Original Article

Pulse wave velocity distribution in a cohort study: from arterial stiffness to early vascular aging

Pedro G. Cunha[a,b,c], Jorge Cotter[a,b,c], Pedro Oliveira[d,e], Isabel Vila[a], Pierre Boutouyrie[f], Stéphane Laurent[f], Peter M. Nilsson[g], Angelo Scuteri[h], and Nuno Sousa[b,c]

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By contrast with other southern European people, north Portuguese population registers an especially high prevalence of hypertension and stroke incidence. We designed a cohort study to identify individuals presenting accelerated and premature arterial aging in the Portuguese population. Pulse wave velocity (PWV) was measured in randomly sampled population dwellers aged 18–96 years from northern Portugal, and used as a marker of early vascular aging (EVA). Of the 3038 individuals enrolled, 2542 completed the evaluation. Mean PWV value for the entire population was 8.4 m/s (men: 8.6 m/s; women: 8.2 m/s; $P < 0.02$). The individuals were classified with EVA if their PWV was at least 97.5th percentile of *z*-score for mean PWV values adjusted for age (using normal European reference values as comparators). The overall prevalence of EVA was 12.5%; 26.1% of individuals below 30 years presented this feature and 40.2% of individuals in that same age strata were placed above the 90th percentile of PWV; and 18.7% of the population exhibited PWV values above 10 m/s, with male predominance (17.2% of men aged 40–49 years had PWV > 10 m/s). Logistic regression models indicated gender differences concerning the risk of developing large artery damage, with women having the same odds of PWV above 10 m/s 10 years later than men.

Conclusion: The population PWV values were higher than expected in a low cardiovascular risk area (Portugal). High prevalence rates of EVA and noteworthy large artery damage in young ages were found.

Keywords: arterial stiffness, cardiovascular risk, early vascular aging, epidemiology, large artery, Portugal, pulse wave velocity

Abbreviations: BP, blood pressure; c-f PWV, carotid–femoral pulse wave velocity; CVD, cardiovascular disease; CVRFs, cardiovascular risk factors; ERVC, European reference values collaboration; EVA, early vascular aging; HR, heart rate; TOD, target organ damage

INTRODUCTION

Changes in arterial wall structure are part of the aging process and occur as a result of mechanical, biochemical, or metabolic insults. These changes are attenuated by local repair mechanisms [1]. Arterial stiffness progresses with age and can be accelerated by different factors, high blood pressure (BP) being one of the most relevant [2]. The impact of these factors on arterial stiffness is significant in younger and older individuals as well as in men and women, and across different countries [3,4]. Other contributors to this unsuccessful aging process can be related to early-life determinants (fetal programming, intrauterine growth retardation, low birth weight, postnatal growth pattern) [5] and genetic determinants, concerning different aspects of arterial stiffness heritability that range from arterial wall composition to transcriptional pathways related to gene expression [6–9].

Early vascular aging (EVA) is a concept with growing interest and relevance [1,5,10–14]. It corresponds to unsuccessful aging: the normal aging process is accelerated and arteries display characteristics typically observed at older (chronological) ages. The early identification of individuals at increased absolute [15] and relative cardiovascular risk when compared with individuals with the same age is critical; measurement of arterial stiffness through pulse wave velocity (PWV) fulfills part of this issue [16]. This group of individuals would benefit from clinical intervention to reduce risk through cardiovascular risk factor (CVRF) control [17] and healthy lifestyle behaviors: exercise [18], diet [19], and lower salt consumption [20]. This is called the aggressive decrease of atherosclerosis modifiers strategy [11].

Arterial stiffness measurement is particularly useful to obtain a comprehensive insight of the accumulated effect of different CVRF through an extended time window, in the

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[a]Department of Internal Medicine, Center for the Research and Treatment of Arterial Hypertension and Cardiovascular Risk, Guimarães – Centro Hospitalar do Alto Ave, [b]Life and Health Science Research Institute (ICVS), School of Health Science, University of Minho, Guimarães, [c]ICVS/3B's – PT Government Associate Laboratory, Braga/Guimarães, [d]Departamento de Estudo de Populações, Instituto de Ciências Biomédicas Abel Salazar, [e]Instituto Saúde Pública, EPI Unit, Universidade do Porto, Porto, Portugal, [f]Department of Pharmacology and INSERM U970, Assistance Publique Hôpitaux de Paris, Université Paris Descartes, Paris, France, [g]Department of Clinical Sciences, Lund University, Skane University Hospital, Malmö, Sweden and [h]San Raffaele Pisana IRCCS, Rome, Italy AQ1

