Original Article

Reference Values in White Europeans for the Arterial Pulse Wave Recorded by Means of the SphygmoCor Device

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Measurement of blood pressure together with applanation tonometry at the radial artery allows the reproducible assessment of various indexes of arterial stiffness, including the peripheral (PP_p) and central pulse pressures (PP_c) and the peripheral (AI_p) and central augmentation indexes (AI_c). We defined preliminary diagnostic thresholds, using the distributional characteristics of these hemodynamic measurements in a reference population. We randomly recruited 870 subjects from 3 European populations. PP_p was the average difference between systolic and diastolic blood pressure measured five times at one home visit. For measurement of PP_c, AI_p and AI_c, we used the SphygmoCor device. We selected subjects without hypertension, diabetes, dyslipidemia in need of medical treatment or previous or concomitant cardiovascular disease. The study population included 228 men and 306 women (mean age 34.9 years). All hemodynamic measurements were curvilinearly related to age, and AI_p and AI_c were lower in men than in women. In men at age 40, the upper 95% prediction bands of the relations of the hemodynamic measurements with age approximated 60 mmHg for PP_p, 40 mmHg for PP_c, 90% for AI_p, and 30% for AI_c. For PP_c, AI_p and AI_c, these thresholds must be adjusted for age, leading to lower and higher thresholds at younger and older age, respectively. In addition, in women of any age, the AI_p and AI_c thresholds must be increased by 10% and 7%, respectively. Pending validation in prospective outcome studies, distributional characteristics of arterial stiffness indexes in a reference population can be used to generate operational thresholds for use in clinical practice. (*Hypertens Res* 2006; 29: 475–483)

***Key Words*: arterial stiffness, augmentation index, diagnosis, pulse pressure, pulse wave analysis**

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Introduction

Arterial stiffness is a precursor of premature cardiovascular disease. This important risk factor remains underused in routine clinical practice for risk prediction, partly because until recently its measurement required special ultrasound equipment and highly trained observers and partly because operational thresholds to diagnose an abnormal elevation of arterial stiffness do not exist.

About a decade ago, O'Rourke and other investigators developed applanation tonometry into a simple and reproducible method to assess various indexes of arterial stiffness (*1*–*3*). A validated algorithm permits transformation of peripheral arterial to central aortic waveforms (*4*–*6*). Analysis of the shape and timing of the waveforms allows the measurement of central and peripheral pulse pressures and central and peripheral systolic augmentation (*7*). In the present paper, we evaluated the distribution of these indexes in subjects enrolled in the European Project on Genes in Hypertension (EPOGH). In the absence of an outcome-driven reference frame, we used the distribution of the aforementioned indexes in normotensive subjects without cardiovascular disease to determine preliminary thresholds distinguishing normal from abnormally elevated values.

Methods

Study Population

The EPOGH Study was conducted according to the principles outlined in the Helsinki declaration for investigations in human subjects. The Ethics Committee of each institution approved the protocol. Participants gave informed written consent.

Three EPOGH centers opted to take part in vascular phenotyping. They randomly recruited nuclear families of Caucasian extraction, including offspring with a minimum age of 10 years in Belgium and 18 years in the two other countries. Overall, the response rate was 82%. Of 870 participants recruited in Cracow (Poland, $n=302$), Hechtel-Eksel (Belgium, $n=380$) and Pilsen (the Czech Republic, $n=188$), we discarded 30 from analysis because the recorded pulse wave was of insufficient quality. We administered a standardized questionnaire to obtain information on each subject's medical history, smoking and drinking habits and use of medications. The blood pressure phenotype was the average of 5 consecutive readings obtained at one home visit. Hypertension was defined as a blood pressure of at least 140 mmHg systolic or 90 mmHg diastolic or as the use of antihypertensive drugs. Using body mass index <25 kg/m^2, 25–30 kg/m^2 and ≥ 30 kg/m^2 as thresholds, we classified subjects as those with normal weight, overweight and obesity. Subjects with fasting blood glucose of at least 6.7 mmol/l or who were receiving treatment with insulin or oral antidiabetic agents were considered to have diabetes mellitus. To generate a healthy sample, we excluded 306 participants because of hypertension ($n=251$) or diabetes ($n=14$), because they required drug treatment for dyslipidemia ($n=12$), or because they had previous or concomitant cardiovascular disease, such as coronary heart disease, heart failure, stroke, transient ischemic attack, or intermittent claudication ($n=170$). The overall number of participants statistically analyzed totaled 534.

