The Syndrome of Variant Angina
Culminating in Acute Myocardial Infarction

JOHN E. MADIAS, M.D.

SUMMARY Ten patients 28-54 years old with recurrent attacks of variant angina (chest pain associated with transient ST-segment elevation) culminating in acute myocardial infarction were studied. Systemic blood pressure and heart rate remained unchanged or decreased during chest pain. Diagnosis of myocardial infarction was made on the basis of pathognomonic enzyme changes and T-wave inversions persisting for several weeks (seven patients) or development of Q waves (three patients). Complications were similar to the ones previously observed in conventional myocardial infarction. None of these patients died. Past history was characterized by absence of effort angina. Exercise stress testing after infarction was normal, and coronary arteriography revealed a spectrum of pathology, ranging from normal arteriograms to three-vessel disease. Intraaortic balloon pumping was ineffective in two patients, but subsequent coronary bypass surgery shortly after myocardial infarction was not followed by further attacks of chest pain. Follow-up of these patients revealed a benign course. Alcohol drinking and cigarette smoking appeared to be very prevalent in this group.

VARIANT ANGINA has been associated with a high incidence of myocardial infarction.1-6 Some investigators have suggested that the variant pattern of angina ceases after myocardial infarction,1 2 6 although others have reported persistent episodes of variant angina after myocardial infarction.6 5 Despite a voluminous literature on the subject of variant angina,14 starting with descriptions of cases as early as the 1930s, little evidence directly links episodes of variant angina with actual occurrence of myocardial infarction during the same hospital admission.5 6 and the temporal association of these two entities with the emerging clinical syndrome has not been delineated.

We report 10 patients who suffered recurrent transient episodes of chest pain associated with ST-segment elevation in the ECG, which progressed to acute myocardial infarction. Attacks of variant angina continued in a few patients after myocardial infarction. The clinical, electrocardiographic, and arteriographic characteristics, along with profiles of the risk factors in this syndrome, are presented and discussed.

Materials and Methods

Eight men and two women with a mean age of 41 ± 2.7 years (sem; range 28-54 years) were observed in the coronary care unit (CCU) of Boston City Hospital. The patients experienced acute myocardial infarction in the midst of recurrent episodes of variant angina and had multiple ECGs recorded during hospitalization. Variant angina was defined as a syndrome characterized by recurrent transient angina occurring at rest without provocation, transient ST-segment elevation with return of the ECG to the baseline after subsidence of angina, and completely pain-free intervals of varying duration (from hours to days) interspersed with attacks of angina. Blood pressure and heart rate during chest pain were either unchanged or decreased, compared with values obtained before the onset of angina. Routine procedures included continuous electrocardiographic monitoring and blood sampling for cardiac enzymes two or three times daily for the initial 2 days, once a day thereafter for as long as the patients remained in the CCU, and more often if clinically warranted. Oxygen at 3 l/min via nasal prongs was administered routinely, and diazepam was given for sedation when indicated. No intramuscular injections were administered during hospitalization.17 The precordial of each patient was marked for accurate repositioning of the V lead of the electrocardiograph. Evaluation of the chest pain episodes included recording 12-lead ECG and blood pressure during and after the attacks, and charting information pertaining to blood pressure and heart rate before the attacks, duration of chest pain episodes, and response to drugs. Sublingual nitroglycerin or isosorbide dinitrate were used to abort the attacks of chest pain. Morphine sulfate was used intravenously in patients unresponsive to nitrates. In addition, these patients were treated with oral or chewable isosorbide dinitrate, nitroglycerin ointment applied to the skin, and oral propranolol hydrochloride. Lidocaine and procainamide were used as clinically indicated for arrhythmia suppression. The upper-normal limit of creatine kinase (CK) in our institution is 75 mIU/ml, and myocardial fraction of CK (MB-CK) normally does not exceed 3% of the total CK, using the Helena CK isoenzyme electrophoresis procedure, Helena Laboratories, Beaumont, Texas. Eight patients underwent cardiac catheterization, which included measurements of intracardiac pressures, left ventricular cineangiography in the right and left anterior oblique projections, and coronary cineangiography with multiple visualizations of coronary arteries in various right and left oblique projections before and after administration of nitroglycerin. We did not attempt to induce spasm in these patients during cardiac catheterization. The presence of a recent myocardial infarction, the demonstration of coronary lesions in

