A novel echocardiographic method as an indicator of endothelial dysfunction in patients with coronary slow flow

H. SIMSEK, M. SAHIN, Y. GUNES¹, S. AKDAG, M.A. AKIL², A. AKYOL, H.A. GUMRUKCUOGLU, M. YAMAN

Cardiology Department, Faculty of Medicine, Yuzunci Yil University, Van, Turkey
¹Cardiology Department, Hisar Intercontinental Hospital, Istanbul, Turkey
²Cardiology Department, Faculty of Medicine, Dicle University, Diyarbakir, Turkey

Abstract. – BACKGROUND: To improve clinical outcomes, noninvasive imaging modalities have been proposed to measure and monitor atherosclerosis. Endothelial dysfunction is considered the first stage in the development of atherosclerosis. Brachial artery flow-mediated dilation (FMD) has been impaired in patients with coronary slow flow (CSF). Recently, color M-mode derived propagation velocity of descending thoracic aorta (aortic propagation velocity-AVP) was shown to be an ultrasonographic marker for atherosclerosis.

AIM: To assess endothelial function in patients with CSF and the correlation of AVP with FMD.

MATERIALS AND METHODS: FMD and AVP were measured in 90 patients with CSF and 39 patients having normal coronary arteries (NCA) detected by coronary angiography.

RESULTS: Compared to patients with normal coronary arteries patients having CSF had significantly lower AVP (39.1±8.4 vs. 53.7±12.7 cm/s, p < 0.001) and FMD (5.6±3.2 vs. 17.6±4.4%, p < 0.001) measurements. There were significant correlations between AVP and FMD (r = 0.524, p < 0.001).

CONCLUSIONS: Transthoracic echocardiographic determination of color M-mode propagation velocity of descending aorta is a simple practical method and correlates well with coronary slow flow and brachial endothelial function.

Key Words: Color M-mode, Coronary slow flow, Endothelial function, Flow mediated dilatation, Propagation velocity.

Introduction

Coronary slow flow (CSF) is a phenomenon characterized by delayed opacification of coronary arteries in the absence of epicardial occlusive disease, in which many etiological factors such as microvascular and endothelial dysfunction and small vessel disease have been implicated³⁴.

In an effort to improve clinical outcomes, noninvasive imaging modalities have been proposed to measure and monitor atherosclerosis. Endothelial dysfunction is considered the first stage in the development of atherosclerosis and other cardiovascular diseases⁵. The status of the vascular endothelium may, therefore, serve as a marker of inherent atherosclerotic risk in an individual. It has been reported that an impaired brachial artery flow-mediated dilatation (FMD) may reflect a vascular phenotype prone to atherosclerosis⁵⁷. Atherosclerosis is a generalized disease that, although mainly manifested in medium-sized vessels, also present in the great vessels, such as the thoracic aorta. Atherosclerosis leads to increased arterial resistance through thickening and stiffening of the arterial wall. Increased aortic resistance secondary to atherosclerosis may be reflected with a decrease in flow propagation speed within the arterial lumen. Recently, we have shown that color M-mode derived propagation velocity of descending thoracic aorta (AVP) was associated with coronary artery disease (CAD)⁸.

Several studies have investigated the relationship between coronary slow flow phenomenon and endothelial dysfunction as a probable etiology and brachial endothelial function assessed by flow mediated dilatation of brachial artery has been found to be associated with CSF⁹⁰. Although we have previously found a significant association between AVP and FMD in patients with coronary artery disease¹¹ the situation might not be same in patients with CSF. In this study, we investigated the association of FMD and AVP in patients with CSF.
Materials and Methods

Ninety patients with angiographically proven CSF but otherwise normal epicardial coronary arteries and 39 healthy subjects were selected from patients who had undergone diagnostic coronary arteriography because of suspected coronary artery disease and were found to have normal epicardial coronary arteries other than CSF. Coronary slow flow was defined according to the TIMI frame count (TFC) method, and the subjects with a TFC greater than 2 standard deviations (SD) from the published normal range for the particular vessel were accepted as having CSF. Patients with a history of congestive heart failure, coronary artery disease including spasm, plaque, or ectasia, valvular heart disease, hyperthyroidism, chronic obstructive pulmonary disease, ventricular preexcitation, atrioventricular conduction abnormalities and those taking medications known to alter cardiac conduction were excluded from the study. The study had been approved by the hospital Ethics Committee. All participants were informed about the study and their consents were obtained.

