

Ventricular–arterial coupling indices reflect early stage of left ventricular remodelling in atrial fibrillation

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Abstract

Background: Atrial fibrillation (AF) associated with adverse atrial and ventricular remodelling and with extracellular matrix dysfunction initiating myocardial fibrosis. Ventricular–arterial coupling (VAC) plays a pivotal role in cardiac and aortic adaptation to pathological conditions. The purpose of this study was to examine the effect of paroxysmal AF on fibrotic remodelling reflected in structural and functional changes in left ventricle and large arteries and their coupling.

Material and methods: We carefully selected women and men aged from 40 to 75 years, with paroxysmal AF and sinus rhythm on admission to the hospital, with preserved left ventricle (LV) systolic function, and the carotid-femoral pulse wave velocity (PWV) within normal range. In transthoracic echocardiography LV systolic and diastolic function, stroke volume (SV), and global longitudinal strain (GLS) were assessed. The brachial blood pressure was simultaneously recorded during echocardiographic recording of blood flow velocity in LV outflow track. Following VAC parameters were analysed: arterial elastance (Ea) and LV elastance (Ees). Two-dimensional speckle tracking was used to derive novel VAC parameter PWV to LV GLS ratio.

Results: In univariable regression model the Ees increased significantly with AF history duration ($p = 0.001$), moreover Ees was higher in women than in men ($p = 0.002$). Ea/Ees ratio decreased significantly with AF history duration ($p = 0.005$). In multivariable regression models, AF duration was also negatively associated with Ea/Ees ratio, and positively related to Ees.

Conclusion: The relationship between AF and LV function is complex and potentially bi-directional. Despite normal LV function, paroxysmal AF can contribute to abnormal heart-vessel coupling, indicating early ventricular remodelling due to arrhythmia, this observation seems to be more pronounced in women.


Key words: atrial fibrillation; arterial elastance; myocardial remodelling; ventricular elastance

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Introduction

Atrial fibrillation (AF) affects nearly 60 million people worldwide [1]. Despite the development of pharmacotherapy, arrhythmia remains one of the main causes of ischaemic strokes [2] and heart failure [3]. The frequency and severity of arrhythmia episodes are closely related to vascular and myocardial remodelling [4]. The standard transthoracic echocardiography (TTE) as the pivotal diagnostics technique does not fully reflect the myocardial dysfunction and does not take into account the influence of decreasing compliance of the aorta on the function of the left ventricle (LV). The important role of ventricular–arterial coupling (VAC) in the pathophysiology of cardiac disease has recently been raised [5]. Heart–vessel coupling constantly changes to match ventricular end-systolic and arterial elastance [6]. Abnormalities found in VAC often precede changes detectable in traditional transthoracic echocardiography. In addition, it has been noticed that VAC parameters differ in women and men both in physiological conditions [7] and in heart diseases [8]. VAC is characterized by the LV contractile function and the load against the arterial circulation. This interaction determines cardiovascular performance and capability and can be calculated by linking ventricular and arterial elastances. Arterial elastance and LV elastance are measured as end-systolic pressure to stroke volume ratio and end-systolic pressure to end-systolic volume ratio respectively [6]. However, there are novel methods that allow for a more in-depth analysis of left ventricular remodelling and abnormal interaction of the left ventricle with aorta, such as ratio of the aortic stiffness measured using the pulse wave velocity (PWV) and global longitudinal strain (GLS) of the left ventricular fibres [9]. AF is also associated with extracellular matrix (ECM) dysfunction initiating atrial fibrosis and atrial dilation [4]. Atrial fibrosis is characterized by a multifactorial process that includes abnormal activation, proliferation and differentiation of fibroblasts and causes excessive synthesis and irregular deposition of ECM proteins including matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) [10]. Atrial remodelling, i.e. structural and functional changes, are caused by heart disease (haemodynamic changes, mechanical stretching), systemic processes (hormonal changes, pro-inflammatory cytokines, ageing), but also may be secondary to atrial fibrillation itself [4]. The degree of atrial remodelling is commensurate with the number of atrial fibrillation episodes or its type (paroxysmal, persistent, permanent). On

the other hand, a large number and long duration of atrial fibrillation episodes cause atrial fibrosis. However, the relationship between atrial fibrillation burden and atrial fibrosis is complex and not linear. This means that a higher level of collagen deposition in the atria does not always result in more frequent attacks of arrhythmias and its progression towards a persistent or permanent type [4]. The purpose of this study was to examine the effects of long-term paroxysmal AF on structural and functional changes in large arteries as well as left ventricle and their interaction in patients with preserved LV ejection fraction, particularly in relation to sex.