Hemodynamic Measurements

To ensure a steady state, the vascular measurements were obtained under standardized laboratory conditions in a quiet examination room, after subjects had rested for 15 min in the supine position. Subjects refrained from smoking, heavy exercise, and drinking alcohol or caffeinated beverages for at least 2 h prior to examination. We recorded during an 8-s period the radial arterial waveform at the dominant arm by applanation tonometry. We used a high-fidelity SPC-301 micromanometer (Millar Instruments, Inc., Houston, USA) interfaced with a laptop computer running the SphygmoCor software, version 6.31 (AtCor Medical Pty. Ltd., West Ryde, Australia). We discarded recordings when the systolic or diastolic variability of consecutive waveforms exceeded 5% or when the amplitude of the pulse wave signal was less than 80 mV. We calibrated the pulse wave by measuring blood pressure immediately before the recordings. From the radial signal, the SphygmoCor software calculates the aortic pulse wave by means of a validated and population-based generalized transfer function. The radial augmentation index was defined as the ratio of the second to the first peak of the pressure wave expressed as a percentage. The aortic augmentation index was the difference between the second and first systolic peak given as a percentage of the aortic pulse pressure. Peripheral and central pulse pressure were defined as the difference between systolic and diastolic blood pressure derived from the brachial blood pressure measured at the subjects' homes and from the aortic pulse wave, respectively.

Statistical Analysis

For database management and statistical analysis, we used SAS software, version 8.1 (SAS Institute Inc., Cary, USA). The central tendency and the spread of the data are reported as the mean±SD. Departure from normality was evaluated by Shapiro-Wilk's statistic (*8*) and skewness by the computation of the coefficient of skewness, *i.e.*, the third moment about the mean divided by the cube of the standard deviation (*9*). The normal distribution was used to determine the significance of the coefficient of the skewness (*9*). We compared means, medians and proportions by means of a large sample z test, Wilcoxon's test and the χ^2 statistic, respectively. Our statistical methods also included single and multiple linear regression (*10*). To evaluate the possible differences between men and women in the regression slopes of the hemodynamic

Table 1. Results of Reproducibility Study

	Coefficient of variation (%)			
	Belgium	Czech Republic	Poland	
	Intraobserver	Intraobserver	Intraobserver	Interobserver
Peripheral augmentation index	2.76	2.20	≤2.56	5.30
Central augmentation index	2.20	1.28	≤2.48	4.90

