Original Article

Association between Brachial Flow-Mediated Dilation and Calcium Score in Patients with Symptomatic CAD

Faezeh Tabesh, Mozhgan Amooali, Reihaneh Zavar, Amirreza Sajjadieh Khajouei[1]

Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, [1]Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Endothelial function plays an important role in the protection of vessels from atherosclerosis. Detection of endothelial dysfunction by non-invasive methods (flow-mediated dilation) and its association with other imaging modalities (calcium score in coronary computed tomography [CT] angiography) is still controversial. In this study, we aim to investigate the association between endothelial function evaluated by flow-mediated dilation (FMD) and calcium score evaluated by coronary CT. **Methods:** In this cross-sectional study, 124 patients with known coronary artery disease (CAD, positive calcium score) were enrolled. FMD as an indicator of endothelial function was evaluated in these participants. FMD less than 7.1%was considered abnormal. Correlation between calcium score and severity of calcification(calcium score above 100 considered as the cutoff point of the high score) and glow-mediated dilation was obtained using the linear regression model. **Results:** The association between calcium score and FMD was strongly significant ($P < 0.001$). Among individuals with low calcium scores, only 15 (18.1%) had abnormal FMD findings, but the majority of individuals with high calcium scores (95.1%) had abnormal FMD findings. **Conclusions:** Our findings provide strong evidence of association between FMD, a marker of vascular endothelial dysfunction, and intensity of coronary atherosclerosis, as assessed by the calcium score on the CCTA.

Keywords: *Atherosclerosis, computed tomography, coronary artery disease*

Introduction

Cardiovascular disease is a great burden to health systems worldwide.[1] Twenty percent of patients who experienced cardiac events die in the first year of diagnosis.[2] Atherosclerotic process begins from childhood and is the most common cause of cardiovascular disease. Coronary endothelial dysfunction is an independent predictor of cardiovascular disease risk and cardiac events.[3] The endothelium protects vessels from stiffness and atherosclerosis and its progression by secreting nitric oxide.[4] Endothelial cells also play an important role in initiating and regulating arterial calcification.[5]

Early detection of endothelial dysfunction by non-invasive modalities can lead to early prevention and treatment of this condition and consequently decrease the burden of cardiovascular diseases. Non-invasive evaluation of endothelial function is an inexpensive and reasonable test that can show the cumulative cardiovascular risk and response to treatment in patients.[6] Flow-mediated dilation (FMD) has been the most widely used non-invasive modality among all developed methods for the evaluation of endothelial function. Recent studies have demonstrated that the brachial artery FMD technique has a strong relationship with coronary artery endothelial function.[7] Forearm measurement of FMD can potentially reveal the extent and severity of coronary artery atherosclerosis. It correlates with coronary endothelial function and the prognosis of patients.[8] Changes in endothelial function cause morphological atherosclerotic changes and may lead to clinical consequences.[9]

Coronary artery calcification (CAC) is an important marker of the presence and severity of atherosclerotic coronary artery disease (CAD).[10] Altered coronary blood flow in the presence of CAC may affect the progression of atherosclerosis, which is one of the determinants of the complexity of CAD.[11] Cardiac computed tomography (CT) is an accurate modality

How to cite this article: Tabesh F, Amooali M, Zavar R, Sajjadieh Khajouei A. Association between brachial flow-mediated dilation and calcium score in patients with symptomatic CAD. Int J Prev Med 2023;14:128.

Address for correspondence:
Dr. Amirreza Sajjadieh Khajouei, Department of Internal Medicine, Isfahan University of Medical Sciences, BOX: 8158388994, Isfahan, Iran.
E-mail: Amirrezasajjadie hkhajouei@gmail.com

Access this article online

Website: www.ijpvmjournal.net/www.ijpm.ir

DOI: 10.4103/ijpvm.ijpvm_143_22

Quick Response Code:

for the calculation of calcium scores. The total CAC score calculated using automated analysis software, called the calcium score, is related to the severity and extent of atherosclerosis.[12]

In recent years, studies revealed controversial results in the evaluation of the relationship between FMD and calcium score; but due to the importance of the issue and the need to predict atherosclerotic disorders earlier, we aimed to investigate the association between endothelial function evaluated by FMD and calcium score on coronary CT angiography in this study. Symptomatic patients with CAD (confirmed by positive calcium score on coronary CT angiography) but without other risk factors of atherosclerosis that affect both FMD and CAC participated in the study. In this study, we aimed to find the relationship between FMD and calcium score that can lead to the earlier and less expensive diagnosis of early stages of CAD and implementation of preventive strategies.