Material and methods

Study population

The study group was recruited prospectively among patients hospitalized at the Department of Cardiology, Interventional Electrophysiology and Hypertension of the University Hospital in Krakow between 2019–2021. Out of patients with paroxysmal atrial fibrillation who were scheduled for pulmonary vein isolation (PVI) procedure, we carefully selected women and men aged between 40 and 75 years, with sinus rhythm on admission to the hospital. Additionally, the inclusion criteria included: preserved left ventricle systolic function and the carotid-femoral pulse wave velocity (PWV) within the normal range [11]. The exclusion criteria were established coronary artery disease, moderate or severe valvular heart disease, secondary arterial hypertension, poorly controlled essential arterial hypertension, cardiomyopathy, chronic kidney disease at stage 3 or higher, type 1 diabetes, morbid obesity, severe chronic obstructive pulmonary disease and severe bronchial asthma. The study was conducted according to the Helsinki declaration for Investigation of Human Subjects. The Jagiellonian University Ethics Committee approved the study protocol. All participants submitted a written informed consent. We used a standardized questionnaire to obtain information on the medical history, including comorbidities, duration of the AF history, frequency and intensity of atrial fibrillation attacks, use of medication, and data on habits and lifestyle. Anthropometric and demographic data were also collected.

Echocardiographic and vascular measurements

Transthoracic echocardiography was performed in patients to assess the dimensions of the heart chambers, left ventricular systolic and diastolic

function, segmental and global contractility, left ventricular ejection fraction, stroke volume, measurements of the left atrium and left ventricular global longitudinal strain. The echocardiography was performed using Vivid 9 ultrasound devices equipped with a 1.5–3.6 MHz array transducer probe (General Electric Healthcare, Milwaukee, Wisconsin, United States). For offline analyses at least three consecutive heart cycles were recorded during breath-hold according to the current recommendations [12] and digitally stored on workstation running EchoPAC software. Ejection fraction (EF), left ventricle end diastolic volume (LVEDV), and left ventricle end systolic volume (LVESV) were calculated using Simpson biplane method. Left ventricular mass was calculated based on the method of Devereux et al. [15] and then adjusted for body surface area for obtaining the left ventricular mass index. Blood flow velocity and velocity time integral (VTI) in left ventricle outflow tract (LVOT) was recorded by placing the pulsed Doppler sample in the LVOT below the aortic valve. LVOT diameter was measured in a parasternal long axis about 0.5 to 1.0 cm apical to the annulus and then LVOT cross-sectional area was calculated. Stroke volume (SV) was obtained as the product of LVOT area and LVOT VTI. Antero-posterior left atrial (LA) end-systolic dimension was measured in parasternal long axis view and LA volume from the Simpson method [14] using apical 4- and 2- chamber views at the end of ventricular systole was also calculated as well as LA volume indexed to the subjects' body surface area (LAVI). Early diastolic peak flow velocity (E), late diastolic peak flow velocity (A) and their ratio (E/A) were determined from the transmitral flow signal. The early (e') and late (a') diastolic velocities of septal and lateral mitral annulus and the E/e' ratio was obtained from tissue Doppler recordings. The left ventricular global longitudinal strain was measured by manually tracing the endocardial border of apical four, two and three chamber view (at a framerate of 60–80 frames/s). Longitudinal strain curves were automatically processed and the average peak strain value of all three views was calculated. During echocardiographic recording of blood flow velocity in LVOT the brachial blood pressure (peripheral systolic blood pressure (pSBP) and brachial pulse wave were simultaneously recorded by SphygmoCor device (AtCor Medical Pty Ltd, West Ryde, New South Wales, Australia) running software Version XCEL. From the brachial signal, the SphygmoCor software estimated the aortic pulse wave and subsequently the central systolic blood pressure (cSBP). Peripheral and central pulse pressures were defined

as the difference between systolic and diastolic blood pressure. We assessed carotid-femoral PWV using SphygmoCor device too. A pressure-sensitive tonometer was placed over the right common carotid artery and a second one over the right femoral artery. The PWV was computed as a quotient of the measured distance covered between the two recorders and the transit time measured. PWV was averaged from at least 10 cardiac cycles. The measurements were performed in agreement with the expert consensus document on the measurement of aortic stiffness in daily practice using PWV [15].

Ventricular-arterial coupling parameters

We calculated classical parameter of VAC which reflects an interplay between the heart and the arterial system as a ratio of arterial elastance and left ventricle elastance. Arterial elastance (E_a) was measured as a ratio of end-systolic pressure (ESP) and stroke volume, where ESP was estimated as peripheral systolic blood pressure multiplied by 0.9 [5]. Left ventricle elastance (E_{es}) was calculated as a ratio of ESP and LVESV. Finally, the E_a/E_{es} ratio was calculated [5]. The formulas for E_a/E_{es} calculation are as follows:

$$E_a = \frac{ESP}{SV} = \frac{0,9 * SBP}{SV}, E_{es} = \frac{ESP}{LVESV}$$

where E_a — arterial elastance; E_{es} — ventricular elastance; ESP — end systolic pressure; LVESV — left ventricle end-systolic volume (Simpson's method); SBP — systolic blood pressure; SV — stroke volume (Doppler's method)

Additionally, we calculated the newly proposed VAC parameter — the ratio of PWV and GLS.