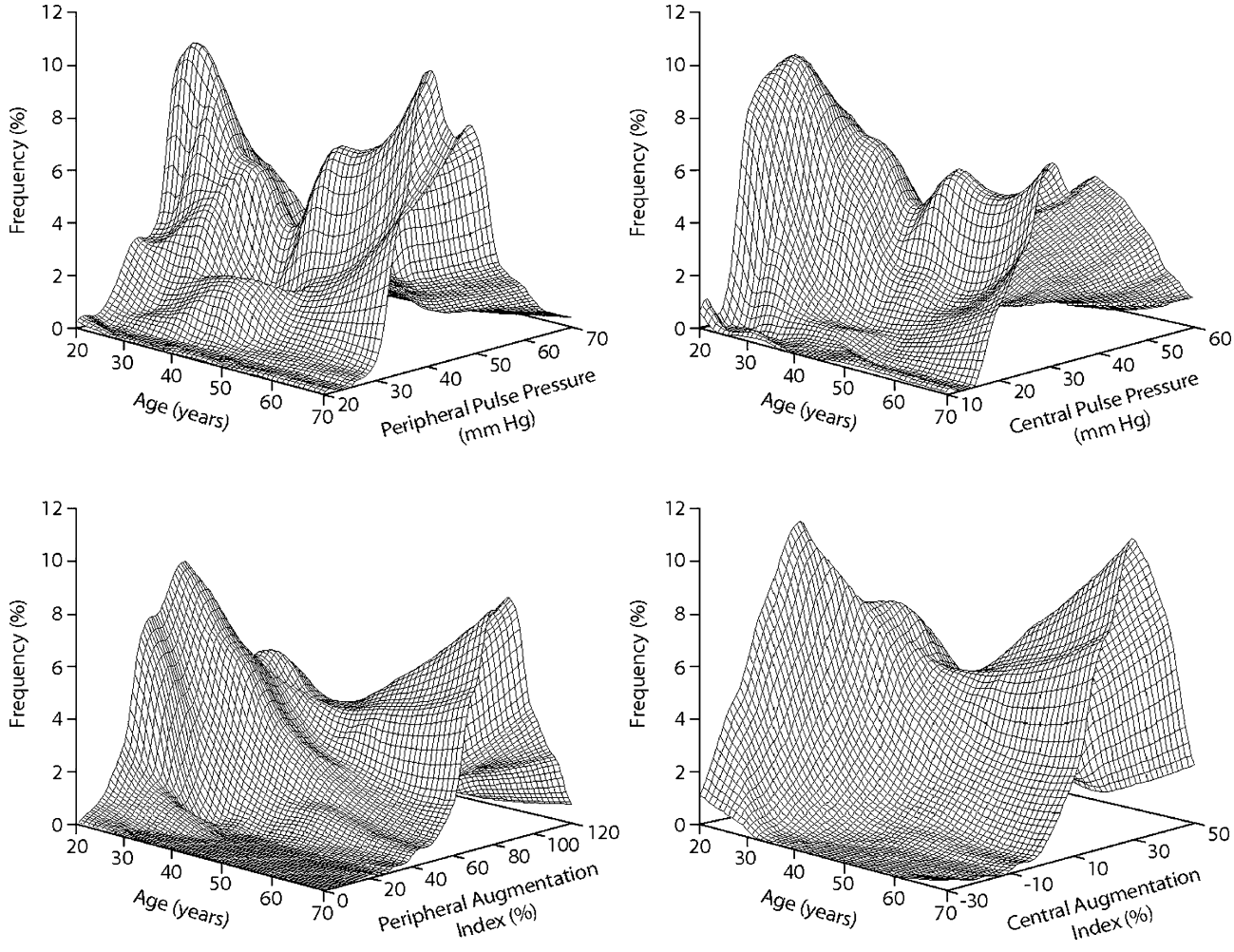

Fig. 1. *The distribution of peripheral and central pulse pressures and peripheral and central augmentation indexes in 534 healthy individuals by age.*

measurements on age, we tested whether the interaction terms with age and age squared significantly increased the explained variance (*10*).

In each center, the observers involved in the present study took part in a reproducibility study of the SphygmoCor measurements. By repeat examination of 10–12 subjects we computed the coefficient of variation as the ratio of the mean difference between repeat measurements to the standard deviation of the differences multiplied by 100 (*11*, *12*).

