# SLOW CORONARY FLOW MAY BE A SIGN OF DIFFUSE ATHEROSCLEROSIS: Contribution of FFR and IVUS

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## Summary

*Slow coronary flow (SCF) 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 implicated. We aimed to investigate the epicardial resistance in relation to SCF by using fractional flow reserve (FFR) and intravascular ultrasound (IVUS). Both have been combined to disclose the related epicardial flow resistance and the arterial anatomy. The study population consisted of 19 [8 (42.1%) male, 11 (57.9%) female; age=55.9±9.4 years] patients with SCF. As compared to expected normal values (1.0), FFR values (0.83±0.13) were significantly lower (p=0.0001). In patients with SCF, a strong negative correlation was seen between TIMI frame count and FFR (r=0.551, p<0.05). On IVUS investigation, the common finding was longitudinally extended massive calcification throughout the epicardial arteries and increased intimal thickness (0.59±0.18mm). A negative correlation between intimal thickness and FFR was determined (r=0.467, p<0.05). In conclusion, we demonstrated decreased FFR in patients with SCF. Decreased FFR levels have been attributed to increased resistance in epicardial coronary arteries due to diffuse atherosclerotic disease which has been demonstrated by IVUS.* ***(Arch Turk Soc Cardiol 2003;31:270-8)***

***Key words:*** *Diffuse atherosclerotic disease, fractional flow reserve, slow coronary flow*

## Özet

### Yavaş Koroner Akım Diffüz Aterosklerozun bir Bulgusu Olabilir: FFR ve IVUS Çalışması

*Yavaş koroner akım, epikardiyal koroner arterlerin tıkayıcı hastalığının yokluğunda koroner arterlerin opak madde ile geç dolması ile karakterize bir fenomendir. Bu fenomen etiyolojikli küçük damar hastalığı ve endotelyal disfonksiyon gibi bir çok etiyolojik faktörler suçlanmıştır. Bizim çalışmamızın amacı, fraksiyonel akım rezervi (FFR) ve intravasküler ultrason (IVUS) kullanarak, yavaş koroner akım ile epikardiyal rezistans arasındaki ilişkiyi araştırmaktı. Çalışmaya toplam 19 yavaş koroner akım saptanan hasta alındı (8 erkek %42.1 ve 11 kadın %57.9). Yaş ortalamaları 55.9±9.4 yıl idi. Bu hastaların FFR değerleri (0.83±0.13) beklenen normal değerlerle (1.0) karşılaştırıldığı zaman oldukça düşük olduğu tespit edildi (p= 0,0001) Yavaş koroner akımlı hastalarda TIMI frame count ve FFR arasında güçlü negatif korelasyon bulundu. (r=-0.551. p<0,05). IVUS incelemesinde epikardiyal arterler boyunca longutidinal uzanan masif kalsifikasyon ve intimal kalınlıkta artma tespit edildi. (0.59±0.18mm). İntimal kalınlık ile FFR arasında negatif korelasyon bulundu. (r=-0.467. p<0,05) Sonuç olarak, bu çalışma yavaş koroner akımlı hastalarada FFR daki azalmayı göstermiştir.*

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*Yavas koroner akımlı hastalarda azalmış FFR seviyeleri IVUS ile gösterilen diffüz aterosklerozun neden olduğu epikardiyal koroner arterlerin rezistansındaki artışa bağlı olabilir.* ***(Türk Kardiyol Dern Arş 2003;31:270-8)***

