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Epicardial adipose tissue thickness in patients with chronic obstructive pulmonary disease having right ventricular systolic dysfunction

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Abstract. – OBJECTIVE: The aim of the present study was to evaluate epicardial fat thickness (EFT) in patients with chronic obstructive pulmonary disease (COPD) having right ventricular systolic dysfunction (RVSD).

PATIENTS AND METHODS: This study was comprised of 98 patients with COPD and 40 healthy controls. All the study participants underwent 2-dimensional, pulsed and tissue-doppler transthoracic echocardiographic examination for the measurements of EFT and parameters of right and left ventricular functions. Patients with COPD were divided into mild and severe RVSD groups according to right ventricular fractional area changes (RVFACs).

RESULTS: Age, gender, prevalence of diabetes mellitus, hypertension, body-mass-index (BMI) and dyslipidemia were similar between COPD patients and controls, as were between mild, and severe RVSD groups. Prevalence of smoking were higher in COPD patients than in controls. Right ventricular end-diastolic diameter, myocardial performance index and peak pulmonary systolic pressure were found to be higher in COPD patients, while tricuspid annular plane systolic, excursion, isovolumic accelerating time, EFT and EFT/BMI were found to be lower in COPD patients. COPD patients with severe RVSD had thinner EFT and lower EFT/BMI values than those with mild RVSD (4.10 ± 0.77 vs 5.48 ± 1.28 mm, $p < 0.001$, respectively).

CONCLUSIONS: The present study shows that the EFT decreases in patients with COPD and it is also associated with the degree of RVSD. Therefore, evaluating EFT in patient with COPD may provide information about the severity of the disease.

Key Words:
Chronic obstructive pulmonary disease, Echocardiography, Epicardial fat thickness, Right ventricular dysfunction.

Abbreviations

BMI: body-mass-index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; ECG: electrocardiography; EFT: epicardial fat thickness; ET: total ejection time; IVA: isovolemic acceleration time; IVCT: interventricular contraction time; IVRT: interventricular relaxation time; HDL-C: high density lipoprotein cholesterol; MPI:myocardial performance index; LDL-C: low density lipoprotein cholesterol; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; PAH: pulmonary arterial hypertension; RV: right ventricul; RVSD: right ventricular systolic dysfunction; RVFACs: right ventricular fractional area changes; sPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible air flow obstruction[1]. One of the most serious cardiovascular complications associated with COPD is pulmonary arterial hypertension (PAH), which develops secondary to chronic hypoxia, followed by right ventricular hypertrophy, dilatation and failure leading to chronic cor pulmonale[2,3]. The relationship between epicardial fat thickness (EFT) and coronary artery disease (CAD), metabolic syndrome, and left ventricular dysfunction has been shown in previous studies[4-9]. However, the relationship between EFT and right ventricular systolic dysfunction (RVSD) have not been studied thoroughly yet. We hypothesized that patients with COPD have diminished EFT, which may reflect altered me-

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tabolism. It was, therefore, the aim of our study to examine EFT in patients with COPD and its association with RVSD severity.

Patients and Methods

Study Population

Ninety-eight consecutive patients with newly diagnosed COPD who have not received any treatment and 40 age- and sex-matched control subjects were included in the present study. Patients with COPD were further divided into groups according to the severity of RVSD, which was assessed by right ventricular fractional area change (RVFAC) on transthoracic echocardiography. Accordingly, mild RVSD was defined as RVFAC 17-31% and severe RVSD as RVFAC < 17%. Patients with coronary artery disease (CAD), left ventricular systolic heart failure (EF < 50%), moderate to severe mitral and/or aortic valvular heart disease, congenital heart disease, atrio-ventricular conduction abnormalities, pericardial effusions, moderate to severe renal or liver disease, thyroid disorders, anemia, electrolyte imbalances, any systemic inflammatory or infectious disease and inadequate transthoracic echocardiographic imaging were excluded. All subjects had sinus rhythm and gave written informed consent. The study was carried out in accordance with the principles of the Declaration of Helsinki and approved by the local Ethics Committee.

