

Brachial flow-mediated vasodilatation in predicting the complexity of coronary artery disease

Wisnu Sakulat, Budi S. Pikir, Eka Prasetya Budi Mulia, Maya Qurota A'yun

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Hospital, Surabaya, Indonesia

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SOUHRN

Cíl: Přestože již byla identifikována řada rizikových faktorů rozvoje aterosklerózy, lze stále obtížně předpovídat, jak tyto faktory interagují při stanovování endotelové funkce a rozvoje ischemické choroby srdeční (ICHS). Neinvazivní vyšetření endotelové funkce se často provádí metodou endotel-dependentní vazodilatace pažní tepny (flow-mediated vasodilatation, FMD). Spolehlivost metody FMD jako zástupného ukazatele závažnosti ICHS zatím nebyla jednoznačně potvrzena. Cílem této studie bylo zjistit korelaci mezi výsledky naměřenými metodou FMD a závažností ICHS s použitím skóre SYNTAX jako spolehlivějších a jednodušších diagnostických nástrojů.

Metoda: Naše studie měla průřezové uspořádání s nenáhodným účelovým vzorkováním. Údaje od pacientů po koronarografickém vyšetření jsme shromažďovali v období od října do prosince 2015. Závažnost ICHS se vypočítávala pomocí skóre SYNTAX. Endotelová funkce se hodnotila metodou FMD pažní tepny s použitím dopplerovského ultrazvuku. Korelace mezi hodnotami FMD a skóre SYNTAX se zjišťovala pomocí Pearsonova korelačního testu.

Výsledky: Do studie jsme zařadili 40 pacientů s ICHS přijatých na kliniku kardiologie nemocnice Dr. Soetomo General Hospital. Průměrný věk pacientů byl $55,38 \pm 9,27$ roku, 85 % ($n = 34$) z nich byli muži, 67 % ($n = 27$) mělo hypertenzi, 80 % ($n = 32$) framinghamské skóre vysokého rizika a u 27,5 % ($n = 21$) bylo podle klasifikace SCORE přítomno středně vysoké riziko. Před katetrizací byla stanovena diagnóza postakutního koronárního syndromu u 65 % ($n = 27$) pacientů s průměrnou hodnotou skóre SYNTAX $33,21 \pm 10,86$. Byla zjištěna těsná, negativní a statisticky významná korelace mezi hodnotou FMD a skóre SYNTAX ($r = -0,787$ a $p < 0,0001$). Čím je hodnota FMD nižší, tím je ICHS závažnější.

Závěr: Při použití skóre SYNTAX vykazuje metoda FMD těsnou a negativní korelaci se závažností ICHS. Nižší hodnota FMD predikuje závažnější ICHS.

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ABSTRACT

Goal: A number of atherosclerosis risk factors have been identified, but it remains difficult to predict how these factors interact in determining the endothelial function and development of coronary artery disease (CAD). Non-invasive assessment of endothelial function is commonly undertaken using the flow-mediated vasodilatation (FMD) technique. The use of FMD as a surrogate indicator for the complexity of CAD remains largely unknown. This study aimed to determine the correlation between FMD with the complexity of CAD based on SYNTAX score for better and simpler diagnostic tools.

Methodology: This was a cross-sectional study with purposive sampling. We collected data from a patient who underwent coronary angiography from October to December 2015. The SYNTAX score was calculated to determine the complexity of CAD. Endothelial function was evaluated by FMD using brachial artery Doppler ultrasonography. Correlation between FMD and SYNTAX score was evaluated using the Pearson correlation test.

Result: We enrolled 40 CAD patients admitted to cardiology ward of Dr. Soetomo General Hospital, mean age 55.38 ± 9.27 years old, 85% ($n = 34$) male, 67% ($n = 27$) has hypertension, 80% ($n = 32$) has high risk Framingham score, and 27.5% ($n = 21$) has moderate risk according SCORE score. Pre-catheterization diagnosis was post-acute coronary syndrome in 65% ($n = 27$) with the mean SYNTAX score being 33.21 ± 10.86 . There was a strong negative and significant correlation between FMD and SYNTAX score ($r = -0,787$ and $p < 0,0001$). The lower the FMD value predicts the higher complexity of CAD.

