Clinical Medicine Research
2015; 4(1): 21-26
Published online February 9, 2015 (http://www.sciencepublishinggroup.com/j/cmr)
doi: 10.11648/j.cmr.20150401.15
ISSN: 2326-9049 (Print); ISSN: 2326-9057 (Online)

Spontaneous Coronary Dissection as an Expression of Coronary Artery Disease: Correlation with Vasospasm

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To cite this article:
Fumimaro Takatsu, Kenji Takemoto. Spontaneous Coronary Dissection as an Expression of Coronary Artery Disease: Correlation with Vasospasm. *Clinical Medicine Research.* Vol. 4, No. 1, 2015, pp. 21-26. doi: 10.11648/j.cmr.20150401.15

Abstract: Background: Artificial coronary artery dissection is observed occasionally during percutaneous coronary intervention. However, "spontaneous" coronary artery dissection (SCAD) is not common and we tried to clarify its characteristics. Methods and Results: We reviewed the serial diagnostic coronary angiograms of 21,500 patients retrospectively. Sixty-two patients showed linear, longitudinal defects that were considered to be the angiographic expression of SCAD, in at least one major coronary artery. Vasospasm was shown in 38 patients. Among the remaining 24 subjects, 18 patients had chest pain even after all coronary narrowings of ≧50 %were treated with coronary intervention or bypass surgery. Chest pain was relieved promptly with sublingual administration of nitrate. Thus, 56 patients (90.3%) with SCAD were demonstrated or considered to have vasospasm. Fifty-two patients of these 56 individuals showed significant (≧50%) narrowing in at least one of the major coronary arteries. In the remaining 4 subjects, 3 patients subsequently developed significant coronary artery disease. Comparison of coronary risk factors was done in the 38 patients shown to have vasospasm and 144 patients with ordinary coronary artery disease. Smoking was more common in the group with vasospasm but there was no difference with regard to the other risk factors. Conclusion: SCAD seems to be an expression of coronary artery disease. However, vasospasm is a common factor in these patients.

Keywords: Coronary Artery Dissection, Coronary Vasospasm, Smoking

1. Introduction

Artificial coronary artery dissection is observed occasionally during percutaneous coronary intervention (PCI). However, "spontaneous" coronary artery dissection (SCAD) is less common. Several authors [1, 2] have reported SCAD in women having acute coronary syndromes during the post-partum period. Other authors [3, 4] have reported patients having connective-tissue diseases, some systemic congenital diseases, or fibromuscular dysplasia associated with SCAD. Various diagnostic approaches, results of medical follow-up, surgical treatment or treatment with PCI, as well as reviews on >400 cases with SCAD have been described [5, 6]. However, the authors of those studies did not analyze the cause of SCAD. Although a few authors [7, 8] have suggested a relationship between coronary vasospasm and SCAD, a systematic study on this correlation is lacking. Only 2 cases of vasospasm during angiography have been reported [7, 9]. In the present study, we tried to clarify the relationship between coronary vasospasm and SCAD.

2. Methods

We reviewed all the coronary angiograms of 21,500 consecutive patients who underwent diagnostic arteriography from January 1980 to April 2002 retrospectively. Thereafter, we used intravascular ultrasound (IVUS) in the treatment of subjects with significant coronary narrowing and the definition of SCAD became complex. So, we did not include patients who had coronary angiography after May 2002. All coronary angiograms were analyzed by two experienced angiographers (FT and KT). A total of 10,329 patients had narrowing of≧50% in at least one major coronary artery and 1,531 subjects without significant narrowing of a coronary artery had a coronary vasospasm. The remaining 9,640 subjects comprised patients who had PCI but no diagnostic angiography in our institute, cardiomyopathies, valvular heart diseases, atypical chest pain without coronary narrowing or vasospasm. After obtaining written informed consent,

