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Hannes Holm, Martin Magnusson, Amra Jujić, Nicola Riccardo Pugliese, Erwan Bozec, et al.. Ventricular–arterial coupling (VAC) in a population-based cohort of middle-aged individuals: The STANISLAS cohort. *Atherosclerosis*, 2023, 374, pp.11-20. 10.1016/j.atherosclerosis.2023.04.010 . hal-04093347

**HAL Id: hal-04093347**

**<https://hal.univ-lorraine.fr/hal-04093347>**

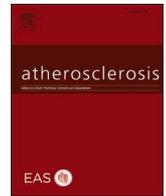
Submitted on 10 May 2023

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## Ventricular–arterial coupling (VAC) in a population-based cohort of middle-aged individuals: The STANISLAS cohort

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### ARTICLE INFO

#### Keywords:

Ventricular arterial coupling  
Hypertension  
Cardiovascular  
Echocardiography

### ABSTRACT

**Background and aims:** Data exploring normal values of different ventricular–arterial coupling (VAC) parameters and their association with anthropometric and cardiovascular (CV) factors are scarce. We aim to report values of two different methods of VAC assessment according to age and sex and explore their association with CV factors within a large population-based cohort of middle-aged individuals.

**Methods:** For 1333 (mean age  $48 \pm 14$ ) individuals participating in the 4th visit of the STANISLAS cohort, VAC was assessed by two methods [1]: arterial elastance ( $E_a$ )/end-systolic elastance ( $E_{es}$ ) and [2] Pulse wave velocity (PWV)/Global longitudinal strain (GLS).

**Results:** The mean values of  $E_a/E_{es}$  and PWV/GLS were  $1.06 \pm 0.20$  and  $0.42 \pm 0.12$ , respectively. The two methods of VAC assessment were poorly correlated (Pearson's correlation coefficient  $r = 0.14$  (0.08; 0.19)). Increased PWV/GLS was associated with older age and a higher degree of cardiovascular risk factors (i.e., BMI, blood pressure, LDL, diabetes, hypertension) in the whole population as well as in the parent generation. In contrast, higher  $E_a/E_{es}$  were associated with decreasing age, and lower prevalence of risk factors in the whole cohort but neutrally associated with risk factors in the parent generation.

**Conclusions:** Higher PWV/GLS is significantly associated with CV factors regardless of age. In contrast, worse  $E_a/E_{es}$  is associated with a better CV risk profile when considering individuals aged 30 to 70 but neutrally associated with CV factors when considering only older patients. These results may suggest that PWV/GLS should preferably be used to explore VAC. In addition, age-individualized threshold of  $E_a/E_{es}$  should be used.

### 1. Introduction

The interplay between the heart and the arterial system has recently gained much attention since interventions that improve both myocardial and vascular function may delay the progression to heart failure, valvular heart disease and possibly even improve prognosis [1]. The coupling between the heart and arteries, commonly named ventricular-arterial coupling (VAC) [1,2], depends on the efficiency of energy transfer from the left ventricle, which pumps blood into the arterial system to maintain organ perfusion. Today, the assessment of VAC in clinical practice is being facilitated by advances in cardiac

imaging. Traditionally, VAC has been defined as the combined marker of arterial and myocardial function, expressed as  $E_a/E_{es}$  ratio, where  $E_a$  reflects arterial elastance (an indicator of arterial load on the left ventricle) and  $E_{es}$  ventricular elastance (an indicator of the contractility and systolic stiffness of the left ventricle) [3]. The  $E_a/E_{es}$  ratio has shown to be a key determinant of heart failure (HF) and increased arterial stiffness, both independently associated with impaired microcirculation causing damage to the end organs such as the kidneys and the brain [1,4,5]. A newer parameter, Pulse wave velocity (PWV)/Global longitudinal strain (GLS) may be a superior marker of VAC compared to the traditional echocardiographic-derived  $E_a/E_{es}$  [6]. This may be explained by

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<https://doi.org/10.1016/j.atherosclerosis.2023.04.010>

Received 17 January 2023; Received in revised form 15 April 2023; Accepted 21 April 2023

Available online 22 April 2023

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the fact that it combines the gold standard for arterial stiffness assessment and LV systolic function. Yet, as highlighted by the consensus document of the ESC Working [1], the optimal marker to assess VAC that should be implemented in practice is not yet established. In addition, data exploring normal values of these two different VAC variables and their association with anthropometric variables and CV factors are scarce and rely on observations of small cohorts. In a recently published article by Pugliese et al., abnormal values of PWV/GLS were directly associated with greater HF severity and worse functional capacity. It was additionally shown that patients with heart failure with preserved ejection fraction (HFpEF) compared to reduced ejection fraction (HFrEF) presented with worse PWV/GLS values [7]. We intended to present the values of  $E_a/E_{es}$  and PWV/GLS in a large population-based cohort of healthy middle-aged individuals and explore their relationship with age, sex and CV factors.

## 2. Patients and methods

### 2.1. Study population

The STANISLAS (*Suivi Temporaire Annuel Non-Invasif de la Santé des Lorrains Assurés Sociaux*) cohort is a single-centre familial longitudinal cohort including 4295 participants (1006 families) from the Nancy region of France, who were first recruited during 1993–95 at the Centre for Preventive Medicine [8]. The families were deemed healthy and free of declared acute and/or chronic illnesses in order to assess the effect of genetic variability of intermediate phenotypes on the transition toward disease. The second and third visits were performed 5 and 10 years later, respectively. Between 2011 and 2016, 1705 subjects of the original cohort participated in the 4th (STANISLAS-V4) re-examination, including screening for cardiovascular risk assessment. Of these

subjects, we excluded 131 subjects with prevalent cardiac diseases or LV dysfunction ( $EF < 50\%$ ) and 241 additional subjects without echocardiography at the 4th visit or with at least one missing parameter among pulse wave velocity (PWV), global longitudinal strain (GLS), arterial elastance ( $E_a$ ) and end-systolic elastance ( $E_{es}$ ). Finally, the study population included 1333 participants (mean age  $48 \pm 14$  years), Fig. 1. The research protocol has received an ethical approval by the local ethics committee (Comité de Protection des Personnes Est III—Nancy—France) and all study participants have been given a written informed consent in order to participate.

### 2.2. Clinical assessment

Clinical evaluation included information regarding past medical history, symptoms suggestive of any cardiovascular illness, and anthropometric measurements (height, weight, and waist). Body mass index (BMI) was calculated as kilograms per square meter, and data regarding the study participants' medication were collected. Peripheral systolic (SBP) and diastolic (DBP) blood pressure was measured three times with an interval of 1 min, using an electronic sphygmomanometer. Hypertension was defined as self-declared hypertension and/or treatment with antihypertensive agents. Pre-diabetes was defined as a fasting plasma glucose (FPG) between 100 mg/dL and 125 mg/dL and/or a glycated hemoglobin between 5.7% and 6.4%. Diabetes was defined as a FPG  $\geq 126$  mg/dL or a glycated hemoglobin  $\geq 6.5\%$  or a random plasma glucose  $\geq 200$  mg/dL with symptoms of hypoglycemia or previous diagnosis of diabetes or anti-glycemic drug therapy [9]. Information regarding the physical activity of the participants was self-reported and divided into three activity levels [1]; low [2], moderate [3], high.