Echocardiography

All echocardiographic examinations (Vivid 7 Pro, GE Vingmed, Milwaukee, WI, USA) were performed in all patients with the 4-Mhz transducer of Vivid 7 pro (GE Vingmed, Milwaukee, WI, USA). Interpretation of echocardiographic examinations was performed by a cardiologist who was blinded to the clinical and demographic details of the study population. During echocardiographic examination, 1-lead electrocardiography (ECG) was recorded continuously, and three consecutive cycles were averaged for every measured parameter. Two-dimensional, pulsed and tissue Doppler measurements were performed according to the criteria of the American Society of Echocardiography[10]. The following two-dimensional echocardiographic parameters were measured: left ventricular end-diastolic diameter (LVEDD, mm), left ventricular end-systolic diameter (LVESD, mm), left ventricular ejection fraction (LVEF, %), EFT and RVSD. The LVEF was estimated using Simpson's rule. The EFT was measured according to a previously described and validated method[11]. Briefly, the epicardial fat was identified as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium, and it was measured perpendicularly on the free wall of the right ventricle at the end diastole in three cardiac cycles. The maximum value at any site was measured, and the average value was calculated. RVSD was assessed via RVFAC, which was calculated in the apical four-chamber view by the ratio of the difference between the end-diastolic and end-systolic RV areas to the end-diastolic RV area. The normal range of RVFAC is between 32-60%; therefore, values between 25-31% were considered to be mild RVSD, and values ≤ 17 were considered to be severe RVDS[12]. We determined the phase of COPD by using the guidelines established by the Global Initiative for COPD (GOLD)[13].

By placing the pulsed-wave Doppler against the RV free wall and tricuspid annulus junction in the apical four-chamber view, the isovolemic acceleration time (IVA) was measured by dividing the baseline-peak velocity during isovolumic contraction to the peak myocardial velocity during isovolumic contraction. In addition, by placing the M-mode tracing at the lateral free wall and tricuspid annulus junction in the apical four-chamber view, the tricuspid annular plane systolic excursion (TAPSE) was measured, with RV dysfunction being defined as a TAPSE value of less than 2 cm[14]. The myocardial performance index (MPI) was calculated by dividing the sum of the RV lateral wall interventricular contraction time (IVCT) and interventricular relaxation time (IVRT) by the total ejection time (ET)[15].

Laboratory Analysis

Blood was obtained by venipuncture at 8:00 am after a 12-h overnight fast. Plasma for glucose and all lipids were analyzed on the same day. Total cholesterol, HDL-C and triglycerides were measured by enzymatic methods using an autoanalyzer (Beckman Coulter AU5800, Fullerton, CA, USA). LDL-C levels were calculated with the Friedewald equation[16].

Statistical Analysis

Statistical analysis was performed using the SPSS for Windows version 15.0 software (SPSS Inc., Chicago, IL, USA). All continuous variables

were expressed as means ± SD, and categorical variables were defined as numbers and percentages. Additionally, categorical data was compared using a chi-square test, and continuous variables were compared between the groups using Student's *t*-test or the Mann-Whitney U test, depending on whether they were distributed normally or not, which was determined with the Shapiro-Wilk test. Furthermore, analysis of variance (ANOVA) and least significant difference (LSD) from post-hoc tests were used for intragroup comparisons of the continuous variables. Finally, Pearson's correlation analysis was used to estimate the relationship between the test parameters, and p value of < 0.05 was considered to be statistically significant.

Results

Baseline clinical and laboratory data of the study participants are listed in Tables I and II. COPD patients and controls were similar with regard to age, gender, diabetes mellitus (DM), hypertension, dyslipidemia, and BMI. However, there was a significant difference in smoking habits as there were more smokers in the COPD group ($p < 0.001$). Similarly, there was no significant difference regarding age, gender, DM, hypertension, dyslipidemia and BMI between patients with mild and severe RVSD. But, smoking was more prevalent in severe COPD subgroup than in control group (Table II).

