Alternans of the ST Segment in Prinzmetal’s Angina

MORRIS J. KLEINFELD, M.D., AND JOHN J. ROZANSKI, M.D.

SUMMARY Alternans of the elevated ST segment (STEA) was found in 8 of 21 patients (38%) with Prinzmetal’s variant angina. In addition to STEA, all eight patients had varying cardiac arrhythmias: multiple premature ventricular depolarizations in eight, ventricular tachycardia in five, and ventricular fibrillation in three. There was no consistent temporal relationship between the occurrence of STEA and the cardiac arrhythmias. Alternans occurred during periods when no arrhythmias were present. All eight patients underwent coronary angiography. Spontaneous coronary artery spasm was documented angiographically in three patients including two who had minimal or no coronary atherosclerotic disease. Six patients had severe, fixed, occlusive coronary artery disease. Possible mechanisms for STEA include: 1) failure of regions of myocardium to depolarize on alternate beats due to variation in conductance and refractoriness between ischemic and nonischemic zones of myocardium, and 2) electrical alternans of the transmembrane action potential during phases 2 and 3 (repolarization) caused by changes in the rate and extent of electrolyte transfer across cell membranes during ischemia.

It is postulated that STEA is an electrocardiographic sign in the surface ECG of a dysequilibrium of refractory periods during ischemia and reflects an unstable electrical state of the myocardium.

Patient Selection and Methods

The criteria used for the selection of patients with Prinzmetal’s angina were 1) the presence of multiple episodes of reversible ST-segment elevation greater than 2 mm in more than one lead of a standard 12 lead electrocardiogram; 2) the absence of evolutionary changes of myocardial infarction on serial electrocardiograms; and 3) the absence of elevation of serum creatine phosphokinase (CPK), lactic dehydrogenase (LDH), or glutamic oxaloacetic transaminase (SGOT). The diagnosis of alternans of the ST segment or ST-T complex was based on the occurrence of consecutive alternation in the configuration of the ST segment or ST-T complex in the presence of a regular cardiac rate. This did not include the common alternation of the ventricular complex encountered with coupled sinus beats and extrasystoles. In addition, a stable baseline was an essential requirement. Conditions known to be associated with electrical alternans, such as pericardial effusion,4 cardiac tamponade,6 certain drug intoxications,6 serum electrolyte abnormalities,10,11 and the long QT syndromes14,15 were ruled out. All patients were monitored continuously in a coronary care unit and episodes of ST segment elevation were recorded. All eight patients with STEA underwent coronary arteriography and two underwent exercise stress testing. Provocative induction of coronary artery spasm by parasympathomimetic agents or ergot derivatives was not done.
Selected Case Histories

The relevant data on all patients studied are presented in table 1.

Patient 1

This 40-year-old man experienced attacks of angina at rest for six months prior to admission but was able to maintain his normal physical activity. His blood pressure (BP) was 130/90 mm Hg and pulse (P) was 90/min. Physical examination, electrocardiogram, chest X-ray, and cardiac enzymes were normal. Repeated episodes of ST-segment elevation occurred with chest pain in leads V₁ and V₃ and were associated with VPDs. During his hospitalization, he had 12 episodes of ventricular tachycardia and/or fibrillation which required defibrillation. Alternans of the elevated ST segment was observed in several instances to precede the ventricular tachycardia and at other times occurred as an isolated finding (fig. 1). During cardiac catheterization, three episodes of ST-segment elevation occurred spontaneously without chest pain. Two of these episodes progressed to ventricular tachycardia and ventricular fibrillation. In both instances STEA preceded the occurrence of ventricular tachycardia. Spasm producing an 80% occlusion of the proximal left anterior descending coronary artery (LAD) occurred during the ST-segment elevation. The spasm resolved after nitroglycerin administration and all coronary vessels appeared normal. Ten milligrams of isosorbide dinitrate given sublingually every four hours prevented subsequent attacks of Prinzmetal's angina. After discharge, the patient discontinued the use of this medication and he remained free of angina during a six month follow-up.