Conclusion: FMD has a strong and negative correlation with the complexity of CAD based on SYNTAX score. The lower the FMD value predicts the higher complexity of CAD.

Keywords:

CAD complexity

Endothelial dysfunction

FMD

SYNTAX score

Address: Budi S. Pikir, MD, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Hospital, Surabaya, Indonesia, e-mail: bsp49@fk.unair.ac.id

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Introduction

Atherosclerosis is the most common cause of coronary, carotid, and peripheral artery disease. The progressiveness of atherosclerosis causes narrowing of the arterial vessels, characterized by the occurrence of endothelial dysfunction, vascular inflammation, and accumulation of lipids, calcium, and debris cells in the tunica intima of arterial walls. The development of atherosclerosis results in plaque formation, vascular remodeling, acute obstruction, and chronic vascular lumen, abnormal blood vessel flow, and decreased blood supply to target organs.^{1,2}

In the past two decades, several models of risk factor stratification have been developed to estimate a person who has a cardiovascular disorder at a certain time, one of which is the Framingham Heart Study (FSH). Multifactorial risk assessments that are often used in clinical practice are useful for patient selection and administration of therapy to reduce the incidence of cardiovascular disease by controlling modifiable factors. However, research shows that 25% of patients who suffer from acute myocardial infarction only have 1–2 risk factors or are classified as low risk.³

Atherosclerosis is a process that begins with the occurrence of endothelial function disorders that have an important role as a barrier between blood circulation and blood vessel walls.⁴ endothelial regeneration, inhibition of leukocyte chemotaxis, and platelet adhesion. Endothelium damage induced by atherosclerosis leads to the reduction in bioactivity of endothelial NO synthase (eNOS). Early detection of endothelial dysfunction can be used for prevention before the onset of atherosclerotic plaque, and it can be evaluated using flow mediated vasodilatation (FMD). Brachial arterial ultrasonography, which can also be used for evaluation of therapy whether or not there is an improvement in endothelial function.⁵

Coronary angiography examination is the gold standard for diagnosis of atherosclerotic heart disease complexity. Coronary diagnostic catheterization provides information about the location of the lesion, the number of blood vessels that have lesions, the degree of obstruction, and the presence or absence of collateral circulation. Various scoring systems have been used to quantify the characteristics of coronary lesions by angiography, and SYNTAX score is one of the most used scoring systems which is proven to be associated with the level of CAD complexity and short and long-term cardiovascular outcomes.⁶

This study aimed to analyze the asymmetrical relationship between parameters of flow mediated vasodilatation (FMD), endothelial function and the complexity of coronary artery disease according to SYNTAX score.

Material and methodology

This study was conducted in October 2015–December 2015 in the cardiac outpatient clinic, echocardiography unit, and cardiovascular intervention and diagnostic installation (IDIK) Dr. Soetomo General Hospital, Surabaya after getting ethical clearance from local institutional review board. The research sample was taken by purposive sampling, with inclusion criteria of male or female patients undergoing elective coronary angiography examination at Dr. Soetomo General Hospital in October–December 2015 and fulfilling the appropriate and uncertain criteria for diagnostic coronary angiography⁷ and willing to participate in the study and signed informed consent. Subjects with a history of coronary intervention with either coronary angioplasty or coronary bypass surgery, suffering from chronic kidney disease, suffering from or having a history of stroke, and peripheral arterial disease was excluded from the study. Cardiovascular risk factors were evaluated and assessed according to the Framingham risk score and SCORE (Systematic Coronary Risk Evaluation).

