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MAIN ARTICLE

Association of epicardial fat thickness with clinical and polysomnographic parameters in non-obese obstructive sleep apnoea patients

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Abstract

Objectives: This study aimed to investigate the relationship of epicardial fat thickness with severity of obstructive sleep apnoea, and clinical and polysomnographic parameters, and to determine independent predictors for epicardial fat thickness.

Methods: A total of 84 patients with a body mass index of less than 30 kg/m^2 and suspected sleep-disordered breathing were included in the study. The correlations of epicardial fat thickness with polysomnographic and clinical data, and severity of obstructive sleep apnoea, were investigated.

Results: Mean epicardial fat thickness was 3.75 ± 1.07 mm in the study group ($n = 62$) and 2.97 ± 0.62 mm in the control group ($n = 22$) ($p < 0.001$). There were significant positive correlations between epicardial fat thickness and: apnoea/hypopnoea index, oxygen desaturation index 3 and minimum oxygen saturation, as well as with age, body mass index, and neck and waist circumferences.

Conclusion: Non-obese obstructive sleep apnoea patients have thicker epicardial fat compared to controls. Oxygen desaturation index 3 has a strong correlation with epicardial fat thickness and is an independent predictor of it.

Key words: Visceral Adipose Tissue; Sleep Apnea Syndromes; Echocardiography; Hypoxemia; Obesity

Introduction

Epicardial fat is situated between the myocardium and visceral pericardium. It covers more than three-quarters of the heart's surface.[1] It is a visceral fat tissue and has different characteristics to other adipose tissues. The adipocytes in epicardial fat are smaller than those in subcutaneous fat and visceral fat in other sites in the body, and the number of adipocytes per gram of tissue is greater.[1] Epicardial fat surrounds the coronary arteries, acts as a paracrine gland, and secretes pro-atherogenic and proinflammatory hormones, and cytokines.[2] Interleukin 6, tumour necrosis factor alpha, adipocytokines and leptin are some of the cytokines released from it.[3,4]

Relationships between epicardial fat thickness and inflammation, vascular dysfunction, oxidative stress, atherosclerosis, and clinical and subclinical coronary artery disease have been shown. In addition, thick epicardial fat tissue has been reported to be a cardiovascular risk factor, independent of other classical risk factors.[5] Thick epicardial fat is also a metabolic risk factor, and has been associated with metabolic syndrome.[6]

Obstructive sleep apnoea (OSA) syndrome is a respiratory disorder of sleep characterised by recurrent episodes of obstructive breathing, caused by repetitive partial or complete collapse of the upper airway.[7] Its prevalence has been reported as 4 per cent in adult males and 2 per cent in adult females.[8] Apnoea and hypopnoea in OSA usually occur together with oxyhaemoglobin desaturations. Individuals with OSA experience sudden arousals from sleep, sleep is fragmented and daytime sleepiness may result. Obstructive sleep apnoea has been associated with mortality and morbidities such as cognitive disorders.[9] It is also a reportedly serious risk factor for systemic arterial hypertension, coronary artery disease, heart failure and stroke. Sympathetic activation due to apnoea and hypopnoea, endothelial dysfunction due to inflammation and oxidative stress, and metabolic dysfunction are the main reasons for the increased risk of cardiovascular diseases in OSA.[10]

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Obstructive sleep apnoea has been associated with inflammation.[9] It was demonstrated that the levels of proinflammatory cytokines, chemokines and adhesion molecules were higher in OSA patients compared to controls, and treatment with continuous positive airway pressure (CPAP) caused a reduction in those markers.[11] The most important factor starting the inflammatory process in OSA is intermittent hypoxia, which is specific to OSA, and characterised by fast re-oxygenation after short desaturations related to apnoea and hypopnoeas.[11]

Epicardial fat thickness has been linked to OSA, and it was previously reported that epicardial fat is significantly thicker in obese OSA patients compared to controls.[12–14] To our knowledge, no studies in the English literature have investigated epicardial fat thickness in non-obese patients with OSA.

This study aimed to determine epicardial fat thickness in non-obese OSA patients using echocardiography, and to compare the results with controls. In addition, we investigated the correlations between epicardial fat thickness and OSA severity, and clinical and polysomnographic data, and discussed the importance of intermittent hypoxia on epicardial fat thickness, independent of obesity.

