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The Association Between Epicardial Adipose Tissue and Coronary Artery Disease: an Echocardiographic Cut-off Point

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ABSTRACT

Introduction: EAT is an independent factor in coronary artery disease (CAD). The objective of the current study was to define an echocardiographic cut-off point for EAT and to determine its diagnostic value in predicting the increase in CAD risk. **Methods**: Two hundred patients underwent coronary artery angiography for diagnosis of CAD and transthoracic echocardiography for measurement of EAT on the right ventricle (RV), RV apex and RV outlet tract. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the EAT cut-off points in the three above-mentioned areas for predicting the severity of CAD were measured. The relation between the EAT and CAD risk factors was evaluated as well. **Results**: EAT was independent from gender, height, hypertension, diabetes, HDL, total cholesterol, ejection fraction, acute coronary syndrome, and the location of the coronary artery stenosis in the coronary artery in all three anatomical areas. EAT on RV and RV apex had a significant relation with CAD ($P \leq 0.05$). Overall, RV EAT$\geq$ 10 mm and RV apex EAT $\geq$ 8 mm had sensitivity and PPV of more than 70% in predicting coronary stenosis $\geq$ 50% and acute coronary syndrome (ACS) and RVOT EAT $\geq$ 13 mm is of PPV=83.5% for predicting coronary stenosis $\geq$ 50%. **Conclusion**: EAT thickness has an acceptable diagnostic value for predicting severe coronary artery stenosis and ACS. Therefore, non-invasive EAT thickness measurement could be of great assistance to clinicians for detecting the patients at risk and helping them to undergo supplementary evaluations with invasive approaches.

Introduction

EAT (Epicardial Adipose Tissue) is defined as adipose tissue situated within the pericardium. EAT originates from the splanchnopleuric mesoderma (such as the mesenteric and omental fat deposit), and its blood supply is provided from coronary arteries. EAT is of more interest than paracardial adipose tissue because of its close anatomic relationship with the myocardium. (EAT) is believed to have an independent correlation with coronary artery disease (CAD)[1]; while body mass index (BMI) measurement is the most efficient and easiest method of evaluating metabolic factors. Abdominal obesity has been proven to be associated with the highest risk of CAD in both males and females which can be evaluated by measuring waist circumference (WC); WC of more than 35 inches and 40 inches in females and males respectively is associated with increased risk of CAD.[2] In the study of Chambers *et al*., increase in CRP serum levels was 17% more common and of more correlation with central obesity in the Asian aborigines than Europeans.[3] EAT is correlated with age, visceral adipose tissue, waist, BMI, serum CRP and insulin resistance.[4] In the study of Eunmi Park and coworkers, the mean EAT was 5.36 mm. Multivariable analyses revealed that EAT could be used as an independent predictive factor of the acute cardiac events within 30 days.[5] In the study of Feyter *et al*., the mean EAT was 10.91±1.9 mm in the patients undergone coronary angiography. In this study as well, the independent role of EAT from abdominal obesity, BMI and other coronary risk factors in CAD was emphasized.[6] Considering the differences observed in the mean EAT in patients and lack of evidence on the diagnostic value of EAT in predicting CAD, in the present study we tried to determine cut-off point for right ventricular (RV) epicardial fat by echocardiography and to evaluate its predictive value in diagnosing patients at risk of increased risk of coronary artery disease.

Materials and methods

In this cross-sectional-diagnostic study, from May 2010 to April 2012, we selected 200 patients who underwent

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coronary artery angiography for the evaluation of suspected coronary artery disease (as a gold standard) in Shahid Madani Heart Center (Tabriz, Iran) and their risk factors for CAD were evaluated. Exclusion criteria from the study were as follow: Poor image quality and simultaneous severe valvular disease. All subjects underwent echocardiographic examination before or early after coronary angiography with commercially available equipment (Vivid 7 Vingmed ultrasound GE Norway).

