

ORIGINAL ARTICLE

Determinants of Arterial Stiffness and Vascular Aging in the Older Adult

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Abstract

Background: Arterial stiffness (AS) is recognized as an important and independent risk factor for cardiovascular diseases (CVD).

Objective: This study was aimed at identifying the main determinants of AS in the elderly.

Design and Methods: This was an observational, cross-sectional study of elderly participants. Blood pressure (BP) and parameters of arterial function were measured using a validated device. Clinical and demographic data, global cardiovascular risk, health-related quality of life, dietary profile and cognition data were evaluated. Blood samples were collected for biochemical profiling of the participants. Handgrip strength test was performed. Student's t-test and the χ^2 or Fisher exact tests were used for between-group comparisons as adequate. Correlational analysis was performed with the Pearson correlation coefficients and linear regression analysis. A two-tailed $p < 0.05$ was considered significant.

Results: Fifty-four participants (81.8 ± 8.8 years; 65-94 years) were included in the study. Central BP was 132.7 ± 23.7 mmHg and 51.5 ± 15.7 mmHg, respectively, for aortic systolic and pulse pressures. Mean pulse wave velocity (PWV) was 12.9 ± 2.1 m/s and augmentation index $30.1 \pm 12.9\%$. The proportion of participants with abnormal AS (increased PWV) was 27.8%. Participants with abnormal AS had higher brachial and central BP, higher BMI and higher abdominal fat. Functionality and nutritional status were worse in participants with abnormal AS. Regression analysis indicated age, brachial and central BP and vascular resistance as main determinants of AS.

Conclusions: Abnormal AS is a common finding in the elderly and is highly associated with hypertension, functional decline and impairment of kidney function. (Int J Cardiovasc Sci. 2020; 33(4):349-356)

Keywords: Vascular Stiffness; Hypertension; Pulse Wave Analysis; Cardiovascular Diseases; Comorbidity; Risk Factors.

Introduction

Population aging is a major challenge for the upcoming decades, as the estimated share of European people aged 65 years or over will increase up to 30% by 2060.¹ Aging, particularly arterial aging,² is associated with increased comorbidity; cardiovascular diseases (CVD) account for most of health problems of the elderly and are the leading cause of death and disability.³ Also, older adults are at higher absolute cardiovascular risk.⁴

Cardiovascular risk assessment has been mainly focused on standard variables such as age, gender, concomitant diseases, blood pressure (BP), cholesterol,

and smoking habits, among others. However, other risk factors have emerged, as is the case of arterial stiffness (AS), which is an increasingly recognized risk factor for CVD.^{5,6} In addition to invasive methods, AS can be measured using non-invasive devices. For example, the Mobil-O-Graph is an oscillometric device that calculates central pressures and velocities from the analysis of the brachial pulse pressure wave velocity and was validated in comparison with non-invasive⁷⁻¹⁰ and invasive^{11,12} methods.

Central arteries stiffen with age, which affects its buffering function and the normal ventricular-arterial coupling, and consequently reduces the hemodynamic effectiveness of the heart. This causes an increase in

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the pulse wave velocity (PWV) and an earlier return of the reflected waves, leading to an increase of both systolic blood (SBP) and pulse pressure (PP). Therefore, aging-related hypertension (HT) is characterized by a significant increase in SBP and no change or even a decrease in diastolic blood pressure (DBP), and the predominant phenotype in elderly people is thus isolated systolic hypertension (ISH).¹³ In addition, it is also known that the arterial stiffening process is accelerated by HT.¹⁴

Frailty has also been linked with CVD in the elderly, and cardiovascular risk factors, in turn, predict frailty.¹⁵ Handgrip strength (HGS) has been proved to be a reliable indicator¹⁶ of frailty,¹⁷ and therefore, an indicator of functional decline.

AS is influenced by several factors, such as age, BP, metabolic profile, genetics, medication, body composition, lifestyle, among others.^{5,6} Although these factors have been widely studied in the general population and in particular clinical settings, such as HT, diabetes, dyslipidemia and chronic kidney disease, little evidence exists concerning the elderly population. Therefore, the aim of this study was to identify the main determinants of AS in the elderly.