Methods

Patients' setting

This cross-sectional study was held up in …, Iran, from September 2019 to September 2020. All participants were assigned a full written and informed consent form. The ethics committee of. approved all steps of the study (…).

One hundred twenty-four outpatient participants aged 35–60 years who were referred for coronary computed tomography angiogram (CCTA) due to symptoms suggestive of CAD and who were otherwise healthy (no prior history of diabetes mellitus, hypertension, and hyperlipidemia) and had calcium score equal or more than 1 (based on Agatston score) were enrolled in the study.[13] Participants also did not take medications that altered FMD. CAD symptoms defined clinically in this study were retrosternal pressure, a choking sensation or pain that may radiate to the left arm, jaw, neck, or back, brought on predictably by exertion or by emotional upset and relieved after sublingual nitroglycerin consumption or cessation of exertion.[14]

Measurements

According to the indication diagnosed by the referring physician, participants underwent coronary CT angiography. These participants underwent brachial artery ultrasound to calculate FMD as the indicator of endothelial function. The standard method was used to measure FMD.[15] The examination was performed in a silent room with constant temperature. The fasting patient was lying in the supine position. Patients were prohibited from consuming caffeine, high-fat foods, and vitamin C for 8 to 10 hours before the examination. The left arm was used to check the FMD. All measurements were performed with a GE Vivid 3 ultrasound device and a 10-MHz linear probe. The size of the brachial artery was measured at rest, then the artery was occluded for 5 minutes using a blood pressure measuring cuff 50 mmHg above systolic blood pressure, then the cuff was deflated and the diameter of the brachial artery was measured again. FMD was calculated as the percentage change in peak vessel diameter from the baseline value. Percentage of FMD ([peak diameter − baseline diameter]/baseline diameter) was used for analysis. FMD below 7.1% is considered abnormal.[16]

Calcium score measurement was done by non-contrast-enhanced CT imaging with Philips ICT 256 slice system with the standard protocol of KV at 120, rotation time at 330 ms, slice thickness of 2.5 mm, and prospective ECG-gated protocol. CAC above one Agatston score was considered as positive CAC. According to previous studies, patients with calcium score less than 100 were categorized as low calcium score.[17] Agatston score calculation software was also used. It was calculated by multiplying the number of voxels with calcification by the volume of each voxel, including all voxels with an attenuation >130 HU.

Statistical analysis

For baseline variables, descriptive statistics (proportions and mean ± standard deviation) were used. Data on categorical variables were presented as the percentage of cases. Fisher's exact test was used for categorical variables. The linear regression model was used to determine the relationship between quantitative variables. P values <0.05 were considered to be statistically significant. The entire data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 20, (SPSS Inc. Chicago).

Results

One hundred twenty-four patients (70 of them male) with positive CAC were enrolled in the study. FMD was done for all of them. According to previous studies, 7.1% was considered as cutoff point for FMD. Demographic characteristics are shown in Table 1. Male dominancy was seen in the group with a high calcium score (80.5%, $P < 0.001$). The mean age of patients was 58.31 ± 9.90 and 59.59 ± 12.88 in the low and high calcium score group, respectively, without significant difference ($P = 0.54$). The mean body mass index (BMI) in patients with low calcium scores was 25.51 ± 3.92 and 26.07 ± 3.77 in patients with high calcium scores. There

Table 1: Demographic characteristics among patients with low and high calcium score

	Calcium Score		Statistical Value	*P*
	Low	High		
Age [mean±SD]	58.31±9.90	59.59±12.88	−0.608	0.54[a]
BMI [mean±SD]	25.51±3.92	26.07±3.77	−0.761	0.45[a]
Male [*n* (%)]	37 (44.6%)	33 (80.5%)	14.395	<0.001[b]
Positive FH [*n* (%)]	27 (32.5%)	22 (53.7%)	5.126	0.024[b]

[a]obtained based on *t*-test. [b]obtained based on Chi-squared test

were no significant differences between the BMI of the two groups (P = 0.45). Fifty-three point seven percent of patients with high calcium scores had a positive family history of CAD in comparison to 32.5% of in-group patients with low calcium scores (P = 0.024).

