Original Article

Relationships between subendocardial perfusion impairment, arterial stiffness and orthostatic hypotension in hospitalized elderly individuals

Francesco Fantin[a], Anna Giani[a], Federica Macchi[a], Giulia Amadio[a], Andrea P. Rossi[a], Elena Zoico[a], Gloria Mazzali[a], and Mauro Zamboni[b]

Background: Orthostatic hypotension is an independent risk factor for cardiovascular morbidity and mortality. Arterial stiffness has been shown to be a pathophysiological mechanism linking orthostatic hypotension and increased cardiovascular risk. This study aims to evaluate the relationship between arterial stiffness, orthostatic hypotension and subendocardial viability ratio (SEVR) and moreover to identify the main predictors of orthostatic hypotension, carotid-femoral pulse wave velocity (PWV-cf) and SEVR.

Methods: Seventy-five patients were enrolled (mean age 82.95 ± 6.45) in Verona's AOUI Geriatric ward. They underwent blood pressure, heart rate, body weight measurements and also comorbidity, arterial stiffness (PWV-cf measured by applanation tonometry), SEVR and biochemical indexes.

Results: Prevalence of orthostatic hypotension was 46.6%. Even after adjustment for age, sex, glomerular filtration rate and mean arterial pressure, SEVR values corrected for arterial oxygen and haemoglobin content were statistically lower in orthostatic hypotension patients ($P = 0.05$) and PWV-cf values were statistically higher in orthostatic hypotension individuals ($P = 0.042$). In a binary logistic regression, PWV-cf was the only significant predictor of orthostatic hypotension (odds ratio 1.123; $P = 0.039$; confidence interval = 1.006–1.17).
In a backward logistic regression model sex, creatinine clearance and orthostatic hypotension were significant predictors of SEVR corrected for O_2 content. Mean arterial pressure, creatinine clearance and orthostatic hypotension were significant predictors of PWV-cf.

Conclusion: This study shows that orthostatic hypotension is related to increased arterial stiffness, confirming its higher prevalence in elderly patients. Orthostatic hypotension was also associated with reduced values of corrected SEVR, showing a relevant consequence of orthostatic hypotension on subendocardial perfusion impairment.

Keywords: orthostatic hypotension, pulse wave velocity, subendocardial viability ratio

Abbreviations: AIx, augmentation index; CCI, Charlson Comorbidity Index; Corrected SEVR, sub-endocardial viability ratio value corrected for oxygen content and haemoglobin; MAP, mean arterial pressure; PP, pulse pressure; PPa [%], pulse pressure amplification; PWVcf, pulse wave velocity carotid-femoral; SEVR, subendocardial viability ratio

INTRODUCTION

Orthostatic hypotension is a frequent and often underdiagnosed cardiovascular disorder, widely common among elderly individuals, showing higher prevalence among hospitalized patients [1]. It is an independent risk factor for both cardiovascular morbidity and all-cause mortality [2,3] and it is associated with higher incidence of syncope, coronary heart disease, stroke and hospitalization [4,5]. Orthostatic hypotension increases the burden of functional impairment: it is associated with higher risk of falling, dementia and cognitive impairment [6], cerebrovascular disorders and stroke [7].

Previous studies showed a strong relation between orthostatic hypotension and several cardiovascular diseases, widespread among geriatric population (older than 65 years), for example heart failure, coronary heart disease, myocardial infraction and atrial fibrillation [8]. Orthostatic hypotension is also frequently related to arterial hypertension, showing higher incidence among hypertensive patients with poor BP levels control [9].

The high prevalence of orthostatic hypotension among elderly individuals can be explained by the frequent conditions of volume depletion, dehydration, immobilization, impaired post-prandial response, deconditioning and frailty [10]. Furthermore, orthostatic hypotension can be

Journal of Hypertension 2021, 39:2379–2387

[a]Section of Geriatric Medicine, Department of Medicine and [b]Section of Geriatric Medicine, Department of Surgery, Dentistry, Pediatric and Gynecology, University of Verona, Verona, Italy

Correspondence to Francesco Fantin, MD, PhD, Clinica Geriatrica, Ospedale Maggiore, Piazzale Stefani 1, University of Verona, –Verona 37126, Italy. Tel: +39 045 8122537; fax: +39 045 8122043; e-mail: francesco.fantin@univr.it

Received 14 April 2021 **Revised** 1 June 2021 **Accepted** 18 June 2021

DOI:10.1097/HJH.0000000000002944

considered one of the pathophysiological expressions of vascular ageing, characterized by arterial wall stiffening and previous studies already described an impaired baroceptor sensitivity due to reduced arterial wall compliance [11].

Pulse wave analysis (PWA) is a noninvasive method, which is considered the gold standard technique to evaluate arterial stiffness [12,13], and a valid instrument in cardiovascular risk assessment [14]. Pulse wave velocity (PWV) can be analysed in different arterial segments, describing both elastic arteries by the carotid-femoral PWV (PWV-cf), and peripheral muscular arteries by carotid-radial PWV (PWV-cr) [15].

Furthermore, PWA can provide information about subendocardial perfusion, by subendocardial viability ratio (SEVR) calculation. SEVR is a noninvasive estimation of myocardial workload, oxygen supply and perfusion [16], and it can be obtained by applanation tonometry. Firstly defined by Buckberg *et al*. in 1972 [17], it represents the ratio between diastolic pressure time index (DPTI) and systolic pressure time index (SPTI). DTPI, which is the area under the diastolic phase in the aortic pulse wave profile, estimates myocardial oxygen supply, whereas STPI (the area under the systolic phase) represents cardiac tissue oxygen consumption [18]. Therefore, low values of SEVR indicate an impaired subendocardial perfusion [17].

Several studies described the possible relations between SEVR and many pathological conditions, such as hypertension [19], peripheral arterial disease [20], aortic stenosis [21], chronic kidney disease [22], but, to our knowledge, less is known about the relationship between SEVR and orthostatic hypotension.

As orthostatic hypotension, arterial stiffness and SEVR reduction can be considered different expressions of the same ageing process, their relationship should be further analysed. The aims of the present study were to quantify the prevalence of orthostatic hypotension among hospitalized geriatric patients, to analyze the possible relationship between arterial stiffness, OH and SEVR and to identify the possible predictors of orthostatic hypotension, PWV-cf and SEVR.

MATERIALS AND METHODS

Individuals

Consecutive in-patients, aged over than 65 years, hospitalized at the Geriatric Section of Verona University Hospital, for any cause, between August and September 2019, were prospectively enrolled. Critically ill patients and individuals who could not assume the upright position were excluded. Patients were evaluated after achievement of clinical stability, not during the acute phase of illness.

