ORIGINAL PAPER

Epicardial fat amount is associated with the magnitude of left ventricular remodeling in aortic stenosis

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Abstract

Both genetic and environmental factors interact to control left ventricular (LV) remodeling in the context of aortic stenosis (AS). Epicardial adipose tissue (EAT) is a specific visceral adipose tissue with paracrine properties in close contact with the myocardium. We sought to assess determinants of EAT amount and its association with the magnitude and pattern of LV remodeling in patients suffering from severe AS. Between January 2014 and September 2017, we prospectively explored consecutive patients referred to our Heart Valve Center for SAVR presenting with severe AS and normal left ventricular ejection fraction ($> 50\%$). Comprehensive transthoracic echocardiography (TTE) including assessment of LV remodeling and EAT amount were performed. 202 patients were included. EAT was significantly larger in elderly, diabetic and obese patients. EAT thickness was correlated positively with indexed LV mass in AS ($r^2 = 0.21$; $p < 0.0001$) as well as severe LV remodeling pattern. Importantly, this observation persisted after adjustment for other factors associated with LV remodeling ($\beta \pm SE = 1.74 \pm 0.34$; $p < 0.0001$). Large amounts of EAT are positively and independently associated with more pronounced and severe LV remodeling in severe AS. Further exploration regarding the impact of functional properties of EAT on LV remodeling is required.

Keywords Aortic stenosis · Epicardial adipose tissue · Left ventricle remodeling · Hypertrophy · Obese

Introduction

In patients with aortic stenosis (AS), left ventricular hypertrophy (LVH) develops as a response to chronic pressure overload. This ventricular remodeling is primarily adaptive, reducing wall stress and preserving systolic cardiac function.

Yet, LVH initiates a vicious circle leading to diastolic dysfunction, myocardial fibrosis, dilation, and finally heart failure [1]. Accordingly, LVH is associated with increased risk of cardiac events and poor prognosis in AS before and after surgical aortic valve replacement (SAVR) [2–4].

Genetic and environmental factors interact with the LV remodeling process in AS. Several studies reported these past few years that obesity, the metabolic syndrome, and type 2 diabetes are associated with more pronounced LVH [5–7].

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However, the nature of the link between these metabolic disorders and cardiac remodeling is still poorly understood.

Visceral adipose tissue is a major source of adipokines and cytokines promoting insulin resistance and cardiovascular disorders in obese and diabetic patients [8]. Epicardial adipose tissue (EAT) is a visceral adipose tissue in close contact with the myocardium. Being located around the heart underneath the visceral pericardial layer, EAT is in direct contact with the epicardium [9]. EAT is thus a first-class candidate to modulate the function of the myocardium and coronary vasculature [10].

Interestingly, EAT amount and its secretory/paracrine properties are altered in both obesity and type 2 diabetes [8, 11]. Moreover, visceral adipose tissue amount is independently associated with indexed left ventricular mass (LVMi) in patients with moderate AS [12].

Nevertheless, to our knowledge, there is no study on the specific association between EAT and ventricular remodeling in AS.

In the present study, we hypothesized that increased EAT amount is associated with poorer LV remodeling in AS.

Methods

Study population and design

From January 2014 to September 2017, we prospectively studied consecutive patients with severe AS referred to our Heart Valve Center (CHU Lille) for SAVR. Patients with reduced left ventricular ejection fraction ($< 50\%$) were excluded **to get a homogeneous population**. Patients with another significant valvular disease, a medical history of previous cardiac surgery or congenital heart disease were also excluded.

The local ethics committee approved the protocol and patients gave informed consent.

Cardiac imaging

A comprehensive transthoracic echocardiography (TTE) was performed in all patients before after cardiac surgery using a commercially available ultrasound machine (Vivid E9, GE Healthcare, Little Chalfont, UK) and stored for off-line analysis (EchoPAC version 201.0.0; GE Vingmed Ultrasound, Horten, Norway). All measures were performed according to current guidelines, particularly for the assessment of AS, and LV structure and function [13].