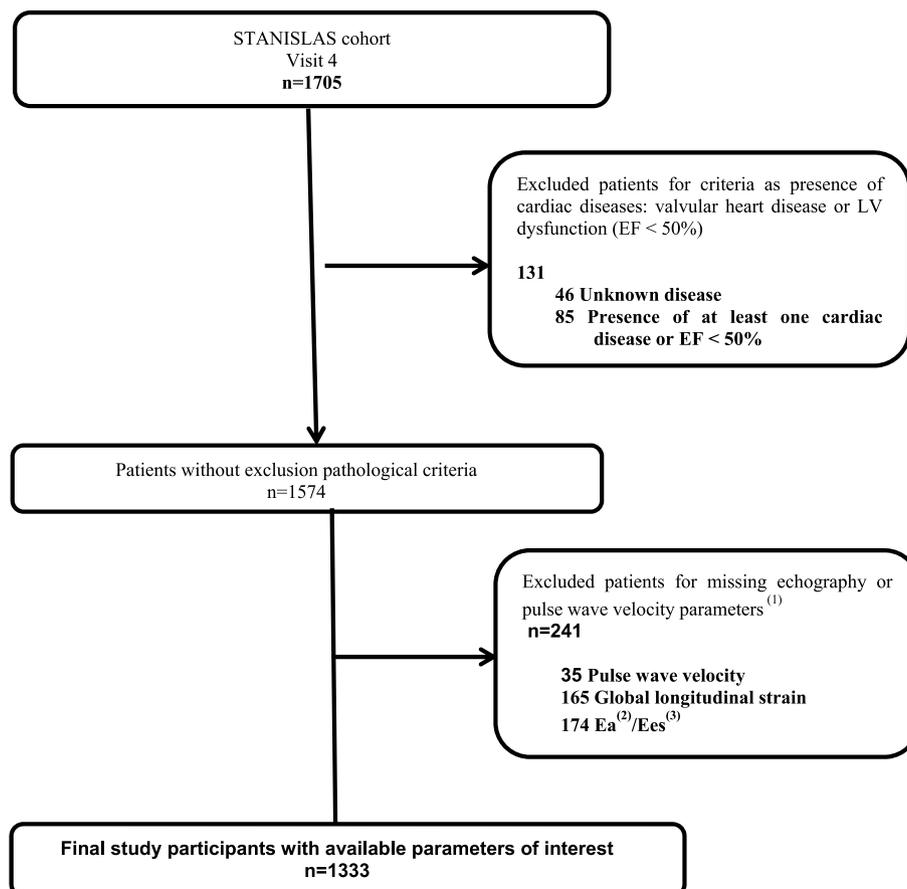


Fig. 1. Flowchart of study population.

### 2.3. Pulse wave velocity

The measurement of Carotid to femoral pulse wave velocity (C-f-PWV) was assessed with Complior® (Alam Medical, France) and Sphygmocor® CVMS (AtCor, Australia) devices in accordance with the recommendations of the European Network for Noninvasive Investigation of Large Arteries [10]. The mean value of two measurements was used to calculate the PWV. In cases when 2 measurements exhibited a difference > 0,5 m/s, a third measurement was performed and PWV was presented as the median value of the three measurements. Measurements were performed by four trained operators. The protocol has previously been presented in detail [8].

### 2.4. Echocardiography

Conventional transthoracic echocardiograms (TTE) were obtained with a commercially available standard ultrasound scanner (Vivid 9, General Electric Medical Systems, Horten, Norway) using a 2.5 MHz phased-array transducer (M5S). All studies were performed by experienced sonographers. The examination included long and short parasternal views as well as the standard apical views. In every view, 2-D Doppler and Tissue Doppler Imaging (TDI) with and without color were obtained. LVEF was calculated using the biplane Simpson's method. In order to obtain global longitudinal strain (GLS), speckle tracking echocardiography was performed to assess the LV systolic deformation in the three apical views: 4-chamber, 3-chamber and 2-chamber views. The software (Q analysis software, Echo PAC PC version 110.1.0, GE Healthcare) automatically calculated the time from the beginning of the QRS complex to the peak early positive (P) systolic (S) and global (G) strain of each segment. The mean strain value of all LV segments ( $n = 17$ ) was subsequently used in order to estimate the global value. As GLS is defined by the change in length as a proportion to baseline length, it is presented as a percentage of LV deformation. Hence, an improvement in the LV systolic function will result in increasingly negative strain values. GLS below  $-16\%$  is considered abnormal [11]. Intra- and inter-observer analyses for multilayer Global peak systolic longitudinal strain (transmural, subendocardial, and subepicardial) have been evaluated on fifty patients within the population. All intra-observer intraclass correlation coefficients (ICC) were  $>0.75$  and inter-observer ICCs were  $>0.70$  (the majority being  $>0.80$ ) [12].

### 2.5. VAC variables

The estimation of arterial load (numerator in the VAC equation) is commonly derived from effective arterial elastance ( $E_a$ ): the ratio of end-systolic pressure (ESP) divided by stroke volume (SV) (ESP/SV) [13]. End-systolic pressure (ESP) is calculated as brachial systolic blood pressure  $\times 0.9$ .  $E_a$  is sensitive to vascular resistance, pulsatile load and heart rate. By contrast,  $E_{es}$  is a load-independent measure of LV contractility and reflects the slope of the end-systolic pressure-volume relationship, originating from the principles of the classical pressure-volume curve as ESP divided by end-systolic volume normalized for body surface area (ESVi): ESP/ESVi [14]. Hence,  $E_a/E_{es}$  (ESP/SV)/(ESP/ESVi) can be further simplified as  $ESV/SV$ , after eliminating ESP in the equation.  $E_{es}$  is affected by LV chamber stiffness and geometry and has an inverse correlation with LV mass. The gold standard method for estimating  $E_{es}$  is the multi-beat invasive method by intraventricular catheterization. However, the non-invasive method by Chen et al. is commonly used as in the current study. According to the Chen derived formula,  $E_{es}$  can be calculated non-invasively by the formula:  $E_{es} = (DBP - [End(est) \times SBP \times 0.9]) / End(est) \times SV$  where DBP and SBP are diastolic and systolic arm-cuff BPs, the SV is Doppler-derived stroke volume, and  $End(est)$  is the estimated normalized ventricular elastance at the onset of ejection.

VAC was assessed by two different methods [1]:  $E_a/E_{es}$  and [2] PWV/GLS. Since  $E_a$  and  $E_{es}$  share the same units (mmHg/ml), the ratio is

unitless, Fig. 2.

### 2.6. Statistics

Group differences in continuous variables across quartiles of PWV/GLS and  $E_a/E_{es}$  were compared using one-way ANOVA test or Kruskal–Wallis depending on the normality of the distribution, whereas categorical variables were compared using  $\chi^2$  or exact fisher test as appropriate and were expressed as number (proportion as percentage). Continuous variables were expressed as mean  $\pm$  standard deviation (SD). Pearson correlation test was used to study the correlation between  $E_a/E_{es}$  and PWV/GLS with  $p < 0.05$  considered to be significant. All analyses were performed using SAS version 9.4.6 (SAS Institute Inc., Cary, N.C., USA) and R version 3.6.1 (2019-07-05).

