

## Brachial endothelial function and carotid intima-media thickness in patients with coronary artery disease

Marjan Mahdavi-Roshan<sup>1,2</sup>, Arsalan Salari<sup>2</sup>, Javad Nasrollah zadeh<sup>\*3</sup>, Mehrnaz Doostdar-Sanaye<sup>1</sup>

<sup>1</sup>Department of Community Medicine; Faculty of Medicine; Guilan University of Medical Science, Rasht, Iran

<sup>2</sup>Guilan interventional Cardiovascular Research Center, Heshmat Hospital, Guilan University of Medical Sciences, Rasht, Iran

<sup>3</sup>Department of Clinical Nutrition & Dietetics, National Nutrition and Food Technology Research Institute, Faculty of Nutrition Sciences and Food Technology, ShahidBeheshti University of Medical Sciences, Tehran, Iran

\*Corresponding Author: email address: [jnasrollahzadeh@gmail.com](mailto:jnasrollahzadeh@gmail.com) (J. Nasrollah zadeh)

### ABSTRACT

Endothelial dysfunction and carotid intima-media thickness are 2 indicators of subclinical cardiovascular disease. The aim of study was to analyze brachial flow mediated dilation(FMD) and carotid intima media thickness (CIMT)in patients with coronary artery disease, and investigate the relationship between endothelial function, CIMT and coronary artery disease risk factors.56 men and women aged between 25 to 75 years with coronary artery disease were recruited. FMD and CIMT was measured by B-mode ultrasonography. Data were presented as mean  $\pm$  SE. Pearson correlation coefficients were used to evaluate associations and T-test and Chi-square tests were used for quantitative and qualitative variables. *P*-values < 0.05 were considered to indicate statistically significant differences. The mean age of subjects was 59.37 $\pm$ 1.28 years. The frequencies of one, two and three-vessel coronary artery disease were 61%, 35.1% and 3.9%, respectively. The mean of CIMT in patients was 0.79 $\pm$ 0.02 mm, and 65.5% of patients had CIMT more than 0.8 mm.The mean of FMD was 4.79 $\pm$ 0.55% and 65.4% of patients had FMD lower than 5.3%. CIMT was correlated directly with number of diseased vessels, age andtotal cholesterol and was correlated inversely with HDL-C.Non-invasive measurement of FMD and CIMT are interrelated techniques that probably assess the same atherosclerotic process from functional and anatomic viewpoints.In these patients an increase in CIMT and decrease in FMD may warrant more aggressive risk factor control through the beginning of effective medical treatment.

**Keywords:** endothelial function; carotid intima media thickness; coronary artery disease

### INTRODUCTION

Ultrasound technique, as anoninvasive method, to evaluate brachial artery flow mediated dilatation (FMD) has recently been much used in the study of arterial physiology.The dilatation response with increased blood flow is mainly mediated by nitric oxide released from arterial endothelial cells[1]. Studies have shown that brachial FMD response is correlated with coronary endothelial function and impaired brachial FMD is related to the prevalence and extent of coronary atherosclerosis and predicts cardiovascular events[2].

Measurement of carotid intima-media thickness (CIMT) by ultrasound is a marker of vessel atherosclerosis. Increased CIMT is correlated with cardiovascular risk factors and the severity of coronary atherosclerosis and predicts cardiovascular events in population groups[3, 4]. Evidence of alterations in these two factors could provide a non-invasive method for early detection of an atherosclerotic process that will remain asymptomatic for many years before manifesting clinically, thereby providing a marker of this process with long-term prognostic value [5, 6]. In recent years, considerable interest has focused on

analyzing the indicators of atherosclerosis and determining their clinical usefulness; it has even been suggested that they could be future risk markers [4, 7, 8].

Because of the prevalence and socioeconomic importance of atherosclerosis, a great deal of effort is centered on its prevention and risk markers. Although several investigators in other countries have examined the relationships between FMD and CIMT and cardiovascular risk factors, previous studies often were limited to healthy subjects or high risk subjects. To our knowledge, few studies have investigated endothelial function and CIMT (as non-invasive techniques) in patients with coronary artery disease, or correlation between FMD, CIMT and cardiovascular risk factors, in Iran. For this reason the aim of study was two-fold: 1) to analyze brachial FMD and CIMT in patients with coronary artery disease, and 2) investigate the relationship between FMD, CIMT and coronary artery disease risk factors.

