The value of epicardial adipose tissue thickness for outcome prediction of patients undergoing coronary artery bypass grafting surgery

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Background: The significant association between epicardial adipose tissue and cardiovascular risk factors as well as outcome of ischemic heart diseases has been recently proposed. We determined the association between epicardial adipose tissue thickness and in-hospital as well as 3-month outcome after coronary artery bypass grafting surgery (CABG). **Materials and Methods:** This cross-sectional study was performed on 78 consecutive patients who underwent CABG in our heart center. Associations between epicardial adipose tissue thickness and in-hospital as well as 3-month outcome after CABG were measured by logistic regression and value of epicardial fat thickness evaluated by receiver operating characteristic (ROC) curve analysis. **Results:** Patients in-intensive care unit (ICU) suffered a variety of events, which many of them were insignificant, but 23 events (29.4%) of 78 were considered as important. The most frequent complication occurred in ICU was atrial fibrillation (9%). The frequency of 3-month complications was 6.4%, including 3.8% rehospitalization, 1.3% reoperation, and 1.3% cardiac death. Ninety-day mortality rate was 1.3%. Mean epicardial adipose tissue thickness was significantly higher in those with in-ICU complications than those without complication (7.64 ± 2.80 mm vs. 6.16 ± 2.29 mm, $P = 0.015$); however, the difference for 90-day complications was statistically nonsignificant. According to ROC curve analysis, measuring epicardial adipose tissue thickness could moderately predict in-ICU complication (area under the curve = 0.65 8, 95% confidence interval: 0.536–0.779, $P = 0.017$). The best cut-off point of this adipose tissue thickness for predicting in-ICU complication was 6.5 mm with sensitivity of 65.9% and specificity of 58.8%. **Conclusion:** Epicardial adipose tissue thickness is a useful predicting parameter for in-ICU complications after CABG.

Key words: Complication, coronary artery bypass graft, epicardial adipose tissue, epicardial fat pad

INTRODUCTION

Epicardial adipose tissue (epicardial fat tissue or epicardial fat pad) is a visceral adipose tissue around the heart that is particularly deposited around subepicardial coronary vessels.[1] In physiological conditions, the fat tissue consists about 20% of the heart volume, and there is no fascia tissue between muscular tissue of the heart and epicardial fat.[2-4] Because of the especial situation of epicardial adipose tissue adjacent to the myocardium and also due to pro-inflammatory substances produced in this tissue, this adipose tissue acts through two mechanisms including local effects and paracrine effects.[5,6] The prominent cells in epicardial fat are adipocytes, ganglia of interconnecting nerves, and immune cells.[7,8] Due to this cellular variety, epicardial adipose tissue has several functions including myocardial protection against high levels of free fatty acids in the blood, energy production at a time when rising demand in the myocardium, myocardial protection against hypothermia, and protection and secretion of pro-inflammatory and preatherogenic biomarkers such as tissue necrotizing factor alpha, interleukin-6, neural growth factor, resistin, and angiotensin.[9-11] In addition,

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epicardial adipose tissue can act as a main source of adipocytokines that involve in the development of coronary atherosclerosis.[6] In fact, epicardial adipose tissue expresses various genes for coding cytokines associated with coronary atherosclerosis.[12,13] The association between epicardial adipose tissue and cardiovascular risk factors has been also shown in some studies. It has been well demonstrated that in obese individuals, thickness and volume of epicardial adipose tissue is more accurate indicator than peripheral fat and also anthropometric indices.[14] Moreover, this adipose tissue in epicardium is associated with inducing metabolic syndrome and its main components including insulin resistance, dyslipidemia, and hypertension.[15] Thus, it is now hypothesized that epicardial adipose tissue may also predict development of coronary atherosclerosis, extension of cardiac ischemic events and also causes poor outcome in ischemic heart disease. Considering that coronary artery bypass grafting (CABG) is an important part of management in ischemic heart disease, finding interfering factors in CABG outcome is crucial. In the present study, we evaluated whether epicardial adipose tissue thickness is a contributing factor in complications after CABG surgery. Besides, our innovation in this study was direct measurement of epicardial adipose tissue at surgery that may be more reliable compared to imaging method.

MATERIALS AND METHODS

Study design and participants
This cross-sectional study was performed on 78 consecutive patients who underwent CABG in Sina hospital, Isfahan, Iran, from April 2014 to July 2015 (Research project number: 15010101922043). The convenient sampling method was applied, and the sample size was calculated based on 5% of Type I error and 80% power.

All patients were candidate for the surgery based on angiography reports of significant coronary artery disease (CAD) and gave written informed consent before surgery.