Correspondence to Pedro Guimarães Cunha, Center for the Research and Treatment of Arterial Hypertension and Cardiovascular Risk, Serviço de Medicina Interna do Hospital de Guimarães, Centro Hospitalar do Alto Ave; Life and Health Science Research Institute (ICVS), University of Minho, Rua dos Cutileiros, Creixomil, Guimarães 4810, Portugal. E-mail: pedrocunha@ecsaude.uminho.pt

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vascular aging process [11]. Longitudinal follow-up of this measurement could also identify those whose clinical intervention has failed to achieve CVRF control and regression/stabilization of early arterial stiffness signs [21]. Carotid–femoral (c-f)PWV reference values adjusted to age, sex, and influencing CVRF have been recently published [16], allowing the clinician to compare an individual's measure of arterial damage against the expected value for that same age.

By contrast with other southern European people, northern Portuguese population registers an especially high stroke incidence [22]. Previous reports published on this population have related increased arterial stiffness to salt intake and prevalence of hypertension (HTN); however, no study was designed to assess EVA patterns. Assessment of arterial wall damage as a marker of increased risk to the development of cardiovascular disease (CVD), cardiovascular events, and all-cause mortality [15,23] is therefore of particular interest, in this geographic area.

We designed a large-scale population-based cohort study to accurately establish the prevalence of several CVRF and determine the distribution of PWV values and signs of pathological arterial stiffness. The aim was to identify individuals presenting accelerated and premature arterial aging, through age-adjusted analysis, or those who have PWV values above the 10 m/s threshold [24].

PATIENTS AND METHODS

The methodology employed in this study has already been detailed elsewhere [25,26]. Briefly, a representative sample of the population from two adjacent cities (Guimarães and Vizela) was randomly selected and evaluated on two different occasions at least 3 months apart, after signing a written consent form approved by an Ethics Committee. In Portugal, every citizen must be registered in the Primary Community Healthcare Centre (PCHCC) of his/her residence area. Comparing the characteristics of citizens living in Guimarães/Vizela (Statistics Portugal for the year 2006) and the same information of those with an actual registry in one of the PCHCC facilities operating in the two cities, the difference between both the lists was inferior to 2%, therefore allowing the consideration that, for practical use, the populations enrolled in PCHCC and living in Guimarães/Vizela are virtually the same. Therefore, participants have been randomly selected from the list of citizens currently living in Guimarães and Vizela.

Considering that there was no available estimate of the prevalence of EVA or large artery damage for the Portuguese population, the sample selection was based considering the estimated prevalence of HTN in Portugal. A sample size of at least 2339 participants was required to achieve 2% precision in an estimated prevalence of HTN of 41.2%. Thus, a sample of the adult population (>18 years of age) stratified by age was defined previewing the necessity of including 4000 individuals (95% confidence interval with an estimation error inferior to 2%, considering a 25% safety margin to cope with nonadherence and dropout rate between visits).

Anticipating a higher nonadherence and dropout rates on younger and professionally active individuals, the number of randomized individuals to enroll was stratified unevenly according to their age (2000 individuals would be <35 years of age, 1000 individuals would have 35–65 years of age, and 1000 individuals would be >65 years).

The estimation of PWV values for the population was adjusted by age and sex agreeing to the known distribution of these characteristics in the population of the two cities, according to Statistics Portugal for the year 2006.

The lists of randomized individuals were delivered to the corresponding family doctors so that they could contact and enroll them, and obtain the written consent to participate. It was therefore clear that only randomly assigned individuals could be enrolled and that no volunteers or physician-selected individuals would be included. If the individual refused, the general practitioner could not replace him/her with a volunteer or with someone from his/her practice. Only randomized individuals were accepted.

Individuals were observed in the morning, fasting overnight, and carrying their usual drug prescriptions. No intake of caffeinated beverages or tobacco use was allowed. The participants underwent a standardized workup including medical history, and biologic and arterial measurements. Trained physicians performed BP measurements at every occasion; training sessions performed prior to the beginning of the study insured standardization of BP and PWV measurements. BP was measured three times (at each visit) with participants in a sitting position, after a 15-min resting period, taken with 2 min interval, using the validated OMRON-705IT device. During their first visit, patients were AQ3
then placed in the supine position and c-fPWV was measured using the Sphygmocor device.

Measured PWV values were standardized and normalized to allow us to compare the obtained values with the ones published as European reference [16] (details in Supplemental Material, http://links.lww.com/HJH/A474).