LV remodeling assessment

LV mass was calculated using M-mode recordings according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging [13, 14]. LV mass was indexed to body height in the allometric power of 2.7 to get indexed LV mass (LVMi) [15]. LV hypertrophy (LVH) was defined using the common cutoff values, i.e. LVMi > 46.7 g/m$^{2.7}$ in women and > 49.2 g/m$^{2.7}$ in men.

Relative wall thickness (RWT) was calculated from TTE measures as the following ratio: ($2 \times$LV posterior wall thickness/LV end diastolic diameter).

Considering both LVMi and RWT, patients were classified as having one of the 4 LV remodeling patterns using the following criteria: (1) normal pattern: absence of LVH and RWT < 0.42; (2) concentric remodeling: absence of LVH and RWT ≥ 0.42; (3) concentric hypertrophy: presence of LVH and RWT ≥ 0.42; and (4) eccentric hypertrophy: presence of LVH and RWT < 0.42.

Epicardial adipose tissue assessment

EAT was measured as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium with TTE. EAT thickness was measured off-line with EchoPac (GE Healthcare), perpendicularly to the free wall of the right ventricle at end-systole in 3 cardiac cycles in the parasternal long-axis view as previously described [16]. Inter-observer reproducibility for this measurement was high with intraclass correlation coefficient of 0.93 IC [0.88; 0.96].

To further validate this method, EAT amounts were compared between TTE and cardiac magnetic resonance (CMR) in 84 patients explored for a LVH. The correlation between these two techniques was good in our center (r = 0.64, p = 0.0001) (Supplemental Fig. 1).

Statistical analysis

Statistics were performed with MedCalc v16.4 (Olstead, Belgium). Continuous variables were tested for normality with Shapiro test, and are given as mean $\pm$ SD. t-test and linear regression were performed for bi-variate analysis. Categorical variables are given as the number (percentage) of patients with the respective attribute and compared with Chi-square test.

Pearson correlation was used to explore the link between EAT thickness and LVMi. Chi-square for trend was used to assess relations between EAT amount and LV remodeling patterns, patients being divided on EAT thickness median. Multivariable linear regression analysis was performed to identify variables independently associated with LVMi. Variables with a p value < 0.10 on univariable analysis were entered into the multivariable models.

A value of $p < 0.05$ was considered statistically significant. Figures were drawn with GraphPad Prism version 5.0.

Results

A total of 202 patients referred for a first SAVR were included. Patients' characteristics are summarized in Table 1. Mean age was 69 ± 10 years. The population was made of 62% of male and a third had diabetes. 79% of them were overweight (43%) or obese (36%). Regarding medications, half of the patients was treated with beta-blockers or ACE inhibitors/ARBs.

EAT amount was larger in older ($p = 0.0063$), hypertensive ($p = 0.016$) and diabetic patients ($p < 0.0001$) with higher BMI ($p < 0.0001$) in bi-variate analysis (Table 2). Conversely, gender was not associated with EAT thickness. After adjustment by multilinear regression, older age ($p = 0.01$), higher BMI ($p < 0.0001$) and diabetes mellitus ($p = 0.008$) remained significantly associated with larger EAT amount.

After splitting the population in half according to LVMi median, patients with higher LVMi had higher BMI

Table 1 Patients' characteristics (n = 202)