## 3. Results

### 3.1. Patient characteristics

The study population had a mean age of  $48 \pm 14$  years, and a half (52%) were female. Four percent ( $n = 52$ ) had diabetes and 19% ( $n = 257$ ) had prevalent hypertension, Supplementary Table 1. The mean values of  $E_a/E_{es}$  and PWV/GLS were  $1.06 \pm 0.20$  and  $0.42 \pm 0.12$  m/s %, respectively (Table 1). The two methods of VAC assessment were poorly correlated with a Pearson correlation coefficient at 0.14 (0.08; 0.19) in the whole population and 0.24 (0.17; 0.31) in the parent generation, Fig. 3. The correlation between the parameters included in the VAC formulas (GLS, PWV,  $E_a$ ,  $E_{es}$ ) is shown in Supplementary Figs. 1 and 2.

### 3.2. Age and sex differences for VAC

$E_a$ ,  $E_{es}$  and PWV all increased with age ( $p < 0.001$ ), whilst GLS did not ( $p = 0.81$ ).  $E_a/E_{es}$  was significantly lower in older participants in the whole population ( $p < 0.001$ ), while no significant difference was observed in the parent generation ( $p = 0.30$ ), Table 3. In contrast, PWV/GLS increased by older age in the whole population as well in the parent generation ( $p < 0.001$ ), Table 2. Although both  $E_a$  ( $p < 0.001$ ) and  $E_{es}$  ( $p < 0.001$ ) were significantly higher in female participants, no sex difference was found for  $E_a/E_{es}$  ( $p = 0.12$ ). Females, as compared to male participants, exhibited lower PWV/GLS values ( $0.39 \pm 0.10$  vs  $0.45 \pm 0.13$  m/s% respectively,  $p < 0.001$ ) in the whole population and the parent generation. Female participants had lower PWV ( $8.04 \pm 1.42$  vs  $8.83 \pm 1.93$  m/s respectively,  $p < 0.001$ ) and higher GLS ( $21.22 \pm 2.97$  vs  $20.03 \pm 2.63\%$  respectively,  $p < 0.001$ ) compared to male participants.

### 3.3. Association of VAC with echocardiographic variables and cIMT

In the whole cohort and the parent generation, higher ratios of PWV/GLS were inversely related to LVEF ( $p < 0.001$ ). LVMi and cIMT gradually and significantly increased with higher PWV/GLS (in the whole cohort and the parent generation).

In the whole cohort, LVEF was significantly lower, and LVMi was significantly higher with higher  $E_a/E_{es}$  both in the whole cohort and in the parent generation. In contrast, cIMT was not significantly higher in participants with higher  $E_a/E_{es}$  in the parent generation.

### 3.4. Association of VAC with CV variables

In the whole population, higher  $E_a/E_{es}$  was associated with lower DBP ( $p < 0.001$ ) and LDL ( $p = 0.001$ ). Further, hypertension ( $p = 0.018$ ) was less frequent by increased ratios of  $E_a/E_{es}$ . Better estimated glomerular filtration rate (eGFR  $p < 0.001$ ) and lower prevalence of antihypertensive treatment was observed by increased  $E_a/E_{es}$  ratios. In the parent generation,  $E_a/E_{es}$  was significantly associated with none of

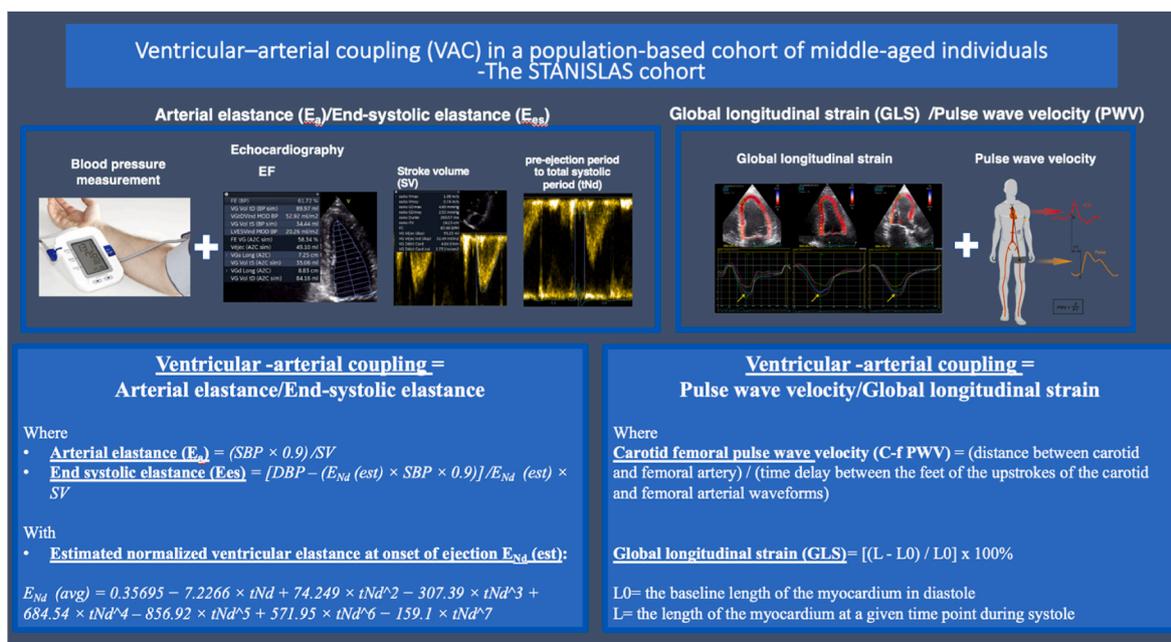


Fig. 2. Graphical figure illustrating how VAC was assessed using two methods ( $E_a/E_{es}$  and  $PWV/GLS$ ).

Table 1

Mean values of parameters included in the VAC formulas ( $GLS$ ,  $PWV$ ,  $E_a$ ,  $E_{es}$ ).

	Whole cohort (n = 1333)	According to sex		p-value	According to age (years)				p-value
		Men (n = 638)	Women (n = 695)		<40 (n = 531)	40-50 (n = 69)	50-60 (n = 442)	>60 (n = 291)	
Variables related to $E_a/E_{es}$									
$E_{es}$ , mmhg/ml	1.48 ± 0.45	1.38 ± 0.43	1.57 ± 0.45	<0.0001	1.35 ± 0.38	1.45 ± 0.49	1.56 ± 0.45	1.59 ± 0.48	<0.0001
$E_a$ , mmhg/ml	1.52 ± 0.40	1.44 ± 0.40	1.60 ± 0.38	<0.0001	1.47 ± 0.36	1.54 ± 0.40	1.56 ± 0.41	1.57 ± 0.43	0.0003
$E_a/E_{es}$	1.06 ± 0.20	1.07 ± 0.20	1.05 ± 0.19	0.12	1.11 ± 0.19	1.09 ± 0.21	1.02 ± 0.19	1.01 ± 0.20	<0.0001
Variables related to $PWV/GLS$									
Pulse wave velocity ( $PWV$ ), m/s	8.41 ± 1.73	8.83 ± 1.93	8.04 ± 1.42	<0.0001	7.43 ± 0.97	7.94 ± 0.84	8.71 ± 1.46	9.87 ± 2.13	<0.0001
Global longitudinal strain ( $GLS$ ), -%	20.65 ± 2.87	20.03 ± 2.63	21.22 ± 2.97	<0.0001	20.65 ± 2.61	20.42 ± 2.83	20.74 ± 3.04	20.60 ± 3.10	0.81
$PWV/GLS$ , m/s %	0.42 ± 0.12	0.45 ± 0.13	0.39 ± 0.10	<0.0001	0.37 ± 0.08	0.40 ± 0.07	0.43 ± 0.11	0.49 ± 0.15	<0.0001
$PWV/LVEF$ , m/s %	13.00 ± 2.93	13.77 ± 3.21	12.29 ± 2.43	<0.0001	11.25 ± 1.92	11.97 ± 1.93	13.12 ± 2.46	14.86 ± 3.66	<0.0001