Definition of early vascular aging

The primary definition of EVA was based upon the age-adjusted normal population of the European reference values collaboration (ERVC) [16]. Accordingly, EVA was defined as a PWV of at least 97.5th percentile of *z*-score for mean PWV values adjusted for age, using the normal population PWV values as comparator. The normal population in the ERVC included the so-called normotensive 'healthy' individuals, as they did not have any known CVRF or CVD and presented optimal or normal BP [16]. In a separate exercise, we also tested another definition of EVA wherein we included individuals with PWV values 2 standard deviation (SD) above the mean PWV value determined as reference for someone with his/her age and BP class; as comparator, we used the reference population values also presented by the ERVC [16] – the total reference population in that collaboration included individuals with high–normal to Grade 3 BP (untreated), dyslipidemia (untreated), smokers, and no diabetes or established CVD [16].

We also considered the existence of arterial target organ damage by dichotomizing PWV values above 10 m/s or below [24].

Statistical analysis

Statistical methodology concerning population sampling, database elaboration, and management, as well as

predefined statistical analysis have already been addressed elsewhere [25]. Prevalence of different studied characteristics was estimated and calculated by demographic characteristics (age group, sex, education level) and risk factors. Linear regression models were studied with PWV as the dependent variable and with independent variables that included age, age^2, sex, SBP (mean of four measurements), heart rate (HR), BMI, years of education, tobacco use, family history of premature CVD, antihypertensive medication use, fasting glucose, lipid profile, mean estimated glomerular filtration rate, C-reactive protein, antidiabetic treatment, antilipidic treatment, and known CVD.

To avoid collinearity problems, age and SBP were standardized by their mean and SD. Logarithmic transformation of PWV values was performed to guarantee a normal homocedastic distribution. Because of detected interactions between sex and major risk factor, we created separate models for men and women. Logistic regression models were constructed to study contributing variables to both the development of large artery damage (PWV $>$ 10 m/s) and EVA. Again, as men and women presented a different discriminative value of age for large artery damage, two different models, based on gender, are presented (Figure SM1 and Supplemental Material, http://links.lww.com/HJH/A474).

RESULTS

From the initial 4000 randomized individuals, 962 could not participate (these individuals either refused to participate, were no longer residents, or were either pregnant or bedridden). From the 3038 enrolled, the dropout rate was 16.1%, between the two clinical observations defined in the study [25,26]. The individuals who dropped out of the study were similar in terms of age, sex, and years of education when compared with the adherent individuals [26].

AQ4 The distribution of population by age class and sex, their clinical characteristics, and mean values of PWV distribution stratified and adjusted for age/sex are summarized in Table 1. In Table 2, we present the prevalence of relevant biologic characteristics (CVRFs, CVD, pharmacologic treatments used), stratified by age class. The adjusted mean PWV value for the entire population was 8.4 m/s (8.2 m/s for women; 8.6 m/s for men). Men had an average 0.6 m/s

AQ5 higher PWV than women ($P < 0.001$). The sex difference in PWV values was observable in any age class ($P < 0.02$) and it increased with advancing age: from 0.4 m/s in individuals below 30 years to 1.3 m/s in individuals of at least 70 years. Regression analysis showed that in males, the increase in PWV depended quadratically on age. In females, a linear model best described this association and in addition to age, SBP and HR were significantly associated with PWV ($R^2 = 0.44$). In males, in addition to age and age^2, SBP, HR, and fasting glucose were also significant variables associated with PWV ($R^2 = 0.49$). Stepwise regression showed that the main associations, by order of importance, were with age, SBP, and HR. The observed differences between genders justify the adoption of gender-specific regression models Table 3.

TABLE 1. Clinical characteristics of 2542 individuals studied

	Total
Number of cases/female %	2542 / 55
Mean age (years)	45.5
Mean BMI (kg/m^2) (SD)	26.6 (4.6)
Mean SBP/DBP (mmHg)	129.8/76.8
Hypertension (%)	31.6
Diabetes (%)	9.1
Dyslipidemia (%)	75.1
Years of education: $\leq$4/5–9/10–12/$>$12 (%)	53.7/22.3/15.7/7.8
Current/former/no smoker (%)	18.8/16.1/65.1
Antihypertensive treatment (%)	22.0
Antidiabetic treatment (%)	6.7
Use of lipid-lowering drugs (%)	17.7
Established cardiovascular disease (%)	5.0