	Total population (n = 202)	Low LVMi (n = 102)	High LVMi (n = 100)	p value
Clinical data				
Age (years)	68.8 ± 9.7	67.9 ± 10.4	69.6 ± 9.0	0.22
Gender (male) n (%)	125 (61.9)	67 (65.7)	58 (58.0)	0.26
BMI (kg/m²)	28.9 ± 4.9	27.8 ± 4.6	29.9 ± 4.9	**0.002**
Normal n (%)	43 (21.3)	31 (30.4)	12 (12.0)	**0.001**
Overweight n (%)	87 (43.1)	44 (43.1)	43 (43.0)	0.98
Obese n (%)	72 (35.6)	27 (26.5)	45 (45.0)	**0.006**
Hypertension n (%)	148 (73.3)	74 (72.5)	74 (74.0)	0.82
Diabetes mellitus n (%)	72 (35.6)	26 (25.5)	46 (46.0)	**0.002**
Smoking n (%)	55 (27.2)	25 (24.5)	30 (30.0)	0.38
NYHA class	2.09 ± 0.7	2.09 ± 0.7	2.10 ± 0.7	0.97
Class I n (%)	5 (2.5)	1 (1.0)	4 (4.0)	
Class II n (%)	23 (11.4)	15 (14.7)	8 (8.0)	
Class III n (%)	122 (60.4)	60 (58.9)	62 (62.0)	
Class IV n (%)	52 (25.7)	26 (25.5)	26 (26.0)	
Euroscore 2 (%)	1.50 [1.05; 2.30]	1.41 [0.97; 2.20]	1.53 [1.13; 2.44]	0.10
Treatments				
Beta-blockers n (%)	71 (35.1)	33 (32.4)	38 (38.0)	0.40
ACE inhibitors/ARBs n (%)	100 (49.5)	50 (49.0)	50 (50.0)	0.89
Oral anti diabetic n (%)	71 (35.1)	26 (25.5)	45 (45.0)	**0.004**
Insulin therapy n (%)	21 (10.4)	5 (4.9)	16 (16.0)	**0.01**
Biology				
NT-pro-BNP (ng/l)	396 [180; 1052]	367 [158; 718]	401 [236; 1455]	0.17
Creatinine (mg/l)	9.0 [8.0; 10.3]	9.0 [8.0; 10.1]	9.0 [7.7; 10.9]	0.19
Cockroft et Gault (ml/min)	79.5 [67.0; 98.0]	81.0 [68.0; 99.3]	78.0 [63.5; 93.0]	0.37
Cardiac imaging				
Peak Ao velocity (m/s)	4.40 [4.14; 4.79]	4.39 [4.14; 4.60]	4.50 [4.15; 4.90]	0.07
Mean Ao gradient (mmHg)	50.5 [42.5; 60.3]	50.0 [42.0; 55.1]	52.0 [43.9; 63.8]	**0.01**
iEOA (cm²/m²)	0.34 [0.29; 0.42]	0.34 [0.30; 0.42]	0.35 [0.29; 0.42]	0.95
LVEF (%)	61.3 ± 9.3	62.3 ± 7.2	60.2 ± 35.7	0.11
LA area (cm²)	24.5 ± 8.0	23.1 ± 5.7	25.9 ± 9.7	**0.01**
ZVA (mmHg/ml/m²)	5.1 [4.2; 6.1]	5.1 [4.3; 6.0]	5.1 [4.1; 6.5]	0.59
LVMi (g/m²·⁷)	54.9 ± 14.1	44.0 ± 6.9	66.1 ± 10.4	**< 0.0001**
EAT thickness (mm)	6.9 ± 3.0	5.7 ± 2.4	8.1 ± 3.1	**< 0.0001**

Bold value represents p < 0.05 between Low LVMi and High LVMi

ACE angiotensin-converting enzyme; *Ao* aortic; *ARBs* Angiotensin II receptor blockers; *BMI* body mass index; *EAT* epicardial adipose tissue; *iEOA* indexed effective orifice area; *LA* left atrium; *LVEF* left ventricular ejection fraction; *LVMi* left ventricular mass index; *NYHA* New York Heart Association; *ZVA* valvuloarterial impedance

Table 2 Determinants of epicardial adipose tissue thickness (n = 202)

