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CLINICAL RESEARCH

Epicardial adipose tissue volume is associated with left ventricular remodelling in calcific aortic valve stenosis

Le volume de graisse épicardique est associé au remodelage ventriculaire gauche au cours du rétrécissement aortique calcifié

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KEYWORDS
Aortic valve stenosis;
Adipose tissue;

Summary
Background. — The severity of left ventricular (LV) remodelling is only partially related to the severity of aortic valve stenosis; additional factors, including diabetes, insulin resistance,

Abbreviations: BMI, body mass index; BSA, body surface area; CT, computed tomography; EAT, epicardial adipose tissue; LDL, low-density lipoprotein; LV, left ventricle/ventricular; LVMI, left ventricular mass indexed to body surface area; RWT, relative wall thickness.

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Left ventricular remodelling

obesity and metabolic syndrome, may play important roles. Epicardial adipose tissue (EAT), now considered as a metabolically active organ, is also linked to these factors.
Aim. — To analyse the association between EAT volume measured using computed tomography and LV remodelling in a prospective cohort of patients with aortic stenosis.
Methods. — Consecutive asymptomatic patients with at least mild degenerative aortic stenosis enrolled in a prospective cohort that aimed to assess the determinants of aortic stenosis occurrence and progression constituted our population.
Results. — We enrolled 143 patients (78 ± 5 years; 65% men). Mean LV mass and EAT volume were 219 ± 64 g and 134 ± 56 mL, respectively. LV hypertrophy was diagnosed in 86 patients (60%), and concentric hypertrophy (32%) was the main remodelling pattern. EAT was associated with body mass index ($P < 0.001$) and body surface area ($P < 0.001$), but not with age ($P = 0.33$) or aortic stenosis severity (all $P > 0.10$). EAT was correlated with LV mass ($r = 0.41$; $P < 0.0001$), and after adjustment for age, sex, body mass index/body surface area, hypertension, waist circumference, low-density lipoprotein cholesterol and aortic stenosis severity, EAT was independently associated with LV mass ($P = 0.01$/$P = 0.02$). Similar results were found when EAT and LV mass index (adjusted for body surface area) were considered instead of absolute values ($P = 0.04$).
Conclusions. — In this prospective cohort of patients with aortic stenosis, EAT volume was independently associated with LV mass. Further studies are warranted to elucidate the underlying mechanisms of this link.

MOTS CLÉS
Rétrécissement aortique calcifié ;
Graisse épicardique ;
Remodelage ventriculaire gauche

Résumé
Contexte. — L'amplitude du remodelage ventriculaire gauche (VG) n'est que partiellement associée à la sévérité du rétrécissement aortique calcifié (RAC). Des facteurs additionnels comme le diabète, l'obésité et le syndrome métabolique pourraient également influencer ce remodelage. La graisse épicardique (GE) est un organe métaboliquement actif, également associée à ces facteurs.
Objectif. — Notre objectif était d'analyser l'association entre volume de GE mesuré par scanner et remodelage VG.
Méthodes. — Notre population d'étude était constituée de patients consécutifs asymptomatiques, ayant un RAC au moins modéré, inclus dans une cohorte prospective visant à évaluer les déterminants de l'apparition et de la progression du RAC.
Résultats. — Parmi les 143 patients (78 ± 5 ans ; 65 % d'hommes) inclus, la masse VG et le volume de GE étaient respectivement de 219 ± 64 g et 134 ± 56 mL. Une hypertrophie VG a été diagnostiquée chez 86 patients (60 %). L'hypertrophie concentrique (32 %) était le principal type de remodelage observé. La GE était associée à l'indice de masse corporelle (IMC) ($p < 0{,}001$) et à la surface corporelle (BSA) ($p < 0{,}001$), mais ni à l'âge ($p = 0{,}33$) ni à la sévérité du RAC ($p > 0{,}10$). La GE était corrélée à la masse VG ($r = 0{,}41$; $p < 0{,}0001$) et après ajustement sur l'âge, le sexe, le rapport IMC/BSA, l'hypertension artérielle, le périmètre abdominal, le taux de LDL-cholestérol et la sévérité du RAC, la GE était indépendamment associée à la masse VG ($p = 0{,}01$/$p = 0{,}02$).
Conclusions. — Dans cette cohorte prospective de patients souffrant de RAC, le volume de GE était indépendamment associé à la masse VG. Des études complémentaires sont nécessaires pour élucider les mécanismes physiopathologiques sous-jacents.