PWV mean values (m/s)	Total	Male	Female
$<$30 years (249/311)	7.1	7.3	6.8
30–39 years (236/334)	7.7	7.9	7.4
40–49 years (122/154)	8.3	8.5	8.1
50–59 years (136/160)	8.5	8.6	8.5
60–69 years (141/169)	9.9	10.3	9.5
70–79 years (145/157)	10.8	11.6	10.2
$\geq$80 years (22/25)	11.4	12.1	11.0
All (1051/1310)	8.4	8.6	8.2

Numbers in brackets correspond to the number of male (M) and female (F) individuals (M/F) in each age class. PWV, pulse wave velocity; SD, standard deviation. AQ8

Early vascular aging

Using the above-mentioned z-scores methodology, every individual was ranked within his/her age strata. We present the percentage of individuals placed above the 90th, 95th, and 97.5th percentile of predicted PWV for their age class in Fig. 1.

EVA was recorded in 12.5% of the total population. Strikingly, 19.3% of individuals below 40 years and 26.1% of individuals below 30 would be classified as EVA individuals, that is, one out of every four young adults. In Supplemental Material, http://links.lww.com/HJH/A474, the calculation of EVA prevalence using the 2SD above the mean PWV value adjusted for age and BP class is presented (using the European 'reference' population values) – Figure SM2, http://links.lww.com/HJH/A474. With this alternative method of calculation, observations of the same nature can be made regarding the high prevalence of EVA, notably at ages below 50 years. With any of the methods applied, there was a significantly higher prevalence of EVA individuals of the male gender in age classes below 40 years.

In Table SM3, http://links.lww.com/HJH/A474, we AQ6 present the biologic characteristics of individuals below 50 years of age classified as having EVA, by comparison with those classified as normal arterial aging within the same age strata. The EVA individuals presented higher male prevalence, mean BP, HTN prevalence, and a slight increase in mean HR, but lower high-density lipoprotein cholesterol levels. In Table SM4, http://links.lww.com/HJH/A474, we show the results of the logistic regression analysis of EVA. Identified variables were age below 30 years [odds ratio (OR) = 3.2], male sex (OR = 1.4), BP above or equal to the high–normal category ($OR_{optimal}$

TABLE 2. Prevalence (percent) of relevant biological characteristics stratified by age group (crude rates)

Age (years)	Current smokers	Former smokers	Diabetes	Dyslipidemia	HTN	CKD	CVD	HTN treatment	Diabetes treatment	Lipid treatment
<30	30.2	7.8	0.4	49.5	2.7	0.4	0.2	0.7	0.2	0.7
30–39	25.9	9.7	1.2	68.1	10.8	0.7	0.5	3.6	0.5	1.9
40–49	26.6	19.6	6.6	81.8	25.2	1.4	1.7	12.6	4.9	8.4
50–59	13.8	21.1	14.8	88.5	44.7	1.7	7.9	31.9	11.2	31.3
60–69	8.7	20.9	25.1	91.3	71.7	4.4	9.0	53.2	20.2	43.1
≥70	2.4	25.1	23.3	90.8	79.9	13.7	21.2	60.9	14.1	44.4

CKD, chronic kidney disease; CVD, cardiovascular disease (including ischemic stroke, hemorrhagic stroke, acute coronary syndromes, coronary heart disease, coronary artery bypass surgery, and peripheral artery disease); HTN, hypertension.

$_{BP} = 1$; $OR_{high-normal\ BP} = 1.7$; $OR_{Grade\ 1\ BP} = 3.1$, and $OR_{Grade\ 2/3\ BP} = 9.4$), HR above 75 bpm (OR = 1.7), and diabetes (OR = 2.8).

Large artery damage

We also aimed to know how many individuals presented PWV values over the established high-risk cutoff of 10 m/s. Figure 2 exhibits the age and sex-adjusted estimate of the prevalence of individuals with measurements above this value.

Men had a higher prevalence of high-risk arterial stiffness both globally ($X^2 = 32.4$, $P < 0.001$) and particularly in the age groups 30–39 ($X^2 = 4.5$, $P < 0.05$), 60–69 ($X^2 = 8.9$, $P < 0.01$), and at least70 years ($X^2 = 16.9$, $P < 0.001$). Overall, a prevalence rate of 18.7% was observed in the population (after adjustment for age and sex). Our attention was drawn to the estimates obtained for the age classes below 50 years, where prevalence can reach as high as 14.1% (ages 40–49 years), with higher figures being recorded in men (17.2%). The fact that 7.2% of men in the age class of 30–39 years exhibited large artery damage is a noticeable finding. Logistic regression analysis models showed that age above 40 years and BP are variables increasing the risk of developing large artery damage; the logistic models for PWV above 10 m/s also evidence the difference between genders. Observing Figure SM1, http://links.lww.com/HJH/A474, it becomes clear that for a 50% probability of developing PWV above 10, and for the same BP level, the corresponding chronological age for males and females differs approximately by 10 years (higher for men); for a given age, the difference in probability of developing PWV above 10, within the same BP class, is approximately 15% (higher for men). HR is also a contributor, especially for women (OR = 2.2), and diabetes status contributes to the development of arterial stiffness in men (OR = 1.9) (Table SM5, http://links.lww.com/HJH/A474).

