WW Med 2023 Vol 3 issue: 2

Worldwide Medicine

Original Article

Role of thoracic periaortic adipose tissue in major adverse cardiovascular events in heart failure

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Received: 3 may 2021 / Accepted: 7 Aug 2021

Background: Adipose tissue is defined as a complex endocrine organ that exerts various regulatory functions and has effects on the cardiovascular system. Previous studies have shown that epicardial adipose tissue is associated with heart failure (HF) and cardiovascular outcome. The effect of thoracic periaortic fat tissue (PFT) on this issue is unknown. We aimed to investigate the relationship between PFT and long-term clinical outcomes in patients with HF.

Material and Method: This retrospective cohort study included 71 patients with HF and 45 patients without HF. We calculated their PFT volumes by examining multi-detector computed tomography images with special software. Adverse cardiac events occurring within one year were recorded.

Results: Adverse cardiac events were seen in 23 of the patients during follow-up. Only one of the events was in the healthy group. In the HF group, there was a statistically significant PFT volume compared to the healthy group (54.5 (41.2-66.5) vs. 42.1 (29.9-52.7), p= 0.014). Logistic regression analysis showed that PFT was an independent predictor of MACE (hazard ratio [HR]: 0.96; 95% CI: 0.94-0.99; p = 0.027).

Conclusion: The study has shown for the first time in the literature that PFT volume can be a useful parameter in predicting adverse cardiac events in the follow-up of patients with HF.

Keywords: Heart failure, mortality, thoracic periaortic adipose tissue, thoracic periaortic fat tissue

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DOI: 10.5455/ww.1614791716

1. Introduction

Heart failure (HF) is a clinical syndrome affecting approximately 1% to 2% of the world population. It is clinically characterized by nonspecific symptoms such as labored breathing, fatigue, and distention [1].

HF cases can be classified according to etiology, in addition to symptoms and ejection fraction (EF). While valvular heart diseases, and epicardial and endocardial abnormalities may potentially play a role in the etiology, the underlying cause is generally myocardial disease [2].

In addition to the usual risk factors such as obesity, acute coronary syndrome (ACS), hypertension (HT), and infection, an abnormally high deposition of visceral adipose tissue may also contribute to the development of HF. Adipose tissue mainly consists of subcutaneous lipid-storing connective tissue cells and plays an active role in metabolism and endocrine hormone production, as well as storage [3].

Most of the current information available is about epicardial adipose tissue (EAT). It has effects on cardiac remodeling, insulin resistance, and the renin-angiotensin-aldosterone system (RAAS). These interactions through various pathways, such as the paracrine and endocrine pathways, have direct or indirect effects on HF and cardiovascular diseases [4].

Studies on PFT, one type of adipose tissue, are, however, limited. PFT is known to have a dense parasympathetic neural network, and has been shown to be associated with arrhythmias [5]. Most studies have excluded patients with HF, and have related HF to long-term adverse cardiovascular events in healthy individuals [6]. The difference between patients with HF and a healthy population, and the long-term effects of HF in patients are not clear. This study aimed to investigate the use of PFT in patients with HF and healthy individuals in predicting adverse cardiovascular events in the long term.

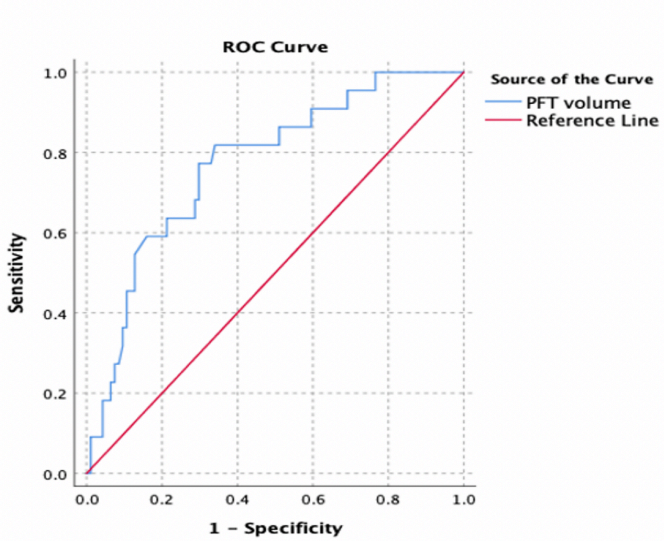

Figure 1. The study's flow chart

2. Materials and Methods

2.1. Patient Population

In this single-center retrospective cohort study, one years' medical records of 116 patients who were followed up in our cardiology clinic were evaluated after a multislice computed tomography scan (MSCT). We planned to include 200 patients in the study. However, we excluded 28 patients with no cross-sectional image, 15 patients with incomplete archive files, and 41 patients without long-term follow-up (Figure 1). In addition to 71 patients over 18 years old with HF, we also selected 45 age-matched individuals with coronary artery disease (CAD) but without HF as the healthy group.