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most of these patients (vide infra), the persistence of attacks of variant angina in the early phase of their hospitalization, and the occasional unresponsiveness of pain to nitroglycerin discouraged us from inducing coronary spasm. Intraaortic balloon counterpulsation, as a therapy for persistent chest pain and for stabilization during cardiac catheterization, and coronary bypass surgery were available to the patients when such procedures were deemed necessary. The first two patients were observed in 1973, the third in 1975, and the remaining seven within the past 16 months.

Results

Risk Factors

Four patients had a history of hypertension (table 1), took antihypertensive drugs sporadically, and had high blood pressure, at least during the early phase of hospitalization. All 10 patients had a history of smoking; some smoked more than 40 cigarettes per day. Patient 9 had a past history of myocardial infarction, with persistent pathognomonic Q waves in his inferior ECG leads. Six patients had a family history of myocardial infarction. Close relatives of four of these six suffered a myocardial infarction at an age less than 40 years. One patient had five relatives, and another four, with a history of myocardial infarction, mostly fatal. There was a history of angina on exertion in only one patient. Five patients had a history of angina at rest from 1 week to 7 months before admission. Four (patients 2, 3, 6 and 8) had chest pain episodes mostly at about the same time of the day or night. Five patients did not have a history of angina before their admission to the hospital. Patient 2 had a documented episode of variant angina while hospitalized on a previous admission. Nine patients drank alcohol (table 1); two drank at social occasions, three drank daily, and four were alcoholics. None of these patients had diabetes or lipid abnormalities.

Clinical Presentation

Some patients were seized by chest pain while driving to work in the morning (nos. 1 and 5), at rest (nos. 2, 3, 4, 6 and 10), during sleep (no. 8), or while performing mild activity (nos. 7 and 9). Five patients (1, 2, 5, 6 and 7) had multiple episodes of chest pain in the few hours preceding their admission. The remaining patients suffered recurrent episodes of chest pain during the 2 days before admission. Patient 3 had similar episodes for 1 week before admission. The duration of these episodes ranged from less than 5 to as long as 60 minutes. Some episodes responded to nitroglycerin (in patients 2, 9 and 10), completely or partially. Often nitroglycerin did not abort the pain, which abated gradually after several minutes. Chest pain was occasionally associated with weakness, diaphoresis, nausea and vomiting. The characteristics of chest pain during hospitalization were similar to the attacks experienced before admission, although episodes of angina in the hospital were often more prolonged. All patients suffered multiple chest pain episodes in the hospital, except patient 6, who experienced chest pain

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Age/Sex</th>
<th>Race</th>
<th>Hx. hypertension</th>
<th>Smoking</th>
<th>F. Hx. of myocardial infarction</th>
<th>Angina at rest</th>
<th>Angina on exertion</th>
<th>Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43/M</td>
<td>W</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<td>-</td>
<td>DD</td>
</tr>
<tr>
<td>2</td>
<td>37/M</td>
<td>W</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+ 6.5 mos*</td>
<td>-</td>
<td>AL</td>
</tr>
<tr>
<td>3</td>
<td>54/F</td>
<td>W</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ 2 yrs</td>
<td>-</td>
<td>SD</td>
</tr>
<tr>
<td>4</td>
<td>28/M</td>
<td>PR</td>
<td>-</td>
<td>+</td>
<td>+, U136</td>
<td>-</td>
<td>-</td>
<td>AL</td>
</tr>
<tr>
<td>5</td>
<td>31/M</td>
<td>W</td>
<td>-</td>
<td>+</td>
<td>+, F155</td>
<td>-</td>
<td>-</td>
<td>AL</td>
</tr>
<tr>
<td>6</td>
<td>41/M</td>
<td>BL</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+ 7 mos</td>
<td>-</td>
<td>SD</td>
</tr>
<tr>
<td>7</td>
<td>51/M</td>
<td>W</td>
<td>-</td>
<td>+</td>
<td>+, B 45</td>
<td>-</td>
<td>-</td>
<td>DD</td>
</tr>
<tr>
<td>8</td>
<td>50/F</td>
<td>W</td>
<td>+</td>
<td>+</td>
<td>+, M150, F155, S140</td>
<td>+ 1 wk</td>
<td>+ 1 wk</td>
<td>ND</td>
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<tr>
<td>9</td>
<td>34/M</td>
<td>W</td>
<td>-</td>
<td>+</td>
<td>+, B 40</td>
<td>+ 1 mos†</td>
<td>-</td>
<td>DD</td>
</tr>
<tr>
<td>10</td>
<td>43/M</td>
<td>W</td>
<td>-</td>
<td>+</td>
<td>+, F150, B36, B38, S38</td>
<td>-</td>
<td>-</td>
<td>AL</td>
</tr>
</tbody>
</table>