Background

With an increasing prevalence, calcific aortic valve stenosis is the most common valvular heart disease in industrialized countries, and represents a significant economic burden [1]. The pressure overload induced by the progressive narrowing of the aortic valve is not the sole trigger for the hypertrophic response of the left ventricle (LV). Indeed, recent findings demonstrate that the severity of left ventricular (LV) hypertrophy as well as the patterns of LV hypertrophy are only partially related to aortic stenosis severity [2,3]. Additional factors, including diabetes, insulin

resistance, obesity and metabolic syndrome, have been suggested as potential factors influencing the occurrence of LV remodelling [4—6]. Interestingly, these factors have also been linked to epicardial adipose tissue (EAT) [5], which had long been considered as an inert tissue providing, at best, mechanical protection to the heart, until the demonstration of its role as a metabolically active organ, producing inflammatory cytokines and mediators [5]. In light of these findings, we hypothesized that an interaction may exist between EAT and the myocardium, leading to adverse LV remodelling. Therefore, we sought to analyse the association between computed tomography (CT)-based EAT volume quantification and LV remodelling in a prospective cohort of asymptomatic patients with aortic valve stenosis.

Methods

The study population comprised consecutive asymptomatic patients with aortic valve stenosis enrolled between January 2008 and January 2013 in an ongoing prospective cohort, COFRASA (COhorte Française de Rétrécissement Aortique du Sujet Agé). The purpose of COFRASA is the evaluation of the determinants of aortic stenosis occurrence and progression. Inclusion criteria were at least mild degenerative aortic stenosis, defined as a mean pressure gradient > 10 mmHg, whether the valve structure was bicuspid or trileaflet. Exclusion criteria were more than mild associated valvular disease, LV outflow tract obstruction, aortic stenosis secondary to rheumatic valve disease or radiotherapy, history of infective endocarditis and severe respiratory or renal insufficiency defined as a creatinine clearance $\leq$ 30 mL/min. For the present study, patients with pacemakers and/or defibrillators were excluded because of device-related artefacts occurring during CT examinations, leading to inaccurate EAT volume quantification. Patients with history of myocardial infarction were also excluded because of potential adverse LV remodelling unrelated to aortic valve stenosis. Clinical, biological and echocardiographic evaluations were performed at study entry for all patients. CT measurements were performed blinded to any clinical and echocardiographic information. All patients provided written informed consent, and the study was approved by the regional ethics committee.

Medical history, cardiovascular risk factors and medications were recorded prospectively. A complete physical examination and an electrocardiogram were performed at study entry. Weight, height, waist circumference, body surface area (BSA) and body mass index (BMI) measurements were collected. Obesity was defined as a BMI > 30 kg/m^2. According to the National Cholesterol Education Program's Adult Treatment Panel III, the presence of at least three of the following criteria defined metabolic syndrome :

- waist circumference > 102 cm in men and > 88 cm in women;
- serum triglyceride concentration $\geq$ 1.7 mmol/L;
- high-density lipoprotein cholesterol < 1.04 mmol/L in men and < 1.29 mmol/L in women;
- blood pressure $\geq$ 130/85 mmHg or taking hypertension medication;
- fasting glucose $\geq$ 5.6 mmol/L or taking diabetes mellitus medication [7].

Patients were considered asymptomatic in the absence of dyspnoea, angina and syncope.

All patients underwent comprehensive Doppler echocardiography at study entry. Two-dimensional LV cavity diameters, wall thickness and left atrial volume were measured, and LV mass was calculated using Devereux's formula [8]. LV hypertrophy was defined as a LV mass indexed to BSA (LVMI) > 115 g/m^2 in men and > 95 g/m^2 in women [8]. Diastolic measurements of LV internal diameter and posterior wall thickness, and relative wall thickness (RWT) calculated using the formula 2*posterior wall thickness/LV internal diameter, were used to distinguish four patterns of LV geometry: normal geometry (normal LVMI and an RWT $\leq$ 0.42); concentric remodelling (normal LVMI index and an RWT > 0.42); concentric hypertrophy (increased LVMI and an RWT > 0.42); and eccentric hypertrophy (increased LVMI and an RWT $\leq$ 0.42) [8]. Aortic stenosis severity assessment was based on peak velocity, mean pressure gradient and aortic valve area calculated using the continuity equation [9]. In accordance with current recommendations, mild aortic stenosis was defined as an aortic valve area between 1.5 and 2 cm^2, moderate aortic stenosis by an aortic valve area between 1 and 1.5 cm^2 and severe aortic stenosis by an aortic valve area < 1 cm^2 [9]. LV ejection fraction was assessed using the biplane Simpson method or visually, and was considered normal if $\geq$ 50%.