Laboratory tests including extracellular matrix metalloproteinases

In fasting patients, during recruitment, before PVI procedure, venous blood samples were taken and standard laboratory tests were performed including blood count, activated partial thromboplastin time (APTT), international normalized ratio (INR), creatinine, sodium, potassium, glucose levels, lipid profile, thyroid stimulating hormone (TSH), C-reactive protein (CRP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP). Additionally, the concentrations of matrix metalloproteinase 9 (MMP-9), matrix metalloproteinase 3 (MMP-3) and tissue inhibitor of metalloproteinases 1 (TIMP-1) were determined with the Human Total MMP-3 Immunoassay, Human MMP-9 Immunoassay, and Human TIMP-1 Immunoassay kit (Quantikine ELISA, Bio-Techne).

Statistical methods

Statistical analysis was carried out in R software, version 4.0.5 and version 9.4 (SAS Institute, Cary, NC, USA). Nominal variables are described by number of observations n and % frequency while continuous variables by mean \pm standard deviation (SD) or median (quartile 1; quartile 3 — Q1; Q3), depending on distribution. Distribution normality was assessed with Shapiro-Wilk test as well as based on skewness and kurtosis values.

Relationship between VAC parameters and other continuous variables was verified with Pearson or Spearman correlation as well as with linear regression. In regression analysis, unadjusted and adjusted univariate models were created. Covariates forced into adjusted models were: sex, age, BMI and history of AF, MMP3 and heart rate. Multicollinearity between independent variables and covariates was verified with variance inflation factors (VIFs) and no high intercorrelation was identified, i.e. no VIFs exceeded level of 10 (VIFs achieved ranged from 1.06 to 2.19) [16].

Results

The study group of 51 participants with paroxysmal atrial fibrillation (mean age 57.8 years) included 14 women and 37 men. Table 1 gives clinical characteristics of the study group. The duration of AF history and severity of AF symptoms were similar in men and women. There were no differences in the prevalence of cardiovascular risk factors and their treatments between men and women. Blood pressure parameters, glucose level and lipid profile were within normal range in the studied group. Women in comparison to men had lower creatine and MMP3 level (Tab. 1).

Table 2 summarizes haemodynamic characteristics presented by sex. Among echocardiographic parameters both the ejection fraction and average GLS, according to recruitment criteria, were in normal range (mean EF for all 62%); however, women were characterized by slightly better GLS than men. There were no sex differences in left ventricle diastolic function parameters. Stroke volume of left ventricle was larger in men than in women.

Among arterial parameters the pulse wave velocity was similar in men and women while the augmentation index was significantly higher in women. Moreover, women were characterized by higher left ventricular end systolic elastance and lower ventricular–arterial coupling calculated as the ratio of arterial and left ventricle elastance (Tab. 2).

The results of the correlation analysis between the ventricular — arterial coupling parameters and the AF duration, metalloproteinases, arterial stiffness, or left ventricle function parameters in the entire study group are presented in Table 3. The highest correlation coefficients were found for: AF duration and left ventricle elastance or Ea to Ees ratio (respectively 0.35; -0.33), for MMP3 and GLS (0.37), and for PWV and GLS (0.35).

In univariable regression model the left ventricle elastance increased significantly with AF duration. Moreover, Ees was higher in women than in men (Fig. 2). The ventricular–arterial coupling measured as Ea to Ees ratio decreased significantly with AF duration and was lower in women than in men (Fig. 3).

In multivariable regression models, AF duration was also negatively associated with Ea to Ees ratio, and positively related to Ees, moreover sex was significant covariate in those analyses (Tab. 4).

Discussion

In the current study, ventricular–arterial coupling parameters were analysed in the group of patients with paroxysmal AF in whom myocardial function was within normal range based on echocardiography. Myocardial remodelling, due to heart abnormal working conditions during atrial fibrillation paroxysms, is a multifactorial process. In the studied group the ratio of arterial to left ventricular elastances (Ea/Ees) significantly decreases with the duration of AF history, moreover Ea/Ees was lower in women than in men. The main contributor of ventricular–arterial decoupling was an increase in left ventricular elastance which was especially pronounced in women while compared to men. What is worth noting in our study, with the increase in GLS (decrease in absolute value, GLS is a negative parameter) and, consequently, with the decrease in the PWV to GLS ratio, the level of metalloproteinases and their inhibitors increased, which indicates active remodelling yet at the enzymatic level.

Complex structural and electrical changes in the atria and ventricular myocardium are directly related to the pathophysiological processes initiated by AF. Advanced atrial fibrosis is linked to more frequent AF paroxysms, the development of a persistent form of the arrhythmia, and diminished antiarrhythmic medication therapy efficacy [4]. Increasing amount of fibrotic tissue in the myocardium is one of the key factors in cardiac remodelling. Connective tissue fibre formation and its redistribution modify cardiac shape to adapt to

Table 1. Clinical characteristics, data are presented as number (%) or mean \pm standard deviation or median and interquartile range (Q1; Q3)