Materials and methods

Study population

A total of 84 patients with a body mass index (BMI) of less than 30 kg/m^2, admitted to our otorhinolaryngology clinic with complaints suggesting sleep-disordered breathing, and who had undergone polysomnography between March 2014 and January 2015, were included in the study. Patients and controls with a BMI of more than 30 kg/m^2, hypothyroidism or hyperthyroidism, primary heart disease, chronic obstructive or restrictive pulmonary disease, uncontrolled hypertension, and craniofacial abnormalities, were excluded, as were smokers and those who used hypnotic drugs.

All patients provided written informed consent. The study protocol was approved by the Ethics Committee of the University.

Clinical measurements

Patients who were admitted to our otorhinolaryngology out-patient clinic with snoring, witnessed apnoea, daytime sleepiness and fatigue were evaluated, with a pre-diagnosis of sleep-disordered breathing. Detailed medical histories of the patients were obtained, and the individuals were questioned regarding the presence of any diseases and use of any drugs. The validated Turkish version of the Epworth Sleepiness Scale was used to analyse daytime sleepiness.[15]

The patients' waist circumference (measured just above the iliac crest while the patient was standing) and neck circumference (measured at the level of the cricothyroid membrane) were measured (in centimetres) and recorded. Body mass index (in kg/m^2) was used to determine obesity.

All patients underwent detailed ENT examinations, including fibre-optic nasopharyngolaryngoscopy and the Müller manoeuvre, and they were evaluated for the presence of any abnormalities that may be causing upper airway obstruction. A whole-night polysomnography was ordered in cases where there was any suspicion of sleep-disordered breathing.

Polysomnography

All included patients underwent technician-attended whole-night polysomnography, performed with an Embla® S4500 system in the sleep laboratory of our hospital. Polysomnography recordings were obtained between 10 pm and 6 am (8 hours). The following measures were recorded: six-channel electroencephalography (two occipital, two central and two frontal channels); right and left electrooculography; electrocardiography; chin, and right and left tibialis muscle electromyography; oronasal pressure; thoracal and abdominal respiratory efforts; pulse oximetry; position; and snoring sound. The polysomnographic data were scored manually by a certified and experienced physician in accordance with the (American Academy of Sleep Medicine) *AASM Manual for the Scoring of Sleep and Associated Events*, version 2.[16]

An apnoea was defined as a drop in the peak signal excursion by 90 per cent or more of the pre-event baseline, with the duration of the 90 per cent or higher drop in sensor signal lasting for 10 seconds or more. Hypopnoea was scored when the peak signal excursions dropped by 30 per cent or more of the pre-event baseline, for 10 seconds or longer, in association with either 3 per cent or higher arterial oxygen desaturation or an increase in the number of arousals.[16] The apnoea/hypopnoea index was calculated by dividing the number of apnoea/hypopnoea events by the number of hours of sleep. Oxygen desaturation index 3 was calculated by dividing the number of 3 per cent drops in oxygen saturation by the number of hours of sleep. The minimum oxygen saturation was recorded.

Echocardiography

Standard transthoracic echocardiography was performed by the same cardiologists in all patients, using a Philips ultrasound system (Epiq 7 G machine; Andover, Massachusetts, USA), within 48 hours of admission. Standard views, including the left lateral decubitus and supine positions, were obtained. Epicardial fat was defined as the relatively echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium. Epicardial fat thickness was measured at the end of diastole, on the free wall of the right ventricle from the parasternal long- and short-axis views, as previously described.[17] The maximum values at any site were measured and the average value was calculated. The intra-observer correlation coefficient was 0.95.

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Study groups

Patients with an apnoea/hypopnoea index of 5 events per hour or more were included in the OSA (study) group, and those with apnoea/hypopnoea index of less than 5 events per hour were included in the control group. There were 62 patients in the study group and 22 patients in the control group. The two groups were compared in terms of epicardial fat thickness.

The study group was divided into three subgroups based on OSA severity, according to the apnoea/hypopnoea index: (1) mild OSA = 5–14.99 events per hour; (2) moderate OSA = 15–29.99 events per hour; and (3) severe OSA = 30 or more events per hour. The three patient subgroups were compared with each other, and each subgroup was compared to the control group regarding epicardial fat thickness.

