Coronary slow flow: Benign or ominous?

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Abstract

Objective: Coronary slow flow phenomenon has been arbitrarily defined as delayed coronary blood flow in the absence of obstructive coronary artery disease. The present study sought to investigate the clinical features, natural history, and outcomes of affected patients.

Methods: In this prospective cross-sectional study, 217 consecutive patients who had undergone coronary angiography and showed features of coronary slow flow phenomenon were evaluated for demographic and coronary risk factor profile, as well as clinical outcomes, at baseline and following treatment.

Results: The study population consisted of 165 (76%) males and 52 (24%) females. The mean age of patients was 52.6±10 years. Mean ejection fraction was 48.2±5.4, 39.3% had diabetes, 43.3% had hypertension, 49.8% was a cigarette smoker, 41.9% had dyslipidemia, and 15% had a familial history of cardiac disease. Forty-nine percent was detected to have abnormal hsCRP levels. The most prevalent presenting complaint was atypical chest pain. Fifty-four percent of patients had slow blood flow in all three vessels. Thirty-six people had undergone repeat coronary angiography in a follow-up period of 5-7 years due to persisting or worsening clinical symptoms, of whom 6 (16.6%) showed significant coronary artery stenosis. Eight (22.2%) had mild CAD, and the rest still showed coronary slow flow without significant stenosis. The most common complaint during follow-up and after initiation of medical therapy was nonanginal chest pain.

Conclusion: Patients with coronary slow flow phenomenon are predisposed to atherosclerosis and obstructive coronary artery disease. Therefore, this pathology should not be considered as a totally benign condition. Primary and secondary cardiovasculature preventive measures should be constituted and seem worthwhile in this patient population.

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Keywords: coronary slow flow, coronary artery disease, atherosclerosis

Introduction

One of the most challenging scenarios in cardiovascular medicine is the practical approach to patients presenting with sample clinical evidence of obstructive coronary artery disease, including retrosternal chest discomfort, multiple coronary artery disease risk factors, and abnormal noninvasive tests, in whom coronary angiography reveals patent coronary vessels that are opacified with a noticeable delay after dye injection, or the so-called "coronary slow flow phenomenon" (1-3). Although this phenomenon has been recognized for many decades, there is still no firm or convincible pathophysiologic explanation. Some studies have mentioned microvascular or endothelial dysfunction (4-6), while others consider it a preliminary stage of atherosclerosis coronary disease (7, 8). There also still remain multiple questions and controversies regarding the point over whether this pathology is limited to coronary arteries or is a manifestation of systemic vascular or endothelial disease (8-10). As the pathophysiology and natural history of this disorder are yet controversial, there is no anonymous treatment strategy (2, 11, 12). Previous observational studies have concluded that these patients have a good prognosis (1, 2, 8, 10). But, a comprehensive study evaluating the long-term prognosis and effective pharmacologic treatment is still lacking.

The present study aimed to evaluate the clinical course of slow flow coronary phenomenon and the response to conventional treatment protocols in these patients.

Methods

A cohort of 3287 patients who underwent coronary angiography between 2006-2013 in our center and had normal epicardial

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coronary arteries was assessed in this cross-sectional study. We used standard Judkins technique for left heart catheterization and standard views using right and left, caudal, and cranial angulations. Angiograms of patients were reassessed, and TIMI frame counts were determined for each coronary artery by two interventional cardiologists (MAS and MM) (11). Images were acquired at 15 frames/s, and all frames were multiplied by 2. LAD frame counts were divided by 1.7 for correction of the longer length of this vessel. A frame count above 27 for all vessels (after correction for LAD as described above) was considered to be slow flow based on accepted previous methods (11). We collected our data on the day of catheterization before the patients were discharged. A total of 217 patients fulfilled the criteria for slow flow phenomenon in our study.

Those with slow flow coronary arteries and concomitant disorders, like valvular heart disease (more than mild), cardiomyopathy, pulmonary arterial hypertension (pulmonary artery systolic pressure above 25 mm Hg in transthoracic echocardiography), and coronary ectasia, were excluded from the study.

Demographic data regarding age, sex, and cardiovascular risk factors (hypertension, diabetes, dyslipidemia, cigarette smoking, and familial history of cardiovascular disease) were recorded.

Baseline ECG changes, echocardiographic data, non-invasive test results, and hsCRP levels were also collected. Blood samples for measurements of hsCRP were obtained from does diagnose with slow flow on the day of coronary angiography. Patients were followed for a mean of 5.5±2 years after the initial angiography, during which regular office visits were conducted, and the presence, absence, worsening, or alleviation of subjective and objective clinical symptoms, hospital admissions, noninvasive tests, or repeat coronary angiography data were recorded.