$GLS$ , global longitudinal strain;  $PWV$ , pulse wave velocity;  $E_a$ , arterial elastance;  $E_{es}$ , End systolic elastance.  $PWV$  and  $PWV/GLS$  have skewed distributions.

the CV variables (BMI, SBP, DBP, hypertension, diabetes), Table 3.

In the whole cohort, higher  $PWV/GLS$  was associated with higher BMI ( $p < 0.001$ ), SBP ( $p < 0.001$ ), DBP ( $p < 0.001$ ) and plasma triglycerides ( $p < 0.001$ ) and LDL ( $p = 0.002$ ). Within the parent generation, LDL ( $p = 0.028$ ) exhibited a decreasing pattern across higher quartiles of  $PWV/GLS$ . Lower values of HDL were seen across increasing quartiles of  $PWV/GLS$  in the whole population ( $p < 0.001$ ) as well as in the parent generation ( $p < 0.001$ ). By increasing quartiles of  $PWV/GLS$ , increasing kidney abnormalities were observed (eGFR  $p < 0.001$ , urine albumin/creatinine index,  $p < 0.001$ ) and diabetes ( $p < 0.001$ ) and hypertension ( $p < 0.001$ ) were more frequent, Table 2. Further, higher prevalence of antihypertensive treatment ( $p < 0.001$ ) and lipid-lowering drugs (statins) ( $p < 0.001$ ) were seen by increasing ratios of  $PWV/GLS$ .

#### 4. Discussion

Within a large population-based cohort, we here present the values of two different methods of VAC assessment, which could serve as reference values in the future. While exploring the relationship of these variables with age, sex and CV factors, higher  $PWV/GLS$  (reflecting a

VAC mismatch) was associated with increasing age and CV risk (hypertension, obesity and hyperlipidemia). In contrast, and counterintuitively, higher  $E_a/E_{es}$  ratios were inversely associated with CV factors when considering the whole cohort (which covers a wide range of ages) and neutrally associated with CV factors when considering only older patients. Even more counterintuitively, younger patients had worse  $E_a/E_{es}$ , thus suggesting that ageing would improve artery-to-heart coupling. These results suggest that  $PWV/GLS$  may be preferably used to assess VAC and that age-specific thresholds should be used for  $E_a/E_{es}$ . To the best of our knowledge, this study is by far the largest exploring VAC assessment in middle-aged individuals and may thus provide reference values of VAC according to age and sex.

Since VAC ultimately reflects the function and efficiency of the cardiovascular system, its use might provide a better understanding of pathophysiologic mechanisms of CV diseases. Since CV risk factors can affect the heart through LV remodeling related to pressure- and volume overload and central arteries stiffening, VAC has been suggested as a promising novel biomarker to assess cardiovascular risk. Since Sungawa et al. first described (1983) the assessment of VAC based on systolic multiple invasive time-varying pressure-volume ratios, advances in

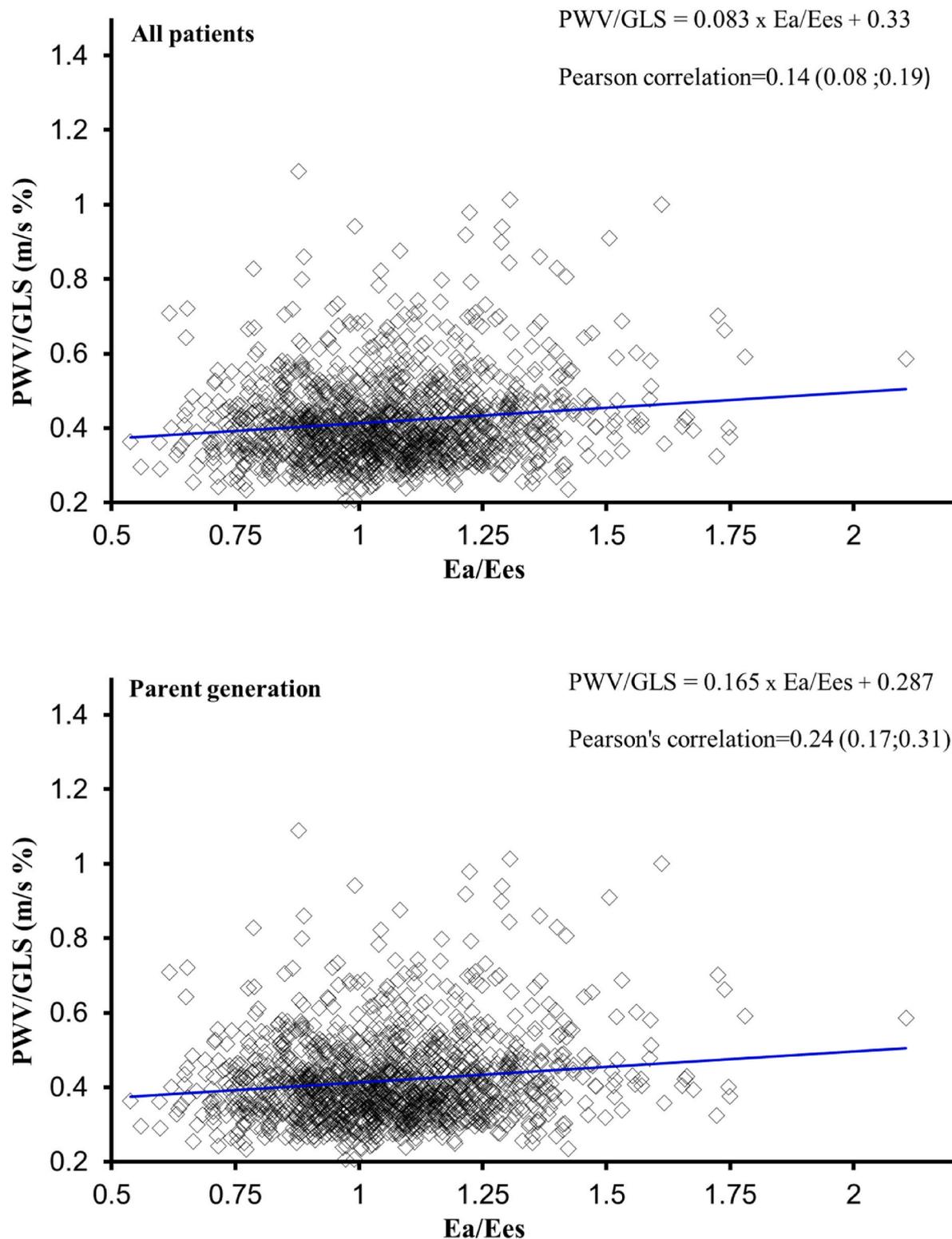


Fig. 3. Correlation between Ea/Ees and PWV/GLS.