The frequency of high and low calcium scores and normal and abnormal FMD are shown in Table 2.

The association between calcium score and FMD was strongly significant (correlation coefficient = −0.829; P < 0.001). Among individuals with low calcium scores, only 15 patients (18.1%) had abnormal FMD findings, but the majority of individuals with high calcium scores, that is, 39 patients (95.1%) had abnormal FMD findings [Table 3]. Participants who had normal FMD were highly unlikely to have a high calcium score (4.9%).

The sensitivity and specificity of FMD for predicting calcium score were 95% and 82%, respectively. Positive predictive value (PPV) and negative predictive value (NPV) were 72% and 97%, respectively.

Discussion

In this study, we evaluated the association between FMD (an indicator of endothelial function) and calcium score in CCTA in patients with positive calcium scores which revealed a strong association between abnormal FMD and high calcium score (defined as greater than 100). Interestingly, we also found that participants who had normal FMD were highly unlikely to have a high calcium score (4.9%), which means a high NPV of normal FMD for calcification of coronary arteries. As atherosclerotic risk factors can affect both FMD and CAC and act as confounding risk factors, patients with these risk factors were excluded to evaluate just the association of CAC and FMD. Also, we excluded patients with zero calcium scores in our study because previous studies showed normal FMD among these participants.[18]

Table 2: Frequency of patients with high and low calcium score and normal/abnormal FMD

	Frequency (*n*)	Percentage (%)
Calcium Score		
Low	83	66.9
High	41	33.1
FMD		
Abnormal	54	43.5
Normal	70	56.5

There is a correlation between endothelium-mediated vasodilation and coronary response.[19] Previous studies that evaluated the association between FMD and atherosclerosis revealed conflicting results. Early studies have shown an association between FMD and angiographic findings,[20] but larger recent studies have shown that there is no significant association between FMD and angiographic findings.[21,22] Chan *et al*.[23] showed that there was no significant association between impaired FMD and the risk of cardiovascular events. Another study showed that patients with two vessels and three vessel diseases had lower FMD than patients with single vessel disease.[24] Another study showed that patients with left main disease on coronary angiography had lower FMD than other patients.[25] These studies can lead to the hypothesis that the FMD results are more disrupted in more extensive CAD. This is in line with our findings of lower FMD in higher calcium scores and not just the positive calcium score.

Also, the controversial results may be due to the study patients' characteristics; for example, higher frequency of non-calcified plaques which are more vulnerable in patients with acute coronary syndrome who usually underwent coronary angiography instead of coronary CT angiography.

However, the relationship between FMD and subclinical markers of atherosclerosis has not been established well.[26] Our results revealed a strong association between FMD—a marker of vascular endothelial dysfunction—with vascular atherosclerotic load assessed by the calcium score on the CCTA.

Various studies have shown that both FMD and calcium scores independently predict the incidence of CAD events in a variety of populations.[27,28] FMD evaluates vascular function in response to shear stress, and CCTA represents the anatomical marker of atherosclerosis.[29,30] Lakshmanan *et al*.[31] also showed that brachial FMD was independently associated with the presence and extent of subclinical atherosclerosis in the CCTA, but in comparison to our study they did not exclude the patients with traditional coronary risk factors affecting the FMD and calcium score. They also considered a lower cutoff point (4.5%) for FMD for predicting a higher calcium score.

The present study revealed that FMD less than 7.1% could predict CADs evaluated by coronary artery calcium scoring.

The sensitivity and specificity of FMD with a cutoff value of 7.1% for the diagnosis of endothelial dysfunction are

Table 3: Association between calcium score and FMD

FMD	Calcium Score		*P**	Regression Coefficient (95% CI)*	
	Low	High		Crude	Adjusted
Non-normal	15 (18.1%)	39 (95.1%)	<0.001	−9.28 (−10.41, −8.16)	−9.07 (−10.27, −7.87)
Normal	68 (81.9%)	2 (4.9%)			

*obtained based on Fisher's exact test. **obtained based on linear regression. Models were adjusted by gender and FH

53% and 70%, respectively.[16] In studies that CCTA used as a gold standard test, the cutoff point of 4.5% for FMD in patients with positive CAC (0 < CAC < 100) was useful. In this scenario, the sensitivity and specificity of FMD are 62.2% and 66.7%, respectively.[3] Given the exclusion of patients with cardiovascular risk factors in our study, determining a cutoff value of less than 7.1% would be most useful for estimating a high level of CACs (above 100).