Results

Characteristics of the Participants

Men and women had similar mean age (range, 12.0–81.3 years; 5th–95th percentile interval, 18.3–58.5 years). Of the 534 participants, 83 men (36.4%) and 72 women (23.5%) were smokers and 112 men (49.1%) and 35 women (11.4%) reported a daily alcohol intake of at least 5 g. Among smok-

Table 2. Characteristics of Participants by Gender

Characteristic	Men (n=228)	Women (n=306)
Anthropometric measurements		
Age (years)	34.6±13.4	35.1±13.6
Height (cm)	177.1±6.4	164.5±6.7
Weight (kg)	78.8±13.1	64.4±12.3
BMI (kg/m^2)	24.8±3.6	23.5±4.3
Peripheral arterial measurements		
Systolic blood pressure (mmHg)*	121.4±8.7	114.8±10.2
Diastolic blood pressure (mmHg)*	76.3±8.1	71.7±8.5
Pulse pressure (mmHg)*	45.0±8.9	43.1±7.7
Augmentation index (%)	54.6±18.3	65.3±20.5
Pulse rate (beats/min)	64.9±11.3	68.4±9.4
Central arterial measurements		
Systolic blood pressure (mmHg)	106.2±10.6	101.7±12.3
Diastolic blood pressure (mmHg)	76.2±9.7	72.0±8.7
Pulse pressure (mmHg)	30.0±7.0	29.7±7.9
Augmentation index (%)	7.2±14.6	15.1±16.3

Values are mean±SD or number of subjects (%). All gender differences were significant ($p \leq 0.01$) with the exception of age ($p=0.67$) and central pulse pressure ($p=0.65$). BMI, body mass index. *Based on the average of five blood pressure readings at the subjects' homes.

ers, median tobacco use was 9 cigarettes per day (range, 1–40/day). Among regular drinkers, median alcohol consumption was 19.7 g/day (range, 5–86 g/day). Among men, 86 (37.7%) and 18 (7.9%) were overweight or obese. Among women, these numbers were 66 (21.6%) and 24 (7.8%), respectively.

Distribution of the Hemodynamic Measurements

The results of the reproducibility study in each center are summarized in Table 1. In all subjects, the distributions of the peripheral and central pulse pressures departed from normality and were positively skewed ($p<0.001$). The coefficients of skewness were 0.42 and 0.64, respectively. Similarly, the peripheral and central augmentation indexes were not normally distributed ($p<0.0001$), with coefficients of skewness amounting to 0.19 and −0.15, respectively. Figure 1 shows the distributions of these hemodynamic measurements by age. In all 534 subjects, pulse pressure averaged 43.9 mmHg (95% confidence interval [CI], 43.2–44.6 mmHg) peripherally and 29.9 mmHg (CI, 29.3–30.5 mmHg) centrally. The augmentation indexes averaged 60.7% (CI, 59.0–62.4%) peripherally and 11.7% (CI, 10.3–13.0%) centrally. Table 2 lists the peripheral and central arterial characteristics by gender.

Hemodynamic Measurements in Relation to Sex and Age

Tables 3 and 4 provide detailed statistics for the peripheral and central pulse pressures and for the peripheral and central systolic augmentation indexes by sex and age. Peripheral pulse pressure was on average 2.0 mmHg (CI, 0.5–3.4 mmHg) higher in men than women. Men and women had similar central pulse pressure. Men had peripheral and central systolic augmentation indexes that were on average 10.7% (CI, 7.3–14.0%) and 7.8% (CI, 5.1–10.5%) lower than in women.

As shown in Figs. 2 and 3, the peripheral and central pulse pressures and the peripheral and central augmentation indexes were curvilinearly related to age. The partial regression coefficients relating the arterial measurements to age (linear and curvilinear terms) were similar in men and women for the peripheral and central augmentation indexes ($p \geq 0.15$), but not for the peripheral and central pulse pressures ($p \leq 0.002$).

Proposal for Diagnostic Thresholds

To determine diagnostic thresholds, we rounded the upper limit of the 95th prediction bands for middle-aged men (40 years) downwards to the nearest value ending in zero. This procedure yielded the following thresholds: 60 mmHg for peripheral pulse pressure, 40 mmHg for central pulse pressure, 90% for the peripheral augmentation index, and 30% for the central augmentation index.