*Documented variant angina.
†Sudden death; no documented myocardial infarction.
‡Previous inferior myocardial infarction.

Abbreviations: Hx. = history; F. Hx. = family history; + = positive Hx.; − = negative Hx.; U = uncle; M = mother; F = father; S = sister; B = brother; W = white; PR = Puerto Rican; BL = black; AL = alcoholic; DD = daily drinker; ND = nondrinker; SD = social drinker; † = death.
on only two occasions. Chest pain attacks occurred over periods ranging from 3–15 days. No diurnal distribution patterns of the pain were observed in the hospital. Some episodes were brief and self-limited; others responded to nitroglycerin, but often morphine sulfate was required for relief. A few patients (nos. 1, 3 and 8) had no pain for intervals of 1–3 days between attacks of variant angina. Occasionally chest pain episodes occurred just before scheduled administration of nitrates (patients 1 and 3).

Electrocardiographic Data

Transient ST-segment elevations were noted in the ECGs of all patients during chest pain episodes. Reciprocal changes ranged from minimal to marked. ECGs after abatement of chest pain returned to normal in all 10 patients. However, after recurrent attacks of pain associated with transient ST-segment elevation (with subsequent return to the baseline), ECGs revealed persistent symmetrically inverted T waves (fig. 1). Such T waves often deepened progressively after each recurrent episode of chest pain. ST-segment elevation was recorded in anterior leads in six patients; two patients showed changes in inferior leads, and two patients revealed changes in both anterior and inferior leads (table 2). Other ECG changes during transient chest pain episodes were ST-segment depressions (fig. 2C), normalization of previously inverted T waves, peaking of T waves, increase or decrease of R wave amplitude (fig. 2C), disappearance of S waves (fig. 2B), and widening of QRS complex with development of monophasic curves (fig. 3). During several chest pain episodes, six patients displayed unchanged ECGs. Clinical episodes were indistinguishable from the ones associated with alterations in the ECG. Four patients had ST-segment elevation in the monitored ECG during pain-free periods. The final ECG in seven patients showed deep, symmetrical T-wave inversions in the same leads which displayed ST-segment elevation during variant angina (fig. 1). Two patients (8 and 9) showed ECG evidence of transmural anterior myocardial infarction (fig. 4) with Q waves and ST- and T-wave evolutionary changes. Patient 8 had persistent ST-segment elevation suggestive of a ventricular aneurysm; a gated blood pool radionuclide scan was positive for that diagnosis. Patient 10 showed persistent mild ST-segment elevation, deepening of pre-existing nonpathological Q waves and a positive technetium-99m pyrophosphate scan for myocardial infarction. T-wave inversions in the seven patients persisted from 2 weeks to 3 months (table 2).