***Anahtar kelimeler:*** *Diffüz aterosklerotik hastalık, fraksiyonel akım rezervi, yavaş koroner akım*

Slow coronary flow (SCF) is a phenomenon characterized by delayed opacification of coronary arteries in the absence of epicardial occlusive disease. As was introduced by Tambe AA et al.[1] in 1972 for the first time, many etiological factors such as microvascular dysfunction, coronary vasospasm and small vessel disease have been implicated[1-5]. In general, typical chest pain with angiographically normal coronary arteries is well known as syndrome X[6]. However, SCF differs in a distinct manner in which hightened epicardial resistance plays the major role as well as do the histopatological abnormalities involving microvasculature[4,5]. Accordingly, some post-mortem studies revealed a co-incidence of epicardial and microvascular disease[7,8]. On the other hand some studies have shown the evidence of diffuse atherosclerosis despite angiographically normal coronary arteries[9-14]. Besides, all patients with proven microvascular disease do not have SCF. Thus, it still remains to be determined whether or not either microvascular or epicardial resistance is related to slow flow.

Fractional flow reserve (FFR), which is an index of focal epicardial stenosis may show surprisingly low or even below the threshold values in angiographically normal patients[15]. Therefore in this study, both FFR and intravascular ultrasound (IVUS) have been combined to disclose the arterial anatomy and the related epicardial flow resistance of the coronary arteries of the patients with slow flow. To our knowledge, there is no evidence of FFR measurements in literature regarding slow flow patients to date. Thus, we aimed to investigate the epicardial resistance in relation with SCF.

## METHODS

### Study population

The study population consisted of 19 [8(42.1%) male, 11 (57.9%) female; age=55.9±9.4 years] patients with slow coronary flow, who underwent coronary angiography because of typical and quasi-typical symptoms of angina between January 2001 and June 2002 at the University Clinic of Mersin University. All patients had otherwise normal coronary angiograms except slow coronary flow, which was determined by quantitative measures. The patients who suffered from one of the following diseases or associated disorders were excluded from this study; myocardial and/or valvular heart disease, tortuous coronary vessels, myocardial bridge, coronary ectasis, a proximal lumen diameter less than 3 mm, diabetes mellitus, hypertension and left ventricular hypertrophy. The patients who complied with study design were called back within the following month and were comprehensively imformed about the procedure. Only 19 out of 45 patients were suitable and accepted such a procedure. After signed imformed consent was obtained, all concomitant medication was stopped 48 hours prior to the procedure. The study was carried out according to the principles of the Declaration of Helsinki and approved by Mersin University, School of Medicine İnvestigational Review Board.

### Coronary angiography and TIMI frame count

Coronary angiography was applied by femoral approach using standard Judkins technique. Coronary arteries in left and right oblique planes and cranial and caudal angles were demonstrated. Left ventricular and aortic pressures were obtained. During the coronary angiography, lopromide (Ultravist-370, Schering AG) was used as contrast agent and was manually injected (6-8 ml contrast agent at each position). Proximal coronary lumen diameter was measured by Quantitative computer-assisted (QCA) facility and those with a caliber of 3 mm or more were enrolled for further SCF measurements. For the quantitative measurement of coronary blood flow, the time elapsed from the appearance till the contrast agent reached the distal end of left anterior descending artery, circumflex artery

and right coronary artery in terms of cineframe count was considered to be the TIMI frame count. Thereafter, the final count was substracted from the initial and the exact TIMI frame was calculated for the given artery[16,17]. However, it was divided by 1.7 when left anterior descending coronary artery was the case for adjusted correction. TIMI frame counting was undertaken by 2 separate cardiologists. In case of conflict the frames were referred to a third one. The corrected cut-off values due to the length, for normal vizualization of coronary arteries were 36.2±2.6 frames for LAD, 22.2±4.1 frames for left circumflex coronary artery, 20.4±3 frames for right coronary artery[16]. Any values obtained above these tresholds were considered slow coronary flow. All TIMI frame counts were measured in matched projections with use of Medcon Telemedicine Technology (version 1.900, Israel).

