



Association of Echocardiographic Epicardial Fat Thickness and Carotid Intima Media Thickness with the Severity of Coronary Artery Disease

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ABSTRACT

Background: Coronary artery disease remains the main cause of death despite several preventive programs. Epicardial adipose tissue is a visceral fat depot of the heart located along the large coronary arteries and on the surface of ventricles and apex. Intima media thickness is commonly recognized as the initial stage in the development of atherosclerosis. The development of ultrasound machines, advances in echocardiographic devices and high resolution transducers facilitate comprehensive analysis of epicardial fat thickness (EFT) and carotid –intima media thickness (C-IMT).

Aim: To investigate the relationship of echocardiographic epicardial fat thickness (EFT) and carotid –intima media thickness (C-IMT) with the severity of coronary artery disease.

Methods: A cross sectional multicenter diagnostic accuracy study carried out at Ibn Al-Nafis Cardiovascular Hospital, Ibn Al- Bitar Cardiology Center and Ghazi Al-Hariri Hospital –Iraqi Center for Cardiology during the period between October 2016 and May 2017 assessing. History regarding demographic data and risk factors was taken. Two dimensional transthoracic echocardiographic measurements were done. EFT was measured from parasternal long axis view perpendicular to the right ventricular free wall. C-IMT was measured according to that recommended by the American society of echocardiography (ASE).

Results: The current study demonstrated that the EFT has a direct and significant correlation with the number of involved vessels (P value < 0.001, r= 0.770). The validity of EFT to discriminate between multiple vessels disease and no vessel involvement is excellent (AUC= 0.984, cut point > 8mm, sensitivity=92.9%, specificity= 93.3%). There is inverse and significant correlation between ejection fraction (EF) and three vessels disease (P value

< 0.001, r= -0.507). Also there is a direct and significant correlation between C-IMT and severity of CAD. ROC analysis for validity of C-IMT to discriminate between multiple vessels disease and no vessel involvement is excellent (AUC= 0.961, cut point > 1.04mm, sensitivity=92.9%. specificity=86.7%). C-IMT is fair to discriminate between single vessel disease and no vessel involvement (AUC=0.738, cut point > 0.84mm, sensitivity 100%), so if correlated with age, C-IMT above 0.84 can be used as a cut off point for the prediction of CAD. Finally, EFT and C-IMT are more likely to reflect severity of CAD than their ratio.

Conclusions: C-IMT and EFT are simple and reproducible parameters that can be used as a screening tool for the presence and severity of CAD especially before symptoms appearance in high risk patients

Key words: Epicardial Fat Thickness, Carotid Intima-Media Thickness, Coronary Artery Disease, Echocardiography.

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INTRODUCTION

Atherosclerosis is a known predisposing factor for CVD, which has a long asymptomatic latent period, thus providing an opportunity for early preventive interventions^[1]. Although atherosclerosis occurs in the general population, some people are at greater risk for developing coronary artery disease.^[2]

Coronary artery disease is the single largest cause of death in the developed countries and is one of the leading causes of disease burden in developing countries as well^[3], in addition to its cost regarding health care services, medications, percutaneous intervention and surgery^[4] It is estimated that if all forms of major CVD were eliminated, life expectancy would rise by almost 7 years^[5].

Cardiac catheterization is the gold standard for diagnosis^[6]. It determines the presence, location and severity of coronary artery disease. Nonetheless, its high cost, mortality rate (about 0.1%), and morbidity rate (1%–5%) limit its use as a routine screening tool^[7].

Epicardial adipose tissue is a visceral fat depot of the heart located along the large coronary arteries and on the surface of ventricles and apex. Intima media thickness is commonly recognized as the initial stage in the development of atherosclerosis^[8]. The aim of the study was to investigate the relationship of Echocardiographic EFT and C-IMT with the severity of coronary artery disease.

Methods

A cross-sectional multicenter diagnostic accuracy study carried out at Ibn Al-Nafis Cardiovascular

Hospital, Ibn Al-Bitar Cardiac Center and the Iraqi Center for Cardiac Diseases during the period between October 2016 and May 2017, assessing C-IMT and EFT. After exclusion of those with poor window, pericardial effusion, history of prior revascularization whether by stenting or coronary artery bypass graft and those with lack of written informed consent, patients preselected to undergo coronary angiography were included in the study.