Cardiac CT imaging was performed at baseline using an MX 8000 IDT 16 CT scanner (Philips Medical Systems, Andover, MA, USA) or a 64-row LightSpeed VCTTM machine (GE Healthcare, Fairfield, CT, USA). A prospective electrocardiogram-triggered scanning protocol at 75% of the RR interval was performed, with contiguous non-overlapping 2.5 mm thick slices, from the right pulmonary artery to the diaphragm, without using contrast media [10]. All data were transferred to a dedicated workstation for postprocessing and image analysis (ADW 4.6; GE Medical Systems, Milwaukee, WI, USA).

EAT was defined as the adipose tissue found between the myocardium and the pericardium. The pericardium was traced manually by scrolling through the slices from the right pulmonary artery to the diaphragm by an experienced clinician blinded to patients' clinical and echocardiographic data (first author). Using a thresholding method, EAT was isolated by defining a window of −250 to −30 HU corresponding to the density of fat [10]. Total EAT volume was automatically obtained by multiplying the sum of all measured areas by the slice thickness (Fig. 1).

Continuous variables are expressed as mean $\pm$ standard deviation, median (25th percentile; 75th percentile) or number of patients (percentage). The distribution of variables was assessed using the Shapiro-Wilk normality test. As EAT volume was not normally distributed, a log transformation was used. Comparisons between quartiles of LV mass and between patterns of LV remodelling were performed using one-way analysis of variance, the χ^2 test or the Wilcoxon/Kruskal—Wallis test, as appropriate. Correlation analysis was performed using Spearman's correlation coefficient. The relationship between EAT volume and LV mass was assessed in univariate and multivariable analyses after adjustment for confounding factors, using the standard least squares fitting method. Interobserver and intraobserver variabilities were assessed using the intraclass

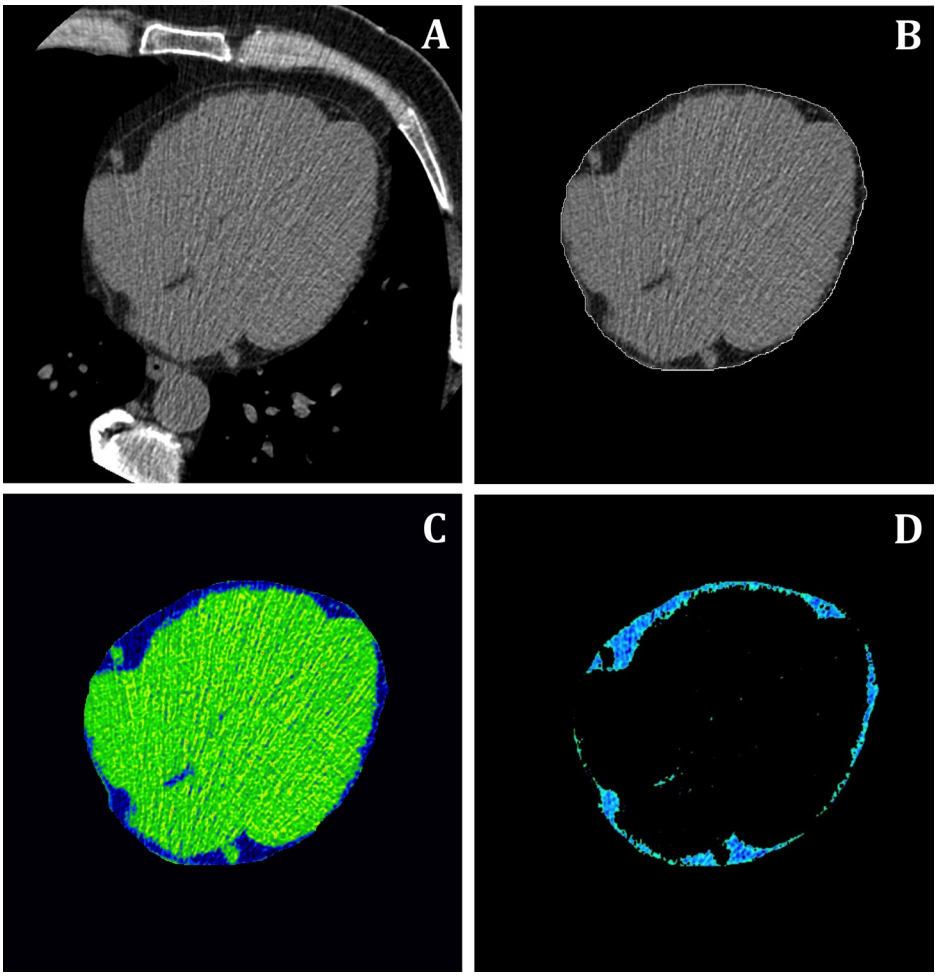

Figure 1. Quantification of epicardial adipose tissue (EAT) volume using computed tomography (CT). A. Native CT axial slice of the heart. B. Segmentation of EAT by manually tracing the pericardium. C. A colour map was used to illustrate the contrast between EAT and other cardiac structures within the pericardium. D. A threshold of −250 to −30 HU corresponding to the density of fat was applied to isolate EAT.