Methods

Study design, population and ethical considerations

This was a cross-sectional, observational, study of participants enrolled in the AGA@4life project. The aim of the AGA@4life project is to evaluate the effects of different interventions (psychological, physical and nutritional therapy) on the promotion of an active and healthy aging. This preliminary analysis aims at identifying the main determinants of baseline AS of the elderly enrolled in the project. The study population was recruited from a day care center in Portugal (*Associação para a Defesa do Idoso e da Criança - ADIC, Vilarinho, Portugal*). People aged above 65 years, of both genders, physically autonomous and with no prior history of cerebrovascular or neurological disorders were invited to participate in the study. The study enrolled 54 elderly volunteers aged between 65 and 94 years, who agreed to participate, i.e., by convenience sampling.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Polytechnic Institute of Coimbra. Anonymity and confidentiality of the collected data

were assured. The study was conducted for scientific purposes only, and thus, there's no conflict of interest to be declared. All participants signed an informed consent prior to the study.

Blood pressure and arterial stiffness

AS was obtained by pulse wave analysis (PWA) using the AGEDIO device (IEM, Stolberg, Germany), which uses the Mobil-O-Graph validated technology for recording brachial blood pressure (bBP) and performing PWA.⁷⁻¹⁰ Oscillometric measurement of bBP provides brachial SBP (bSBP) and brachial DBP, mean arterial pressure (MAP) and pulse pressure (PP), as well as heart rate (HR). Immediately after the measurement of bBP, the cuff is reinflated at diastolic phase for approximately 10 seconds, while continuously recording brachial pulse waves with a high-fidelity pressure sensor.⁷⁻¹⁰ Brachial SBP and bDBP are used for calibrating the pulse waveforms. Afterwards, the device's software (HMS, version 5.1) applies a generalized transfer function, the ARCSolver algorithm, to reconstruct the aortic pulse waveforms.⁷⁻¹⁰ Wave separation analysis is implemented by decomposition of the aortic pulse waveform into forward (incident) and backward (reflected) pulse waves. These data together with aortic characteristic impedance, age and gender allow the estimation of oscillometric PWV. After quality check, the main parameters derived from the PWA are obtained, including: PWV, which is estimated from the reconstructed aortic pulse waveform, taking into consideration the characteristic impedance and age, and assuming a three-element Windkessel model;⁹ the augmentation pressure (AP), the augmentation index (AIx) and the heart-rate adjusted augmentation index (AIx@75), all of them measures of the augmentation component of the aortic SBP, dependent on the timing of the reflected wave; total vascular resistance (TVR), also derived from the ARCSolver algorithm. Increased AS was classified considering the reference values for PWV, i.e., two standard-deviations (SDs) above the reference PWV values, adjusted for age and gender.⁵

Overall procedure

Participants were enrolled in the study in January 2018. During February and March 2018, multidisciplinary diagnostic evaluation of each participant was performed at baseline, comprising the analysis of relevant demographic and clinical information, including comorbidities, ongoing treatments, diet, physical activity,

cardiovascular risk profile and history of falls. The HGS was measured in the dominant hand using a Jamar hydraulic hand dynamometer (measured in Kg/f), with participant seated with shoulder adducted, elbow flexed 90° and forearm in neutral position.^{18,19} Individuals were instructed to exert maximal grip strength for five seconds, only once.

The Portuguese version of the physical exercise self-efficacy questionnaire was used to evaluate the individual's self-confidence regarding the practice of physical activities.²⁰ Diet profile was evaluated with the Portuguese version of the mini nutritional assessment.²⁰ Cognitive function was evaluated at baseline using the Cambridge Neuropsychological Test Automated Battery (CANTAB - Cambridge Cognition, Cambridge, UK) platform.^{21,22} AS and brachial and central BP were also measured, and blood samples were collected for biochemical analysis.

Statistical Analysis

Data were compiled in Excel 2016 (Microsoft Office, Redmond, WA), checked for quality, and then imported into SPSS Statistics version 24 (IBM, Armonk, NY) for statistical analysis. Post-hoc statistical power was checked with the GPower software version 3.1.9.2 (Universität Kiel, Germany) providing a power coefficient > 0.9 for a medium effect size. The distribution of variables was tested for normality by Kolmogorov-Smirnov's test, and the homogeneity of variances was addressed with the Levene's test. Variables with a non-normal distribution were log-transformed. A simple descriptive statistic method was applied for demographic and clinical characterization. Data are presented as mean ± SD for continuous variables, and as frequency (%) for categorical variables. Comparisons between independent groups were performed with Student's t test for continuous variables, and with the χ^2 or Fisher's exact tests for categorical data. For between-group comparisons, adjustments to age and/or gender were made. Pearson correlation coefficients (r) was calculated with AS (PWV) as the dependent variable. Univariable and multivariable linear regression analysis were also performed with AS (PWV) as the dependent variable and adjusting to age and gender in the multivariable model. Assumptions for linear regression were previously checked, including the presence of a linear relationship, normal distribution and homoscedasticity of errors, as well as independence of the observations. A two-tailed $p < 0.05$ was considered significant.