Epicardial fat was defined as an echo-free space between the outer wall of the myocardium and the visceral layer of pericardium observed in the parasternal long axis view (Figure 1 and 2). It was measured at the point on the free wall of RV along the midline of the ultrasound beam at end systole. All studies were performed by well-trained Echocardiologist. Epicardial fat thickness was measured at parasternal long axis view at anterior aspects proximal and distal to RV outlet tract (RVOT), and modified long axis view used to measure of RV apical fat pad thickness. LVEF was assessed by M-Mode method, and LV mass index was estimated using M-Mode formula LV Mass=$1.04\times[(IVST+LVID+ PWT)_3-(LVID)_3]\times 0.8 +0.6$.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the EAT cut-off points in RV, RV apex and RVOT for diagnosing severity degree of CAD were measured. For statistical analysis, SPSS version 17.0 (SPSS Inc, Chicago, IL, USA) was used. Independent samples t-test for comparing quantitative variables and chi-square test for qualitative variables between the subgroups created by each EAT cut-off points were used. The correlation between quantitative variables was analyzed using Pearson correlation test. P-value ≤ 0.05 was considered statistically significant.

Results

From 200 patients, 19 people were excluded from the study due to having exclusion criteria and from the 181 studied patients, epicardial fat pad was measured on the RVOT area (180 people), right ventricle (174 people) and RV Apex (177 people). Fifty six percent of the studied patients were male; 68.4% and 32.9% of the patients had hypertension and diabetes respectively. The most common lipid abnormality was increased LDL (≥ 100 mg/dl; 63.9%). The prevalence of normal coronary angiography, 1VD, 2VD and 3VD were 24.1%, 21.8%, 20.7% and 33.3% respectively while 72.7% of patients with CAD had severe coronary stenosis (≥ 50%). The most common vessel with stenosis was LAD with the prevalence of 53%. Stable angina, unstable angina, NSTEMI (Non-ST Elevation MI) and STEMI (ST Elevation MI) were observed in 18.8%, 28.3%, 8.4% and 24.5% of the patients respectively. The relation between epicardial fat of the different areas with CAD risk factors were evaluated separately; there was a significant correlation between RVOT fat pad thickness and waist circumference, serum CRP and ST-T changes in ECG. Other parameters were of no significant relation with RVOT FP thickness. On the RV area, a significant relation was observed between RVFP thickness and waist circumference and ST-T changes. On the RV Apex, the only significant correlation observed was between RV Apex thickness and ST-T changes in ECG (Table 1). Only RVOT fat pad was of significant relation with metabolic disorders including serum CRP level and increased LDL and TG. In all three studied areas, there was a significant correlation between increase in EAT and ST-T changes in ECG and increase in Posterior Wall Thickness (PWT), weight, waist circumference and BMI (Table 2). A significant correlation was observed between RVOT fat pad and the number of affected vessels considerable coronary artery stenosis (≥ 50%; P= 0.004) and severe coronary artery disease (2 or 3 vessels involvement; P= 0.021). In addition, a significant correlation was detected between RV Apex FP and considerable coronary artery stenosis (≥50%; P= 0.019; Table 3). RV Apex FP ≥ 13 mm was of specificity of 62.6% and predictive value of 63.5% for severe coronary artery disease (P= 0.021) whereas it was of specificity of 71.4% and predictive value of 83.5% for considerable coronary artery disease (P= 0.004;Table 4). The correlation between EAT and BMI was statistically significant however weak in all three areas (Figure 3a, b, c).