Finally, putting side by side both the prevalence of individuals that contributed PWV values above the median and the expected 90th percentile (using the normal 'healthy' population as comparator) and the prevalence of individuals with PWV above 10 m/s (Fig. 3), we were able to describe the coexistence of both early and late signs of vascular aging in this population.

DISCUSSION

We present for the first time in a population-based study in Portugal, the mean values of PWV distributed by age category and sex. The main finding is that PWV values are markedly higher than expected from the European reference values, especially in younger individuals and males. We sought to describe how individuals' PWV values from a so-called low CVR area rank relative to European references [16]. We confirmed a clear increase of PWV with age, as well as higher mean levels of PWV in men, similar to descriptions in other reports [27].

Only few studies have characterized the distribution of PWV values using comprehensive population-based samples. A recent publication from Uruguay [28] reports population reference values higher than those published here and in the ERVC, hinting (as previously suggested [27]) that ethnic and geographic differences could explain different CVD geographic patterns. The Bogalusa Heart study [29], the Enigma study [30], and the ARYA study [31] reported mean PWV values for individuals below 40 years that are lower than those found in the city of Guimarães/

TABLE 3. Linear regression models for pulse wave velocity as dependent variable, following logarithmic transformation

Variables	Males				Females			
	Coefficients (SE)	Standardized coefficients	*P* values	R^2 incremental	Coefficients (SE)	Standardized coefficients	*P* values	R^2 incremental
Age	0.117 (0.007)	0.461	<0.001	0.411	0.113 (0.007)	0.474	<0.001	0.392
Age^2	0.034 (0.007)	0.109	<0.001	0.421	–	–	–	–
SBP	0.059 (0.007)	0.216	<0.001	0.466	0.058 (0.007)	0.239	<0.001	0.425
HR	0.003 (0.001)	0.134	<0.001	0.485	0.003 (0.001)	0.123	<0.001	0.439
Fasting glucose	0.001 (0.0003)	0.069	0.005	0.492	–	–	–	–
Constant	1.847 (0.039)	–	<0.001	–	1.904 (0.035)	–	<0.001	–
R^2		0.492				0.439		

Explanatory variables studied in the regression model: years of schooling, smoking, antihypertensive treatment, antidiabetic treatment, use of lipid-lowering drugs, prevalence of established cardiovascular disease, mean fasting glucose, family history of premature cardiovascular disease, BMI, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, mean estimated glomerular filtration rate, and C-reactive protein. HR, heart rate; PWV, pulse wave velocity; SE, standard error.

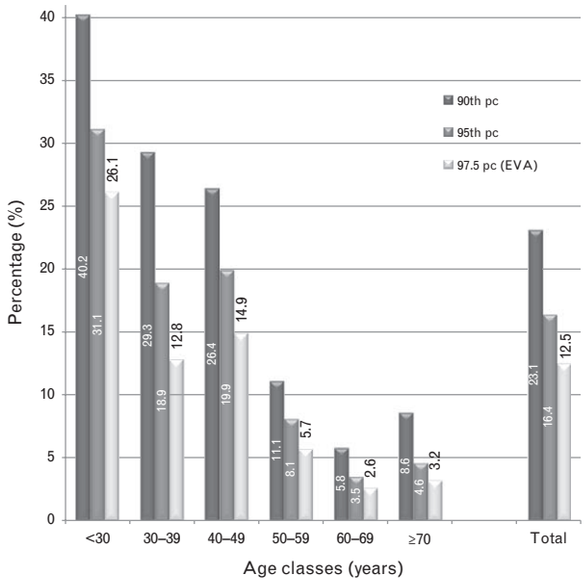

FIGURE 1 Prevalence of early vascular aging (EVA) stratified by age and showing percentage of individuals above the 90th and 95th percentile of pulse wave velocity (PWV) *z*-score values, using normal 'healthy' European individuals as comparators. These high values above expected percentiles in the population are complementary explained by analyzing distribution histograms of PWV and PWV *z*-scores as well as the difference in mean PWV values between the healthy European reference values collaboration population and the Guimarães/Vizela population, presented in Supplementary Material ~~– SM6 to SM8~~, http://links.lww.com/HJH/A474. pc, percentile.