Clinical data	All	Women	Men	p*
Number	51 (100.0)	14 (27.5)	37 (72.5)	0.001
Age [years]	57.76 \pm 8.74	59.93 \pm 6.75	56.95 \pm 9.35	0.21
BMI [kg/m ²]	29.13 \pm 4.28	30.24 \pm 5.74	28.71 \pm 3.59	0.37
Physically active	28 (54.9)	8 (57.1)	20 (54.0)	0.84
Current smoking	7 (13.7)	0	7 (18.9)	0.09
Alcohol intake	18 (35.3)	2 (14.3)	16 (43.2)	0.053
AF duration [years]	5.66 \pm 4.75	6.04 \pm 3.64	5.51 \pm 5.15	0.73
AF episodes [number/week]	0.25 (0.04;1.00)	0.38 (0.10; 1.00)	0.25 (0.01; 1.00)	0.38
EHRA symptom scale				
I	7 (13.7)	0	7 (18.9)	0.37
Ila	10 (19.6)	3 (21.4)	7 (18.9)	
Ilb	23 (45.1)	8 (57.2)	15 (40.6)	
III	9 (17.6)	3 (21.4)	6 (16.2)	
IV	2 (3.9)	0	2 (5.4)	
Drugs				
Antiarrhythmics	45 (88.2)	13 (92.9)	32 (85.5)	0.53
Anticoagulants	44 (86.3)	10 (71.4)	34 (91.9)	0.058
Statins	26 (51.0)	7 (50.0)	19 (51.3)	0.93
ACEI/ARB	30 (58.8)	7 (50.0)	23 (62.2)	0.43
Comorbidities				
Hypertension	33 (64.7)	9 (64.3)	24 (64.9)	0.97
Hypercholesterolemia	28 (54.9)	7 (50.0)	21 (56.8)	0.66
Diabetes type 2	3 (5.9)	0	3 (8.11)	0.37
Laboratory tests				
Creatinine [μ mol/L]	81.94 \pm 14.24	71.5 \pm 11.39	85.9 \pm 13.26	0.0007
Total cholesterol [mmol/L]	4.35 \pm 1.04	4.43 \pm 1.02	4.32 \pm 1.06	0.74
HDL-C [mmol/L]	1.29 \pm 0.33	1.38 \pm 0.30	1.26 \pm 0.34	0.30
LDL-C [mmol/L]	2.46 \pm 0.89	2.42 \pm 0.85	2.47 \pm 0.91	0.88
Triglycerides [mmol/dL]	1.28 \pm 0.63	1.38 \pm 0.88	1.25 \pm 0.53	0.52
Glucose [mmol/L]	5.41 \pm 0.61	5.23 \pm 0.45	5.48 \pm 0.65	0.23
TSH [μ U/mL]	1.74 \pm 1.25	2.01 \pm 1.63	1.64 \pm 1.08	0.34
hs-CRP [mg/L]	2.89 (1.01; 4.74)	3.22 (1.01; 4.90)	2.83 (1.00; 4.71)	0.94
NT-proBNP [pg/mL]	164.50 (71.75; 273.75)	178.25 (59.0; 288.0)	133.97 (50.0; 223.0)	0.26
Metalloproteinases				
TIMP1 [ng/mL]	76.89 (67.76; 88.07)	78.42 (70.80; 88.07)	76.13 (66.50; 87.06)	0.25
MMP3 [ng/mL]	12.66 (8.37; 16.64)	7.42 (6.70; 9.36)	14.17 (10.15; 20.26)	0.001
MMP9 [ng/mL]	43.93 (34.14; 80.99)	36.53 (32.35; 81.41)	44.43 (34.54; 80.89)	0.19
Peripheral and central BP				
Peripheral SBP [mm Hg]	121.42 \pm 13.33	123.1 \pm 13.18	120.9 \pm 13.53	0.65
Peripheral DBP [mm Hg]	65.72 \pm 8.51	65.30 \pm 8.87	65.85 \pm 8.53	0.86
Heart rate [beats/min]	63.53 \pm 11.27	65.5 \pm 11.73	62.94 \pm 11.24	0.55
Central PP [mm Hg]	45.02 \pm 11.57	48.2 \pm 6.97	44.06 \pm 12.57	0.33
Peripheral PP [mm Hg]	55.63 \pm 11.63	57.8 \pm 8.99	54.97 \pm 12.37	0.51
MAP [mm Hg]	83.67 \pm 8.39	85.40 \pm 10.44	83.15 \pm 7.79	0.46

p for between gender differences; ACEI — angiotensin-converting enzyme inhibitors; AF — atrial fibrillation; ARB — angiotensin receptor blockers; BMI — body mass index; DBP — diastolic blood pressure; EHRA — European Heart Rhythm Association; MAP — mean arterial pressure; MMP3 — matrix metalloproteinase 3; MMP9 — matrix metalloproteinase 9; PP — pulse pressure; SBP — systolic blood pressure; TIMP1 — tissue metalloproteinase inhibitor 1

Table 2. Haemodynamic parameters, data are presented as mean \pm standard deviation