Table 1. The relation between epicardial fat pad in different anatomical areas and the coronary artery disease risk factors and angiography results

EAT location		EAT on RV Apex			EAT on RV			EAT on RVOT		
		<8mm	≥8mm	P	<10mm	≥10mm	P	<13mm	≥13mm	P
Male		(37)60%	(63) 54%	0.516	(33) 9.56 %	(63)54.3%	0.872	(54) 56.8%	(48) 56.4%	1
Hypertension		(39) 64%	(83) 71%	0.384	(40) 69%	(79) 68.1%	1	(69)72.6%	(54) 63.5%	0.25
Waist circumference		(29) 47.5%	30(35) %	0.212	(30)51.7%	(78) 67.2%	0.047	(54) 57%	(63) 73%	0.002
Diabetes		(18)29.5%	(40) 34.7%	0.589	(20)35.1%	(37)31.9%	0.804	(25) 26.5%	(33) 38.8%	0.113
Serum CRP	negative	(41) 67.5%	(71)5.61%	0.44	(36) 62.1%	(74) 63.8%	0.755	(67)70.7%	(48)57.7%	0.026
	+1	6%(4)	12 (14) %		(7) 12.1%	(11) 9.5%		(10)10.5%	(8)9.5%	
	+2	(13) 21.6%	(19) 16.3%		(12)20.7%	(20) 17.2%		(16)8.16%	(16)19.8%	
	+3	(3)4.9%	(10) 8%		(3) 5.2%	(9) 7.8%		2%(2)	(11) 13%	
	+4	0%	(2).2%		0 %	(2) 1.7%		0%	(2) 2%	
ST-T changes in ECG		(32)52.5%	(81)69.8%	0.034	(People 29) 50.9%	(People 82)70.7%	0.012	(54) 56.8%	(62) 72.9%	0.036
Heart block		(5)8.2%	(12)10.3%	0.847	(People 4)6.9 %	(People 13) 11.2%	0.527	(9) 9%	(8)9.5%	1
Smoking		(20)32.7%	(37)31.8%	1	(People 18)31 ٪	(People 37) 31.9%	1	(30)31.6%	(29)34.2%	0.839
Statines		(18)29.5%	(30) 25.8%	0.733	(People 18)31 ٪	(People 29) 25.9%	0.507	(24)25.2%	(24)28.2%	0.778

Table 2. The correlation between basic and clinical variables with epicardial fat pad in different anatomical areas

EAT location	EAT on RV Apex			EAT on RV			EAT on RVOT		
	<8mm	≥8mm	P	<10mm	≥10mm	P	<13mm	≥13mm	P
Age (year)	58.1± 10.7	58.9± 11.9	0.804	56.1 ±11.2	59.7 ±11.6	0.048	58.7 ±11.6	58.3 ±11.2	0.828
Height (cm)	163.4±10	164 ±9.9	0.691	163.2± 9.5	163.8± 10.3	0.738	163 ±8.9	164.6 ±11	0.274
Weight (kg)	73.2± 10.7	77.6 ±13	0.023	72.8 ±10.5	77.6 ±13.1	0.015	73.7 ±10.8	78.7 ±13.4	0.007
Waist circumference (cm)	99.3± 9.9	102.4 ±12	0.212	98.45± 9.8	103 ±12.4	0.013	99.8 ±11.3	103 ±12.1	0.066
Serum LDL (mmol/dl)	114 ±36.1	116 ±34.9	0.706	37.7±111	116 ±34.5	0.374	108.4± 25.2	121.8 ±34	0.004
Serum HDL (mmol/dl)	37.6 ±5.4	37.3± 6.4	0.891	37.3 ±5.8	37.2 ±6.3	0.897	37.4 ±6.4	36.9 ±5.9	0.566
Serum Cholestrol (mmol/dl)	180.5 ±45	178.6 ±41	0.775	172 ±46.6	182 ±40.8	0.173	174 ±46.1	184.2 ±37	0.113
Serum TG (mmol/dl)	180.6 ±87	165.1± 81	0.241	165.6 ±95	172.5 ±78	0.616	165 ±90.4	176.3 ±74.5	0.037
Ejection Fraction (EF%)	48.7± 8.2	46.6 ±8	0.098	48.16 ±8	47 ±8	0.383	47.9 ±7.8	46.3 ±8.6	0.2
Intraventricular Septum Thickness (IVST mm)	11.1 ±1.8	12 ±2	0.013	11.3± 2	11.8 ±2	0.118	11.3 ±1.9	12 ±2	0.019
Left ventricle internal diameter (LVID mm)	48.1 ±6.1	48.6 ±8	0.68	47± 6.2	48.6 ±7.6	0.193	47.2 ±6.5	49.6± 8.1	0.028
Posterior wall thickness (PWT mm)	10.1 ±1.4	11 ±2	0.004	10.2 ±1.4	11 ±2	0.007	10.5± 1.5	11 ±2.1	0.043
LV Mass (gr)	189± 52	213 ±72	0.065	184 ±55.3	213± 70.8	0.008	190 ±60.8	221± 69.7	0.09
Body Mass Index (kg/m^2)	27.5 ±4.3	28.9± 5	0.02	27.3± 4	29± 5.1	0.029	27.9± 4.6	29 ±4.9	0.002

