Inappropriate Microvascular Constriction Produced Transient ST-Segment Elevation in Patients With Syndrome X

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Objectives. The aim of this project was to study the responsible site(s) and underlying cardiac disease(s) of patients with transient ST-segment elevation and normal coronary angiograms.

Background. Transient ST-segment elevation has been demonstrated in patients with variant angina or unstable angina. In those patients, epicardial coronary arteries, not microvessels, are always the responsible site for the transient ST-segment elevation.

Methods. This study consisted of three cases with a transient ST-segment elevation and normal coronary angiograms. Treadmill testings were performed before coronary angiography in all cases. Coronary angiography was undertaken during the control state and during ST-segment elevation and, when possible, a Doppler guide wire was positioned in the left anterior descending artery (LAD). Coronary responses to vasodilators were observed. Finally, cardiac biopsy was performed and pathologic observation was conducted.

Results. All three cases had significant ST-segment depression during treadmill testing in II, III, aVF and V_{1-6} leads; however, no angiographic coronary stenosis was demonstrated and vasospasm was not provoked. A transient ST-segment elevation associated with chest pain was observed in V_{1-6} leads, but normal coronary angiograms during ST-segment elevation were observed in every case. Coronary blood flow (CBF) velocity profile remained normal during ST-segment elevation. In one case, vasodilator responses to the LAD during ST-segment elevation were also measured. A 0.5 mg intracoronary injection of nitroglycerin increased CBF velocity (220%), but ST-segment elevation was not normalized and chest pain persisted. A 10 mg intracoronary injection of papaverine (PVN) further increased CBF velocity up to 340%, and this normalized ST-segment elevation and relieved chest pain quickly. Either endothelium-dependent coronary flow reserve (CFR) measured with a 100 μg intracoronary infusion of acetylcholine, or flow-dependent CFR by a 10 mg intracoronary injection of PVN was reduced in one of two cases measured. Pathologic findings supported syndrome X as the underlying cardiac disease in all cases.

Conclusions. These findings suggested a new clinical implication involving transient ST-segment elevation mimicking variant angina and normal coronary angiograms in patients with syndrome X. The major responsible site for this phenomenon was suggested to be coronary arterioles of less than 200 μm in diameter.

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Angiographic coronary stenosis used to be demonstrated during every attack of transient ST-segment elevation. The responsible mechanism was thought to be epicardial coronary vasospasm (1–3) or unstable angina (3). On the other hand, syndrome X is diagnosed by chest pain, exercise-induced ST-segment depression and the absence of either significant epicardial coronary stenosis or vasospasm (4–7). Some patients with syndrome X have some pathologic changes around microvessels themselves and sometimes the myocardium. However, there has been no report so far of a spontaneous attack manifesting ST-segment elevation mimicking variant angina in patients with syndrome X.

We observed transient ST-segment elevation mimicking variant angina and normal coronary angiograms in three cases with chest pain. Thus, the aim of this study was 1) to study the responsible site(s) for ST-segment elevation, 2) to investigate the underlying cardiac disease(s) and 3) to examine vasodilator responses to acetylcholine (Ach) and papaverine (PVN).