correlation coefficient in 20 patients selected at random. A *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using JMP 10 software (SAS institute, Cary, NC, USA).

Results

During the study period, 143 consecutive patients were enrolled prospectively. Clinical, biological, echocardiographic and CT characteristics of the population are presented in Table 1. The mean age was 78 ± 5 years, and 93 (65%) patients were male. Criteria for metabolic syndrome were met in 56 (39%) patients. Mean LV ejection fraction was 64 ± 4%, mean aortic valve area was 1.35 ± 0.38 cm^2, mean pressure gradient was 26 ± 16 mmHg and mean peak velocity was 3.2 ± 0.8 m/s; severe aortic stenosis was diagnosed in 25 (17%) patients.

Absolute LV mass was 219 ± 64 g [median 220 (172; 254) g], and LVMI was 117 ± 30 g/m^2 (median 115 (93; 138) g/m^2). LV hypertrophy was diagnosed in 86 patients (60%) and concentric hypertrophy (32%) was the main pattern of LV remodelling, followed by normal geometry (29%), eccentric hypertrophy (28%) and concentric remodelling (11%). In the univariate analysis, determinants of LV mass were mean pressure gradient ($P = 0.03$) and peak velocity ($P = 0.02$). Mean pressure gradient ($P = 0.03$) and peak velocity ($P = 0.02$) were significantly higher in patients with LV hypertrophy, and significantly different across the four different patterns of LV geometry ($P = 0.04$ and $P = 0.045$, respectively). Results are presented in Table 2. Moderate correlations were found between LV mass and aortic stenosis severity assessed by mean pressure gradient ($r = 0.25$; $P = 0.002$), peak velocity ($r = 0.26$; $P = 0.002$) or aortic valve area index ($r = -0.27$; $P = 0.001$), and between LV mass and low-density lipoprotein (LDL) cholesterol concentration ($r = -0.26$; $P = 0.002$). No correlation was found between LV mass and aortic valve area ($r = -0.05$; $P = 0.55$).

EAT volume followed a non-normal distribution ($P < 0.0001$), with a mean value of 134 ± 56 mL, and a median value of 122 (97; 162) mL. The interobserver and intraobserver agreement rates for the measurement of EAT volume were 0.943 (95% confidence interval 0.836—0.980) and 0.980 (95% confidence interval 0.947—0.993), respectively, showing excellent reproducibility.

EAT volume was significantly higher in men than in women (141 ± 56 vs. 121 ± 54 mL; $P = 0.02$) and in patients with

Table 1 Clinical, biological, echocardiographic and computed tomography characteristics according to patterns of left ventricular remodelling.