A detailed clinical history and physical examination were recorded for each patient. Clinical data included age, sex, blood pressure (BP), heart rate (HR) and body weight measurement (Salus scale, Milan, Italy). Possible orthostatic hypotension risk factors were noted, such as arterial hypertension, diabetes, chronic kidney disease (defined as the presence of an estimated glomerular filtration rate (eGFR), by the Cockroft-Gault equation, lower than 60 ml/min per 1.73 m^2) and Parkinson's disease. Smoking habit was also investigated. If a recent echocardiographic evaluation was available, left ventricular ejection fraction and the presence of diastolic dysfunction were registered.

The study was approved by the Ethical Committee of the University of Verona. All participants gave informed consent to be involved in the research study.

Comorbidity

Charlson Comorbidity Index (CCI) was calculated for each patient. The scoring scheme is based on the presence of a list of 19 pathological conditions, each one is assigned a weight from 1 to 6 points; the sum of the weights for all concurrent diseases is then corrected by age. Charlson age adjusted index ranges from 0 to 43 points, but a score higher than 5 points predicts poor clinical outcomes [23].

The total number of medications was also registered; the use of hypotensive drugs (ACE-inhibitors, angiotensin receptor blockers, calcium channel blockers, oral or intravenous diuretics, alpha-blockers, beta-blockers) was investigated, and the number of hypotensive medications was reported.

Blood pressure measurement and orthostatic hypotension evaluation

Brachial BP was measured twice in a time frame of 15 min using an aneroid sphygmomanometer (Heine Optothechnik, Gilching, Germany) in the non-dominant arm of the individual, in the supine position, after 5 min of rest. The average of the readings was considered as the individual's BP. Mean arterial pressure (MAP) was then derived. BP was then measured 1, 3 and 5 min after assuming orthostatic position. HR was registered each time. According to ESC guidelines [24], orthostatic hypotension was defined as a reduction in SBP of at least 20 mmHg or in DBP of at least 10 mmHg.

Arterial stiffness and subendocardial viability ratio evaluation

The BP was measured immediately prior to tonometric recording. The PWA was performed noninvasively using a small portable device called PulsePen (Diatecne, Milan, Italy) [25]. Its software, WPulsePen 2.0.1, provides central aortic pressure values, an assessment of arterial pulse wave contours, an estimation of reflection waves and measurements of PWV. PulsePen determines the PWV by a single probe placed at two sites in rapid succession, using the electrocardiogram trace as reference.

The PWV was calculated as distance between the measurement sites divided by transit time delay between femoral and carotid pulse wave and expressed in meters per second.

The distance of the pulse wave transit was the difference between the distance from supra-sternal notch to femoral point of application of the tonometer and the distance from carotid point of tonometer application and the supra-sternal notch. The time delay was measured between the feet of the peripheral artery (femoral or radial) and carotid waveforms. The foot of the wave is defined at the end of diastole when the steep rise of the waveform begins.

PWA provide information about different arterial segments, as it can analyse both elastic arteries by the carotid-femoral PWV (PWV-cf) and peripheral muscular arteries by carotid-radial PWV (PWV-cr) [15]. Increased aortic stiffness, described as augmented PWV-cf, predicts higher cardiovascular risk.

By means of the same software, other indices were then calculated: first, pulse pressure (PP), strongly related to cardiovascular risk and coronary heart disease [26,27], was derived as the difference between SBP and DBP. Also, pulse pressure amplification (*PPa*%) was calculated; it represents the increment of peripheral PP as compared to the central PP, and it relates to age, sex and body composition. PPa% is described as the ratio between the difference of brachial PP (*pPP*) and ascending aorta PP (*cPP*):

$$PPa = \frac{pPP - cPP}{cPP}$$

PulsePen software also defines the augmentation pressure, which is the systolic pressure increment caused by the reflection wave (from the periphery to the centre), and the augmentation index (AIx), which is the ratio between augmentation pressure and PP.

PulsePen Software, by PWV traces analysis, provides SEVR measurement, which represents an indirect estimation of myocardial perfusion, relative to left ventricle workload. SEVR is obtained by the following formula: SEVR = DPTI/SPTI. DTPI, which is the area under the diastolic phase in the aortic profile, estimates myocardial oxygen supply, and it is defined by the formula: DPTI = ([mean diastolic aortic pressure−mean diastolic left ventricular pressure] ×diastolic time); whereas STPI (the area under the systolic phase) represents cardiac tissue oxygen consumption, defined as SPTI = mean systolic aortic pressure (corresponding to left-ventricular mean systolic pressure) ×left-ventricular ejection time [18]. As SEVR is described as DTPI/STPI ratio, it indirectly reflects the adequacy of subendocardial perfusion.

A critical value for SEVR of 0.5 has been suggested [28], lower values may represent insufficient subendocardial perfusion, as indicated by a corresponding reduction of the ratio of subendocardial/subepicardial flow per gram of left-ventricular myocardium [18].

Subendocardial oxygen supply depends both on coronary flow and on arterial oxygen saturation, and it can be compromised in case of severe anaemia or hypoxia. Therefore, SEVR should be adjusted for arterial oxygen concentration, converting the measure of myocardial blood flow supply (*DTPI*) into a measure of myocardial oxygen delivery [18]. The correction is obtained by multiplying SEVR by the arterial oxygen content (CaO_2) [29], as follows: $SEVR \times CaO_2 = CaO_2 \times DTPI / STPI$.

The blood oxygen content was determined using the following formula: $CaO_2 = 1.34 \times$ blood haemoglobin concentration (g/dl) × arterial oxygen saturation (%) $+0.003 \times$ arterial pressure of oxygen (mmHg).

According to previous evidences, the critical value for SEVR CaO_2 was considered 10; lower values may represent a significant reduction in oxygen supply [29].

Biochemical analysis

Venous blood samples for all metabolic assessments were obtained after the individuals fasted overnight. Plasma glucose was measured with a glucose analyser (Beckman Instruments Inc, Palo Alto, California, USA). Cholesterol and triacylglycerol concentrations were determined with an automated enzymatic method (Autoanalyzer; Technicon, Tarrytown, New York, USA). High-density-lipoprotein (HDL) cholesterol was measured by using the method of Warnick and Albers. LDL cholesterol was calculated using the Friedwald formula. Creatinine was measured by a modular analyser (Roche Cobas 8000; Monza, Italy); eGFR was calculated by Cockroft-Gault formula.