provocation of vasospasm was initiated in > 80% of patients (subjects with PCI only, cardiomyopathies or valvular heart diseases were excluded). After conventional diagnostic angiography, provocation of vasospasm was undertaken first with ergonovine maleate administered by intravenous, intra-aortic, or intra-coronary injection. After 1995, if no vasospasm was provoked by ergonovine, then acetylcholine was injected following the method of Yasue et al. [10]. For patients admitted for acute coronary syndromes, provocation was done > 4 months after treatment of critical lesions because a provocation test is considered to be dangerous in such situations. The diagnosis of vasospasm was based on at least one of two criteria [11, 12, Table1]. The first was spontaneous ST segment elevation on electrocardiography that resolved spontaneously or with the administration of nitrates. The second criterion was total or subtotal occlusion of at least one major coronary artery during diagnostic angiography that was spontaneous or induced by administration of ergonovine or acetylcholine in coronary arteries without narrowing of ≧ 50%.

Table 1. *Diagnosis of Coronary Vasospasm*

	n	Spasm during angiography*	Spontaneous ST elevation	Clinical Suspicion
Dissection	27	24 (88.9%)	7**	3
Slit	35	14 (40%)	0	15

n = number of patients
*transient total occlusion or subtotal occlusion with distal filling delay spontaneously during angiography or provoked with ergonovine or acetylcholine in sites without significant narrowing
**all 7 patients showed spasm on angiography

Patients having at least one of the following criteria were excluded.

(i): a "spastic", non- occlusive response on provocation test; (ii): provoked spasm only at the site with coronary narrowing of ≧50%; (iii): history of strong trauma to the chest; (iv)：pregnant patients or within 1 year of delivery; (v): linear defects only in the phase of acute coronary syndromes (because in these cases defects are thought to be an intraluminal thrombus); (vi): absence of pain and/or discomfort in the chest.

Incidentally, none of our study subjects was within 1 year of delivery.

2.1. Definition of "Dissection" and "Slit"

Intraluminal linear and longitudinal defects in coronary arteries longer than three- times the luminal diameter were defined as "dissection" and those of shorter length as "slit".

2.2. Control Patients

One hundred and forty-four patients with coronary narrowing > 75% in at least one major coronary artery but with no positive or equivocal response in the provocation test were selected randomly from 10,329 subjects with significant coronary narrowing. Patients with chest pain at rest or during sleep were excluded. Subjects with SCAD were not included.

2.3. Coronary Risk Factors

Patients who underwent diagnostic coronary arteriography were hospitalized for 1 - 2 days before the angiographic study. Blood samples were obtained on the morning of the study after an overnight fast. In patients admitted to hospital due to acute myocardial infarction or unstable angina, laboratory analyses of lipids and blood glucose (i.e., for the diagnosis of diabetes mellitus (DM)) were carried out >2 months after hospitalization. If patients were receiving drugs that could affect these data, we obtained the recordings before drug administration. Hypertension was defined as a systolic blood pressure ≧ 140 mmHg and/or a diastolic blood pressure ≧ 90mmHg. Patients with DM were defined according to the criteria proposed by Alberti et al. [13]. Patients taking anti-diabetic agents (including insulin) were considered to have DM. As for smoking, patients smoke cigarette even one a day at the first diagnostic angiogram or first admission for treatment of acute coronary syndrome were defined as current smokers. And patients who had never smoked in his life were defined as "never smokers".

2.4. Statistical Analyses

Table 2. *Baseline characteristics**

n	Spasm with SCAD	Coronary Narrowing without Spasm	p
	38	144	
Male/Female	30/8	110/34	0.40
Age (years)	52.6±1.8	54.5±6.7	0.22
Current Smoker	21 (70%)	57 (39.6%)	0.004
Never smoke	6 (16.2%)	57 (39.6%)	0.004
Hypertension	7 (23.3%)	62 (43.1%)	0.408
DM	10 (33.3%)	58 (40.3%)	0.124
BMI	23.5±3.0	24.1±2.9	0.279
Total cholesterol **	229.1±37.7	237.9±54.5	0.400
Triglyceride**	157.5±91.6	181.6±101.3	0.230
HDL-cholesterol**	52.8±8.8	44.6±6.9	0.018
Uric acid*	5.7±1.5	6.1±1.7	0.310

