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ABSTRACT

Background: Carotid-femoral pulse wave velocity (PWV) is a direct measure of aortic stiffness used in the stratification of cardiovascular risk. Its clinical application in Latin America has been limited by the absence of reference values. The objective of this study was to establish PWV reference values among adults referred to a specialized cardiology center for 24-hour ambulatory blood pressure monitoring (ABPM) in Medellín, Colombia.
Methods: A descriptive study of 3,160 records of adult (older than 18 years) patients without pharmacological treatment assessed for PWV using a Mobil-O-Graph® 24-hour PWA device (IEM, Stolberg, Germany) and 24-hour ABPM with hemodynamic parameters based on suspected hypertension or hypotension was conducted. Patient records were categorized by decade of age and sub-divided based on the following 24-hour ABPM categories: normal (< 130/80 mmHg), grade I hypertension (between 130–150/80–90 mmHg), and grade II hypertension (> 150/90 mmHg).
Results: PWV increased with age (r = 0,894; p < 0,001) and blood pressure category (ρ = 0,081; p < 0,001); the age-related increase was more pronounced among the patients in the higher blood pressure categories. Measures of central tendency and dispersion regarding PWV are presented, and reference values are proposed from the 90th percentile based on the age and 24-hour ABPM categories.
Conclusions: PWV is directly related to age and blood pressure and can be predicted using a simple equation that includes these two variables. To stratify the cardiovascular risk of patients and make clinical decisions, the 90th percentile based on the age and 24-hour ABPM categories is recommended as a cut-off.

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Adult; atherosclerosis; vascular stiffness; blood pressure; pulse wave velocity; ambulatory blood pressure monitoring

Introduction

Cardiovascular disease is a chronic clinical condition that represents a great burden for global public health due to its high morbidity and mortality (1). For this reason, the evaluation of cardiovascular risk has become highly relevant because it has allowed researchers to stratify populations and establish prevention and treatment measures (2). For this evaluation, in addition to classical risk factors and biochemical markers (2), other predictive methods for assessing the structure and function of the large arteries have been developed (3) based on the concept of arterial stiffness. These changes in arterial function can be evaluated non-invasively and are predictive of premature vascular damage (4).

To quantify arterial stiffness, various methods have been used (5); however, carotid-femoral pulse wave velocity (PWV), which is obtained via tonometry, is the reference technique (6). More recently, other validated methods based on the oscillometric technique have been used (7). These methods estimate the speed of systolic pulse pressure waves along the aorta and large vascular branches (8). Broadly speaking, the volume of blood ejected from the heart in systole expands the ascending aorta and generates a pulse pressure wave that propagates through the aorta depending on its properties. The propagation speed of this wave indicates the degree of arterial stiffness; a faster speed reflects greater vascular rigidity, which depends both on mean arterial pressure values as well as on arterial wall properties (9,10). When the PWV increases systolic pressure and pulse pressure may also increase (11), and these effects are related to target organ damage and cardiovascular complications (12,13).

An increased PWV is observed in people with older age, and various pathologies such as diabetes, hypertension, or kidney disease (14). These conditions result from the pathophysiological changes in anatomic arrangement of the elastin and collagen in the arterial media (15–17).

As such, this method of evaluation has contributed to diagnostic, therapeutic, and prognostic approaches, and it is considered as a tool for the stratification of cardiovascular risk (9). The clinical utility of PWV has been defined based on the reference values of special groups (16,18–20) or according to expert consensus (21). Previous studies conducted in different countries have combined efforts to describe reference values for the general population using different methods of obtaining the PWV (22–25); however, few studies have accounted for blood pressure measurements (26,27). Importantly, the

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results of these studies cannot be extrapolated to other populations such as Latin Americans with risk factors (28).

PWV reference values have been described among healthy Latin American populations (29–32). To the authors' knowledge, no studies have been published concerning people with broad age ranges and different blood pressure values most associated with cardiovascular risk. Establishing PWV reference values for patients who exhibit cardiovascular risk factors and who also attend a specialized hypertension clinic to perform 24-hour ambulatory blood pressure monitoring (ABPM) with hemodynamic parameters might contribute to a better clinical decision-making. For this reason, the objective of the current study was to describe these PWV characteristics and establish reference values based on a large number of adults who attended a specialized cardiology center for 24-hour ABPM and did not receive pharmacological antihypertensive treatment.