Inclusion criteria:

Patients who underwent diagnostic coronary angiography were included. Patients with minimal atherosclerotic lesion < 50% in coronary arteries or no lesion considered as control group. Patients with coronary artery stenosis of 70% or more in one or more coronary arteries (LAD, CX or RCA) or 50% or more in left main stem were enrolled as cases of CAD [9].

History regarding demographic data and risk factors was taken. Ejection fraction was measured by M-mode method from parasternal long axis view. EFT was measured from parasternal long axis view perpendicular to the right ventricular free wall. C-IMT was measured according to that recommended by the American society of echocardiography (ASE) [10].

Then, results of the whole study sample were revised according to angiographic findings. 72 patients were included in the CAD group while 60 patients with no CAD considered as control group.

Statistical Analysis:

SPSS version 20.0.0, Minitab 17.1.0, Med Clac 14.8.1 software package was used to make the statistical analysis. P value was considered to be significant if less than 0.05.

Results

Epicardial fat thickness (EFT) and carotid –intima media thickness (C-IMT) in a total of one hundred thirty two (132) patients preselected to undergo coronary angiography. Results of the whole study sample were revised according to angiographic findings. 72 patients were included in the CAD group while 60 patients with no CAD considered as control.

There was no significant difference in age, height, weight, BMI and sex between control and CAD groups as illustrated in table (1).

All risk factors (except family history of premature CAD) were significantly more prevalent in patients with CAD compared to control as illustrated in table (2).

Epicardial fat thickness (EFT): there was significant difference in the EFT between the two groups, as there was an increase in the EFT as the number of vessels affected increased with a P value <0.001 as illustrated in table (3).

Ejection fraction (EF): There was no much reduction in ejection fraction in patients with no vessel involvement and those with one and /or two vessels involvement, but there was a significant reduction in ejection fraction among patients with three-vessel disease as illustrated in table (3).

C-IMT: there was a significant difference in the C-IMT between the two study groups in such a way as the number of vessels involved increased, the mean C-IMT increased, as illustrated in table (3).

As the number of vessels involvement increases the patients will be in a higher quartile regarding epicardial fat thickness (EFT), e.g. all patients (100%) with three-vessels disease were in quartile 4 of epicardial fat thickness versus 67.7% in patients with two-vessels disease, as illustrated in table 4.

Similarly, as the number of vessels involvement increases the patients will be in a higher quartile (Q₄) regarding Carotid Intima Media Thickness(C-IMT), e.g. all patients (100%) with three- vessels disease were in quartile 4 of epicardial fat thickness versus 67.7% in patients with two-vessels disease, as illustrated in table 5.

Of notice, there is similarity in the pattern of EFT and C-IMT distribution in the quartiles as illustrated in tables 4 and 5.

Both EFT and C-IMT were **fair** (since AUC was between 0.7 – 0.79) to discriminate single vessel disease from no coronary artery disease with optimum cut point of >5.66 and >0.84 respectively, offering more sensitivity and negative predictive value (less false negative), as illustrated in table 6

Both EFT, C-IMT had excellent (since AUC between 0.9 – 0.99) to discriminate multiple vessel disease from no vessel involvement with optimal cut point of >8.0 and >1.04 respectively, while EFT/C-IMT had fair ability to discrimination as there was a balance in sensitivity and specificity and predictive value, as illustrate in table 7

Table 1: demographic data of studied groups

Variables	Control	CAD	P value
Age (years)	57.0 ± 10.9	60.0 ± 10.1	0.140
Height (m)	1.7 ± 0.1	1.7 ± 0.1	0.181
Weight (kg)	76.2 ± 9.8	78.2 ± 12.6	0.327
BMI (kg/m ²)	27.4 ± 3.0	28.6 ± 4.4	0.070
Sex			0.266
Female (44)	23 (38.3%)	21 (29.2%)	
Male(88)	37 (61.7%)	51 (70.8%)	
BMI groups			0.446
Normal(30)	15 (25.0%)	15 (20.8%)	
Over weight(64)	31 (51.7%)	33 (45.8%)	
Obese (38)	14 (23.3%)	24 (33.3%)	

Table 2: Atherosclerotic risk factors in studied groups.