## **MATERIALS AND METHODS**

Subjects, men and women aged between 25 to 75 years with coronary artery disease that were recruited from the Rajaei Cardiovascular, Medical and Research Center, a university-affiliated medical center, from August 2013 to April 2014, for this cross-sectional study. Exclusion criteria included: recent acute coronary syndrome (<6 months), present smokers, diabetes, renal disease. All participants were from urban regions. All subjects gave written and informed consent and the study was approved by the National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences Ethics Committee. CIMT was measured and analyzed by a single radiologist blinded to the subjects' details using a LOGIQ7 ultrasound machine. All subjects were examined in a supine position and measurements were conducted in a quiet environment. CIMT was determined by measuring the distance between the lumen-intima and media-adventitia border of the vascular wall with the use of electronic calipers. Each ultrasonic scan was performed in the anterior, lateral, and posterior projections of the right and left carotid arteries. Three CIMT measurements were made on the near and far walls of the left and

right common carotid arteries, carotid bifurcation, and internal carotid. The mean CIMT was calculated by averaging the values of CIMT measured.

After a 10 min rest in a temperature controlled laboratory (21°C), endothelial function was assessed. To assess brachial FMD, the right brachial artery diameter was measured both at rest and during reactive hyperemia. Brachial FMD was assessed based on guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery (2002). In Reactive hyperaemia was induced by inflating a blood pressure cuff placed around the forearm to a pressure of 250 mm Hg for 5 minutes. The brachial artery is imaged above the antecubital fossa in the longitudinal plane. Measurements of arterial diameter were performed at a fixed distance from an anatomic marker at rest and at 30, 60, and 90 seconds after cuff release. The vessel diameter in scans after reactive hyperemia was expressed as the percentage relative to the resting scan. The greatest value between 30 and 90 seconds was used to derive the maximum FMD. Fasting blood samples were taken from patients. Laboratory measurements (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, Apolipoprotein A<sub>1</sub>, Apolipoprotein B and hs-CRP) were measured using commercially available kits (Pars Azmoon, Iran).

Statistical Package for Social Sciences version 11.5 was used for all statistical analysis. Data were presented as mean  $\pm$  SE. Pearson correlation coefficients were used to evaluate associations and T-test and Chi-square tests were used for quantitative and qualitative variables. P-values < 0.05 were considered to indicate statistically significant differences.

## **RESULTS**

The mean age of 56 subjects was 59.37 $\pm$ 1.28 years. 43 subjects (76.8%) were male and 13 subjects (23.2%) were female. Of 56 patients, 18 patients (32.1%) had hypertension. The frequencies of one, two and three-vessel coronary artery disease were 61%, 35.1% and 3.9%, respectively. The mean of CIMT in patients was 0.79 $\pm$ 0.02 mm, and 65.5% of patients had CIMT more than 0.8 mm. In our study over weight

patients had higher CIMT than normal weight patients but this difference wasn't significant ( $p=0.22$ ). There wasn't any significant difference in CIMT, between men and women ( $p=0.83$ ).

The mean of FMD in patients was  $4.79 \pm 0.55\%$  and 65.4% of patients had FMD lower than 5.3%. In our study over weight patients had lower FMD than normal weight patients but this difference wasn't significant ( $p=0.56$ ). There wasn't any significant difference in FMD, between men and women ( $p=0.72$ ). Based on CIMT, patients divided into 2 groups. Subjects that had CIMT < 0.8 mm and Subjects that had carotid IMT  $\geq$  0.8 mm. Base on brachial FMD, patients also divided into 2 groups. Subjects that had FMD > 5.3% and Subjects that had FMD  $\leq$  5.3%. Difference in cardiovascular risk factors in patients, base on

carotid IMT and brachial FMD have shown in table 1 and table 2.