Methods and materials

A descriptive study was conducted that included 3,160 records of patients who attended the Centro Clínico y de Investigación SICOR, Soluciones Integrales en Riesgo Cardiovascular, Medellín (Colombia) for 24-hour ABPM with hemodynamic parameters between January 2015 and July 2017.

PWV and ABPM records

We examined the records provided by health insurers or independent physicians of patients who underwent PWV measurement and 24-hour ABPM with hemodynamic parameters based on the suspicion of hypertension, white coat hypertension, masked hypertension, or hypotension. The records of patients older than 18 years were included. We excluded the records of pregnant women, people who received antihypertensive treatment (diuretic, β-Blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and calcium antagonists) and those who exhibited sustained arrhythmia.

Prior to the installation of the 24-hour ABPM equipment, PWV measurements were recorded. A nurse completed a written document that included demographic and clinical information, anthropometric measures, and pharmacological treatment if present, following a pre-defined protocol (33).

Measuring PWV

The PWV measurement in this study was recorded from a seated position using the Mobil-O-Graph® 24-hour PWA device (IEM, Stolberg, Germany), which estimated the following hemodynamic parameters via oscillometry: PWV, central aortic pressure, cardiac index, stroke volume, systemic vascular resistance, and augmentation index. This device was connected to a cuff located on an upper extremity. The size of the cuff was selected based on the arm diameter of each patient.

The principle for recording PWV consists of examining the oscillometric pressure curves from plethysmography and the pulsatile pressure changes in the arteries of the upper extremities (34). The fluctuation in pulsatile pressure during the inflation of the cuff induces periodic changes (oscillations) in pressure that are measured using the device. This fluctuation in the pressures is analyzed as the difference between the start of the first wave and the beginning of the second (or reflected) wave, thereby calculating PWV (34).

The Mobil-O-Graph® 24-hour PWA (IEM, Stolberg, Germany) software was used, which decomposes the times of the detected systole and diastole waves as the basis for the mentioned calculations and additional hemodynamic measures. This method was validated after comparison with a measurement taken using a central catheter; a Pearson's correlation coefficient of 0.81 and an average difference in repeated measurements of 0.5 m/s were reported (95% CIs = −0.47 to 0.57 m/s) (34). A sub-sample of 52 patients from this study was used to compare the estimated PWV with measurements using SphygmoCor® (*Atcor Medical Blood Pressure Analysis System*, Sydney, Australia); an Pearson's correlation coefficient of 0.71, intraclass correlation coefficient of 0.71 and a mean difference between the two methods of 0.05 m/s (95% CIs = −0.35 to 0.47 m/s) were found.

After measuring PWV, each record was downloaded to an institutional computer through an infrared connection into the HMS CS database (IEM, Stolberg, Germany) where the information was stored. The PWV records obtained were downloaded to an Excel (Microsoft, Redmond, Washington, United States) file from the registration system that enabled the information to be stored on a systematized platform.

ABPM

Then, a device for 24-hour ABPM was installed for each patient (i.e., the Mobil-O-Graph® NG [IEM, Stolberg, Germany] or the Custo-Screen® [Custo, Munich, Germany]), which was secured at the waist using a belt (33). Both devices were previously validated (35,36), and they use the oscillometric measurement method. Cuffs were used based on the diameter of the non-dominant arm, and blood pressure was measured every 15 minutes throughout the day (6:00–22:00) and every 30 minutes throughout the night (22:00–6:00). All patients who provided measurements at least 20 times per day and seven times per night were considered as having provided satisfactory records. Subsequently, each record was downloaded into the institutional database.

Statistical analysis

Initially, an exploratory analysis of the data was conducted to detect errors in the coding of the variables, including possible inconsistencies in the data, lost data, and outliers. This analysis also allowed us to become familiar with the basic distribution characteristics of the variables. Age was categorized into seven groups: < 30, 30–39, 40–49, 50–59, 60–69, 70–79, and > 80 years. Blood pressure was categorized based on 24-hour ABPM into three groups: < 130/80 (normal), 130/80–150/90 (grade I hypertension), and > 150/90 mmHg (grade II hypertension). Body mass index was categorized into three groups: < 25 (normal), 25–30 (overweight), and > 30 kg/m^2 (obesity).

The Shapiro Wilk test was used to evaluate whether the variables came from a normally distributed population throughout the sample based on age and blood pressure. To describe the quantitative variables, means, standard deviations, medians, and percentiles were used. Proportions were used to describe the categorical variables.