imaging have evolved [15]. In 2001, Chen et al. were the first to describe the non-invasive single-beat method to assess  $E_{es}$  by including parameters such as systolic and diastolic brachial blood pressures, echo-Doppler stroke volume (SV), echo-derived ejection fraction (EF) and an estimated normalized ventricular elastance at arterial end-diastole ( $E_{Nd}$ ) [3]. Previous studies have shown that the optimal value of VAC derived from the  $E_a/E_{es}$  ratio should range from 0.5 to 1 reflecting the state when the stroke work of the left ventricle is ideal [16,17]. Hence, when

arterial load ( $E_a$ ) increases to the point when  $E_a/E_{es} > 1$ , a VAC mismatch appears with subsequent lower left ventricle contractile efficiency [18]. This mismatch in VAC is often seen as the effect of increasing age and development of hypertension. Yet, the increase of  $E_a$  is met by a simultaneous increase of  $E_{es}$  (index of LV contractility/stiffness) which offset the increase in VAC despite the presence of hypertension and increasing age [19]. The  $E_a/E_{es}$  ratio is still today the most acknowledged method to assess VAC and has been shown to be a strong predictor

**Table 2**  
Patients' characteristics across quartiles of PWV/GLS.

Characteristics	All patients, n = 1333				p-value	Parent generation, n = 738				p-value
	PWV/GLS <0.34	0.34 ≤ PWV/GLS <0.40	0.40 ≤ PWV/GLS <0.46	PWV/GLS ≥0.46		PWV/GLS <0.37	0.37 ≤ PWV/GLS <0.43	0.43 ≤ PWV/GLS <0.52	PWV/GLS ≥0.52	
	(n = 334)	(n = 332)	(n = 334)	(n = 333)		(n = 184)	(n = 185)	(n = 184)	(n = 185)	
	m ± SD/n (%)	m ± SD/n (%)	m ± SD/n (%)	m ± SD/n (%)		m ± SD/n (%)	m ± SD/n (%)	m ± SD/n (%)	m ± SD/n (%)	
Age, years	40 ± 13	46 ± 13	48 ± 14	57 ± 11	<0.0001	58 ± 4	59 ± 4	60 ± 4	62 ± 5	<0.0001
Sex (n (%) female)	254 (76.0%)	176 (53.0%)	145 (43.4%)	120 (36.0%)	<0.0001	131 (71.2%)	102 (55.1%)	83 (45.1%)	66 (35.7%)	<0.0001
Weight, kg	67.8 ± 13.7	71.4 ± 13.5	75.4 ± 14.9	77.6 ± 14.4	<0.0001	69.5 ± 12.9	71.9 ± 14.2	74.9 ± 14.4	79.4 ± 14.1	<0.0001
Height, m	1.66 ± 0.09	1.69 ± 0.09	1.70 ± 0.10	1.69 ± 0.09	<0.0001	1.63 ± 0.09	1.66 ± 0.09	1.67 ± 0.09	1.69 ± 0.08	<0.0001
BMI, kg/m <sup>2</sup>	24.5 ± 4.2	25.0 ± 4.0	26.0 ± 4.4	27.1 ± 4.7	<0.0001	26.0 ± 3.9	25.8 ± 3.8	26.6 ± 4.3	27.8 ± 4.7	<0.0001
SBP, mmHg	116.8 ± 11.2	122.4 ± 13.1	126.8 ± 13.9	135.0 ± 15.8	<0.0001	120.8 ± 12.4	126.8 ± 14.1	130.6 ± 14.7	139.2 ± 16.4	<0.0001
DBP, mmHg	67.4 ± 7.3	71.1 ± 7.6	73.3 ± 8.5	77.2 ± 8.8	<0.0001	70.4 ± 7.9	73.5 ± 8.0	75.3 ± 8.5	78.1 ± 9.4	<0.0001
Current smoking	89 (26.7%)	65 (19.6%)	90 (26.9%)	58 (17.4%)	0.003	22 (12.0%)	28 (15.1%)	21 (11.4%)	21 (11.4%)	0.65
Hypertension	34 (10.2%)	50 (15.1%)	64 (19.2%)	109 (32.9%)	<0.0001	47 (25.5%)	51 (27.6%)	55 (30.1%)	79 (42.9%)	0.001
Pre-diabetes	88 (26.4%)	95 (29.2%)	120 (36.6%)	141 (43.3%)	<0.0001	92 (50.3%)	89 (48.6%)	88 (48.1%)	87 (48.3%)	0.98
Diabetes	2 (0.6%)	4 (1.2%)	10 (3.0%)	36 (11.0%)	<0.0001	3 (1.6%)	3 (1.6%)	11 (6.0%)	31 (17.2%)	<0.0001
Physical activity										
High	102 (36.7%)	100 (34.7%)	112 (40.6%)	99 (38.7%)		71 (46.4%)	60 (38.7%)	62 (40.8%)	58 (41.1%)	
moderate	73 (26.3%)	78 (27.1%)	76 (27.5%)	55 (21.5%)	0.38	34 (22.2%)	48 (31.0%)	37 (24.3%)	34 (24.1%)	0.60
Low	103 (37.1%)	110 (38.2%)	88 (31.9%)	102 (39.8%)		48 (31.4%)	47 (30.3%)	53 (34.9%)	49 (34.8%)	
EF (%)	66.2 ± 5.8	65.5 ± 5.9	64.8 ± 6.2	64.5 ± 6.2	0.0009	67.8 ± 5.6	66.3 ± 5.9	65.9 ± 6.2	65.0 ± 5.7	<0.0001
Medications										
Antihypertensive treatment	24 (7.2%)	46 (13.9%)	53 (15.9%)	98 (29.4%)	<0.0001	39 (21.2%)	46 (24.9%)	49 (26.6%)	71 (38.4%)	0.002
Angiotensin II receptor antagonist	13 (3.9%)	21 (6.3%)	23 (6.9%)	53 (15.9%)	<0.0001	18 (9.8%)	21 (11.4%)	24 (13.0%)	41 (22.2%)	0.003
Statins	10 (3.0%)	21 (6.3%)	37 (11.1%)	74 (22.2%)	<0.0001	19 (10.3%)	31 (16.8%)	41 (22.3%)	51 (27.6%)	0.0002
LVMI, g/m <sup>2</sup>	68.3 ± 14.6	73.6 ± 18.2	76.9 ± 18.0	81.5 ± 18.7	<0.0001	76.3 ± 16.8	76.3 ± 17.3	81.0 ± 19.7	83.2 ± 19.2	0.0002
cIMT, μm	555.37 ± 111.61	611.24 ± 146.32	628.66 ± 141.03	692.85 ± 138.76	<0.0001	667.47 ± 139.14	683.80 ± 123.22	707.96 ± 128.74	727.77 ± 132.59	<0.0001
Total cholesterol g/l	2.06 ± 0.39	2.15 ± 0.39	2.14 ± 0.40	2.17 ± 0.40	0.001	2.31 ± 0.36	2.29 ± 0.39	2.24 ± 0.38	2.18 ± 0.38	0.005
Triglycerides, g/l	0.90 ± 0.42	0.98 ± 0.53	1.05 ± 0.54	1.20 ± 0.62	<0.0001	1.02 ± 0.46	1.07 ± 0.61	1.13 ± 0.53	1.21 ± 0.58	0.0007
HDL cholesterol, g/l	0.60 ± 0.13	0.60 ± 0.15	0.57 ± 0.14	0.56 ± 0.13	<0.0001	0.63 ± 0.13	0.63 ± 0.15	0.59 ± 0.14	0.56 ± 0.13	<0.0001
LDL cholesterol, g/l	1.28 ± 0.33	1.36 ± 0.33	1.36 ± 0.35	1.37 ± 0.35	0.002	1.47 ± 0.33	1.45 ± 0.34	1.43 ± 0.33	1.37 ± 0.34	0.028
Creatinine, mmol/L	0.07 ± 0.01	0.07 ± 0.01	0.07 ± 0.01	0.07 ± 0.01	<0.0001	0.07 ± 0.01	0.07 ± 0.01	0.07 ± 0.02	0.07 ± 0.01	0.002
eGFR CKD-EPI formula, ml/min/1.73m <sup>2</sup>	103.74 ± 14.39	98.48 ± 14.28	96.76 ± 15.65	90.48 ± 14.27	<0.0001	89.03 ± 10.70	88.99 ± 11.27	86.97 ± 13.00	88.19 ± 11.71	0.58
Urine albumin/creatinine	0.91 ± 2.05	0.74 ± 0.66	0.92 ± 1.66	1.36 ± 2.70	<0.0001	0.95 ± 2.14	0.85 ± 0.97	1.18 ± 1.76	1.38 ± 2.34	0.042