Results

The study enrolled 54 participants (70% women), with a mean age of 81.8 ± 8.8 years (range: 65-94 years). About 5% of the participants were smokers and 5% were former smokers. Twenty percent of the participants had family history of cardiovascular disease. Hypertension was observed in 80% of the participants, and 64% were under anti-hypertensive treatment. Dyslipidemia accounted for 60% of the participants, with 48% medicated with statins, and diabetes was identified in 26% of the participants, all of them medicated accordingly. Main characteristics are presented in Table 1.

Mean PWV was 12.9 ± 2.1 m/s. Significant differences were observed between genders, with males presenting higher BP and PWV. The proportion of participants

Table 1 - Demographic and clinical characteristics of the study population (n = 54)

	Mean ± SD
Age (years)	81.8 ± 8.8
Body mass index (Kg/m ²)	26.9 ± 4.3
Systolic BP (mmHg)	146.8 ± 37.7
Diastolic BP (mmHg)	79.7 ± 75.8
Heart rate (bpm)	68.2 ± 10.9
Aortic systolic BP (mmHg)	132.7 ± 23.7
Aortic pulse pressure (mmHg)	51.5 ± 15.7
AIx@75 (%)	30.1 ± 12.9
Cardiac output (L/m)	4.8 ± 1.1
Haematocrit (SI)	39.7 ± 5.2
Total Cholesterol (mg/dL)	181.8 ± 39.0
HDL Cholesterol (mg/dL)	42.7 ± 8.5
LDL Cholesterol (mg/dL)	128.5 ± 36.2
Triglycerides (mg/dL)	140.6 ± 51.8
Glycemia (mg/dL)	114.7 ± 56.4
Creatinine (mg/dL)	0.8 ± 0.2
C-reactive protein (mg/dL)	0.4 ± 0.6
Microalbuminuria (mg/L)	42.7 ± 82.5
Haemoglobin A1c (%)	5.3 ± 1.7
Pulse wave velocity (m/s)	12.9 ± 2.1

BP: blood pressure; AIx@75 : augmentation index corrected for heart rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

with abnormal PWV, according to the reference values adjusted for age,⁵ was 27.8% (n = 15). Participants with abnormal PWV were significantly older, had significantly higher brachial and central BPs, higher Aix@75 and higher vascular resistance, lower HGS and worse nutritional status (Table 2).

Univariable linear regression with PWV as dependent variable detected a significant association with age, gender, BP, vascular resistance, creatinine and HGS (Table 3). In multivariable analysis (adjusted for age and gender), BP (particularly the PP component), vascular resistance and handgrip maintained a significant association with PWV.

Also, the presence of hypertension was significantly associated with PWV. PWV increased exponentially with age, as depicted in Figure 1, which occurred in a similar manner in men and women; however, a steeper increase

was observed in hypertensive participants, indicating a shift in the expected trend of arterial ageing, where hypertension accelerates the rate of AS with age.

Pulse wave velocity was also significantly and inversely correlated with HGS (Figure 2; Pearson $r = -0.512$; $p = 0.001$).

Discussion

Considering the current evidence recognising AS, and particularly PWV, as a strong and independent determinant of cardiovascular risk,⁶ we performed a study aimed at identifying the main determinants of AS in the very old, identifying the factors that may accelerate arterial ageing and, thereby potential routes for preventive actions targeting the maintenance of vascular health. The study enrolled 54 participants with mean age

Table 2 - Comparative profiles of the participants as a function of the presence of abnormal arterial stiffness (aortic pulse wave velocity)

