218	0.595	0.488–0.702	0.022
MAP_2	218	0.579	0.472–0.685	
Right Carotid Wall Hypertrophy				
MAP_1	1628	0.681	0.651–0.710	<0.001
MAP_2	1628	0.667	0.637–0.696	
Left Carotid Wall Hypertrophy				
MAP_1	1631	0.674	0.645–0.704	<0.001
MAP_2	1631	0.634	0.634–0.693	
Aortic Stiffness				
MAP_1	1763	0.750	0.723–0.778	<0.001
MAP_2	1763	0.731	0.703–0.760	

Abbreviations: DBP, diastolic blood pressure; MAP, Mean arterial pressure; PP, pulse pressure; ROC, receiver operating characteristic.
$MAP_1 = DBP + 0.412 \times PP$.
$MAP_2 = DBP + 0.33 \times PP$.

and diastolic pressure.[27,28] In addition, mean rather than systolic BP is the preferred metric in the intensive care unit to guide therapy.[29] The superiority of MAP over the SBP was also observed in the BOSHI study,[30] which compared measurements of maternal home BP with clinic BP before 20 weeks of gestation to determine associations with the risk of delivering a lower-birth-weight infant. It was reported that high maternal home DBP and MAP, but not SBP, before 20 weeks of gestation was independently associated with a higher risk of lower infant birth weight than clinic DBP and MAP.[30]

In clinical practice, there are several situations in which it is essential to monitor MAP levels. For example, in patients with sepsis, vasopressors are often titrated based on the MAP. According to the guidelines of the Surviving Sepsis Campaign,[31] it is recommended that MAP should be maintained $\geqslant 65$ mm Hg. In addition, treatment of patients with stroke or head injury may depend on the patient's MAP, whereas the admission MAP, as assessed using the form factor 0.3, in patients with stroke is an important parameter.[32] Another recent but critical application of MAP is the calibration of devices for the noninvasive estimation of central aortic BP.[33–35] A common method for the calibration of recorded arterial pulse waves relies on the use of MAP and DBP values, which strongly affect the accuracy of measurements.[36]

However, until now, clinical practice has traditionally relied on the noninvasive auscultatory method to measure SBP and DBP. By contrast, MAP constitutes the sole parameter physically measured by the most current oscillometric techniques, but these values are often not reported. Thus, alternatively, MAP is calculated using a formula, most often one of those examined in this study. It should be noted, however, that current practice guidelines have been slow to integrate MAP evaluation in vital sign monitoring. For example, Cardiology and Hypertension Societies define hypertension based on SBP and DBP measurements only.[37] By contrast, the Society for Critical Care Medicine[38] has utilized both systolic and mean arterial blood pressure for defining sepsis-induced hypotension, whereas MAP is used as a therapeutic target.

Association of MAP with target organ deterioration

In this study, we found that MAP is positively associated with LVM, which is consistent with previous findings.[39–41] However, the present study showed that the MAP calculation using a form factor of 0.412 is better related to LVM than MAP values derived from the form factor 0.33 (1/3). Furthermore, MAP_1 (*vs.* the traditional MAP_2) was a better discriminator of subjects with LV hypertrophy. Similarly, all MAP values were positively related with the right and left carotid wall mass, which is consistent with previous studies,[42–44] but again, MAP_1 was the strongest determinant of the carotid wall mass. Finally, aortic stiffness, as assessed by carotid-to-femoral PWV, was positively related with MAP levels.[45,46] MAP_1 yielded the highest correlation coefficient and was also a better discriminator of subjects with increased aortic stiffness ($PWV > 10\ m\ s^{-1}$). Of the seven examined methods for MAP estimation, the internal proprietary algorithm of the utilized automated oscillometric device provided MAP values, which had the lowest association with the parameters of target organ damage.

Notably, all formulas using a single form factor for the estimation of MAP based on brachial BP measurements have inherent flaws when applied to different populations. However, in the Asklipeios Study,[5] Segers *et al.* found that the values of the form factor at the brachial artery for different age groups and gender are close to the value of 0.4. Furthermore, there is a non-negligible amplification of SBP between the brachial and the radial artery,[5] which suggests that the use of the MAP_6 method may include an additional source of error in MAP estimation. More importantly, in a previous invasive study providing intra-arterial pressures at the brachial artery, it was observed that the mean pressure at the upper arm is underestimated when calculated using the traditional formula of adding one-third of the pulse pressure to the diastolic pressure.[47] Conversely, this underestimation can be avoided by adding 40% of the pulse pressure to the diastolic pressure,[47] suggesting that the use of the form factor 0.4 yields more accurate MAP estimations compared to invasive measurements. The above studies[5,47] further support our findings. Undoubtedly, invasive studies are needed to examine the accuracy of the various methods and techniques for the noninvasive estimation of MAP and larger scale studies are needed in different populations to further determine whether the most accurate MAP estimation is translated to superior clinical relevance.

Limitations

This study did not evaluate the accuracy of each different MAP estimation, which could ideally be achieved by comparison of the estimated MAP values with directly measured MAP through the intra-arterial, continuous recording of blood pressure waves. Therefore, substantial and thorough reasoning for which method of MAP estimation should be considered the most accurate cannot be derived by the present analysis. Consequently, these findings regarding the highest correlation to target organ deterioration should not be confused with better accuracy.

Unfortunately, LVM was assessed only in a small number of patients ($N = 218$) compared to the total population ($N = 1878$). In addition, there were no available data with which to test the association of MAP_7 with LVM.

CONCLUSIONS

In the existing literature, it is evident that MAP is most frequently calculated by the MAP_2 formula. This formula is basically derived using the widely applied rule of thumb that assumes a form factor of one-third (33%). However, it has been previously found that 'this

value is too low and that the one-third rule to estimate mean arterial pressure should be reconsidered.'[5]

In many published studies, which formula was used for the MAP calculation is often unknown. In the present study, we demonstrated that the estimation of MAP using the form factor value 0.412 provides values that are more strongly related with cardiovascular parameters compared with MAP determined by the traditional formula, which uses the form factor value 0.33. More importantly, we found that the parameters of target organ deterioration, such as left ventricular and carotid wall hypertrophy as well as increased aortic stiffness, are better related with MAP_1 than MAP_2 values. This evidence supports that MAP_1 may have a superior diagnostic or even prognostic ability compared with the traditional formula (MAP_2), but this should be investigated further. In addition, future invasive validation studies are required to determine the accuracy of the different MAP estimates using the various available formulas compared with intra-arterially measured mean arterial pressures.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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