

Flow Mediated Dilation and Its Correlation with Coronary and Systemic Atherosclerosis in Patients Scheduled for Surgical Myocardial Revascularization

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Purpose: The study aimed to evaluate endothelial dysfunction (ED), assessed through flow mediated dilation (FMD), in individuals with severe coronary artery disease (CAD) scheduled for coronary artery bypass graft surgery (CABG). Additionally, we examined the association between the severity of ED evaluated through FMD and the extent of atherosclerosis at the coronary arteries level (SYNTAX I score), carotid arteries and peripheral arteries.

Methods: The study included 84 participants recruited between January 2020 and June 2021. Doppler ultrasonography was used to assess both FMD and the degree of carotid artery stenosis. SYNTAX I score was calculated based on coronary angiography, and peripheral artery disease (PAD) was evaluated using computed tomography.

Results: FMD was used as a surrogate for assessing ED. We found no statistical difference between men and women [4.46 (1.03–6.75) in women versus 2.55 (0.95–6.13 in men; $p=0.21$). A significant association was observed between FMD and SYNTAX score ($p < 0.001$). A lower FMD corresponded to a higher SYNTAX score, reflecting an extensive burden of coronary atherosclerosis. Furthermore, ED, as measured by FMD, was indicative of carotid atherosclerosis and PAD, as evidenced by lower FMD in patients with severe carotid plaques ($p < 0.001$) and severe PAD ($p < 0.01$).

Conclusion: FMD might be a reliable tool to assess systemic atherosclerosis, ED in the brachial artery being related to carotid artery plaque, CAD and peripheral lower limb ischemia.

Keywords: flow mediated dilation, SYNTAX I score, carotid stenosis, peripheral artery disease, coronary artery by-pass graft, coronary artery disease

Introduction

Endothelial dysfunction (ED) encompasses various aspects, ranging from vascular tonus alteration [reduced nitric oxide (NO) vasodilator response] to proinflammatory and prothrombotic status, reduced antioxidant activity, excess synthesis of adhesion molecules and a pro-proliferative status in smooth vascular muscle cells. ED was identified in all stages of ischemic cardiomyopathy: it is present before the formation of atherosclerotic plaque and persists throughout the disease, including acute coronary syndromes.¹ The impairment of ED is implicated in the origin and development of atherosclerotic cardiovascular disease (CVD).²

ED emerges early in the progression of cardiovascular disease. Previous large-scale studies involving healthy populations with cardiovascular risk factors have shown that certain individual risk factors are associated with reduced FMD (flow-mediated dilation).^{3,4} Endothelial function is especially altered in subjects diagnosed with diabetes mellitus.^{5,6}

Previous research established significant correlations between FMD, as a tool for ED assessment, and the severity of CAD (based on the SYNTAX score).^{7,8} Furthermore, FMD appears to be associated with carotid artery atherosclerosis^{9,10} and PAD.¹¹

The aim of the present study was to assess ED, as measured by FMD, in patients with severe CAD undergoing CABG. We also assessed the severity of CAD using the SYNTAX I score and conducted screenings for carotid artery plaque and PAD. Finally, we tested the hypothesis that FMD was associated with CAD and systemic atherosclerotic burden (as identified in the carotid and lower limb territories).

Material and Methods

We prospectively included 84 patients with chronic coronary disease and severe coronary lesions requiring CABG, between January 2020 and June 2021. The study protocol obtained ethical clearance from the Ethical Committee of Transylvania University and adhered to the principles outlined in the Helsinki Declaration and the Code for Good Clinical Practice. A written Informed Consent was obtained from all patients.

Patients with acute coronary syndromes, subclavian artery stenosis, associated significant valvular disease, severe hepatic/renal failure, recent/active bleeding, coagulation disorders, and active malignancy were excluded from the study.