Parameters	All	Women	Men	p*
Echocardiographic data				
LVMI [g/m ²]	97.98 \pm 19.67	97.28 \pm 20.78	98.26 \pm 19.52	0.87
LVEDV [mL]	104.17 \pm 25.11	93.21 \pm 24.63	109.1 \pm 24.09	0.048
LVESV [mL]	41.86 \pm 14.06	35.43 \pm 13.66	44.76 \pm 13.45	0.038
Stroke volume [mL]	62.08 \pm 8.63	56.66 \pm 8.65	64.15 \pm 7.79	0.013
Ascending aorta diameter [mm]	33.75 \pm 2.85	32.72 \pm 3.04	34.09 \pm 2.75	0.17
LAVI [mL/m ²]	41.03 \pm 12.04	40.11 \pm 11.77	41.40 \pm 12.29	0.74
RVID [mm]	36.82 \pm 3.33	36.57 \pm 2.82	36.91 \pm 3.54	0.75
GLS (%)	-18.97 \pm 2.89	-20.25 \pm 2.86	-18.46 \pm 2.79	0.049
Transmitral E/A ratio	1.15 \pm 0.41	1.17 \pm 0.29	1.29 \pm 0.44	0.34
Mitral annular e' [cm/s]	8.99 \pm 3.37	8.22 \pm 1.35	9.29 \pm 3.87	0.32
E/e' ratio	7.92 \pm 1.94	7.61 \pm 1.98	8.03 \pm 1.95	0.52
Arterial data				
PWV [m/s]	9.03 \pm 1.45	8.38 \pm 1.29	9.23 \pm 1.45	0.10
Alx (%)	33.28 \pm 15.05	45.10 \pm 12.19	29.69 \pm 14.09	0.003
VAC components				
Ea [mm Hg/mL]	1.77 \pm 0.34	1.95 \pm 0.42	1.72 \pm 0.29	0.07
Ees [mm Hg/mL]	2.77 \pm 1.13	3.61 \pm 1.27	2.52 \pm 0.97	0.006
Ea to Ees ratio	0.71 \pm 0.21	0.58 \pm 0.14	0.74 \pm 0.22	0.046
PWV to GLS ratio	-0.49 \pm 0.13	-0.40 \pm 0.08	-0.51 \pm 0.13	0.019

Alx — augmentation index; Ea — arterial elastance; Ees — left ventricular end systolic elastance; GLS — global longitudinal strain; IVSd — interventricular septal end diastole thickness; LAVI — left atrium volume indexed to body surface area; LVEDV — left ventricle end diastolic volume; LVEF — left ventricle ejection fraction; LVESV — left ventricle end systolic volume; LVIDd — left ventricular internal diameter end diastole; LVMI — left ventricle mass indexed to body surface area; LVPWd — left ventricular posterior wall end diastole thickness; PWV — pulse wave velocity; RVID — right ventricle internal diameter

Table 3. Correlations of ventricle — arterial coupling and its components

Variable	Ea [mm Hg/mL]		Ees [mm Hg/mL]		Ea/Ees		PWV [m/s]		GLS (%)		PWV/GLS	
	rho	p	rho	p	rho	p	rho	p	rho	P	rho	p
Atrial fibrillation time [years]	0.08	0.596	0.35	0.023	-0.33	0.028	0.13	0.42	-0.10	0.494	0.06	0.721
BMI [kg/m ²]	-0.39	0.009	-0.20	0.204	-0.07	0.643	0.45	0.002	0.31	0.028	-0.48	0.001
TIMP1 [ng/mL]	-0.02	0.882	0.18	0.253	-0.20	0.196	0.15	0.32	0.29	0.049	-0.20	0.194
MMP3 [ng/mL]	-0.11	0.486	-0.35	0.021	0.22	0.158	0.13	0.41	0.37	0.010	-0.37	0.015
MMP9 [ng/mL]	0.03	0.836	0.09	0.549	-0.01	0.984	0.20	0.059	0.07	0.617	-0.22	0.156
PWV [m/s]	0.07	0.664	-0.01	0.973	0.12	0.447	-	-	0.35	0.023	-	-
LVEF (%)	-0.12	0.458	0.28	0.070	-0.39	0.009	-0.39	0.009	-0.63	<0.001	0.63	<0.001
LAVI [mL/m ²]	-0.42	0.006	-0.41	0.006	0.04	0.811	-0.20	0.86	-0.18	0.209	0.13	0.398
GLS (%)	-0.05	0.76	-0.21	0.047	0.22	0.16	0.07	0.617	-	-	-	-

Statistically significant correlations ($p < 0.05$) are highlighted in bold. BMI — body mass index; Ea — arterial elastance; Ees — left ventricular end systolic elastance; GLS — global longitudinal strain; LAVI — left atrium volume indexed to body surface area; LVEF — left ventricle ejection fraction; MMP3 — matrix metalloproteinase 3; MMP9 — matrix metalloproteinase 9; PWV — pulse wave velocity; TIMP1 — tissue metalloproteinase inhibitor 1

new circumstances [4]. The extracellular matrix (ECM), an acellular component of the heart that contains a variety of fibres with collagen predominating, and the cellular components of the myocardium, are both involved in this adaptation process [4]. Increased expression of MMP-9 has been

observed in the atrial tissue and blood serum of patients with AF, and the MMP-9 levels appear to be positively associated with the stage of AF [17, 18]. In our study we did not reveal the relation of metalloproteinases concentration with duration of AF history (data not shown); however, MMP-9