CIMT was correlated directly with age ( $r = 0.43$ ,  $p = 0.001$ ), total cholesterol ( $r=0.25$ ,  $p=0.05$ ) and number of diseased vessels ( $r = 0.24$ ,  $p = 0.07$ ) and inversely with HDL-C ( $r=-0.28$ ,  $p=0.03$ ). In addition, in patients with CIMT  $\geq$  0.8, the correlation between CIMT and increased number of diseased vessels was more significant ( $r = 0.55$ ,  $p = 0.000$ ). There wasn't any significant correlation between FMD and risk variables. In our study there wasn't significant correlation between FMD and CIMT.

Patients with CIMT  $\geq$  0.8 mm were older and had significantly higher total cholesterol and lower ejection fraction, ApolipoproteinA<sub>1</sub> and HDL-C than Patients with CIMT < 0.8 mm.

**Table 1.** Clinical characteristics in coronary artery disease patients base on CIMT and FMD measures

	patients CIMT			patients FMD		
	CIMT <0.8 mm (N=19)	CIMT $\geq$ 0.8 mm (N=36)	<i>p</i> - value	FMD>5.3% (N=18)	FMD $\leq$ 5.3% (N=34)	<i>p</i> -value
Age (years)	56.21 $\pm$ 1.94	61.16 $\pm$ 1.59	0.04	57.82 $\pm$ 1.44	59.21 $\pm$ 3.63	0.08
Sex (% male)	14(73.7%)	28(77.8%)	0.74	14(77.8%)	25(73.5%)	0.74
Body mass index(kg/m <sup>2</sup> )	25.07 $\pm$ 0.66	26.11 $\pm$ 0.63	0.30	26.08 $\pm$ 1.10	25.39 $\pm$ 0.48	0.66
Coronary artery disease						
One vessel disease	13(68.4%)	23(63.9%)	0.20	10(55.6%)	23(67.6%)	0.31
Two or three vessel disease	6(31.6%)	13(36.2%)		8(44.4%)	11(32.4%)	
Hypertension(%)	6(31.6%)	12(33.3)	0.61	4(22.2%)	12 (35.3)	0.34
Systolic BP (mmHg)	116.53 $\pm$ 3.78	120 $\pm$ 2.43	0.41	115.83 $\pm$ 3.33	119.68 $\pm$ 2.71	0.39
Diastolic BP (mmHg)	74.05 $\pm$ 2.82	75.04 $\pm$ 1.81	0.56	74.05 $\pm$ 2.99	75.35 $\pm$ 1.83	0.69
Ejection Fraction (%)	45.83 $\pm$ 1.20	41.57 $\pm$ 1.98	0.05	45 $\pm$ 1.80	43.97 $\pm$ 1.44	0.66

Data represent mean  $\pm$  SE or percentages and number of subjects for dichotomous measures. CIMT, carotid intima media thickness; FMD, flow mediated dilation; PCI, percutaneous coronary intervention ; CABG, coronary artery bypass graft surgery; BMI, body mass index; BP, blood pressure

**Table 2.** Biochemical characteristics in coronary artery disease patients base on CIMT and FMD measures

	patients CIMT			patients FMD		
	CIMT <0.8 mm (N=19)	CIMT $\geq$ 0.8 mm (N=36)	<i>p</i> - value	FMD>5.3% (N=18)	FMD $\leq$ 5.3% (N=34)	<i>p</i> -value
Cholesterol (mg/dL)	101.42 $\pm$ 4.12	113.94 $\pm$ 5.08	0.05	107.67 $\pm$ 8.24	112 $\pm$ 4.05	0.59
Triglycerides(mg/dL)	69.52 $\pm$ 9.35	71.70 $\pm$ 7.09	0.85	72.20 $\pm$ 6.39	74.05 $\pm$ 11.05	0.88
LDL-C(mg/dL)	51.89 $\pm$ 2.80	58.02 $\pm$ 3.50	0.18	54.16 $\pm$ 5.72	58.76 $\pm$ 3.67	0.53
HDL-C(mg/dL)	36.66 $\pm$ 1.54	31.36 $\pm$ 1.62	0.03	33.83 $\pm$ 1.84	35.29 $\pm$ 1.66	0.58
hs-CRP(mg/dL)	3.20 $\pm$ 0.81	4.24 $\pm$ 0.87	0.38	3.91 $\pm$ 1.15	4 $\pm$ 0.82	0.96
ApolipoproteinA <sub>1</sub> (mg/dL)	103.56 $\pm$ 4.07	95.57 $\pm$ 3.51	0.04	103.94 $\pm$ 3.93	99.64 $\pm$ 4.23	0.46
ApolipoproteinB(mg/dL)	51.63 $\pm$ 3.61	59.52 $\pm$ 3.45	0.12	56.27 $\pm$ 5.32	58.02 $\pm$ 3.11	0.76
Lipoprotein a	28.48 $\pm$ 3.69	31.86 $\pm$ 2.75	0.47	28.89 $\pm$ 2.72	32.71 $\pm$ 3.62	0.40

