ORIGINAL RESEARCH

Quantification of Cardiac Adipose Tissue in Failing and Nonfailing Human Myocardium

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BACKGROUND: Because body mass index (BMI) is generally used clinically to define obesity and to estimate body adiposity, BMI likely is positively correlated with epicardial adipose tissue (EAT) level. Based on echocardiography, previous outcomes on this matter have varied from almost absent to rather strong correlations between BMI and EAT. The purpose of our study was to unambiguously examine EAT content and determine if correlations exist between EAT content and BMI, cause of heart failure, or contractile force.

METHODS AND RESULTS: We qualitatively scored 150 human hearts ex vivo on EAT distribution. From each heart, multiple photographs of the heart were taken, and both atrial and ventricular adipose tissue levels were semiquantitatively scored. Main findings include a generally higher EAT content on nonfailing hearts compared with end-stage failing hearts (atrial adipose tissue level 5.70 ± 0.13 vs. 5.00 ± 0.12, $P<0.001$; ventricular adipose tissue level 5.14 ± 0.16 vs. 4.57 ± 0.12, $P=0.0048$). The results also suggest that EAT quantity is not strongly correlated with BMI in nonfailing (atrial adipose tissue level $r=0.069$, ventricular adipose tissue level $r=0.14$) or failing (atrial adipose tissue level $r=-0.022$, ventricular adipose tissue level $r=0.051$) hearts. Atrial EAT is closely correlated with ventricular EAT in both nonfailing ($r=0.92$, $P<0.001$) and failing ($r=0.87$, $P<0.001$) hearts.

CONCLUSIONS: EAT volume appears to be inversely proportional to severity of or length of time with heart failure based on our findings. Based on a lack of correlation with BMI, it is incorrect to assume high EAT volume given high body fat percentage.

Key Words: BMI ■ cardiomyopathy ■ heart failure ■ obesity ■ pathogenesis

eart failure is the leading cause of death globally, with the number of affected individuals expected to increase by 46% by 2030.[1–3] Risk factors for heart failure include, but are not limited to, coronary artery disease, diabetes, high blood pressure, and obesity. Independently, obesity is a worldwide epidemic. As of 2018, 42.4% of adults in the United States were obese.[4] As of 2021, the number of US states that reported at least 35% of residents were obese has nearly doubled since 2018.[5]

Obesity is diagnosed and categorized according to body mass index (BMI, kg/m^2), with 25.0 to 29.9 being overweight and a BMI >30 being obese. Individuals with obesity have an increased amount of adipose tissue, with an accumulation of adipose tissue in certain areas of the body. Accumulation of adipose tissue in the abdominal region is linked to comorbidities and all-cause mortality, whereas an accumulation of adipose tissue in the lower region of the body is linked with a decrease in cardiovascular disease after adjustment for total body fat mass.[6,7] One of the most prominent characteristics of the human heart at first glance is the thickness and breadth of adipose tissue covering the epicardium (epicardial adipose tissue [EAT]; intrapericardial fat layer in direct contact with myocardium). However, the relationship between obesity and EAT quantity is controversial.

The body of literature surrounding EAT is growing. Many recent studies have described relationships between EAT and clinically relevant topics including, but

What Is New?

- A subjective quantification system of cardiac adipose tissue was established by visual examination of multiangle human cardiac photographs to yield an overall adipose tissue score.
- Correlation analyses of the adipose tissue score and physiologic parameters revealed the amount of adipose tissue content is not strongly correlated with body mass index, and atrial adipose tissue score is significantly correlated with ventricular adipose tissue score in end-stage failing and nonfailing human hearts.
- Nonfailing human hearts have higher adipose tissue content compared with end-stage failing hearts.

What Are the Clinical Implications?

- Lower adipose tissue score for end-stage failing hearts supports the hypothesis that failing myocardium is shifted toward a lipid-focused metabolism compared with nonfailing counterparts.
- Reduced epicardial adipose tissue in patients with heart failure potentially poses a threat of reduced energy availability to the myocardium as fat content decreases over time and presents a prognostic index considering epicardial fat content directly proportional to severity of and/ or length of time with heart failure.
- Lack of correlation of adipose tissue score with body mass index suggests an assumption of high epicardial fat content based on metrics of obesity are not appropriate.

Nonstandard Abbreviations and Acronyms

AATS	atrial adipose tissue score
ATS	adipose tissue score
EAT	epicardial adipose tissue
VATS	ventricular adipose tissue score

not limited to inflammation,[8] atherosclerosis,[9] acute coronary events,[10] and significantly with arrhythmia[11–13] and diabetes.[14–16] It has been reported that EAT deposition (as thickness or volume) is strongly correlated with obesity.[17–19] However, noninvasive methods of quantification of EAT, such as echocardiography, have the disadvantage of subjectivity, as it is hard to distinguish adipose tissue from nonadipose tissue over the entire organ. In addition, some studies have quantified EAT as assessment of the thickness of EAT in a specific location,[20] whereas the distribution of EAT may not be uniform, and thus a single location may

not necessarily reflect the overall EAT of a subject. For the past decade, we have studied contractile function in isolated myocardium muscle preparations from the right ventricle and left ventricle, and while obtaining these human hearts for dissection, we noticed human hearts widely vary in EAT content. Upon visual examination of the ex vivo heart we observed EAT content ranging from small trace amounts running along the length of the coronary arteries (pericoronary fat) to being nearly completely encased.