We excluded the patients with chronic renal failure, active infection, malignant disease, cerebrovascular disease, rheumatic valvular disease, congenital heart disease, moderate and severe valvular diseases. We obtained the weight and height values of the patients from their files and thus calculated their body mass indices (BMI) using the formula BMI = body weight (kg) / height (m^2). We obtained the hemogram and biochemical values, which were determined using venous blood samples from the patients' files before MSCT.

2.2. Definitions

Follow-up data were obtained from hospital records or by interviewing the patients or their families in person or by phone. The mean follow-up duration was 12 months. The main end point of study is the long-term presence of MACE. MACEs consisted of three parameters: cardiovascular death, HF-related hospitalization, and new-onset atrial fibrillation (NOAF). Cardiovascular death includes sudden cardiac death, death due to HF and fatal ventricular arrhythmias. Hospitalization due to HF was defined as hospitalization for acute decompensated chronic HF. NOAF was defined as an irregular rhythm in which P-waves could not be detected using electrocardiography with a complaint of new-onset palpitations.

2.3. Echocardiographic Examination

Echocardiographic examinations were performed on all patients using the Vivid 7 Pro device (GE, Norway) and a 2.5-MHz probe. The LVEF values were calculated using the modified Simpson method. The TTE examinations were performed in accordance with the imaging guidelines recommended by the American and European Societies [7].

2.4. Multislice Computed Tomography

All thoracic periaortic examinations were performed by the same radiologist. Images were taken with 320-slice MSCT (Aquilion One Vision Edition, Toshiba Medical Systems, Nasu, Japan) and then analyzed. When measuring

PFT, −200 and 50 Hounsfield units in the thorax that extended from the area of the carina area to the diaphragm below and in front of the esophagus, the vertebral corpus margin on the posterior, the lateral vertebral corpus on the right, and the costovertebral joint on the left surrounding the thoracic aorta were accepted as adipose tissue (Figure 3). The volumes were calculated by manual drawing with custom software (Vitrea Workstation Version 6.8.0, Minnesota, USA) [8].

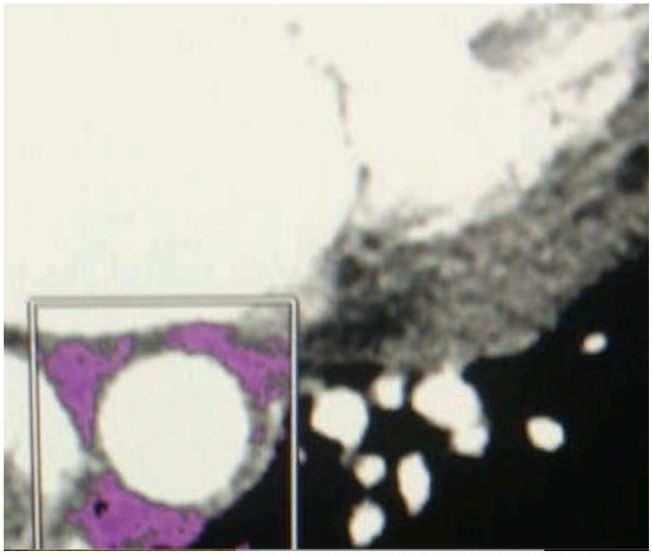

Figure 2. Receiver operating characteristic (ROC) curve of periaortic fat volumes for long-term major adverse cardiac events

2.5. Statistical Analysis

Statistical analyses were performed using SPSS 21.0 (SPSS Inc, Chicago, IL, USA) program. After analyzing the distribution of variables, the continuous variables were shown as mean ± standard deviation, while the categorical variables were expressed as percentages and numbers. The Student's t-test and Mann-Whitney U-test were used to compare parameters with normal distribution and without normal distribution, respectively. The chi-square test was used to compare the odds ratios of categorical variables. Correlation analyses were performed to investigate the associations between PTF volume and the other parameters. Logistic regression analysis was performed using the backward elimination method to determine the effect of the variables. 95% confidence intervals were calculated with standardized beta coefficients. A receiver operating characteristic (ROC) analysis was performed to determine the ability of the PFT volume to predict MACEs. A p value <0.05 was considered statistically significant. Post-hoc power analysis (effect size 0.60, alpha error: 0.05 and 71 patients in group 1 and 45 patients in group 2) was performed with G*Power software version 3.1.9.6 pro- vided a 0.8774417 power for the independent samples t-test.