Blood Pressure and Heart Rate Changes During Variant Angina

During recurrent episodes of variant angina, a reduction of blood pressure and heart rate was always noted in two patients. Two patients showed either a reduction of these two parameters (fig. 2C) or no change (fig. 2B), and three showed no changes in heart rate and blood pressure during episodes of pain. Two patients showed either no changes (fig. 3) or elevation of blood pressure and heart rate during episodes of variant angina. Finally, one patient showed no change, reduction of blood pressure and heart rate, and increase in blood pressure with unchanged heart rate during different episodes of variant angina. Changes in blood pressure and heart rate varied from minimal to marked. No correlation was found between the magnitude and the form (ST-segment elevation, depression, or T-wave alterations) of ECG, and the changes in blood pressure and heart rate noted during episodes of variant angina in individual patients or in the group.
TABLE 2. Changes in Blood Pressure and Heart Rate During and ECG Data During and Following Episodes of Variant Angina

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Transient ECG changes during V.A.</th>
<th>Change in BP and HR during V.A.</th>
<th>ECG changes following V.A.*</th>
<th>Duration of ECG changes following V.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+ST V1-V6; NLT; T; NO }</td>
<td>NO } or ↑BP, ↑HR</td>
<td>T↓ V1-V6</td>
<td>2 months</td>
</tr>
<tr>
<td>2</td>
<td>+ST V1-V6, R↑, S↓; T; NO }</td>
<td>NO }</td>
<td>T↓ V1-V6</td>
<td>2 weeks</td>
</tr>
<tr>
<td>3</td>
<td>+ST 1, AVL, V1-V6; T↓</td>
<td>NO }</td>
<td>T↓ V1-V6</td>
<td>2 months</td>
</tr>
<tr>
<td>4</td>
<td>+ST 1, 2, AVL, V1-V6</td>
<td>↓BP, ↓HR</td>
<td>T↓ 1, 2, AVL, AVF, V1-V6</td>
<td>3.5 weeks</td>
</tr>
<tr>
<td>5</td>
<td>+ST 2, 3, AVF; -ST 2, 3, aVF; NO }</td>
<td>NO }</td>
<td>T↓ 2, 3, aVF</td>
<td>2 weeks</td>
</tr>
<tr>
<td>6</td>
<td>-ST 1, 2, 3, aVF, V1-V6; +ST 1, aVL, V1-V6, R↑; widening QRS V1-V6; R↑, S↓</td>
<td>NO } or ↓BP, ↓HR</td>
<td>T↓ V1-V6</td>
<td>3 weeks</td>
</tr>
<tr>
<td>7</td>
<td>+ST V1-V6; T↑, V1-V6</td>
<td>↓BP, ↓HR</td>
<td>T↓ V1-V6</td>
<td>3 weeks</td>
</tr>
<tr>
<td>8</td>
<td>-ST 1, 2, aVL, aVF; +ST 1, aVL, V1-V6; -ST 2, 3, aVF, V1-V6; T↓ V1-V6; R↑ V1-V6; NO }</td>
<td>NO } or ↓BP, ↓HR</td>
<td>T↓ 1, AVL, V1-V6; +ST and QS 1, aVL, V1-V6</td>
<td>3 months</td>
</tr>
<tr>
<td>9</td>
<td>+ST V1-V6; NO }</td>
<td>NO } or ↓BP, ↓HR</td>
<td>T↓ V1-V6; +ST and QS V1-V6; T↓ V1-V6</td>
<td>2.5 months</td>
</tr>
<tr>
<td>10</td>
<td>+ST 2, 3, aVF; NO }</td>
<td>NO } or ↑BP, ↑HR</td>
<td>NO }; +ST 2, 3, aVF; qR 2, 3, aVF</td>
<td>1.5 months</td>
</tr>
</tbody>
</table>

Abbreviations: V.A. = Variant angina; NO } = No change; BP = Blood pressure; HR = Heart rate; +ST = ST-segment elevation; -ST = ST-segment depression; T↓ = T-wave inversion; T↑ = Peaking of T wave; NLT } = Normalization of T-wave inversion; R = R wave; S = S wave; ↑ = increase; ↓ = decrease. *Data under the heading "ECG changes following V.A." refer to the discharge ECG, except for cases 8, 9 and 10, which in addition include changes in ECG after recurrent episodes of variant angina.

Enzymatic Data

Peak enzyme values were noted on day 1 to day 15 of the hospitalization. In seven patients, abnormally high percentages of MB-CK confirmed the diagnosis of acute myocardial infarction. Modest elevations of peak CK were noted in a few patients, but the values were more than 500% higher than the initial and/or final values of CK in the same patients. Four patients showed re-elevation of CK after a sequence of decreasing values, which suggests an extension of the original myocardial necrosis (table 3). One patient had two such re-elevations. These additional peaks of CK were preceded by transient, often prolonged episodes of variant angina.