Statistical analysis

Data were analysed with IBM SPSS Statistics version 20 software for Mac (IBM, Los Angeles, California, USA). The results were expressed as means ± standard deviations. The Pearson correlation test was used to measure the linear association among variables. The Tukey honest significant difference test was used as the post-hoc test. Differences between the groups were analysed with analysis of variance for continuous variables. Multivariate linear regression analysis was performed to determine whether the variables were independent predictors for epicardial fat thickness. All *p*-values presented are two-tailed, and values of less than 0.05 are considered to be statistically significant.

Results

In total, 84 patients with a BMI of less than 30 kg/m^2 (62 OSA patients and 22 controls), who had undergone polysomnography, were included in the study. There were 52 males and 10 females in the study group, and 18 males and 4 females in the control group. The clinical and polysomnographic data of the study and control groups are presented in Table 1. Polysomnography results indicated that of 84 patients, 10 (11.9 per cent) had mild, 17 (20.2 per cent) had moderate and 35 (41.7 per cent) had severe OSA.

The distribution of epicardial fat thickness in the study and control groups is presented in Table 2. Epicardial fat was significantly thicker in the OSA group ($p < 0.001$). Post-hoc analysis indicated that epicardial fat was significantly thicker in the severe OSA group compared to the controls ($p = 0.012$) (Figure 1).

Correlation analysis

Age, BMI, neck circumference and waist circumference showed significant positive correlations with epicardial fat thickness. There was no significant correlation between epicardial fat thickness and Epworth Sleepiness Scale scores (Table 3).

Epicardial fat thickness showed a significant and positive correlation with apnoea/hypopnoea index ($p = 0.04$). Epicardial fat thickness was also highly and positively correlated with oxygen desaturation index 3 ($p < 0.001$) (Figure 2). On the other hand, epicardial fat thickness was negatively correlated with minimum oxygen saturation ($p = 0.001$) (Table 3).

Multivariate regression analysis was performed to determine independent predictors for epicardial fat thickness. Only oxygen desaturation index 3 was found to be an independent predictor of epicardial fat thickness ($p = 0.036$) (Table 4).

Discussion

In our study, we showed for the first time in the English literature that epicardial fat was significantly thicker in non-obese OSA patients when compared to controls. It was also shown for the first time that oxygen desaturation index 3 was an independent predictor of epicardial fat thickness.

Thick epicardial fat is a cardiometabolic risk factor independent of other classical risk factors.[1] It has been associated with cardiovascular diseases, diabetes mellitus, gestational diabetes and metabolic syndrome. Kim *et al.* performed a study on 209 patients, and showed correlations between epicardial fat thickness

TABLE I
CLINICAL AND POLYSOMNOGRAPHIC DATA OF THE STUDY AND CONTROL GROUPS

Characteristic	OSA group*		Control group†	
	Range	Mean ± SD	Range	Mean ± SD
Age (years)	25–75	47.43 ± 12.56	19–56	38.68 ± 10.98
BMI (kg/m^2)	17.90–29.80	26.74 ± 2.30	19.15–29.70	24.50 ± 3.26
Neck circumference (cm)	31–51	40.07 ± 3.42	32–47	39.28 ± 3.75
Waist circumference (cm)	80–140	102.59 ± 8.88	81–109	97.20 ± 7.51
ESS score	1–17	7.21 ± 4.49	0–15	3.95 ± 4.58
AHI (events per hour)	6.5–102.4	41.72 ± 26.14	0–4.9	2.60 ± 1.35
ODI3‡	4–96.5	38.22 ± 31.79	0–15.00	2.88 ± 4.53
Minimum oxygen saturation (%)	53–93	81.77 ± 8.79	79–94	88.87 ± 5.27

*$n = 62$; †$n = 22$. ‡Values represent the number of 3 per cent drops in oxygen saturation divided by the number of hours of sleep. OSA = obstructive sleep apnoea; SD = standard deviation; BMI = body mass index; ESS = Epworth Sleepiness Scale; AHI = apnoea/hypopnoea index; ODI3 = oxygen desaturation index 3

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TABLE II
EPICARDIAL FAT THICKNESS OF THE STUDY AND CONTROL GROUPS

Group*	Range (mm)	Mean ± SD (mm)
Control	2.00–4.90	2.97 ± 0.62
Total OSA	1.61–6.10	3.75 ± 1.07
Mild OSA	2.1–5.2	3.68 ± 0.90
Moderate OSA	1.61–5.4	3.63 ± 1.06
Severe OSA	2.6–6.1	3.82 ± 1.14

