
ORIGINAL RESEARCH

The assessment of atherosclerosis on vascular structures in patients with acute coronary syndrome

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Abstract

Introduction: Endothelial dysfunction plays a crucial role in the process of atherosclerotic diseases and has been accepted as an early stage of atherosclerosis. Carotid intima-media-thickness (CIMT) and flow-mediated-dilatation (FMD) of the brachial artery have been recommended as noninvasive methods to assess endothelial structure and function. Angiographic properties of patients with acute coronary syndrome (ACS) are closely associated with cardiovascular events. In this study, we investigated the relation of atherosclerotic properties of coronary, brachial and carotid arteries with CIMT, FMD and coronary angiography in patients with ACS.

Methods: We enrolled 133 patients who were diagnosed with ACS into this study. Exclusion criteria were known coronary artery disease, diabetes mellitus and hypertension. Coronary angiography, CIMT and FMD were measured in all patients. The numbers of major stenotic coronary ves-

sels with $\geq 50\%$ or $\geq 70\%$ were defined as diseased vessel. Gensini score was used to evaluate the severity of atherosclerosis. Morphologic properties of stenotic lesion were defined. Cutoff levels were 7% for FMD and 0.9 mm for CIMT.

Results: Mean age was 59.7 ± 11.8 years. FMD, CIMT and Gensini score were $8.3 \pm 5.9\%$, 0.80 ± 0.19 mm and 7.8 ± 3.5 , respectively. Only 44% of patients with ACS had impaired FMD. Gensini score, number of diseased vessels and number of critical lesions were higher in patients with impaired FMD. (Gensini: 8.7 ± 3.6 vs. 7.0 ± 3.1 , $p=0.009$, diseased vessels: 2.7 ± 0.4 vs. 2.3 ± 0.7 , $p<0.0001$, critical lesions: 3.0 ± 2.1 vs. 2.2 ± 1.4 , $p=0.02$). Increased CIMT was found in only 33% of patients. Gensini score and number of diseased vessels were significantly higher in patients with increased CIMT. Significant but weak correlations were found between CIMT, FMD and angiographic severity of coronary atherosclerosis. Angiographic properties and le-

sion morphology were similar between CIMT and FMD groups.

Conclusion: There appears to be a relationship between CIMT, FMD and severity of coronary atherosclerosis in patients with ACS. However, in patients with ACS, morphologic properties of stenotic lesions are not associated with CIMT and FMD in brachial artery.

Endothelial dysfunction and atherosclerosis are common and well known problems of the vascular system. Endothelial dysfunction plays a crucial role in the process of atherosclerotic disease because of the regulatory functions of the endothelium.¹ It has been accepted as an early stage of atherosclerosis² and it plays an important role in the development, progression, and clinical complications of atherosclerosis.^{3,4} Several studies suggest that the presence of endothelial dysfunction is an independent predictor of cardiovascular events.^{5,6}

Coronary angiography provides visual information about the properties of coronary atherosclerosis and plaque characteristics. Angiographic properties of patients with acute coronary syndrome (ACS) are closely associated with cardiovascular events and mortality rate.⁷ The more stenotic coronary lesions have higher rates of progression to occlusion and myocardial infarction.^{8,9} The number of significantly diseased coronary vessels is also a predictive variable of survival⁷ and properties of stenotic lesions are one of the major predicting factors for cardiac events and mortality.¹⁰ Patients with ACS have unstable plaque characteristics compared to patients with stable angina.¹¹ Therefore, it is important to understand the plaque characteristics and its related factors.

Endothelial dysfunction can be detected in peripheral arteries with high resolution ultrasound. Carotid intima media thickness (CIMT) and flow-mediated dilatation (FMD) of the brachial artery have been recommended as noninvasive methods to assess endothelial and smooth muscle function.¹² While an increase in CIMT is an early morphological change in atherosclerosis, FMD reflects a functional impairment of the

endothelium before morphological changes can be detected.

Atherosclerosis is a systemic process and it affects all vascular system. Although closely associated, there is limited information about the combined evaluation of atherosclerotic status in all vascular bed in patients with ACS. In this study, we aimed to investigate the relationship of atherosclerotic properties of coronary, brachial and carotid artery with CIMT, FMD and coronary angiography, in non-diabetic and non-hypertensive ACS patients. We also investigated angiographic properties of stenotic lesions in coronary arteries and their relation to other vascular systems.