Complications

Evidence of ventricular irritability was noted in all patients (table 3). One patient suffered an episode of ventricular fibrillation. Other complications included pericarditis in two patients, Dressler's syndrome in two patients, congestive heart failure in one patient, and transient incomplete right bundle branch block in one patient. Four patients (1, 3, 4 and 6) had an extension of myocardial necrosis. These patients had recurrent episodes of variant angina following the initial myocardial infarction. Intravenous balloon counterpulsation was initiated in two patients (nos. 3 and 9) because of persistent chest pain on days 9 and 2 of admission, respectively. Episodes of variant angina persisted despite balloon pumping. These two patients underwent emergency aortocoronary bypass surgery, which did not result in further ECG changes from those present after their myocardial infarction (table 2, fig. 4). In patient 9, we saw the area of infarction during surgery. There were no deaths in this group of 10 patients.

Follow-up Data

Follow-up ranged from 5.5-69.5 months. Seven patients remained asymptomatic. Patient 8 suffered one, and patients 2 and 5 suffered multiple chest pain episodes at rest or on exertion, and were admitted to the hospital for evaluation. No evidence of recurrent myocardial infarction was noted. Patient 2 has been asymptomatic for the past 37 months. While patient 2 had experienced pain at rest only, patients 5 and 8 had suffered pain at rest and on exertion (table 3). Currently all patients are asymptomatic, except for patient 5, who is frequently admitted with a history of chest pain and negative work-up.

Exercise Stress Test

Patients 1, 2, 4, 5 and 7 had a normal exercise stress test 3 years, 4, 3, 4 and 4 months, respectively, after acute myocardial infarction. Patient 9 had a normal exercise stress test 2 months after myocardial infarction and cardiac surgery. All six patients reached heart rates over the 85% maximum of predicted values.
VARIANT ANGINA AND MYOCARDIAL INFARCTION/Madias

Cardiac Catheterization

Coronary pathology ranged from normal coronary anatomy to three-vessel disease (table 4). Coronary spasm was not observed during arteriography in these patients, and we did not attempt to induce it. ST-segment elevation during variant angina predicted the location of coronary lesions, documented at angiography in patients with coronary artery disease. Visualization of the left ventricle revealed normal function in two patients, segmental contraction abnormalities in five patients, and a ventricular aneurysm in one patient (no. 9). Ejection fraction was normal (≥ 55%) in six patients and abnormally decreased in two patients (nos. 6 and 9).

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Other Observations

Thrombocytosis was detected in patient 6. Patient 7 had a history of Raynaud’s disease. Three patients (2, 4 and 5) had histories of chest pain at rest precipitated by drinking alcohol. Attacks of variant angina occurred in patient 10 in the hospital after smoking and while eating. This patient’s brother allegedly suffered from variant angina.

Discussion

Electrocardiographic, clinical and arteriographic characteristics of these patients were similar to those noted in association with variant angina.\(^1\)\(^-\)\(^6\)\(^,\)\(^18\)\(^-\)\(^20\) Variant angina often occurs at a young age,\(^3\) but family history of mostly fatal infarction at a young age has not been previously noted. Smoking and alcohol drinking precipitated attacks of variant angina in our patients, as previously reported.\(^10\)\(^,\)\(^21\) The role of Raynaud’s disease (a vasoreactive state) and thrombocytosis in our patients’ illness could not be explained. Contrary to the common course, these patients with variant angina did not stabilize, but progressed to acute myocardial infarction. Their course, however, could be easily differentiated from the clinical and ECG sequence of conventional acute myocardial infarction.\(^22\) The patients were asymptomatic between attacks of spontaneous angina and their ECGs returned to baseline after cessation of pain, until they finally developed myocardial infarction.