This study was approved by our Center's Ethics Committee, and all patients signed an informed consent form authorizing the use of their information for analysis on the day of catheterization after confirmation of slow flow. After patients were transferred to the ward, data were collected using a form after explaining the study's purpose and protocol, with reassurance that the study would not interfere with their treatment drugs.

Statistical analysis

Continuous variables are expressed as mean±standard. Categorical data are presented as percent frequencies. One-sample Kolmogorov-Smirnov test was used to investigate the normal distribution for continuous variables. Comparison of the variables before and after the follow-up was performed using McNemar test. Data were analyzed using SPSS 15.0 for Windows (SPSS Inc, Chicago, Illinois, USA). A p value <0.05 was considered statistically significant.

Results

The study population consisted of 165 (76%) males and 52 (24%) females; the mean age of participants was 52.6±10 years.

Table 1. Demographic and clinical characteristics of subjects with slow flow

Variables	Slow flow (n=217)
Demographics	
Age, year	52.06±10.5
Male	76%
Comorbidities	
HTN (%)	43.3%
DM (%)	32.3%
Dyslipidemia (%)	41.9%
Nicotine use (%)	49.8%
Familial history for CAD (positive)	15.2%
hs-CRP (above 2 mg/L)	56%
LVEF (%) at time of admission	48.2±5.7%
EKG changes (%)	76.03%
ST depression	39.6%
T wave inversion	29.3%
ST depression and T wave inversion	27.1%
LBBB and RBBB	7.3%
Without EKG change	23.9%
LVEF (%) in follow up period	46.6±4.8%

CAD - coronary artery disease; DM - diabetes mellitus; EKG - electrocardiogram; HTN - hypertension; LBBB - left bundle branch block; LVEF - left ventricular ejection fraction; RBBB - right bundle branch block

Seventy (32.3%) patients had diabetes, 94 (43.3%) had hypertension, 91 (41.9%) had dyslipidemia, 108 (49.8%) were smokers, and 33 patients had a family history of cardiovascular disease. Fifty-six percent had hsCRP levels more than 2 mg/L, and 43.3% had hsCRP levels below 2 mg/L. Mean left ventricular ejection fraction of the patients was 48.2±5.7%. From 217 patient of our study population, 109 patients (50.2%) had undergone noninvasive tests, including exercise stress testing (60.5%), stress echocardiography (8.4%), and myocardial perfusion imaging or MPI (31.1%) that showed abnormal results (Table 1). All patients had undergone a coronary angiography due to presentation with acute coronary syndromes, including non-ST elevation myocardial infarction (positive troponin I)/unstable angina (NSTEMI/UA), typical chest discomfort or atypical chest pain accomplished by exertional dyspnea, and, for EKG changes, abnormal noninvasive tests, as shown in the Table 2.

The coronary angiography results showed that 118 (54%) patients had slow flow coronary phenomenon in all 3 vessels, 43 (20%) had it in 2 vessels, and 56 (25%) patients had this abnormality in a single coronary artery. There was no statistically significant difference in the prevalence of traditional cardiovascular risk factors between these three groups (p value=0.4). All patients had been started on medical therapy after the initial diagnosis of slow flow coronary phenomenon, as shown in Table 3. Of the patients mentioned above during a mean follow-up period of 5.5±2 years, 36 patients had undergone a repeat

Table 2. Symptoms before and after treatment

	Symptoms before treatment (n=217)	Symptoms after treatment (n=204)	*P*
Unstable angina (%)	30%	3.4%	<0.001
Typical chest pain (%)	25.3%	4.4%	<0.001
Atypical chest pain (%)	40.5%	17.1%	0.03
Dyspnea on exertion (%)	5.1%	2.4%	0.04
Non-angina chest pain (%)	0%	43.6%	<0.001
Asymptomatic (%)	0%	28.9%	<0.001

Table 3. Drugs used in patients

Drugs	n (%)
Beta-blocker (%)	74.2%
ACEI (%)	95.5%
Ca. channel blocker (%)	67.3%
Aspirin (%)	94.9%
Clopidogrel (%)	33.6%
Anti-depressant (%)	28.6%
Statins (%)	94.9%
ACEI - angiotensin-converting enzyme	

coronary angiography (once) because of symptom recurrence or alleviation. Non-invasive tests during follow-up (MPI: 21 patients and stress echocardiography in 8 patients) for 29 (80.5%) of these patients were abnormal. Catheterization showed that 22 patients were still slow flow, 8 patients had developed mild coronary artery disease (luminal stenosis <50%), and 6 patients had developed significant coronary stenosis. Thirteen patients were lost to follow-up. Mean echocardiographic systolic LV function showed no significant changes during follow-up compared with echocardiographic systolic LV function at the time of admission.

