

# The Effect of Epicardial Fat on the Right and Left Ventricular Function in Subjects with Various Etiological Types of Pulmonary Arterial Hypertension

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## ABSTRACT

**Background:** Little is known on the effect of epicardial fat in pulmonary arterial hypertension (PAH). Therefore, the present study sought to perform a comparative analysis on the influence of epicardial fat thickness (EFT) on the right and left ventricular function, between three different etiological varieties of pulmonary arterial hypertension: caused by congenital heart defects (atrial septum defects with left to right shunt), by systemic sclerosis, and by myocardial ischemia. **Materials and Methods:** This is a prospective observational study on 50 patients with documented PAH (systolic pulmonary artery pressure – PASP of >35 mmHg). The thickness of the epicardial adipose tissue was evaluated by 2D cardiac ultrasound, on the free wall of the right ventricle, during end-diastole, in the long parasternal axis view. The patients were divided into three study groups: Group 1 – PAH determined by congenital heart defects with left to right shunts (atrial septum defects, n = 25); Group 2 – PAH induced by systemic sclerosis (n = 12); Group 3 – PAH induced by myocardial ischemia (n = 13). **Results:** The average age was 54.48 ± 10.78 years, 30% (n = 15) of subjects were males, with a mean body mass index of 24.65 ± 4.40 kg/m<sup>2</sup>, EFT was 9.15 ± 2.24 mm, and the PASP was 41.33 ± 5.11 mmHg. Patients in Group 3 were more likely to smoke (p = 0.025) and presented a significantly lower LVEF, compared to the other groups (Group 1: 60% ± 6 vs. Group 2: 60% ± 7 vs. Group 3: 48% ± 7, p < 0.0001). The largest EFT was found in Group 3 (11.08 ± 2.39 mm), followed by Group 2 (9.14 ± 2.03 mm), and Group 1 (8.16 ± 1.57 mm) (p = 0.0003). The linear regression analysis found no significant correlations between EFT and other echocardiographic parameters: PASP (r = -0.228, p = 0.118), LVEF (r = -0.265, p = 0.06), TAPSW (r = 0.015, p = 0.912), TEI (r = 0.085, p = 0.552), RVEDD (r = -0.195, p = 0.173), RA area (r = -178, p = 0.214), and LA diameter (r = 0.065, p = 0.650). **Conclusions:** Epicardial fat thickness was found to be significantly higher in patients with PAH induced by myocardial ischemia, followed by those with systemic sclerosis and congenital heart defects, respectively. EFT did not influence the echocardiographic parameters for left and right ventricular function in patients with pulmonary arterial hypertension of different etiologies.

**Keywords:** pulmonary arterial hypertension, epicardial fat thickness, systemic sclerosis, atrial septum defects, myocardial ischemia

## INTRODUCTION

### Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) represents an increase in the pulmonary arterial pressure above 25 mmHg, triggered by a progressive rise in pulmonary vascular resistance due to vasoconstriction, vascular remodeling, fibrosis, and inflammation.<sup>1</sup> Several studies have identified the presence of proinflammatory cytokines as promoters of PAH, including interleukins, tumor necrosis factor, and autoantibodies, which advocate for the autoimmune inflammatory pathogenesis of the disease.<sup>2,3</sup> Vessel remodeling and increased vascular resistance in the pulmonary arterial circulation leads to overload of the right cardiac chambers, with right ventricular hypertrophy, tricuspid regurgitation, and subsequent right atrial remodeling, and in case of associated right ventricle ischemia or fibrosis, the evolution is towards right cardiac failure. The clinical presentation of PAH includes shortness of breath, syncope during physical exertion, fatigue, chest pain, or even death due to right ventricular failure, while the clinical examination reveals signs of increased pressure in the right heart, jugular distension, hepatojugular reflex, peripheral edema, and hepatomegaly.<sup>4,5</sup>