Vizela. Most of these studies were performed in either healthy or lower CVRF populations (when compared with our cohort).

Other population studies have been conducted in older individuals [32,33], normotensives, and untreated hypertensive patients [34], as well as a subset of 998 healthy normotensive individuals in the Anglo-Cardiff Collaborative Trial trial [35]. In this latter study, as well as in the Baltimore Longitudinal Study of Aging [36] and again in the data we are presenting here, the existence of a nonlinear progression of PWV with age is registered, evidencing a much steeper increase from mid-life onward, more pronounced in men.

Noticeably, in our (so-called) low-risk population, significantly higher than expected PWV values are being recorded: 80–84% of individuals under 50 years have a PWV value above the expected median value for their age class in the normal ('healthy') population of the ERVC (Fig. 3) [16]. The male gender prevalence was expected, and it also reflects either the higher prevalence of CVRF or increased mean levels of several variables that are known to influence PWV (mainly BP) in males (data not shown).

The independent predictive value of PWV concerning cardiovascular events/mortality in population-based studies has been well established [37], and goes beyond the CVR stratification achieved by use of well accepted risk scores [38,39]. Therefore, when comparing the mean values of our population with those of the normal 'healthy' population [16], it is relevant to state that, compared with individuals with no CVRF or established CVD, our individuals below 50 years present mean PWV values that are overall 1 m/s higher. Knowing that an increase in 1 m/s in PWV is related to an increase in cardiovascular events, cardiovascular mortality, and overall mortality by 14, 15, and 15%, respectively [15], our findings raise apprehension. We cannot exclude that part of the difference between our population and the ERVC could be attributed to methodological differences even if standardization and staff training took place before screening. Still, recent evidence has emphasized that c-fPWV improves CVR prediction and reclassifies individuals at risk for CVD events, especially concerning individuals below 61 years of age and particularly regarding stroke [23].

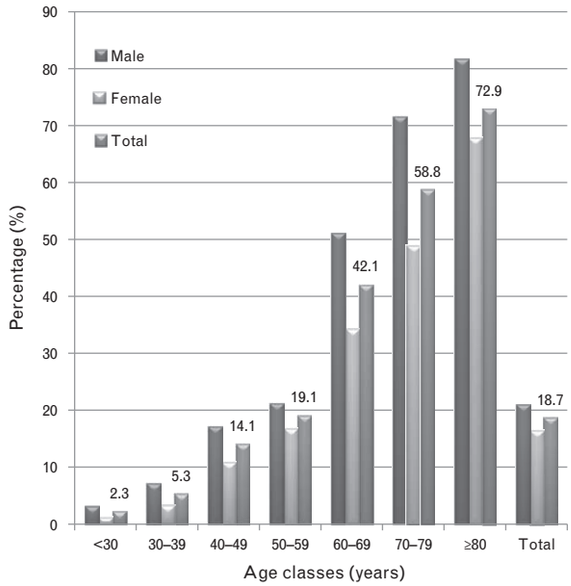

FIGURE 2 Percentage of individuals presenting carotid–femoral pulse wave velocity value above the 10 m/s high-risk cutoff, stratified by age and sex.

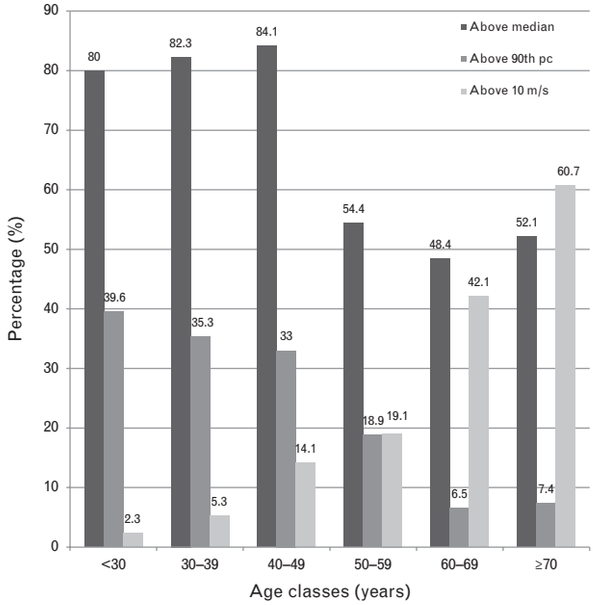

FIGURE 3 Percentage of individuals above the median and above the 90th percentile of the normal pulse wave velocity value expected for age, and above the 10 m/s cutoff (stratified by age decade). pc, percentile.