Methods

Study population

We enrolled 133 patients diagnosed with ACS into the study. Exclusion criteria were: known coronary artery disease (CAD) (documented by coronary angiography or a history of coronary intervention), history of diabetes mellitus or fasting plasma glucose levels >110 mg/dl, history of hypertension or newly diagnosed hypertension (resting blood pressure \geq 140/90 mm Hg) or use of antihypertensive medications. Patients using antihyperlipidemic agent were also excluded from the study. All patients underwent angiography and had a severe lesion (stenosis >75%) in at least one coronary artery. Baseline demographic data and a complete clinical history were collected for each patient. Coronary angiography, CIMT and FMD of the brachial artery were measured in all patients.

Measurements of FMD

All patients underwent ultrasound assessment of brachial artery diameter before hospital discharge by the same operator. Endothelium-dependent function, measured as FMD was assessed using a 7.5-MHz linear array transducer (Vivid 7, GE-Vingmed Ultrasound AS, Horten, Norway) according to guidelines for the ultrasound assessment of the brachial artery.¹² All va-

soactive drugs, smoking, caffeine, exercise and food were discontinued for 12 hours before endothelial function testing. Subjects were positioned supine with the arm in a comfortable position for imaging the brachial artery. The brachial artery was imaged above the antecubital fossa in the longitudinal plane. For FMD, baseline measurements of brachial artery diameter were first obtained. Then a sphygmomanometric cuff was placed on the left arm above the antecubital fossa. The cuff was inflated to 50 mmHg above the patient's systolic blood pressure to occlude the arteries for 5 minutes and then deflated. Post-occlusion diameter of the brachial artery was obtained one minute after cuff deflation. Measurements were taken at end diastole (onset of the R-wave of continuously recorded electrocardiography) of five cardiac cycles and averaged for each scan. Flow-mediated dilatation was defined as the relative percentage change relative to the baseline diameter of the brachial artery. Flow-mediated vasodilatation was defined as $(\text{reactive hyperemia diameter} - \text{baseline diameter}) / \text{baseline diameter} \times 100\%$. A cut-off value of $\geq 7\%$ has been proposed to represent a normal FMD (12, 13). The intra-observer coefficient (CV) of variation for FMD measurements was 4.7 %.

Evaluation of properties of coronary atherosclerosis

The number of major coronary vessels with $\geq 50\%$ or $\geq 70\%$ luminal stenosis (lumen diameter reduction) was scored from 1 to 3 as diseased vessel (right, left anterior descending, and circumflex arteries). Left main stenosis $\geq 50\%$ was scored as two vessel disease if there was no lesion $\geq 50\%$ in the other vessels. Coronary stenotic lesions with $\geq 50\%$ or $\geq 70\%$ luminal stenosis were defined as critical lesions.

Gensini score

Gensini score was used to evaluate the severity of atherosclerosis.¹⁴ The most severe stenosis in each of eight coronary segments was graded from 1 to 4 (1-49% lumen diameter reduction: 1 point, 50-74%

stenosis: 2, 75-99% stenosis: 3, 100% occlusion: 4) to give a total score of between 0 and 32. This score therefore gives an index of the severity of coronary atherosclerosis.

Coronary thrombus was defined as a filling defect surrounded by contrast media in the absence of calcification and dissection. Total occlusion was defined as the absence of any anterograde opacification. Coronary calcification was defined as the visualization of any coronary calcified lesion viewed by angiography. Coronary collateral flow was assessed according to Rentrop collateral flow classification. Lesion morphology was defined as Braunwald type A, B, C according to the standard American Heart Association / American College of Cardiology classification.¹⁵

Biochemical analysis

Blood samples were obtained at early morning hours following overnight fasting for lipid profiles (Thermo Clinical LabSystem), high sensitive C-reactive protein (hs-CRP) (Dade-Behring®) and other parameters.

Statistical analysis

Statistical analysis was performed with SPSS version 13.0 for Windows (SPSS Inc., Chicago, Illinois) and data were expressed as mean \pm SD. For continuous variables, differences between groups were compared with a Student t-test. Chi-squared test was used for nominal data. Pearson or spearman correlation coefficients between various parameters were calculated. A p value of < 0.05 was considered statistically significant.