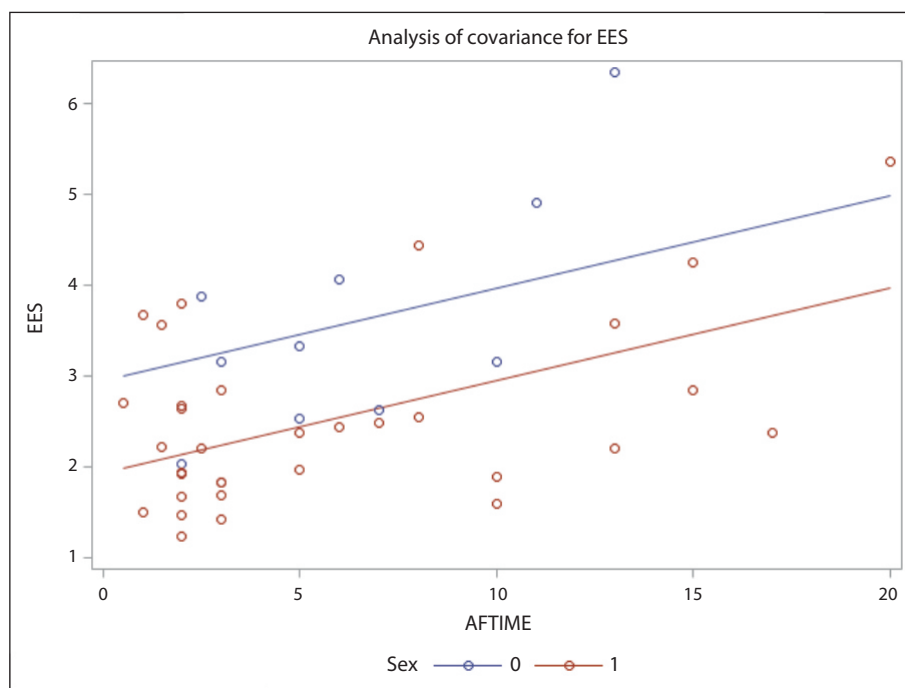


Figure 2. Relationship of ventricular–arterial coupling component with atrial fibrillation history duration. Model: Sum of Squares 19.9; $p < 0.001$; p for sex = 0.002; p for AFTIME 0.001. EES — left ventricle elastance; AFTIME — atrial fibrillation history duration; sex 0 — women; sex 1 — men

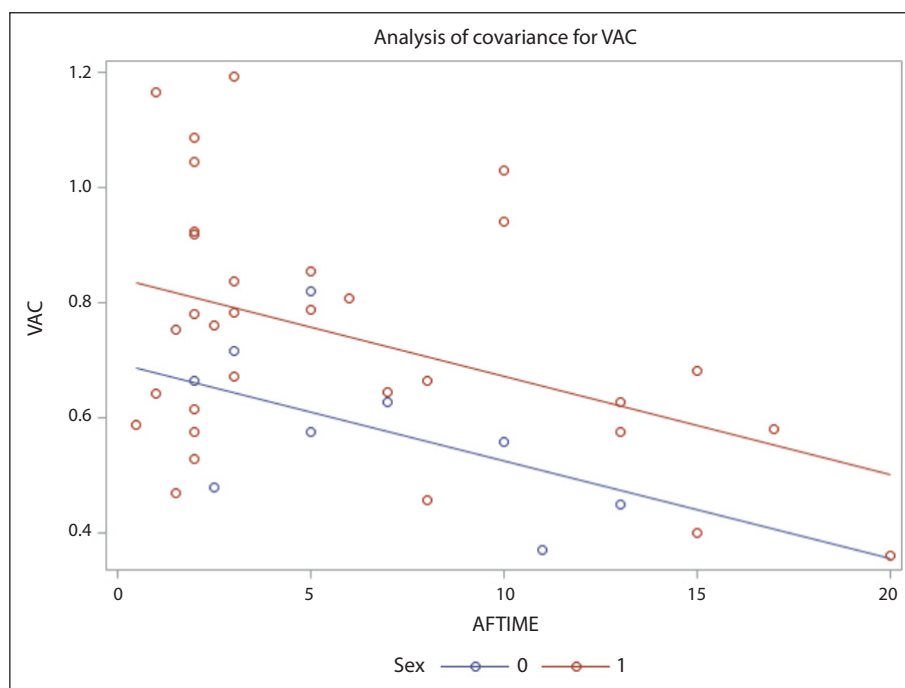


Figure 3. Relationship of ventricular–arterial coupling with atrial fibrillation history duration. Model: Sum of Squares 0.48; $p = 0.003$; p for sex = 0.03; p for AFTIME 0.005. VAC — ventricular–arterial coupling; AFTIME — atrial fibrillation history duration; sex 0 — women; sex 1 — men

level increases with frequency of AF episodes — but correlation analyses did not reach statistical significance (0.25; $p = 0.06$), which could be

explained by relatively low number of AF episodes per week in the studied group. A structural change in the heart chambers affects its function and con-