Statistical analysis

Results are shown as mean value ± standard deviation (SD). Variables not normally distributed were log-transformed before analysis. Pearson correlation analyses were used to test association between SEVR, PWV-cf, AP, AIx and other variables. Independent samples *t*-tests were used to compare baseline characteristics of male and female population and of patients with and without orthostatic hypotension. ANOVA and ANCOVA analyses were performed to study SEVR and PWV-cf, even after age, sex MAP and eGFR adjustment. Multiple backward regression analysis valued the combine effects of age, sex, MAP, CCI, orthostatic hypotension presence and eGFR on SEVR-CaO_2 and PWV-cf. Binary regression analysis was performed to evaluate orthostatic hypotension predictors, considering age, sex, MAP, eGFR and PWV-cf as independent variables.

A significance threshold level of 0.05 was used throughout the study. All statistical analyses were performed using SPSS 23.0 version for Windows (IBM, Armonk, New York, USA).

RESULTS

The main characteristics of the study population are summarized in Table 1. Seventy-five individuals with a mean age of 82.95 ± 6.45 years were evaluated, of whom 38 were women and 37 were men. Women were significantly older than men ($P = 0.03$). The prevalence of orthostatic hypotension was 46.6%.

Creatinine values were higher in men than in women ($P = 0.006$).

No significant differences were observed between male and female in SBP and DBP, MAP, and HR. Augmentation pressure, AIx and *PPa*% also did not differ between the two populations.

PWV-cf did not differ between men and women. On the contrary, both SEVR and SEVR values corrected for oxygen content and haemoglobin were significantly lower in the female population ($P = 0.002$ and $P = 0.01$, respectively).

Regarding comorbidity, men appeared to be affected by a higher number of diseases than women ($P = 0.008$), although the two populations did not differ in terms of score obtained on the CCI.

Table 2 summarizes univariate correlations between SEVR, SEVR corrected for oxygen content and haemoglobin, PWV-cf and the main study variables.

TABLE 1. Characteristics of the study population

$n = 75$	Total ($n = 75$)	Women ($n = 38$)	Men ($n = 37$)	P (women vs. men)
Age (years)	82.95 ± 6.45	84.53 ± 6.81	81.32 ± 5.72	0.030
Blood glucose Level (mg/dl)	98.26 ± 24.49	104.58 ± 28.34	93.19 ± 18.44	0.043
Haemoglobin (g/dl)	11.37 ± 1.73	11.14 ± 1.75	11.61 ± 1.70	0.241
Creatinine (μmol/l)	93.61 ± 41.51	80.84 ± 34.38	106.73 ± 44.48	0.006
Creatinine Clearance (ml/min)	52.58 ± 20.68	49.33 ± 20.59	55.92 ± 20.51	0.169
Total cholesterol (mg/dl)	136.13 ± 43.22	145.82 ± 48.42	125.29 ± 34.08	0.040
HDL cholesterol (mg/dl)	42.54 ± 15.62	41.35 ± 15.58	43.82 ± 15.79	0.510
Triglyceride (mg/dl)	101.61 ± 47.57	113.76 ± 53.84	87.56 ± 34.91	0.018
Orthostatic SBP (mmHg)	109.72 ± 14.11	109.05 ± 14.14	110.41 ± 14.243	0.681
Orthostatic DBP (mmHg)	67.71 ± 8.22	66.61 ± 7.58	68.84 ± 8.78	0.243
Clinostatic SBP (mmHg)	123.29 ± 13.72	121.11 ± 12.48	125.40 ± 14.69	0.182
Clinostatic DBP (mmHg)	71.16 ± 8.10	69.58 ± 7.87	72.70 ± 8.13	0.100
PP orthostatic (mmHg)	42.01 ± 9.82	42.45 ± 10.31	41.57 ± 9.41	0.700
MAP orthostatic (mmHg)	83.28 ± 9.02	82.29 ± 8.19	84.30 ± 9.80	0.339
PP clinostatic (mmHg)	52.12 ± 10.37	51.52 ± 9.16	52.70 ± 11.52	0.632
MAP clinostatic (mmHg)	88.53 ± 9.09 ±	86.76 ± 8.63	90.27 ± 9.30	0.099
HR at rest (bpm)	74.19 ± 8.88	76.50 ± 8.065	71.81 ± 9.15	0.021
HR in orthostatism (bpm)	80.34 ± 10.09	82.44 ± 9.75	78.41 ± 10.15	0.092
AIx%	10.98 ± 16.85	10.29 ± 18.90	11.68 ± 14.67	0.722
AP (mmHg)	7.24 ± 4.82	7.59 ± 5.12	6.89 ± 4.54	0.536
PPa%	15.63 ± 15.68	17.53 ± 17.59	13.68 ± 13.40	0.289
PWV-cf (m/s)	13.00 ± 5.39	13.26 ± 5.62	12.79 ± 5.99	0.728
SEVR	1.20 ± 0.27	1.10 ± 0.24	1.30 ± 0.27	0.002
Corrected SEVR	16.17 ± 4.61	14.72 ± 3.80	17.43 ± 4.99	0.010
Length of stay (days)	12.53 ± 6.98	12.41 ± 5.87	12.66 ± 8.15	0.893
CCI	5.63 ± 1.68	5.58 ± 1.73	5.68 ± 1.65	0.805
Number of diseases	4.40 ± 1.62	3.92 ± 1.62	4.89 ± 1.49	0.008
Number of drugs	5.55 ± 2.04	5.13 ± 2.11	5.97 ± 1.89	0.073
Number of antihypertensive drugs	0.63 ± 0.75	0.47 ± 0.65	0.78 ± 0.82	0.074

AIx, augmentation index; AP, augmentation pressure; CCI, Charlson Comorbidity Index; Corrected SEVR, subendocardial viability ratio value corrected for oxygen content and haemoglobin; MAP, mean arterial pressure; PP, pulse pressure; *PPa* [%], pulse pressure amplification; PWV-cf, pulse wave velocity carotid-femoral; SEVR, subendocardial viability ratio.

A significant negative correlation was found between corrected SEVR and age ($r = -0.241$ and $P = 0.04$), between corrected SEVR and PPA ($r = -0.259$ and $P = 0.027$) and between PWV-cf and both SEVR ($r = -0.294$ and $P = 0.012$) and corrected SEVR ($r = -0.309$ and $P = 0.009$).