**Coronary pressure measurements and calculation of FFR**

Using standard femoral approach with Judkins technique, 7F guiding catheter with no side holes was placed in the coronary ostium. Coronary pressure measurement [aortic (Pa) and distal coronary pressure (Pd)] measurement was performed with a 0.014-inch fiber-optic high-fidelity pressure-monitoring wire (Pressure-guide, Radi Medical). Heparin (10000 IU IV) was administered before the procedure. After calibration, this fiber-optic wire was introduced into a 7F guiding catheter and advanced to its tip. At that point, equality of pressures registered by the guiding catheter and the fiber-optic wire was verified. The wire was then advanced into the coronary artery and positioned in distal end. Pa and Pd were monitored continuously during the procedure. After the pressures had been stabilized, maximum coronary hyperemia was obtained by intracoronary adenosine (15 $\mu$g in the right or 20 $\mu$g in the left coronary artery was infused)[18]. FFR was calculated as the ratio of mean hyperemic distal coronary pressure measured by pressure wire to mean aortic pressure measured by the guiding catheter (FFR=Pd/Pa)[19]. If there is no resistance along an artery, there is no pressure decline and FFR equals unity. The larger the resistance to blood flow, the larger the decline in pressure and thus, the smaller FFR. Therefore, FFR as the ratio of distal to proximal coronary pressures is an index of the resistance to flow along the epicardial vessel and, conversely; 1-FFR represents to what extent (expressed in percent) the segment of epicardial artery located between two measurement points (Pa and Pd, respectively) contributes to the total resistance to maximal myocardial flow[15]. The measurement was performed twice, and FFR was taken as the average of both measurements.

**Intravascular ultrasound**

All patients enrolled in the study underwent subsequent IVUS investigation at the same setting with FFR measurement. "Endosonics In Visions Imaging System" was utilised during IVUS. After intracoronary injection of 2 mg of isosorbide dinitrate, the imaging catheter had a 30 frames/second maximum frame rate and 20-MHz single-piezoelectric crystal transducer mechanically rotating at 1,800 rpm within a 3.5-F monorail catheter (The Endosonic Visions Five-64 F/X catheter) was then advanced over the guide wire (0.014-inch fiber-optic high-fidelity pressure-monitoring wire (the same guide wire used in FFR) into the coronary artery as distally as possible and was then carefully pulled back to continuously image the wall morphology. The size of Judkins catheter was used to calibrate the length of the coronary segment. Images were analysed frame by frame and having the external elastic lamina border manually traced, maximal and minimal intimal thicknesses were measured within the same segment. The following criteria 13 were chosen for lesion characteristics and severity. Atherosclerotic lesion; in any segment 5 mm intimal thickness, eccentric lesion; if maximal thickening exceeded two fold minimal thickening the lesion was considered eccentric, calcified lesion; focal or diffuse calcification leading to acoustic shadowing. All images were recorded on recordable compact disc for subsequent data analysis. Each IVUS image was analyzed off-line by two independent experienced IVUS analysts.

**Myocardial perfusion scintigraphy (MPS)**

All patients underwent MPS investigation 24 hrs prior to the FFR and IVUS measurements. Both stress and rest images were taken after Tc-99m sestamibi. All

images were taken using Siemens ECAM 2000 gamma camera. Initial images were at 45 RAO position and 32 slices were taken in 30 min till 180 degrees was reached. Standard Bruce protocol was used for stress images. After 85 % of target heart rate (220-age) was achieved 814-1110MBq (22-30mCi) Tc-99m sestamibi injection was done allowing exercise for another 1-2 minutes. SPECT method was used for image interpretitation[20].

**Statistical analysis**

Statistical analysis was performed using SPSS 10.0 (SPSS, Chicago, Illinois) software. Categoric variables were expressed as counts and percentages. Continuous variables were expressed as means SD. Given the fact that FFR is universally 1.0 in otherwise normal coronary arteries, all FFR results were compared using the test value of 1.0 of "One-sample T" test. When gender was considered as to the FFR results Mann-Whitney U test was used. Pearson correlation test was used to Fig. out any relation between TIMI frame count, proximal artery diameter and intima–media thickness. All hypothesis testing was 2-tailed. A p value of <0.05 was considered significant.