2.6. Statement of Ethics

This study was in compliance with the principles outlined in the Declaration of Helsinki. The study protocol was approved by local Ethics Committee for Clinical Investigations (decision no: 2020–13).

3. Results

The study involved 116 patients. The demographic and clinical variables of all the groups are given in Table 1. There was no statistical difference between the groups in terms of HT, DM and BMI. In the lipid panel analysis, LDL-C values were statistically higher in the healthy group (p=0.003). After a one-year follow-up of the patients, there had been 23 significant adverse cardiac events (MACEs). We observed all-cause mortality in three patients, hospitalization for HF in eight patients, and NOAF in 12 patients. One of the newly diagnosed AF patients was in the healthy group. Correlation analysis revealed negative correlations between LVEF and PFT volume ($r = -0.339$, $p < 0.001$) (Table 2). In the logistic regression analysis, the contributions of independent predictors for MACEs were calculated using the backward elimination method. It was determined that PFT volume (HR: 0.96; 95% CI: 0.94-0.99; P = 0.027) and LVEF (HR: 1.058; 95% CI: 1.018-1.099; P = 0.004) values were strong and independent predictors of MACEs (Table 3). ROC curve analysis showed that PFT volumes higher than 41 could predict significant adverse cardiac events in the long term [(p <0.001) (with 90% sensitivity and 40% specificity, 0.771 area under the curve 95% CI: 0.666-0.876)] (Figure 2).

Table 1. General characteristics of the patients

Variables	Heart failure (n=71)	Healthy group (n=45)	P value
Age (years)	67±11,7	63±12,4	0,084
Female n (%)	16 (22%)	23 (51%)	0,002
HT n (%)	37 (52%)	23 (51%)	0,916
DM n (%)	36 (50%)	17 (38%)	0,173
BMI (kg/m^2)	26,55±1,57	26,73±1,52	0,557
Smoking n (%)	15 (21%)	8 (18%)	0,659
Glucose (mg/dl)	112,80±27,95	113,44±27,21	0,903
Creatinine (mg/dL)	1,06±0,26	0,88±0,21	<0,001
TSH (mU/L)*	2,1 (1,16-3,06)	2,1 (1,2-2,6)	0,907
LDL-C (mg/dL)*	115 (99-140)	145 (117-164)	0,003
HDL-C (mg/dL)*	45 (39-55)	53 (45-57)	0,006
Triglyceride (mg/dL)*	120 (98-159)	145 (108-180)	0,340
Total cholesterol (mg/dL)*	171 (142-200)	190 (164-230)	0,102
Hemoglobin g/dL	12,79±1,84	13,47±1,49	0,119
Trombosit count (x10^3 μL)	230,62±75,59	247,58±64,44	0,368
Drugs (n, %)			
ASA	62 (87,3)	37 (82,2)	0,449
ACEI/ARB	67 (94,4)	40 (88,9)	0,306
Beta blocker	60 (84,5)	40 (88,9)	0,505
Statin	59 (83,1)	38 (84,4)	0,849
Furosemide	54 (76,1)	0 (0)	<0,001

LVEF (%)*	30 (25-38)	60 (58-64,5)	<0,001
LA*	35 (30-42)	35 (28-38)	0,258
PFT volume (ml)*	54,5 (41,2-66,5)	42,1 (29,9-52,7)	0,014
Outcomes			<0,001
Cardiovascular death	3	0	
HF related hospitalisations	8	0	
Atrial fibrillation	11	1	

The bold values represents as Statistically significant p<.05 values. DM: Diabetes mellitus; HT: Hypertension; LDL-C: Low-density lipoprotein; TSH: Thyroid Stimulating Hormone; HDL-C: High-density lipoprotein; ACEI: Angiotensinogen converting enzyme inhibitor, ARB: Angiotensin receptor blocker, ASA: Acetylsalicylic acid LVEF: Left ventricle ejection fraction; LA: Left atrial PFT: Periaortic tissue volume; HF: Heart failure. *: Data presented as a median with (per 25-75).