Table 3. The correlation between coronary angiography variables with epicardial fat pad in different anatomical areas

VARIABLE		RV Apex(<8mm)	RV Apex(≥8mm)	P	RV (<10mm)	RV(≥10mm)	P	RVOT (<13mm)	RVOT(≥13mm)	P
Number of the affected vessels in angiography	Normal	(21)34.5%	(22)18.9%	0.12	(16)27.6%	(26)22.4%	0.56	(31)32.6%	(12)14%	0.012
	1VD	(13)21.3%	(25)21.7%		(15)25.9%	(23)19.8%		(21)22.2%	(18)21.4%	
	2VD	(11)18%	(26)22.4%		(11)19%	(25)21.6%		(19)20%	(18)21.1%	
	3VD	(16)26.2%	(43)37%		(16)27.6%	(42)36.2%		(24)25.2%	(37)43.5%	
Location of the stenosis	Multiple	(8)20%	(21)22.5%	0.17	(12)28.6%	(16)17.8%	0.19	(13)20.4%	(17)23.2%	0.94
	Ostium	(3)7.5%	(3)3.2%		(3)7.1%	(3)3.3%		(2)3.2%	(4)5%	
	Proximal	(13)32.5%	(32)34%		(10)23.8%	(36)40%		(23)35.9%	(24)32.8%	
	Mid	(14)35%	(29)30.8%		(15)35.7%	(26)28.9%		(21)32.9%	(22)31%	
	Distal	(2)5.2%	(9)9.5%		(2)4.8%	(9)10%		(5)7.8%	(6)8%	
Vessel	LM	(1)2.5%	(3)3.2%	0.69	(1)2.4%	(3)3.3%	0.78	(2)3.1%	(2)2.7%	0.78
	LAD	(23)57.5%	(50)53.3%		(23)54.8%	(47)52.2%		(38)59.3%	(35)47.9%	
	LCX	(5)12.5%	(15)15.9%		(8)19%	(12)13.3%		(8)12.5%	(12)16.7%	
	RCA	(9)22.5%	(22)23.4%		(7)16.7%	(23)25.6%		(13)20.3%	(19)26%	
	Dia	(2)5%	(1)1%		(2)4.8%	(2)2.2%		(1)1.5%	(3)4%	
	OM	0%	(3)3.2%		(1)2.4%	(3)3.3%		(2)3.1%	(2)2.7%	
Considerable coronary stenosis[1]		(37)60.7%	(91)78.4%	0.01	(39)67.2%	(87)75%	0.36	(60)63.1%	(71)83.5%	0.004
Acute coronary syndrom[2]		(30)69.7%	(77)5.78%	0.36	(31)72.1%	(74)77.1%	0.675	(49)73.1%	(61)79.2%	0.509
Severe coronary stenosis[3]		(27)44.2%	(68)6.58%	0.6	(27)46.6%	(66)56.9%	0.259	(43)45.2%	(54)63.5%	0.021

[1]Stenosis ≥ 50% in coronary arteries , [2]Unstable angina or acute MI, [3] 2 or 3 Vessel Disease