The FMD was measured by brachial artery suppressed with a sphygmomanometer cuff of 50 mmHg from the systolic blood pressure or a maximum pressure of 220 mmHg at the distal cubital fossa (forearm), and the cuff was removed and then the brachial artery diameter was measured at the 1st, 3rd and 5th minute. The result was done by calculating the difference between brachial artery diameters 1 minute after provocation and reduced by initial diameter. Result of less than 5% is considered to be abnormal. The diameter of the brachial artery was measured in the diastolic end phase by referring to the beginning of the QRS complex electrocardiographic. The measurement used vivid 7 GE echocardiography. The SYNTAX score calculation was done after a coronary angiogram obtained. Data obtained from the examination results were analyzed using Pearson correlation using SPSS.

Table 1 – Baseline characteristics of subjects

Variable	n (%) / mean \pm SD ^a
Gender	
Man	34 (85)
Women	6 (15)
Age (years)	55.38 \pm 9.27
40–49	12 (30)
50–59	15 (37.5)
\geq 60	13 (32.5)
Cardiovascular risk factors	
Hypertension	27 (67)
Diabetes mellitus	17 (42)
Dyslipidemia	19 (47.5)
Smoking	29 (72)
Heredity	4 (10)
Framingham score	
Low risk	2 (5)
Intermediate risk	6 (15)
High risk	32 (80)
SCORE score	
Low risk	2 (5)
Moderate risk	21 (52.5)
High risk	11 (27.5)
Very high risk	6 (15)
Pre cath diagnosis	
Post-acute coronary syndrome	27 (67.5)
Stable angina	10 (25)
Etc.	3 (7.5)
Post cath diagnosis	
Normal	3 (7.5)
Single vessel disease	5 (12.5)
Double vessel disease	11 (27.5)
Triple vessel disease	21 (52.5)

^a Numerical data is displayed in mean \pm SD (standard deviation) while ordinal data is in percentage.

Table 2 – Distribution of mean FMD value and SYNTAX score

Variable	Mean±SD
Flow mediated vasodilatation (%)	6.01±2.60
SYNTAX score	24.99±13.61

and SCORE scores. On the assessment of risk factors using the Framingham score, most subjects were in the high-risk category with 32 subjects (80%). Whereas in the assessment using SCORE, the highest subjects were in the moderate risk category with 21 subjects (52%). Subjects

Table 3 – FMD value (%) based on subject characteristics

Variable	Category	n	Mean±SD	p value
Age (years)	40–49	12	8.03±3.20 ^a	0.003
	50–59	15	5.26±1.94 ^b	
	≥60	13	5.00±1.56 ^b	
Gender	Male	34	5.87±2.53	0.434
	Female	6	6.78±3.13	
Hypertension	Yes	27	5.45±2.36	0.052
	No	13	7.15±2.79	
Diabetes mellitus	Yes	17	5.21±1.35	0.098
	No	23	6.59±3.14	
Dyslipidemia	Yes	19	5.43±1.74	0.193
	No	21	6.52±3.14	
Smoking	Yes	29	5.76±2.42	0.345
	No	11	6.65±3.06	
Heredity	Yes	4	5.62±1.16	0.763
	No	36	6.05±2.72	
Framingham score	Low risk	2	12.50±0.71 ^a	<0.0001
	Intermediate risk	6	6.43±1.22 ^b	
	High risk	32	5.52±2.29 ^b	
SCORE score	Low risk	2	9.85±4.45	0.061
	Moderate risk	21	6.39±2.66	
	High risk	11	4.87±1.94	
	Very high risk	6	5.47±1.80	
Pre cath diagnosis	Post ACS	27	5.43±1.79 ^a	0.005
	Stable angina	10	6.26±3.09 ^{ab}	
	Etc.	3	10.33±3.78 ^b	
Post cath diagnosis	Normal	3	13.5±0.71 ^a	<0.0001
	Single vessel disease	5	8.02±0.78 ^b	
	Double vessel disease	11	5.80±1.80 ^c	
	Triple vessel disease	21	4.63±1.01 ^d	

a,b,c,d Different superscript letters at mean ± standard deviation showed significantly different results.