To assess the influence of risk factors (e.g., body mass index) and sex on PWV, an analysis of covariance was first performed after adjusting for age and mean arterial pressure. In addition, a simple linear regression model was used to establish the relationship between PWV and the mean arterial blood pressure of the 24-hour ABPM. A statistical significance level of α = 0.05 was set for all analyses, and the IBM® software SPSS version 20.0 (SPSS Inc., Chicago, Illinois) was used to examine the data.

Ethical aspects

The Institutional Ethics Committee approved this study. Prior to the installation of the equipment for the current diagnostic evaluation, informed consent was obtained to use the results of the examination for research purposes. The health research rules of Resolution 008430 of 1993 from the Ministry of Social Protection of Colombia and the principles of the Declaration of Helsinki in its latest revision were taken into account (37).

Results

Of the total 11,380 records, 8,162 belonged to patients who had exclusion criteria; 25 belonged to children under 18 years old; and 33 had missing information and were removed (Figure 1). The included records were of patients with an average age of 50.7 ± 14.0 years; 49.9% were male, 17.2% were obese, and 58.9% had blood pressure measurements greater than 130/80 mmHg (Table 1).

Although PWV was higher in men and lower in those who were obese, differences in age and mean blood pressure were observed by sex and body mass index. After adjusting for age and mean arterial pressure, however, the differences in PWV between sex and body mass index categories were 0.1 m/s (Table 2).

PWV increased with age (r = 0,894; p < 0,001) and blood pressure categories (ρ = 0,081; p < 0,001); the age-related increase was more pronounced among the patients in the higher blood pressure categories. Figure 2 shows a graphic representation of the mean PWV by the age and 24-hour ABPM blood pressure categories. Table 3 shows the mean ± 2 standard deviations, median, 5th 10th, and 90th, 95th percentile values of the PWV for each age and 24-hour ABPM category.

Among the age categories, a linear regression offered the best fit of the observed data when the mean arterial blood pressure of the 24-hour ABPM was included as the independent variable. The linear regression equations for each of the age categories are shown in Table 4. Although the ß coefficient for the mean arterial blood pressure of the 24-hour ABPM was similar across the different age categories, the intercept increased by 4-fold when the under-30 category was compared with the > 80 years category (Table 4).

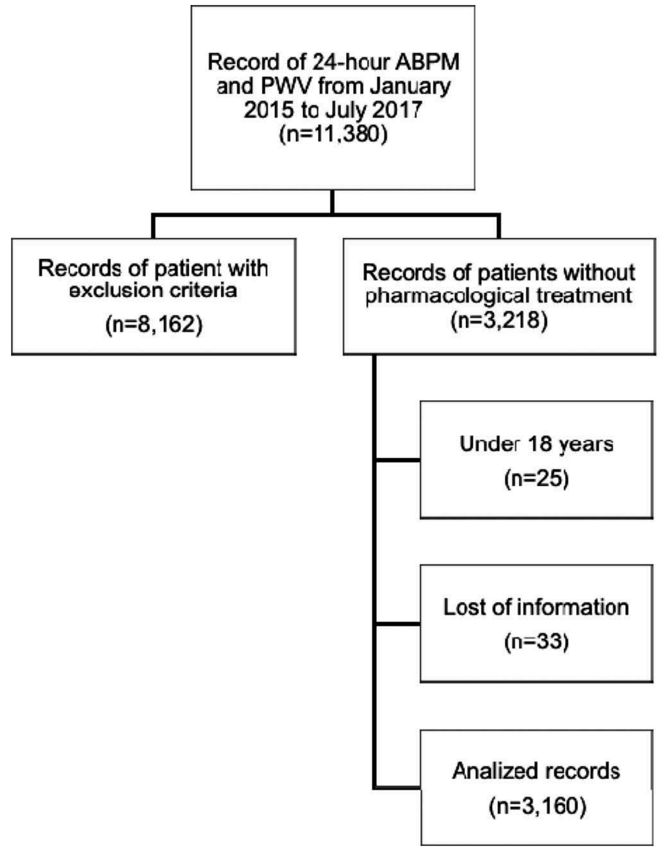

Figure 1. Flowchart showing how records were included.
ABPM: 24-hour ambulatory blood pressure monitoring; PWV: pulse wave velocity.