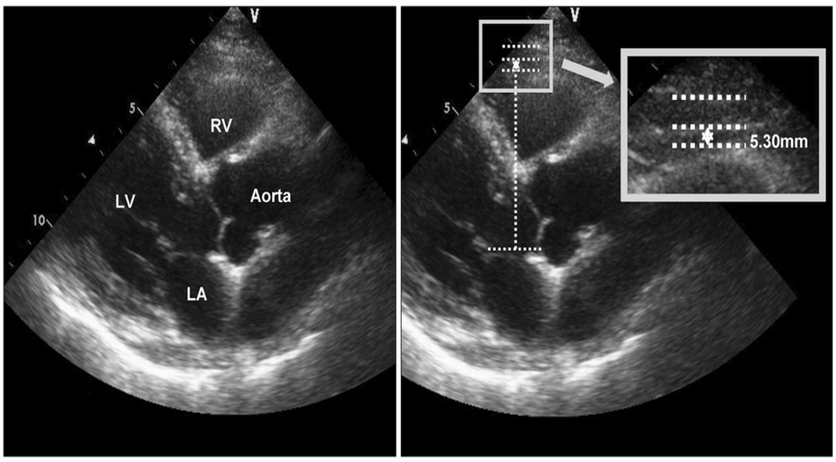

Figure 1. Example of measurement of epicardial fat thickness.Epicardial fat was identified as an echo-free space in the pericardial layers on the twodimensional echocardiography and its thickness was measured perpendicularly on the free wall of the right ventricle at end-diastole.

Table 4. Diagnostic value of epicardial fat pad in predicting coronary artery disease and its degree

Variable		Acute coronary syndrome (unstable angina or myocardial infarction)	Considerable coronary stenosis (>50%)	Severe coronary artery disease (2 or 3 vessel disease)
EFP (Apex RV ≥ 8 mm)	Sensitivity	72	71	71.5
	Specificity	38.2	48.9	41.4
	PPV (%)	78.5	78.4	58.6
	NPV (%)	30.2	39.3	55.7
	P-value	0.362	0.019	0.069
EFP on (RV≥ 10 mm)	Sensitivity	70.4	69	70.9
	Specificity	35.2	39.5	38.2
	PPV (%)	77.08	75	56.9
	NPV (%)	27.9	32.7	53.4
	P-value	0.675	0.368	0.259
EFP on (RV Outlet≥ 13 mm)	Sensitivity	55.4	54.2	55.6
	Specificity	53	71.4	62.6
	PPV (%)	79.2	83.5	63.5
	NPV (%)	26.8	36.8	54.7
	P-value	0.509	0.004	0.021

PPV= Positive predictive value; NPV= Negative predictive value, EFP= Epicardial fat pad, RV= Right Ventricle

Discussion

Similar to the study of Shemirani and Hosseini, our study confirmed the independent correlation between EAT and CAD and its degree over the RV area. However, unlike their study, RV EAT had a correlation with age and BMI in our study.[1] Similar to the study of SG-Ah, our study revealed that there was a correlation between RV EAT and waist circumference, age and BMI and EAT measurements using echocardiography could predict the risk of being affected by coronary artery disease and its extend and degree. However, the Cut-off point of our study for different areas of the epicardium was higher than the previous studies (13 mm in RVOT, 10 mm on RV and 8 mm on RV apex). In the study of S-G Ahn, the mean epicardial fat thickness was 4, 3 and 1.5 mm in the patients with unstable angina, atypical chest pain and stable angina respectively.[4] Unlike the study of Park, our study does not confirm the predictive value of EFP in the occurrence of cardiac events. The Cut-off point of our study for EFP was higher than this study (5.36 mm). However, unlike the study of Park, it did not predict acute cardiac events based on EAT thickness.[5]

