Slow Coronary Flow is Associated with Carotid Artery Dilatation

FATMA YIGIT, ALPAY TURAN SEZGIN, SENOL DEMIRCAN, GOKNUR TEKIN, TANSEL EROL and HALDUN MUDERRISOGLU

Baskent University School of Medicine, Department of Cardiology, Adana, Turkey

YIGIT, F., SEZGIN, A.T., DEMIRCAN, S., TEKIN, G., EROL, T. and MUDERRISOGLU, H. Slow Coronary Flow is Associated with Carotid Artery Dilatation. Tohoku J. Exp. Med., 2006, 209 (1), 41-48 — Slow coronary flow (SCF) in a normal coronary angiogram is a well-recognized clinical entity, but its etiopathogenesis remains unclear. Carotid intima-media thickness (CIMT) is a noninvasive marker of atherosclerosis. The aim of this study was to investigate the CIMT and diameter of carotid and coronary artery in relation to SCF. Twenty-four patients with angiographically diagnosed SCF (51 ± 7 years), and 26 age-matched subjects with normal coronary flow (NCF) (52 ± 8 years) in the coronary angiography were enrolled. Coronary flow rates were documented by thrombolysis in myocardial infarction (TIMI) frame count (TFC), a simple method for evaluating coronary blood flow. Carotid and coronary artery diameters and CIMT were measured. Mean TFC was significantly higher in patients with SCF than in patients with NCF (p < 0.001). There were no significant differences regarding maximum (p = 0.84) and mean CIMT (p = 0.61). On the other hand, carotid lumen (p = 0.03) and coronary artery diameters (p = 0.001) were significantly greater in patients with SCF than in subjects with NCF. There was a significant relation between mean coronary artery diameter and TFC (p = 0.004, 95% CI for OR: 1.61-11.87). In conclusion, these findings suggest that CIMT is not altered in patients with SCF as compared with those with NCF. However, carotid and coronary artery diameters are increased in patients with SCF as compared to those with NCF. Because the common carotid artery can be assessed in nearly every patient, carotid artery dilatation may be used as an early indicator for SCF. ——— slow coronary flow; carotid intima-media thickness; carotid artery diameter; coronary artery diameter

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Slow coronary flow (SCF) is identified by detection of slow dye progression in the coronary arteries during selective coronary angiography (Tambe et al. 1972). Histopathologic studies have revealed coronary microvascular disease in some patients who exhibit SCF (Mosseri et al. 1986; Mangieri et al. 1996), but this has not been extensively studied. It remains to be determined whether or not diffuse atherosclerotic disease in the epicardial vessels and microvessels of the heart wall is associated with SCF.

New noninvasive tools have been developed to detect subclinical atherosclerosis. These methods, which measure parameters such as carotid intima-media thickness (CIMT), added a new dimension to cardiovascular research and clinical
cardiology practice (Kasliwal et al. 2004). Measurement of CIMT is a safe, standardized, validated method that has many advantages, including portability, existence of a large reference database, and relatively low cost (Barth 2002).

Recently, it has been shown that vascular endothelial function is impaired in patients with SCF by brachial artery flow-mediated dilatation technique (Sezgin et al. 2003). However, no study has been reported to investigate the role of CIMT in patients with SCF. Therefore, we aimed to measure CIMT and carotid and coronary artery diameters in SCF in an attempt to clarify the mechanism of SCF.

**METHODS**

**Study population**

The prospective study was conducted between 2004 and 2005. Twenty-four patients with angiographically diagnosed SCF (19 men and 5 women; mean age, 51 ± 7 years), and 26 age-matched subjects with normal coronary flow (NCF) (19 men and 7 women; mean age 52 ± 8 years) were enrolled (Table 1). We performed coronary angiography because they had angina and coronary risk factors. Subjects were excluded if they had one or more of the following diseases or associated conditions: evidence of obstructive coronary artery disease, coronary ectasia, myocardial bridge, major coronary spasm, myocardial and/or valvular heart disease, connective tissue disorder, uncontrolled hypertension, or any other systemic disease, except for diabetes mellitus. As well, negative results on an exercise test were required in order to distinguish SCF from cardiac syndrome X, is characterized with chest pain, exercise-induced ischemic ST-segment changes and angiographically normal coronary arteries (Pasqui et al. 2005). Written informed consent was obtained from all participants.

**Exercise testing**

Exercise testing was done using the standard Bruce protocol, and each subject was tested after a 3-day period in which no anti-ischemic drugs were taken.

**Coronary angiography**

Selective coronary angiography was performed in all subjects via a femoral approach. Left ventriculography was performed and the ejection fraction was calculated. The diameters of the epicardial coronary arteries were measured using a computerized quantitative coronary angiography analysis system (Vepro, Medimage, Pfungstadt, Germany).