Table 2. Results of correlation analyses between PFT volume and other parameters

Abbreviations in Table 1

Variables	PFT volume	
	r	p
Age	0,130	0,163
BMI	-0,143	0,125
LDL-C	-0,148	0,112
LA	0,016	0,861
LVEF	-0,339	<0,001

Table 3. Predictors of long-term major adverse cardiovascular events in multiple regression model

	HR	95% CI	P
Step 1			
PFT volume	0,969	0,969-0,940	0,044
LVEF	1,063	1,019-1,109	0,004
BMI	1,084	0,769-1,529	0,644
Age	0,992	0,946-1,041	0,784
HT	0,589	0,192-1,805	0,354
DM	1,144	0,388-3,372	0,807
Total cholesterol	1,000	0,985-1,014	0,958
Smoking	1,125	0,287-4,406	0,866

Creatinine	1,775	0,227-13,873	0,584
Step 8			
PFT volume	0,968	0,941-0,996	0,027
LVEF	1,058	1,018-1,099	0,004

R^2=0.23, Model statistics p<0.001. CI: Confidence interval; HR: Hazard ratio, Abbreviations in Table 1

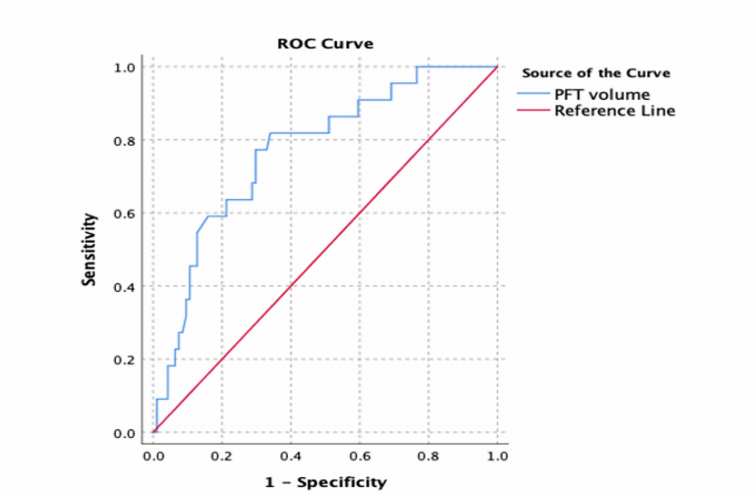

Figure 3. MSCT images depicting periaortic adipose tissue measurement

4. Discussion

This study is the first to investigate the effect of PFT volume values on MACEs in long-term follow-up in HF and healthy individuals. We determined that the PFT volumes were higher in HF patients compared to healthy individuals, and were independent predictors of MACEs.

Although ischemic heart disease is the most common cause of HF, it has no accepted standard etiological classification. HT, DM, obesity, and arrhythmias are the usual risk factors [9]. Obesity has become an important health problem all over the world, and increasing BMI values correlate with an increase in adverse cardiac outcomes. Increases in the volume of fat, secondary to increased BMI values, and impaired pro-inflammatory and anti-inflammatory responses have been blamed for this [10]. Although the effects of PFT values on the vascular system were different in other studies, we observed no differences between the groups in terms of BMI. The PFT values were higher in the patients with HF compared to healthy individuals and were associated with MACEs [11]. We think that PFT is a more specific tissue to focus on compared to epicardial adipose tissue. The results of other studies support this theory. As a matter of fact, a positive correlation was observed between epicardial adipose tissue and LDL-C levels and BMI in one previous study, whereas, in the current study, no correlation was observed between PFT volume, LDL-C values, and BMI values [12]. Repeated hospitalizations in patients with a diagnosis of HF are associated with increased mortality [13].

PFT is not only a dynamic organ but also a fat deposit affecting systemic organs. In the current study, there were more episodes of atrial fibrillation in patients with HF. LA diameter plays an important role in the development of AF. In hypertrophic cardiomyopathy patients, a relationship has been shown between NOAF and LA diameter [14]. Although there was no difference between the groups in terms of LA diameters in the current study, the more frequent incidence of AF in the group with high PFT volumes suggests that PFT may play a role in the etiology of AF.

In the current study, the volume of PFT was measured in patients who underwent MDCT for various indications, showing that PFT volume is associated with the long-term frequency of MACE, and that MACEs are an independent predictor.

Limitation

This was a retrospective and single-center study and thus has limitations: it is difficult to generalize the present findings to the general population, and the results will need to be confirmed with multi-center and larger studies.

Conclusion

We have suggested that PFT is not only adipose tissue, but is also a hitherto understudied fat deposit that affects systemic organs, which thus needs to be further studied. PFT volume can be useful as a marker for predicting MACEs in patients with HF.

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