Our goal in this study was to subjectively quantify EAT by visual examination of cardiac photographs from our organ collections and measure correlations of EAT content with BMI, cause of heart failure (ischemic vs nonischemic), and myocardial contractility. Our methodology for quantifying EAT yields a single score for atrial adipose tissue and ventricular adipose tissue that combines the thickness of EAT as well as the percentage of the heart that is covered with EAT.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. End-stage failing hearts were acquired from patients undergoing cardiac transplantation at The Ohio State University Wexner Medical Center. Informed consent was obtained from the cardiac transplant patients. Nonfailing hearts were acquired from organ donors through the Lifeline of Ohio Organ Procurement organization (LOOP). These hearts are retrieved from organ donors whose hearts do not match the inclusion criteria for transplantation, or whose hearts do meet criteria, but a matching recipient was not identified. Exclusion criteria for transplantation includes cardiac abnormalities, infection with HIV, suspected intravenous drug use, age, a history of hypertension with visible impact on the heart, or current noncardiac inflammation. Per research guidelines, hearts were not retrieved nor included in the study from donors deemed "high risk" from infection with HIV, suspected intravenous drug use, or other behaviors putting the patient at risk for HIV. All human tissue experiments were approved by the Institutional Review Board of The Ohio State University and in accordance with the Declaration of Helsinki.

Hearts were procured and handled identically regardless of their source. Hearts were retrieved directly in the operating room, and the coronary arteries were flushed immediately with cold cardioplegic solution (in mM; 110 NaCl, 16 KCl, 16 MgCl$_2$, 10 NaHCO$_3$, and 0.5 CaCl$_2$; pH 7.4) and thereafter transferred to the laboratory in cold cardioplegic solution. The cardioplegic solution was stored on ice until time of use. After flushing of the arteries, the heart was transported to the laboratory in clean cold cardioplegic solution inside a cooler. The

left ventricle of the heart was transferred to cold modified Krebs–Henseleit solution containing 2,3-butanedione monoxime. Photographs from multiple angles were captured of every heart, including cross-sections of the atria and ventricles. The hearts were weighed, and several dimensions of the heart were recorded (whole heart width, height, and overall base diameter; diameter of aorta, aortic valve, pulmonary artery, tricuspid valve, and mitral valve; wall and adipose tissue thickness).

In order to test contractile performance of myocardial tissue, thin, linear trabeculae were isolated from the left and/or right ventricle of each heart with the use of a stereo dissection microscope.[21,22] Trabeculae were transferred to custom-made setups to measure the force and kinetics of the muscle at 1 Hz. The setup contained circulating Krebs–Henseleit solution (with omission of 2,3-butanedione monoxime) at 37 °C. Calcium (1 M $CaCl_2$) was slowly added to the solution to reach 2 mM. Trabeculae were gradually stretched to reach optimal length and the force and kinetics of the muscles were recorded upon stabilization.

A 3-part adipose tissue scoring system was developed to score all hearts based on the distribution and thickness of the adipose tissue on the atria and ventricles. The hearts were given a score between 0 and 7 for the approximate adipose tissue distribution or coverage (Table 1) across either the atria or ventricles. A lower score correlates with less adipose tissue coverage. The hearts were also scored between 0 and 3 for the thickness (Table 2) of the adipose tissue, if applicable. The distribution and thickness scores are incorporated into an overall atrial adipose tissue score (AATS) and a ventricular adipose tissue score (VATS) as shown in Table 3. Figure 1 shows examples of human hearts with a low, medium, and high ATS. Scoring individuals (n=11) assigned each heart an AATS and VATS based on the multidimensional photographs. The 11 individuals who scored the hearts typically assist in the logistical procurement of human hearts. They were trained to score by examining test pictures, in which they were told what was deemed a very

Table 1. Adipose Distribution Determination for Adipose Tissue Score

Adipose distribution	
0	0%
1	1%–15%
2	15%–30%
3	30%–45%
4	45%–60%
5	60%–75%
6	75%–90%
7	90%–100%

The table is issued to determine the percentage of the heart (atria and ventricle) that is covered with adipose tissue.

Table 2. Adipose Thickness Determination for Adipose Tissue Score

Adipose thickness	
0	NA
1	Low
2	Medium
3	High

The thickness of the adipose tissue is separated into 4 categories (NA/ not applicable, low, medium, and high). Each category corresponds with a number (0–4).

lean heart (score 1), a heart with a very large amount of adipose tissue (score 7), and a few in between. Thereafter, they were asked to score all 150 hearts in 1 scoring session taking into account the criteria in Tables 1 and 2. The individuals were blinded to the biometric data of the heart, that is, they had no knowledge of disease state, age, sex, BMI, etc. The scores were averaged for each heart and were used for correlation analyses. The advantage of this scoring system is that it can be done by taking a few photographs (takes a few seconds) at the time of procurement and the semiquantitative analysis can be done later. The hearts are thereafter immediately used for physiological, histological, and biochemical studies and as such need to be processed rapidly to ensure viability of the tissue for live tissue experimentation. It is simply not feasible to physically dissect all the adipose tissue and quantify exactly by weighing, as this would take a long time (possible upwards of an hour) and would negatively interfere with many planned experiments on this tissue. An analysis of the individual scores allowed us to test reproducibility of the scoring system; on the 7-point scale, the average SD of the score of the 11 individuals who scored the hearts was less than 1 point. Overall, the average SD of an individual who scored compared with overall average was less than 0.5 points.