Hypertension was defined as systolic blood pressure values greater than 140/90 mmHg according to the 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines.¹² The criteria for diagnosing diabetes included a fasting blood glucose level >7.0 mmol/L, a 2-hour plasma glucose value >11.1 mmol/L during a 75-g oral glucose tolerance test, glycated hemoglobin (HbA1c) >6.5%, or, in patients with classic symptoms of hyperglycemia or a hyperglycemic crisis, a random plasma glucose >11.1 mmol/L.¹³ For ease of analysis, we included patients with a total plasma cholesterol level >5.2 mmol/l or high-density lipoprotein plasma concentration <1 mmol/l in the dyslipidemia group.¹⁴

To diagnose CAD and evaluate its severity according to the SYNTAX I score, coronary angiogram was performed. The SYNTAX I score was determined using the number of diseased arteries, the location, and the aspect of atherosclerotic plaques (<https://syntaxscore.org/>). Carotid anatomy was evaluated using Doppler ultrasonography. For practical purposes, we documented the stenosis of the internal carotid artery. Carotid artery stenosis was defined as mild (<50%), moderate (50–69%), and severe (70–99%).¹⁵

PAD was diagnosed based on symptoms, clinical signs, Doppler ultrasonography, and its severity was evaluated using computed tomography angiography. PAD was classified in 6 groups (0-no PAD; 1-mild stenosis <25%; 2-moderate stenosis 25–50%; 3-moderate to severe stenosis 50–75%; 4-critical stenosis 75–99%; 5-occlusion) based on computed tomography angiography.^{16,17}

Prior to the FMD measurement, the subjects had to fast for at least six hours, refrain from physical exertion, and not consume caffeine or smoke for the previous twenty-four hours.^{18–22} For a minimum of ten minutes, patients were kept in a quiet room in the supine posture. The vascular linear probe operating in 2D mode at 7.5–12 MHz was used to measure FMD. To create reactive hyperemia, the occlusion cuff was wrapped around the forearm and inflated for five minutes to a pressure 50 mmHg higher than the systolic blood pressure. During reactive hyperemia, the diameter change was continuously assessed. The diameter of the brachial artery was measured basally (before the cuff was inflated), 3 minutes after the cuff was deflated, 60–90 seconds after maximal reactive hyperemia, and 3–10 cm above the antecubital fossa. FMD was calculated as percentage index according to current guidelines.²³ Flow-mediated dilation is usually expressed as the percentage increase in post cuff-release vessel diameter relative to the baseline diameter. There is ongoing discussion on the normal reference levels. In accordance with recent research, we considered a value <6.5% as indicative for ED.²⁴

Statistics

Data were analyzed using Microsoft Office Excel 2019 and JASP 0.19 software. Patient demographics and characteristics were compared using the *T*-test, Chi-square and Mann–Whitney *U*-tests. To ascertain correlations in the analyzed data, 2-tailed Pearson (for normally distributed variables), Spearman (for skewed distribution) and one way ANOVA tests were employed, with statistical significance set at $p < 0.05$.

Results

We included patients aged 46–88 years, 79.76% of the studied population being male. The mean age was 64.25 ± 7.24 for males and 68.41 ± 10.44 for females. The studied population was composed of overweight patient, with a mean BMI (body mass index) of 28.07 kg/m^2 for males and 29.48 kg/m^2 for females. Arterial hypertension and dyslipidemia were the most common cardiovascular risk factors identified. Smoking was reported in 22.38% of males and 11.76% of females, while type 2 diabetes mellitus was present in 38.8% of males and 41.17% of females. Clinical characteristics of the subjects, based on their gender, are displayed in Table 1.

An example of FMD measurement is presented in Figure 1 (Figure 1a: the basal diameter and velocity of the brachial artery and Figure 1b: peak diameter and velocity of the brachial artery measured during maximal reactive hyperemia).

We observed a significant correlation between FMD and SYNTAXI score ($r=0.898$; $p<0.001$), indicating that a low FMD corresponds to severe coronary atherosclerosis (Figure 2).

To evaluate the correlation between FMD and the presence and severity of carotid atherosclerotic disease, patients were divided into three groups according to the severity of carotid artery stenosis assessed using carotid ultrasound examination: group 1 [20 patients, 23.81% with mild carotid artery stenosis ($<50\%$)], group 2 [34 patients, 40.47% with moderate carotid artery stenosis ($50\text{--}69\%$)], and group 3 [30 patients, 35.71% included patients with severe carotid artery atherosclerosis ($70\text{--}99\%$)]. Figure 3 depicts the relation between FMD and the severity of carotid atheroma.