GLS, global longitudinal strain; PWV, pulse wave velocity; LDL, low density lipoprotein; HDL, high density lipoprotein; cIMT, carotid intima media thickness; EF, ejection fraction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVMI, left ventricle myocardial index; eGFR, estimated glomerular filtration rate. GLS (absolute value); age, triglycerides, urine albumin/creatinine and eGFR have skewed distributions.

of mortality [4,20,21]. In HFREF patients, increasing ratios has been strongly associated with worsening of NYHA-class, higher levels of natriuretic peptides as well as rehospitalization and mortality [4]. Still, several disadvantages with the use of  $E_a/E_{es}$  as an approach of measuring VAC have been raised, including the fact that  $E_a$  is highly influenced by systemic vascular resistance and heart rate, together accounting for 98% of the variability of  $E_a$  [5]. Also,  $E_a$  assumes a constant ejection time which disqualifies it as a pure maker of arterial load [22, 23]. Further,  $E_a$  is insensitive to changes pulsatile arterial load (systolic wave reflections), thereby not reflecting arterial stiffness which is highly

affected by cardiovascular diseases such as hypertension and heart failure [4,24,25]. Hence, although  $E_a/E_{es}$  provides useful insights into the mechanical characteristics of VAC, the insensitivity of the LV loading sequence may make it difficult to implement when analyzing VAC in cases with diastolic dysfunction [26].

In the current study, we observed lower values of EF by increasing quartiles of  $E_a/E_{es}$ . Owing to the inverse relationship between  $E_a/E_{es}$  and EF ( $E_a/E_{es} = 1/LVEF - 1$ ), these findings are expected. Normal EF range between 0.5 and 0.65 corresponds to  $E_a/E_{es}$  between 0.54 and 0.82 [26]. Due to the disadvantages of the  $E_a/E_{es}$  approach, more novel methods of