The presented regression models allowed an explanation of 44–49% of the recorded PWV values in our population. Associations with age and SBP were not surprising, as they have been extensively documented [40]. For HR, the known strength of association is positive [33,40–42] but weaker [40], a fact also reproduced here, with HR only increasing significantly the risk of large artery damage in women. The association of fasting glucose with PWV and the increased risk of development of large artery damage with diabetes were only observed for men, results that are partially in line with data from the Framingham and the Whitehall studies [33,42] but conflicting with the majority of findings in the literature [40], a fact that cannot be dissociated from the differences in prevalence of this condition for both genders.

Early vascular aging

These results have a significant relevance for cardiovascular prevention and raise several questions about not only the CVR profile of our population but also concerning the need for emergent clinical and public health measures. First, we have shown that, whatever the method used to determine its prevalence, there is an overwhelming higher prevalence of EVA in younger age classes, especially below the age of 40. As expected, EVA has proven to be a useful concept to identify individuals at risk in younger age classes where it was more prevalent; the relative decline in EVA prevalence after the age of 50 years accompanies the expected steeper increase of PWV after that age, as has been shown in different trials [35]. This could mean that differences according to EVA prevalence will become more visible in younger age groups, reflecting differential biological aging of the arterial tree, but that convergence applies to older age groups when the impact of chronological aging in general overrides the differential biological aging, more visible in younger individuals. This is in line with epidemiological findings that PWV is a relatively stronger cardiovascular risk marker in middle-aged individuals than in the elderly [23]. The other complementary explanation is survival bias, a phenomenon related to selective better survival in individuals with low PWV.

We observed that males were particularly afflicted by EVA across all age classes, a fact that cannot be dissociated from the overall higher CVRF levels/prevalence in males. Estimation of EVA prevalence is difficult in the absence of consensus on its definition. In addition, the analysis is not focused in outliers in a distribution, but rather with a global shift of the distribution of real values compared with predicted values. It is more conservative to say that the real EVA prevalence should lie within the values determined by both definitions used here (>97.5th percentile of normal mean PWV values stratified by age or >2SD of the mean PWV adjusted to BP class – see Supplemental Materials, http://links.lww.com/HJH/A474). This would provide a global prevalence of EVA between 8.7 and 12.5%, and the following prevalence rate intervals could be determined for every age class: 20.1–26.2% (<30 years), 10.0–12.8% (30–39 years), 7.2–14.9% (40–49 years), 2–5.7% (50–59 years), 1.6–2.6% (60–69 years), and 1.1–3.2% (≥70 years). In addition, we found that 40.2% of individuals in the age class below 30 years and 26.4–29.3% of individuals in the age classes 40–49 and 30–39 years, respectively, are above the 90th percentile of PWV *z*-score. This impressive result means that even if not strictly considered as EVA individuals, over 34.7% of individuals below 40 years are above the 90th percentile of PWV expected for their age: these individuals also have significant added risk for the development of CVD (pointing out the fact that their mean PWV value is at least 1 m/s above their normal/reference counterparts [15,16]). They deserve a particularly strict follow-up, as proposed elsewhere [12].

HR appears as one of the variables associated with EVA. The frequency of individuals exhibiting HR above 75 bpm is slightly higher across all age groups, in particular in the 30–39 years group. Looking at Table SM3, http://links.lww.com/HJH/A474, the absolute difference in HR between EVA and non-EVA individuals is rather small (2 bpm in the whole population, 3.1 and 3.6 bpm in the age groups 30–39 and 40–49 years, respectively). This raises the question of the real biological explanation of this statistical finding, for example, a relatively increased activity of the sympathetic nervous system. On the other hand, could specific genetic alterations [9] associated with early, prolonged 'environmental' stressors (mediated through sympathetic nervous system) result in stiffer than average arteries? The significance of HR as a determinant of EVA may support this hypothesis.

To explain this increased EVA prevalence in our population, one cannot forget the importance of increased average BP and pulse pressure. Individuals with EVA have significantly higher SBP (Table SM3, http://links.lww.com/HJH/A474), way above the minimum exposure risk for the development of CVD.