During the follow-up period, the most prevalent symptom of patients was nonanginal chest pain as compared to atypical angina pain at first presentation. Clinical symptoms showed a statistically significant improvement after initiation of medical therapy (p<0.001).

Discussion

Coronary slow flow phenomenon is a frequent angiographic finding with obscure pathophysiology (1-3, 8). Considering the existing controversy on the treatment and long-term prognosis of these patients in the current literature, the present study sought to investigate the natural history of these patients. The prevalence of coronary slow flow was 6.6% in our study, which we believe, considering the relatively adequate sample size, is a reliable result. In a study by Hawkins et al. (11), it was reported to be 5.5%, whereas Mangieri et al. (4) and Beltrame et al. (13) reported a 7% and 1% prevalence, respectively. Higher prevalence appears to be more common in populations that are more vulnerable to atherosclerotic disease; therefore, it has been hypothesized that coronary slow flow phenomenon is a primary stage of atherosclerosis, with microvascular or endothelial dysfunction being implicated, as well (7, 8, 11, 14).

The data on demographic variables are also generally limited in the literature. In our study, 76% of the patients were male. Some studies have reported male gender as a predictor of coronary slow flow phenomenon, while others have found no relation between sex and slow flow phenomenon (9). The mean age of our patients was 52±10 years, which compares well with previous studies that reported these patients to be generally younger than those with obstructive coronary arteries (11). In our study, there was no statistically significant relationship between traditional cardiovascular risk factors and coronary slow flow phenomenon, but some studies have observed that these patients are more likely to suffer from metabolic disorders, including impaired fasting glucose, high triglyceride, low high-density cholesterol, and high HbA1c, perhaps because these abnormalities enhance the progression of the main underlying disorder (microvascular or endothelial dysfunction) (15, 16). Most of our patients had mild systolic dysfunction that seemed to be due to baseline microvascular and endothelial dysfunction compared to those with normal epicardial coronary arteries (17, 18).

Also, 56% of the study population had hsCRP levels of more than 2 mg/L at baseline; however, we do not have follow-up data in this regard. There is still controversy regarding the existence of a clear and positive relationship between hsCRP and slow coronary flow phenomenon (19, 20). Further research in this regard seems worthwhile.

All patients with noninvasive tests performed before catheterization had abnormal test results that seemed to be related with the pathophysiologic process of this disease (i.e., microvascular and endothelial dysfunction). Evidence of perfusion abnormality in noninvasive tests must justify anti-ischemic treatment strategies in these patients (8, 13, 21, 22).

There is also considerable controversy regarding presenting clinical symptoms before coronary angiography. We found atypical chest discomfort to be the most common, and non-anginal chest pain was the most frequent symptom after the first angiography and initiation of medical treatment. Some studies report atypical chest pain as the most common (11), whereas others found typical chest pain to be the most prevalently reported symptom (23). In a study of Beltrame et al. (13), resting chest pain that required urgent admission was also mentioned (12).

In our study, patients were followed for mean of 5.5 years after initiation of anti-ischemia and anti-anginal medication. Fourteen (6.4%) patients were found to have developed different degrees of coronary artery stenosis during follow-up, and there were no significant differences in traditional coronary artery disease risk factors between these patients and others. To the best of our knowledge, no previous studies have had this length of follow-up. However, as the limited number of our patients had

developed coronary artery disease and because atherosclerosis is known to have a slowly progressive course (24), we could not establish a significant statistical relation between the slow coronary flow phenomenon and rate of atherosclerotic progression; however, these results emphasize the need for further evaluation of the fate of atherosclerotic disease in this group and that the coronary slow flow phenomenon might not be absolutely benign. The alleviation of symptoms during follow-up showed that patients benefit from risk factor modification and anti-anginal and anti-ischemic therapy. This is also in accordance with previous studies that reported that these patients benefit from antiplatelet therapy (11). Statins and nebivolol, possibly via improvement of endothelial function and reduction of inflammation, and diltiazem have also been reported to be used with some success in these patients (25-28).

Study limitations

The aim of our study was to evaluate the course and response to treatment in this patient population, considering the limited existing clinical data in this regard. We did not choose a control group and believe that further comparison between those with normal coronary arteries and coronary slow flow should be the subject of future studies. However, we compared the cardiovascular risk of our patients with the risk calculated by the Framingham risk scoring system for age- and risk factor-matched patients.

Conclusion

Coronary slow flow is not a totally benign phenomenon, and affected individuals benefit from and deserve to be offered the full spectrum of primary and secondary cardiovascular preventive measures.

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