PAH is categorized in 5 subgroups, according to its etiology, as follows: subgroup 1 – idiopathic or familial PAH; subgroup 2 – PAH caused by left heart failure (systolic, diastolic, or valvular); subgroup 3 – PAH caused by respiratory disorders with pulmonary fibrosis, including bronchial asthma, emphysema, interstitial lung disease, or chronic obstructive pulmonary disease; subgroup 4 – PAH caused by chronic pulmonary embolism; subgroup 5 – unclear or multifactorial pathomechanisms.<sup>6</sup>

Although the most cited causes for PAH include pulmonary and left-sided heart disease, congenital cardiac diseases with systemic to pulmonary shunt are associated with pulmonary arterial hypertension.<sup>7</sup> PAH has been reported in around 9–35% of cases with open or closed atrial septum defect, but the pulmonary vascular disease can be prevented if the left to right shunt is corrected before the development of Eisenmenger syndrome or shunt reversal occurs.<sup>8</sup>

Left ventricular failure caused by myocardial ischemia is characterized by increased filling pressures, either due to diastolic dysfunction or mitral regurgitation, which in turn triggers pulmonary venous hypertension and postcapillary pulmonary hypertension. This complex mechanism will lead to endothelial dysfunction and pulmonary vascular remodeling, which in time, will resemble the changes that

are present in patients with primary pulmonary hypertension.<sup>9,10</sup>

Autoimmune diseases, such as systemic sclerosis, often present PAH as a complication, and studies have shown that approximately 8–12% of patients with systemic sclerosis present different stages of PAH.<sup>11,12</sup> Moreover, PAH occurring as a complication of systemic connective tissue disorders is associated with significantly higher mortality rates in comparison to patients with other forms of PAH, including the idiopathic form.<sup>13</sup>

### Epicardial fat in various clinical settings

Epicardial adipose tissue has been widely researched for its impact on several cardiovascular disorders including ischemic heart disease, acute coronary syndromes, heart failure, and metabolic syndromes.<sup>14,15</sup> Furthermore, epicardial fat was found to be increased in several autoimmune disorders such as systemic sclerosis, psoriasis, or polyarthritis. Epicardial fat volume, measured by cardiac computed tomography, has been shown to be larger in patients with systemic sclerosis compared to controls, and patients with associated PAH present larger epicardial fat volumes compared to those with systemic sclerosis without PAH.<sup>16–18</sup> Also, epicardial fat thickness (EFT) has been associated with the severity of pulmonary disorders that are known for being associated with pulmonary hypertension, and EFT is associated with a higher extent of right ventricular remodeling in patients with chronic obstructive pulmonary disorders.<sup>19</sup>

Little is known on the effect of epicardial fat in pulmonary arterial hypertension. Therefore, the present study sought to perform a comparative analysis on the influence of EFT on the right and left ventricular function, between three different etiological varieties of pulmonary arterial hypertension: caused by congenital heart defects (atrial septum defects with left to right shunt), by systemic sclerosis, and by myocardial ischemia, with the help of 2D transthoracic echocardiography.

## MATERIALS AND METHODS

This is a prospective observational study that included 50 patients with documented PAH, with a systolic pulmonary artery pressure of >35 mmHg, as measured with Doppler echocardiography. All patients underwent a complete 2D transthoracic echocardiography examination with assessment of the following parameters: (a) for left cardiac chambers: left ventricular ejection fraction (LVEF), left atrium diameter, tissue Doppler (septal and lateral e'); and

(b) for right cardiac chambers: pulmonary arterial systolic pressure (PASP), right ventricular end-diastolic diameter (RVEDD), tricuspid annular plane systolic excursion (TAPSE), right atrium area, right ventricular myocardial performance index (Tei index).

The thickness of epicardial adipose tissue was evaluated by 2D cardiac ultrasound, on the free wall of the right ventricle, during end-diastole, in the long parasternal axis view, with the ultrasound beam perpendicular to the aortic annulus. Epicardial fat was viewed as a hypoechoic space between the free wall of the right ventricle and the visceral epicardial membrane.