*(This table does not include 24 patients with SCAD but no improved spasm)
SCAD = spontaneous coronary dissection, n = number of patients, DM = diabetes mellitus, BMI =body mass index (kg/m^2), HDL = high-density lipoprotein, **All continuous variables expressed as mean±standard deviation and mg/dL

Continuous variables are the mean±standard deviation. All factors were first examined by a univariate analysis using the Students' *t* - test for continuous variables and for other characteristics with the chi-square test. A level of significance of $p < 0.1$ by univariate analysis (Table 2) was examined further by multiple logistic regression analysis. We also conducted a stepwise forward selection procedure to identify characteristics that independently influence vasospasm. In this

analysis, the dependent variable was vasospasm. Independent variables comprised the body mass index (BMI, in kg/m^2), smoking, DM, hypertension, as well as serum levels of total cholesterol, triglyceride, high-density lipoprotein - cholesterol (HDL-C) and uric acid.

3. Results

Sixty-two patients showed dissections or slits in at least one of the major coronary arteries upon diagnostic angiography. Among these 62 subjects, 27 showed coronary dissection as defined above and 24 (88.9%) showed definite vasospasm upon angiography. Spontaneous ST elevation was recorded in 7 of those subjects. Two patients with effort angina and rest angina showed considerable dissection in the left main trunk. They had urgent bypass surgery to the left anterior descending artery and left circumflex artery. After bypass surgery, they refused to undergo a test of vasospasm provocation. Those 2 patients had chest pain at rest even after successful bypass surgery. They had angiography before discharge from hospital; all bypasses were patent and the right coronary arteries did not show significant narrowing. Their chest pain vanished promptly upon sublingual administration of nitroglycerin. Then, we gave diltiazem (100-200mg a day), which suppressed chest pain completely. One patient with dissection had chest pain at rest that vanished promptly with sublingual administration of nitrate. He showed no spasm upon provocation with ergonovine. The angiographic study of this patient was done before 1994, so acetylcholine was not used. Thus, almost all patients having dissection on coronary angiography were shown or suggested to have vasospasm.

Thirty-five patients were shown to have a slit as defined above. Fourteen subjects (40%) of these 35 subjects showed vasospasm on arteriography. Among the remaining 21 subjects, 3 patients, although they had chest pain at rest or at night and upon effort, we could not undertake a provocation test of vasospasm due to considerable allergy to the contrast medium. These 3 subjects had successful PCI and follow-up coronary arteriography showed no significant residual narrowings. Even after PCI, their chest pain at rest continued. Chest pain was relieved promptly with sublingual administration of nitrate. Four patients, who showed severe two - vessel disease, had successful bypass surgery. The ergonovine test was negative in these 4 patients but, they had chest pain at rest even after successful surgery. Chest pain also vanished immediately with sublingual administration of nitrate and their symptoms subsided after they had 100-200mg of diltiazem. One patient with a severe narrowing in one vessel had angina upon effort as well as at rest and the ergonovine test was negative. This patient had successful PCI without restenosis and after PCI chest pain at rest remained but vanished promptly with administration of sublingual nitrate. Another patient had chest pain only at rest and during sleep and the ergonovine test was also negative in this subject. Six patients with slits showed an equivocal response to ergonovine maleate. All had chest pain at rest or during sleep and none had lesions or symptoms suggestive of unstable angina. The angiographic study of these 12 patients with a negative or equivocal response to ergonovine, like the patient with dissection, was done before 1994, so acetylcholine was not employed. Thus, 38 patients (61.3%) with SCAD were shown or considered to have vasospasm and an additional 18 (29.0%) were suggested to have vasospasm clinically.

3.1. Symptoms of these 38 Patients

One patient had chest pain on effort unrelated to time. Four had chest pain on effort only in the early morning. Three patients had chest pain upon exposure to the cold. Five suffered sudden myocardial infarction and they had chest pain at rest after myocardial infarction. The remaining 25 subjects had chest pain at rest or during sleep as well as upon effort. The interval between the first report of chest discomfort and diagnostic angiography was 62.7±77.1 months and the frequency of chest pain before angiography was 17±27 times.