	Univariable		Multivariable	
	$\beta \pm SE$	p	$\beta \pm SE$	p
Gender (male)	−0.69 ± 0.43	0.11		
Age (years)	**0.06 ± 0.02**	**0.0063**	**0.05 ± 0.02**	**0.0103**
BMI (kg/m²)	**0.33 ± 0.04**	**< 0.0001**	**0.25 ± 0.04**	**< 0.0001**
Diabetes mellitus n (%)	**2.01 ± 0.42**	**< 0.0001**	**1.07 ± 0.39**	**0.0083**
Hypertension n (%)	**1.17 ± 0.46**	**0.016**	–	–
Mean aortic gradient (mmHg)	−0.003 ± 0.01	0.84		
Beta blockers	−0.43 ± 0.44	0.33		
ACE inhibitors/ARBs	**0.98 ± 0.46**	**0.03**	–	–

Bold value represents p < 0.05 between Low LVMi and High LVMi

p-value by t-test or linear regression in bivariate analysis. Regression coefficient, standard errors and p-value from multivariate linear regression model constructed with all variables with p < 0.10 in bivariate analysis

ACE angiotensin converting enzyme; *ARBs* angiotensin II receptor blockers; *BMI* body mass index
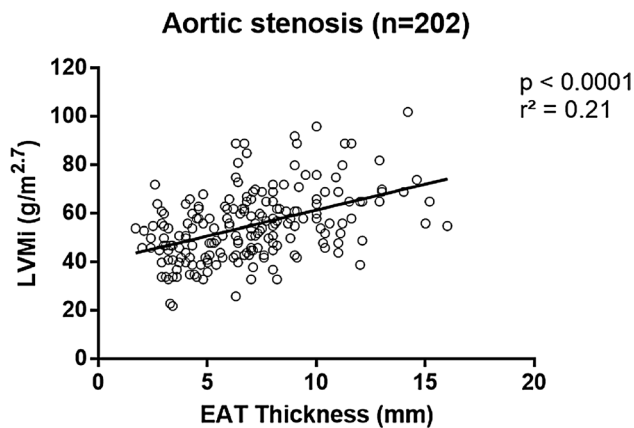
Fig. 1 Correlation between EAT amount and LV mass. r^2 and p-value by Pearson correlation and drawn line by linear regression

(29.9 ± 4.9 vs. 27.8 ± 4.6 kg/m², p = 0.002), were more frequently diabetic (46 vs. 25%, 0.002), with higher mean aortic gradient (52.0 [43.9; 63.8] vs. 50.0 [42.0; 55.1] mmHg, p = 0.01) and higher EAT thickness (8.1 ± 3.1 vs; 5.7 ± 2.4 mm, p < 0.001). This minimal difference between mean aortic gradient can be merely due to inter/intra-observer variability and suggest that other factors can impact LV remodeling in AS.

We next explored the link between EAT amount and LVMi, an index of LV remodeling magnitude. Interestingly, LVMi correlated positively with EAT thickness ($r^2 = 0.21$, p < 0.0001) (Fig. 1). This association between EAT thickness and LVMi remained significant even after adjustment for other determinants of LVMi (Table 3). Overall the results were the same whatever the normalization of the LVM (Supplemental Table 1).

To further evaluate the link between LV remodeling and EAT, we explored whether EAT amount correlated with patterns of LV remodeling.

Very few patients (20; 9.9%) displayed an absence of remodeling. 52 (25.7%) patients had concentric LV remodeling, 104 (51.5%) concentric LV hypertrophy and 26 (12.9%) eccentric LV hypertrophy. Interestingly, the magnitude of LV remodeling was associated with EAT amount (p < 0.0001 by Chi-square for trend; Fig. 2).

Thus, in addition to the association between EAT quantity and LV mass, EAT amount was associated with a more severe LV remodeling pattern in AS.

Discussion

Exploring patients suffering from severe AS, we demonstrate that EAT amount is positively correlated with the extent of LVMi and with a more pathological remodeling pattern. Importantly, this observation persisted even after adjustment for other factors associated with LV remodeling.