The results of RV echocardiographic parameters and RV EFT are shown in Table 1 and Table 2. IVA and TAPSE were found to be lower in COPD groups when compared with the controls (2.3 ± 0.5 vs 2.6± 0.4 m/s^2, $p < 0.002$; 20.0 ± 3.4 vs 25.0 ± 2.1 mm, $p < 0.001$, respectively). On the other hand, MPI and systolic pulmonary arterial pressure (sPAP) were found to be higher in COPD group in comparison to the controls (0.60 ± 0.14 vs 0.46 ± 0.10, $p < 0.001$; 46.1 ± 20.0 vs 23.8 ± 2.6, respectively; $p < 0.001$).

When RV EFT values were compared, patients with COPD exhibited lower values than in the controls (4.92 ± 1.20 vs 6.35 ± 1.10 mm, $p < 0.001$) (Table I, Table II and Figure 1). Moreover, the results of the subgroup analysis indicated that the EFT is thinner in patients with severe RVSD than in those with mild RVSD (4.10 ± 0.77 vs 5.48 ± 1.28 mm, $p = 0.001$). A significant positive correlation was detected between EFT and both TAPSE and IVA (r = 0.522, $p = 0.001$ and r = 0.444, $p = 0.001$, respectively). There was also a significant negative correlation between EFT and both MPI and sPAP (r= -0.555, $p = 0.001$ and r = 0.746, $p = 0.001$, respectively) (Table III).

The EFT/BMI ratio were measured in each group by dividing the EFT by BMI to show that

Table I. Baseline characteristics and echocardiographic parameters of the study population.

Variable	COPD group (n = 98)	Control group (n = 40)	*p*
Age, years	67.0 ± 9.8	70.0 ± 5.5	0.06
Gender, female/male	35/63	15/25	0.84
BMI, kg/m^2	24.1 ± 2.9	25.2 ± 3 .1	0.85
Diabetes, n (%)	4 (4%)	0	0.19
Dyslipidemia, n (%)	4 (4%)	4 (%10)	0.17
Hypertension, n (%)	4 (4%)	0	0.19
Smokers, n (%)	57 (58%)	9 (22%)	< 0.001
LVEDD, mm	44.8 ± 4.2	46.3 ± 5.0	0.12
LVESD, mm	28.5 ± 3.2	29.5 ± 3.3	0.52
LVEF, %	55.6 ± 2.1	55.8 ± 2.0	0.90
RVEDD, mm	30.3 ± 3.4	23.7 ± 1.7	< 0.001
TAPSE, mm	20.0 ±3.4	25.2 ± 2.1	< 0.001
MPI	0.60 ± 0.14	0.46 ± 0.10	< 0.001
IVA, m/s^2	2.3 ± 0.5	2.6 ± 0.4	< 0.002
sPAP, mmHg	46.1 ± 2.0	23.8 ± 2.6	< 0.001
EFT, mm	4.92 ± 1.20	6.35 ± 1.10	< 0.001
EFT/BMI, mm/kg/m^2	0.20 ± 0,04	0.25 ± 0.03	< 0.001

COPD: chronic obstructive pulmonary disease; BMI: body mass index; EFT: epicardial fat tissue thickness; IVA: isovolumic accelerating time; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MPI: myocardial performance index; RVEDD: right ventricular end-diastolic diameter; sPAP: peak systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion.

Table II. Baseline characteristics and echocardiographic parameters of the study population according to the degree of RVSD.