Results

Characteristics of subjects

We enrolled 40 subjects with baseline characteristics, as described in Table 1. The composition of 40 research subjects consisted of 34 males (85%) and six females (15%). The youngest of the subject was 40 years old, and the oldest was 75 years old. The most commonly found cardiovascular risk factors were smoking (72%), followed by hypertension (67%). The calculation of the global cardiovascular risk score used in this study is the Framingham

who underwent coronary angiography were dominated by post-acute coronary syndrome (ACS) patients (67.5%). Post-coronary angiography revealed that most diagnoses were triple vessel disease (52.5%).

Examination of FMD value and SYNTAX score

The minimum value of FMD was 2.3%, and the maximum value was 14%, and the FMD mean was 6.01±2.60% (Table 2). The mean SYNTAX score in this study was 24.99±13.61, with a minimum SYNTAX score of 0, and a maximum SYNTAX score is 52 (Table 2).

Distribution of FMD based on subject characteristics

Table 3 shows that FMD values were lower in the older age group but did not differ significantly in the age group 50–59 and >60 years. In the ≥ 60 -year age group, FMD mean was $5.00 \pm 1.56\%$. Mean FMD was also found to be lower in men and subjects with major cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, and smoking, even though it was not statistically significant. Based on the assessment of global cardiovascular scores, FMD values were found to be lowest in the high-risk group according to SCORE, with mean $4.87 \pm 1.94\%$. Based on the diagnosis, it was found that subjects with post ACS and triple vessel disease had lower FMD values. The mean FMD values in post ACS subjects were $5.43 \pm 1.79\%$, and in triple vessel disease subjects, FMD mean values were $4.63 \pm 1.01\%$.

Distribution of SYNTAX score based on subject characteristics

Table 4 shows that the SYNTAX score is higher in the older age group, but not significantly different in the age group 50–59 and >60 years. In the age group ≥ 60 years, the mean SYNTAX score was 30.42 ± 13.75 . SYNTAX scores were also found to be higher in men and subjects with major cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, and smoking. Statistically, a significant difference was found in subjects with hypertension risk factors compared to subjects without hypertension.

This study also showed that based on the assessment of global cardiovascular scores, the higher the SYNTAX score was higher in the Framingham/SCORE risk group, which was also higher. With the highest mean value obtained in the high-risk group according to SCORE, which is 32.14 ± 10.85 ,

Table 4 – SYNTAX score based on subject characteristics

Variable	Category	n	Mean \pm SD	p value
Age (years)	40–49	12	15.50 \pm 11.84 ^a	0.010
	50–59	15	27.87 \pm 11.42 ^b	
	≥ 60	13	30.42 \pm 13.75 ^b	
Gender	Male	34	25.35 \pm 13.31	0.691
	Female	6	22.92 \pm 16.40	
Hypertension	Yes	27	28.09 \pm 13.66	0.036
	No	13	18.54 \pm 11.44	
Diabetes mellitus	Yes	17	29.71 \pm 11.64	0.058
	No	23	21.50 \pm 14.14	
Dyslipidemia	Yes	19	27.05 \pm 12.18	0.368
	No	21	23.12 \pm 14.83	
Smoking	Yes	29	26.72 \pm 13.19	0.194
	No	11	20.41 \pm 14.25	
Heredity	Yes	4	22.00 \pm 8.45	0.650
	No	36	25.32 \pm 14.11	
Framingham score	Low risk	2	0.00 \pm 0.00 ^a	0.008
	Intermediate risk	6	19.50 \pm 7.66 ^b	
	High risk	32	27.58 \pm 13.06 ^c	
SCORE score	Low risk	2	12.50 \pm 17.60 ^a	0.028
	Moderate risk	21	20.45 \pm 12.20 ^a	
	High risk	11	32.14 \pm 10.85 ^b	
	Very high risk	6	31.92 \pm 15.27 ^{a,b}	
Pre cath diagnosis	Post ACS	27	27.48 \pm 12.98 ^b	0.044
	Stable angina	10	23.55 \pm 12.46 ^b	
	Etc.	3	7.33 \pm 2.68 ^a	
Post cath diagnosis	Normal	3	0.00 \pm 0.00	0.0001
	Single vessel disease	5	9.60 \pm 1.94 ^a	
	Double vessel disease	11	23.10 \pm 5.75 ^b	
	Triple vessel disease	21	33.21 \pm 10.86 ^c	