**Table 3**  
Patients' characteristics across quartiles of  $E_a/E_{es}$ .

Characteristics	All patients, n = 1333					Parent generation, n = 738				
	$E_a/E_{es}$ <0.92	$0.92 \leq E_a/E_{es}$ <1.04	$1.04 \leq E_a/E_{es}$ <1.18	$E_a/E_{es} \geq 1.18$	p-value	$E_a/E_{es}$ <0.88	$0.88 \leq E_a/E_{es}$ <1.00	$1.00 \leq E_a/E_{es}$ <1.14	$E_a/E_{es} \geq 1.14$	p-value
	(n = 322)	(n = 333)	(n = 349)	(n = 329)		(n = 185)	(n = 184)	(n = 185)	(n = 184)	
	m ± SD/n (%)	m ± SD/n (%)	m ± SD/n (%)	m ± SD/n (%)		m ± SD/n (%)	m ± SD/n (%)	m ± SD/n (%)	m ± SD/n (%)	
Age, years	53 ± 12	48 ± 14	46 ± 14	45 ± 14	<0.0001	60 ± 5	59 ± 4	59 ± 4	60 ± 5	0.30
Sex (n (%) female)	165 (51.2%)	181 (54.4%)	198 (56.7%)	151 (45.9%)	0.031	90 (48.6%)	89 (48.4%)	112 (60.5%)	91 (49.5%)	0.053
Weight, kg	74.0 ± 15.2	71.5 ± 13.3	71.7 ± 14.7	75.1 ± 14.9	0.002	74.8 ± 14.9	73.6 ± 13.1	72.5 ± 14.9	74.8 ± 14.2	0.35
Height, m	1.68 ± 0.10	1.68 ± 0.09	1.69 ± 0.09	1.70 ± 0.10	0.003	1.66 ± 0.10	1.67 ± 0.09	1.66 ± 0.09	1.67 ± 0.09	0.4
BMI, kg/m <sup>2</sup>	26.3 ± 4.6	25.2 ± 3.8	25.2 ± 4.4	26.0 ± 4.8	0.001	26.9 ± 4.3	26.4 ± 3.9	26.3 ± 4.2	26.7 ± 4.6	0.51
SBP, mmHg	126.2 ± 14.6	124.5 ± 15.6	124.4 ± 15.4	126.0 ± 14.8	0.26	127.9 ± 15.5	129.4 ± 14.2	129.4 ± 17.9	130.7 ± 15.9	0.43
DBP, mmHg	74.0 ± 8.3	72.3 ± 8.8	71.5 ± 9.0	71.3 ± 8.9	0.0003	74.1 ± 8.2	75.6 ± 8.6	73.8 ± 9.6	73.7 ± 9.1	0.13
Current smoking	56 (17.4%)	73 (21.9%)	82 (23.5%)	91 (27.7%)	0.019	22 (12.0%)	25 (13.6%)	24 (13.0%)	21 (11.4%)	0.92
Hypertension	81 (25.2%)	59 (17.7%)	65 (18.7%)	52 (15.9)	0.018	60 (32.4%)	51 (27.7%)	62 (33.7%)	59 (32.2%)	0.63
Pre-diabetes	140 (44.3%)	109 (32.8%)	106 (31.0%)	89 (27.6%)	<0.0001	97 (52.7%)	88 (48.4%)	87 (48.1%)	84 (46.2%)	0.64
Diabetes	16 (5.1%)	9 (2.7%)	15 (4.4%)	12 (3.7%)	0.46	11 (6.0%)	10 (5.5%)	13 (7.2%)	14 (7.7%)	0.82
Physical activity										
High	100 (38.0%)	105 (38.0%)	107 (36.9%)	101 (37.5%)		72 (47.1%)	54 (36.2%)	63 (40.6%)	62 (43.1%)	
moderate	78 (29.7%)	72 (26.1%)	73 (25.2%)	59 (21.9%)	0.44	36 (23.5%)	43 (28.9%)	42 (27.1%)	32 (22.2%)	0.57
Low	85 (32.3%)	99 (35.9%)	110 (37.9%)	109 (40.5%)		45 (29.4%)	52 (34.9%)	50 (32.3%)	50 (34.7%)	
EF, %	69.4 ± 5.6	66.3 ± 4.8	64.3 ± 5.1	61.2 ± 5.6	<0.0001	70.3 ± 5.3	66.8 ± 5.0	65.2 ± 4.9	62.7 ± 5.8	<0.0001
Medications										
Antihypertensive treatment	70 (21.7%)	49 (14.7%)	54 (15.5%)	48 (14.6%)	0.040	52 (28.1%)	44 (23.9%)	56 (30.3%)	53 (28.8%)	0.56
Angiotensin II receptor antagonist	42 (13.0%)	20 (6.0%)	29 (8.3%)	19 (5.8%)	0.002	29 (15.7%)	27 (14.7%)	26 (14.1%)	22 (12.0%)	0.77
Statins	36 (11.2%)	31 (9.3%)	37 (10.6%)	38 (11.6%)	0.80	29 (15.7%)	29 (15.8%)	42 (22.7%)	42 (22.8%)	0.12
LVMI, g/m <sup>2</sup>	75.0 ± 17.3	73.9 ± 17.8	74.0 ± 18.4	77.3 ± 18.6	0.053	78.2 ± 16.8	77.1 ± 18.8	78.6 ± 18.0	82.9 ± 19.8	0.015
cIMT, μm	651.53 ± 132.25	619.54 ± 135.46	608.20 ± 155.22	611.38 ± 146.04	0.0003	690.69 ± 123.99	692.56 ± 118.54	693.94 ± 150.94	710.65 ± 135.18	0.45
Total cholesterol, g/l	2.19 ± 0.36	2.14 ± 0.42	2.11 ± 0.38	2.07 ± 0.41	0.0005	2.25 ± 0.37	2.24 ± 0.39	2.29 ± 0.38	2.23 ± 0.38	0.37
Triglycerides, g/l	1.06 ± 0.58	0.99 ± 0.53	1.06 ± 0.55	1.02 ± 0.50	0.035	1.06 ± 0.45	1.11 ± 0.67	1.18 ± 0.55	1.08 ± 0.50	0.061
HDL cholesterol, g/l	0.58 ± 0.14	0.60 ± 0.15	0.58 ± 0.13	0.56 ± 0.14	0.005	0.59 ± 0.14	0.60 ± 0.15	0.60 ± 0.13	0.61 ± 0.15	0.53
LDL cholesterol, g/l	1.40 ± 0.32	1.34 ± 0.35	1.33 ± 0.33	1.30 ± 0.35	0.001	1.45 ± 0.32	1.42 ± 0.34	1.45 ± 0.34	1.40 ± 0.34	0.38
Creatinine, mmol/L	0.07 ± 0.01	0.07 ± 0.01	0.07 ± 0.01	0.07 ± 0.01	0.46	0.07 ± 0.01	0.07 ± 0.02	0.07 ± 0.01	0.07 ± 0.01	0.18
eGFR CKD-EPI formula, ml/min/1.73m <sup>2</sup>	93.07 ± 14.99	96.82 ± 15.00	98.98 ± 15.55	100.46 ± 15.06	<0.0001	88.38 ± 11.96	87.34 ± 12.45	88.36 ± 10.97	89.10 ± 11.42	0.55
Urine albumin/creatinine	1.03 ± 1.62	0.82 ± 0.72	1.05 ± 2.48	1.02 ± 2.33	0.064	0.99 ± 1.09	1.09 ± 1.83	1.16 ± 2.40	1.12 ± 2.00	0.82

$E_a$ , arterial elastance;  $E_{es}$ , end-systolic elastance; LDL, low density lipoprotein; HDL, high density lipoprotein; cIMT, carotid intima media thickness; EF, ejection fraction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVMI, left ventricle myocardial index; eGFR, estimated glomerular filtration rate.

GLS (absolute value); age, triglycerides, urine albumin/creatinine and eGFR have skewed distributions.

VAC assessment, including the use of PWV/GLS ratio, has been suggested. Up to this date, only one study has compared PWV/GLS to the conventional  $E_a/E_{es}$  method. Ikonomidis et al. showed in 299 hypertensive subjects that PWV/GLS were more correlated with increased carotid intima media thickness (cIMT), coronary flow reserve and diastolic dysfunction than the traditional echocardiographic method ( $E_a/E_{es}$ ) [6]. In accordance with these findings, the current study shows that VAC mismatch shown as an increased PWV/GLS ratio is associated with increased cIMT whereas a lower  $E_a/E_{es}$  (i.e. better VAC) is associated with a counterintuitive increase of cIMT.

The novelty of PWV/GLS approach has been attributed to its implementation of gold standard methods to assess arterial stiffness (PWV) and myocardial contractility (GLS). With every heartbeat, a pulse

wave is generated and travels through the arterial tree. At reflection sites, such as points of branching or changes of material properties in the arterial walls, the forward wave will be reflected and travel back towards the heart, arriving at the heart during the diastolic phase and therefore have little impact on LV contraction in healthy individuals [27, 28]. Age-related artery stiffening results in faster pulse wave propagation (increased PWV) through the arterial tree and, therefore, earlier pulse wave reflection during the systolic phase when the left ventricle still contracts. In order to overcome the increased pressure, the LV will increase its mass through hypertrophy of myocytes with a subsequently enlarged wall thickness of the LV. Subsequently, elevated PWV has been shown to be highly associated with impaired LV strain, which is supposed to be attributed to an elevation of LV afterload [29,30]. Further,

LV longitudinal function is more susceptible than LV radial function to be affected by increased LV afterload [31,32]. These data actually support our findings and provide convincing evidence for the inerrant superiority of PWV/GLS on the classical  $E_a/E_{es}$  approach.

Further, in a recently published article by Pugliese et al., abnormal values of PWV/GLS were directly associated with greater HF severity and worse functional capacity. Interestingly, this was particularly observed for patients with heart failure with preserved ejection fraction (HFpEF) [7]. This highlights another benefit of PWV/GLS compared to  $E_a/E_{es}$  which is commonly normal in HFpEF patients due to simultaneous increases in both  $E_a$  and  $E_{es}$  [33].

The absence of association between  $E_a/E_{es}$  and surrounding CV risk factors could be attributed to the lack of manifested cardiovascular disease in the STANISLAS cohort, as both methods of VAC assessment have previously demonstrated an association with prevalent cardiovascular disease.

