

Relation of Increased Epicardial Fat After Fontan Palliation to Cardiac Output and Systemic Ventricular Ejection Fraction

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Epicardial fat produces multiple proinflammatory cytokines and is associated with adverse cardiovascular events. Inflammation and resultant endothelial dysfunction may play a role in progressive myocardial dysfunction among adults with single ventricle physiology after Fontan palliation, but the potential impact of increased epicardial fat volume (EFV) has not been studied. This study sought to determine if there is greater EFV in Fontan patients compared with a group of repaired tetralogy of Fallot (rTOF) patients. We retrospectively measured EFV manually on cardiac magnetic resonance imaging in Fontan patients, ≥ 15 years, and 1:1 age, sex, and body mass index–matched patients with rTOF. EFV was indexed to body surface area. A random subset of studies was re-measured to assess intra- and interobserver reliability. Fontan patients ($n = 63$, median age 21.6 years, 51% male, mean body mass index 24.2 ± 5.6 kg/m²) had a larger indexed EFV compared with matched rTOF patients (75.3 ± 29.2 ml/m² vs 60.0 ± 19.9 ml/m², $p = 0.001$). In Fontan patients, indexed EFV was inversely correlated with ventricular ejection fraction ($r = -0.26$, $p = 0.04$) and cardiac index ($r = -0.33$, $p = 0.01$). Intra- and interobserver reliabilities of the indexed EFV measurements in both groups were excellent (intraclass correlation coefficient ranges from 0.93 to 0.97). In conclusion, indexed EFV is higher in Fontan patients compared with patients with rTOF and is associated with lower ventricular ejection fraction and cardiac index. Increased EFV could play a role in the failing Fontan circulation, but longitudinal studies are necessary to establish any causative role. © 2018 Elsevier Inc. All rights reserved. (Am J Cardiol 2018;■■■:■■■–■■■)

Adult patients with Fontan palliation are at risk of progressive myocardial dysfunction as they age. The factors leading to the failing Fontan circulation are poorly understood, and the potential effect of epicardial fat on this population has not been studied. Epicardial fat is the adipose tissue located between the myocardium and the visceral pericardium. This adipose tissue is immunologically active—producing multiple proinflammatory and proatherogenic cytokines.¹ Given the proximity to epicardial coronary arteries, this adipose tissue may modulate the coronaries through the secretion of these cytokines.² There is a growing body of literature that has shown an association between the amount of epicardial fat and the adverse cardiovascular outcomes.^{3–5} The cytokines secreted by epicardial fat may play a role in coronary microvascular dysfunction.^{6–9} Increased epicardial

fat causing coronary endothelial dysfunction could have grave consequences in any patient with single ventricle physiology. The aims of this study are to compare epicardial fat volume (EFV) in a population of adolescent and adult Fontan patients by cardiac magnetic resonance imaging (MRI) to a group of repaired tetralogy of Fallot (rTOF) patients and to evaluate its association with other cardiac indices in individuals with Fontan anatomy including ventricular ejection fraction and cardiac index.

Methods

Fontan patients age ≥ 15 years at the time of a cardiac MRI performed at our institution between November 2007 and February 2014 were evaluated. Patients with diabetes mellitus, autoimmune conditions, or on dialysis were excluded due to the known association between these conditions and increased epicardial fat. Subjects were also excluded due to image artifact obscuring epicardial fat or if the study was incomplete due to claustrophobia or unavailable images. The most recent MRI was included for individuals with multiple MRI studies during the study period. The comparison group of rTOF anatomy was chosen because tetralogy of Fallot repair is a two-ventricle physiology with shared early childhood sternotomy and pericardial entry. Patients with rTOF, who had a cardiac MRI performed at our institution during the study period, were eligible for matching. The same exclusion criteria

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also applied to the rTOF group, and patients were matched 1:1 with Fontan patients based on sex, age (± 6 years), and body mass index (BMI) (± 6 kg/m² within each of the following BMI categories: underweight [≤ 18.5 kg/m²], normal [18.5 to 25.0 kg/m²], overweight [25.0 to 30.0 kg/m²], and obese [>30 kg/m²]). This study was approved by the University of Michigan Institutional Review Board.

Cardiac MRI studies were performed using a 1.5 T scanner (Philips Intera Achieva or Ingenia, Best, The Netherlands). Cine images were obtained with a breath hold, electrocardiographic-gated, segmented k-space, steady-state free precession sequence. These images were analyzed using commercially available software (cvi42; Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Epicardial fat is defined as the fat between visceral pericardium and myocardium to differentiate it from pericardial fat. The border between epicardial and pericardial fat was determined by inspection of the entire cine series in all slices, and pericardial fat was excluded. Areas of epicardial fat were traced manually on consecutive end-systolic short-axis images, beginning at the systemic atrioventricular valve and ending at the last slice containing cardiac adipose tissue as previously described^{10,11} (Figure 1). The areas obtained for each slice were multiplied by the slice thickness and resulting volumes summed together to yield the EFV. No patient had a pericardial effusion. EFV was indexed to body surface area (BSA). Cardiac index was calculated as the sum of flow in the superior vena cava and inferior vena cava, indexed to BSA. Atrioventricular valve regurgitation for Fontan subjects was measured by standard MRI methods.