## RESULTS

All clinical and angiographic characteristics as well as rest and maximal hyperemia FFR variables of the patients are given in Table 1. Two patients had left bundle branch block. On ECG during contrast injection at angiography, 5 patients had a ST segment depression of 1-2 mm and another 3 had typical anginal pain. Three patients out of 5 had a FFR value of less than 0.75. FFR values are universally 1.0 in otherwise normal coronary arteries using one-sample T test, all others were compared to 1.0 as percentage. As compared to expected normal value of unity, FFR values were significantly lower ($p<0.0001$). Furthermore 5 patients (26.3%) had a FFR value of less than 0.75, which was considered to be the cut-off value. Three out of 19 patients had perfusion defects signifying myocardial ischemia on SPECT and the values were 0.58, 0.63 and 0.73 (Fig. 1A and 1B).

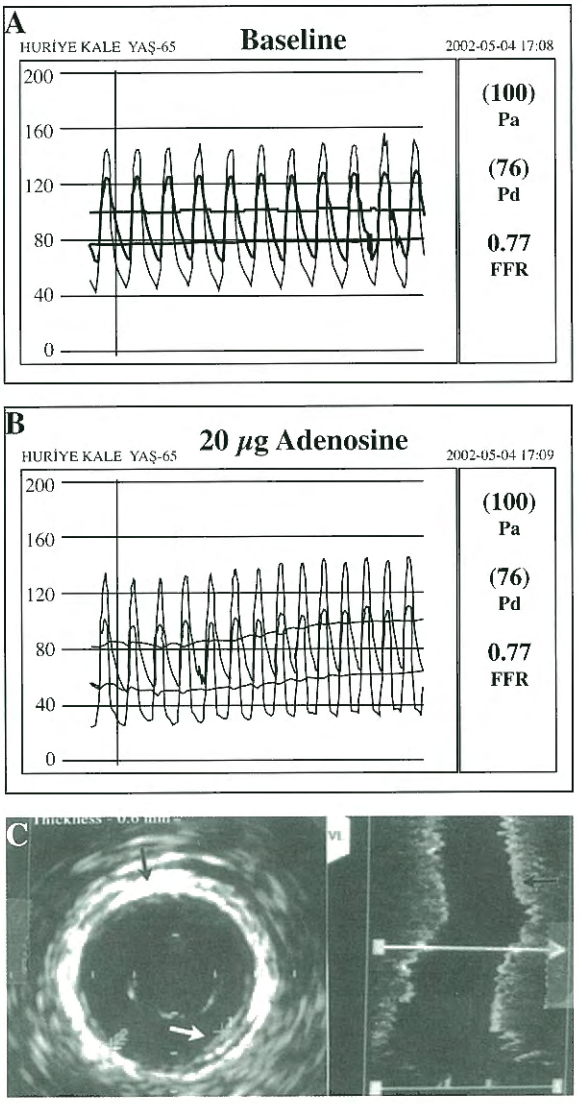


***Figure 1:*** *In a patient with SCF and reversible defect on SPECT: (A) baseline fractional flow reserve (FFR) = 0.77, (B) After adenosine infusion; FFR=0.58, (C) IVUS; longitudinally extended diffuse calcification throughout the epicardial artery and intimal thickness.*

When FFR values were compared to gender, FFR values were lower and nonsignificant in males showed no significant difference (male sex, 0.77 vs female sex, 0.88, $p>0.05$). No positive correlation was determined between either reference vessel diameter or age and FFR values. In patients with SCF, a strong negative correlation was seen between

TIMI frame count and FFR (r=0.551, p<0.05), (Fig. 2A). Mean vessel diameter was 3.60 mm and no correlation existed between FFR and TIMI frame count. TIMI frame count for LAD (n=13) was=57.3112.52 frames, for LCX (n=2) was=44.002.83 frames, and for RCA (n=4) was=41.255.44 frames. Upon IVUS investigation, the common finding was longitudinally extended massive calcification throughout the epicardial arteries in 13(68.4%) patients and regional calcification in 6(31.6%) patients. Mean intimal thickness was 0.590.18mm and in 13(68.4%) patients eccentric lesions were observed (Fig. 1C). A negative correlation between intimal thickness and FFR was determined (r= 0.467, p<0.05), (Fig. 2B).