Lower limb PAD was diagnosed in 11 (16.41%) of the male population. The female population included in the study did not have associated PAD. PAD was classified in 6 groups (0-no PAD; 1-mild stenosis $<25\%$; 2-moderate stenosis $25\text{--}50\%$; 3-moderate to severe stenosis $50\text{--}75\%$; 4-critical stenosis, $75\text{--}99\%$; 5-occlusion) based on computed tomography angiography. Out of the 84 patients enrolled 73 did not have associated PAD, 4 patients had moderate lower limb PAD ($25\text{--}50\%$), 4 patients had moderate-to-severe PAD ($50\text{--}75\%$), and 3 patients associated critical stenosis ($75\text{--}99\%$) in the lower limbs. The difference between mean FMD for patients with PAD and those without diagnosed PAD was statistically significant at a p value of 0.001. The relation between FMD and PAD is presented in Figure 4.

Table 1 Baseline characteristics of the subjects according to gender

Variables	Male (N = 67)	Female (N= 17)	P Value
Age (years; mean $\pm$ st dev)	64.25 $\pm$ 7.24	68.41 $\pm$ 10.44	0.058 ^a
BMI (kg/m^2 ; mean $\pm$ st dev)	28.07 $\pm$ 4.30	29.48 $\pm$ 3.89	0.225 ^a
Hypertension (N, %)	64, 95.51	15, 88.23	0.257 ^b
Smoking status (N, %)	15, 22.38	2, 11.76	0.330 ^b
Dyslipidemia (N, %)	63, 94.03	17, 100	0.302 ^b
Diabetes (N, %)	26, 38.80	7, 41.17	0.858 ^b
Carotid artery stenosis(N*, %)	52, 77.61	12, 70.58	0.218 ^b
PAD (N,%)	11, 16.41	0, 0	0.360 ^b
SYNTAX I score (median, min-max)	30.5, 17–48	26, 17–54	0.120 ^c
FMD(%; median, min-max))	2.55, 0.95–6.13	4.46, 1.03–6.75	0.214 ^c

Notes: ^at test, ^bChi-square, ^cMann–Whitney U-test; N*: patients with carotid artery stenosis $>50\%$;

Abbreviations: st dev, standard deviation; BMI, body mass index; PAD, peripheral artery disease; FMD, flow-mediated dilation; min, minimum; max, maximum.