Table 4. Multivariable regression of ventricular — arterial coupling and its components with atrial fibrillation duration

	Model			
	R-square	p	Mean square	p
Ea [mm Hg/mL]	0.16	0.37		
Sex [0-women; 1-men]			0.19	0.20
Age [years]			0.15	0.26
AF duration [years]			0.01	0.75
BMI [kg/m ²]			0.02	0.70
MMP3 [ng/mL]			0.07	0.45
Heart rate [beats/min]			0.01	0.84
Ees [mm Hg/mL]	0.46	0.0008		
Sex [0-women; 1-men]			9.03	0.002
Age [years]			0.22	0.60
AF duration [years]			10.9	0.001
BMI [kg/m ²]			0.62	0.39
MMP3 [ng/mL]			0.59	0.40
Heart rate [beats/min]			3.02	0.06
Ea to Ees ratio	0.50	0.0004		
Sex [0-women; 1-men]			0.17	0.01
Age [years]			0.01	0.62
AF duration [years]			0.21	0.009
BMI [kg/m ²]			0.02	0.41
MMP3 [ng/mL]			0.05	0.19
Heart rate [beats/min]			0.24	0.004
PWV to GLS ratio	0.43	0.002		
Sex [0-women; 1-men]			0.08	0.01
Age [years]			0.09	0.008
AF duration [years]			0.01	0.79
BMI [kg/m ²]			0.07	0.019
MMP3 [ng/mL]			0.01	0.45
Heart rate [beats/min]			0.01	0.51

AF — atrial fibrillation; BMI — body mass index; Ea — arterial elastance; Ees — left ventricular end systolic elastance; GLS — global longitudinal strain; LAVI — left atrium volume indexed to body surface area; LVEF — left ventricle ejection fraction; MMP3 — matrix metalloproteinase 3; PWV — pulse wave velocity

tributes to dysregulation of left ventricle – arterial interaction.

VAC is a concept describing the interaction of left ventricle and the vascular system in terms of volume and pressure relationship. It is estimated as the ratio of arterial elastance and ventricular elastance. It should be emphasized that under physiological conditions, the mechanical energy transferred from the heart to the vessels is greatest when both arterial and ventricular elastance are approximately equal [19]. Haemodynamic parameters such as systemic blood pressure, heart rate, stroke volume, anatomical parameters — left ventricular remodelling, left atrial enlargement, left ventricular size, sex and age affect the VAC value. In addition, VAC

depends on the used drugs, and so, for example, Ea is most affected by pressor amines, vasodilators, diuretics, beta-blockers, while Ees is most affected by inotropic drugs [20]. VAC behaves differently according to different pathological conditions. In systolic left ventricular failure, ventricular elastance decreases significantly and vascular elastance remains unchanged or increases (due to decrease in stroke volume and cardiac output, then tissue hypoperfusion, activation of sympathetic nervous system and subsequently vasoconstriction), causing an increase in the Ea/Ees ratio [5]. A similar increase in the Ea/Ees ratio is observed in arterial hypertension, but it is mainly expressed by an increase in vascular elastance and a decrease in ventricular elastance [5].

In case of tachycardia, both Ees and, to a greater extent, Ea increase, which causes an increase in the Ea/Ees ratio [20]. The Ea/Ees ratio in heart failure with preserved ejection fraction is insensitive to abnormal VAC states as both Ees and Ea have a tendency to increase [5]. What has been shown in our study, with the increase in the duration of atrial fibrillation history, the elastance of the left ventricle increases significantly — potentially as a consequence of paroxysmal arrhythmia, while arterial elastance increases to lesser extent consequently giving a significant decrease in the Ea/Ees ratio. As we observed relatively young patients (mean age 57.8 years) with history of paroxysmal AF of about 6 years, significant increase in Ees may be considered a compensatory mechanism. With aging, stiffening of the aorta may lead to an increase in Ea, resulting in symptoms of heart failure with preserved left ventricular ejection fraction.

Myocardial remodelling with aging and due to chronic diseases differs between men and women [21, 22]. Studies have shown that women naturally express fibrosis-related genes and proteins differently than men. Those associated with the TGF/Smad3 pathway, in particular, appeared to be up-regulated in females with long lasting AF, promoting an aggravation of fibrosis remodelling [23]. Transforming growth factor beta (TGF- β) is responsible for increasing the synthesis of metalloproteinases and their inhibitors [24]. Although no sex differences in MMP-9 and TIMP-1 concentrations have been observed in our study, women had lower MMP-3 level than men. In the majority of studies looking at cardiac remodelling, MMP-3 is one of the enzymes with higher concentration in men compared to women [25];, MMP-3 concentration is also significantly higher in men in physiological conditions [26].