Exclusion criteria include
Those with unwillingness, presence of valvular heart disease, and surgery other than CABG.

During operation, the occurrence of arrhythmia, cross-clamp time, cardiopulmonary bypass (CPB) time, need for cardioversion, need to balloon pump and its usage time, and also need to more than one inotrope were recorded. After surgery, ventilation time (>48 h), time for inotrope use (more than 48 h), or postoperative complications including atrial fibrillation (AF), ventricular arrhythmias, heart blocks, raising blood pressure, gastrointestinal bleeding, reoperation, local infection, myocardial infarction (MI),

renal failure, pericardial effusion, respiratory distress, length of intensive care unit (ICU) stay, length of hospital stay, and in-hospital death were also recorded. After discharge, all patients were followed for 3 months in terms of assessing death as well as complications such as stroke, MI, or congestive heart failure.

Study variables' assessment
At first, baseline characteristics and clinical history including cardiovascular risk factors were collected by interviewing and recorded at the data gathering form. Weight was measured by use of SECA Alpha 750 digital scales and height was measured by a stadiometer from the ground surface to the tip of the outstretched plant. The body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. Blood pressure was assessed using a sphygmomanometer marked as Alpha Kinase 2. Fasting blood sugar and lipid profile were also measured by especial kits (KERNEL model), 24 h preoperatively. Epicardial adipose tissue was measured on the thickness of adipose tissue. By scalpel, the epicardium was cut 2 cm below the right ventricular outflow tract (with the highest fat tissue thickness) for 5 mm to the level of myocardium. Then, a cylindrical steel rod with a thickness of 2 mm was inserted to the cutoff point. The maximum thickness of epicardial adipose tissue was obtained by determining front of rod to adipose tissue and measuring it by a steel caliper.

Statistical analysis
All data were entered in statistical software. The statistical software, SPSS version 16.0 for windows (SPSS Inc., Chicago, IL, USA), was used. Basic results were presented as quantitative and categorical variables. Kolmogorov–Smirnov test was applied to test variables normality. According to the normality test results, Mann–Whitney-U-test or independent-*t*-test was used to test significant difference between patients with and without complications. Chi-square or Fisher's exact test was used to test dependence of categorical variables. The correlations were tested using Pearson's or Spearman's Rank order correlation tests, according to the normality condition. The association between epicardial adipose tissue thickness and outcome was assessed using the multiple logistic regression analysis when adjusted for baseline variables. $P \leq 0.05$ was considered as statistical significance. The predictive value of epicardial adipose tissue thickness on complications was assessed using the receiver operating characteristic (ROC) curve analysis.

RESULTS

The study population consisted of 78 patients, age 39–80 years of age (65 men and 13 women, mean age 63.66 ± 8.40 years). Functional capacity of patients stratified by New York Heart Association (NYHA) functional class,

in which 9.0% had NYHA class Score I, 87.2% had NYHA class Score II, and 3.8% had NYHA class Score III. Time of MI to surgery was measured and 3.8% of patients experienced this event within the 1–7 days, 3.8% within 22–90 days, while 25.6% had history of MI 90 days before of admission time. Angiographic data showed single-vessel disease in 1.3% of patients, two-vessel disease in 14.1%, and three-vessel disease in 83.3%. Furthermore, 3.8% had left main lesion [Table 1]. Forty-one percent of patients were diabetic, 32.1% were hypertensive, 9.0% had dyslipidemia, and 7.7% were smoker. The mean BMI was 27.82 ± 3.92 kg/m^2. 7% had no known cardiovascular traditional risk factors. Mean preoperative left ventricular ejection fraction was 52.50 ± 11.90%. Based on our analysis, 2.6% had history of lung disease such as chronic obstructive pulmonary disease, 6.4% had renal insufficiency, and 19.2% had history of cerebrovascular diseases. The mean CPB time was 76.56 ± 15.92 min, and mean cross-clamp time was also 45.51 ± 1.15 min.

With respect to intraoperative complications, 2.6% needed excess doses of inotropes, 3.8% needed intra-aortic balloon pump insertion, 5.1% experienced cardiac arrhythmias, 1.3% had cardiac arrest, and in 1.3% of patients, epicardial pacemaker were required.

Total in-ICU unwanted events are shown in Table 2. The most frequent in-ICU complication was AF (9%) and inotrope use for more than 48 h (6.4%). Bleeding >1000 cc (3.8%) and fever (7.7%) were other common unwanted events in ICU. Mortality was reported in only 1.3% of patients during ICU management course. Mean total ICU stay was 2.48 ± 1.54 days and mean total hospital stay was 6.29 ± 2.85 days. Three-month complication was recorded in 6.4% of patients including rehospitalization due to angina in 3.8%, reoperation in 1.3%, and cardiac death due to progressive heart failure in 1.3% [Table 2]. Ninety-day mortality rate was calculated as 1.3%.