Several studies have described the role of FMD in predicting cardiovascular events. Currently, the European Society of Cardiology Working Group on peripheral circulation advocates evaluating FMD as a research tool only.[32] Accordingly, our findings could introduce FMD as an accurate, less expensive, and conventional modality to improve risk classification in CAD patients.

Limitations

The present study was performed on a limited number of participants. Further studies with larger sample sizes are recommended. Also, this study was observational and included all the limitations of this type of study.

Conclusion

Finally, our findings provide evidence of a strong association between FMD—a marker of vascular endothelial dysfunction—with vascular atherosclerotic load, as assessed by the calcium score. These results suggest the possibility of the usage of FMD as a low-cost non-invasive test to predict the burden of atherosclerosis.

Financial support and sponsorship

This study was supported by Isfahan University of Medical Science [Grant number, 398014, IR.MUI.MED.REC.1398.095].

Conflicts of interest

There are no conflicts of interest.

Acknowledgments

Nil.

Ethical Considerations:

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Code of Ethics:

IR.MUI.MED.REC.13983095

Authors' Contributions:

FT and AS contributed to the concept and design of the study. MA, FT, AS, and RZ contributed to the analysis and interpretation of the data. MA, FT, and AS contributed to the critical revision of the article and writing of the manuscript. All authors reviewed the manuscript.

Received: 27 Apr 22 **Accepted:** 27 Oct 22
Published: 30 Nov 23

References

1. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, *et al*. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation 2011;123:e18-209.
2. Kolansky DM. Acute coronary syndromes: Morbidity, mortality, and pharmacoeconomic burden. Am J Manag Care 2009;15:S36-41.
3. Halcox JPJ, Schenke WH, Zalos G, Mincemoyer R, Prasad A, Waclawiw MA, *et al*. Prognostic value of coronary vascular endothelial dysfunction. Circulation 2002;106:653-8.
4. Oikonomou E, Siasos G, Tsigkou V, Bletsa E, Panoilia M-E, Oikonomou IN, *et al*. Coronary artery disease and endothelial dysfunction: Novel diagnostic and therapeutic approaches. Curr Med Chem 2020;27:1052-80.
5. Cola C, Almeida M, Li D, Romeo F, Mehta JL. Regulatory role of endothelium in the expression of genes affecting arterial calcification. Biochem Biophys Res Commun 2004;320:424-7.
6. Lekakis J, Abraham P, Balbarini A, Blann A, Boulanger CM, Cockcroft J, *et al*. Methods for evaluating endothelial function: A position statement from the European Society of Cardiology Working Group on Peripheral Circulation. Eur J Cardiovasc Prev Rehabil 2011;18:775-89.
7. Broxterman RM, Witman MA, Trinity JD, Groot HJ, Rossman MJ, Park S-Y, *et al*. Strong relationship between vascular function in the coronary and brachial arteries: A clinical coming of age for the updated flow-mediated dilation test? Hypertension 2019;74:208-15.
8. Teragawa H, Ueda K, Matsuda K, Kimura M, Higashi Y, Oshima T, *et al*. Relationship between endothelial function in the coronary and brachial arteries. Clin Cardiol An Int Index Peer-Reviewed J Adv Treat Cardiovasc Dis 2005;28:460-6.
9. Schechter AN, Gladwin MT. Hemoglobin and the paracrine and endocrine functions of nitric oxide. N Engl J Med 2003;348:1483-5.
10. Williams MC, van Beek EJR, Hill AT, Murchison JT. Coronary Artery Calcification on Thoracic Computed Tomography Is an Independent Predictor of Mortality in Patients With Bronchiectasis. J Thorac Imaging 2021;36:166-73.
11. Gökdeniz T, Kalaycıoğlu E, Aykan AÇ, Boyacı F, Turan T, Gül İ, *et al*. Value of coronary artery calcium score to predict severity or complexity of coronary artery disease. Arq Bras Cardiol 2014;102:120-7.
12. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, *et al*. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 2008;359:2324-36.
13. Firnhaber JM, Mounsey AL, Firnhaber GC. How should we use the coronary artery calcium score to predict cardiovascular risk? J Fam Pract 2011;60:368-9.
14. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, *et al*. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J 2020;41:407-77.
15. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, *et al*. Guidelines for the ultrasound

assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002;39:257-65.
16. Maruhashi T, Kajikawa M, Kishimoto S, Hashimoto H, Takaeko Y, Yamaji T, *et al*. Diagnostic criteria of flow-mediated vasodilation for normal endothelial function and nitroglycerin-induced vasodilation for normal vascular smooth muscle function of the brachial artery. J Am Heart Assoc 2020;9:e013915.
17. Hanifehpour R, Motevalli M, Ghanaati H, Shahriari M, Ghasabeh MA. Diagnostic accuracy of coronary calcium score less than 100 in excluding coronary artery disease. Iran J Radiol 2016;13:e16705.
18. Li J, Flammer AJ, Nelson RE, Gulati R, Friedman PA, Thomas RJ, *et al*. Normal vascular function as a prerequisite for the absence of coronary calcification in patients free of cardiovascular disease and diabetes. Circ J 2012;76:2705-10.
19. Arbab-Zadeh A. Stress testing and non-invasive coronary angiography in patients with suspected coronary artery disease: Time for a new paradigm. Heart Int 2012;7:e2.
20. Schrock NW. The theory of asset choice: Simultaneous holding of short and long positions in the futures market. J Polit Econ 1971;270-93.
21. Frick M, Schwarzacher SP, Alber HF, Rinner A, Ulmer H, Pachinger O, *et al*. Morphologic rather than functional or mechanical sonographic parameters of the brachial artery are related to angiographically evident coronary atherosclerosis. J Am Coll Cardiol 2002;40:1825-30.
22. Juonala M, Viikari JSA, Laitinen T, Marniemi J, Helenius H, Rönnemaa T, *et al*. Interrelations between brachial endothelial function and carotid intima-media thickness in young adults: The cardiovascular risk in young Finns study. Circulation 2004;110:2918-23.
23. Chan L, Shaw AG, Busfield F, Haluska B, Barnett A, Kesting J, *et al*. Carotid artery intimal medial thickness, brachial artery flow-mediated vasodilation and cardiovascular risk factors in diabetic and non-diabetic indigenous Australians. Atherosclerosis 2005;180:319-26.
24. Kaku B, Mizuno S, Ohsato K, Murakami T, Arai Y, Nio Y, *et al*. The correlation between coronary stenosis index and flow-mediated dilation of the brachial artery. Jpn Circ J 1998;62:425-30.
25. Nemoto T, Minami Y, Yamaoka-Tojo M, Sato T, Muramatsu Y, Kakizaki R, *et al*. Impaired flow-mediated dilation and severity and vulnerability of culprit plaque in patients with coronary artery disease. Int Heart J 2019;60:539-45.
26. Schroeder S, Enderle MD, Baumbach A, Ossen R, Herdeg C, Kuettner A, *et al*. Influence of vessel size, age and body mass index on the flow-mediated dilatation (FMD%) of the brachial artery. Int J Cardiol 2000;76:219-25.
27. Perticone F, Ceravolo R, Pujia A, Ventura G, Iacopino S, Scozzafava A, *et al*. Prognostic significance of endothelial dysfunction in hypertensive patients. Circulation 2001;104:191-6.
28. Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: Mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. J Am Coll Cardiol 2005;46:807-14.
29. Lerman A, Zeiher AM. Endothelial function: Cardiac events. Circulation 2005;111:363-8.
30. Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. Radiology 2003;228:826-33.
31. Lakshmanan S, Shekar C, Kinninger A, Birudaraju D, Dahal S, Onuegbu A, *et al*. Association of flow mediated vasodilation and burden of subclinical atherosclerosis by coronary CTA. Atherosclerosis 2020;302:15-9.
32. Vlachopoulos C, Xaplanterisa P, Aboyansb V, Brodmannc M, Cífkovád R, Cosentino F, *et al*. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. Atherosclerosis 2015;241:507-32.