TABLE 2. Univariate correlations between subendocardial viability ratio, corrected subendocardial viability ratio, pulse wave velocity carotid-femoral and the main variables of the study

	R		
$n = 75$	SEVR	Corrected SEVR	PWV-cf
Age	−0.164	−0.241*	0.214
SEVR	//	0.701*	−0.294*
Corrected SEVR	0.701*	//	−0.309*
PWV-cf	−0.294*	−0.322*	//
PPa	−0.223	−0.259*	0.047
Aix	0.069	0.059	−0.002
AP	0.074	0.142	−0.152
SBP	0.026	0.239	0.147
DBP	0.043	0.208	0.118
PP	0.002	0.175	0.144
MAP	−0.016	0.176	0.194
Blood glucose level	−0.316*	−0.130	0.049
Total cholesterol	−0.074	0.084	−0.149
HDL cholesterol	0.137	0.306*	−0.149
LDL cholesterol	−0.085	0.023	−0.186
Triglyceride	−0.244*	−0.208	0.164
Creatinine clearance	0.105	0.287*	−0.330*

AIx, augmentation index; AP, augmentation pressure; corrected SEVR, subendocardial viability ratio value corrected for oxygen content and haemoglobin; MAP, mean arterial pressure; PP, pulse pressure; PPa, pulse pressure amplification; PWV-cf, carotid – femoral pulse wave velocity; SEVR, subendocardial viability ratio.
*$P < 0.05$, significant correlation.

SEVR was negatively related with fasting glucose level ($r = -0.316$ and $P = 0.007$) and with triglyceride values ($r = -0.244$ and $P = 0.046$); adjusted SEVR was positively related to HDL cholesterol value ($r = 0.306$ and $P = 0.011$).

SEVR was significantly correlated with creatinine clearance ($r = 0.287$ and $P = 0.014$); on the contrary, we found a negative association between creatinine clearance and PWV-cf ($r = -0.330$ and $P = 0.005$), and AIx ($r = -0.255$ and $P = 0.027$).

Table 3 highlights the main differences between patients with orthostatic hypotension (35 individuals) and patients without (40 individuals).

Orthostatic hypotension patients were found to have lower body weight (61.89 ± 13.19 vs. 68.93 ± 14.80 kg, $P = 0.034$) and lower haemoglobin values (10.94 ± 1.41 vs. 11.73 ± 1.91, $P = 0.048$). No significant differences were observed in other biochemical parameters.

No differences were found in number of diseases or CCI score between the study groups. No statistically significant difference was observed between the two populations regarding either the total number of medications taken or specifically the number of antihypertensive drugs.

Moreover, there was no significant difference about the prevalence of diabetes mellitus, hypertension and chronic renal failure in the group of patients with and without orthostatic hypotension (data not shown in Table).

PWV-cf was significantly higher in patients with orthostatic hypotension than in patients without (14.36 ± 3.83 vs.

TABLE 3. Comparison of the main study variable between sub-groups of patients with and without orthostatic hypotension

n = 75	OH patients (*N* = 35)	Patients without OH (*N* = 40)	*P*
Age (years)	84.42 ± 4.98	81.65 ± 7.32	0.062
Weight (kg)	61.89 ± 13.19	68.93 ± 14.80	0.034
Blood glucose level (mg/dl)	98.03 ± 27.95	99.78 ± 21.33	0.760
Haemoglobin (g/dl)	10.94 ± 1.41	11.73 ± 1.91	0.048
Creatinine (μmol/l)	91.00 ± 42.33	95.90 ± 41.18	0.613
Creatinine clearance (ml/min)	51.47 ± 20.46	53.55 ± 21.07	0.668
Total cholesterol (mg/dl)	131.39 ± 34.44	140.13 ± 49.54	0.397
HDL cholesterol (mg/dl)	41.15 ± 12.42	43.74 ± 18.03	0.491
LDL cholesterol (mg/dl)	69.65 ± 77.52	31.14 ± 44.21	0.405
Triglyceride (mg/dl)	101.09 ± 36.49	102.05 ± 55.92	0.934
Orthostatic SBP (mmHg)	106.94 ± 11.45	112.15 ± 15.82	0.111
Orthostatic DBP (mmHg)	66.46 ± 7.75	68.80 ± 8.54	0.220
Clinostatic SBP (mmHg)	124.85 ± 15.98	122.00 ± 11.59	0.396
Clinostatic DBP (mmHg)	72.12 ± 8.29	70.38 ± 7.95	0.365
PP orthostatic (mmHg)	40.48 ± 6.66	43.35 ± 11.84	0.210
MAP othostatic (mmHg)	82.21 ± 8.47	84.21 ± 9.47	0.342
PP clinostatic (mmHg)	52.72 ± 13.12	51.62 ± 7.54	0.671
MAP clinostatic (mmHg)	89.70 ± 9.63	87.58 ± 8.62	0.332
HR at rest (bpm)	74.14 ± 9.40	74.23 ± 8.50	0.968
HR in orthostatism (bpm)	78.85 ± 9.16	81.63 ± 10.79	0.249
AIx%	11.18 ± 16.09	10.80 ± 17.68	0.923
AP (mmHg)	6.49 ± 4.69	7.90 ± 4.89	0.210
PPa%	17.86 ± 12.77	13.68 ± 17.77	0.252
PWV-cf (m/s)	14.36 ± 5.83	11.78 ± 4.69	0.041
SEVR	1.20 ± 0.24	1.20 ± 0.30	0.935
Corrected SEVR	15.01 ± 3.35	17.23 ± 5.34	0.039
Length of stay (days)	14.13 ± 8.18	10.96 ± 5.26	0.077
CCI	5.91 ± 1.65	5.38 ± 1.69	0.168
Number of diseases	4.66 ± 1.66	4.18 ± 1.56	0.200
Number of drugs	5.54 ± 1.80	5.55 ± 2.24	0.988
Number of antihypertensive drugs	0.51 ± 0.74	0.73 ± 0.75	0.227

AIx, augmentation index; AP, augmentation pressure; CCI, Charlson Comorbidity Index; Corrected SEVR, subendocardial viability ratio value corrected for oxygen content and haemoglobin; MAP, mean arterial pressure; OH, Orthostatic Hypotension; PP, pulse pressure; *PPa* [%], pulse pressure amplification; PWV-cf, carotid-femoral pulse wave velocity; SEVR, subendocardial viability ratio.

11.78 ± 4.69, $P = 0.041$). The difference between the two populations remained significant even after adjustment for age, sex, GFR and MAP ($P = 0.042$) (Fig. 1a).

Regarding SEVR, no significant differences were observed between the two populations; however, SEVR values corrected for oxygen content and haemoglobin were significantly lower in patients with orthostatic hypotension (15.01 ± 3.35 vs. 17.23 ± 5.34, $P = 0.039$), even after adjustment for age, sex, GFR and MAP ($P = 0.05$) (Fig. 1b).