Variable	Severe RVSD (RVFAC < 17%) (n = 40)	Mild RVSD (RVFAC 25-31%) (n = 58	Controls (RVFAC 32-60%) (n = 40)	p
Age, years	67.0 ± 9.5	66 ± 10	70.0 ± 5.5	0.10
Gender, female/male	11/29	24/34	15/25	0.36
BMI, kg/m^2	23.7 ± 3.3	24.4 ± 2.6	25.2± 3.1	0.1
Diabetes, n (%)	2 (5%)	2 (3.4%)	0	0.39
Dyslipidemia, n (%)	0	4 (6.8%)	4 (10%)	0.14
Hypertension, n (%)	14 (35%)	29 (50%)	19 (47%)	0.22
Smokers, n (%)	22 (55%)	35 (60%)	9 (22.5%)	0.01
LVEDD, mm	43.0 ± 3.4	45.0 ± 4.6	46.3 ± 5	0.03
LVESD, mm	27.3 ± 3.1	29.2 ± 3.1	29.5 ± 3.3	0.004
LVEF, %	55.2 ± 2.0	55.9 ± 2.0	55.8 ± 2.0	0.22
RVEDD, mm	33.8 ± 1.9	27.9 ± 1.1	23.7 ± 1.7	< 0.001
TAPSE, mm	17.0 ± 2.3	22.0 ± 2.3	25.0 ± 2.1	< 0.001
MPI	0.7 ± 0.2	0.52 ± 0.11	0,46 ± 0.1	< 0.001
IVA, m/s^2	1.9 ± 0.3	2.5 ± 0.4	2.6 ± 0.4	< 0.001
sPAP, mmHg	68.0 ± 8.8	30.0 ± 5.1	23.0 ± 2.6	< 0.001
EFT, mm	4.10 ± 0.77	5.48 ± 1.28	6.35 ± 1.18	< 0.001
EFT/BMI, mm/kg/m^2	0.17 ± 0.03	0.22 ± 0.04	0.25 ± 0.03	< 0.001

BMI: body mass index; EFT: epicardial fat tissue thickness; IVA: isovolumic accelerating time; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MPI: myocardial performance index; RVEDD: right ventricular end-diastolic diameter; RVSD: right ventricular systolic dysfunction; RVFAC: right ventricular fractional area change; sPAP: peak systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion.

EFT in each group is independent from the BMI values. The EFT/BMI was 0.25± 0.03 in the control group, 0.22 ± 0.04 in the mild RVSD group and 0.17 ± 0.38 in the severe RVSD group, and the differences were significant for all groups ($p < 0.001$) (Table II and Figure 2).

Discussion

The present report showed that EFT decreases in patients with COPD who have RVSD and it is associated with the degree of RVSD. The relationship between EFT and RVSD have been studied for the first time in our study.

Epicardial adipose tissue has a smaller adipocyte size but higher rates of fatty acid uptake and secretion than other visceral fat depots[17,18]. However, epicardial fat has some vital benefits such as serving as a buffer, absorbing fatty acids, and protecting the heart against high fatty acids levels. In addition, it is used as a local energy source at times of high demand by channeling fatty acids to the myocardium[18]. In fact, the body of evidence shows that epicardial fat is an extremely active organ that produces several bioactive adipokines[17].

It was shown that epicardial fat reduction in heart failure, coronary heart disease, and metabolic syndrome was directly related to an increase in cardiovascular events[4-9]. Additionally, many complex and diverse metabolic processes such as insulin resistance, HT, and dyslipidemia

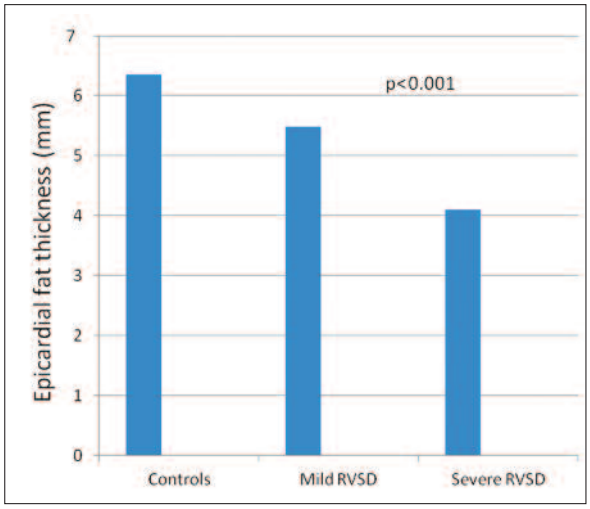

Figure 1. EFT in control, mild RVSD and severe RVSD groups. EFT, epicardial fat thickness; RVSD, right ventricular systolic dysfunction.