Data represent mean  $\pm$  SE or percentages and number of subjects for dichotomous measures. CIMT, carotid intima media thickness; FMD, flow mediated dilation; PCI, percutaneous coronary intervention ; CABG, coronary artery bypass graft surgery; BMI, body mass index; BP, blood pressure

## **DISCUSSION**

The present study demonstrate that there was a trend towards increased CIMT in patients with coronary artery disease and severity of coronary artery disease was correlated with increased CIMT. The maximal intima-media thickness equal or greater than 0.8 mm at the far wall of the carotid artery, was selected as the highest value for comparison[9].

Some studies compared CIMT with the incidence of clinically symptomatic coronary artery disease and the extent or incidence of coronary artery disease on angiograms. However, the results of these studies are rather discrepant. Our observations about correlation between CIMT and the extent of coronary artery disease are consistent with several previous studies [10-12]. Kablak-Ziembicka et al[11] found a strong association between coronary artery status, verified by coronary angiography, and mean aggregate IMT in carotid arteries. In contrast, in Furumoto et al [13] and Adams et al[14] study, there was no linear correlation between IMT and the extent of coronary artery disease.

Since both the sensitivity and specificity of echocardiography or treadmill testing are limited, the CIMT measurements of the carotid arteries may help significantly to diagnosing the status of patients with atypical chest pain or patients with a number of cardiovascular risk factors. In these patients an increase in CIMT may be a decisive factor in recommending coronary angiography and may warrant more aggressive risk factor control through the beginning of effective medical treatment. Dysfunction of endothelial cells is probably the earliest event in the process of lesion formation hence, the concept that assessment of endothelial function may be a useful prognostic tool for coronary artery disease[15].

The predictive value of FMD for cardiovascular events is still not well established. Based on Koyoshi et al [16] study, the cut-off level of brachial FMD that had the greatest sensitivity and specificity for the diagnosis of coronary artery disease is 5.3%. In our study, the mean of FMD in patients was 4.79% and a reduction in FMD was found in patients with coronary artery disease.

Several studies have investigated the relationship between and endothelial function and coronary

disease, and a significant decrease in endothelial function was found in patients with angiographically proven coronary disease as compared to persons without this condition[13, 15, 17].

Patients with reduced FMD may be instructed to initiate life style modifications and other primary preventive measures. Upon FMD measurements, images were obtained every 30 seconds after cuff dilation so that maximal vasodilation could have been obtained accurately. Recovery of FMD may be used as a surrogate marker for evaluating the efficacy of different preventive measures for atherosclerotic coronary artery disease. And also brachial artery FMD may become a useful tool for screening patients with coronary artery disease [13].

In this study there was no linear correlation between FMD and cardiovascular risk factors. In Maruhashi et al[18] study, endothelial function that assessed by FMD, significantly correlated with cardiovascular risk factors, including age, Body Mass Index, systolic and diastolic blood pressure, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol. Our Study had Limitations. First, the study was cross-sectional. Second, non-invasive measurements were performed after various treatments. Coronary artery disease patients were taking medications such as, antidiabetic medications that might modify the measurements of FMD.

## **CONCLUSION**

In this study there was a trend towards increased CIMT and a reduction in FMD in patients with coronary artery disease, and severity of coronary artery disease was correlated with increased CIMT. In conclusion, although further study is needed, our data suggest that non-invasive measurement of endothelial function and intima-media thickness are interrelated techniques that probably assess the same atherosclerotic process from functional and anatomic viewpoints, respectively, allowing non-invasive assessment of cardiovascular risk in patients with risk factors.