Transthoracic Echocardiographic Examination

The echocardiographic examination was performed at rest, with the patient in the left lateral decubitus position, using a commercially available echocardiographic device (Vivid 3, General Electric) with a 3.0 MHz transducer according to established standards, by two experienced echocardiographers who were blinded to the clinical data and ongoing therapy. From suprasternal window, at supine position, color M-mode Doppler recordings were obtained with the cursor parallel to main flow of direction in descending aorta. Color Doppler Nyquist limit is adapted to 30-50 cm/s and switching to M-mode with recorder sweep rate of 200 mm/s, an M-mode spatio-temporal velocity map with the shape of a flame is displayed (Figure 1). If the slope of flame was unclear baseline shifting was used to change the aliasing velocity until a clear delineation of isovelocity slope was seen. Aortic flow propagation velocity was then calculated from dividing the distance between points corresponding to the beginning and end of the propagation slope, to the duration between corresponding time points. Thus, AVP corresponds to the velocity at which the flow is propagating down the artery. Mean of at least three measurements was recorded as AVP value.

Assessment of Brachial Artery Flow-Mediated Dilatation

For the assessment of endothelial function flow-mediated dilatation of the brachial artery was measured. All groups were abstained from

Figure 1. Measurement of descending aorta propagation velocity (AVP): in a patient with coronary slow flow (A) and in a patient with normal coronary arteries (B).
AVP and FMD in CSF

Caffeine containing drinks for at least 12 h. They were kept in supine position in a stable room temperature between 20 and 25°C during the ultrasonographic examination. In order to best visualize the brachial artery, the arm was comfortably immobilized in the extended position and brachial artery was scanned in the longitudinal section 3-5 cm above the antecubital fossa. After optimal transducer positioning, the skin was marked for reference for later measurements and arm was kept in the same position throughout the study. All measurements of the brachial artery lumen diameter were assessed at the end-diastole (timed by the QRS complex) and were calculated as the average of the measurements obtained during three consecutive cardiac cycles. After recording baseline measurements, the cuff was inflated to 200 mmHg (or 50 mmHg higher than systolic blood pressure) for 5 min to create a transient forearm ischemia. Subsequently, the cuff was deflated and the arterial diameter was measured at 30, 60, 90 and 180 s after deflation. The maximum diameter in any of these measurements was used in the calculation of FMD according to the following formula: (maximum diameter during reactive hyperemia - diameter at baseline) \times 100 / (diameter at baseline).

The intra- and inter-observer variations were less than 10% for AVP and FMD, less than 5% for CIMT and all were nonsignificant.

**Statistical Analysis**

Quantitative variables are expressed as mean±standard deviation and qualitative variables as numbers and percentages. Differences between independent groups were assessed by Student’s t-test for normally distributed quantitative variables and Mann-Whitney’s U-test for variables without normal distribution and Chi-square test for qualitative variables. Pearson correlation analysis was used to assess the correlations between variables. All tests were performed in the SPSS for Windows, version 10.0. All results were considered statistically significant at the level of \( p < 0.05 \).

**Results**

The distributions of sex, age, smoking, body mass index and lipid parameters were similar between the study groups, LDL-cholesterol was slightly higher in patients with CSF but the difference did not reach statistical significance. Compared to patients with normal coronary arteries mean TFC level was significantly higher and AVP and FMD levels were significantly lower among patients having CSF (Table I). There were significant correlations between AVP and FMD (\( r = 0.524, p < 0.001 \)) (Figures 2 and 3).

**Discussion**

In this study, we found that AVP measured by transthoracic echocardiography is decreased in patients with CSF and significantly correlated with FMD.