	Overall population ($n = 143$)	No LV hypertrophy ($n = 57$)	LV hypertrophy ($n = 86$)	P	Normal geometry ($n = 41$)	Concentric remodelling ($n = 16$)	Concentric hypertrophy ($n = 46$)	Eccentric hypertrophy ($n = 40$)	P
Clinical characteristics									
Age (years)	78 ± 5	77 ± 5	79 ± 6	0.09	77 ± 5	78 ± 5	79 ± 6	79 ± 5	0.35
Men	93 (65)	42 (74)	51 (59)	0.08	29 (71)	13 (81)	27 (59)	24 (60)	0.30
BMI (kg/m^2)	28 ± 5	27 ± 5	28 ± 5	0.10	27 ± 5	27 ± 4	29 ± 6	28 ± 4	0.15
BSA (m^2)	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.93	1.8 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	0.76
Waist circumference (cm)	101 ± 13	100 ± 13	102 ± 13	0.26	99 ± 14	102 ± 12	103 ± 13	102 ± 13	0.54
Hypertension	110 (77)	43 (75)	67 (78)	0.73	30 (73)	13 (81)	32 (70)	35 (88)	0.22
Diabetes mellitus	30 (21)	14 (25)	16 (19)	0.39	9 (22)	5 (31)	7 (15)	9 (23)	0.57
Hypercholesterolaemia	85 (59)	35 (61)	50 (58)	0.70	26 (63)	9 (56)	27 (59)	23 (58)	0.94
Metabolic syndrome	56 (39)	20 (35)	36 (42)	0.42	14 (34)	6 (38)	24 (52)	12 (30)	0.16
Biological characteristics									
Creatinine clearance (mL/min)	73 ± 21	73 ± 19	72 ± 23	0.46	74 ± 17	72 ± 23	71 ± 20	74 ± 24	0.88
Total cholesterol (mmol/L)	5.0 ± 1.1	4.9 ± 1.0	5.0 ± 1.2	0.59	4.9 ± 1.1	4.9 ± 1.0	5.0 ± 1.2	5.1 ± 1.2	0.91
LDL cholesterol (mmol/L)	2.8 ± 0.9	2.8 ± 0.9	2.8 ± 1.0	0.61	2.8 ± 0.9	2.7 ± 0.7	2.8 ± 1.0	2.9 ± 1.0	0.83
HDL cholesterol (mmol/L)	1.6 ± 0.5	1.6 ± 0.6	1.6 ± 0.5	0.67	1.7 ± 0.7	1.4 ± 0.5	1.5 ± 0.4	1.6 ± 0.5	0.14
Triglycerides (mmol/L)	1.3 ± 0.8	1.2 ± 0.7	1.4 ± 0.8	0.48	1.1 ± 0.5	1.6 ± 0.9	1.5 ± 1.0	1.2 ± 0.5	0.08
Echocardiographic variables									

Table 1 (*Continued*)

	Overall population ($n = 143$)	No LV hypertrophy ($n = 57$)	LV hypertrophy ($n = 86$)	*P*	Normal geometry ($n = 41$)	Concentric remodelling ($n = 16$)	Concentric hypertrophy ($n = 46$)	Eccentric hypertrophy ($n = 40$)	*P*
LV mass (g)	219 ± 64	170 ± 40	251 ± 56	< 0.0001	165 ± 42	184 ± 31	269 ± 58	231 ± 47	< 0.0001
LVMI (g/m^2)	117 ± 30	91 ± 14	135 ± 25	< 0.0001	88 ± 14	96 ± 12	144 ± 26	125 ± 19	< 0.0001
Aortic valve area (cm^2)	1.35 ± 0.38	1.39 ± 0.36	1.31 ± 0.40	0.21	1.38 ± 0.35	1.43 ± 0.39	1.26 ± 0.41	1.37 ± 0.38	0.41
Mean pressure gradient (mmHg)	26 ± 16	21 ± 7	30 ± 19	0.03	21 ± 8	20 ± 6	34 ± 23	24 ± 12	0.04
Peak velocity (m/s)	3.2 ± 0.8	2.9 ± 0.4	3.4 ± 1.0	0.02	2.9 ± 0.5	2.9 ± 0.4	3.6 ± 1.1	3.1 ± 0.7	0.045
Severe aortic stenosis	25 (17)	6 (11)	19 (23)	0.07	4 (10)	2 (13)	14 (32)	5 (13)	0.03
LV ejection fraction (%)	64 ± 4	64 ± 3	63 ± 5	0.53	65 ± 2	63 ± 4	63 ± 5	64 ± 4	0.15
CT characteristics									
EAT volume (mL)	134 ± 56	121 ± 47	142 ± 60	0.05	115 ± 45	138 ± 49	147 ± 63	136 ± 56	0.08
EAT volume index (mL/m^2)	71 ± 26	65 ± 21	76 ± 28	0.03	62 ± 20	72 ± 24	78 ± 30	73 ± 26	0.07

Data are expressed as mean ± standard deviation or number (percentage). BMI: body mass index; BSA: body surface area; CT: computed tomography; EAT: epicardial adipose tissue; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LV: left ventricle; LVMI: left ventricular mass indexed to body surface area.

Table 2 Factors associated with left ventricular mass in univariate and multivariable analysis after adjustment for age, sex, hypertension, body mass index, waist circumference, low-density lipoprotein cholesterol concentration, aortic valve mean pressure gradient and epicardial adipose tissue volume.