Methods

We selected three consecutive cases (2 women and 1 man) from October 1, 1996 to December 22, 1997, who had a transient ST-segment elevation during cardiac catheterization and normal coronary angiograms. Before the coronary angiography, Holter 24-h monitoring (Marquette Electronics, Inc., Wisconsin) treadmill testing with modified Bruce protocol or modified Balke protocol using a Case 15 (Marquette Electronics, Inc., Wisconsin) echocardiographic examination with a 2.5 or 3.75 MHz transducer (Toshiba SSH-160A, Kawasaki, Japan) were performed. Control coronary angiography was performed initially and provocation of coronary vasospasm was done by an intracoronary infusion of acetylcholine (Ach).
(50 μg to the right coronary artery and 100 μg to the left coronary artery) if normal coronary angiograms had been obtained. Five French of Judkins type catheters for both coronary arteries were used to conduct the angiography using a biplane cineangiography (Philips Polydiagnost, The Netherlands). During a spontaneous attack of ST-segment elevation, coronary angiography of the left coronary artery was done as quickly as possible because the elevated ST-segments in all cases had been observed in V_4–6 leads. Then, coronary blood flow (CBF) velocity was measured with a 0.014" of Doppler guide wire (FloWire, Cardiometrics, Inc., California) at segment 7 of the left anterior descending artery (LAD). Coronary responses to an intracoronary injection of vasodilators (0.5 mg of nitroglycerin [NTG] and 10 mg of papaverine [PVN]) were observed during ST-segment elevation, if possible. After the transient ST-segment elevation had disappeared completely, control CBF velocity at segment 7 of the LAD was measured. Then, Ach (100 μg) was again infused into the left coronary artery to measure endothelium-dependent coronary flow reserve (CFR). After this procedure, PVN (10 mg) was injected into the left coronary artery to determine flow-dependent CFR. Finally, cardiac biopsy from the right ventricle was undertaken to determine pathologically the underlying cardiac disease.

**Results**

**Patients’ characteristics** (Table 1). Three cases with normal sinus rhythm showed a spontaneous attack of ST-segment elevation. All of the cases had a history of anginalike chest pain at rest, but did not have a clear history of chest pain during exercise. In all three cases, chest pain used to last for a long time, over 30 min, and a sublingual NTG administration sometimes failed to relieve chest pain, which suggested a psychologic influence upon the chest pains. All the cases had periodic recurrences of chest pain in a 1-year period without any provocation factors. Case 2 had hypertension and Hashimoto disease with normal thyroid function, but the other two cases had no other diseases. No one had either a smoking habit or relatives with similar symptoms.

Before admission, cases 1 and 2 had been administered nitrate, calcium antagonist, beta-adrenergic blocking agents and antidepressant, but case 3 had had no medication.

### Table 1. Summary of Patients’ Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
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<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>75</td>
<td>73</td>
<td>58</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td><strong>Chest pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>During exercise</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>(−)</td>
<td>(+)</td>
<td>(−)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td><strong>Treadmill</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak HR (/min)</td>
<td>121</td>
<td>133</td>
<td>140</td>
</tr>
<tr>
<td>% of maximum HR* (%)</td>
<td>83</td>
<td>91</td>
<td>87</td>
</tr>
<tr>
<td><strong>ST-segment depression</strong></td>
<td>II, III, aVF, V_4–6</td>
<td>II, III, aVF, V_4–6</td>
<td>II, III, aVF, V_4–6</td>
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</tbody>
</table>

*HR = heart rate.

**Treadmill testing. Holter 24-h monitoring and echocardiography.** Holter 24-h monitoring demonstrated some episodes of significant ST-segment depression in all cases during daily activities. However, their chest symptoms sometimes did not coincide with episodes of ST-segment depression, and episodes of significant ST-segment depression without any symptoms similar to silent ischemia were seen. No episode of ST-segment elevation was observed before coronary angiography.

Treadmill testing was performed with modified Bruce protocol in cases 2 and 3, and with modified Balke protocol in case 1. Treadmill testing was ended by satisfying the criteria of diagnostic ST-segment depression (Table 1). The magnitude of maximum ST-segment depression was 2.0 mm in V_5 and V_6 leads in case 1, 2.0 mm in V_5 lead in case 2 and 1.5 mm in III lead in case 3. Anginalike chest pain was not provoked in any of the cases by treadmill testing, even during peak exercise.

Echocardiographic examination demonstrated either no abnormal wall motion or normal-looking echocardiograms at rest. Thus, neither underlying myocardial disease, including cardiac hypertrophy, nor valvular disease, except for angina or anginalike disorders, was found in any of the cases. Systolic and diastolic function were not impaired either. Ejection fraction of the left ventricle was 75% in case 1, 60% in case 2 and 58% in case 3.