In Our study, there was no significant correlation between EAT thickness and number of affected vessels in coronary angiography or location of the stenosis.The study of Feyter indicated a completely independent role of EAT from abdominal fat, BMI and other CAD risk factors and even EAT being independent from CAD incidence which is different from our study in this regard.[6] The results obtained from our study revealed no significant relation between ejection fraction and EFP in all three anatomical areas; yet a significant relation could be observed between age and EFP on RV which is in contrast with the study of Sironi.[7] However, no relation between blood pressure and EFP was found in both studies. Our study was in line with the study of Singh regarding the relation between EFP and LV Mass and increased LDL levels.[8] The study of Fox et al., similar to our study, confirmed the direct correlation between EFP and BMI, LV Mass and waist circumference in both males and females.[9] In all three anatomical areas, a significant correlation was observed between EFP and increased BMI, weight, waist circumference and PWT and increase in ST-T changes which is in accordance with the similar studies.[10-12] Our results showed that EAT was associated with coronary artery disease, particularly EAT increased in patients with significant CAD, defined as percent diameter stenosis >50%; this correlation was significant for EAT location of RVOT with diameter of ≥13mm.The results obtained from our study were in line with findings of Yun and colleagues.[13]

Epicardial Adipose Tissue is a true visceral fat tissue found around the heart, attached to the free wall of right ventricle, left ventricular apex and atrium. Epicardial adipose tissue has been suggested by the previous studies to be strongly correlated with abdominal fat deposits which could be explained due to having a common embryogenesis pathway. In Our study, significant correlations were observed between waist circumferences and EAT thickness ≥ 13mm on RVOT and between ST-T changes in ECG and EAT thickness on RVOT≥ 13mm which could be considered unique findings not observed in the similar previous studies .There were also no significant correlation between EAT thickness and ACS presentation of patients in the present study; the results of this study are in contrast to findings of the study of Ito *et al*., which showed EAT assessed by CT was an independent predictor of ACS in patients with CAD.[14] Echocardiographic epicardial fat measurement is of numerous advantages both clinically and in the research realm including low cost, ease of accessibility, rapid application, and good reproducibility. However, to accept echocardiographic epicardial fat thickness as a routine clinical assessment of cardiovascular risk, further studies and evidence are required.

Conclusion

EAT measurement could be used as a quantitative indicator of metabolic disorders and systemic atherosclerosis and also as a key for CAD Risk Stratification. RVOT fat pad is in relation with metabolic disorders including increased serum LDL, TG and CRP, and waist circumference. EAT over the RV and RV Apex has an independent relation with CAD. High diagnostic and predictive values of EAT for being affected by severe coronary artery disease and severe coronary arteries stenosis were obvious in our study.

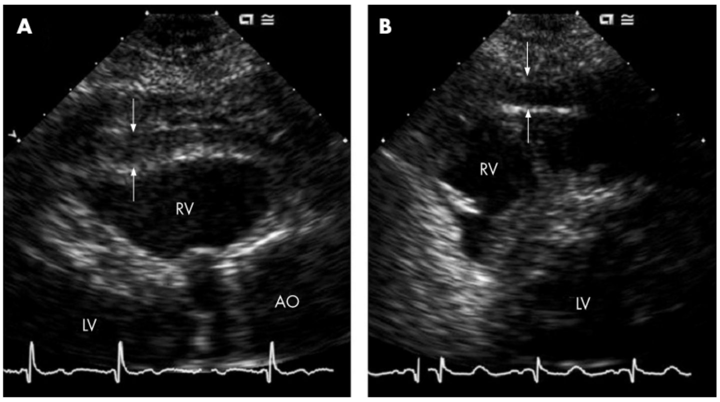

Figure 2. Echocardiographic measurement of epicardial adipose tissue (EAT).(A) Parasternal long-axis view; (B) parasternal short-axis view at the mitral valve level. AO, aorta; LV, left ventricle; RV, right ventricle. Anterior echo-lucent space between the linear echo-dense parietal pericardium and the epicardium was considered to be EAT (arrows). Mediastinal fat, seen as an echo-lucent area located above the parietal pericardium, was not included in the EAT measurement.