	P (univariate analysis)	*P* (multivariable analysis)
Age	0.45	
Sex	< 0.0001	< 0.0001
Hypertension	0.45	
BMI	< 0.0001	0.02
Waist circumference	< 0.0001	
LDL cholesterol concentration	0.001	
Aortic valve mean pressure gradient	< 0.0001	< 0.0001
EAT volume	< 0.0001	0.01

BMI: body mass index; EAT: epicardial adipose tissue; LDL: low-density lipoprotein.

metabolic syndrome (157 ± 60 vs. 119 ± 48 mL; $P = 0.001$), but did not differ between patients with severe and non-severe aortic stenosis (136 ± 72 vs. 134 ± 52 mL; $P = 0.60$). No association was found between EAT volume and hypertension ($P = 0.63$) or diabetes mellitus ($P = 0.20$). Moderately strong correlations with BSA ($r = 0.50$; $P < 0.0001$), BMI ($r = 0.52$; $P < 0.0001$) and waist circumference ($r = 0.59$; $P < 0.0001$) were found, but there was no correlation with age ($r = -0.08$; $P = 0.33$). EAT volume was weakly correlated with the concentration of triglycerides ($r = 0.35$; $P < 0.0001$), and was not correlated with creatinine clearance ($r = -0.01$; $P = 0.89$) or LDL cholesterol concentration ($r = -0.03$; $P = 0.70$). No correlation was found between EAT volume and echocardiographic parameters of aortic stenosis severity, assessed by aortic valve area ($r = 0.03$; $P = 0.76$), mean pressure gradient ($r = 0.10$; $P = 0.23$) or peak velocity ($r = 0.12$; $P = 0.16$).

EAT volume was greater in patients with than without LV hypertrophy (142 ± 60 vs 121 ± 47 mL; $P = 0.05$; Fig. 3A), and a positive correlation between LV mass and EAT volume was observed ($r = 0.41$; $P < 0.0001$) (Fig. 2). In the univariate analysis, EAT volume was associated with LV mass ($P = 0.04$). In the multivariable analysis, after adjustment for age, sex, hypertension, BMI, waist circumference, LDL cholesterol concentration and mean pressure gradient, EAT volume was independently associated with LV mass ($P = 0.01$). Replacing mean pressure gradient with aortic valve area ($P = 0.002$) or BMI with BSA ($P = 0.02$) in the multivariable model did not influence the result (Table 2). Using LVMI and EAT volume index instead of absolute values did not affect our conclusions in the multivariable analysis ($P = 0.04$). An independent association between EAT volume and LV mass was observed in the multivariable analysis in the subgroup of patients with moderate and severe aortic stenosis ($P = 0.02$). There was a strong trend towards an association between the pattern of LV remodelling and EAT volume ($P = 0.08$) (Table 1 and Fig. 3B).

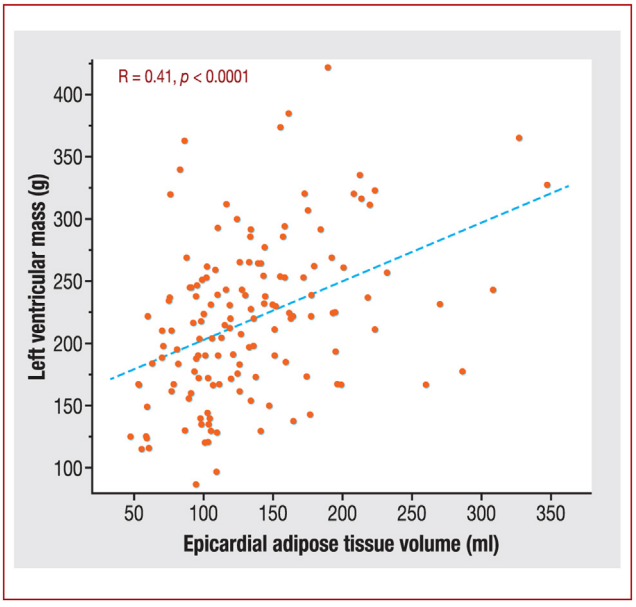

Figure 2. Correlation between left ventricular mass and epicardial adipose tissue volume.

Discussion

In this prospective cohort of asymptomatic patients with at least mild aortic valve stenosis, we found that EAT volume was independently associated with LV mass. CT-based EAT volume quantification was highly reproducible, with excellent intraobserver and interobserver variability.