Table 5 lists the changes in hemodynamic measurements associated with female sex and with each 10-year deviation from 40 years. Because in our reference sample, sex and age had only minor effects on peripheral pulse pressure, the proposed 60 mmHg threshold might be applicable to both sexes and throughout the age range studied in the present analysis. Along similar lines, central pulse pressure was similar in the both sexes. The 40 mmHg threshold might therefore be applicable to middle-aged men and women. For women, the proposed thresholds for peripheral and central augmentation indexes need to be increased by approximately 10% and 7%, respectively.

The aforementioned thresholds for central pulse pressure and peripheral and central augmentation indexes need to be adjusted for age according to the curvilinear relationships as described in Figs. 2 and 3 and Table 5. In young adults (20 years), these thresholds need to be decreased by approximately 3 mmHg, 24% and 19%, respectively. By contrast, at older age (60 years), the proposed cut-off points should be increased by 7 mmHg, 14% and 11%, respectively. Consideration of the significant sex by age interaction terms for the peripheral and central pulse pressures did not materially change the proposed thresholds. Table 6 shows the proposed thresholds for men and women across the age classes. Standardization of the peripheral and central augmentation

Table 3. Peripheral and Central Pulse Pressures

	Men					Women				
	Age group					Age group				
	<30	30–39	40–49	≥50	All	<30	30–39	40–49	≥50	All
Number	106	51	33	38	228	134	64	56	52	306
Peripheral (mmHg)										
Mean	47.3	43.3	41.4	44.1	45.0	42.8	40.8	43.9	45.6	43.1
SD	9.8	6.8	8.3	7.3	8.9	8.8	5.9	7.3	6.2	7.7
P5	34.0	31.6	30.4	32.4	32.0	29.2	30.8	32.4	36.4	30.4
P10	36.4	35.2	31.2	33.6	34.4	32.0	33.6	35.2	39.2	33.6
P50	46.8	44.0	39.1	43.8	44.0	41.8	40.6	42.0	45.0	42.0
P90	59.6	50.8	52.8	53.2	56.0	56.0	47.6	54.4	53.6	54.4
P95	67.2	51.6	56.8	56.8	62.4	58.8	51.6	55.2	56.8	56.4
Central (mmHg)										
Mean	28.8	30.5	29.2	33.5	30.0	26.1	28.5	31.6	38.5	29.7
SD	6.8	5.4	7.2	8.1	7.0	5.6	5.9	7.0	8.7	7.9
P5	19.0	22.3	14.6	19.0	20.3	19.0	21.0	19.9	27.0	19.9
P10	21.0	23.8	21.0	24.6	22.0	20.0	21.9	22.8	28.6	20.5
P50	28.8	29.3	28.6	31.6	29.2	25.6	27.8	32.2	37.6	28.3
P90	37.9	37.7	38.1	47.0	39.2	34.5	35.8	38.8	50.8	39.0
P95	40.4	40.1	43.1	49.6	41.6	36.5	38.4	45.0	54.9	44.9

P5, P10, P90 and P95 indicate percentile values, respectively.