Risk factors	Total (n=132)	Control(n=60)	CAD(n=72)	P value
Hypertension	Negative (47)	28 (46.7%)	19 (26.4%)	0.015
	Positive (85)	32 (53.3%)	53 (73.6%)	
DM	Negative (94)	51 (85.0%)	43 (59.7%)	0.001
	Positive (38)	9 (15.0%)	29 (40.3%)	
Smoking	Negative (90)	48 (80.0%)	42 (58.3%)	0.008
	Positive (42)	12 (20.0%)	30 (41.7%)	
Alcohol drinking	Negative (126)	60 (100.0%)	66 (91.7%)	0.032
	Positive (6)	0 (0.0%)	6 (8.3%)	
Family History of Premature CAD	Negative (110)	52 (86.7%)	58 (80.6%)	0.348
	Positive (22)	8 (13.3%)	14 (19.4%)	
Dyslipidemia	Negative (110)	55 (91.7%)	55 (76.4%)	0.019
	Positive (22)	5 (8.3%)	17 (23.6%)	

Table 3: Relation between Echo variables and number of affected coronary arteries

Parameters	Number of coronary arteries involved				P value
	0 (control)	1	2	3	
EFT (mm)	5.75 ± 1.63	6.93 ± 0.85	8.90 ± 0.71	9.97 ± 0.85	<0.001
EF %	65.61 ± 3.80	67.87 ± 2.16	63.65 ± 3.21	52.27 ± 6.33	<0.001
C-IMT(mm)	0.87 ± 0.16	1.00 ± 0.09	1.15 ± 0.07	1.35 ± 0.11	<0.001
EFT/C-IMT	6.61 ± 1.38	6.94 ± 0.67	7.78 ± 0.63	7.39 ± 0.45	<0.001

Table 4: Distribution of EFT in patients with and without CAD

	Number	Q1	Q2	Q3	Q4
		EFT < 5.877	5.877 ≤ EFT < 7.2	7.2 ≤ EFT < 8.707	EFT ≥ 8.707
No. CAD	60	30 (50.0%)	17 (28.3%)	12 (20.0%)	1 (1.7%)
Single vessel	30	3 (10.0%)	15 (50.0%)	12 (40.0%)	0 (0.0%)
Two vessels	31	0 (0.0%)	0 (0.0%)	10 (32.3%)	21 (67.7%)
Three vessels	11	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (100.0%)

Table 5: Distribution of mean intima-media thickness (IMT) in patients with and without CAD

	Number	Q1	Q2	Q3	Q4
		IMT < 0.87	0.87 ≤ IMT < 1.00	1.0 ≤ IMT < 1.13	IMT ≥ 1.13
No. CAD	60	30 (50.0%)	17 (28.3%)	12 (20.0%)	1 (1.7%)
Single vessel	30	3 (10.0%)	15 (50.0%)	12 (40.0%)	0 (0.0%)
Two vessels	31	0 (0.0%)	0 (0.0%)	10 (32.3%)	21 (67.7%)
Three vessels	11	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (100.0%)

Table 6: ROC analysis of the validity of EFT, C-IMT and EFT/C-IMT ratio in the discrimination between single vessel CAD and no vessel involvement

	AUC	P value	Cut point	Sensitivity	Specificity	PPV	NPV
EFT	0.722	<0.001	>5.66	96.7%	48.3%	48.3%	96.7%
C-IMT	0.738	<0.001	>0.84	100%	48.3%	49.2%	100%
EFT/C-IMT	0.593	0.121	-	-	-	-	-

Table 7: ROC analysis of the validity of EFT, C-IMT and EFT/C-IMT ratio in the discrimination between multiple vessels CAD and no vessel involvement.

	AUC	P value	Cut point	Sensitivity	Specificity	PPV	NPV
EFT	0.984	<0.001	>8	92.9%	93.3%	90.7%	94.9%
C-IMT	0.961	<0.001	>1.04	92.9%	86.7%	83.0%	94.5%
EFT/C-IMT	0.793	<0.001	>7.2	81.0%	75.0%	69.4%	84.9%

Discussion

Our findings are consistent with Kulkarni who has indicated that diabetes, hypertension, obesity, hyperlipidemia and smoking are strong predictors of CAD.^[11] In our study we found that positive family history of premature CAD, a non-modifiable risk factor was not significant for CAD (P value =0.348). Thus, the most important risk factors for CAD among our patients are amenable to medical and lifestyle interventions. This finding was partially consistent with Kulkarni who indicated that while positive family history of premature CAD does not appear to impact general disease risk, it does significantly increase early onset of CAD (P value=0.03).^[11] In the Framingham Heart Study, a family history of premature heart disease was associated with an excess risk for an adverse cardiovascular outcome.^[12]