Only a handful of studies have focused on the role of EAT in the pathophysiology of aortic valve stenosis. Parisi et al. hypothesized that EAT may participate in the inflammatory burden of aortic stenosis [11]. Capoulade et al. found that increased total adiposity and CT-measured abdominal visceral adipose tissue was associated with LV hypertrophy in patients with aortic stenosis [12]. This result corroborates our findings, as EAT originates from splanchnopleuric mesoderm, and shares a common embryologic origin with mesenteric and omental fat, while paracardial fat is a different entity, situated within the mediastinum, and originating from primitive thoracic mesenchymal cells [5]. Mahabadi et al. found that EAT thickness, quantified using transthoracic echocardiography, was significantly associated with severe aortic stenosis, independent of traditional risk factors [13]. In contrast, our results did not show any association between CT-based measurement of EAT volume and

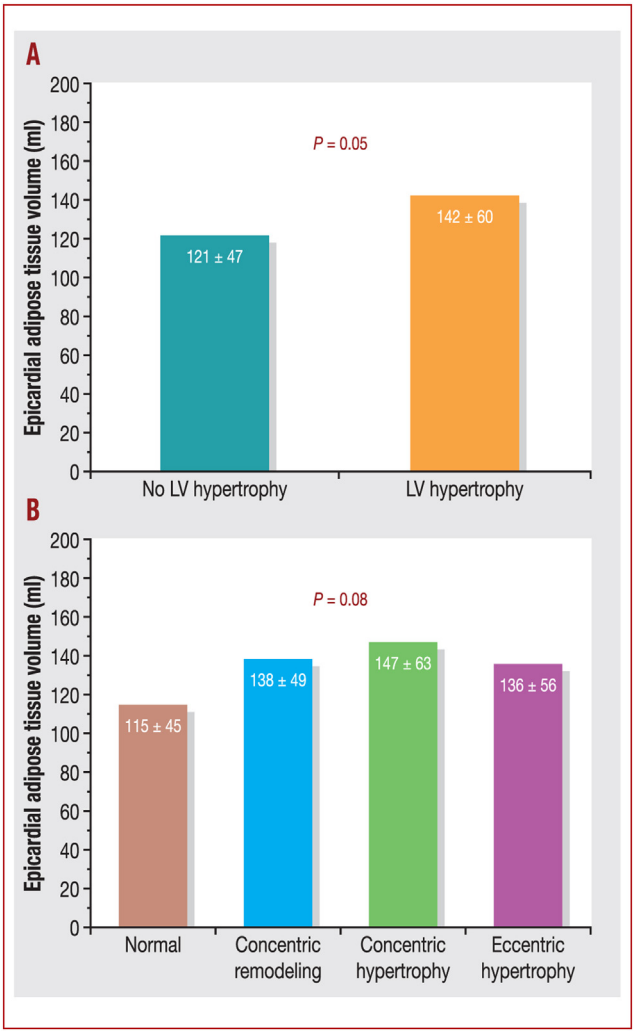

Figure 3. A. Epicardial adipose tissue (EAT) volume according to the presence or absence of left ventricular (LV) hypertrophy. B. EAT volume according to patterns of LV remodelling.

echocardiographic parameters of aortic stenosis severity. In a recent publication, Coisne et al. showed that EAT thickness measured perpendicularly to the free wall of the right ventricle in the echocardiographic parasternal long-axis view was independently associated with increased LV remodelling in aortic stenosis [14]. We have confirmed and extended this result by measuring EAT volume using CT, which is the gold standard technique for the evaluation of EAT.

Highlighting the anatomical characteristics of EAT is essential to understand its interaction with the myocardium. Under normal conditions, EAT is mainly found in the interventricular and atrioventricular grooves, extending to the apex, and to a lesser extent in the subepicardial region of appendages and within the free walls of the atria, with a minor, but non-negligible, amount of EAT expanding into the myocardium [5]. It is important to emphasize that there is no structure, such as a fascia, between EAT and the myocardium, and this proximity has prompted major questions in recent years about a potential interaction between these two components. In a population of elderly women with lifestyle-related diseases and preserved ejection fraction, Watanabe et al. found a significant relationship between EAT thickness and early impairment of LV systolic function [15]. EAT volume has also been associated with impaired diastolic function [16]. The nature of the interaction between EAT and the myocardium is still only partially understood, and the main hypothesis is that EAT may increase the local inflammatory burden as it secretes cytokines and chemokines. The inflammatory role of EAT has been more widely studied in coronary artery disease, and most studies suggest that it may participate in the progression of coronary artery disease through local inflammatory mechanisms [17]. Thus, EAT has been associated with coronary and vascular calcifications [18], coronary atherosclerosis progression [19,20] and coronary events, independent of traditional cardiovascular risk factors [21]. Aortic stenosis and coronary atherosclerosis share common risk factors, such as smoking, hypertension, diabetes and increased concentrations of LDL cholesterol and lipoprotein(a) [22–24]. While previous publications have suggested that inflammation and atherogenesis may intervene in the process of valve calcification [25], we hypothesize that it may also have a local effect on the development of adverse LV remodelling.