EAT, clinical metabolic disorders, and LV remodeling

The human heart is coated with fat, which is in direct contact with the epicardium and is a source of free fatty acids, adipokines, and inflammatory cytokines [17]. Sharing a common microcirculation with the myocardium, EAT is believed to directly interact with cardiomyocytes in both physiology and pathology through paracrine signaling. Growing evidence supports this paradigm. On the one hand, EAT amount and quality have been shown to be altered by aging and metabolic disorders associated with high incidence of cardiovascular disease (CVD) [18, 19]. On the other hand, epidemiological studies demonstrated a

Table 3 Determinants of indexed left ventricular mass normalized to height$^{2.7}$ (n = 202)

	Univariable		Multivariable	
	β ± SE	p	β ± SE	p
Gender (male)	− 1.77 ± 2.04	0.38		
Age (years)	0.10 ± 0.10	0.33		
BMI (kg/m^2)	**0.84 ± 0.20**	**< 0.0001**	0.19 ± 0.21	0.36
Diabetes mellitus n (%)	**6.26 ± 2.03**	**0.0024**	2.08 ± 1.90	0.27
Hypertension n (%)	1.57 ± 2.23	0.48		
Mean aortic gradient (mmHg)	**21.6 ± 7.8**	**0.006**	**0.20 ± 0.06**	**0.0003**
ZVA (mmHg/ml/m^2)	− 2.87 ± 8.2	0.73		
LVEF (%)	− 0.15 ± 0.11	0.17		
EAT (mm)	**2.13 ± 0.29**	**< 0.0001**	**1.74 ± 0.34**	**< 0.0001**
Euroscore II (%)	3.18 ± 3.79	0.40		

Bold value represents p < 0.05 between Low LVMi and High LVMi

p-value by t-test or linear regression in bivariate analysis. Regression coefficient, standard errors and p-value from multivariate linear regression model constructed with all variables with p < 0.10 in bivariate analysis

BMI body mass index; *EAT* epicardial adipose tissue; *LVEF* left ventricular ejection fraction; *ZVA* valvuloarterial impedance

Fig. 2 Patterns of LV remodeling according to EAT amount. Patients were divided in two groups according to EAT thickness median. p-value by Chi-square for trend
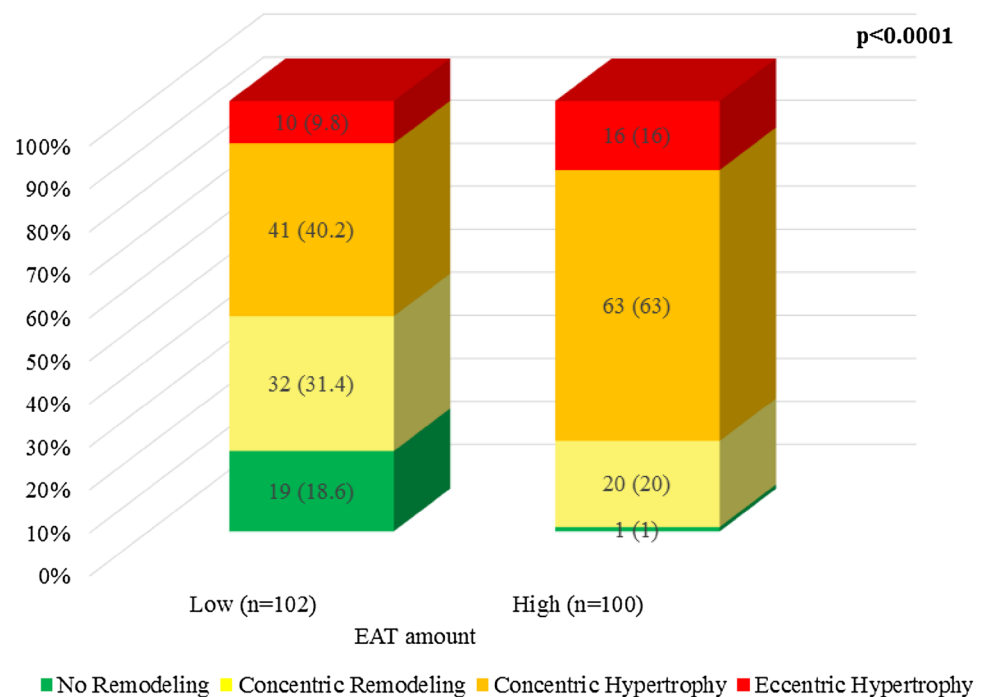
clear positive correlation between EAT volume and/or pro-inflammatory phenotype with CVD incidence and severity. Large EAT amounts, quantified by TTE [19], CT scan [20] or CMR [21], are consistently associated with severe coronary artery disease. Hirata et al. showed that infiltration of macrophages in EAT is enhanced in patients with coronary artery disease together with a shift of macrophage polarization toward a pro-inflammatory state, i.e. an increased M1/M2 macrophage ratio [22]. These results suggested that EAT