Thus, manifestations of CAD are due to an interaction of several unfavorable genetic and environmental factors. In recent years, there has been tremendous progress in sequencing the human genome, along with advances in molecular and population genetics that will pave the way for identification of genes and their potential role in expression of underlying atherosclerosis.^[13]

ROC analysis for validity of EFT in the discrimination between multiple vessels disease from no vessel involvement was excellent (AUC=0.984), cut point > 8mm, sensitivity 92.9% and specificity 93.3%. These findings are consistent with Jin-Won Jeong et al, who established that epicardial fat thickness has a good association with the severity of coronary artery disease.^[14] Shirmani et al reported EFT thickness as an independent predictor of CAD among other well-known risk factors^[15], while Chaowalit et al did not find significant correlation between EFT and the number of atherosclerotic coronary arteries.^[16]

Echocardiographic measurement of epicardial fat quantity is limited to the assessment of EFT on the free wall of the right ventricle. In addition, measuring epicardial fat thickness at end diastole will lead to a deformation by epicardial fat compression.^[16,17] This may be the reason for the discrepancy in the results reported by some studies.

In this study we found that patients with three vessels disease had significant reduction in ejection fraction, Farouk Mookadam et al find that EFT > 5mm was associated with lower ejection fraction^[18]. Also Farouk Mookadam et al and Liu J, Fox CS, Hickson DA, May WL, Ding J, Carr JJ, et al found that EFT is inversely associated with ejection fraction.^[18, 19] EFT seems to increase with age^[20, 21, 22] which agrees with our findings.

The present study showed that carotid artery IMT was higher in patients with angiographically confirmed CAD than in patients with normal coronary arteries. The number of patients with normal IMT decreases as the number of involved coronary arteries increases.

Our observations are consistent with several previous studies. Granér M. et al found a strong association between coronary artery status, verified by coronary angiography, and mean aggregate IMT in carotid arteries.^[23] Likewise, in our study mean aggregate IMT increased with advancing CAD. In the present study, the cut point in the case patients was 0.84mm which is similar to that reported by Kasliwal RR et al (intima-media thickness of 0.83±0.20 mm).^[24]

Kablak- ziembicka et al showed that there was an increase in CIMT as the CAD progressed and patients with CIMT value of 1.15 mm had 94% higher risk of CAD.^[25] which agrees to our findings in that C-IMT of > 1.04 mm have a sensitivity of 92.9% to discriminate patients with multiple vessels disease from no vessel involvement.

The current study shows that EFT/C-IMT ratio had mild direct relationship with the number of involved vessels (P-value <0.001). To date there is no published study that examine the effect of EFT/ C-IMT ratio as a predictor of CAD, to compare with.

Limitations of the study

The limitations are inherent in the study design, which recruited subjects undergoing coronary angiography for a suspected clinical diagnosis of CAD. In addition, being a multicenter study, echocardiographic measurements were not done by a single Echocardiographer.

Conclusions

Echocardiographic epicardial fat thickness a non-invasive parameter, easily evaluated, inexpensive, reproducible and direct measure of visceral fat. It can be considered as a predictive factor for CAD especially before symptoms appearance in high-risk patients. C-IMT measurement is an independent predictor of CAD. It has a good correlation with the severity of coronary atherosclerosis. EFT and C-IMT are more likely to reflect severity of coronary artery disease than their ratio.

References

1. McMahan C, Gidding S, Viikari J, et al. Association of pathobiologic determinants of atherosclerosis in youth risk score and 15-year change in risk score with carotid artery intima-media thickness in young adults (from the