3.2. Site of SCAD and Spasm

Spasm was demonstrated only in the same coronary artery showing SCAD in 20 patients (none of these spasm sites had a narrowing of≧50%). Among these 20 subjects, spasm was also shown in the segment proximal or distal to the segment showing SCAD in 18 patients. In 7 patients, spasm was provoked in the artery showing SCAD as well as in other vessels. Eleven patients showed spasm only in the artery without SCAD.

3.3. Coronary Narrowing

Among 62 patients, 58 subjects had significant (≧50%) coronary narrowing in at least one major coronary artery. Two patients had lesions in the left main trunk, 3 had three-vessel disease, 13 had two- vessel disease and 40 had a lesion in one vessel. In the remaining 4 subjects without significant narrowing of the coronary arteries, 3 patients developed significant coronary narrowings in subsequent studies. All 4 patients were demonstrated or considered to have vasospasm.

3.4. Coronary Risk Factors

All 56 patients shown or considered to have vasospasm had some coronary risk factors (DM, obesity, hypertension, family history of coronary artery disease, smoking, low level of serum HDL-C or elevated levels of total cholesterol, triglyceride, uric acid or low-density lipoprotein in serum).

We compared the coronary risk factors of 38 patients with SCAD shown to have vasospasm and 144 patients having coronary artery disease but no spasm, who were selected randomly from 10,329 subjects with significant narrowing (Table 2).

Continuous variables were distributed normally. There were no significant differences with regard to age, sex, BMI, frequency of hypertension, DM, or serum levels of total cholesterol, triglyceride and uric acid between the two groups. Current smokers were definitely ($p = 0.004$) more closely associated with vasospasm and SCAD. HDL-C levels were lower in patients who had coronary narrowing of≧50% but

no vasospasm (p = 0.018).

3.5. Multivariate Analyses

Table 3. *Results of multiple logistic regression analysis*

Characteristics	OR	95% CI	p
Current Smoker	3.93	1.63-9.47	0.002
HDL-C	1.03	1.00-1.05	0.016

OR=odds ratio; CI=confidence interval; HDL -C=high-density lipoprotein-cholesterol

Multivariate analyses again demonstrated that smoking was associated with vasospasm with dissections or slits (relative risk, [RR], 3.93; 95% confidence interval, [CI], 1.63-9.47). HDL-C levels were slightly lower (but not significantly) in patients with coronary narrowing ≧ 50% but without vasospasm (RR, 1.03; 95% CI, 1.00-1.05).

4. Discussion

There have been several reports of SCAD not being caused by chest trauma or during PCI [1-6]. SCAD is observed in acute coronary syndromes or in the sudden death of women post-partum [1, 2]. Other causes of SCAD are connective-tissue diseases [3], systemic congenital diseases such as Ehlers-Danlos syndrome, fibromuscular dysplasia [4] as well as in cocaine abuse. Common coronary artery disease can be expressed as coronary dissection. Some authors [7, 8] have suggested a correlation between coronary vasospasm and SCAD but a systematic study on the relationship between them has not been done. Mark et al. [7] reported a 50-year-old female, who had ST elevation in the inferior leads on chest pain that was relieved with nitrate. Coronary angiography showed a definite dissection in the posterior descending artery. During the angiographic study, spontaneous chest pain with ST elevation in the inferior leads arose. At this time, the posterior descending artery was occluded transiently. Nishikawa et al. [8] described 4 patients with considerable dissection upon angiography after they suffered myocardial infarction. Two of these patients had chest pain at rest before infarction. They suggested the possibility of vasospasm in these cases but the authors did not try to demonstrate vasospasm with Holter recordings or with provocation of vasospasm in the angiographic study. Roth et al. [1] reviewed 103 cases who sustained myocardial infarction post-partum and 41 of these showed coronary artery dissection. Among these, only 2 subjects were shown to have vasospasm. SCAD, like aortic dissection, can be caused by cystic medial necrosis or inflammation. However, none of the cases reported here had aortic dissection, systemic congenital diseases, connective-tissue disorders, chronic inflammatory diseases or abused cocaine. Other possible causes of dissection include strong force to the coronary arteries (e.g., chest trauma) or extreme physical activity. As reported by Roth et al., pregnancy and delivery can give rise to various mechanical or hormonal stresses to the vascular system. Eight of our cases were females but the intervals between their last delivery and the onset of chest pain was > 20 years, and we excluded patients with a history of forceful trauma to the chest. In some patients, the site of SCAD and spasm demonstrated by angiography was different. Using repeat provocation in the angiographic study, Ozaki et al. [14] reported arteries showing spasm that occasionally changed in the follow-up study. Thus, in the 11 patients showing spasm only in arteries without SCAD, spasm could be provoked in a vessel showing SCAD if spasm provocation was repeated in the follow-up study.