All echocardiography evaluations were performed with a Vivid E9 Ultrasound system (General Electric Vingmed Ultrasound, Horten, Norway). All patients signed a written informed consent before being included in the study, and the research was approved by the Ethics Committee for Scientific Research of the University of Medicine and Pharmacy of Tîrgu Mureş, Romania.

All patients underwent complete evaluation of cardiovascular risk factors, comorbidities, and demographic characteristics.

The total number of patients included 3 different etiological types of PAH: Group 1 – PAH determined by congenital heart defects with left to right shunts, more specifically with various types of atrial septum defects (n = 25); Group 2 – PAH induced by connective tissue disorders, more specifically by systemic sclerosis (n = 12); Group 3 – PAH induced by myocardial ischemia (n = 13).

Statistical analysis was performed with GraphPad Prism 6 statistical software (GraphPad Software, Inc., San Diego, USA), and a two-tailed p value of <0.05 was considered statistically significant. To test the normality of distribution for numerical data, D'Agostino Pearson normality test was used, continuous data was shown as mean ± standard deviation and median respectively, and categorical variables were expressed as percentages and integer values. Pearson and Spearman coefficients were used for correlation analysis.

## RESULTS

The average age of the study population was  $54.48 \pm 10.78$  years, and 30% (n = 15) of the subjects were males. The mean body mass index was  $24.65 \pm 4.40$  kg/m<sup>2</sup>, epicardial fat thickness was  $9.15 \pm 2.24$  mm, and the PASP was  $41.33 \pm 5.11$  mmHg.

The echocardiographic parameters for the total study population and patient comorbidities are listed in Table 1.

The comparative analysis between the three PAH etiological categories showed that there was a significantly

higher percentage of smokers in the ischemic PAH group (p = 0.025), but no other significant difference was observed, more specifically with regard to age (p = 0.267), gender (p = 0.09), body mass index (p = 0.679), or cardiovascular risk factors (Table 2).

Analysis of the echocardiographic parameters showed that patients in Group 3 (PAH induced by myocardial ischemia) presented a significantly lower LVEF compared to the other groups, as both groups had a mean LVEF above 60% (Figure 1). No significant difference was found between the three patient categories in relation to the RVEDD (Group 1:  $31.34 \pm 2.69$  mm vs. Group 2:  $31.92 \pm 1.73$  mm vs. Group 3:  $30.92 \pm 2.25$  mm, p = 0.584), the TAPSE value (Group 1:  $25.04 \pm 5.94$  mm vs. Group 2:  $25.75 \pm 2.30$  mm vs. Group 3:  $24 \pm 4.41$  mm, p = 0.670), the TEI index (Group 1:  $0.46 \pm 0.41$  vs. Group 2:  $0.59 \pm 0.38$  vs. Group 3:  $0.39 \pm 0.64$ , p = 0.393), left atrium diameter (Group 1:  $38.12 \pm 6.26$  mm vs. Group 2:  $37.58 \pm 5.97$  mm vs. Group 3:  $39.85 \pm 3.84$  mm, p = 0.566), or the PASP value (Group 1:  $41.84 \pm 5.28$  vs. Group 2:  $41.83 \pm 5.52$  vs. Group 3:  $39.88 \pm 4.47$ , p = 0.502).

The largest EFT was found in Group 3 – myocardial ischemia PAH ( $11.08 \pm 2.39$  mm), followed by Group 2 – systemic sclerosis PAH ( $9.14 \pm 2.03$  mm) and Group 1 – congenital heart defects PAH ( $8.16 \pm 1.57$  mm), the difference being statistically significant (p = 0.0003) (Figure 2).

