Lack of Compensatory Enlargement at Sites of Coronary Vasospasm: Identification by Ultrasound and Successful Treatment with Stenting

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Summary: The case of a young man with spontaneous vasospasm at two sites in his left anterior descending coronary artery is described. Intravascular ultrasound demonstrated mild eccentric atherosclerosis with smaller total artery cross-sectional area (defined as the external elastic membrane) compared with reference segments. Impaired compensatory enlargement (remodeling) in response to mild atherosclerosis may derive from one or more biologic mechanisms that are also responsible for vasospasm. This characteristic is easily identified by intravascular ultrasound. In this case, coronary stenting of the vasospastic sites led to excellent long-term control of symptoms more than 1 year after intervention.

Key words: coronary spasm, compensatory enlargement, intravascular ultrasound

Introduction

Focal coronary vasospasm is an important cause of variant angina.¹ Although vasospasm may occur in arterial segments with or without angiographic evidence of atherosclerosis,² atherosclerotic changes are typically seen with intravascular ultrasound even in angiographically normal coronary arteries.^{3,4} Case series using intravascular ultrasound have described mild concentric thickening of the intima and the sonolucent (medial) layer of vasospastic segments compared with reference segments after vasorelaxation with nitroglycerin.^{3,4} We describe a case of variant angina with spontaneous vasospasm in two segments associated with a smaller total

artery area compared with reference segments. This finding supports an association between coronary vasospasm and impaired compensatory enlargement (remodeling) in response to mild atherosclerosis.

Case History

A 41-year-old man was admitted to the hospital for further investigation of angina which was precipitated by sudden increases in physical activity following periods of rest and associated with rapid nonsustained monomorphic ventricular tachycardia (VT).

He had a history of intermittent chest pain starting 6 years earlier when he was admitted to another hospital with chest discomfort and transient anterior ST elevation on his electrocardiogram (ECG). During coronary angiography, he developed focal spontaneous spasm of the mid left anterior descending (LAD) coronary artery. He was treated with verapamil, but had recurrent symptoms, and repeat angiography showed a 30% eccentric lesion in the mid LAD artery. Isosorbide dinitrate was substituted for verapamil. He was first evaluated at our institution 2 years prior to his current presentation and had a normal exercise test to stage 7 of the Bruce protocol with a maximum heart rate of 157 beats/min.

Three months prior to his current admission, the patient developed his usual angina. Angiography at another hospital showed no change, and amlodipine and vitamin E (400 IU/day) were added. Another exercise test to the same workload was normal. Since that time, he had experienced chest discomfort and palpitations that occurred when he suddenly exercised after a long period of rest. His current admission was precipitated by symptoms while riding an exercise bike, associated with 6 mm ST elevation and a 25 beat run of VT documented by an event recorder.

The patient was an otherwise healthy long distance runner (30 miles/week) who did not smoke, had no history of hypertension, dyslipidemia, family history of premature coronary artery disease, or history of illicit drug use. He had a history of radiation therapy to the thymus gland as a child (75 Roentgens). His physical examination, ECG, and cardiac-specific enzyme levels remained normal during his admission.

He had an exercise test which was modified at his request. He lay down for 1 h prior to the test and then immediately started running on the treadmill. Within 2 min he developed

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Received: June 13, 1999

Accepted with revision: September 23, 1999

FIG. 1 (A) Spontaneous coronary vasospasm at two sites in the left anterior descending artery (arrows), associated with angina and ST elevation on the electrocardiogram. (B) Resolution of spasm with intracoronary nitroglycerin.

his usual anginal symptoms and had > 2 mm ST elevation in leads V₄–V₅ associated with nonsustained monomorphic VT.

Cardiac Catheterization

At cardiac catheterization, the patient spontaneously developed angina and had spasm at two discrete sites within the LAD coronary artery (proximal 60%, mid 95%) (Fig. 1). Following the administration of intracoronary (200 µg), sublingual (0.4 mg), and intravenous (25 µg/min) nitroglycerin, there was no residual stenosis at the proximal site and a 30% stenosis

at the more distal site of spasm which had been noted previously (Fig. 1).

Intravascular Ultrasound

Intravascular ultrasound (2.9F 30 MHz Microview, Cardiovascular Imaging Systems, Sunnyvale, Calif.) of the LAD showed a mild eccentric plaque at the proximal site of spasm, an eccentric calcified plaque at the distal site of spasm, mild concentric intimal thickening between the sites of spasm, and no intimal thickening in the proximal or distal artery (Fig. 2).

FIG. 2 Intravascular ultrasound of left anterior descending artery after nitroglycerin. Scale 1.0 mm/division. (A) Proximal reference segment of the left anterior descending artery (LAD) showing no intimal thickening. (B, D) Proximal and distal vasospastic sites showing absent compensatory enlargement compared with reference segments and eccentric plaque. (C) Reference segment between sites of spasm. (E) Distal reference segment showing no intimal thickening.