Analyses of coronary risk factors demonstrated smoking to be more frequent in patients with vasospasm, a finding that was in accordance with our previous reports [11, 12]. There were no significant differences in all the other risk factors analyzed in this study. Thus, although SCAD is considered to be an expression of coronary artery disease, in many cases, vasospasm frequently overlaps and spasm can cause SCAD in these subjects.

5. Limitations of the Study

We defined coronary dissections and slits only upon angiography. Hence, we do not know if more patients with or without vasospasm could have had SCAD demonstrated with IVUS or optical coherence tomography (OCT). These more forceful methods for detecting or excluding coronary dissection are usually employed in PCI. In routine angiographic studies for the diagnosis of CAD, however, obtaining written informed consent is very difficult because of the potential risk and expense. Moreover, almost all the patients in the present study had angiography before IVUS or OCT became used so routinely. We found coronary narrowing ≧50% in vessels not showing SCAD in almost all patients. With respect to analyses of coronary risk, except for smoking, there were no differences between the SCAD group and control coronary artery disease group. Thus, SCAD could be an expression of conventional coronary artery disease. However, our study cohort of 38 patients may not have been sufficiently large to discuss the differences in coronary risk factors between the two groups. Consequently, further studies with more patients with SCAD are necessary for risk factor analyses.

6. Conclusion

This was the first study researching the cause of SCAD in a systematic manner. In 62 cases having SCAD, 38/62 (61.2%) were shown to have coronary vasospasm. An additional 18 patients (29.0%) were considered to have vasospasm clinically. With regard to long dissection, 24/27 (88.9%) were proved to have coronary spasm. Thus, patients showing SCAD must be followed up very carefully with calcium antagonists, nicorandil or long acting nitrates even if there is no definitive proof of vasospasm

Funding Sources

We did not receive any financial support and this study does

not involve a conflict of interest.

This study is not published in part or in its entirety, nor has it been presented in any congress or scientific meeting.

Figure Legends

Representative Case (Figure 2, 3)