*As determined by polysomnography. SD = standard deviation; OSA = obstructive sleep apnoea

TABLE III
CORRELATIONS OF EPICARDIAL FAT THICKNESS WITH OTHER VARIABLES STUDIED

Variable	Pearson correlation coefficient	*P*-value
Age	0.108	0.005
BMI	0.338	0.002
Neck circumference	0.238	0.031
Waist circumference	0.372	0.001
ESS	0.196	0.079
AHI	0.225	0.04
ODI3	0.475	<0.001
Minimum oxygen saturation	−0.372	0.001

BMI = body mass index; ESS = Epworth Sleepiness Scale; AHI = apnoea/hypopnoea index; ODI3 = oxygen desaturation index 3

and coronary artery disease and coronary artery calcium levels.[18] It has also been demonstrated that epicardial fat thickness is an independent risk factor for coronary artery disease.[17] Similarly, Hajsadeghi *et al.* showed a correlation between epicardial fat thickness and coronary artery disease, and reported epicardial fat thickness to be a risk factor (independent of other risk factors) for major adverse cardiac events, after follow up of their 245 patients for a period of 48 months.[5]

Epicardial fat thickness was shown to be associated with type 2 diabetes mellitus[19] and gestational diabetes.[20] Mohar *et al.* demonstrated that epicardial fat thickness was correlated with coronary artery disease severity in patients with type 2 diabetes mellitus.[21] Epicardial fat thickness was also associated with metabolic syndrome. Pierdomenico *et al.* performed a meta-analysis, and reported the results of 9 studies on 1030 patients with metabolic syndrome.[6] The authors reported that epicardial fat was thicker in patients with metabolic syndrome when compared to those who did not have metabolic syndrome.[6]

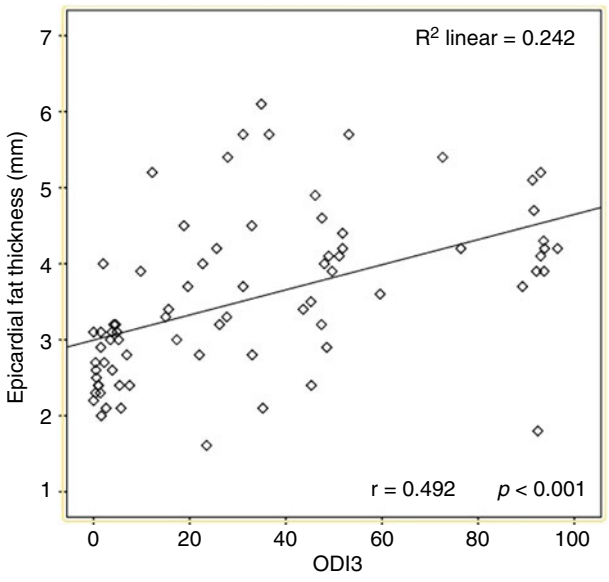

FIG. 1
Relationship between epicardial fat thickness and oxygen desaturation index 3 (ODI3).

Various methods, such as multi-detector computed tomography (CT), magnetic resonance imaging (MRI) and echocardiography, have been used to determine epicardial fat thickness. A number of studies used multi-detector CT to measure the volume of epicardial fat,[5,6,18,22] and it was reported that echocardiographic measurements were compatible with the measurements performed using multi-detector CT.[6] Some other studies have used MRI to measure epicardial fat thickness;[22] however, it is not a preferred modality as it is expensive and there may be limited access to MRI facilities.

Echocardiography is an inexpensive, non-invasive, easy-to-use and widely employed method to measure epicardial fat thickness. Furthermore, a number of studies have shown that echocardiographic measurements of epicardial fat thickness are compatible with measurements obtained using other techniques.[1,12–14,18–20] We preferred echocardiography to measure epicardial fat thickness in our study.