Other authors have proposed a role of stress hormones acting on the endothelium as well as media smooth muscle layer for contraction, suggesting that PWV increases not only as a reflection of arterial wall structure modification (elastin degeneration, collagen material increase) [6,17] but also with increased vascular smooth muscular cell tonus [43]. At this point, we cannot offer an explanation for the influence on these results of early-life determinants or other proposed contributors to accelerated vascular aging as (short-term) BP variability [44] or salt consumption (recent studies in Portugal have reported the average individual salt consumption as reaching 10.7 g/day in adults, and 7.8 g/day in 10–12-year-old children [45,46]).

Large artery damage (pulse wave velocity above 10 m/s)

The observation that 18.7% of our population (mean age of 47 years) displays large artery damage is novel and surprising. In Copenhagen [39], Framingham [38], and Vobarno [47], significantly older aged populations registered the prevalence of large artery damage between 23.6 and 31.7%. In our population, for the age class 60–70 years, 42% of the individuals would have large artery damage. We have not seen data including the prevalence of increased PWV in the adult population stratified by age class and sex presented elsewhere. Still, values observed in younger age classes are striking. Logistic regression models concerning

PWV above 10 m/s have been discussed previously, mainly obviating the role of age and BP in the development of large artery damage, with differences between genders observed only in the magnitude of risk increase.

Strengths and limitations

The strength of our approach resides on having set up an evaluation of an homogenous population living in adjacent cities in the same region of northern Portugal and using a very large random sample representative of all adult age classes, levels of education, and professional status. The study also has clear limitations. Only one measurement of PWV was performed per individual. A white coat effect cannot be excluded, particularly in younger individuals. The precise definition of EVA is questionable in the absence of a general definition. PWV might not be sufficient for characterizing EVA, and it could also include other cardiovascular or age-related target organ damage variables [48]. We also used the reference value data to characterize EVA. This set of data is valuable, but not immune to bias as it was collected over a variety of locations, using various techniques, and included individuals defined as healthy or bearing risk factors on a post-hoc basis; on another perspective, we cannot exclude that a historic cohort effect could have some influence in our results, when we compare our data with the data from the ERVC (that included cohorts analyzed over 20 years ago).

CONCLUSION

Consistently, whether looking at mean absolute PWV values, prevalence of EVA based on distribution (>97.5 percentile or >2SD over mean for age categories) or prevalence of large artery damage (PWV > 10 m/s), we observed a pattern of increased signs of arterial damage, portraying a cardiovascular risk picture different from what could be expected in a low cardiovascular risk country as Portugal. As Portugal has paradoxically one of the highest rates of stroke in Europe, finding that the general population has skewed distribution of PWV with much higher values might be particularly meaningful when recent evidence shows that c-fPWV improves CVR prediction, especially for stroke [23]. At the same time, the fact that c-fPWV has a higher predictive value in younger ages suggests that we cannot disconnect the high prevalence of EVA from large artery damage in young ages, and stroke (or other CVD) at older age. Only the longitudinal follow-up of this cohort will provide answers to these questions.

The high prevalence of EVA together with the impressive percentage (34.7%) of individuals below 40 years who are above the 90th percentile of the expected PWV value for their age and BP class is clearly worrisome, increasing also the need for better knowledge of prevalence and early control of CVRF as well as tighter risk stratification and inherent clinical intervention.

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There are no conflicts of interest. AQ7

Conflicts of interest

Please refer to the Supplemental Material, http://links.lww.com/HJH/A474.

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Reviewers' Summary Evaluations

Reviewer 1

This paper is focused on the study of the north Portuguese population with a known high prevalence of HTN and stroke. The author studied pulse wave velocity (PWV) in 3038 subjects. The results show that in this population PWV values were higher than expected. Strengths of this work are certainly the large population evaluated, the state of the art method and the correct methodologic approach, including the statistical analysis. A weakness is the absence of other important clinical parameters, which would have helped in mechanistic explanations.

Reviewer 2

The authors assessed early vascular aging (EVA) by measuring pulse wave velocity (PWV) in subjects aged 18–96 years. They compared the measured PWV values with those published in the European Reference Values Project (RVP). They considered a subject to be at risk for EVA when the PWV value exceeded the 97.5th percentile of the value found in the subgroup of RVP called 'healthy subjects'. The values were stratified according to age decades. The overall prevalence of EVA was 12.5%, the highest prevalence being in the youngest subjects aged below 30 years; on the contrary, when the absolute cut-off value of PWV >10 m/s was taken, the prevalence of pathologic values increased steeply with age.

Studying the relative increase of PWV, i.e. comparing the measured value with the reference value at the same age (and blood pressure) group, seems a sound approach to discover arterial pathological changes at a young age. This may be a good approach for early prevention in the future.

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