As shown by binary logistic regression (Table 4), PWV-cf was a significant predictor of orthostatic hypotension with odds ratio (OR) 1.123 [$P = 0.039$ and confidence interval (CI) 1.006–1.17], accounting for 15% of the variance.

Furthermore, a backward logistic regression demonstrated that sex, creatinine clearance and orthostatic hypotension were significant predictors of corrected SEVR, explaining 20.5% of the variance (Table 5).

DISCUSSION

The present study shows, in a group of 75 elderly hospitalized individuals (mean age 82.95 ± 6.45 years), a significant relationship between orthostatic hypotension and subendocardial perfusion impairment. Furthermore, we confirmed the positive relation between increased arterial stiffness and orthostatic hypotension, showing that PWV-cf was the main predictor of orthostatic hypotension in the study population.

In our cohort, the prevalence of orthostatic hypotension was 46.6%: these data are consistent with previous studies, in which the prevalence of orthostatic hypotension in elderly patients in the hospital setting is 50–60% [1]. Higher percentage was also described in a recent study, investigating the prevalence of orthostatic hypotension in a sample of 85 acute patients over 65 years of age admitted to two departments of Internal Medicine. The 75% of patients presented at least one episode of orthostatic hypotension during hospitalization and the 27% were found to have persistent orthostatic hypotension. The latter group was also 3 years older than the group of patients with occasional orthostatic hypotension, and 7 years older than the group without orthostatic hypotension [30].

The high prevalence of orthostatic hypotension in elderly patients is probably due to the physiological changes of ageing, such as decreased baroreceptor sensitivity and autonomic nervous system dysfunction, which impair the response to orthostatism, together with the presence of several favourable conditions (organ disease, volume depletion and prolonged immobility) [31].

Among geriatric population, the incidence and prevalence of orthostatic hypotension should be considered in relation to the presence of some relevant comorbidities. Up to 70% of orthostatic hypotension individuals are affected by hypertension, and orthostatic hypotension presents higher incidence in hypertensive patients with poor BP level control [9]. Furthermore, it is well known that

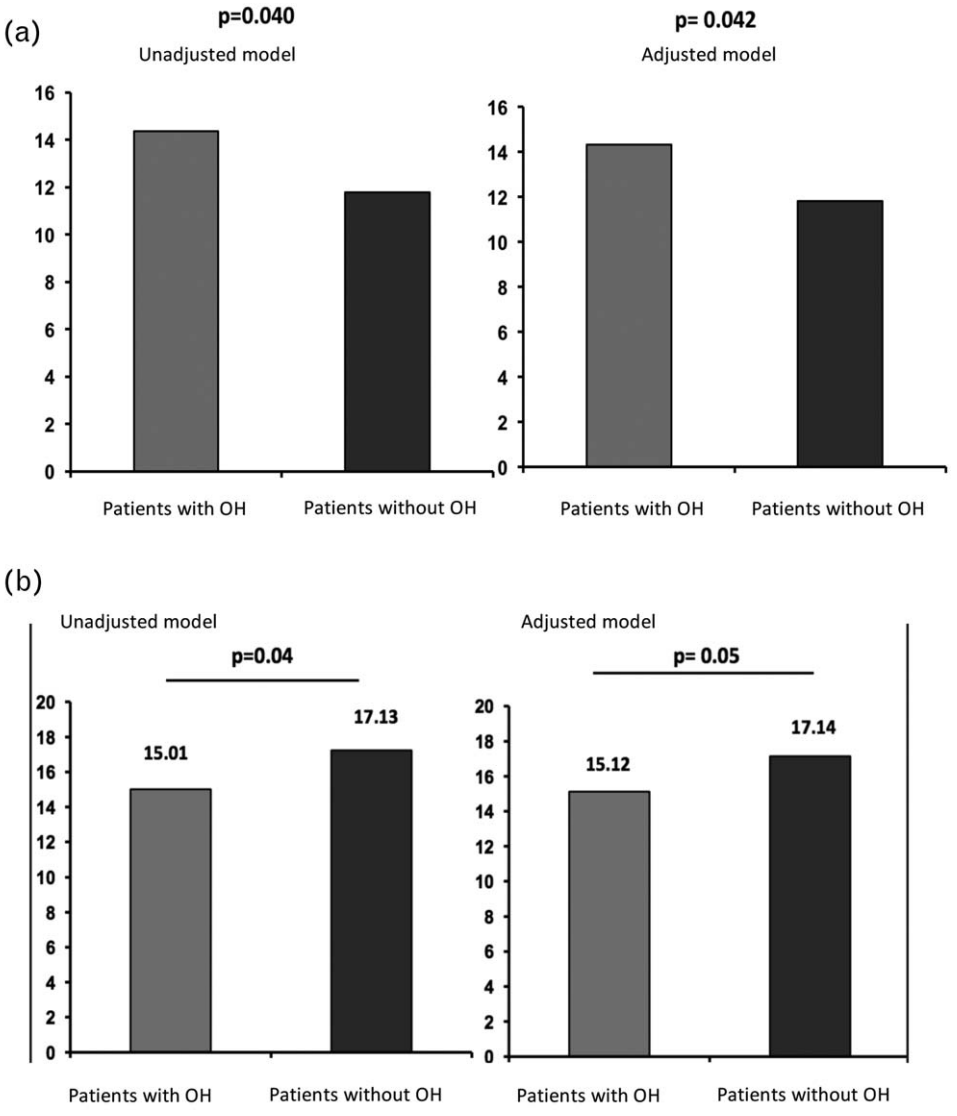

FIGURE 1 Comparison of PWVcf values (a) and corrected SEVR values (b) between patients with or without Orthostatic Hypotension (OH) before and after adjustment for age, sex, GFR and MAP.

orthostatic hypotension is a frequent finding in patients with autonomic nervous system dysfunction, it is related both to primary neurodegenerative disorders, such as Parkinson's disease, and to peripheral neuropathies occurring in several diseases, including diabetes mellitus [32].

In our study, we therefore investigated the prevalence of diabetes mellitus, arterial hypertension and chronic renal failure in patients with and without orthostatic hypotension and in patients without it: the prevalence did not show a significant difference among groups. Only two of 75

TABLE 4. Binary logistic regression considering orthostatic hypotension as a dependent variable and age, sex, SBP, creatinine clearance, corrected subendocardial viability ratio and carotid-femoral pulse wave velocity as an independent variable in study's population (n = 75)

	B coefficient	ES	OR	CI	*P*
Age	0.079	0.048	1.082	0.984–1.190	0.105
Sex	−0.515	0.531	0.598	0.211–1.692	0.332
MAP	−0.027	0.029	0.973	0.919–1.031	0.360
Creatinine clearance	0.014	0.015	1.014	0.985–1.044	0.336
PWV-cf	0.116	0.056	1.123	1.006–1.254	0.039

MAP, mean arterial pressure; PWV-cf, carotid femoral pulse wave velocity.