A total of 150 human hearts (nonfailing n=66; end-stage failing n=84; Table 4) were included and scored by 11 individuals. Lifeline of Ohio Organ Procurement hearts that had a history of cardiac conditions or were suspected to have cardiac conditions upon review were excluded from the study. Failing hearts include ischemic and nonischemic etiologies, as diagnosed and stated in the patients' medical history. Failing hearts that were diagnosed with both ischemic and nonischemic cardiomyopathy were excluded from the study. The youngest patient with heart failure was 19 years of age, the oldest heart was from a 70-year-old patient. The youngest nonfailing heart was of a 19-year-old, the oldest from a 72-year-old individual (average ages shown in Table 4).

Statistical Analysis

An unpaired *t* test, 2 tailed, with 95% CI was used to determine the significance of difference between 2

Table 3. Adipose Tissue Score Determination

Adipose tissue score		
Adipose distribution	Adipose thickness	Score
0%	0	0
1%–15%	0, 1, 2	1
1%–15%	3	2
15%–30%	0, 1, 2	2
15%–30%	3	3
30%–45%	0, 1, 2	3
30%–45%	3	4
45%–60%	0, 1, 2	4
45%–60%	3	5
60%–75%	0, 1, 2	5
60%–75%	3	6
75%–90%	0, 1, 2, 3	6
90%–100%	3	7

The percentage of adipose tissue distribution and the adipose tissue thickness score are used in conjunction to determine the overall adipose tissue score (ATS) for the atria (AATS) and ventricle (VATS).

groups. Normality of distribution was verified. A paired *t* test, 2 tailed, with 95% CI was used to determine the significance of difference between the VATS and AATS. Pearson correlation was used to determine if a correlation was present between 2 variables. A Pearson correlation coefficient (r) above 0.5 was considered a strong correlation. Because we have more parameters on each subject (ie, such as race or ethnicity), but a few data points for some subjects were missing, we opted to test a limited number of variables rather than test a multivariable model to avoid having to exclude subjects' data sets where there was valuable information for almost all parameters on the main interest in our study. GraphPad Prism 9 was used for graphing and statistical analyses. The authors have full access to all data in the study and take responsibility for data integrity and analysis.

RESULTS

The main goal of this study was to determine whether a correlation is present between the BMI and the amount of cardiac adipose tissue in failing and nonfailing human hearts. The impact of the cause of heart failure (ischemic vs. nonischemic cardiomyopathy) on the correlation between BMI and ATS was also investigated. Finally, the developed tension (in mN/mm^2) of trabeculae isolated from the hearts was also compared with the ATS.

In total, 150 total human hearts were scored with the ATS system by 11 individuals. Both nonfailing hearts (n=66) and end-stage failing hearts (n=84)
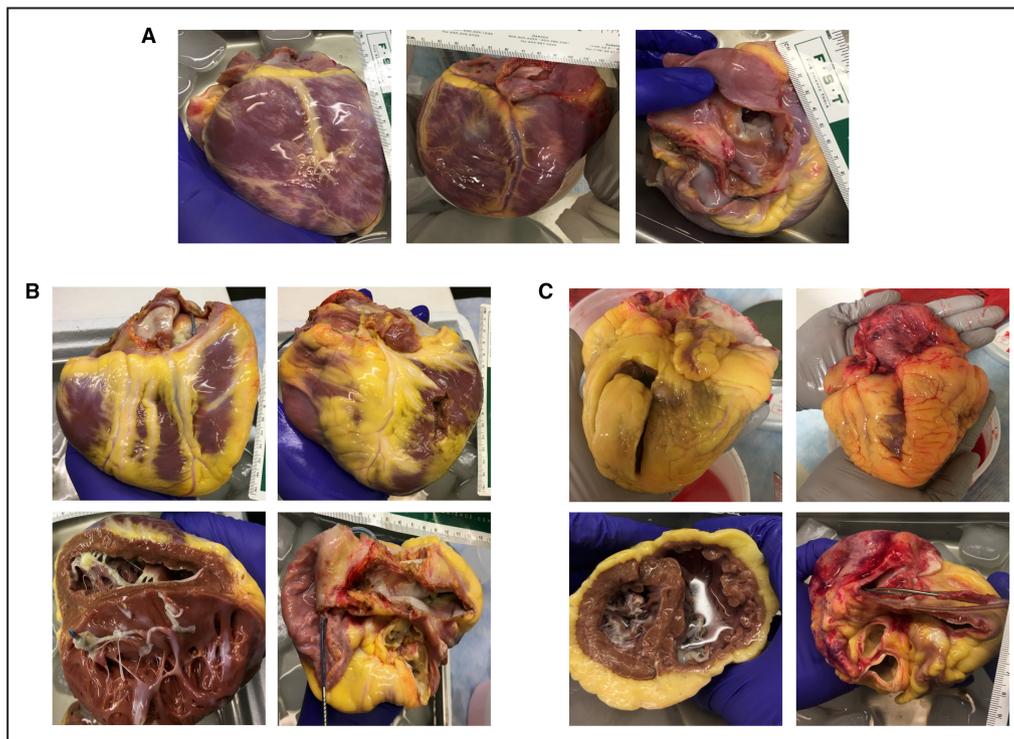