Obstructive sleep apnoea has been associated with coronary artery disease, hypertension, congestive heart failure and cerebrovascular events.[9,10] Some investigators have studied the relationship between OSA and epicardial fat thickness.[12–14] Mariani *et al.* investigated the association between epicardial fat thickness and OSA in 115 obese OSA patients, and demonstrated that epicardial fat thickness increased as OSA severity increased.[12] Similarly, Lubrano *et al.* found a correlation between OSA and epicardial fat thickness in obese OSA patients.[13] In addition, those authors found thicker epicardial fat in patients with OSA and metabolic syndrome, when compared to OSA patients without metabolic syndrome.[13]

Akilli *et al.* included obese and non-obese OSA patients in their study, and investigated the relationship between OSA and epicardial fat thickness by gender.[14] They found significant differences in epicardial fat thickness between severe OSA patients and controls, and mild OSA patients and controls in females; however, they did not find any significant correlation

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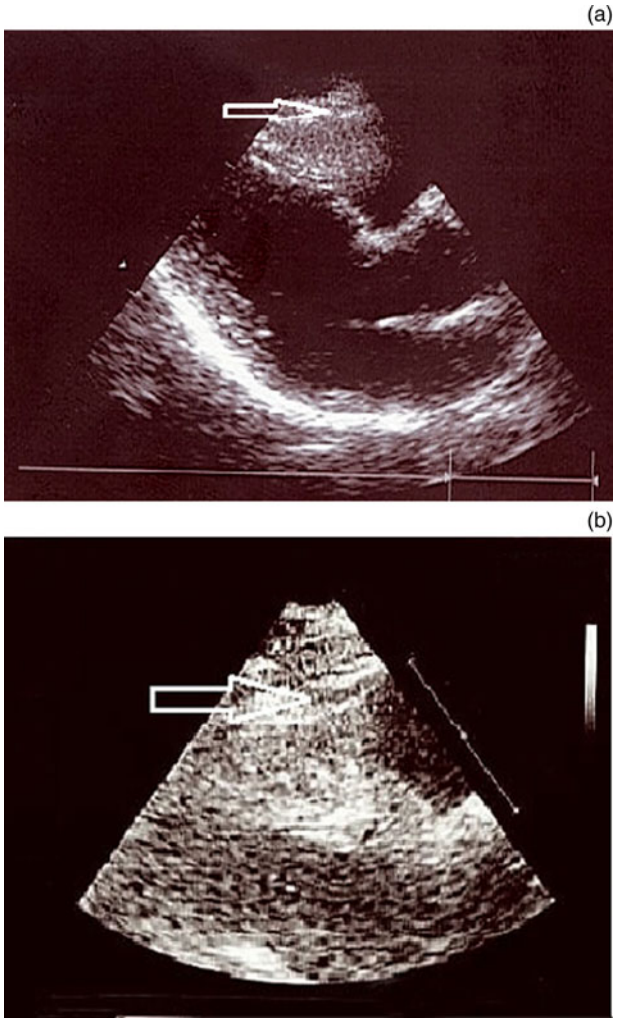

FIG. 2

Measurement of epicardial fat thickness in (a) control individual and (b) patient with obstructive sleep apnoea (OSA). Epicardial fat was identified as an echo-free space in the pericardial layers on the echocardiography, and its thickness was measured perpendicularly on the free wall of the right ventricle at the end of diastole. Epicardial fat tissue was found to be thicker (thick arrow) in the OSA group than the control group (thin arrow).

between epicardial fat thickness and OSA severity in males.[14] Çetin *et al*. investigated the effect of CPAP therapy on epicardial fat thickness.[23] They showed that CPAP treatment reduces epicardial fat thickness volume in patients with OSA.

To our knowledge, no studies in the English literature have investigated the correlation between epicardial fat thickness and OSA in non-obese OSA patients. We performed our study on non-obese OSA patients, and found significantly higher epicardial fat thickness in non-obese OSA patients when compared to controls. In addition, epicardial fat thickness showed a positive correlation with apnoea/hypopnoea index. In our study, we showed for the first time that epicardial fat was thicker in OSA patients, independent of obesity.

Although a number of studies have shown that obesity, OSA, metabolic syndrome, cardiovascular diseases and epicardial fat thickness were interrelated, it is not easy to unravel the complex relationships between them. Our study is important, as we excluded obese patients, and showed a correlation between OSA and epicardial fat thickness, independent of obesity. We believe that our study provides important data to interpret the aforementioned complex relationships.