	Normal PWV (n = 39)	Abnormal PWV (n = 15)	p-value
Age, years	78.8 ± 8.2	88.7 ± 1.3	< 0.001
Females, %	66.0	80.0	0.693
BMI, Kg/m ²	27.0 ± 4.3	26.4 ± 4.5	0.705
Brachial SBP, mmHg	137.0 ± 35.0	175.3 ± 31.6	0.004
Brachial DBP, mmHg	79.4 ± 17.8	83.7 ± 1.2	0.368
Brachial PP, mmHg	63.4 ± 18.8	91.6 ± 29.4	0.001
Heart rate, bpm	69.7 ± 11.7	64.0 ± 7.2	0.162
Total cholesterol, mg/dL	180.5 ± 40.8	185.9 ± 34.6	0.741
HDL cholesterol, mg/dL	43.0 ± 8.6	42.0 ± 9.2	0.762
Creatinine, mg/dL	0.8 ± 0.2	0.9 ± 0.3	0.070
Hypertension, %	70.0	100.0	0.050
Aortic SBP, mmHg	127.0 ± 21.7	150.9 ± 20.8	0.004
Aortic PP, mmHg	46.8 ± 12.8	65.3 ± 15.9	0.001
AIx@75, %	28.0 ± 13.8	36.5 ± 7.4	0.020
Vascular resistance	1.3 ± 0.2	1.7 ± 0.4	0.006
Handgrip strength, Kg/f	17.5 ± 8.1	12.1 ± 4.8	0.020
Mini nutritional assessment, score	23.5 ± 7.1	19.7 ± 4.1	0.040
PWV, m/s	12.1 ± 1.7	15.6 ± 0.9	< 0.001

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; HDL: high-density lipoprotein; Aix@75: augmentation index corrected to heart rate; PWV: pulse wave velocity.

Table 3 - Univariable and multivariable linear regression analysis with pulse wave velocity as dependent variable

Variable	Univariable			Multivariable*		
	β	CI	p-value	β	CI	p-value
Age, years	0.213	0.171; 0.255	< 0.001	-	-	-
Gender	1.554	0.091; 3.016	0.038	-	-	-
BMI, Kg/m ²	0.036	-0.103; 0.203	0.669	0.046	-0.044; 0.136	0.308
Brachial SBP, mmHg	0.020	0.002; 0.038	0.027	0.021	0.015; 0.028	< 0.001
Brachial DBP, mmHg	0.001	-0.045; 0.047	0.961	0.035	0.013; 0.057	0.002
Brachial MAP, mmHg	0.037	0.004; 0.075	0.031	0.043	0.031; 0.054	< 0.001
Brachial PP, mmHg	0.053	0.029; 0.076	< 0.001	0.037	0.028; 0.047	< 0.001
Heart rate, bpm	-0.046	-0.111; 0.018	0.155	0.004	-0.034; 0.041	0.848
Aortic SBP, mmHg	0.037	0.010; 0.065	0.010	0.039	0.030; 0.047	< 0.001
Aortic PP, mmHg	0.082	0.045; 0.120	< 0.001	0.057	0.041; 0.072	< 0.001
AIx@75	0.053	0.001; 0.106	0.050	0.022	-0.010; 0.053	0.167
Vascular resistance	3.701	1.876; 5.526	< 0.001	2.039	1.035; 3.043	< 0.001
Total cholesterol, mg/dL	0.005	-0.015; 0.025	0.621	-0.001	-0.012; 0.010	0.801
HDL cholesterol, mg/dL	-0.014	-0.106; 0.078	0.762	-0.008	-0.058; 0.041	0.731
Triglycerides, mg/dL	0.008	-0.007; 0.023	0.261	0.004	-0.005; 1.219	0.620
Glycaemia, mg/dL	0.015	0.002; 0.028	0.025	-0.001	-0.010; 0.007	0.745
Creatinine, mg/dL	3.777	0.320; 7.233	0.033	1.684	-0.268; 3.636	0.088
Microalbuminuria, mg/L	0.009	0.001; 0.018	0.071	-0.001	-0.007; 0.004	0.611
Handgrip strength, Kg/f	-0.114	-0.180; -0.047	0.001	-0.049	-0.097; -0.001	0.046
MNA, score	-0.071	-0.297; 0.155	0.526	-0.008	-0.128; 0.113	0.895

* adjusted for age and gender; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure; AIx@75: augmentation index corrected to heart rate; HDL: high density lipoproteins; MNA: mini nutritional assessment.

of 81.8 ± 8.8 year. From these, 80% had HT, which, *per se*, is an important CVD risk factor, and even more considering that only 64% of these hypertensive participants were under anti-hypertensive treatment.