FIG. 3 Reference segment between spasm sites showing total vessel area bound by the external elastic lamina (outer circle) and lumen area (inner circle).

Three diastolic frames from the intravascular ultrasound study of these five sites were digitized from super VHS tape. Computerized planimetry (TapeMeasure, INDEC Systems, Mountain View, Calif.) was used to measure the external elastic membrane (EEM) cross-sectional area (CSA) and lumen CSA for each image, and averages were reported for each site (Fig. 3). There was excellent intraobserver variability for the measurement of lumen and EEM CSA from eight segments 1 week apart ($r = 0.99$).

The lumen CSA and area percent stenosis (plaque area/EEM CSA) at the sites of spasm were not critically reduced (proximal site: lumen CSA = 10.42 mm^2 , 16% stenosis; distal site: lumen CSA = 11.70 mm^2 , 23% stenosis). The total artery size (area bound by the EEM) was reduced at the two sites of spasm compared with the reference segments (Fig. 4).

A 3.5 mm Palmaz-Schatz stent (Johnson & Johnson Interventional Systems, Warren, N.Y.) was deployed at each spasm site. The patient's drug regimen was changed to ticlopidine 250 mg b.i.d. for 4 weeks, nifedipine XL 60 mg q.d., diltiazem 30 mg t.i.d., isosorbide dinitrate 20 mg t.i.d., vitamin E 400 IU q.d., and aspirin. On the following day he had a normal exercise test (modified in a similar manner) and completed 10 min

without symptoms, ECG changes, or VT. At 1 year of follow-up, he has had no recurrence of angina, and exercise testing through Stage 8 of the Bruce protocol has remained normal.

Discussion

Severe coronary vasospasm without significant atherosclerosis is a relatively infrequent cause of angina. Coronary vasospasm can be spontaneous or provoked by ergonovine, methergine, or acetylcholine.^{2,4-10} Coronary vasospasm is usually treated with calcium-channel blockers and/or nitrates, and most patients experience an improvement in symptoms.⁵ Patients with coronary vasospasm associated with ventricular arrhythmias, as in our case, have a higher risk of sudden death.¹¹

The mechanisms responsible for coronary vasospasm remain uncertain. Cigarette smoking and the withdrawal of vasodilator medications are strongly associated with coronary vasospasm.^{2,9,12,13} Radiation therapy has been implicated as a cause of premature coronary artery disease.^{14,15} However, in contrast to the findings here, it is usually noted with higher dose mediastinal radiation and characteristically involves the ostia or most proximal portions of the main coronary arteries. A deficiency in the basal bioavailability of nitric oxide at sites of coronary vasospasm may be partly responsible for this condition,⁷ although some studies have not supported this hypothesis.⁶ Oxidative stress may be higher at sites of coronary vasospasm, and this can reduce the availability of nitric oxide at these sites. In support of this theory, one study has suggested that vitamin E supplements may help to reduce symptoms in patients with vasospasm.¹⁶

Although coronary vasospasm can be associated with significant coronary stenoses, little or no disease is found frequently with angiography. Previous studies with intravascular ultrasound have shown concentric thickening of the intima leading edge and sonolucent (medial) layers of the artery at vasospastic compared with control sites.^{3,4} This patient had a conspicuous pattern of mild eccentric plaque and a reduced total artery area (EEM) present only at the sites of spasm. The

FIG. 4 Total artery area (EEM) and lumen area measured by computer planimetry at the five sites from Figure 2. The vasospastic sites had a reduced total artery area compared with reference sites consistent with a lack of compensatory enlargement.

smaller total artery area at the sites of spasm suggests a lack of compensatory enlargement or maladaptive shrinkage of the vessel.

The mechanisms of compensatory enlargement of coronary arteries in the setting of atherosclerosis are not well understood. Vascular remodeling is regulated by promoters and inhibitors of cellular migration, growth, and the activity of enzymes involved in the degradation and synthesis of extracellular matrix.¹⁷ Many of these factors have vasoactive properties^{17,18} and provide a plausible mechanism for a link between changes in vasomotor tone and vascular remodeling.

Angioplasty for spasm is associated with a high rate of restenosis.^{19,20} There are few reports of stenting for spasm with varying success for up to 3 to 6 months after the procedure.^{21–24} Our patient continued to be free of symptoms more than 1 year after stenting for spasm refractory to pharmacologic therapy. As his medical regimen was also changed at the time of stenting, it is possible that this contributed to the good clinical outcome.

Conclusion

Severe coronary vasospasm causing ventricular arrhythmias but with minor angiographic disease occurred at sites of eccentric rather than concentric plaque, and with a reduced total artery area compared with reference segments. Lack of compensatory enlargement may be a pathologic characteristic of coronary spasm in vessels with no or minimal angiographic disease. In this case, coronary stenting led to excellent long-term control.

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