**Documentation of slow coronary flow**

Slow coronary flow was diagnosed using the thrombolysis in myocardial infarction (TIMI) frame-count method (Gibson et al. 1996). The TIMI frame-count (TFC) method is a simple, reproducible, objective, quantitative index of coronary flow velocity. Coronary flow

| Table 1. Clinical characteristics of slow and normal coronary flow patients |
|-----------------------------|-----------------------------|-----------------------------|---------|
| Patients                    | SCF (n = 24) | NCF (n = 26) | p       |
| Age, years                  | 51 ± 7        | 52 ± 8       | 0.5     |
| Female, n                   | 5             | 7            | 0.23    |
| Smoking, n                  | 8             | 7            | 0.76    |
| Smoking duration, pack-years| 37 ± 34       | 25 ± 18      | 0.40    |
| Diabetes, n                 | 6             | 5            | >0.99   |
| Diabetes duration, years    | 4.2 ± 3.7     | 5.3 ± 4.2    | 0.65    |
| Hypertension, n             | 8             | 12           | 0.24    |
| Hypertension duration, years| 8.2 ± 6.3     | 5.3 ± 3.6    | 0.24    |
| Hyperlipidemia, n           | 14            | 14           | 0.78    |
| Heredity, n                 | 5             | 5            | >0.99   |
| Body mass index (kg/m²)     | 31 ± 5        | 30 ± 4       | 0.70    |
| Ejection fraction           | 65 ± 10       | 64 ± 9       | 0.74    |

SCF, slow coronary flow; NCF, normal coronary flow. Values are means ± s.d.
was quantified objectively by 2 independent observers using the corrected TFC (CTFC) method. These examiners were blinded to the clinical details of each individual case. Any disagreements were resolved by a third observer. The first frame used for counting was the first frame in which dye fully entered the artery. The last frame used for the left anterior descending artery (LAD) was the frame in which frame dye first entered the mustache segment. The last frame used for the circumflex artery (Cx) was the frame in which dye first entered the distal bifurcation segment. The last frame used for the right coronary artery (RCA) was the frame in which dye entered the first branch of the posterolateral artery. Specifically, to identify this frame we first ran the cine film past the point of initial opacification of the endpoint branch, and then reversed it frame by frame until the endpoint branch disappeared. Once this location on the film was identified, the frame count for each artery was determined by subtracting the number of the first frame from the number of the last frame.

The normal frame counts for LAD are 1.7 times greater than the mean for Cx and RCA. Hence, the longer LAD frame counts were corrected by dividing by 1.7 to derive the CTFC as described earlier (Gibson et al. 1996). We calculated mean CTFC for each patient and control subjects by adding the CTFCs for the LAD, Cx and RCA, and then dividing the total by 3. All patients had frame counts greater than 2 standard deviations above the overall CTFC for the controls, and this was taken to indicate SCF.

All CTFC were determined from matched projections using the brand name, “Medcon Telemedicine Technology” (version 1.900, Tel Aviv, Israel).

**Carotid artery ultrasonography**

CIMT was determined using a high-resolution ultrasound system equipped with a 13-MHz transducer (Vivid 7, General Electric, Fairfield, CT, USA). Longitudinal scans were done of the distal 2.0 cm of each common carotid artery, immediately proximal to the origin of the bifurcation. Three measurements of CIMT were recorded for each carotid artery (right and left) and these values were averaged to obtain the mean CIMT for both vessels combined. CIMT was measured offline using computer software (M’ATH, Paris, France) that automatically records IMT to within 0.001 mm. The distance from the luminal-intimal interface of the near wall to that of the far wall was defined as the lumen diameter. Lumen diameter was also measured as the distance from the adventitia of the near wall to the adventitia of the far wall and it was termed adventitia-adventitia distance (Fig. 1). Carotid plaque was defined as a focal thickening of the vessel wall relative to its adjacent wall, with protrusion into the lumen. For analysis, plaques were defined as simple or complex depending upon their extent, echogenic composition and surface characteristics, as proposed by Lombardo and colleagues (Lombardo et al. 2004).

Fig. 1. Digitized images of the common carotid artery and the bulb. The references lines in the proximal of the artery indicate where the analysis was done. The picture on the left shows the carotid intima-media measurement (small thick arrow) in a patient with normal coronary flow, whereas the picture on the right shows the carotid artery adventitia-adventitia distance (long thick arrow) and luminal diameter (short thick arrow) measurement in the same patient. The thin arrows indicate the bulb. Bulb is the largest part of carotid artery.