Discussion

The primary contribution of this study is the provision of PWV reference values for patients with suspected alterations in blood pressure. These values were obtained using the oscillometric method that was validated by the previous literature. The results were presented by age and blood pressure categories based on their relationship with the investigated variable. These findings contribute to the construction of the cardiovascular risk stratification tools for the Latin American population.

Arterial rigidity has been proposed as an additional independent cardiovascular risk marker for the clinical assessment of patients; however, the diversity of available methods and the lack of reference values prevent a distinctive criterion based on patient characteristics. The most recent expert recommendation regarding the cut-off point as a predictor of cardiovascular events was 10 m/s with 80% of the carotid-femoral distance (21); however, this value does not consider differences based on age or blood pressure.

In this sense, several researchers have suggested cut-off points for PWV. In a French population, the 10th and 90th percentile values were reported (18). For patients without pharmacological treatment (i.e., lipid-lowering, hypoglycemic, and anti-hypertensive drugs), these values were 7.1 and 10.6 m/s, respectively; for patients receiving treatment, these values were 7.7 and 12.2 m/s, respectively (18). In another French population, a cut-off of 13 m/s showed a satisfactory predictive capacity for atherosclerosis and a high risk of

Table 1. Demographic, anthropometric and hemodynamic characteristics of the patients to whom the records were made.

Demographic, anthropometric, clinics and hemodynamic characteristics	Men (n = 1,578)		Women (n = 1,582)		All (n = 3,160)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	48.1	13.5	53.3	14.1	50.7	14.0
Weight (kg)	83.5	12.6	66.4	11.4	74.9	14.7
Height (m)	1.7	0.1	1.6	0.1	1.7	0.1
Body mass index (kg/m2)	27.5	3.5	25.8	4.1	26.7	3.9
Systolic blood pressure in consulting room (mmHg)	135.1	15.3	132.0	16.2	133.5	15.9
Diastolic blood pressure in consulting room (mmHg)	87.8	10.9	82.6	11.6	85.2	11.6
Mean arterial pressure in consulting room (mmHg)	109.4	11.3	105.2	12.1	107.3	11.9
Pulse pressure (mmHg)	47.2	13.3	49.3	13.9	48.3	13.6
Heart rate (beats/min)	73.7	11.9	75.8	12.0	74.8	12.0
Systolic volume (mL)	71.1	12.7	64.1	11.2	67.6	12.5
Cardiac ouput (L/min)	5.1	0.7	4.8	0.7	4.9	0.7
Peripheral vascular resistance (mmHg/mL*s)	1.3	0.2	1.3	0.2	1.3	0.2
Central systolic pressure (mmHg)	124.7	13.9	122.8	15.4	123.8	14.7
Central diastolic pressure (mmHg)	89.4	10.9	84.2	11.6	86.8	11.5
Augmentation index (%)	20.2	10.8	30.6	11.4	25.4	12.3
Reflection coefficient (%)	62.1	8.5	65.8	7.8	63.9	8.3
	%	n	%	n	%	n
Diabetes	3.1	49	2.7	43	2.9	92
Dyslipidemia	11.7	185	16.7	264	14.2	449
Current smoker	4.8	76	2.7	43	3.8	119
Ex-smoker	5.2	82	1.4	22	3.3	104
Alcohol (one or more drinks per week)	22.1	349	5.6	89	13.9	438

Table 2. Influence of sex and body mass index on pulse wave velocity before and after adjustment for age and mean arterial pressure. Adjustment for age and mean arterial pressure.

Risk factor	n	Age (years) Mean	Mean arterial pressure (mmHg) Mean	Pulse wave velocity before adjustment (m/s)		Pulse wave velocity after adjustment (m/s)	
				Mean	P value	Mean	P value
Gender							
Men	1,578	48.1	109.4	8.0	< 0.001	7.7	0.001
Women	1,582	53.3	105.2	7.5		7.8	
Body mass index							
Normal	1,072	51.9	105.6	7.8	< 0.001	7.8	0.056
Overweight	1,543	50.5	107.9	7.7		7.7	
Obesity	545	47.4	108.5	7.5		7.8	

mortality at 10 years (16). In a Dutch study, the population was divided based on a cut-off of 14 m/s (19). In a Japanese study, a cut-off of 10 m/s was chosen as a criterion for altered PWV, which was used to predict cardiovascular events (20).