Table 4. Peripheral and Central Augmentation Indexes

	Men					Women				
	Age group					Age group				
	<30	30–39	40–49	≥50	All	<30	30–39	40–49	≥50	All
Number	106	51	33	38	228	134	64	56	52	306
Peripheral (%)										
Mean	43.5	57.3	61.4	75.9	54.6	51.0	67.4	77.6	86.2	65.3
SD	13.7	13.5	14.7	15.0	18.3	16.3	14.0	15.2	13.5	20.5
P5	23.7	39.3	41.1	46.2	26.0	24.0	46.1	52.0	64.2	30.1
P10	26.0	44.0	42.7	58.0	32.0	29.4	48.3	57.0	67.4	38.8
P50	43.2	55.3	61.0	78.0	52.6	50.4	67.3	76.9	84.5	65.0
P90	62.0	70.0	79.7	91.8	78.8	73.1	84.0	96.8	108.0	91.1
P95	68.0	79.7	86.4	97.1	86.9	81.8	88.4	105.0	111.8	97.8
Central (%)										
Mean	−1.5	9.4	13.7	23.1	7.2	3.7	16.6	25.5	31.1	15.1
SD	12.1	10.7	11.4	10.6	14.6	14.3	10.2	10.6	8.7	16.3
P5	−20.0	−6.0	−2.5	0.0	−16.0	−20.9	−3.0	8.0	16.5	−15.0
P10	−17.7	−5.5	0.0	6.4	−12.2	−15.9	0.6	10.7	20.0	−8.6
P50	−2.1	8.4	14.0	24.7	6.4	4.0	16.8	25.6	31.2	17.0
P90	14.2	23.8	28.9	33.4	27.3	22.7	27.9	40.0	42.0	35.0
P95	20.0	27.3	35.4	42.8	30.8	27.0	30.5	42.9	44.4	40.0

P5, P10, P90 and P95 indicate percentile values, respectively.

indexes to a heart rate of 60 beats/min did not alter these conclusions.

Discussion

We determined the distributional characteristics of various measures of arterial stiffness in White Europeans by means of

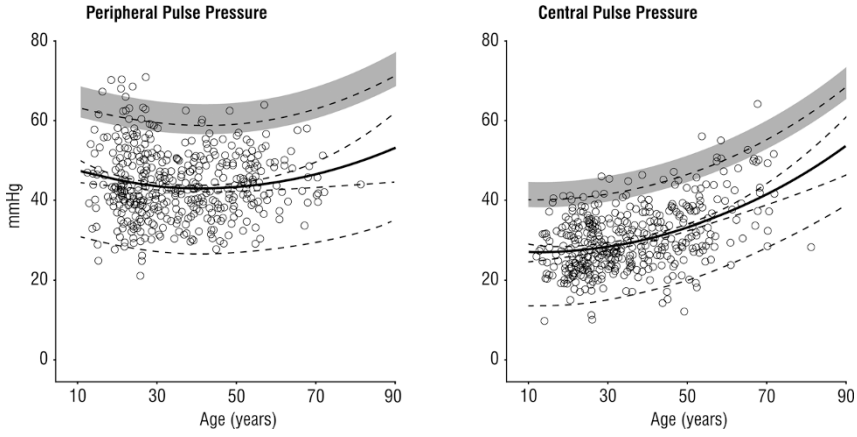

Fig. 2. *Relation of the peripheral and central pulse pressures with age in 534 subjects. Each panel shows the regression line and the 95% prediction bands for mean and individual values of pulse pressure. The shadowed area represents the transition between normal and elevated values.*

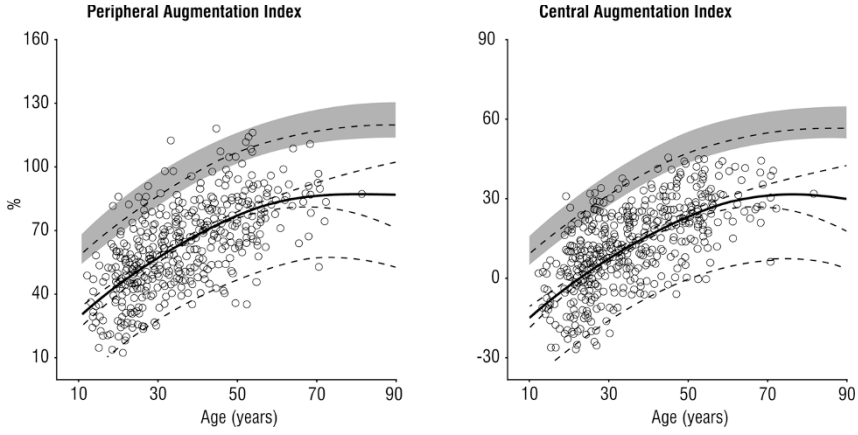

Fig. 3. *Relation of the peripheral and central augmentation indexes with age in 534 subjects. Each panel shows the regression line and the 95% prediction bands for mean and individual values of pulse pressure. The shadowed area represents the transition between normal and elevated values.*