IMT, intima-media thickness; QI, quality index; Std D, standard deviation.
Statistical analyses
Continuous variables are expressed as mean ± S.D. and categorical variables as percentages. P values less than 0.05 were considered statistically significant. The Student’s unpaired t-test was used to compare continuous variables, and the chi-square test was used to compare categorical variables. The Mann-Whitney’s U-test was used to compare continuous variables that were not distributed normally. Multiple logistic regression tests were done using the forward stepwise method.

RESULTS
Patient characteristics
There were no statistically significant differences between the two groups with respect to clinical characteristics (Table 1).

Catheterization data
In all 24 patients, slow flow was detected in all major epicardial vessels. In all 24 cases, the CTFC for all 3 major epicardial coronary arteries and the mean CTFC were significantly greater than 2 standard deviations above the means for these parameters in the control subjects (p < 0.001 for all, Table 2). The mean coronary artery diameters in the SCF group were significantly greater than the corresponding findings in the NCF (p = 0.041 for LAD, p = 0.01 for Cx, p < 0.001 for RCA) (Table 2). Multiple logistic regression analyses showed a significant relation between average coronary artery diameter and average TIMI frame count (p = 0.004, 95% CI for OR: 1.61-11.87).

None of the subjects developed complications during coronary angiography, and all had ejection fractions in the normal range (Table 1).

| Table 2. Coronary artery diameters and thrombolysis in myocardial infarction (TIMI) frame counts of groups |
|----------------------------------|-----------------|-----------------|-----------------|
|                                  | SCF Group (n = 24) | NCF Group (n = 26) | p               |
| LAD CTFC                        | 23.26 ± 7.17     | 8.05 ± 3.24      | < 0.001         |
| CX CTFC                         | 17.67 ± 7.71     | 10.23 ± 3.27     | < 0.001         |
| RCA CTFC                        | 19.75 ± 8.19     | 10.15 ± 4.80     | < 0.001         |
| CTFCm                           | 20.22 ± 6.04     | 9.47 ± 3.23      | < 0.001         |
| LAD diameter (mm)               | 4.2 ± 1.0        | 3.7 ± 0.7        | 0.041           |
| CX diameter (mm)                | 3.8 ± 0.8        | 3.2 ± 0.6        | 0.01            |
| RCA diameter (mm)               | 3.7 ± 0.6        | 3.0 ± 0.7        | < 0.001         |
| Coronary artery diameter (mm)   | 3.9 ± 0.7        | 3.3 ± 0.5        | < 0.001         |

LAD, left anterior descending artery; CX, left circumflex artery; RCA, right coronary artery; CTFC, corrected TIMI frame count; CTFCm, mean corrected TIMI frame count. Values are means ± S.D.

| Table 3. The measurements of common carotid artery and plaque existence in slow and normal coronary flow patients |
|---------------------------------------------------------------|-----------------|-----------------|-----------------|
|                                                               | SCF (n = 24)    | NCF (n = 26)    | p               |
| Max carotid IMT (mm)                                         | 0.869 ± 0.103   | 0.864 ± 0.100   | 0.84            |
| Mean carotid IMT (mm)                                        | 0.710 ± 0.101   | 0.697 ± 0.377   | 0.61            |
| Adventitia-adventitia distance (mm)                          | 7.635 ± 0.811   | 7.147 ± 0.583   | 0.02            |
| Lumen diameter (mm)                                         | 6.247 ± 0.822   | 5.800 ± 0.530   | 0.03            |
| Plaque existence, n (%)                                      | 10 (42%)        | 7 (27%)         | 0.23            |
| Complex plaque existence, n (%)                             | 3 (13%)         | 4 (15%)         | 0.15            |

IMT, intima-media thickness; SCF, slow coronary flow; NCF, normal coronary flow. Values are means ± S.D.
There were no significant differences between the SCF and NCF groups with respect to maximum ($p = 0.84$) and mean CIMT ($p = 0.61$) (Table 3). The SCF group had significantly greater mean adventitia-adventitia distance and significantly greater mean lumen diameter than the NCF group ($p = 0.02$ and $p = 0.03$, respectively).

Complex plaque was detected in 3 (13%) subjects in the SCF group and 4 (15%) subjects in the NCF group ($p = 0.15$).

**DISCUSSION**

The results of the study demonstrate for the first time that carotid artery diameter is increased and CIMT is not changed in patients with SCF when compared with patients with NCF. In addition, the study shows for the first time that patients with SCF and without coronary ectasia have significantly wider coronary artery diameters compared with patients with NCF. Additionally, there was a significant positive correlation between mean CTFC and coronary artery diameter.

Angina, myocardial ischemia, and infarction have been reported to be associated with SCF (Przybojewski and Becker 1986; Kapoor et al. 1998). The patients with SCF had normal exercise stress test. But in the literature positive exercise test was observed in the majority (71%) of SCF patients (Goel et al. 2001). We selected the patients with normal exercise stress test to eliminate cardiac syndrome X.