Linear regression analysis showed that there were no statistically significant correlations between epicardial fat

**TABLE 1.** Clinical and echocardiographic characteristics of the total study population

Echocardiographic parameters	Mean ± SD
LVEF (%)	57.12 ± 7
RVEDD (mm)	31.37 ± 2.36
TAPSE (mm)	24.94 ± 4.86
TEI	0.54 ± 0.40
LA diameter (mm)	38.44 ± 5.62
RA area (mm <sup>2</sup> )	14.78 ± 3.5
T1 (ms)	455.7 ± 110.9
T2 (ms)	317 ± 84.64
RVEDD (mm)	47.96 ± 4.18
LVESD (mm)	31.32 ± 3.92
Septal e' (cm/s)	14.66 ± 2.69
Lateral e' (cm/s)	12.32 ± 2.38
Cardiovascular risk factors	n (%)
Hypertension	15 (30%)
Dyslipidemia	9 (18%)
Obesity	7 (14%)
Smoking	11 (22%)
Previous stroke	9 (18%)

**TABLE 2.** Comparative analysis of clinical characteristics and cardiovascular risk factors between the three etiological PAH groups

	Group 1 (congenital heart defects) n = 25	Group 2 (systemic sclerosis) n = 12	Group 3 (myocardial ischemia) n = 13	p value
Age (years)	52.12 ± 12.23	55.67 ± 9.792	57.92 ± 7.815	0.267
Male gender, n (%)	11 (44%)	2 (16.6%)	2 (15.3%)	0.09
BMI (kg/m <sup>2</sup> )	24.03 ± 3.94	24.97 ± 4.43	25.55 ± 5.30	0.672
Hypertension, n (%)	5 (20%)	3 (25%)	7 (53.8%)	0.053
Dyslipidemia, n (%)	2 (8%)	2 (16.6%)	4 (30.7%)	0.191
Obesity, n (%)	1 (4%)	2 (16.6%)	3 (23%)	0.194
Smoke, n (%)	2 (8%)	3 (25%)	6 (46.1%)	0.025
Stroke, n (%)	2 (8%)	3 (25%)	4 (30.7%)	0.171

thickness, measured by 2D echocardiography, and other echocardiographic parameters (Figure 3).

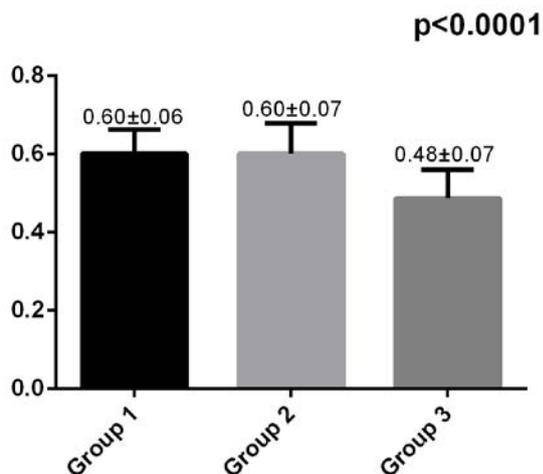
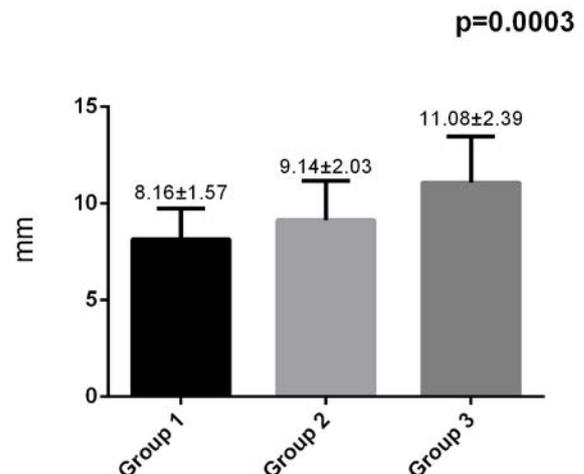
## DISCUSSIONS