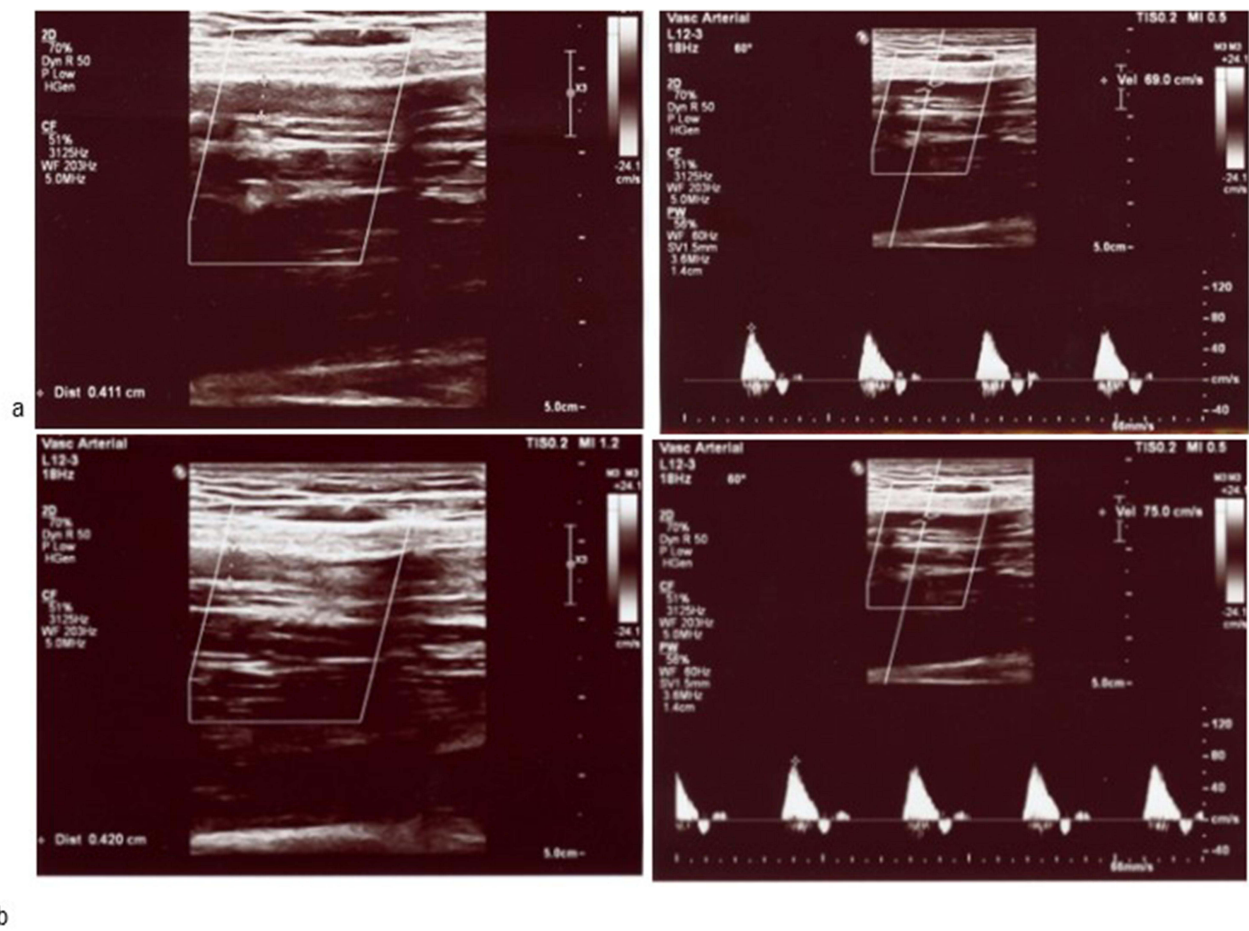


Figure 1 An example of FMD measurement. (a) The basal diameter and velocity of the brachial artery; (b) Peak diameter and velocity of the brachial artery (maximal hyperemia)-the estimated FMD was 2.18%.

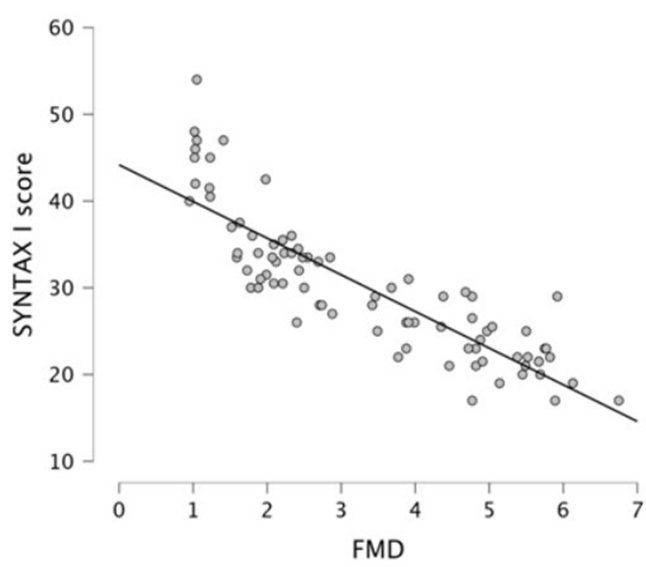


Figure 2 The correlation between SYNTAX score and FMD.