Results

The baseline clinical and biochemical characteristics of the patients are summarized in Table 1. Mean age was 59.7 ± 11.8 years in study population. Most of the patients (65%) had a non-ST-elevation myocardial infarction. Table 2 shows values of CIMT, FMD and angiographic findings. FMD, CIMT and Gensini score

TABLE 1. Baseline clinical and biochemical characteristics

Age (years)	59.7 ± 11.8
Sex male n (%)	119 (86.2)
BMI (kg/m ²)	26.9 ± 3.6
Non smoking	39 (28.3)
Smoking n (%)	99 (71)
0-10 years	5 (3.6)
10-15 years	4 (2.6)
more 20 years	89 (64.5)
BUN (mg/dl)	16.9 ± 5.3
Creatinine (mg/dl)	0.9 ± 0.2
Triglycerides (mg/dl)	121.3 ± 81.6
Cholesterol (mg/dl)	
Total	179.1 ± 39.1
HDL	34.4 ± 10.1
LDL	120.7 ± 32.3
Hs -CRP	22.3 ± 32.3
Uric acid	6.1 ± 1.6
Diagnosis n (%)	
UAP	32 (24%)
NONSTEMI	87 (65%)
STEMI	14 (11%)

UAP: Unstable angina pectoris, NONSTEMI: Non-ST-elevation myocardial infarction, STEMI: ST-elevation myocardial infarction

were $8.3 \pm 5.9\%$, 0.80 ± 0.19 mm and 7.8 ± 3.5 , respectively.

Patients were first divided into two groups: impaired FMD group with FMD value lesser than 7% (n = 58) and normal FMD group with FMD value equal or above 7% (n = 75). Only 44% of patients with ACS had impaired FMD. Gensini score, number of diseased vessel and critical lesion were higher in impaired FMD group than in the normal FMD group (Gensini score: 8.7 ± 3.6 vs. 7.0 ± 3.1 , $p=0.009$, number of diseased vessels: 2.7 ± 0.4 vs. 2.3 ± 0.7 , $p<0.0001$, critical lesion ($\geq 50\%$): 3.0 ± 2.1 vs. 3.0 ± 2.1 , $p=0.02$). Angiographic properties and lesion morphology were similar between two groups (Table 3).

Patients were similarly divided into two groups: increased CIMT group with thickness equal to or greater than 0.9 mm (n = 44) and normal CIMT group with thickness less than 0.9 mm (n = 89). Increased

TABLE 2. Atherosclerotic properties of patients

FMD (%)	8.3 ± 5.9
CIMT (mm)	0.80 ± 0.19
Rentrop grade	1.06 ± 1.25
Gensini score	7.8 ± 3.5
Number of diseased vessel	2.0 ± 1.5
Number of diseased vessel ($\geq 50\%$)	1.8 ± 0.8

Data expressed as mean \pm SD or percentage of all patients.

FMD: Flow-mediated dilatation, CIMT: Carotid intima media thickness

TABLE 3. Comparison of patients with decreased and normal FMD

	FMD $\geq 7\%$ (n:75)	FMD $< 7\%$ (n:58)	p
FMD (%)	12.3 ± 4.6	3.2 ± 2.2	<0.0001
CIMT (mm)	0.79 ± 0.1	0.81 ± 0.2	0.4
Rentrop grade	1.04 ± 0.9	1.02 ± 0.9	0.9
Gensini score	7.0 ± 3.1	8.7 ± 3.6	0.009
Number of diseased vessels ($\geq 50\%$)	1.7 ± 0.7	2.0 ± 0.8	0.047
Number of diseased vessels ($\geq 70\%$)	2.3 ± 0.7	2.7 ± 0.4	<0.0001
Number of critical lesions			
$\geq 50\%$	2.2 ± 1.4	3.0 ± 2.1	0.02
$\geq 70\%$	1.9 ± 1.2	2.3 ± 1.7	0.1
Number of non critical lesions	1.7 ± 1.5	2.4 ± 1.6	0.02
Angiographic findings (% of patients)			
Totally occlusion	40%	45%	0.6
Braunwald A	56%	70%	0.1
Braunwald B	52%	51%	0.4
Braunwald C	60%	46%	0.4
Calcification	2%	4%	0.3
Thrombus	10%	9%	0.8
Left main disease	3%	4%	0.7

Data expressed as mean \pm SD or percentage of all patients.