The mean epicardial adipose tissue thickness was 6.99 ± 2.67 mm, ranged 2.5–14 mm. Mean epicardial adipose tissue thickness was significantly higher in those with in-ICU complications than those without complication (7.64 ± 2.80 mm vs. 6.16 ± 2.29 mm, *P* = 0.015); however, no difference was revealed in mean epicardial adipose tissue thickness between the patients with and without 90-day complications (7.20 ± 1.92 mm vs. 6.98 ± 2.73 mm, *P* = 0.810). More results are presented in Table 3. BMI difference was not significant between patient with and without 3-month complication (27.40 ± 3.213 vs. 27.85 ± 3.974, *P* > 0.05). The difference between fat pad in patients with and without 3-month complication was not reliable, due to very few number of patients with complication.

Table 1: Baseline patients' characteristics

Clinical features	Mean &SD or Number (percent)
Age (years), mean±SD	63.5±8.3
Males, *n* (%)	65 (83.3)
Diabetes, *n* (%)	33 (42.3)
Hypertension, *n* (%)	44 (56.4)
NYHA functional class (II), *n* (%)	68 (87.2)
Hyperlipidemia, *n* (%)	46 (59)
Smoking, *n* (%)	25 (32.1)
3 vessel disease, *n* (%)	65 (83.3)
Previous myocardial infarction, *n* (%)	26 (33.2)

SD=Standard deviation; NYHA=New York heart association

Table 2: The frequency of complications and events in studied patients

Complication/event	*n* (%)
In-ICU complications	
AF	7 (9)
Need for inotrope >48 h	5 (6.4)
Fever	6 (7.7)
More than one inotropes needed	6 (7.7)
Bleeding >1000cc	3 (3.8)
Acute kidney injury	6 (7.7)
Cardiac arrest	1 (1.3)
Need for IABP	1 (1.3)
Need for reoperation	2 (2.6)
3 months' complications	
Rehospitalization	3 (3.8)
Need for reoperation	1 (1.3)
Death due to CHF	1 (1.3)
Unwanted, nonsignificant in-ICU events	
PVCs	8 (10.3)
Pleural effusion	8 (10.3)
Emphysema	1 (1.3)
Sinus tachycardia	4 (5.1)
Delirium	3 (3.8)
PACs	2 (2.6)
Hiccup	3 (3.8)

PACs=Premature atrial contractions; PVCs=Premature ventricular contractions; AF=Atrial fibrillation; CHF=Congestive heart failure; IABP=Intra-aortic balloon pump counter pulsation; ICU=Intensive care unit

There was no significant correlation between mean epicardial adipose tissue thickness and total hospital stay (*r* = 0.020, *P* = 0.863). We also found no association between epicardial adipose tissue thickness and length of ICU stay (*r* =−0.057, *P* = 0.629). Logistic regression analysis showed that high epicardial adipose tissue thickness could effectively predict in-ICU complications (odds ratio = 1.338, 95% confidence interval [CI]: 1.046–1.712, *P* = 0.021). According to ROC curve analysis [Figure 1], measuring epicardial adipose tissue thickness could moderately predict in-ICU complication (area under the curve = 0.658, 95% CI: 0.536–0.779, *P* = 0.017). In this regard, the best cutoff point of the thickness for predicting in-ICU complication was 6.5 mm with a sensitivity of 65.9% and a specificity of 58.8%.

Table 3: Characteristics difference between patients with and without complication (during the surgery and in-intensive care unit hospitalization)

Complications	n	Mean	SD	P
Age (at surgery)				
With	37	65.22	7.500	0.103
Without	37	61.97	9.290	
BMI (at surgery)				
With	10	27.49	1.954	0.77
Without	66	27.49	1.954	
Adipose tissue thickness (at surgery)*				
With	11	9.73	-	<0.05
Without	67	6.54	-	
BMI (ICU)				
With	40	27.49	3.548	0.46
Without	33	28.18	4.444	
Adipose tissue thickness (ICU)				
With	41	7.61	2.845	<0.05
Without	34	6.16	2.285	