Figure 1. **Examples of human hearts with a low, average, and high adipose tissue score.**
A, Example of human heart with a low AATS and VATS. **B**, Example of a human heart with an average AATS and VATS. **C**, Example of a human heart with a high AATS and VATS. AATS indicates atrial adipose tissue score; and VATS, ventricular adipose tissue score.

Table 4. Characteristics of Nonfailing and Failing Hearts

Pathogenesis	Men (n)	Women (n)	Mean age (Years±SD)
Nonfailing	28	38	46.2±14.8
Failing	60	24	54.9±10.5

Nonfailing hearts were retrieved from organ donors via Lifeline of Ohio Organ Procurement. The hearts were unable to be placed for cardiac transplantation. End-stage failing hearts were retrieved from patients undergoing cardiac transplantation at The Ohio State University Wexner Medical Center.

were included. Averages, SD, and SEM were calculated from the scores. Figure 2 shows the distribution of AATS (Figure 2A) and VATS (Figure 2B) for all nonfailing and failing hearts. Remarkably, the nonfailing hearts had a significantly higher AATS compared with failing hearts (5.70±0.13 vs. 5.00±0.12, $P<0.001$, unpaired t test) and also has a significantly higher VATS (5.14±0.16 vs. 4.57±0.12, $P=0.0048$, unpaired t test). When comparing ventricular versus atrial scores, both in the nonfailing and the failing hearts, the atrial score was significantly higher than the ventricular score ($P<0.001$, paired t test). There was no significant difference between women and men in the AATS (respectively, nonfailing: 6.02±0.15 vs. 5.85±0.16, $P=0.42$, and failing: 5.43±0.18 vs. 5.23±0.12, $P=0.35$). Interestingly, although there was no significant difference between women and men in the VATS for the nonfailing hearts (5.33±0.20 vs. 4.97±0.20), women had a significantly higher VATS compared with men (5.24±0.11 vs. 4.63±0.13, $P=0.005$) in the failing hearts.
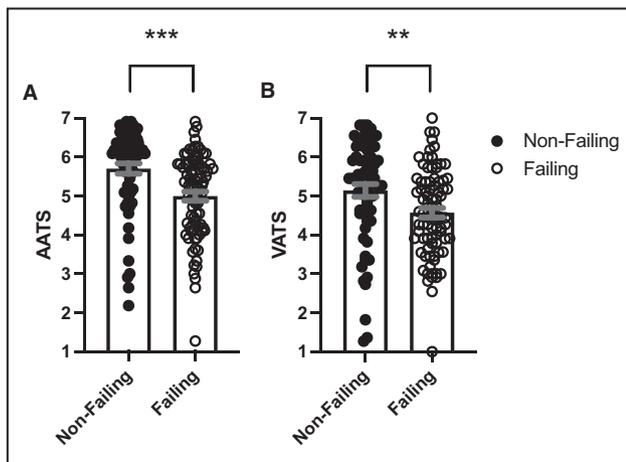
Figure 2. Distribution of AATS and VATS for all nonfailing and failing hearts.
A, Distribution of AATS in nonfailing (n=66; 5.70±0.13 SEM, *** indicates $P<0.001$, unpaired t test) and failing (n=84; 5.00±0.12 SEM) hearts. **B**, Distribution of VATS in nonfailing (n=66; 5.14±0.16 SEM, ** indicates $P<0.01$, unpaired t test) and failing (n=84; 4.57±0.12 SEM) hearts. The average ATS score for each heart was used. The failing category includes both nonischemic and ischemic hearts, unless noted otherwise. AATS indicates atrial adipose tissue score; and VATS, ventricular adipose tissue score.

A strong correlation was present between AATS and VATS for both nonfailing and failing human hearts. Nonfailing hearts ($r=0.92$) have a slightly stronger correlation between AATS and VATS compared with failing hearts ($r=0.87$; Figure 3A). Failing category such as nonischemic and ischemic cardiomyopathy plays only a minor role in affecting the correlation. Nonischemic hearts ($r=0.87$) had a slightly stronger correlation between AATS and VATS compared with ischemic hearts ($r=0.85$; Figure 3B).