In Latin America, PWV reference values and frequency of early vascular aging have been reported with regard to healthy population (29,30,32). In Uruguay, different PWV values were described based on blood pressure and age among 429 patients without a cardiovascular history, in which the 97.5 percentile was adopted as the cut-off (29). In Argentina, an average PWV of 6.84 ± 1.65 m/s was reported in a population of 780 patients without a history cardiovascular disease and blood pressure values within normal limits: PWV increased between 6 and 8% for each decade of life (30). Botto et al. used PWV to describe rates of early vascular aging and found greater frequencies in younger adults (32). All together these studies, showed direct relationship between age and PWV, which may also have been influenced by blood pressure values. These trends were clearly observed in our results.

Aging is widely associated with arterial stiffness. Although an increased arterial stiffness at younger ages may reflect a functional impairment (10), in people with advanced age, this is more related to structural vascular changes independent of blood pressure levels (38) which may have an effect on cognitive function (39). For this reason, the evaluation of the vascular system through PWV should be considered against the expected increase in age. Similarly, the relationship between PWV and the degree of arterial hypertension due to the effect of high blood pressure on arterial elasticity is well known. In light of these considerations, the measurement of PWV as a marker of cardiovascular risk must be account for these individual characteristics. Our results corroborate the findings of other studies regarding the variables that explain PWV. Moreover, they match those reported in the literature, showing the lack of a relationship with other variables such as sex and BMI (26,40).

Our study initially found differences in PWV values according to sex and BMI; after adjusting for potential confounds, however, these differences were marginal. In fact, differences of 0.1 m/s based on gender and BMI categories were similar to those reported in a recent European study (40). For this reason, the equations for estimating PWV were developed taking into account only age and the degree of arterial hypertension. In this sense, the reference values described differ minimally with respect to other studies and PWV values increase with age and blood pressure (25).

We included available information regarding personal history of risk factors including smoking and diabetes. According to the findings, the population studied has low and intermediate cardiovascular risk for the indication of blood pressure monitoring without previous antihypertensive treatment. In addition, we consider the BMI to be a good indicator that groups cardiovascular risk factors (41), because the relationship between weight/height is a common denominator of conditions related to the metabolic syndrome (42). In this regard, we found no relationship between the values of PWV and BMI as other studies have also reported (22).

We recognize that the methodological design used in this work does not allow us to extrapolate the results obtained to the general population. Importantly, the majority of patients referred to this specialized center have pre-paid medical insurance. Therefore, differences might exist in socioeconomic conditions and health status with respect to the general population. However, the results of our study contribute to clinical decision-making.

The measurement of blood pressure in the office may affect that of PWV because the respective calculations of the other hemodynamic variables are performed based on this method. In this sense, the inaccuracy of the data obtained through an isolated blood pressure measurement, as shown by multiple studies (43–46), can affect the determination of PWV. Although we recognize this limitation, importantly, our work highlights the description of PWV based on age and blood pressure categories obtained from 24-hour ABPM.

Recently, to make the determination of arterial stiffness more accessible in clinical practice, the estimation of PWV using equations that consider age and blood pressure in a non-linear way has been proposed (26). The PWV estimated

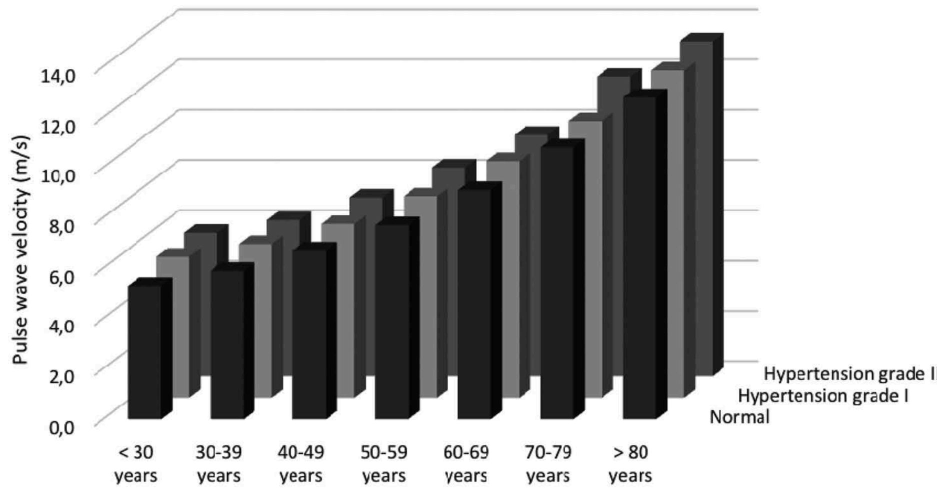

Figure 2. Pulse wave velocity averages according to age categories and blood pressure categories of 24-hour ambulatory blood pressure monitoring (n = 3,160).