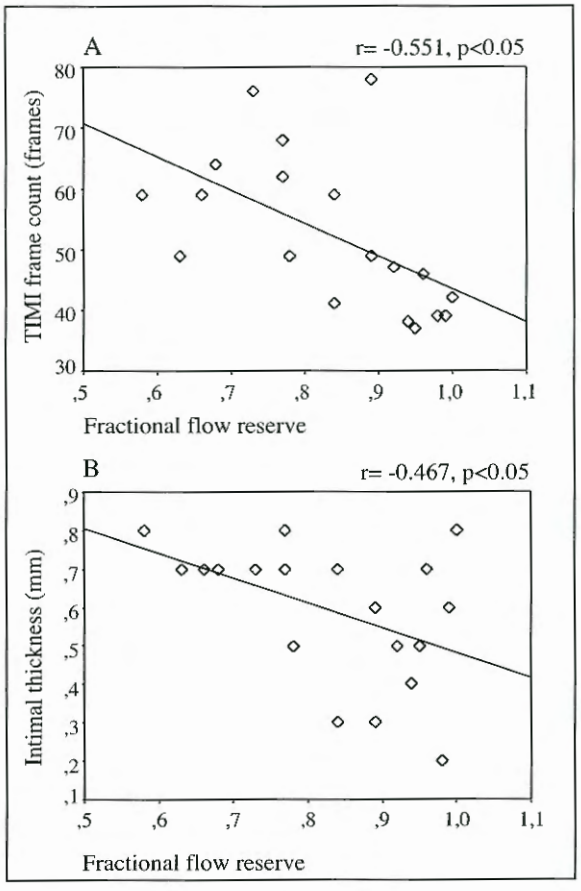


***Figure 2:*** *A) Correlation between fractional flow reserve (FFR) and TIMI frame count, B) Correlation between FFR and intimal thickness.*

Due to the relatively small number of patients involved in the study, coronary artery disease risk factors such as smoking, heredity and lipid parameters etc. were not applied to any kind of statistical methods to Fig. out any possible correlation. All variables investigated are disclosed in Table 2.

| | |
|---|---|
| Age, yr | 55.9±9.4 |
| Female sex, n (%) | 11(57.9) |
| Smoking, n (%) | 7(36.8) |
| Total cholesterol (mg/dl) | 228.0±36.9 |
| Heredity, n (%) | 3(15.8) |
| TIMI frame count (frames) | 52.5±12.8 |
| Coronary localization | |
| Left anterior descending coronary artery n(%) | 13 (68.4) |
| Left circumflex coronary artery n(%) | 4 (21.1) |
| Right coronary artery n(%) | 2 (10.5) |
| Proximal luminal diameter (mm) | 3.6±0.4 |
| Intimal thickness (mm) | 0.59±0.18 |
| Eccentric lesions n(%) | 13(68.4) |
| Baseline Pa (mmHg) | 103.1±18.2 |
| Baseline Pd (mmHg) | 93.9±19.7 |
| Baseline fractional flow reserve (%) | 0.91±0.12 |
| Maximal hyperemia Pa (mmHg) | 98.3±19.9 |
| Maximal hyperemia Pd (mmHg) | 82.4±24.3 |
| Maximal hyperemia fractional flow reserve (%) | 0.83±0.13 |
| Distal-proximal gradient (mmHg) | 15.8±12.1 |