TABLE 5. Multiple backward regression considering the corrected subendocardial viability ratio as dependent variable and age, sex, mean arterial pressure, Charlson Comorbidity Index, creatinine clearance and orthostatic hypotension as an independent variable in study's population ($n = 75$)

	B coefficient	ES	*P*	R^2
Age	0.025	0.097	0.797	
Sex	2.493	1.032	0.019	
MAP	0.071	0.058	0.226	
CCI	−0.344	0.332	0.303	
Creatinine clearance	0.049	0.028	0.081	
OH	1.960	1.032	0.062	0.239
Age	2.430	0.996	0.017	
MAP	0.070	0.057	0.225	
CCI	−0.319	0.315	0.315	
Creatinine clearance	0.046	0.026	0.077	
OH	1.898	0.996	0.061	0.238
Sex	2.329	0.991	0.022	
MAP	0.078	0.057	0.173	
Creatinine clearance	0.056	0.024	0.023	
OH	1.898	0.988	0.044	0.227
Sex	2.454	0.993	0.016	
Creatinine clearance	0.053	0.024	0.032	
OH	2.213	0.985	0.028	0.205

CCI, Charlson Comorbidity Index; MAP, mean arterial pressure.

individuals were affected by Parkinson's disease and they both had orthostatic hypotension. The small sample size could justify these results.

Our findings showed higher PWV-cf in patients with orthostatic hypotension than in patients without it (PWV-cf 14.36 ± 5.83 vs. 11.78 ± 4.69 m/s, $P = 0.041$).

As widely known, PWV-cf measurement represents a noninvasive and reproducible method for the assessment of arterial stiffness; a value higher than 10 m/s is considered an index of subclinical organ damage [14]. Our results confirm previous analyses: a large cross-sectional study led on 3362 elderly individuals showed that patients with orthostatic hypotension were older and had a greater arterial stiffness, measured by PWV-cf, and presented a greater reduction in BP values on assumption of orthostatic position, as compared to individuals without orthostatic hypotension [33].

Structural alterations in the wall of the great vessels, leading to a reduction in arterial compliance together with a consequent reduction in baroreceptor sensitivity, could explain the relationship between arterial stiffness and orthostatic hypotension.

In our study, in line with previous findings, the relationship between arterial stiffness and orthostatic hypotension remained significant even after adjustment for confounding factors such as age, sex, MAP and glomerular filtration rate, suggesting an independent role of arterial stiffness in determining orthostatic hypotension.

To our knowledge, this is the first study that directly investigated the relationship between orthostatic hypotension and SEVR. Our data showed a statistically significant association between orthostatic hypotension and SEVR corrected for oxygen content and haemoglobin, showing lower SEVR values in orthostatic hypotension patients (15.01 ± 3.35 vs. 17.23 ± 5.34, $P = 0.039$). SEVR, which represents the ratio between oxygen supply and oxygen demand by the myocardium and is derived from the analysis of the central pressure curve, is considered a valid index to assess cardiovascular risk and coronary risk [19]. As the oxygen supply to the subendocardium depends not only on coronary flow, but also on the O_2 content of arterial blood, the SEVR value should be corrected for SpO_2 and haemoglobin value. A corrected SEVR value less than 10 reflects insufficient subendocardial vascularization [18].

Several studies identified a significant relationship between prevalence of orthostatic hypotension and risk of major cardiovascular events; from a meta-analysis of 15 prospective observational studies conducted in Europe, the United States and Asia, including individuals aged 45–83 years, from both acute and subacute setting, orthostatic hypotension was found to be an independent predictor of heart failure, coronary artery disease, myocardial infarction and mortality [8]. Although the pathophysiology of the increased cardiovascular risk in orthostatic hypotension patients is not completely clarified, subendocardial perfusion impairment may fill a gap of knowledge about this issue.

In our study, we found reduced corrected SEVR values in orthostatic hypotension patients, still significant even after correction for confounding factors such as age, sex, MAP and glomerular filtration rate, enlightening the relevant subendocardial perfusion impairment in orthostatic hypotension individuals. In our study population, the oxygen content adjusted SEVR was found to correlate negatively and significantly with age ($r = -0.241$, $P = 0.04$), contextualizing SEVR impairment as an expression of vascular ageing.

Moreover, we found a significant negative correlation between PWV-cf and both SEVR and corrected SEVR. This finding corroborates the power of aortic PWV as an index of subclinical organ damage and an independent prognostic element for cardiovascular mortality. Arterial stiffness may contribute to the development of cardiac ischemic damage, especially subendocardial, by reducing oxygen delivery and/or increasing its need. The Rotterdam study, a large population-based study conducted on 2490 elderly individuals, showed that an increase in pulse wave velocity related to an increase in SPTI and a decrease in DPTI, thus, a significant reduction in SEVR, providing a further explanation of the relationship between arterial stiffness and increased cardiovascular morbidity and mortality [34].

These results confirm that there is a significant direct relationship between arterial stiffness and orthostatic hypotension, supporting an independent role of arterial stiffness in the pathogenesis of orthostatic hypotension and its greater prevalence in elderly individuals.

The complex relation between arterial stiffness, SEVR and orthostatic hypotension may be explained by the underlying pathophysiological mechanisms.

Orthostatic hypotension is mostly provoked by an autonomic nervous system dysfunction. In normal condition, the transition from supine to erect position leads to redistribution of intravascular volume with consequent BP drop [35]. Within few seconds, baroceptors activation leads to increased peripheral vascular resistances and HR [35,36], but in case of prolonged up-right standing, other mechanism contributes to BP counter-regulation, such as