^{a,b,c} Different superscript letters at mean \pm standard deviation showed significantly different results.

however, this mean value is not statistically different from the very high-risk group. Based on the diagnosis, subjects with post ACS and triple vessel disease had higher mean SYNTAX scores. The mean SYNTAX score in post ACS subjects was 27.48 ± 12.98 , and in triple vessel disease subjects, the mean SYNTAX score was 33.21 ± 10.86 .

Data analysis of the correlation between FMD and SYNTAX score

The normality of data distribution of FMD and SYNTAX score variable was tested using one-sample Kolmogorov-Smirnov test and showed that data of FMD and SYNTAX score had $p = 0.191$ and $p = 0.954$, respectively, which means the data had a normal distribution ($p \geq 0.05$). The results of the Pearson correlation test showed a significant correlation between the value of FMD and SYNTAX score with a level of significance of correlation with $\alpha = 0.05$ and value of $r = -0.787$ and $p < 0.0001$. The negative r value indicates that the correlation is in the opposite direction, which indicates that the lower the FMD value, the higher the SYNTAX score. The value of r in this study was $0.600 \leq r < 0.800$ indicates that there was a very strong correlation. The value of $p < 0.0001$ indicates that the negative correlation was significant.

Discussion

More than 50 years of epidemiological studies have identified a number of factors related to CAD. Risk factors that were first introduced to the Framingham Heart Study are still the gold standard in the risk stratification of CAD patients. However, several studies indicate the limitations of the Framingham Risk Score in the form of underprediction or overprediction in populations with CAD risk factors. Therefore other markers of atherosclerosis are needed, which are more individualized.⁸ Some new tools or methods can be used to add information and detect atherosclerosis compared to just assessing traditional risk factors that exist. FMD examination in the brachial artery can be used to assess the presence of endothelial dysfunction, which in some studies has shown a correlation with the risk and incidence of CAD.⁸⁻¹¹

It is widely accepted that age, sex, high blood pressure, smoking, dyslipidemia, and diabetes are the main risk factors for cardiovascular disease. Cardiovascular risk factors often do not stand alone and are multifactorial, which interact with each other to aggravate the atherosclerosis process. The 2016 European Society of Cardiology (ESC) guideline on the prevention of cardiovascular disease states that diabetes mellitus is a major risk factor for CAD that can stand alone without having to be accompanied by other risk factors.¹² Data shows that women with diabetes mellitus will experience an increased risk of cardiovascular disease as much as five times, whereas, in men, diabetes mellitus will increase the risk of cardiovascular disease three times more. In this study, diabetes mellitus was a risk factor for CAD with the lowest FMD score and highest SYNTAX score. The lower FMD value indicates a more severe degree of endothelial dysfunction. Whereas the higher the SYNTAX score value indicates, the more complex the CAD. Simova et al. revealed in their study that

diabetic patients had significantly lower FMD values compared with non-diabetic patients.¹³

Many studies have examined the relationship between CAD risk factors and endothelial function. Benjamin et al. showed the relationship between risk factors for CAD and endothelial function in 2883 subjects of the Framingham study.¹⁴ In general, patients with a higher Framingham and SCORE found increasingly severe degrees of endothelial dysfunction marked by low FMD values.⁸ In our study based on the Framingham score, we found a tendency in the decrease of FMD value in the higher risk group, where the lowest FMD value was found in the high-risk group with a significant difference. The difference in FMD values was also found in the higher SCORE risk group, but the value of this difference was not significant.⁹