Table 3. Distribution of pulse wave velocity values according to age categories and 24-hour ambulatory blood pressure monitoring categories (n = 3,160).

Age categories	24-hour ambulatory blood pressure monitoring categories														
	Normal (n = 1,299)					Hypertension grade I (n = 1,391)					Hypertension grade II (n = 470)				
	Mean	(- 2 SD)		(+ 2 SD)		Mean	(- 2 SD)		(+ 2 SD)		Mean	(- 2 SD)		(+ 2 SD)	
< 30 years	5.3	4.3		6.2		5.6	4.6		6.6		5.7	4.5		6.8	
30–39 years	5.9	4.4		7.3		6.1	4.9		7.3		6.2	5.1		7.3	
40–49 years	6.7	5.0		8.3		6.9	5.1		8.7		7.1	5.9		8.4	
50–59 years	7.7	6.1		9.3		8.0	6.3		9.7		8.3	6.1		10.5	
60–69 years	9.1	7.1		11.2		9.4	7.5		11.2		9.6	8.0		11.3	
70–79 years	10.8	9.4		12.2		11.0	9.6		12.4		11.9	8.3		15.4	
> 80 years	12.8	10.7		14.9		13.0	11.1		14.8		13.3	11.1		15.5	
	Median	p5	p10	p90	p95	Median	p5	p10	p90	p95	Median	p5	p10	p90	p95
< 30 years	5.3	4.4	4.6	5.9	6.1	5.6	4.9	5.0	6.3	6.8	5.7	4.2	4.8	6.4	6.6
30–39 years	5.8	5.0	5.2	6.4	6.7	6.0	5.3	5.5	6.7	7.0	6.3	5.5	5.5	6.8	7.0
40–49 years	6.6	5.7	5.9	7.3	7.6	6.8	6.0	6.2	7.6	7.9	7.1	6.1	6.4	8.0	8.1
50–59 years	7.6	6.7	6.9	8.5	8.9	7.9	7.0	7.2	8.9	9.1	8.2	7.1	7.3	9.3	9.8
60–69 years	9.1	8.0	8.2	10.0	10.3	9.3	8.2	8.4	10.2	10.5	9.5	8.5	8.6	10.8	11.2
70–79 years	10.8	9.7	10.0	11.9	12.1	10.9	10.0	10.2	12.0	12.3	11.6	10.3	10.7	13.2	13.6
> 80 years	12.6	11.3	11.4	14.2	14.8	12.8	11.7	11.7	14.5	14.7	13.2	11.2	11.7	15.3	15.7

Table 4. Simple linear regression equations of the relationship between pulse wave velocity and mean arterial pressure of 24-hour ambulatory blood pressure monitoring according to age categories.

Age categories	$PWV = \beta_0 + \beta_1 \times MAP$	R^2
< 30 years	$PWV = 3.271 + 0.023 \times MAP$	0.124
30–39 years	$PWV = 3.937 + 0.021 \times MAP$	0.073
40–49 years	$PWV = 4.321 + 0.026 \times MAP$	0.081
50–59 years	$PWV = 5.191 + 0.028 \times MAP$	0.075
60–69 years	$PWV = 7.345 + 0.020 \times MAP$	0.032
70–79 years	$PWV = 8.060 + 0.031 \times MAP$	0.080
> 80 years	$PWV = 11.070 + 0.020 \times MAP$	0.037

PWV: pulse wave velocity; MAP: mean arterial pressure of 24-hour ambulatory blood pressure monitoring.

from these equations shows a predictive capacity independent of directly measured PWV and the calculation of cardiovascular risk (47). These findings might make us reconsider the need to perform direct measurements of PWV and raise the possibility of using estimation equations such as the one proposed in our study to stratify cardiovascular risk.

Conclusions

PWV is directly related to age and blood pressure and can be predicted with a simple equation using these variables. To stratify the cardiovascular risk of the patients and make decisions in the clinical setting, it is recommended to use the proposed 90th percentile as a cut-off according to age and 24-hour ABPM blood pressure categories.

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Competing interests

The authors declare no competing interests.

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