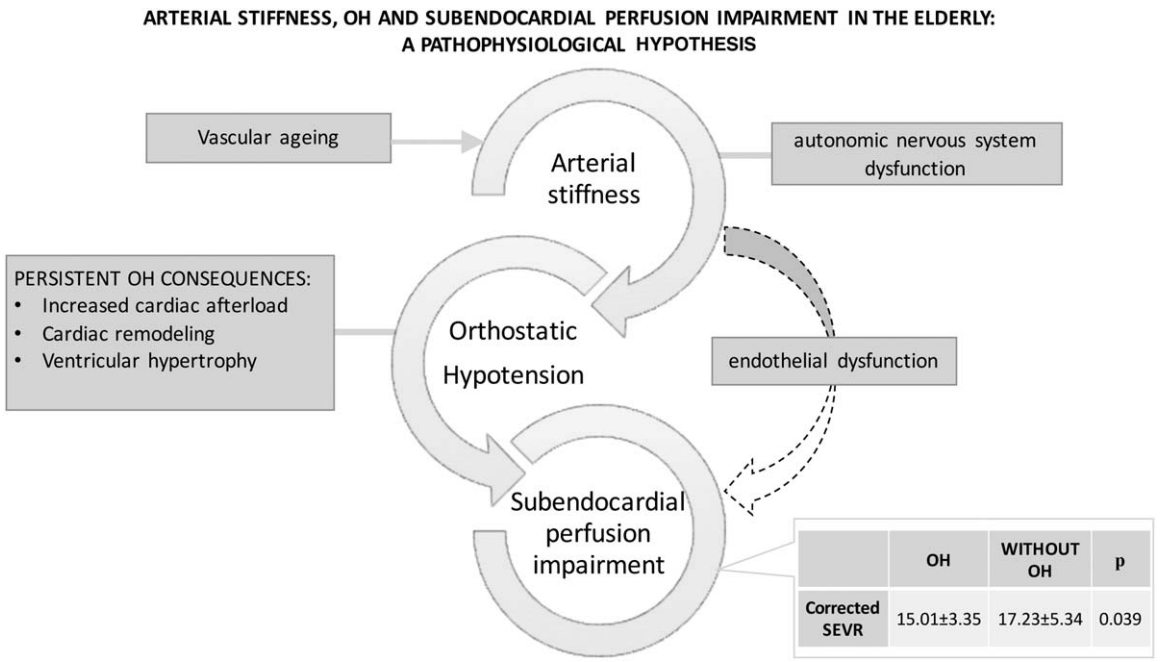

FIGURE 2 Arterial stiffness, orthostatic hypotension and subendocardial perfusion impairment in the elderly: a pathophysiological hypothesis.

vasopressin secretion and renin-angiotensin-aldosterone-system (RAAS) activation [35]. BP variation due to orthostatic hypotension may increase cardiac afterload, and therefore induce ventricular hypertrophy and renal flow impairment.

Furthermore, the repeated activation of neuroendocrine compensatory mechanism may also activate endothelial responses, and the prolonged stimulation of vasoconstrictors (endothelin-1 and vasopressin) may promote atherosclerosis, suggesting a complex network underlaying inflammation, autonomic dysfunction and atherosclerosis [37,38].

Cardiac remodelling due to orthostatic hypotension is probably not completely understood and further research is needed to better understand this complex phenomenon; our data cannot draw pathophysiological conclusion. Nevertheless, we may hypothesize that ventricular hypertrophy along with endothelial dysfunction (which also affects coronary vessels) may play a relevant role on subendocardial perfusion impairment. According to this hypothesis, SEVR reduction may represent an epiphenomenon of the elaborate remodelling process due to orthostatic hypotension. SEVR measurement, also because of the feasibility of the technique, may be performed in the clinical setting to better describe the burden of orthostatic hypotension cardiac consequences (Fig. 2).

The study has some limitations. The small sample size may have affected the statistical significance of some correlations. Furthermore, our article is an observational study and by its nature it is not possible to deduce any causal link between PWV-cf, OH, SEVR and ageing or to draw conclusions regarding clinical outcome in this population. A further limitation is represented by having conducted the assessment of the presence of orthostatic hypotension on a single occasion for each patient: a repeated measurement at different times of hospitalization and after clinical discharge could provide more data on the prevalence of this disease and its correlation with different risk factors. Moreover, patients with atrial fibrillation were not excluded from the study but, in this case, the reliability of PWV-cf and SEVR measurements is controversial. The high prevalence of comorbidities in the elderly may represent a confounding factor, and the relationship between orthostatic hypotension and SEVR may be further analysed in younger and healthier cohorts.

Although there was no significant difference in the number of medications taken by patients with and without orthostatic hypotension, no data were collected regarding the individual categories of medications taken, an element that might differentially affect the occurrence of orthostatic hypotension.

In conclusion, our findings confirm the high prevalence of orthostatic hypotension in elderly hospitalized individuals and describe a significant relationship between orthostatic hypotension and reduced SEVR. The pathophysiological mechanism may be explained by the increased arterial stiffness in orthostatic hypotension patients. The increased arterial stiffness and the impaired subendocardial perfusion in patients with orthostatic hypotension may represent a relevant mechanism to explain the increased cardiovascular risk in these patients.

ACKNOWLEDGEMENTS

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Low PA. Prevalence of orthostatic hypotension. *Clin Auton Res* 2008; Suppl 1:8–13.
2. Masaki KH, Schatz IJ, Burchfiel CM, Sharp DS, Chiu D, Foley D, *et al.* Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart Program. *Circulation* 1998; 98:2290–2295.