FMD: Flow-mediated dilatation, CIMT: Carotid intima media thickness

$p<0.05$ accepted as significant

CIMT was found in only 33% of all patients. Brachial FMD, Gensini score, number of diseased vessel and critical lesion were higher in the increased CIMT group than in the normal CIMT group. (FMD: 6.8 ± 4.5 vs. 8.5 ± 5.7 , $p=0.04$, Gensini score: 9.3 ± 3.6 vs. 7.2 ± 3.1 , $p=0.006$, diseased vessels: 2.2 ± 0.8 vs. 1.6 ± 0.7 , $p=0.001$, critical lesion ($\geq 50\%$): 3.5 ± 2.1 vs. 2.2 ± 1.6 , $p=0.002$). Angiographic properties and le-

TABLE 4. Comparison of patients with normal and increased CIMT

	CIMT < 0.9 mm (n:89)	CIMT ≥ 0.9mm (n: 44)	
CIMT (mm)	0.68	1.03	<00001
FMD (%)	8.5 ± 5.7	6.8 ± 4.5	0.04
Rentrop score	1.04 ± 0.8	1.20 ± 1.0	0.5
Gensini score	7.2 ± 3.1	9.3 ± 3.6	0.006
Number of diseased vessels (≥50%)	1.6 ± 0.7	2.2 ± 0.8	0.001
Number of diseased vessels (≥70%)	2.4 ± 0.5	2.7 ± 0.7	<0.0001
Number of critical lesions			
≥50%	2.2 ± 1.6	3.5 ± 2.1	0.002
≥70%	1.9 ± 1.3	2.7 ± 1.7	0.01
Number of non critical lesions			
	1.7 ± 1.3	2.0 ± 1.6	0.02
Angiographic findings (% of patients)			
Totally occlusion	42%	57%	0.1
Braunwald A	51%	60%	0.1
Braunwald B	51%	60%	0.3
Braunwald C	64%	76%	0.2
Calcification	2%	6%	0.1
Thrombus	9%	10%	0.8
Left main disease	1%	10%	0.05

Data expressed as mean ±SD or percentage of all patients.

FMD: Flow-mediated dilatation, CIMT: Carotid intima media thickness

p<0.05 accepted as significant

sion morphology of patients was similar between two groups (Table 4).

There was a significant but weak correlation between CIMT, FMD and angiographic properties of coronary atherosclerosis. CRP levels were significantly correlated with Gensini score, number of diseased vessel and critical lesion (Table 5).

Discussion

The relationship between FMD in the brachial artery, IMT in carotid artery and degree of coronary atherosclerosis have been investigated in previous studies. These studies suggest that FMD and CIMT may be associated with CAD in different patients groups.¹⁶⁻¹⁹ However, there is insufficient data about the severity

TABLE 5. Correlations between angiographic properties, CIMT, FMD and CRP

	Gensini score	Diseased vessels (≥50%)	Critical lesions (≥50%)	Critical lesions (≥70%)
CIMT	r=.288 p=0.004	r=.294 p=0.003	r=.354 p<0.0001	r=.278 p=0.006
FMD	r=-.230 p=0.015	r=-.167 p=0.04	r=-.174 p=0.006	r=-.234 p=0.002
Hs-CRP	r=.262 p=0.008	r=.294 p=0.003	r=.182 p=0.06	r=.210 p=0.035

FMD: Flow-mediated dilatation, CIMT: Carotid intima media thickness, Hs-CRP: High sensitivity C-reactive protein
p<0.05 accepted as significant

and morphologic properties of atherosclerotic lesions and their relationship with CIMT and FMD in patients with ACS. Thus, the goal of the present study was to investigate FMD, CIMT and degree and properties of coronary atherosclerosis in patients with ACS. We found significant relationship between CIMT, FMD and coronary atherosclerosis. However there was no relationship between these parameters and morphologic properties of atherosclerotic lesions.