EFV was re-measured in a random subset of 30 studies in each group after a gap of at least 1 week from the initial measurement to assess intraobserver reliability. Additionally, a second investigator repeated measurements of a subset of 60 patients to determine interobserver reliability. A senior cardiology fellow performed measurements on the entire study cohort (AML), and a cardiologist with expertise in noninvasive cardiac imaging completed subset measurements (ALD). These measurements were performed independently and blinded to all previous measurements.

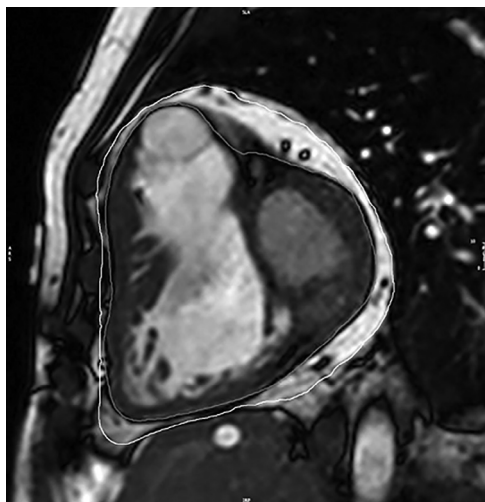


Figure 1. Example of a manual tracing of epicardial fat on a single short-axis image at end-systole.

Data are reported as frequency (percentage) for categorical variables and median and interquartile range or mean \pm standard deviation for continuous variables. Demographic and clinical characteristics were compared between Fontan and rTOF groups using chi-square test or Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables. Fat volume indexed to BSA (or BMI) was compared between Fontan and rTOF groups using Student's *t* test. Pearson or Spearman correlation coefficient, depending on the distributional assumption, was used to assess a correlation of indexed fat volume with cardiac indices and clinical characteristics. Intra- and interobserver reliabilities on EFV measurements were evaluated using intraclass correlation coefficient (ICC) and Bland-Altman limits of agreement. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC). *p* Value <0.05 was considered statistically significant.

Results

During the study period, 74 potential Fontan individuals were identified. Of those, 11 were excluded (5 due to other medical conditions, 3 due to image artifact obscuring epicardial fat, and 3 due to an incomplete study), leaving a total of 63 subjects. There were no significant differences in the demographic and baseline clinical characteristics between the Fontan subjects and the rTOF patients, with the exception of more sternotomies in the Fontan group (Table 1).

Individuals with single ventricle anatomy and Fontan palliation had a significantly larger EFV indexed to BSA compared with rTOF patients (75.3 ± 29.2 ml/m² vs 60.0 ± 19.9 ml/m², $p = 0.001$) (Figure 2). Indexing EFV to BMI demonstrated a similar difference (5.51 ± 1.97 ml/kg/m² vs 4.41 ± 1.47 ml/kg/m², $p = 0.001$). EFV indexed to BSA by single ventricle anatomy subgroups compared with rTOF are displayed in Figure 3.

There was a negative correlation between indexed EFV and both ejection fraction and cardiac index in Fontan patients (Figure 4). Indexed EFV in Fontan patients positively correlated with weight ($r = 0.35$, $p < 0.0001$), BMI ($r = 0.40$, $p < 0.0001$), and age ($r = 0.34$, $p = 0.0001$).

No significant correlation was found between indexed fat volume and number of sternotomies ($r = 0.16$, $p = 0.08$), smoking status (67.1 ± 23.7 for ever-smoker vs 70.5 ± 28.9 for never-smoker, $p = 0.65$), atrioventricular valve regurgitation severity (71.0 ± 34.3 for moderate or above vs 73.5 ± 23.4 for below moderate, $p = 0.78$), or height ($r = 0.06$, $p = 0.50$). There were 6 patients with a history of protein losing enteropathy (PLE) in the Fontan cohort. There was no significant difference in indexed EFV in patients with a history of PLE compared with Fontan patients without a history of PLE (63.0 ± 11.3 ml/m² vs 76.6 ± 30.2 ml/m², $p = 0.31$).

Intraobserver reliabilities of the indexed EFV measurements in both groups were excellent (ICC 0.95 and 0.93 in Fontan and rTOF, respectively). Interobserver reliabilities of the indexed EFV in both groups were also excellent (ICC 0.96 and 0.97 in Fontan and rTOF, respectively). Bland-Altman plots for limits of agreement of the indexed EFV measurements are presented in Figure 5. Intraobserver agreement was similar between the groups, and interobserver agreement was slightly better in patients with rTOF.

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