the SphygmoCor device. In the absence of an outcome-driven reference frame, our study suggests that in middle-aged men, arterial stiffness might be abnormally increased if the following thresholds are exceeded: 60 mmHg for the peripheral pulse pressure, 40 mmHg for the central pulse pressure, 90% for the peripheral augmentation index, and 30% for the central augmentation index. Because central pulse pressure and the peripheral and central augmentation indexes curvilinearly increased with age, the aforementioned thresholds need to be adjusted accordingly. In addition, for the peripheral and central augmentation indexes in women, higher thresholds might be employed.

Prospective studies in which pulse pressure was analyzed as a continuous variable have demonstrated that peripheral pulse pressure has prognostic significance. Asmar and colleagues (*13*) studied 61,724 consecutive subjects, 49% women, between 16 and 90 years old. They found that in women as well as men the mean value of pulse pressure across the age range was close to 50 mmHg. These French investigators suggested 65 mmHg as a diagnostic threshold, which they determined either by adding two standard deviations to the mean or from the 95th percentile. This 65 mmHg threshold is in close agreement with the values of the peripheral pulse pressure (65 mmHg (*14*), or 68 mmHg (*15*)) that were previously reported to be associated with cardiovascular morbidity and mortality. Franklin and colleagues (*16*) also noticed that in middle-aged and older subjects, pulse pressure was an important predictor of cardiovascular risk, because a high systolic and a low diastolic blood pressure were both associated with an adverse outcome.

Table 5. Adjustment of Thresholds in 40-Year Old Men for Other Ages or Female Sex

Adjustment to age and female sex	Estimate (95% CI)	Rounded estimate
Peripheral pulse pressure (mmHg)		
40 → 20 years	+2.0 (+0.3 to +3.6)	+2.0
40 → 30 years	+0.5 (−0.0 to 1.1)	+0.5
40 → 50 years	+0.3 (−0.3 to +1.0)	+0.5
40 → 60 years	+1.5 (−0.2 to +3.3)	+1.5
Female sex	−2.0 (−3.4 to −0.6)	−2.0
Central pulse pressure (mmHg)		
40 → 20 years	−3.2 (−4.5 to −1.8)	−3.0
40 → 30 years	−2.0 (−2.5 to −1.5)	−2.0
40 → 50 years	+2.9 (+2.4 to +3.4)	+3.0
40 → 60 years	+6.7 (+5.2 to +8.1)	+7.0
Female sex	−0.4 (−1.6 to +0.7)	−0.5
Peripheral augmentation index (%)		
40 → 20 years	−24.1 (−26.9 to −21.3)	−24.0
40 → 30 years	−10.8 (−11.9 to −9.8)	−10.0
40 → 50 years	+8.4 (+7.4 to +9.5)	+8.0
40 → 60 years	+14.3 (+11.2 to +17.4)	+14.0
Female sex	+10.0 (+7.7 to +12.6)	+10.0
Central augmentation index (%)		
40 → 20 years	−19.2 (−21.5 to −17.0)	−20.0
40 → 30 years	−8.6 (−9.4 to −7.8)	−8.0
40 → 50 years	+6.6 (+5.7 to +7.5)	+7.0
40 → 60 years	+11.1 (+8.6 to +13.5)	+11.0
Female sex	+7.4 (+5.5 to +9.4)	+7.0

The proposed thresholds in 40-year old men were 60 mmHg and 40 mmHg for the peripheral and central pulse pressures and 90% and 30% for the peripheral and central augmentation indexes, respectively (see Results for further information). Estimates were derived from regression models relating the arterial measurements to sex and the linear and squared terms of age. The adjustment for female sex is cumulative to that for age group. CI, confidence interval.