Patient 3

This 54-year-old man experienced nocturnal angina for 12 days prior to admission. Pulse was 72/min and BP was 100/80 mm Hg. Physical examination, chest X-ray, ECG, and cardiac enzymes were normal. He experienced three to four attacks of Prinzmetal's angina nightly with ST-segment elevation in leads I, aVL, and V₅₋₆ associated with frequent multifocal VPDs, brief runs of ventricular tachycardia, and supraventricular tachycardia. During an episode of supraventricular tachycardia (fig. 2), STEA was observed. Coronary angiography revealed a fixed 90% stenosis of a diagonal branch of the left coronary. The right coronary revealed minimal proximal narrowing. The left coronary artery was bypassed with a saphenous vein graft. Postoperatively, pathological Q waves appeared in leads I, aVL, and V₅₋₆. The patient was free of chest pain during six months of follow-up.

Patient 7

This 60-year-old man experienced three episodes of unconsciousness during the month prior to admission. His BP was 172/95 mm Hg and P was 70/min. Physical examination, chest X-ray and cardiac enzymes were normal. The ECG showed normal sinus rhythm and inverted T-waves in leads I, aVL, and V₁₋₂. Daily episodes of ST-segment elevation occurred in leads V₁₋₃ accompanied by chest pain and VPDs with frequent ventricular bigeminy. During several episodes of Prinzmetal's angina, STEA occurred (fig. 3) and was followed but not preceded by multifocal VPDs, ventricular tachycardia, and ventricular fibrillation. During one of these attacks, 2:1 atrioventricular block occurred unassociated with electrical alternans. Coronary angiography revealed fixed 90% occlusions of both the right coronary artery and left circumflex vessel distal to the first major branch. The LAD had a 60% fixed proximal obstruction. Transient complete heart block occurred during the injection of the right coronary artery. Bypass surgery was attempted but was unsuccessful and the patient died.

Results

A summary of the electrocardiographic and coronary angiographic data is given in table 1. With the exception of the episodes of transient ST-segment elevation, six of the eight patients had normal electrocardiograms, one had T-wave inversions in leads I, aVL, V₁₋₃, and one had minimal

<table>
<thead>
<tr>
<th>Pt/Age/Sex</th>
<th>Basic</th>
<th>ECG Features</th>
<th>Arrhythmias</th>
<th>Coronary Angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/40/M</td>
<td>N</td>
<td>V₁₋₃</td>
<td>Multifocal VPDs, VT, VF</td>
<td>Normal coronaries; spasm of LAD</td>
</tr>
<tr>
<td>2/53/M</td>
<td>N</td>
<td>II, III, aVF</td>
<td>Multiple VPDs, VB</td>
<td>80% stenosis of RCA</td>
</tr>
<tr>
<td>3/54/M</td>
<td>N</td>
<td>V₄₋₆, I, aVL</td>
<td>Multiple VPDs, VB</td>
<td>90% stenosis of diagonal branch of LCA</td>
</tr>
<tr>
<td>4/62/M</td>
<td>N</td>
<td>II, III, aVF</td>
<td>Multiple VPDs, VB, VT</td>
<td>Diffuse obstructive three vessel disease; spasm of RCA</td>
</tr>
<tr>
<td>5/57/M</td>
<td>N</td>
<td>V₁₋₃</td>
<td>Multiple VPDs</td>
<td>90% stenosis of LAD; 90% stenosis of circumflex branch of LCA</td>
</tr>
<tr>
<td>6/42/F</td>
<td>N</td>
<td>II, III, aVF</td>
<td>VPDs</td>
<td>40% stenosis of RCA; spasm of RCA</td>
</tr>
<tr>
<td>7/60/M</td>
<td>T inverted in V₁₋₃</td>
<td>I, aVL, V₁₋₃</td>
<td>Multiple VPCs, VB, VT, VF, 2:1 AV block</td>
<td>40% stenosis of RCA; 90% stenosis of circumflex; 60% stenosis of LAD</td>
</tr>
<tr>
<td>8/64/M</td>
<td>ST↑ I, aVL, V₅₋₆</td>
<td>I, aVL</td>
<td>Multifocal VPDs</td>
<td>70% stenosis of RCA; 90% stenosis of LAD</td>
</tr>
</tbody>
</table>