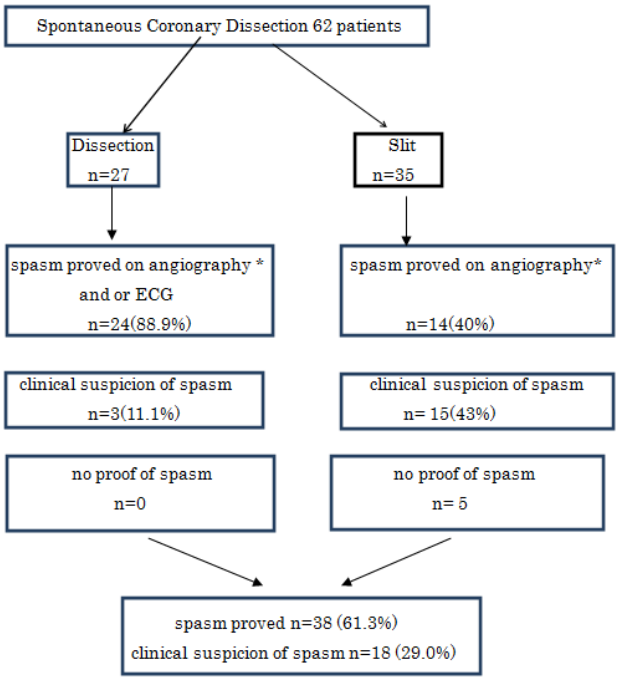

Figure 1. *62 patients with Spontaneous Coronary Dissection*

n=number of patients
(Definition of dissection and slit in methods)
*transient total occlusion or subtotal occlusion with distal filling delay spontaneously during angiography or provoked with ergonovine or acetylcholine in sites without significant narrowing
ECG: electrocardiography

A 64-year-old male had chest pain upon exposure to cold since 1985. He had no coronary risk factors except for smoking. In October 1990, he had severe chest pain for several minutes. Next day his electrocardiogram showed a QS pattern in precordial leads, which was not seen in 1985. He was given sublingual nitroglycerin. After this episode, he had chest pains during sleep on three occasions that vanished promptly with sublingual nitroglycerin. In December 1994, he was referred to our institute for diagnostic coronary angiography. The left anterior descending artery (LAD) showed a remarkably long dissection (Figure 1: first and fourth arrows indicate the beginning and the end of the dissection). In the dissection, ~70% of stenosis was present (second arrow). (Figure 2):.The right coronary artery (RCA) and circumflex artery had only minor irregularities (A and B: A is the same image as Figure 1). Ergonovine maleate (0.2mg, i.v.) provoked occlusion of the RCA and two 90% spasm of LAD (Figure 3C (arrows) and D) Left circumflex artery also showed two 80-90% spasm (Figure 3C). ST segments in the inferior leads and precordial leads were elevated and he had moderate chest pain. Isosorbide dinitrate (5mg) into the RCA promptly resolved occlusions, chest pain and ST elevation. Left ventriculography showed mild antero-apical hypokinesis. We thought that the long radiolucency in the LAD might be a thrombus, so warfarin was begun and prothrombin time/international normalized ratio was kept at 2.62 for about 6 months. After 6 months, coronary angiography was repeated but the findings in the LAD were the same as in those recorded in the first angiogram. Thereafter, he has been free of chest pain with diltiazem (200mg a day) and aspirin (100mg a day).

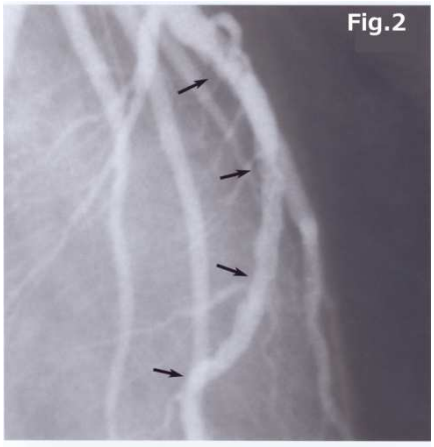

Figure 2. *A typical case with dissection: left anterior descending artery (right anterior oblique view).*

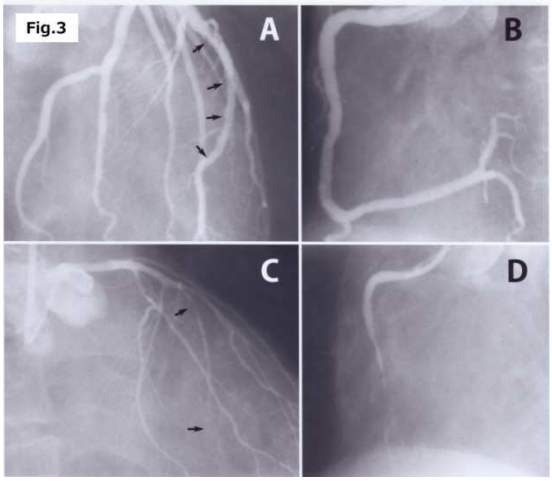

Figure 3. *Same case as in Figure 2: provocation of spasm and right coronary artery.*

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