**Transient ST-segment elevation** (Figs. 1, 2 and 3). In all cases, a transient ST-segment elevation was demonstrated during cardiac catheterization (Figs. 1B, 2B and 3C). In case 1, the ST-segment elevated from V_1 to V_5 leads, and a slight reciprocal ST-segment depression was found in II, III and aVF leads (Fig. 1B). Coronary angiography of the left coronary artery was performed, and CBF velocity in the LAD was measured during the ST-segment elevation. In this case, coronary responses to intracoronary NTG and PVN were measured. Severe chest pain was complained of during ST-segment elevation in this case.
In case 2, the ST-segment elevation was recognized from V1 to V6 leads (Fig. 2B). Increased magnitude of positive T wave was recognized in II, III and aVF leads. Coronary angiography of the left coronary artery was performed and CBF velocity in the LAD was measured during the ST-segment elevation, but coronary responses to vasodilators during the ST-segment elevation could not be investigated because of spontaneous regression of the ST-segment elevation. In this case as in case 1, the patient also complained of severe chest pain during the ST-segment elevation.

In case 3, the ST-segment elevation was found from V1 to V6 leads (Fig. 3C). In addition, an episode of ST-segment depression was also found from V1 to V6 leads and in II, III and aVF leads (Fig. 3B). Because of spontaneous regression of this attack within a few minutes, only coronary angiography could be performed to confirm whether a newly developed coronary stenosis due to coronary spasm had occurred during the ST-segment elevation. There was no complaint of chest pain during ST-segment change in this case.

In all the cases, normal angiograms of the left coronary artery were demonstrated during the ST-segment elevation (Figs. 2D, 3E and 4B). Coronary blood flow velocity profiles during the ST-segment elevation also remained normal in cases 1 and 2.

Changes in each state of average peak velocity (APV) were also demonstrated, as shown in Table 2. Average peak velocity during the ST-segment elevation was 10 cm/s in case 1 (Fig. 5A). An intracoronary NTG infusion (0.5 mg) decreased the severity of chest pain and the magnitude of the ST-segment elevation (Fig. 1C), but did not cure it completely. Average peak velocity was increased to 22 cm/s by NTG infusion (Fig. 5B). After NTG infusion, a 10-mg infusion of intracoronary PVN followed. Papaverine further increased the APV up to 34 cm/s (Fig. 5C) and normalized ST-segment very quickly (Fig. 1D). Chest pain also disappeared quickly after PVN infusion. No significant epicardial coronary stenosis was demonstrated after either NTG infusion (Fig. 4C) or PVN infusion (Fig. 4D), as was the case with the control (Fig. 4A), or during the ST-segment elevation (Fig. 4B).

The co-existence of coronary vasospasm and measurement of CFR (Table 2). A 100-μg infusion of intracoronary Ach to the left coronary artery did not provoke coronary vasospasm in any of the cases, as was also demonstrated for a 50-μg intracoronary infusion of Ach to the right coronary artery. In cases 2 and 3, coronary responses to vasodilators were measured during control state. An intracoronary infusion of Ach (100 μg) increased APV in cases 2 and 3. An intracoronary PVN infusion (10 mg) also increased APV of the LAD in cases 2 and 3. Thus, endothelium-dependent CFR was calculated as 1.2 in case 2 and 2.8 in case 3, while flow-dependent CFR was calculated as 1.5 in case 2 and 2.3 in case 3.
Cardiac biopsy from the right ventricle. In case 1, perivascular fibrosis and fibromuscular dysplasia of the media were clearly demonstrated (Fig. 6A), as were focal interstitial fibrosis and perinuclear halo of the myocardium (Fig. 6B). Perivascular fibrosis was found in the other cases, while fibromuscular dysplasia of the media was found only in case 2. Mild focal interstitial fibrosis was also observed in case 2, while myocardial hypertrophy was documented only in case 3.

Discussion

ST-segment elevation and syndrome X. Transient ST-segment elevation has been demonstrated only in patients with variant angina (1–3) or unstable angina (3). In those patients, epicardial coronary arteries, not microvessels, are always the responsible site for the transient ST-segment elevation. On the other hand, syndrome X is a particular cardiac disorder known as microvascular angina existing in combination with neither atherosclerotic epicardial coronary stenosis nor coronary vasospasm (4–7). This is usually diagnosed by findings of anginalike chest pain, exercise-induced significant ST-segment depression and normal coronary angiograms (4–7).