#### 4.1. VAC in accordance to age and sex

In the current study, GLS was not affected by age. The unchanged or even improved GLS in individuals free from structural heart disease has previously been shown and suggested to be a compensatory mechanism in order to maintain low LV filling pressure in the presence of fibrotic remodeling [34–36]. Hence, the linear increase of PWV/GLS by older age observed in the whole population and in the parent generation is most likely attributed to the elevation of PWV. Several mechanisms have been suggested to explain the age-dependent increase of PWV, including altered neurohormonal signaling, endothelial dysfunction, and alteration in collagen cross-linking and protein composition [37]. In correlation analysis, GLS was positively correlated with PWV (data not shown). We observed that both  $E_a$  and  $E_{es}$  were increased in older individuals in the whole population, which is in line with earlier reports [38]. In a population consisting of 788 individuals aged 60 (SD  $\pm$  9) years, Borlaug et al. have previously shown that both  $E_a$  and  $E_{es}$  increased during a follow-up period of 4 years. Surprisingly however, in our cohort, the ratio of  $E_a/E_{es}$  decreased with higher age, which is explained by a greater increase of  $E_{es}$  relative to  $E_a$ . When focusing on the parent generation (age >50 years), increasing  $E_a/E_{es}$  was not affected by age. The pathophysiologic mechanism behind the increase of  $E_{es}$  is to some extent unclear and usually the increase of  $E_{es}$  is hypothesized to be mainly driven by an increase in  $E_a$  (i.e. arterial load) [39,40]. Alternatively, cardiac and artery stiffening may occur simultaneously during aging due to presence of CV risk factors including oxidative stress, fibrosis and proinflammation [41,42]. This may better explain why a mismatch of  $E_a$  and  $E_{es}$  was observed in our study.

In the current study, we observed a sex difference in VAC assessments where males were more likely to have higher  $E_a/E_{es}$  and PWV/GLS ratios. In a large cross-sectional community-based study of individuals above 45 years old ( $n = 2042$ ), Redfield et al. showed that the decline of  $E_a/E_{es}$  by older age was only observed in female whom also had lower ratios compared to aged-matched male participants [43]. However, both  $E_a$  and  $E_{es}$  were higher in female participants, which was also the case in the current study. It is well established that women have higher large-artery stiffness compared to male and therefore higher  $E_a$ . The sex discrepancy in artery stiffness has been proposed as an effect of higher levels of estradiol which is inversely correlated with aortic impedance seen in women. Coutinho et al. showed in 461 participants without heart failure that female participants had higher aortic impedance ( $Z_C$ ) and lower total arterial compliance (TAC) compared to male subjects. The increased  $Z_C$  seen in females remained significant after adjusting for aortic diameter, suggesting that sex differences in aortic stiffness is not only an effect of body size. Additionally,  $Z_C$  and TAC was significantly associated with  $E_a/E_{es}$  in women only [5].

#### 4.2. Strengths and limitations

To the best of our knowledge, this is the first study that aims to compare two different methods of VAC assessment in regard to age, sex and modifiable surrounding factors of cardiovascular risk. Due to the population-based nature of our cohort, and the high numbers of study participants, this study also allows us to provide reference values of VAC. However, since this study is cross-sectionally designed, causality between VAC and surrounding factors cannot be drawn. Additionally, no information was available regarding the duration of hypertension, diabetes and smoking. The current study is based on clinical data retrieved from a general population without prevalent cardiovascular disease or clinical cardiovascular outcomes. Hence, VAC was only explored in relation to prevalent cardiovascular risk factors. The PWV/GLS and  $E_a/E_{es}$  characterize different features of the cardiovascular system and thereby reflecting VAC from different aspects. This is illustrated by the poor correlation between the two methods which is due to the fact that they do not measure the same energies involved in the ventricular arterial interaction. Finally, the study was undertaken in a defined region with a rather homogeneous genetic background, and other studies should be conducted to ensure the generalizability of our results. Invasive intraventricular catheterization remains the gold standard method to assess VAC ( $E_a/E_{es}$ ). However, this requires expensive specialized equipment and expertise but also comes with an increased procedure risk.

#### 4.3. Conclusion

Higher PWV/GLS is significantly associated with CV factors regardless of age. In contrast, worse  $E_a/E_{es}$  is associated with a better CV risk profile when considering individuals aged 30 to 70 but neutrally associated with CV factors when considering only older patients. These results may suggest that PWV/GLS should preferably be used to explore VAC. In addition, age-individualized threshold of  $E_a/E_{es}$  should be used.

#### Financial support

Dr. Magnusson was supported by grants from the Swedish Medical Research Council, the Swedish Heart and Lung Foundation, the Medical Faculty of Lund University, Skåne University Hospital, the Crafoord Foundation, the Region Skane, Knut and Alice Wallenberg Foundation and the Marianne and Marcus Wallenberg Foundation and by Wallenberg Centre for Molecular Medicine at Lund University.

N.G. and P.R. are supported by public grants overseen by the European Commission (EUF7) and the French National Research Agency (ANR) as part of the second 'Investissements d'Avenir' programme FIGHT-HF (ANR-15-RHU-0004); programme HOMAGE under grant agreement N 305507; and project FIBROTARGETS grant HEALTH-2013-602904.

#### CRedit authorship contribution statement

**H. Holm:** contributed to the design and implementation of the research, to the analysis of the results, Writing – original draft, The first draft of the manuscript was written by H Holm, all authors commented on previous versions of the manuscript. **M. Magnusson:** contributed to the design and implementation of the research, to the analysis of the results, Writing – original draft, The first draft of the manuscript was written by H Holm, all authors commented on previous versions of the manuscript. **A. Jujic:** contributed to the design and implementation of the research, Formal analysis, to the analysis of the results, Writing – original draft, The first draft of the manuscript was written by H Holm, all authors commented on previous versions of the manuscript. **Nicola Riccardo Pugliese:** contributed to the design and implementation of the research, Formal analysis, to the analysis of the results, Writing – original draft, The first draft of the manuscript was written by H Holm, all

authors commented on previous versions of the manuscript. **E. Bozec:** Formal analysis, contributed with statistical analyses, All authors read and approved the final manuscript. **Z. Lamiral:** Formal analysis, contributed with statistical analyses, All authors read and approved the final manuscript. **O. Huttin:** contributed to the design and implementation of the research, Formal analysis, to the analysis of the results, Writing – original draft, The first draft of the manuscript was written by H Holm, all authors commented on previous versions of the manuscript. **F. Zannad:** contributed to the design and implementation of the research, Formal analysis, to the analysis of the results, Writing – original draft, The first draft of the manuscript was written by H Holm, all authors commented on previous versions of the manuscript. **P. Rossi-gno:** contributed to the design and implementation of the research, Formal analysis, to the analysis of the results, Writing – original draft, The first draft of the manuscript was written by H Holm, all authors commented on previous versions of the manuscript. **N. Girerd:** contributed to the design and implementation of the research, Formal analysis, to the analysis of the results, Writing – original draft, The first draft of the manuscript was written by H Holm, all authors commented on previous versions of the manuscript.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Acknowledgments

The authors thank the Centre de Ressources Biologiques Lorrain of Centre Hospitalier Régional Universitaire de Nancy for biobank handling.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2023.04.010>.

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