## **ACKNOWLEDGEMENTS**

The authors wishes to thank Dr Ali Zahedmehr and Dr Ali Mohammad-Zadeh for valuable helps.

**REFERENCE**

1. 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. *Journal of the American College of Cardiology*. 2002;39(2):257-65.
2. Chan SY, Mancini GJ, Kuramoto L, Schulzer M, Frohlich J, Ignaszewski A. The prognostic importance of endothelial dysfunction and carotid atheromaburden in patients with coronary artery disease. *Journal of the American College of Cardiology*. 2003;42(6):1037-43.
3. Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torkko N, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *Jama*. 2003;290(17):2277-83.
4. Juonala M, Viikari JS, 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(18):2918-23.
5. Teragawa H, Kato M, Kurokawa J, Yamagata T, Matsuura H, Chayama K. Usefulness of flow-mediated dilation of the brachial artery and/or the intima-media thickness of the carotid artery in predicting coronary narrowing in patients suspected of having coronary artery disease. *The American journal of cardiology*. 2001;88(10):1147-51.
6. Juonala M, Viikari JS, Rönnemaa T, Marniemi J, Jula A, Loo B-M, et al. Associations of Dyslipidemias From Childhood to Adulthood With Carotid Intima-Media Thickness, Elasticity, and Brachial Flow-Mediated Dilatation in Adulthood The Cardiovascular Risk in Young Finns Study. *Arteriosclerosis, thrombosis, and vascular biology*. 2008;28(5):1012-7.
7. Yeboah J, Burke GL, Crouse JR, Herrington DM. Relationship between brachial flow-mediated dilation and carotid intima-media thickness in an elderly cohort: the Cardiovascular Health Study. *Atherosclerosis*. 2008;197(2):840-5.
8. Kaźmierski M, Michalewska-Włodarczyk A, Krzych ŁJ. Intima-media thickness and flow-mediated dilatation in the diagnosis of coronary artery disease in perimenopausal women. *Pol Arch Med Wewn*. 2010;120(5):181-8.
9. Jadhav UM, Kadam N. Carotid intima-media thickness as an independent predictor of coronary artery disease. *Ind. heart journal*. 2000;53(4):458-62.
10. Visonà A, Pesavento R, Lusiani L, Bonanome A, Cernetti C, Rossi M, et al. Intimal medial thickening of common carotid artery as indicator of coronary artery disease. *Angiology*. 1996;47(1):61-6.
11. 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(11):1286-90.
12. Coppola G, Corrado E, Piraino D, Carella M, Muratori L, Camarda P, et al. Carotid intimal-media thickness and endothelial function in young patients with history of myocardial infarction. *International angiology: a journal of the International Union of Angiology*. 2009;28(2):120-6.
13. Furumoto T, Fujii S, Saito N, Mikami T, Kitabatake A. Relationships between brachial artery flow mediated dilation and carotid artery intima-media thickness in patients with suspected coronary artery disease. *Japanese heart journal*. 2002;43(2):117-25.
14. Adams MR, Nakagomi A, Keech A, Robinson J, McCredie R, Bailey BP, et al. Carotid intima-media thickness is only weakly correlated with the extent and severity of coronary artery disease. *Circulation*. 1995;92(8):2127-34.
15. Verma S, Buchanan MR, Anderson TJ. Endothelial function testing as a biomarker of vascular disease. *Circulation*. 2003;108(17):2054-9.
16. Koyoshi R, Miura S-i, Kumagai N, Shiga Y, Mitsutake R, Saku K. Clinical significance of flow-mediated dilation, brachial intima-media thickness and pulse wave velocity in patients with and without coronary artery disease. *Circ J*. 2012;76:1469-75.
17. Heitzer T, Schlinzig T, Krohn K, Meinertz T, Münzel T. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. *Circulation*. 2001;104(22):2673-8.
18. Maruhashi T, Soga J, Fujimura N, Idei N, Mikami S, Iwamoto Y, et al. Relationship between flow-mediated vasodilation and cardiovascular risk factors in a large community-based study. *Heart*. 2013;99(24):1837-42.