We reported here three cases with spontaneous transient ST-segment elevation. All of the cases satisfied the above criteria as syndrome X. In addition, they also had pathologic findings in the perivascular region or the myocardium itself, which supported the diagnosis of syndrome X.

Previously, ergonovine- or Ach-induced, but not spontaneous, ST-segment elevation with normal coronary angiograms was reported (8,9), and this finding may be consistent with provoked microvascular constriction. Very recently, Yamagishi et al. (10) and Mohri et al. (11) reported a single case with a transient spontaneous ST-segment elevation with normal coronary angiograms. However, neither of the above cases could provide concrete evidence of syndrome X. The former showed no exercise-induced ST-segment changes, and the latter made no report of these changes. Thus, to the best of our knowledge, there has been no clear report demonstrating spontaneous transient ST-segment elevation mimicking variant angina or unstable angina in patients with syndrome X. Furthermore, this would also be the first report providing evidence that small vessels are one of the important responsible sites for angina with ST-segment elevation.

Different vasodilator responses to NTG or PVN and ST-segment elevation in case 1. In case 1, NTG did not normalize the ST-segment elevation or relieve chest pain (Fig. 1C), while PVN did both, relieving chest pain completely (Fig. 1D). It is
known that NTG dilates only vessels greater than 200 μm in diameter (12,13), while PVN dilates both those of greater and lesser diameter (7,14,15). Therefore, these findings suggested that the major responsible site for this ST-segment elevation attack may be vessels of less than 200 μm in diameter, although the vessels greater than 200 μm may play a partial role in this phenomenon.

Figure 4. Coronary angiograms of the left coronary artery in case 1. (A) A control coronary angiogram; (B) a coronary angiogram during the ST-segment elevation; (C) a coronary angiogram after a 0.5-mg intracoronary NTG infusion; (D) a coronary angiogram after a 10-mg intracoronary PVN infusion.

Figure 3. Serial electrocardiography changes and coronary angiograms in case 3. (A) Control electrocardiography at rest. This electrocardiographic was obtained at the end of cardiac catheterization because ST-segment changes (B and C) were observed just after cardiac catheterization was begun. (B) A transient ST-segment depression; (C) the transient ST-segment elevation; (D) a control coronary angiogram; (E) a coronary angiogram during the ST-segment elevation.
CBF velocity profile and the possible cause of transient ST-segment elevation. In cases 1 and 2, CBF velocity profile remained normal during the ST-segment elevation. In case 2, APV during the ST-segment elevation was similar to that during control. These findings may lead to the hypothesis that a heterogeneous distribution of microcirculatory vasoconstriction may occur during ST-segment elevation, but areas with this phenomenon may be significantly large.

The cause of inappropriate vasoconstriction was not clearly understood. Different responses to vasodilators (NTG and PVN) in case 1 indicated that the responsible site was arterioles of less than 200 μm in diameter, as described before. It is surprising that inappropriate vasoconstriction in our cases

**Table 2.** Changes in Average Peak Velocity, Endothelium-Dependent and Flow-Dependent Coronary Flow Reserve of the Left Anterior Descending Artery at Each State

<table>
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<tr>
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<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
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<tbody>
<tr>
<td>Control (cm/s)</td>
<td>(-)</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>During ST-segment elevation (cm/s)</td>
<td>10</td>
<td>29</td>
<td>(-)</td>
</tr>
<tr>
<td>Acetylcholine (cm/s)</td>
<td>(-)</td>
<td>33</td>
<td>85</td>
</tr>
<tr>
<td>Papaverine (cm/s)</td>
<td>(-)</td>
<td>42</td>
<td>68</td>
</tr>
<tr>
<td>EDCFR</td>
<td>(-)</td>
<td>1.2</td>
<td>2.8</td>
</tr>
<tr>
<td>FDCFR</td>
<td>(-)</td>
<td>1.5</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Average peak velocity was measured with a Doppler guide wire. Acetylcholine = a 100 μg intracoronary infusion of acetylcholine. Papaverine = a 10 mg intracoronary infusion of papaverine. EDCFR = endothelium-dependent coronary flow reserve; FDCFR = flow-dependent coronary flow reserve.