<table>
<thead>
<tr>
<th>Table I. Clinical and echocardiographic findings of the study population.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary slow flow (n=90)</strong></td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
</tr>
<tr>
<td>Mean TFC</td>
</tr>
<tr>
<td>AVP (cm/s)</td>
</tr>
<tr>
<td>FMD (%)</td>
</tr>
</tbody>
</table>

It is known that in patients detected with SCF, FMD is significantly impaired compared to the patients with normal coronary flow\(^{10}\). The assessment of flow-mediated dilatation (FMD) of the brachial artery has been widely used as a simple and non-invasive method of determining endothelial function\(^{14}\). It has been shown that FMD is decreased in patients with coronary risk factors\(^{15,16}\), CSF\(^{10}\) and that FMD correlates with invasive testing of coronary endothelial function as well as severity and extent of coronary atherosclerosis\(^{17}\). Systemic endothelial function reflects the propensity of arteries to develop atherosclerosis in response to exposure to cardiovascular risk factors\(^{18}\). Atherosclerosis leads to increased arterial resistance through thickening and stiffening of the arterial wall. Because the increased aortic resistance acts in a manner to decrease the flow propagation speed within the arterial lumen, a similar decrease in aortic flow propagation with increased downstream resistance is logical. In a recent study, we have evaluated aortic strain, aortic distensibility, aortofemoral pulse wave propagation velocity (PWPV) and AVP in 127 patients undergoing coronary angiography. We have found that among clinical and echocardiographic variables AVP was the most significant predictor of CAD and an AVP value of ≤ 41 cm/s, predicted CAD with 82.4 sensitivity and 97.2% specificity (positive predictive value 98.7% and negative predictive value 68.2\%). AVP was also useful to improve diagnostic accuracy of exercise electrocardiography test\(^{19}\). We have also found significant associations between AVP and carotid intima media thickness (CIMT) and FMD in patients having significant coronary atherosclerosis\(^{10}\) or subclinical atherosclerosis\(^{20}\). In this study we found a significant association of AVP with FMD in patients with CSF not having significant coronary atherosclerotic involvement.

Improved noninvasive assessment of global cardiovascular risk is valuable in many situations. Measurement of AVP is an easy and practical method and it may be used in patients referred for noninvasive cardiovascular examination, to improve cardiovascular risk estimation and for better selection of high-risk individuals for additional exams and for institution of preventive measures. This method might improve patient selection for primary prevention of atherosclerosis, with a favorable impact on cost effectiveness in cardiovascular prevention.

**Conclusions**

Coronary slow flow may be associated with impaired endothelial function assessed by AVP measured by transthoracic echocardiography and

**Figure 2.** Error bar of AVP and FMD in patients with and without coronary slow flow, AVP: Color M-mode propagation velocity of descending aorta, FMD: Flow mediated dilatation of brachial artery, CSF: Coronary slow flow, NCA: Normal coronary arteries, SE: Standard error.

**Figure 3.** Scatter plot of AVP for FMD. AVP: Color M-mode propagation velocity of descending thoracic aorta, FMD: Flow mediated dilatation of brachial artery.
AVP and FMD in CSF

FMD an ultrasonographic marker of endothelial function. Transthoracic echocardiographic determination of color M-mode propagation velocity of descending aorta is a simple practical method and correlates well with coronary slow flow and brachial endothelial function.

References

2) SINGH S, KOTHARI SS, BAHIL VK. Coronary slow flow phenomenon: an angiographic curiosity. Indian Heart J 2004; 56: 613-617.
6) TURNER SP. The pathophysiology of the coronary slow flow phenomenon, Thesis (Ph.D.), The University of Adelaide, School of Medical Sciences, 2006.
13) LANG RM, BIERG M, DEVEREUX RB, FLACKS KAMPF FA, FOSTER E, PELLITRA PA, PICARD MH, ROMAN MJ, SEWARD J, SHANEMISE JS, SOLOMON SD, SPENCER KT, SUTTON MS, STEWART WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiography 2005; 18: 1440-1463.