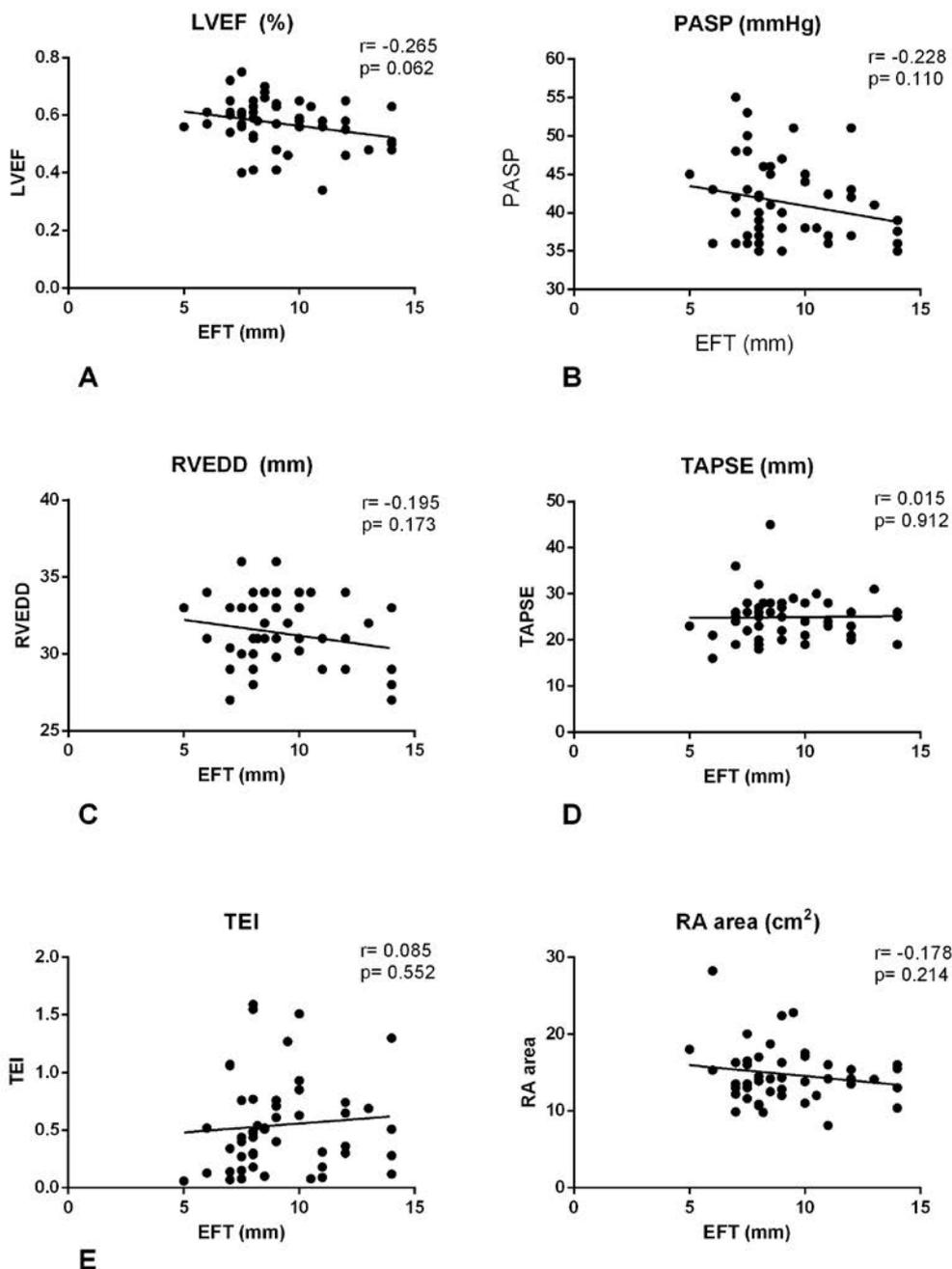
The present study aimed to evaluate the role of epicardial fat thickness, measured with the help of transthoracic cardiac ultrasound, on the right and left ventricular function in patients with 3 etiological varieties of PAH, more precisely PAH induced by atrial septum defect with right to left shunt, PAH induced by left ventricular myocardial ischemia, and PAH induced by systemic sclerosis.