As expected, the results showed age as a strong determinant of PWV and BP, and a significant proportion of participants (28%) had abnormal AS, according to the expected values for age and gender.⁵ This clearly reveals the interplay of chronological ageing with other contributing factors for the progression of AS through the lifespan, and particularly in the old and very old.²³ The dependence of AS on age relates to the decrease in arterial compliance due to a decreased ratio of elastin to collagen, resulting from an enhanced degradation of

elastin and accumulation of stiffer collagen in the arterial media layer.^{13,14}

On the other hand, there is an intrinsic, two-sided relationship between AS and BP. Our study showed that abnormal values of PWV were significantly related with HT, and that increases in both brachial and central systolic and PPs were associated with higher PWV. The increase in the stiffness of central arteries, mostly in older individuals, also contributes to an earlier arrival of the reflected component of the pulse wave, illustrated in the univariable regression analysis with a significant association between PWV and the AIx@75. This would cause an increase in the SBP and no change, or even a decrease in DBP, paving the way to increased

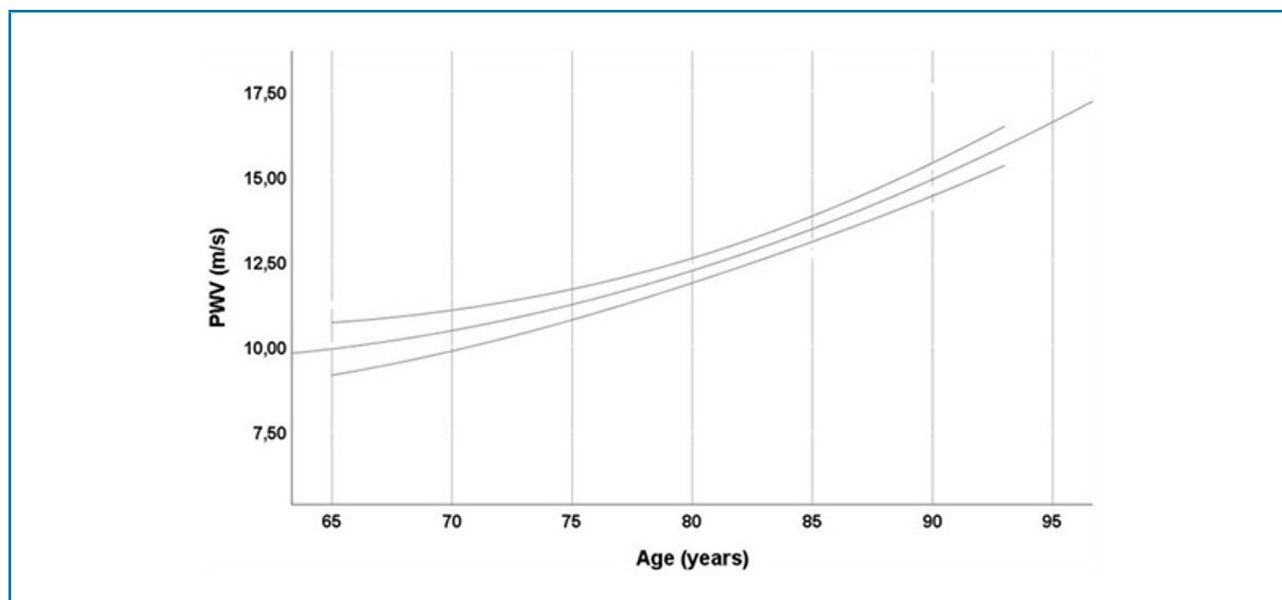


Figure 1 - Aortic pulse wave velocity increase with age.