As shown in Figure 4A, there is no correlation between BMI and AATS in nonfailing ($r=0.069$) and failing ($r=−0.022$) human hearts. There is also no correlation present between BMI and VATS in nonfailing ($r=0.14$) and failing ($r=0.051$) human hearts (Figure 4B). Pathogenesis of the end-stage failing heart, in this study distinguished between ischemic and nonischemic cardiomyopathy, does not affect the correlation between BMI and VATS or AATS. As shown in Figure 4C, there is no correlation between BMI and AATS in nonischemic ($r=−0.026$) nor in ischemic ($r=−0.0040$) human hearts. Similarly, there is not a correlation present between BMI and VATS in nonischemic ($r=0.014$) nor ischemic ($r=0.22$) human hearts (Figure 4D).

As shown in Figure 5, heart weight and body mass of the donors do not have a strong correlation with the ATS of failing hearts. Although there is no correlation between AATS (Figure 5A; $r=0.058$ nonischemic, $r=0.017$ ischemic) or VATS (Figure 5B; $r=0.064$ nonischemic, $r=0.18$ ischemic) and heart weights, the data do suggest that large hearts (>800 g) have high ATS but smaller hearts (<500 g) do not always have low ATS. This holds true for both AATS and VATS (Figure 5A and Figure 5B, respectively). There is also no correlation seen between AATS (Figure 5C; $r=0.060$ nonischemic, $r=0.19$ ischemic) or VATS (Figure 5D; $r=−0.025$ nonischemic, $r=0.15$ ischemic) and body mass. However, as similarly seen with heart weights, the patients with greater body mass tend to have overall slightly higher AATS and VATS, but those with lower body masses do not always have low scores. There is a strong correlation between ATS and age in nonfailing hearts (AATS Figure 5E, $r=0.55$, $P<0.001$; VATS Figure 5F, $r=0.54$, $P<0.001$). A slight correlation is indicated between AATS and age in failing hearts, but no correlation is indicated between age and VATS in failing hearts (AATS Figure 5E, $r=0.23$, $P=0.034$; VATS Figure 5F, $r=0.20$).

Although there is a significant difference seen in developed tension under resting conditions (1 Hz) of trabeculae isolated from nonfailing and failing hearts (Figure 6A; 17.0±1.5 vs. 12.4±1.2, $P<0.05$, unpaired t test), the adipose tissue scores do not correlate with the developed tension under the same conditions (Figure 6B and Figure 6C). As shown in Figure 6B, no correlation is present between AATS and developed tension of nonfailing ($r=−0.081$) and failing ($r=−0.063$)
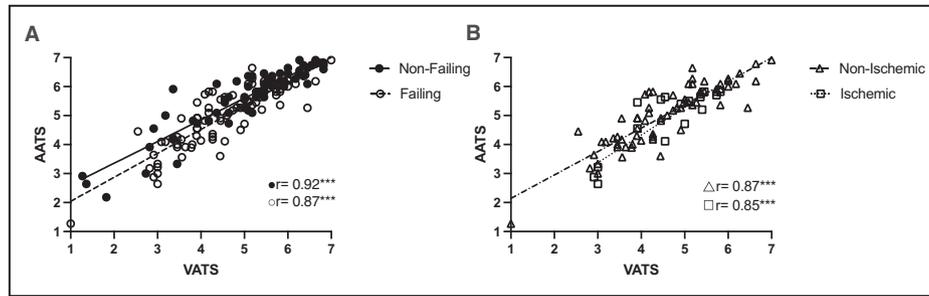
Figure 3. **Correlations of ATS for nonfailing and failing hearts.**
A, Correlation of AATS with VATS of nonfailing (n=66; *r*=0.92) and failing (n=84; *r*=0.87) hearts.
B, Correlation of AATS with VATS of nonischemic (n=68; *r*=0.87) and ischemic (n=16; *r*=0.85).
Pearson correlation was used to measure the linear relationship between AATS and VATS. ***
denotes *P*<0.001. The average ATS score for each heart was used. The failing category includes
both nonischemic and ischemic hearts, unless noted otherwise. AATS indicates atrial adipose
tissue score; ATS, adipose tissue score; and VATS, ventricular adipose tissue score.

hearts. There is also no correlation present between VATS and developed tension of nonfailing (*r*=−0.15) and failing (*r*=−0.027) hearts (Figure 6C).