Sezgin et al. (2003) have demonstrated that brachial artery flow mediated dilatation is impaired in patients with SCF (Przybojewski and Becker 1986; Kapoor et al. 1998). The patients with SCF had normal exercise stress test. But in the literature positive exercise test was observed in the majority (71%) of SCF patients (Goel et al. 2001). We selected the patients with normal exercise stress test to eliminate cardiac syndrome X.

Several explanations can be proposed for the lack of association between CIMT and SCF observed in the study. First, IMT is commonly used as a surrogate marker for atherosclerosis; however use of this parameter is a problem because 1) it assumes uniform thickness throughout the blood vessel and 2) it detects changes primarily in the media, whereas that is confined to the intima atherosclerosis, is a focal phenomenon (Spence 2002). Second, the effect of atherosclerosis itself on coronary flow and vice versa is not well understood. According to preliminary data, in the early phase of atherosclerosis or intensive coronary artery disease risk factors, vasodilatation capacity of coronary resistive arterioles by pharmacologic and physical stress is disturbed before development of angiographic atherosclerotic disease (James 1977). Moreover, there are no unified criteria for distinguishing atherosclerosis as
seen in early plaque formation from thickening of the intimal-media complex (Touboul et al. 2004). Slow coronary run-off caused by coronary microcirculation dysfunction might be responsible for flow turbulence causing inhomogeneous contrast medium distribution at the site of mild plaque; this, in turn, can simulate the presence of a severe complex stenosis.

In the literature, the phenomenon of SCF is well known for coronary artery ectasia (Kruger et al. 1999; Senen et al. 2004). Coronary artery ectasia is defined by segmental or diffuse dilation of the coronary arteries to more than 1.5 the diameter of the adjacent segments of the same artery or of different arteries (Swayne et al. 1983). Several attempts have been made by using CTFC to determine whether SCF is evident in coronary artery ectasia. It has been speculated that slow flow is aggravated with increasing severity of ectasia involvement. It has been suggested that a higher CTFC might reflect disordered resistance vessel function. Kosar and colleagues (Kosar et al. 2005) have found that neither the coexisting stenosis nor the extent of involvement significantly affects CTFC in patients with coronary ectasia. According to the above criteria, patients in the present study did not have coronary ectasia; however, there was a significant difference between the 2 groups regarding epicardial coronary artery diameters.

Papadakis and coworkers, using the CTFC method, have demonstrated that coronary artery ectasia is associated with diminished coronary flow velocity (Papadakis et al. 2001). Although coronary artery ectasia was not found in our patients, we suggest that SCF may play a role in the etiology of coronary ectasia. It could be that SCF is an early finding for coronary ectasia. The abnormal dilatation of the epicardial vessels must be considered a feature of atherosclerotic damage to the coronary circulation. Indeed, increased mortality in association with coronary ectasia has been reported (Papadakis et al. 2001).

Although we used an advanced technique to evaluate carotid artery it can be done with simple duplex ultrasonographic scanning (Cinar et al. 2004). As a conclusion, in the current study indicate that increased coronary and carotid diameter observed in SCF could be an early finding and may be used as an early indicator for SCF.

**Study limitations**

The most significant limitations of the present study are that the sample size of the study was small and we did not measure indicators of vascular endothelial function like von Willebrand factor, ICAM-1, and VCAM-1 to make their data comparable to that of other studies and to elucidate the pathophysiology of endothelial dysfunction in SCF. We did not determine the inter- and intra-observer errors for carotid artery ultrasonography.

The lack of information on endothelial function is a serious limitation of the current study. Another limitation of the present study is that the angiographic definition of normal coronary arteries relies on axial contrast angiograms of the vessel lumen, which underestimates the presence of atherosclerotic plaque (Arnett et al. 1979). Intravascular ultrasound overcomes the limitation of angiography with tomographic images (Potkin et al. 1990). However, we did not have the opportunity to perform intravascular ultrasonography.

Prior studies have shown that the volume, rate, and pressure of the contrast injection as well as the coronary catheter size have little effect on the frame count (Levin et al. 1977; Dodge et al. 1998). Because the timing, volume, and pressure of the contrast injection were not controlled in the present study, these factors may have influenced our measurements of frame count.

**Conclusions**

The results of the study indicate that patients with SCF do not have intima-medial thickening along the carotid wall. On the other hand, both carotid and coronary artery diameter are increased in patients with SCF. The noninvasive nature of carotid artery ultrasonography gives the opportunity for serial, easily repeatable, flow evaluation in these patients. Because the common carotid artery can be assessed in nearly every patient, carotid artery dilatation may be used as an early
indicator for SCF.

References


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