During the initial phase of the natural history of aortic stenosis, LV hypertrophy proves beneficial, restoring wall stress and maintaining cardiac output, but eventually leads to maladaptive LV remodelling associated with a poor prognosis [2,26]. Therefore, the magnitude of LV remodelling may be an interesting component to consider when determining the timing of intervention, and identifying the determinants of adverse LV remodelling in patients with aortic stenosis is an essential task. In a population of patients with moderate-to-severe aortic stenosis, Dweck et al. demonstrated that the severity of LV hypertrophy and the patterns of LV adaptation assessed by cardiac magnetic resonance imaging were not correlated with aortic stenosis severity [3]. These results are consistent with previous publications [27], and suggest that unidentified factors may contribute to LV remodelling. Given that LV hypertrophy is associated with an adverse prognosis [28], identifying these factors is also an important goal. In our study, we found that EAT may be one of these factors, as a statistically significant association between EAT volume and LV remodelling remained after adjustment for known variables linked to LV hypertrophy, namely aortic stenosis severity and hypertension, leading to the hypothesis that adverse LV remodelling in aortic stenosis may not be the sole consequence of increased afterload. Furthermore, we observed a trend ($P = 0.08$) suggesting that EAT volume may influence the pattern of LV remodelling, especially towards concentric hypertrophy. However, statistical significance was not reached, and it is likely that our study lacked sufficient power to clarify this particular point.

Our findings may have important clinical implications. In past publications, LV hypertrophy has been associated with an increased risk of cardiac events in the population of patients with aortic stenosis [26,29], and an increased risk of mortality following aortic valve replacement [30]. Consequently, EAT volume may represent a prognostic factor that could affect disease progression by accelerating and/or worsening adverse LV remodelling in patients with aortic valve stenosis. In the ASTRONOMER trial, metabolic syndrome and insulin resistance were associated with an

increased prevalence of concentric LV hypertrophy and faster progression of LV hypertrophy [4,6]. An association between type 2 diabetes and LV hypertrophy and dysfunction in patients with severe aortic stenosis was also reported [31]. These publications strengthen the hypothesis that therapeutic interventions aiming to reduce EAT volume may represent a window of opportunity to reduce adverse LV remodelling, and therefore delay the timing of intervention.

Integrating CT-based EAT volume assessment into everyday practice is not an arduous task, as it is an accurate, fast, highly reproducible and easily available technique [10]. The imaging protocol does not require any intravenous contrast media administration, and only exposes patients to a very low radiation dose, as EAT volume can be measured on low-dose acquisitions performed for aortic valve calcium scoring assessment [10]. Nevertheless, it is worth emphasizing that, so far, no consensus has been reached on the normal range of EAT volume, and that magnetic resonance imaging and echocardiography have also been proposed to quantify EAT [10]. Transthoracic echocardiography is the front-line exploration imaging modality for aortic stenosis, particularly in patients with mild or moderate disease. It is the most widely available and least expensive technique. EAT thickness is measured using the echocardiographic parasternal long- and short-axis views at end-systole, at the level of right ventricular free wall [10,32]. This approach only allows a partial, linear and two-dimensional measurement of epicardial fat, which is a three-dimensional structure, and distinguishing epicardial and pericardial fat may prove difficult as echocardiography may overestimate EAT volume [33]. In contrast, CT allows sharp EAT volumetric measurement and precise discrimination between pericardial and epicardial fat with higher spatial resolution [10]. Furthermore, the intraobserver and interobserver variabilities of echocardiographic measurements have been shown to be poorer compared with CT [10,32].

Study limitations

Several limitations have to be considered. First, this was a single-centre study with a relatively small population, but it was a proof of concept study. Second, significant overlap of EAT values across LV remodelling categories was observed and, although statistically significant, correlation analysis was far from perfect, suggesting that additional factors influencing LV remodelling indubitably exist. Third, as this was a retrospective study, echocardiographic examinations specifically aimed at measuring epicardial fat thickness were not performed. Finally, we did not analyse the prognostic value of EAT volume in our population. Therefore, further studies on larger populations are required to confirm our results, and to assess the prognostic value of EAT in aortic valve stenosis.

Conclusions

In this prospective cohort of patients with at least mild degenerative aortic valve stenosis, EAT volume was independently associated with adverse LV remodelling. Further studies are warranted to confirm these findings, and to understand the pathophysiological mechanisms and nature of the interaction between EAT and the LV myocardium in patients with aortic valve stenosis.

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Disclosure of interest

The authors declare that they have no competing interest.

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