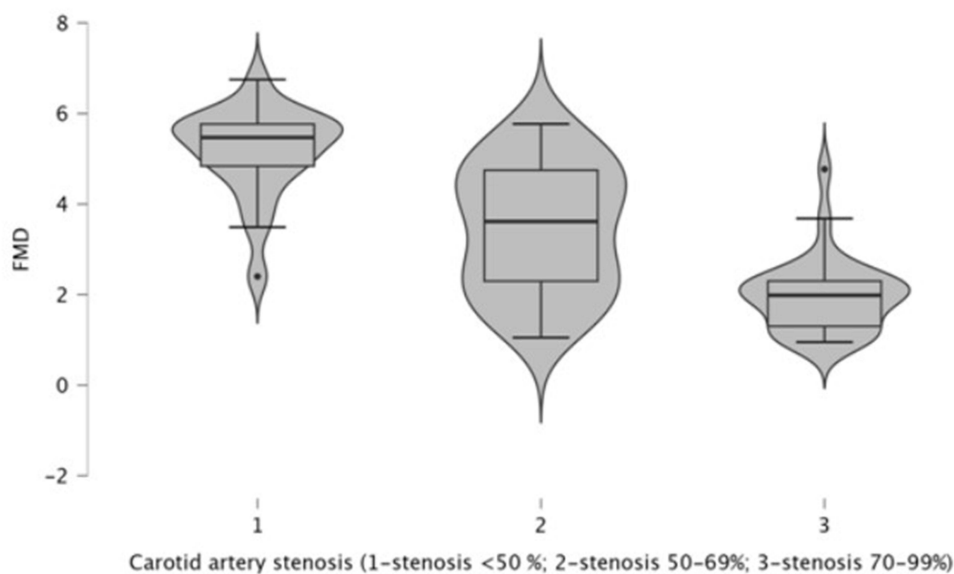


Figure 3 FMD and the severity of carotid artery stenosis ($p<0.001$; p value according to One-Way ANOVA).