***Table 1:*** *Clinical, angiographic and intravascular ultrasound characteristics and fractional flow reserve variables of the patients*

## DISCUSSION

FFR is an index of the resistance to flow along the epicardial vessel. In maximal hyperemia, FFR is independent from microvascular bed and in normal coronary arteries, proximal and distal pressures differ by no more than 1 mm Hg[15,19]. However, in diffuse atherosclerosis with nonstenotic atheroma, intracoronary pressure decreases from proximal to distal by degrees. De Bruyne et al.[15], have found in nonstenotic vessels

***Table 2:*** *Clinical, angiographic, intravascular ultrasound and fractional flow reserve (FFR) variables of patients*

| Patient (no) | Sex/Age | MIPSø | Coronary Localization | TIMI france count (frame)* | Intinal thickness (mm) | Pa (mmHg) | Pd (mmHg) | FFR (ratio) | Pd-Pa (mmHg) | 1-FFR |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M/43 | - | LAD | 76 | 0.5 | 72 | 56 | 0.78 | 16 | 0.22 |
| 2 | F/55 | - | RCA | 47 | 0.3 | 108 | 91 | 0.84 | 17 | 0.16 |
| 3 | M/47 | + | LAD | 96 | 0.7 | 85 | 54 | 0.63 | 31 | 0.37 |
| 4 | F/68 | - | LAD | 86 | 0.5 | 79 | 75 | 0.95 | 4 | 0.05 |
| 5 | F/51 | - | LAD | 47 | 0.2 | 127 | 124 | 0.98 | 3 | 0.02 |
| 6 | M/58 | - | RCA | 57 | 0.8 | 111 | 85 | 0.77 | 26 | 0.23 |
| 7 | M/49 | - | LAD | 83 | 0.7 | 66 | 51 | 0.77 | 15 | 0.23 |
| 8 | F/65 | + | LAD | 98 | 0.6 | 78 | 46 | 0.58 | 32 | 0.42 |
| 9 | F/43 | - | LAD | 104 | 0.7 | 103 | 68 | 0.66 | 35 | 0.34 |
| 10 | F/67 | - | LAD | 61 | 0,6 | 140 | 138 | 0.99 | 2 | 0.01 |
| 11 | F/50 | | RCA | 51 | 0.7 | 71 | 68 | 0.96 | 3 | 0.04 |
| 12 | F/56 | - | LAD | 79 | 0.6 | 101 | 95 | 0.94 | 6 | 0.06 |
| 13 | M/73 | - | RCA | 49 | 0.5 | 90 | 82 | 0.92 | 8 | 0.08 |
| 14 | F/55 | - | LAD | 109 | 0.8 | 111 | 98 | 0.89 | 13 | 0.11 |
| 15 | M/72 | - | LAD | 86 | 0.3 | 104 | 93 | 0.89 | 11 | 0.11 |
| 16 | M/57 | + | LAD | 73 | 0.7 | 101 | 74 | 0.73 | 27 | 0.27 |
| 17 | F/43 | - | LAD | 76 | 0.7 | 92 | 77 | 0.84 | 15 | 0.16 |
| 18 | F/62 | - | LCX | 46 | 0.6 | 111 | 111 | 1.0 | 0 | 00 |
| 19 | M/56 | - | LAD | 79 | 0.7 | 117 | 80 | 0.68 | 37 | 0.32 |

ø Myocardial perfusion scintigraphy, * The corrected TIMI frame count is shown for the left anterior descending artery

with atheroma that the difference averages 10 mm Hg. The present study demonstrates that, in these patients, without angiographically focal stenosis within the coronary tree, a decline in distal coronary pressure leading to FFR values below 1.0 was the surprising finding (0.83±0.13, $p<0.0001$), the difference between distal and proximal pressures averages 15.84±12.11 mmHg and 5 patients of FFR values patients being below the threshold of 0.75. Paradoxically, microcirculation which is the most implicated etiologic factor in SCF[1,4,5] seems to be replaced or to some extent be combined with macrovessel disease which is the single most important finding in this study.