VAC parameters also differ in females and males in normal conditions. Despite having lower systolic blood pressure and pulse pressure than men, young women have reduced small vessel compliance and elevated augmentation index (AIx) [27–29]. Additionally, there are gender disparities in the function of the left ventricle at rest. Healthy women have higher Ees and diastolic stiffness than men [30]. Peak and end-systolic pressure, as well as resting heart rate, are considerably higher in women [30]. Even after accounting for body surface area, there was still a discernible gender difference in arterial elastance (with women having greater arterial elastance index) [30, 31]. The Ea/Ees ratio is lower in women [31]. In our observations, we found that women and men did not differ significantly with regard

of heart rate and blood pressure as well as arterial elastance; however, women had significantly higher Ees while the ratio of Ea to Ees was significantly lower. Accordingly, women are more adversely affected by atrial fibrillation than men.

In our study men had a slightly higher absolute value of GLS than women, with similar PWV values, but the PWV/GLS ratio in women was significantly higher. In general, women tend to have lower PWV than men from adolescence to menopause [32]. Both males and females experience an increase in arterial stiffening with aging, but the increase is steeper in men than women [33]. After menopause, however, women's PWV tends to increase and may approach or even exceed that of men [34]. The group of women in this study was in perimenopausal or postmenopausal age which explains similarity in PWV values with men. In the study on a healthy population, women had less impaired GLS than men [35]. This gender difference in GLS was also shown in studies in patients with comorbidities [36]. Patients with AF have more impaired GLS than healthy population [37]. The PWV to GLS ratio is greater the lower the PWV is, or the smaller (less impaired) GLS is. A reduced PWV/GLS ratio is a marker that reflects the presence of subclinical LV dysfunction and/or increased aortic stiffening, which may both contribute to progression to symptoms and eventually lead to heart failure if left untreated at an early stage when changes are still reversible [38]. Ultimately, it was women who were characterized by better ventricular vascular interaction according to PWV/GLS ratio; however, this parameter was primarily affected by age, not the duration of AF. Thus, the early changes caused by AF are not evident in the PWV to GLS ratio while GLS and PWV remain within normal limits.

Epidemiological studies demonstrate a strong link between AF and heart failure with preserved ejection fraction (HFpEF). Moreover, AF is considered as one of the primary precedents and predictors of the development of HFpEF [39]. The observed early changes in VAC are probably one of the factors causing HFpEF to occur more frequently in women than in men. The development and prognosis of HFpEF have been also linked to a number of comorbidities, including hypertension [40]. Arterial hypertension doubles the risk of developing AF in comparison to normotensives [41, 42] regardless of myocardial remodelling expressed as left atrial enlargement [41]. Arterial hypertension also increases the risk of developing heart failure by three times in women, compared with two times in men [43]. This could be attributed to the fact that women have

a higher augmentation index than men, which results in more end-organ damage, including LV hypertrophy [28, 40]. AF increases the risk of hospitalization due to heart failure 1.63 times in women in comparison with 1.37 times in men [44], suggesting that atrial fibrillation plays more important role in women with HFpEF. Possible explanations for the convergence of AF and HFpEF include i.a. the hypothesis that each phenotype might follow one another sequentially (i.e. elevated left ventricular filling pressure in HFpEF may result in left atrial dilatation, which provokes AF, and conversely, rapid heart rate due to AF may result in LV fibrosis) [39]. In HFpEF, impairment of VAC is related to inflammatory and mechanical overload caused by arterial hypertension and other co-morbidities. In HFpEF increased arterial stiffness and wave reflections raise the LV late systolic pressure [45]. Through the active process of fibrosis and the increase in inflammatory mediators, endothelial dysfunction occurs, nitric oxide production decreases and, consequently, vasoconstriction takes place and peripheral resistance elevates, resulting in an increase in Ea [5]. Due to impaired diastolic function and a decrease in the contractile reserve of the left ventricle, Ees increases [5]. AF is associated with early deterioration of VAC, a marker of heart failure development, emphasizing the need for appropriate pharmacological treatment from an early stage of the disease.

A few limitations of our study should be taken into consideration. First, we presented a relatively small group of patients with atrial fibrillation; however, their ventricular and blood pressure parameters were carefully and extensively phenotyped. The study group consisted of significantly fewer women, but they did not differ from men in terms of risk factors for cardiovascular diseases and the clinical picture of AF. Finally, this was a cross-sectional evaluation of VAC parameters, and the prognostic significance of our results needs to be evaluated in future longitudinal studies.

Conclusion

Despite normal LV function, paroxysmal AF can contribute to abnormal heart-vessel coupling, indicating early ventricular remodelling due to arrhythmia, and it seems more pronounced in women. It should be emphasized, that PWV to GLS ratio do not fully reflect the interaction of the large vessels with the ventricle in paroxysmal atrial fibrillation, and that the elastance of the aorta and the elastance of the left ventricle and their ratio are more adequate

parameters to assess this interaction, but further studies on a larger group are required.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

Ethics statement

The study was conducted according to the Helsinki declaration for Investigation of Human Subjects. The Jagiellonian University Ethics Committee approved the study protocol. All participants submitted a written informed consent.

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Conflict of interest

No conflict of interest.

Author contributions

Each of the co-authors has an equal contribution to the creation of the study.

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