DISCUSSION

This semiquantitative study was primarily designed to correlate the amount of EAT with disease status and BMI. Based on our analyses of EAT visual discrimination by the ATS system, our results demonstrate several main findings. The first is that nonfailing hearts had significantly more EAT than failing hearts. The second main observation is that there is more EAT in the atrial area than in the ventricular area, and this is true for both nonfailing and failing hearts. Third, EAT did not correlate with BMI, nor was EAT different between
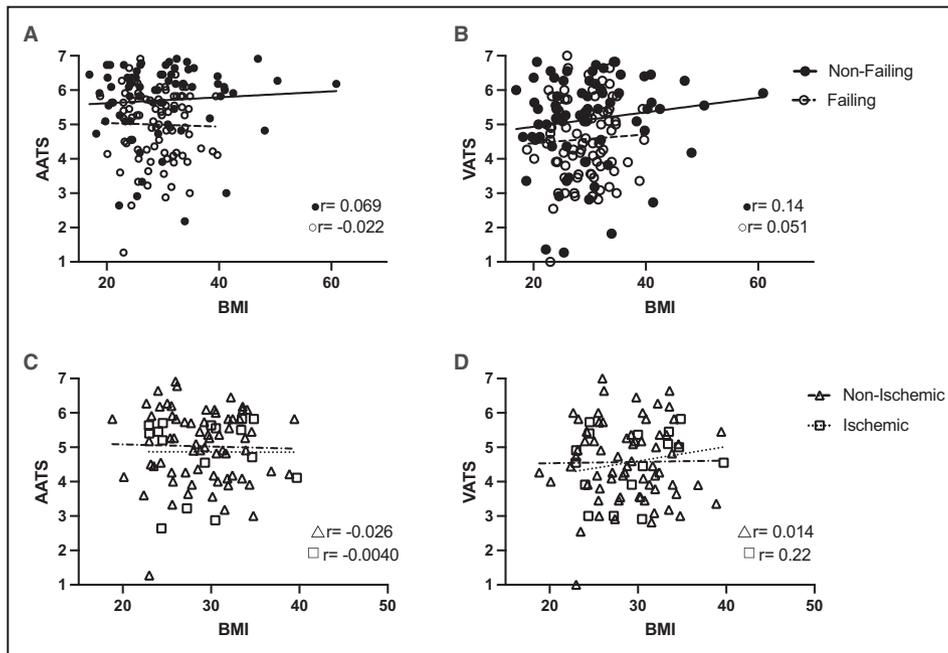

Figure 4. **Correlations of ATS with body mass index.**
A, Correlation of AATS with body mass index (BMI, kg/m^2) of nonfailing (n=66; *r*=0.069) and failing (n=84; *r*=−0.022) hearts. **B**, Correlation of VATS with BMI of nonfailing (n=66; *r*=0.14) and failing (n=84; *r*=0.051) hearts. **C**, Correlation of AATS with BMI of nonischemic (n=68; *r*=−0.026) and ischemic (n=16; *r*=−0.0040) failing hearts. **D**, Correlation of VATS with BMI of nonischemic (n=68; *r*=0.014) and ischemic (n=16; *r*=0.22) failing hearts. Pearson correlation was used to measure the linear relationship between ATS and BMI. The average ATS score for each heart was used. The failing category includes both nonischemic and ischemic hearts, unless noted otherwise. AATS indicates atrial adipose tissue score; ATS, adipose tissue score; and VATS, ventricular adipose tissue score.
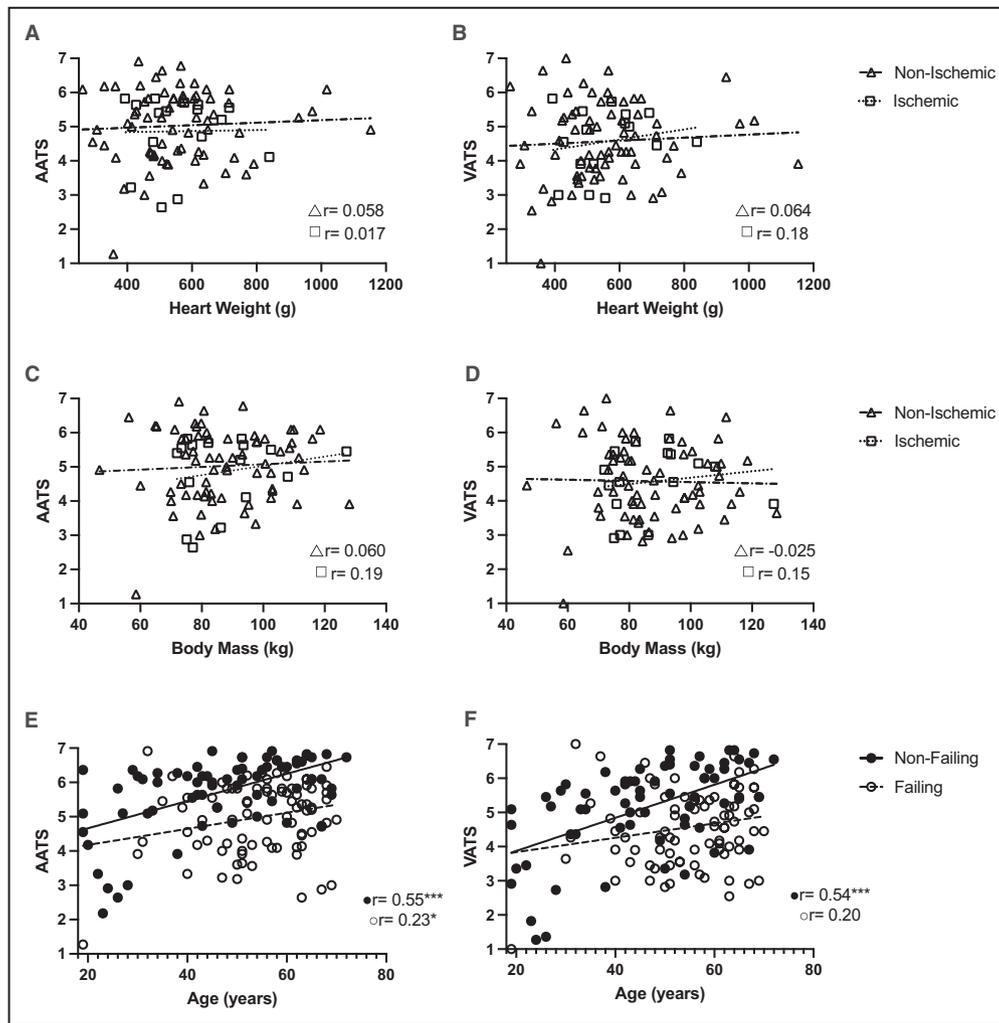
Figure 5. **Correlations of ATS and heart weights, body mass, and ages of patients.**
A, Correlation of AATS and heart weight (g) of nonischemic (n=68; r=0.058) and ischemic (n=16; r=0.017) failing hearts. **B**, Correlation of VATS and heart weight (g) of nonischemic (n=68; r=0.064) and ischemic (n=16; r=0.18) failing hearts. **C**, Correlation of AATS and body mass (kg) of nonischemic (n=68; r=0.060) and ischemic (n=16; r=0.19) failing hearts. **D**, Correlation of VATS and body mass (kg) of nonischemic (n=68; r=−0.025) and ischemic (n=16; r=0.15) failing hearts. **E**, Correlation of AATS and age (years) of nonfailing (n=66; r=0.55) and failing (n=84; r=0.23) patients. **F**, Correlation of VATS and age (years) of nonfailing (n=66; r=0.54) and failing (n=84; r=0.20). Pearson correlation was used to measure the linear relationship between ATS and heart weight, body weight, and age. *** denotes $P<0.001$ and *$P<0.05$. The average ATS score for each heart was used. The failing category includes both nonischemic and ischemic hearts, unless noted otherwise. AATS indicates atrial adipose tissue score; ATS, adipose tissue score; and VATS, ventricular adipose tissue score.