*Mann–Whitney U-test was applied due to nonnormality. ICU=Intensive care unit; BMI=Body mass index; SD=Standard deviation
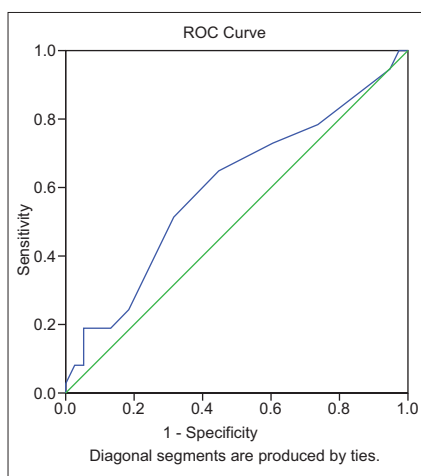

Figure 1: Receiver operating characteristic curve analysis to determine value of epicardial fat thickness to predict in-intensive care unit complication

DISCUSSION

Among all definitive criteria for in-hospital and 90-day outcome of coronary bypass surgery, measuring thickness of epicardial adipose tissue could predict operative complications during ICU stay. According to our findings, the most common in-ICU complications included AF, prolonged inotrope use, and even fever. In fact, it could be supposed that epicardial adipose tissue not only can be related to conductive abnormalities leading arrhythmias, especially in atrial zone, but also may act via effect of cardiopulmonary system leading heart failure and also other noncardiac systems such as increased susceptibility to inflammatory reactions or even infectious conditions. In this regard, by measuring epicardial adipose tissue thickness, predicting increased risk for ICU-related complications after

coronary artery bypass surgery can be possible. However, our study could not reveal the value of epicardial adipose tissue thickness to predict total postoperative morbidity or even prolonged ICU or hospital stay. Very few studies focused the value of epicardial adipose tissue thickness for predicting postoperative complications in patients undergoing revascularization. Whereas more studies emphasized the role of this parameter to predict outcome of patients related to cardiac ischemic events. In a recent study by Hirata *et al.*,[16] epicardial adipose tissue thickness was greater in the CAD group than in the non-CAD group based on echocardiography measurement. In Tanindi *et al.*'s study,[17] thickness more than 7 mm and diabetes were main predictors of cardiovascular death. In a similar study by Kaya *et al.*,[18] epicardial adipose tissue volume contributed to the development of coronary atherosclerotic lesions. Besides the described studies, some others could not demonstrate high value of epicardial adipose tissue thickness for predicting poor outcome in CAD patients. In a study by Romijn *et al.*,[19] epicardial adipose tissue volume had no diagnostic value beyond calcium scoring and cardiovascular risk factors in the detection of hemodynamically significant CAD. Furthermore, Albuquerque *et al.*[20] showed that epicardial adipose tissue thickness, as measured using echocardiography, did not strongly predict major adverse cardiac events in CAD patients. The risk of restenosis in drug-eluting stents was not correlated with epicardial fat thickness, based on echocardiography measurement, in a study by Nikaeen *et al.*[21] It seems that the controversial results can be due to the method of measuring epicardial adipose tissue thickness including echocardiography, MR imaging, or directly by cutting the local tissue as the method applied in our study.

According to our used method for assessing epicardial adipose tissue thickness, this parameter was applicable for assessment of poor in-ICU outcome; however, because of moderate discriminative value obtained by ROC curve analysis, it seems that combining this diagnostic method with other predicting protocols can enhance its accuracy for predicting poor outcome in patients undergoing coronary bypass surgery.

Some studies suggested a variety of mechanisms to explain progression of coronary involvement and thus poor outcome of CAD in those with increased epicardial adipose tissue thickness. As described by Iwayama *et al.*,[22] increased epicardial adipose tissue thickness might play a crucial role in development of CAD through impairment of adiponectin secretion, especially in nonobese patients. Moreover, Pezeshkian and Mahtabipour[23] showed that the significant increase of trans and conjugated fatty acids in epicardial adipose tissue might worsen the formation of atheroma in the related arteries. It presumes that not only the secretion

of cytokines and impairment of adiponectin secretion but also increase of trans and conjugated fatty acids in adipose tissue can well explain the relationship between epicardial adipose tissue thickness and development of CAD and its related poor outcome.

Compare to other studies, we used one of the most accurate way of measuring epicardial adipose tissue thickness by direct measuring during cardiac surgery, although our weakness is not comparing this accurate method with other measuring modalities similar to echocardiography, CT scan, and MRI imagines. Furthermore, because of some limitations in statistical analysis, results must be generalized with caution.

CONCLUSION

Measuring epicardial adipose tissue thickness can be considered as a valuable factor for predicting in-ICU complications, in patients who are undergoing coronary artery bypass surgery. The combination of this index with other predicting parameters for increasing predicting power of poor outcome in patients who underwent CABG is suggested for further studies.

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Conflicts of interest
There are no conflicts of interest.

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