Table 6. Proposed Thresholds for Men and Women by Age

	Proposed thresholds by age				
	Age (years)				
	20	30	40	50	60
Peripheral pulse pressure (mm Hg)					
Men	62	60	**60**	60	62
Women	60	58	58	58	60
Central pulse pressure (mm Hg)					
Men	37	38	**40**	43	47
Women	36	38	40	42	46
Peripheral augmentation index (%)					
Men	66	80	**90**	98	104
Women	76	90	100	108	114
Central augmentation index (%)					
Men	10	22	**30**	37	41
Women	17	29	37	44	48

The diagnostic thresholds (rounded) are based on the upper 95th prediction band of the curvilinear relations between the vascular measurements and age (see Figs. 2 and 3). Table 5 provides information on the adjustment required for age and female gender, using 40-year old men as the central reference point.

The use of thresholds in clinical decision-making might be criticized. Indeed, the association between arterial stiffness and cardiovascular risk is probably continuous without a threshold at which the risk suddenly increases. However, the widespread clinical use of arterial stiffness indexes requires a generally accepted reference frame. Clinicians need to know the transition zone between normal and abnormally elevated values. However, the presently proposed thresholds should never be interpreted as such, but should be integrated in the assessment of a subject's overall absolute cardiovascular risk that is determined by many other risk factors. Absolute cardiovascular risk, rather than a single risk factor, should be the basis for clinical decisions.

Pulse wave velocity and the distance of reflection points to the heart are the main determinants of the peripheral and central augmentation indexes. Wave reflection occurs at sites of changes of arterial impendence along the arterial tree, such as branching points or atherosclerotic plaques. The peripheral and central augmentation indexes increase with age and mean arterial pressure (*7*, *17*) and are inversely related to heart rate (*18*, *19*) and body height (*20*). Mitchell and colleagues (*21*) studied carotid-femoral pulse wave velocity and systolic augmentation at the level of the carotid artery in 188 men and 333 women in the Framingham Heart Study Offspring Cohort. All participants were free from cardiovascular disease, hypertension, dyslipidemia, obesity, and smoking within the 12 months prior to the start of the study. The mean age was 56.6 years. From their article, we calculated the mean values plus two standard deviations. These thresholds for the carotid augmentation index were 33% and 37% in men and women, respectively.

To our knowledge, this is the first study of its sort in White Europeans. However, it should be interpreted within the context of its limitations. Although the age range was wide, we enrolled relatively few subjects older than 60 years. Pulse wave analysis was used to assess the central pulse pressure and the central augmentation index. Such an approach may have led to a small degree of error in central pressure estimation, although the transfer function involved has been previously validated (*1*, *22*). The strong consistency in the relations of the peripheral and central hemodynamic measurements with age excludes any distortion by the transfer function. Nevertheless, the thresholds proposed for central pulse pressure should not be extrapolated to other techniques of measurement. In contrast to the Framingham investigators (*21*), we did not exclude smokers from our reference sample. Smoking may increase the stiffness of large arteries and wave reflection (*23*), but our subjects refrained from smoking for at least 2 h prior to the examination. We also used a high-fidelity pressure transducer to increase the accuracy of the recorded pressure waveforms. Only one observer (Belgium and Czech Republic) or two observers (Poland) per center obtained all vascular measurements.

In conclusion, pending validation in prospective outcome studies, 60 mmHg for the peripheral pulse pressure, 40 mmHg for the central pulse pressure, 90% for the peripheral augmentation index, and 30% for the central augmentation index might be considered as preliminary thresholds to diagnose increased arterial stiffness and wave reflection in male middle-aged White Europeans. The aforementioned thresholds need adjustment for sex and age and should be integrated in an overall cardiovascular risk assessment. Moreover, additional studies in reference populations with a larger sample size are required. Such studies are currently in progress in other centers of the European Project on Genes in Hypertension.

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