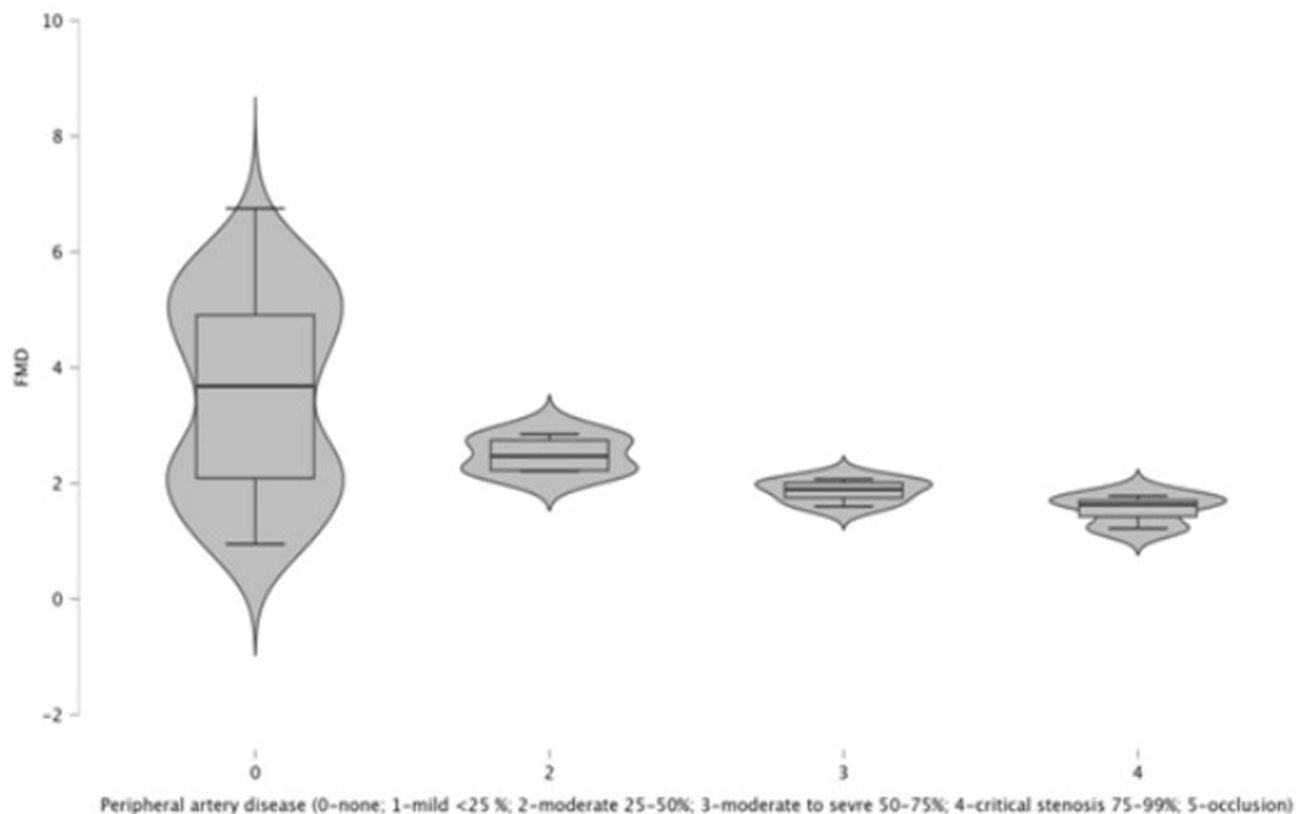


Figure 4 The relation between FMD and PAD ($p<0.001$; p value according to One-Way ANOVA).

Discussion

There were no statistically significant differences between males and females in terms of the clinical characteristics of the studied population (p values are mentioned in Table 1). Both groups exhibited FMD values below the 6.5% (the median was 2.55% in the male group and 4.46% in the female group), which represents the cutoff identified in previous studies

as a marker for acute cardiovascular events.^{23,24} Although the median for FMD in males was lower than in females (2.55% versus 4.46%), the result was not statistically significant ($p=0.214$). As the study involved mainly postmenopausal women (mean age 68.41 ± 10.44 years), our result is in accordance with previous research showing similar FMD values in older men and women.²⁵

Furthermore, FMD values correlated with the SYNTAX I score ($r=0.898$; $p<0.001$), underlining that vasodilator response is diminished in patients with severe CAD. Previous trials have proven that FMD and SYNTAX I score are associated in patients with a low cardiovascular risk, without established coronary artery disease or vascular atherosclerotic disease.^{7,8,26,27} However, little research was carried out on high-risk patients. To our knowledge, the present study is the first to measure brachial FMD in patients with severe CAD scheduled for CABG, and to prove that an important association persists between FMD values and SYNTAX score.

Endothelial dysfunction assessed by FMD is also associated with the presence and severity of carotid plaques. Our study showed that a low FMD value, indicating severe ED, was correlated with severe atherosclerosis in the carotid territory, as well.^{9,28}

To our knowledge, FMD measurement is less commonly used in the field of vascular surgery. However, it has proven to be an important tool for evaluating endothelial function in lower limb artery disease.¹¹ Our study found that a low brachial FMD was associated with severe PAD.

Advancements in the standardization of FMD methodology and analysis have made it a valuable tool for evaluating therapeutic interventions. FMD assessment could also be a useful tool for evaluating ED in patients undergoing CABG in which procedures are conducted to improve endothelial function (for example: antioxidant medication; endogenous release of nitric oxide after ischemic preconditioning). As it is a non-invasive method, FMD can be used multiple times, with virtually no side effects, and it might indicate the effect of experimental therapies earlier, guiding the next steps of researchers (proceeding/discontinuing the study).

Several limitations need mentioning. First, FMD measurement is affected by multiple factors, some of them being corrected before the investigation was carried out (subjects had to fast for at least six hours, refrain from physical exertion, not consume caffeine or smoke for the previous twenty-four hours, maintaining supine posture for at least 10 minutes in a quiet room prior to the examination). A limitation of this study is the small sample size of patients diagnosed with PAD, as only 11 patients were identified with associated lower limb atherosclerosis based on the criteria used. This limited number of PAD cases may affect the findings related to lower limb artery disease and its relationship with endothelial function. Larger studies on PAD patients are needed to confirm and expand upon these results. Further research is needed to validate the results obtained for this category.

Conclusion

First, in patients with severe coronary artery disease scheduled for CABG surgery, endothelial dysfunction, estimated by FMD, is impaired. Second, FMD values correlated with SYNTAX I score, carotid artery plaque and PAD, reflecting the burden of systemic atherosclerosis.

Disclosure

The author(s) report no conflicts of interest in this work.

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