Some biopsy studies of patients with SCF[4,5] showed that SCF could be the result of increased resistance in arterioles[1,4,5]. Mangieri et al.[5] and Kurtoglu et al.[21] have observed remarkable progress in restoring coronary flow when they studied dypyridamole in this group of patients. Adenosine, being a potent vasodilator is one of the most important mediators in regulating coronary flow reserve and autoregulation[22]. On the other hand dipyridamole, inhibits the active uptake of adenosine into vascular endothelium

and erythrocytes and is a pyrimidopyrimidine derivative[23]. Thus, leads to vasodilation and augments the coronary flow. Interestingly, no beneficial effect of nitrogylcerine infusion was observed in the same studies[23,24]. This is simply due to its effects on arteries larger than 200 nm. However it is vice versa for dypyridamole. All these data support the theory that the pathophysiology underlying this disorder is closely related to the microvasculature and has a dynamic character. However, despite intracoronary adenosine infusion (15 g in the right or 20 g in the left coronary artery) FFR was significantly lower in our study. Additionally, there was a strong negative correlation was seen between TIMI frame count and FFR. These findings clearly signify the independent involvement of epicardial arteries in slow flow process. Therefore one can not easily relate all pathopysiologic process to impaired adenosine metabolism. It is authors' opinion that slow coronary blood flow is a complex process involving micro and macro vascular structures based on diffuse atherosclerosis. Accordingly, Von Lider et al.[25] have shown that CFR confirmed the extremely slow blood flow velocity in a patient with SCF but CFR and coronary blood flow proved to be within normal range, and these findings suggest that SCF may not always be due to a microvascular disease. They speculated that SCF may be due to epicardial artery disease.

Another interesting point of the present study was FFR values below the treshold (0.75) in 3 patients with reversible ischemia on SPECT examination (15.8%). Additionally, we also found diffuse calcification and intimal thickening in all segments of the vessels despite the absence of focal stenosis or plaques in coronary angiography of SCF patients. Besides, there was a negative correlation between intimal thickness and FFR. Obviously the ischemia with this subset of patients could have been due to the generalized atherosclerotic involvement of coronary arteries. Accordingly, Gould et al.[26] have observed in patients with diffuse atherosclerosis without statistically significant dipyridamole-induced segmental myocardial perfusion defects caused by flow-limiting stenoses compared with normal control subjects, there was a graded, longitudinal, base-to-apex myocardial perfusion gradient significantly different from normal control subjects, indicating diffuse coronary arterial narrowing by noninvasive positron emission tomography.

**Study limitations**

The current study demonstrates preliminary results concerning heightened resistance of the epicardial arteries in patients with SCF, however some limitations exist. First of all, the results can not be extrapolated to overall coronary tree since the point of interest was the particular vessel which was the one with highest TIMI frame count. Second, since the universal normal value of FFR (1.0) has been accepted and applied virtually, no control group has been established for precise comparison. Similarly no control group existed for IVUS examination. Third, FFR and CFR tecniques have not been combined in the same setting. The major drawback for CFR is that absolute CFR is an index of the serial resistance of epicardial and microvascular vessels and does not distinguish between these two entities and is highly susceptible to hemodynamic parameters[27]. Therefore both FFR and CFR techniques should be interpreted together in the same setting to avoid any possible bias. In conclusion, we studied the patients with SCF and angiographically patent coronary arteries, and demonstrated decreased FFR in the same setting. Decreased FFR levels have been attributed to diffuse disease which has been demonstrated by IVUS signifying decreased elasticity due to diffuse calcification and intimal thickening in all segments of the vessels and nonstenotic atheroma. We conclude that SCF may be a generalized disorder of the whole coronary tree afflicted with diffuse atherosclerosis.

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