Abbreviations: ST↑, ↓ = ST = segment elevation or depression; VPD = ventricular premature depolarization; VB = ventricular bigeminy; VT = ventricular tachycardia; RCA = right coronary artery; LCA = left coronary artery; VF = ventricular fibrillation; LAD = left anterior descending coronary artery; SVT = supraventricular tachycardia.
ST-segment depression in leads I, aVL, V₆. The location of the elevation of ST segment during angina involved the inferior aspect of the heart in three patients and the anterior or anterolateral location in five patients. All patients had ventricular arrhythmias; namely, multiple VPDs in eight patients, ventricular tachycardia in five, and ventricular fibrillation in three. Alternans of the elevated ST segment frequently preceded these arrhythmias, but STEA was also noted as an isolated finding. Sublingual nitrates appeared to be effective in terminating episodes of both STEA and ST elevation. One patient with normal coronary arteries angiographically (patient 1) had a negative exercise stress test while another with minimal coronary artery disease had ST segment elevation during exercise (patient 6). Patient 8 who had Holter monitoring showed both ST-segment elevation and ST-segment depression at different times, both with and without chest pain. Coronary angiography demonstrated severe fixed occlusive disease involving one or more coronary vessels in six patients, one of whom demonstrated coronary artery spasm. Two patients with little or no coronary atherosclerotic disease both demonstrated spontaneous coronary artery spasm. The angiographic findings correlated in seven of eight patients with the location of ST-segment elevation. The exception was patient 8.

Discussion

The finding of STEA in eight of 21 patients during Prinzmetal's variant angina raises the question of whether this form of alternans is specific for Prinzmetal's angina as opposed to classical angina. The studies reported to date do not specifically provide an answer to this question. A review of the literature of Prinzmetal's angina showed a number of illustrations of STEA which have not been commented upon by the different authors. This suggests a lack of awareness of its true occurrence. The use of long-term Holter monitoring can be useful in the detection of STEA and therefore should be more frequently employed. One must, however, recognize the methodologic limitations when interpreting ST changes during Holter monitoring. It is noteworthy that in the present study STEA occurred in patients with and without chest pain. Moreover, this phenomenon was observed in patients with angiographically normal coronary vessels in whom coronary artery spasm was documented, as well as in those having fixed occlusive disease of the coronary arteries.

The occurrence of STEA in Prinzmetal's angina may have an experimental counterpart as judged by the studies of Hellerstein and Liebow and those of Prinzmetal and associates using intermittent occlusion of a major coronary vessel. Hellerstein and Liebow stressed the incidence of STEA in their experimental study. The frequency of STEA increased with the frequency of repeated ligation and release of a major coronary vessel. In the studies by Prinzmetal and associates, reversible ST-segment elevation was produced in dogs by temporary occlusion and release of a large coronary artery. In one of their studies STEA is noted in a number of illustrations, namely, 1A and B, 3A, 4A and 8B, although no specific reference to STEA was made. It is important to note that Prinzmetal and associates have claimed that intermittent occlusion of a large coronary artery in the dog resulting in increased tonus of the vessel can reproduce all the major clinical and electro-
cardiographic features of the variant form of angina in humans.\textsuperscript{18} One may extend these correlations to include STEA as well as ST elevation.

The exact mechanism for STEA in Prinzmetal's angina is still a matter of conjecture. Two mechanisms for STEA are suggested: 1) failure of an ischemic area to depolarize on alternate beats, that is, an increase in refractoriness and decrease in conduction between the ischemic and non-ischemic zones, whereby cells of the ischemic zone remain unresponsive to activation on alternate beats; and 2) alternation of cellular transmembrane action potentials during phases 2 and 3 (repolarization) caused by change in the rate and extent of transfer of electrolytes across myocardial cell membranes.\textsuperscript{20} The experimental demonstration of electrical alternans in single cells of both intact frog hearts and isolated perfused rabbit hearts under conditions of hypoxia lends support to this hypothesis.\textsuperscript{3, 20}

The mechanism for the frequent ventricular arrhythmias may involve temporal dispersion of refractoriness during ischemia which causes fractionation of the wavefront of depolarization, thus predisposing to re-entrant arrhythmias. This mechanism was originally suggested by Wiggers,\textsuperscript{21} Han,\textsuperscript{3} and others.\textsuperscript{2, 3, 21} One may postulate that STEA is an electrocardiographic sign of this dysequilibrium of refractory periods and reflects an unstable electrical state of the myocardium.

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