patients with an ischemic versus a nonischemic cause of heart failure. Lastly, we did not observe a correlation between EAT and contractile function of isolated myocardium in resting condition.

Our first major observation focused on the relationship of EAT to patient heart failure status (failing or nonfailing; Figure 2). Contrary to our expectations, the nonfailing hearts had significantly higher EAT scores than their failing counterparts. Note that the age of the nonfailing group was significantly lower than the age of the failing group. In the nonfailing group, the

EAT moderately increased with age (Figure 5E and F), and thus the generally higher EAT score for nonfailing hearts compared with failing hearts could potentially be higher if age-matching is taken into account, increasing the calculated difference between the failing and nonfailing groups. These data are partially in line with published literature. It has been reported that the amount of EAT increases with age until 20 to 40 years old and thereafter is independent of age.[17] Our data suggest that EAT is strongly correlated with age for all ages included in the study (19–72 years). There was no
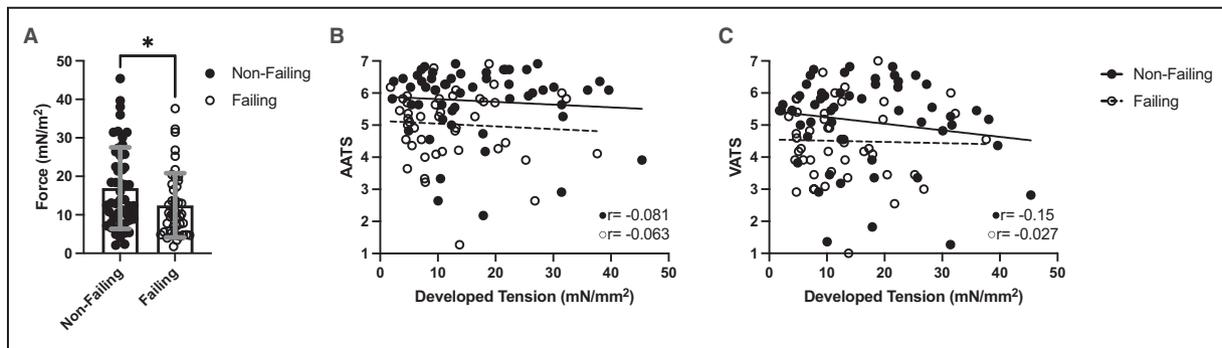
Figure 6. **Mean developed tension and correlation of ATS with developed tension of isolated trabeculae from nonfailing and failing hearts.**

A, Mean developed tension (mN/mm^2) at 1 Hz of isolated trabeculae from nonfailing (n=52; 16.95±1.47 SEM; * indicates $P<0.05$; unpaired t test) and failing (n=46; 12.44±1.23 SEM) hearts. **B**, Correlation of AATS and developed tension (mN/mm^2) at 1 Hz of nonfailing (n=52; $r=-0.081$) and failing (n=46; $r=-0.063$) hearts. **C**, Correlation of VATS and developed tension (mN/mm^2) of nonfailing (n=52; $r=-0.15$) and failing (n=46; $r=-0.027$) hearts. Failing hearts include both nonischemic and ischemic hearts. Pearson correlation was used to measure the linear relationship between ATS and developed tension. The average ATS score for each heart was used. The failing category includes both nonischemic and ischemic hearts. AATS indicates atrial adipose tissue score; ATS, adipose tissue score; and VATS, ventricular adipose tissue score.

significant difference between women and men in the AATS (respectively, nonfailing: 6.02±0.15 vs. 5.85±0.16, $P=0.42$, and failing: 5.43±0.18 vs. 5.23±0.12, $P=0.35$). Interestingly, although there was no significant difference between women and men in the VATS for the nonfailing hearts (5.33±0.20 vs. 4.97±0.20), women had a significantly higher VATS compared with men (5.24±0.11 vs. 4.63±0.13, $P=0.005$) in the failing hearts.