Atherosclerosis is a multifactorial chronic process. This process has different stages and affected by many underlying factors. The assessment of FMD in the brachial artery has been widely used to evaluate endothelial function and atherosclerosis. It was shown that FMD is associated with rapid progression of atherosclerosis and poor cardiovascular prognosis, which explains its predictive value for cardiac events.²⁰ In one study using a cut of level for FMD of < 7%, it was found that FMD is reduced in patients with significant coronary stenosis, but not in patients with mild atherosclerotic changes or in patients with no severe lesion.²¹ In another study, FMD was significantly lower in the triple-vessel disease group than in the single-vessel disease group.²² Severity of coronary stenosis or number of diseased vessels was used to evaluate coronary atherosclerosis in these studies. Therefore, these methods don't give clear information about atherosclerotic status such as early or late stage

or lesion characteristics. In our study, we evaluated the association of coronary atherosclerosis with different parameters and found only a limited relationship between severity of atherosclerosis and FMD.

The mean FMD values vary considerably across populations, ranging from -1.9 to 19.2%.²³ These differences are due to properties of study populations such as risk factors, age, medication use and emotional status. Therefore, demographic properties of patient are important factors for evaluation of FMD levels. There are insufficient data about FMD values in patient with ACS. In our study, the mean FMD of the entire population was above the cut of level (8.3%; range 0-28%). In a previous study, Jambrik Z. et al. assessed whether endothelium-dependent FMD predicted the presence of angiographically assessed CAD in patients with typical or atypical chest pain.²⁴ However, morphologic properties were not evaluated. Frequency of hypertension and diabetes mellitus were 93% and 32% respectively. Optimal cut of value for FMD was accepted as < 8.8%. The FMD value was 13% in non-CAD patients, 12% in one-vessel disease, 7% in two-vessel disease and 6% in three-vessel disease. This study concluded that FMD was a sensitive indicator of the diagnosis of CAD but unable to predict both the extent and the severity of angiographically assessed CAD. In our study, we excluded hypertension and diabetes mellitus. One, two and three vessel disease were observed in 41%, 32% and 25% of patients respectively. We found a significant relationship between FMD and Gensini score ($p < 0.0001$) and number of diseased vessel ($p = 0.02$) but only 44% of patients with ACS had impaired FMD. Consequently, we observed a limited relationship between FMD values and angiographic properties of coronary atherosclerosis in patients with ACS. It should also be considered that FMD may be in the normal range in patients with ACS possibly due to demographic characteristics of the patients or methodology.

Angiographic studies indicated that complex lesion morphology is associated with increased risk of

cardiovascular risk.^{7-9,11} Similar increment in cardiac risk was demonstrated in cases of increased CIMT and decreased FMD in patients with CAD.²⁵ Therefore we aimed to investigate lesion morphology and its relation with CIMT and FMD. The results of the comparison of FMD, CIMT, Gensini score and diseased vessels indicate that these tests are associated with stage of the atherosclerotic process. However, we did not find any significant relationship between FMD, CIMT and angiographically defined lesion properties such as calcification, totally occlusion, thrombus and Braunwald type of stenotic lesion. Frequency of type A, B and C lesion was similar in patients who had normal and increased CIMT and who have impaired and normal FMD. Frequency of total occlusion, thrombus, calcification and left main disease was similar in CIMT and FMD groups. These results suggest that measurement of CIMT and FMD might give inform only about severity of coronary atherosclerosis. These parameters do not appear to reflect status or characteristic of coronary plaques.

Carotid IMT is a marker of atherosclerosis. Although several studies have shown that an increased CIMT is associated with the presence of CAD²⁶⁻²⁸), other studies have indicated a poor correlation between CIMT and the presence of CAD.^{19,29} In a previous study, it was suggested that determination of increased CIMT is not useful in discriminating between presence or absence of CAD. However, it was found that CIMT was associated with the extent of the coronary artery disease.³⁰ Our findings appear consistent with this study. We did not investigate the relation between CIMT and presence or absence of coronary artery disease. We found significant correlation between both the CIMT and FMD and the severity of coronary artery disease. We also found increased CIMT in only 33% of all patients with ACS. This result was interesting and may be important in terms of a possible relationship between CIMT and coronary plaque rupture. We suggest that coronary plaque rupture may occur independently of carotid atherosclerosis. We used a cut of level for CIMT as 0.90 mm but the mean CIMT

for the study population was 0.80 mm. Therefore, demographic characteristics should be considered in interpreting the results of the study.

In conclusion, we observed a potential relationship between CIMT, FMD and severity of coronary atherosclerosis in patients with ACS. However, morphologic properties of stenotic lesions were not associated with CIMT and FMD values in patients with ACS.

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