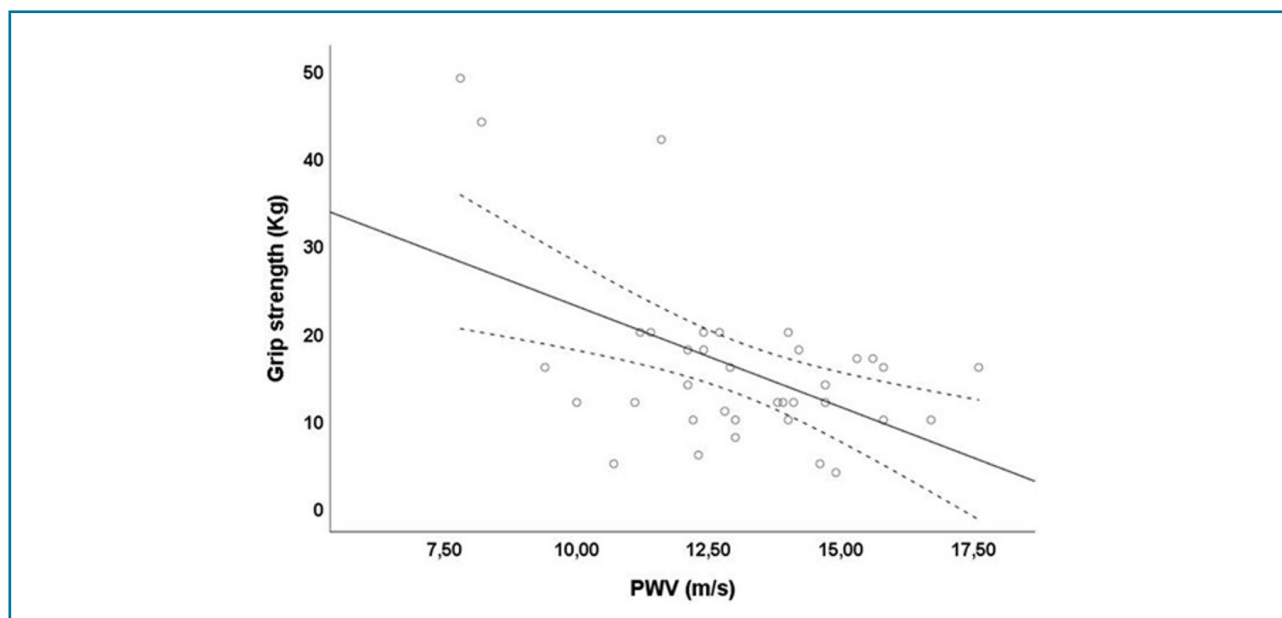


Figure 2 - Aortic pulse wave velocity and handgrip strength.

pulsatility and increased PP.²⁴ These hemodynamic adaptations serve the basis for ISH, which is the most prevailing HT phenotype in the very old.⁵ Conversely, HT has been proved to cause arterial damage that may accelerate AS.^{2,14,23,24} This was also supported by the strong association of BP and vascular resistance with AS demonstrated in the present study.

In addition to the expected association of AS with hemodynamic parameters, a significant association of AS was found with kidney function and overall health parameters. In fact, there was an association of AS with creatinine values, with participants with abnormal AS showing higher mean creatinine levels and worse kidney function, which is in line with previous evidence

demonstrating an independent association between PWV and kidney function.^{25,26} Also, frailty represents a state of greater physiological vulnerability, which further affects the interaction between risk factors, disease progression and the phenotypic expressions of CVD.^{15,17}

The HGS test has been acknowledged as one important marker of frailty and degree of sarcopenia in the elderly.¹⁷ In the present study, we found a significant inverse association of PWV with HGS, with participants with abnormal AS showing significantly lower scores in the HGS test, and thus, greater frailty and worse overall health. This association was also documented in a population analysis derived from the Framingham Heart Study,¹⁵ which corroborates AS as a biomarker that may express the cumulative exposure to risk factors through the lifespan and adaptations of some aspects of biological ageing (abnormal AS) whose course is dissociated from the expected chronological ageing.²⁷⁻²⁹

The present study has limitations that should be considered. The use of a single-point method for assessing arterial properties is a limitation that must be acknowledged³⁰ despite its previous validation.⁷⁻¹² The size of the cohort is limited, even though the post-hoc statistical power analysis provided evidence in favor of its adequacy for the analytical procedures used. The results refer to one single measurement per participant, therefore considerations about age-dependent trends must be taken with caution.

As a future challenge, we seek to explore tailored interventions to improve functionality and overall quality of life, evaluating whether personalized interventions, such as exercise programs, nutritional counselling and drug adherence programs are effective for preventing and/or treating AS and restoring vascular health in the elderly.

Highlights

- Abnormal arterial stiffness is a common finding in older adults and is strongly associated with isolated systolic hypertension.
- Abnormal arterial stiffness is a form of accelerated vascular ageing that is associated with a worse overall cardiovascular risk profile.

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- Frailty and impaired kidney function are strongly associated with arterial stiffness.

- The identification of the main determinants of arterial stiffness in the elder may be instrumental for the design of tailored and effective intervention programs.

Author contributions

Conception and design of the research: Pereira T. Acquisition of data: Pereira T, Costa T. Analysis and interpretation of the data: Pereira T, Costa T. Statistical analysis: Pereira T, Costa T. Obtaining financing: Pereira T. Writing of the manuscript: Pereira T, Costa T. Critical revision of the manuscript for intellectual content: Pereira T, Costa T.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Polytechnic Institute Of Coimbra under the protocol number 8/2018. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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