As this study was designed to report semiquantitative differences, we can only speculate on the underlying cause(s) of significant differences in EAT between nonfailing and end-stage failing hearts. This decreased amount of EAT in heart failure could possibly be related to the weakened cardiac output regulation in failing hearts; the frequency-dependent activation and β-adrenergic response are all negatively affected in heart failure,[21] although the length-dependent activation is preserved. The overall slower and weaker failing heart is also metabolically shifted toward a slower fatty acid-dominant metabolism in heart failure in lieu of faster glucose-dominant metabolism seen in nonfailing hearts.[23] The closest source of fatty acids after intracellular triglyceride droplets is EAT, and as failing hearts use more fatty acids to maintain homeostasis, failing hearts may consequently have lower EAT than nonfailing hearts. This is consistent with the findings of other groups who have studied EAT and heart failure using echocardiography,[24] magnetic resonance imaging,[25] or both.[26] Another possible explanation that warrants further investigation is the lower amount of EAT in patients with heart failure as a result from cardiac cachexia and negative energy balance. A study has reported through analysis with echocardiography, patients with cachexia have significantly lower EAT thickness compared with body weight-stable patients.[27] Adipose tissue wasting,

including EAT, in patients with cachexia is assumed to be caused by an overall net loss of triacylglycerols. This is assumed to be the result of greater stimulation of lipolytic and oxidative pathways, ultimately leading to a decline in the intracellular triacylglycerols.[27]

Our analysis of atrial and ventricular EAT showed atrial EAT is significantly higher than ventricular EAT in both nonfailing and failing hearts. The raw data show a relatively normal distribution of fat score for VATS and a distribution skewed toward the higher end for AATS. This could possibly be due to the normal anatomical distribution of EAT—commonly along the atrioventricular and interventricular grooves, but less so around the 2 atrial appendages and subepicardially in the free walls of the atria.

We then investigated the relationship between subcategorization of heart failure (ischemic or nonischemic) and EAT score. None of the variables correlated with EAT content; however, as described previously, the fat content of the atria is strongly correlated with that of the ventricles in the same patient or donor (Figure 3). This correlation weakens when considering heart failure subcategory. Therefore, the strongest predictor of adipose tissue content on the ventricles is the adipose tissue content on the atria. We hypothesize this is due to the continuous epicardial space from cardiac apex to base and thus biochemical and hormonal signals triggering changes in epicardial adipose tissue will be shared by both the atria and ventricles. Despite the association between ischemic heart disease and fatty acid metabolism, this association is also present in heart failure overall.[24] The shift toward fatty acids may be more pronounced once the heart crosses the functional threshold to failure and overshadow the fatty acid shift that could be attributed to ischemia alone.

When we included BMI into the analysis, we found no correlation between BMI and ATS on neither the atria nor the ventricles (Figure 4). Several studies to date have shown the association between BMI and EAT content is poor in humans by autopsy,[28] echocardiography,[19,29] and magnetic resonance imaging.[30] This could be due to the difficulty in accurately distinguishing EAT from other similarly radiopaque (X-ray/computed tomography), echoic (ultrasound), or magnetically resonant tissues in vivo. In addition, the EAT distribution is not homogenous across the heart, and thus assessment of EAT requires an encompassing evaluation of EAT, at multiple locations of the epicardium. The rather clear lack of a relationship between BMI and EAT underscores the fact that EAT is distinctly different from other adipose tissue deposits, which very clearly positively correlate with BMI. In addition, the prominent negative correlation between heart failure and EAT content bears potential as a possible imaging indicator for the dysfunctional myocardial metabolism characteristic of heart failure.

Cardiac contractility studies were also performed on isolated multicellular preparations from these hearts and when analyzed with respect to EAT score, we found no correlation (Figure 6). As EAT had been shown to be strongly correlated with nonfailing status, and the metabolism of nonfailing hearts is primarily glucose based, the higher EAT content would not necessarily confer a higher metabolic reserve and increased contractile ability.

CONCLUSIONS

The body of literature covering the pathophysiological roles of not only epicardial fat but also myocardial fat, endocardial fat, and pericardial fat is growing because of availability of advanced noninvasive imaging techniques. The deposition of fat in the epicardial space is indeed heterogeneous across the surface of the heart and is influenced by many factors. Our work demonstrates that although a correlation between BMI and EAT is not obviously present in our patient population, EAT content is significantly higher in nonfailing hearts compared with end-stage failing hearts and is significantly higher in atria compared with ventricles.

ARTICLE INFORMATION

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Disclosures

None.

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