3. Xin W, Lin Z, Mi S. Orthostatic hypotension and mortality risk: a meta-analysis of cohort studies. *Heart* 2014; 100:406–413.
4. Rose KM, Tyroler HA, Nardo CJ, Arnett DK, Light KC, Rosamond W, *et al.* Orthostatic hypotension and the incidence of coronary heart disease: the atherosclerosis risk in communities study. *Am J Hypertens* 2000; 13:571–578.
5. Shaw BH, Borrel D, Sabbaghan K, Kum C, Yang Y, Robinovitch SN, *et al.* Relationships between orthostatic hypotension, frailty, falling and mortality in elderly care home residents. *BMC Geriatr* 2019; 19:80.
6. Curreri C, Giantin V, Veronese N, Trevisan C, Sartori L, Musacchio E, *et al.* Orthostatic changes in blood pressure and cognitive status in the elderly: the Progetto Veneto Anziani Study. *Hypertension* 2016; 68:427–435.
7. Rawlings AM, Juraschek SP, Heiss G, Hughes T, Meyer ML, Selvin E, *et al.* Association of orthostatic hypotension with incident dementia, stroke, and cognitive decline. *Neurology* 2018; 91:e759–e768.
8. Ricci F, Fedorowski A, Radico F, Romanello M, Tatasciore A, Di Nicola M, *et al.* Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. *Eur Heart J* 2015; 36:1609–1617.
9. Gangavati A, Hajjar I, Quach L, Jones RN, Kiely DK, Gagnon P, *et al.* Hypertension, orthostatic hypotension, and the risk of falls in a community-dwelling elderly population: the maintenance of balance, independent living, intellect, and zest in the elderly of Boston study. *J Am Geriatr Soc* 2011; 59:383–389.
10. Parashar R, Amir M, Pakhare A, Rathi P, Chaudhary L. Age related changes in autonomic functions. *J Clin Diagnostic Res* 2016; 10:CC11–CC15.
11. Monahan KD, Dinenno FA, Seals DR, Clevenger CM, Desouza CA, Tanaka H. Age-associated changes in cardiovagal baroreflex sensitivity are related to central arterial compliance. *Am J Physiol Heart Circ Physiol* 2001; 281:H284–H289.
12. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, *et al.* Assessment of arterial distensibility by automatic pulse wave velocity measurement: validation and clinical application studies. *Hypertension* 1995; 26:485–490.
13. Van Popele NM, Grobbee DE, Bots ML, Asmar R, Topouchian J, Reneman RS, *et al.* Association between arterial stiffness and atherosclerosis: the Rotterdam study. *Stroke* 2001; 32:454–460.
14. Vlachopoulos C, Xaplanteris P, Aboyans V, Brodmann M, Cífková R, Cosentino F, *et al.* The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation. *Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY Atherosclerosis* 2015; 241:507–532.
15. McVeigh GE, Bratteli CW, Morgan DJ, Alinder CM, Glasser SP, Finkelstein SM, *et al.* Age-related abnormalities in arterial compliance identified by pressure pulse contour analysis: aging and arterial compliance. *Hypertension* 1999; 33:1392–1398.
16. Ekart R, Bevc S, Hojs N, Knehtl M, Dvoršak B, Hojs R. Albuminuria is associated with subendocardial viability ratio in chronic kidney disease patients. *Kidney Blood Press Res* 2015; 40:565–574.
17. Buckberg GD, Fixler DE, Archie JP, Hoffman JI. Experimental subendocardial ischemia in dogs with normal coronary arteries. *Circ Res* 1972; 30:67–81.
18. Salvi P, Revera M, Faini A, Giuliano A, Gregorini F, Agostoni P, *et al.* Changes in subendocardial viability ratio with acute high-altitude exposure and protective role of acetazolamide. *Hypertension* 2013; 61:793–799.
19. Tsiachris D, Tsioufis C, Syrseloudis D, Roussos D, Tatsis I, Dimitriadis K, *et al.* Subendocardial viability ratio as an index of impaired coronary flow reserve in hypertensives without significant coronary artery stenoses. *J Hum Hypertens* 2012; 26:64–70.
20. Scandale G, Dimitrov G, Recchia M, Carzaniga G, Minola M, Perilli E, *et al.* Arterial stiffness and subendocardial viability ratio in patients with peripheral arterial disease. *J Clin Hypertens* 2018; 20:478–484.
21. Müller C, Goliasch G, Schachinger S, Kastl S, Neunteufl T, Delle-Karth G, *et al.* Transcatheter aortic valve replacement (TAVR) leads to an increase in the subendocardial viability ratio assessed by pulse wave analysis. *PLoS One* 2018; 13:1–11.
22. Ekart R, Bevc S, Hojs N, Hojs R. Derived subendocardial viability ratio and cardiovascular events in patients with chronic kidney disease. *CardioRenal Med* 2019; 9:41–50.
23. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994; 47:1245–1251.
24. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, *et al.* 2018 ESC/ESH Guidelines for themanagement of arterial hypertension. *Eur Heart J* 2018; 39:3021–3104.
25. Salvi P, Lio G, Labat C, Ricci E, Pannier B, Benetos A. Validation of a new noninvasive portable tonometer for determining arterial pressure wave and pulse wave velocity: the PulsePen device. *J Hypertens* 2004; 22:2285–2293.
26. Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetière P, *et al.* Pulse pressure: a predictor of long-term cardiovascular mortality in a french male population. *Hypertension* 1997; 30:1410–1415.
27. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. *Circulation* 1999; 100:354–360.
28. Barnard RJ, MacAlpin R, Kattus AA, Buckberg GD. Ischemic response to sudden strenuous exercise in healthy men. *Circulation* 1973; 48:936–942.
29. Brazier J, Cooper N, Buckberg G. The adequacy of subendocardial oxygen delivery: the interaction of determinants of flow, arterial oxygen content and myocardial oxygen need. *Circulation* 1974; 49:968–977.
30. Pasina L, Casati M, Cortesi L, Tettamanti M, Pellegrini R, Oppedisano I, *et al.* Orthostatic hypotension among elderly patients in Italian internal medicine wards: an observational study. *Intern Emerg Med* 2020; 15:281–287.
31. O'Connell MDL, Savva GM, Fan CW, Kenny RA. Orthostatic hypotension, orthostatic intolerance and frailty: the Irish Longitudinal Study on Aging-TILDA. *Arch Gerontol Geriatr* 2015; 60:507–513.
32. Hiorth YH, Pedersen KF, Dalen I, Tysnes OB, Alves G. Orthostatic hypotension in Parkinson disease: a 7-year prospective population-based study. *Neurology* 2019; 93:e1526–e1534.
33. Mattace-Raso FU, Van Der Cammen TJ, Knetsch AM, Van Den Meiracker AH, Schalekamp MA, Hofman A, Witteman JC. Arterial stiffness as the candidate underlying mechanism for postural blood pressure changes and orthostatic hypotension in older adults: the Rotterdam Study. *J Hypertens* 2006; 24:339–344.
34. Guelen I, Mattace-Raso FU, Van Popele NM, Westerhof BE, Hofman A, Witteman JC, Bos WJ, *et al.* Aortic stiffness and the balance between cardiac oxygen supply and demand: the Rotterdam Study. *J Hypertens* 2008; 26:1237–1243.
35. Magkas N, Tsioufis C, Thomopoulos C, Dilaveris P, Georgiopoulos G, Sanidas E, *et al.* Orthostatic hypotension: from pathophysiology to clinical applications and therapeutic considerations. *J Clin Hypertens* 2019; 21:546–554.
36. Ricci F, De Caterina R, Fedorowski A. Orthostatic hypotension: epidemiology, prognosis, and treatment. *J Am Coll Cardiol* 2015; 66:848–860.
37. Johansson M, Ricci F, Aung N, Sutton R, Melander O, Fedorowski A. Inflammatory biomarker profiling in classical orthostatic hypotension: insights from the SYSTEMA cohort. *Int J Cardiol* 2018; 259:192–197.
38. Ibrahim NE, Januzzi JL, Magaret CA, Gaggin HK, Rhyne RF, Gandhi PU, *et al.* A clinical and biomarker scoring system to predict the presence of obstructive coronary artery disease. *J Am Coll Cardiol* 2017; 69:1147–1156.