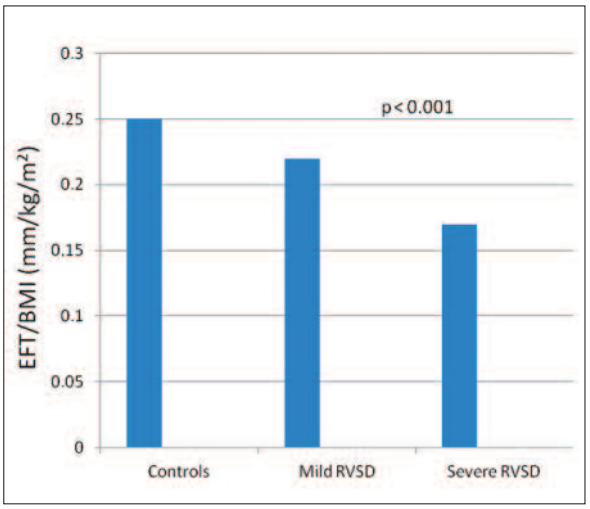

Figure 2. EFT/BMI ratio in control, mild RVSD and severe RVSD groups. BMI, body mass index; EFT, epicardial fat thickness; RVSD, right ventricular systolic dysfunction. Epicardial fat thicknes corrected for body mass index in patients with severe and mild right ventricular systolic dysfunction (RVSD) compared with the controls.

play a role in the increase or decrease of EFT. Moreover, epicardial fat has been suggested to play an independent role in the development and progression of obesity- and diabetes-related cardiac abnormalities[19-21]. In our paper, control group did not differ from the COPD group in terms of DM, hypertension, age, and gender. Because of the confounding effects of some cadiovascular risk factors on EFT, we also calculated EFT/BMI ratio. The results are significantly different between COPD and control groups as well as between COPD subgroups. This was interpreted that besides metabolic processes, there may be also other factors that affect EFT.

COPD is known to have systemic effects, including systemic inflammation, nutritional changes, and adverse effects on the cardiovascular system. Systemic inflammation is discriminated by oxidative stress, activated inflammatory cells and cytokines, and an increase in the plasma levels of acute phase proteins. At the same time, an imbalance between the oxidant-antioxidant status can also be observed[22]. All of these metabolic processes could affect EFT. Nutritional changes, especially weight loss, are seen in patients with COPD. However, the weight loss in these cases is due to the loss of skeletal muscle mass rather than the loss of fat mass[23] and the decrease in *t* EFT found in the COPD group may indicate that it is different from other fat tissues. In our study, smoking was more prevalent in COPD group than in control group. However, we did not find any significant association between smoking and EFT, and this finding is consistent with previous studies.

Tuba et al[9] showed that EFT has been associated with LV volume and dysfunction independently from BMI, and that LV dysfunction was significantly decreased in their patient group. In our study, EFT and RV dysfunction showed a similar relationship that was independent of BMI since the decrease in EFT was parallel with an increase in RVSD. In other words, the EFT showed a proportionate change with a dysfunction that occurred in any part of the heart. This finding may be, in part, explained by the fact that because of its anatomical and functional proximity to the myocardium and its intense metabolic activity, there may present some interactions between the heart and its visceral fat depot[19]. In previous studies[24,25], EFT was evaluated in patients with obstructive sleep apnea, and thinning in EFT was seen with an increase in the degree of sleep apnea that was independent of BMI. Although not specifically declared during this study, it has been thought that there can be a direct relationship between the decrease of EFT and RVSD. It is known that respiratory diseases affects the right ventricular functions in long term. Therefore, the thinning of EFT may be related with RVSD. Although EFT is associated with general adiposity, it was also thought to be related to visceral adiposity in previous studies. These findings are consistent with our findings. Moreover, the positive correlation of EFT with TAPSE and IVA; and negative correlation of EFT with MPI and sPAP indicate that there may be a direct relationship between EFT and RVSD. We speculate that this relationship may represent a continuum in epicardial fat dynamics. As the myocardium becomes more dysfunctional and develops abnormal metabolic needs, the role of epicardial fat as a source of energy or cytokine hemeostasis should decrease; hence, less would be found[26,27].

Finally a previous study in adolescents shows importance of EFT so assessments of EFT in particular during routine echocardiographic examination might be used for the evaulation of cardiovascular disease[28].

Conclusions

We demonstrated that COPD patients had diminished EFT values, which was associated with

the degree of RVSD and it is also associated with the degree of RVSD. Therefore, evaluating EFT in patients with COPD may provide information about the severity of the disease.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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