One must consider the importance of inflammatory events in both OSA and epicardial fat thickness when interpreting the relationship between these two conditions. The levels of inflammatory markers have been shown to be increased in OSA.[24] A number of inflammatory markers, including tumour necrosis factor alpha (TNF-α), interleukins 6 and 8, and C-reactive protein, were found to be higher in OSA patients.[20] Endothelial dysfunction related to the inflammatory process in OSA has been proposed to play a role in the development of cardiovascular diseases.[21,25] In addition to its close location to coronary vessels, epicardial fat acts as a paracrine gland that releases inflammatory markers. It is thought that inflammatory adipokines, such as TNF-α, interleukin 6 and 1b, and monocyte chemoattractant protein-1, are released from epicardial fat, resulting in the development of cardiovascular events.[1] Both OSA and thicker epicardial fat are correlated with inflammatory events.

It has also been suggested that intermittent hypoxia is the event that starts the inflammatory process in OSA.[9–11] Intermittent hypoxia is a unique kind of hypoxia seen in OSA, and is characterised by desaturations related to respiratory events occurring during sleep and arousal, and reperfusion following them.

TABLE IV
MULTIVARIATE REGRESSION ANALYSIS FOR EPICARDIAL FAT THICKNESS

Variable	Unstandardised coefficients		Standardised coefficients	*t*	*P*-value
	B	Standard error	Beta		
Minimum oxygen saturation	−0.001	0.017	−0.008	−0.056	0.956
Age	0.016	0.009	0.202	1.834	0.071
Gender	0.216	0.282	0.079	0.763	0.448
BMI	0.045	0.044	0.119	1.018	0.312
AHI	0.003	0.004	0.076	0.729	0.468
ODI3	0.010	0.005	0.305	2.135	0.036

Dependent variable: epicardial fat thickness. BMI = body mass index; AHI = apnoea/hypopnoea index; ODI3 = oxygen desaturation index 3

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Previous studies that investigated the correlation between epicardial fat thickness and OSA in obese patients only used the apnoea/hypopnoea index, and not intermittent hypoxia parameters, in statistical analyses. When we considered that the event starting the inflammatory process in OSA may be intermittent hypoxia, we felt that data related to hypoxia should be included in the statistical analysis.

The oxygen desaturation index represents the number of times per hour of sleep that the blood oxygen level dropped by a certain degree from baseline. It is believed that an elevation in oxygen desaturation index may lead to increased oxidative stress in the body, which may predispose people to long-term cardiovascular risks, including high blood pressure (hypertension), heart attack, stroke, and memory loss associated with dementia. Therefore, we used oxygen desaturation index 3 and minimum oxygen saturation as variables in the statistical analysis. We believed that oxygen desaturation index 3 was the most important parameter representing intermittent hypoxia in OSA. We found that epicardial fat thickness showed significant correlations with oxygen desaturation index 3 and minimum oxygen saturation.

As stated above, none of the studies that investigated epicardial fat thickness in obese OSA patients used oxygen desaturation index 3 as a variable. Only Akilli *et al.*, who investigated the relationship between epicardial fat thickness and gender, reported a positive correlation between epicardial fat thickness and oxygen desaturation index during rapid eye movement sleep in women.[14] In our study, we report, for the first time, that oxygen desaturation index 3 is an independent predictor of epicardial fat thickness.

- **Thick epicardial fat is a cardiovascular risk factor**
- **It has been associated with obstructive sleep apnoea (OSA), coronary artery disease, obesity, metabolic syndrome and diabetes mellitus**
- **There were significant positive correlations between epicardial fat thickness and apnoea/hypopnoea index, oxygen desaturation index 3 and minimum oxygen saturation**
- **Epicardial fat was significantly thicker in patients with severe OSA**
- **Oxygen desaturation index 3 was an independent predictor of epicardial fat thickness**

Our study has some limitations. First, our sample size is small, in both the study and the control groups. Further studies are needed on larger, non-obese patient cohorts. In addition, new studies should be conducted on both obese and non-obese patients that include intermittent hypoxia parameters as variables.

In conclusion, this study showed for the first time that epicardial fat was thicker in non-obese OSA patients compared to controls. A strong correlation was found between oxygen desaturation index 3 and epicardial fat thickness in non-obese OSA patients. Epicardial fat thickness, independent of obesity, may provide important information on OSA. In addition, oxygen desaturation index 3 is an independent predictor of epicardial fat thickness. Obstructive sleep apnoea should be considered if routine echocardiography reveals increased epicardial fat thickness. Further studies on larger patient cohorts are needed to further clarify this subject.

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