**Figure 5.** Representative CBF profile of the LAD with a Doppler guide wire in case 1. (A) During the ST-segment elevation; (B) after an intracoronary infusion of 0.5 mg of NTG; (C) after an intracoronary infusion of 10 mg of PVN.
exceeded autoregulatory function spontaneously and led to expanded cardiac ischemia. It is known that interaction of several vasoconstrictive substances (6,16–20) and neural stimuli (19) and/or reduced function of vasodilators (21–27) results in vasoconstriction of microvessels. The net effects of some of these factors may exceed autoregulatory function, resulting in elevated ST-segment. Marcus et al. (15) reported that almost 50% of coronary vascular resistance was made by the vessels of less than 100 μm in diameter. During the ST-segment elevation in our cases, therefore, it was not surprising that vessels of less than 100 μm in diameter constituted the responsible site for this phenomenon. Response to PVN during the ST-segment elevation in case 1 may be consistent with this view. The total area with severely reduced blood flow caused by inappropriate vasoconstriction may occupy a significant area producing severe ischemia, but vasoconstriction may occur heterogeneously, as we described, because the normal coronary blood flow profile remained at the proximal site.

Endothelial dysfunction and microvascular dysfunction. Previous reports (28–31) described reduced endothelium-dependent vasodilation assessed by intracoronary infusion of Ach in patients with syndrome X. In our cases, impaired endothelium-dependent vasodilation was demonstrated in case 2 but not in case 3. Since we had only a small number of cases, we could not conclude whether impaired endothelium-dependent vasodilation co-existed in patients with syndrome X combined with transient ST-segment elevation.

Egashira et al. (30) reported that PVN induced lactate production and chest pain, with electrocardiographic change suggesting cardiac ischemia. They presumed that there may be microvascular dysfunction other than endothelial dysfunction in patients with syndrome X because PVN dilated coronary-resistant vessels independently of endothelial function. They also presumed that PVN produced cardiac ischemia due to the coronary steal phenomenon, because different spatial vasodilatory responses to PVN between diseased vessels and normal vessels produced different coronary resistance. From this view, Maseri et al. (6) and others (31,32) have proposed the mechanism responsible for ischemic change of syndrome X as being inappropriate vasoconstriction at the “prearteriolar” level, concomitant with the steal phenomenon due to compensatory “arteriolar” vasodilation. However, our findings, especially the different responses to NTG and PVN in case 1, could not be explained by their hypothesis. We presumed, as described before, that multiple inappropriate vasoconstriction of microvessels of less than 200 μm in diameter in certain areas, not associated with compensatory arteriole dilation, may have been the possible cause for the transient ST-segment elevation.

Maseri et al. (6) suggested adenosine as a possible mediator of anginal pain. Emdin et al. (5) also reported that aminophyllin, an adenosine receptor blocker, improved exercise capacity and exercise-induced chest pain. These data supported the transmural maldistribution hypothesis as a genesis of ischemic change in patients with syndrome X. In this context, our data may also be inconsistent with their hypothesis.

Clinical outcome and implication. Chest pain in cases 1 and 2 could not be controlled completely by several drugs such as nitrate, nicorandil, Ca-antagonist, theophyllin, beta-blocker and antidepressant. The patients had mainly complained of chest pains at rest. Surprisingly, their chest pain disappeared after the administration of the same drugs for relief of chest pain at a period several months later. Maseri et al. (6) described prolonged chest pain and Kaski et al. (4) and Cannon et al. (31) reported the occurrence of chest pain at rest or during mild exercise. As with their patients, ours sometimes had prolonged chest pain at rest which was not relieved by medical treatment. Thus, clinical manifestations may vary, ranging from chest pain without ST-segment change to chest pain with ST-segment elevation in the same patient due to the extent of the area with inappropriate circulation.

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References