might influence atherogenesis in coronary arteries. In the same line, EAT amount and pro-inflammatory activity have been shown to be enhanced in atrial fibrillation patients [23].

Regarding EAT and cardiac remodeling, data from a few autopsy and echocardiographic studies reporting conflicting data are available. Coradi et al., exploring 117 human autopsy hearts, observed a constant ratio in each ventricle between EAT weight and muscle weight, even in presence of cardiac hypertrophy or features of ischemic cardiomyopathy

[24]. The authors thus suggested that during the hypertrophic process, EAT and the ventricles presented a parallel and correlated increase in their masses. It is to be underlined that the etiology of cardiac hypertrophy was not reported in these 60 dead patients classified as having <<hypertrophic hearts>>. Exploring 60 lean-to-obese healthy subjects, Iacobellis et al. showed a consistent positive correlation between EAT amount and LV mass [25]. Moreover, Capoulade et al. found that obesity and excess visceral adiposity (reflected by higher visceral adipose tissue/total adipose tissue ratio) were independently associated with LVH in 124 patients with AS [12]. Taken altogether, our results are consistent with Iacobellis and Capoulade findings and reinforce the concept that clinical conditions such as obesity, diabetes and aging may alter EAT, which in turn may impact the hypertrophic process in patients suffering from AS.

Perspectives

Taken together, our findings indicate that EAT amount is associated with the hypertrophic response in AS. Although the observational design of our study limits any conclusion regarding causality, evidence from basic science strongly supports a role for EAT in cardiac disorders observed in obesity and diabetes.

Yet, the precise mechanisms by which EAT and myocardium are associated in AS patients remain to be determined. Among the numerous adipokines and cytokines secreted by EAT, for only a few mechanistic data are available. Increases in TNFα, IL-10 or IL-6 or decreases in adiponectin signaling interfere with hypertrophic signaling pathways in rodent models and in vitro cardiomyocyte cultures [22]. Further exploration of the functional properties of EAT in the patients suffering from LV remodeling is required. This may open avenues for pharmacological strategies to modulate EAT activity and as such slow down the progression of LV remodeling in AS, specifically in those with obesity and diabetes.

Limitations

Our study has several limitations. First, we used a historical method (M-mode) that may have technical problems to calculate LVM compared to the more recent methods, including 3D. Second, EAT amount was estimated by measuring EAT thickness with TTE [16]. The linear measurement made with TTE on the right ventricular free wall cannot perfectly reflect the distribution and amount of EAT covering the LV. Nerlekar et al. recently found a poor correlation between EAT thickness measured by TTE and EAT area/volume measured by using cardiac computed tomography (CT) (r = 0.29) [26]. Nevertheless, the amount of EAT was low in their patients evaluated with cardiac CT for suspected coronary artery disease. In opposition, we found a good correlation between EAT thickness by TTE and total EAT volume obtained by CMR in our center. Third, we did not report biological parameters such as insulin resistance index, serum triglyceride and cholesterol. This should be done in future studies to better characterize respective effects of obesity, the metabolic syndrome and type 2 diabetes on EAT.

Conclusions

Large EAT amounts are independently associated with more pronounced and severe LV remodeling AS. These new findings combined with previous bench studies argue for EAT being a potential actor of cardiac remodeling in the context of chronic pressure overload.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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