The main findings of the study were: (1) the largest EFT was found in patients from the myocardial ischemia group, followed by those with systemic sclerosis and with congenital heart defects; (2) there were no statistically signifi-

cant correlations between any of the measured echocardiographic parameters for left or right ventricular function and the thickness of the epicardial adipose tissue; (3) subjects with myocardial ischemia were more likely to smoke, and they presented, as expected, a significantly lower left ventricular ejection fraction compared to the rest of the groups.

Epicardial adipose tissue has been proved to be a reliable predictor for myocardial ischemia, the severity of coronary artery disease, as well as the rates of major adverse cardiovascular events in patients with acute coronary syndromes. Likewise, many researchers have connected epicardial fat with established risk prediction tools for acute coronary syndromes such as GRACE (Global Registry for Acute Coronary Events), TIMI (Thrombolysis In Myocardial Infarction) or the angiographic SYNTAX score.<sup>14,20-22</sup>

**FIGURE 1.** Left ventricular ejection fraction between the three etiological PAH groups**FIGURE 2.** Epicardial fat thickness between the three etiological PAH groups



**FIGURE 3.** Correlations between the EFT and echocardiographic parameters for right and left ventricular function, in the overall study population

In addition, the LVEF was significantly lower in patients with PAH induced by ischemic cardiomyopathy, while the other two patient categories both presented a preserved ejection fraction of over 60%. While the lower ejection fraction, illustrative for left ventricular systolic dysfunction, was to be expected, regarding the larger epicardial fat, remains the age-old chicken-egg conundrum as to which came first: are patients at a higher risk for develop-

ing myocardial ischemia due to a larger epicardial adipose tissue, or is it that the epicardial fat thickness develops more because of the already established ischemia?

Being a type of visceral adipose tissue, epicardial fat is believed to influence insulin resistance, to enhance the overall cardiometabolic risk, and to promote a pro-inflammatory status.<sup>23</sup> Several studies have evaluated the impact of an increased epicardial adipose tissue on the clinical

outcomes of patients with autoimmune disorders such as rheumatoid arthritis, psoriasis, or systemic sclerosis.<sup>16-18,22</sup> Fatma *et al.* aimed to study the epicardial adipose tissue in patients with rheumatoid arthritis, as well as its effect on the cardiovascular involvement of the systemic disease. Their study found that EFT was higher in patients with polyarthritis ( $6.6 \pm 2.0$  mm vs.  $5.4 \pm 1.8$  mm,  $p = 0.003$ ) and that EFT was linked to left ventricular diastolic dysfunction, hypertension, or duration of the disease.<sup>24</sup> Long *et al.* sought to determine if the intrathoracic and epicardial fat volumes, assessed with thoracic CT, are linked to the presence of PAH as a marker for clinical severity of systemic sclerosis. Their results revealed that EF volume was significantly associated with the severity of systemic sclerosis, illustrated by the presence of PAH, independent of other cardiovascular risk factors or interstitial pulmonary disease (adjusted OR: 1.010, 95% CI: 1.003-1.018,  $p = 0.007$ ).<sup>18</sup>

Within our study population, the measured pulmonary arterial systolic pressure did not differ between the three groups, although patients with myocardial ischemia presented slightly lower values compared to those with congenital heart defects or with systemic sclerosis, which is known to stimulate pulmonary fibrosis inflammation and vascular remodeling.

## CONCLUSIONS

Epicardial fat thickness was found to be significantly higher in patients with PAH induced by myocardial ischemia, followed by those with systemic sclerosis and congenital heart defects, respectively. In our study, EFT did not influence the echocardiographic parameters for left and right ventricular function in patients with PAH of different etiologies. The largest EFT was found among patients with myocardial ischemia, thus proving, once again, the deleterious effects of the adipose tissue surrounding the heart on coronary artery disease.

## CONFLICT OF INTEREST

Nothing to declare.

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