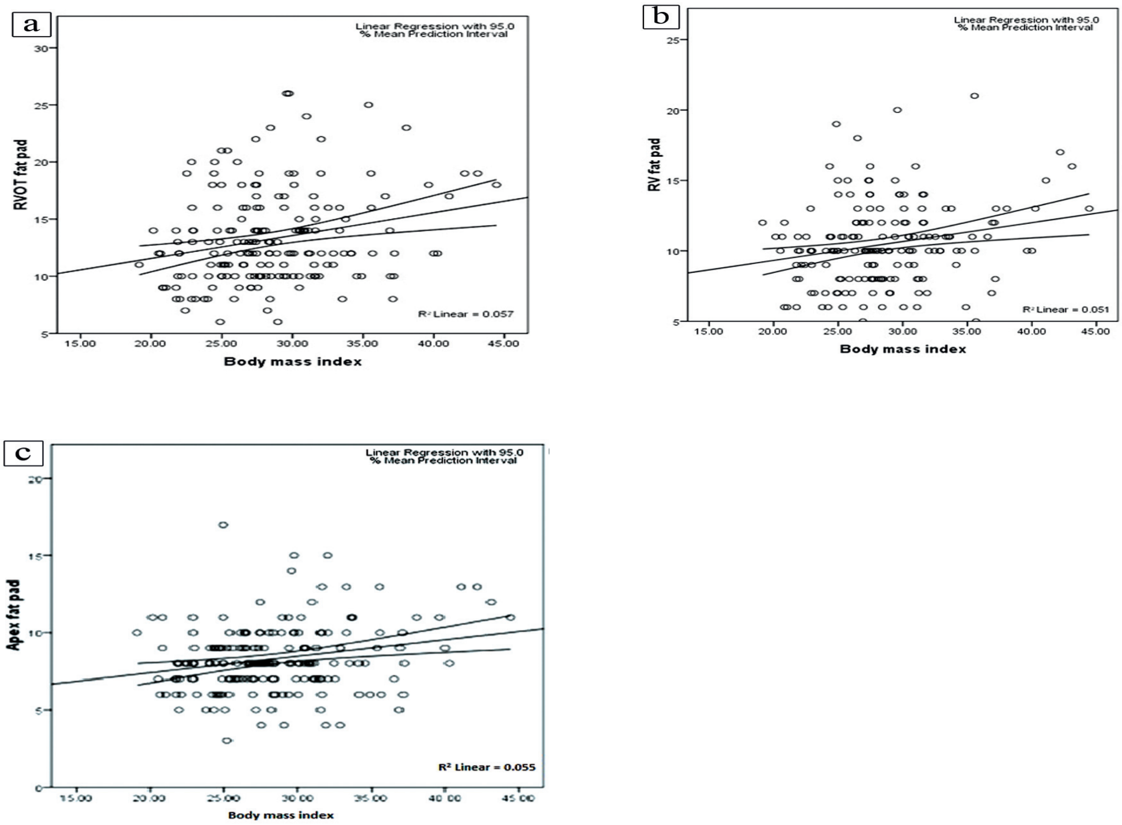

Figure 3. The correlation between body mass index and epicardial adipose tissue) thickness in 3 right ventricle (RV) locations :(a) RV outlet , (b) RV, and (c) RV apex.

Therefore, administration of EAT thickness measurement in the clinical practice could be of tremendous assistance in identifying patients at risk and guiding them in controlling the risk factors appropriately and, if required, undergoing supplementary evaluations with invasive approaches.

Recommendations

Further studies with higher sample volumes to promote the power of the results enabling us to use the findings clinically is recommended. Subsequently with more confidence, we would be able to use EAT in predicting CAD incidence, its degree and the probability of deterioration of the patient status in case of CAD incidence.

Ethical issues: The local ethics committee of Tabriz University of Medical Sciences approved the study and all patients signed informed consent.
Conflict of interests: The authors declare no conflicts of interest.

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