- Cardiovascular Risk in Young Finns Study). *J Am Coll Cardiol.* 2007; 100:1124- 9.
2. Jaggi H, Kearns EH. Risk Factors in Coronary Artery Disease. Missouri: University of Missouri-Columbia School of Health Professions, 2012 Available at: <http://shp.missouri.edu/vhct/case2000/conclusion.htm>.
 3. Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A. Growing epidemic of coronary heart disease in low-and middle-income countries. *Current problems in cardiology.* 2010; 35(2):72-115.
 4. Wael Almahmeed, Mohamad Samir, et al. Coronary artery disease in Africa and the Middle East. *Therapeutic Clinical risk management,* 2012; 8: 65-72.
 6. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2009; 119: 21–181.
 7. Deelstra, M.H. & Jacobson, C. Cardiac catheterization. In: S.L. Woods, E.S.S. Froelicher, S.U. Motzer & E.J. Bridges (eds), *Cardiac Nursing*, 5th edn. Lippincott Williams and Wilkins, Philadelphia, 2005; 20: 459–77.
 8. Olade, R. & Safi, A. (2006). Cardiac catheterization (left heart). eMedicine. Retrieved online on 30th August 2006 from <http://www.emedicine.com/MED/topic2958.htm>
 9. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. *Nat Clin Pract Cardiovasc Med* 2005; 2:536-43.
 10. Eagle KA, Guyton RA, Davidoff R, Edwards Ewy GA, Gardner TJ, et al. guideline update for coronary artery bypass surgery: summary article: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guideline, *Circulation,* 2004; 110: 340-437.
 11. Mitchell CK, Aeschlimann SE, Korcarz CE. Carotid intima media thickness testing: technical considerations. *J Am Soc Echocardiogr* 2004; 17:690- 2.
 12. Prashanth Kulkarni: Family history of coronary artery disease as an additional risk factor associated with coronary artery disease, a descriptive observational study. *Journal of clinical trials in cardiology,* 2015; 2: 1-3.
 13. Lloyd-Jones DM, Nam BH, D'Agostino RB Sr, Levy D, Murabito JM, Wang TJ, Wilson PW, O'Donnell CJ. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *JAMA.* 2004; 291:2204 – 2211.
 14. Higgins M. Epidemiology and prevention of coronary heart disease in families. *Am J Med.* 2000; 108:387–395.
 15. Jin-Won Jeong et al Echocardiographic Epicardial Fat Thickness and Coronary Artery Disease *Circulation J* 2007; 71: 536 –539.
 16. Shemirani H, Khoshavi M. Correlation of echocardiographic epicardial fat thickness with severity of coronary artery disease-an observational study. *Anadolu Kardiyol Derg.* 2012; 12:200-205.
 17. Chaowalit N, Somers VK, Pellikka PA, et al. Subepicardial adipose tissue and the presence and severity of coronary artery disease. *Atherosclerosis.* 2006; 186:354-359.
 18. Djaberi R, Schuijf JD, van Werkhoven JM, et al. Relation of epicardial adipose tissue to coronary atherosclerosis. *Am J Cardiol.* 2008; 102:1602-1607.
 20. Mookadam F, Goel R, Alharthi MS, Jiamsripong P, Cha S. Epicardial fat and its association with cardiovascular risk: a cross-sectional observational study. *Heart Views.* 2010; 11(3):103-8.
 21. Liu J, Fox CS, Hickson DA, May WL, Ding J, Carr JJ, et al. Pericardial fat and echocardiographic measures of cardiac abnormalities: the Jackson Heart Study. *Diabetes Care.* 2011; 34(2):341-6.
 22. Fox CS, Gona P, Hoffmann U, Porter SA, Salton CJ, Massaro JM, et al. Pericardial fat, intrathoracic fat, and measures of left ventricular structure and function: the Framingham Heart Study. *Circulation.* 2009; 119(12):1586-91.
 23. Alexopoulos N, McLean DS, Janik M, Arepalli CD, Stillman AE, Raggi P. Epicardial adipose tissue and coronary artery plaque characteristics. *Atherosclerosis.* 2010; 210 (1):150-4.
 24. Silaghi A, Piercecchi-Marti M-D, Grino M, Leonetti G, Alessi MC, Clement K, et al. Epicardial adipose tissue extent: relationship with age, body fat distribution, and coronaropathy. *Obesity (Silver Spring).* 2008; 16(11):2424-30.
 25. Granér M¹, Varpula M, Kahri J, Salonen RM, Nyssönen K, Nieminen MS, Taskinen MR, Syväne M. Association of carotid intima-media thickness with angiographic severity and extent of coronary artery disease. *Am J Cardiol.* 2006 ;97(5):624-9.
 26. Kasliwal RR, Bansal M, Gupta H, Agrawal S. Association of carotid intima-media thickness with left main coronary artery disease. *Indian Heart J.* 2007;59:50–5.
 27. Kablak-Ziembicka A, Tracz W, Przewlocki T, Pieniazek P, Sokolowski A, Konieczynska M. Association of increased carotid intima-media thickness with the extent of coronary artery disease. *Heart.* 2004; 90:1286–90.