The SYNTAX score is an angiographic scoring system to determine the degree of complexity of CAD. In our study based on cardiovascular risk factors, the highest SYNTAX score was found in subjects aged > 60 years and with risk factors for diabetes mellitus. Based on global cardiovascular scores, high-risk subjects based on Framingham and SCORE had a higher degree of complexity of CAD. Tolunay's study of 205 stable angina patients showed that there was a significant relationship between cardiovascular risk factors assessed by the Framingham and SCORE scores, where the mean subject belonged to the moderate risk according to Framingham and intermediate-risk according to SCORE with a mean SYNTAX score of 13.63 ± 8.68 . High CAD complexity (SYNTAX score > 33) was only found in 5.4% of subjects.¹⁵ Whereas in our study, most subjects were in the high-risk group according to the Framingham and moderate risk based on SCORE where the subjects in this study had a higher mean SYNTAX score of 24.99 ± 13.61 and high complexity of CAD was found in 25% of subjects. This might be caused by Dr. Soetomo hospital as a referral center, so the cases referred to for coronary angiography are cases with a high complexity of CAD.

The results of this study showed that FMD measured by ultrasound in the brachial artery decreased in all patients who experienced CAD (SYNTAX score > 0). The strong and inverse correlation in this study showed that the lower the FMD value, the higher the SYNTAX score. This was consistent with the literature review that the more severe degree of endothelial dysfunction as indicated by the low dilatation of the brachial artery after hyperemia is related to the more complex CAD. Our study also confirmed that systemic endothelial dysfunction reflects the tendency of arteries to undergo the process of atherosclerosis, including the coronary arteries. This research is in line with Manganaro et al. who showed a significant linear relationship between SYNTAX score and FMD, where the low value of FMD was related to the complexity of CAD. Manganaro et al. stated that FMD in the brachial artery is a reliable indicator of the severity of CAD.¹⁰

Although FMD examination can reflect the presence of endothelial dysfunction, until now, there has not been the same standard value regarding the normal value of FMD measurements. In the Manganaro et al. study, FMD values $> 12\%$ were associated with the absence of CAD in coronary angiography and FMD values $< 4\%$ related to the severity and complexity of CAD.¹⁰ Whereas in our study, subjects without CAD (SYNTAX score = 0) had a mean FMD of 13.5 ± 0.71 , subjects with complex CAD (SYNTAX score > 33) were found in the triple vessel disease group with an mean FMD of 4.63 ± 1.01 .

Endothelial function measurement applications as a clinical diagnostic method have some limitations conceptually and practically. It is clear that the data obtained is not intended to replace diagnostic methods that have been clinically accepted in the diagnosis of CAD (for example, stress testing). However, on the other hand, the information provided by the assessment of cardiovascular risk factors is sometimes difficult to translate from the study population to be applied to individual patient care, and vascular endothelium is theoretically related and has a function as a good indicator to assess the global status of the cardiovascular system. However, interpretations of complex phenomena such as endothelial dysfunction cannot rely on a single measurement.

This study had several limitations: the study was not randomized and did not use a control group, ultrasound examination only used one observer, and no intra-observer variability testing was carried out, and this study had a small scope and had not been done multicenter with a wider scope.

Conclusion

This study showed that FMD endothelial function is fairly reliable in predicting the complexity of coronary artery disease according to SYNTAX scores in patients undergoing coronary angiography. Further research is needed to find out whether FMD can be used as a preventive strategy or monitoring of endothelial function improvement in patients with coronary artery disease.

Conflict of interest

None declared.

Funding

None declared.

Ethical statement

This study followed the principles of the Declaration of Helsinki and had been approved by the ethical committees of Dr. Soetomo General Hospital.

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