Some distinctions can be made between the initial phase of the syndrome of variant angina and the intermediate syndrome,\(^23\)\(^-\)\(^26\) also known as preinfarction or unstable angina: 1) history of angina on exertion is common in the latter,\(^23\) while it was noted in only one patient in our group; 2) the exercise stress test, as a rule, is positive in patients with unstable angina,\(^24\)\(^,\)\(^26\) yet it was negative in our cohort; 3) history of angina at rest was present in five of our patients, but this feature is not common in patients with the intermediate syndrome;\(^23\)\(^,\)\(^24\) 4) between attacks of pain our patients were completely asymptomatic, sometimes for several days; this is most unusual in patients with unstable angina, in whom either resolution within 24 to 48 hours, or progression to myocardial infarction, without phases of complete recovery between episodes of pain is the rule; 5) transient ST-segment elevation accompanying spontaneous angina with resolution of both clinical and ECG features is the hallmark of variant angina. Thus, Fischl\(^22\) and Bertolasi\(^22\) and their co-workers excluded patients with these characteristics from their groups of subjects with unstable angina; 6) spontaneous angina in a previous study was invariably accompanied by increased heart rate and blood pressure.\(^27\) The literature on patients with unstable angina either does not refer to these parameters,\(^24\)\(^-\)\(^26\) or confirms the notion that both
### Table 3. Enzymatic Data, Complications, and Follow-up of Patients with Variant Angina and Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Peak CK</th>
<th>MB-CK (%)</th>
<th>Time of peak CK (days)</th>
<th>Complications</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>1</td>
<td>263</td>
<td>—</td>
<td>2</td>
<td>Multifocal PVCs; V.T.; V.F.</td>
<td>59.5 months; asymptomatic</td>
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<tr>
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<td>270</td>
<td>—</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>135</td>
<td>—</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>233</td>
<td>—</td>
<td>2</td>
<td>Rare PVCs</td>
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<td>154</td>
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<td>IABC: CABG</td>
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<tr>
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<td>595</td>
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<td>239</td>
<td>—</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>225</td>
<td>—</td>
<td>3</td>
<td>Rare PVCs; pericarditis</td>
<td>15 months; multiple admissions for chest pain</td>
</tr>
<tr>
<td>6</td>
<td>470</td>
<td>27</td>
<td>1</td>
<td>Multifocal VT; PVCs; couplets, Dressler's</td>
<td>11 months; asymptomatic</td>
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<tr>
<td></td>
<td>435</td>
<td>—</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>186</td>
<td>17</td>
<td>1</td>
<td>Rare PVCs; V.T., IRBBB</td>
<td>7.5 months; asymptomatic</td>
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<td>8</td>
<td>1,050</td>
<td>15</td>
<td>2</td>
<td>Frequent PVCs; pericarditis; CHF; Dressler's</td>
<td>7 months; admission for chest pain</td>
</tr>
<tr>
<td>9</td>
<td>275</td>
<td>20</td>
<td>3</td>
<td>Rare PVCs; IABC; CABG</td>
<td>6.5 months; asymptomatic</td>
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<tr>
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<td>620</td>
<td>17</td>
<td>3</td>
<td>PVCs</td>
<td>5.5 months; asymptomatic</td>
</tr>
</tbody>
</table>

Abbreviations: PVC = premature ventricular contraction; V.T. = ventricular tachycardia; V.F. = ventricular fibrillation; CK = creatine kinase; MB-CK = percentage of myocardium specific isoenzyme of CK; IABC = intraaortic balloon countepulsation; CABG = coronary artery bypass graft; CHF = congestive heart failure; IRBB = incomplete right bundle branch block.

### Table 4. Catheterization Data of Patients with Variant Angina and Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Time of catheterization in relation to the infarction</th>
<th>Coronary arteriography</th>
<th>Left cineventriculography</th>
<th>Ejection fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24 days after</td>
<td>60% RCA; 85% LAD; 75% LCF</td>
<td>normal</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>130 days before</td>
<td>50% LAD; poor degree of branching of all coronary arteries</td>
<td>normal</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>10 days after</td>
<td>98% LAD; 40%; septal; 30% LCF; hypoplastic RCA</td>
<td>mild apical hypokinesis</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>21 days after</td>
<td>normal</td>
<td>mild anteroseptal hypokinesis</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>160 days after</td>
<td>normal</td>
<td>marked inferoseptal hypokinesis</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>31 days after</td>
<td>50% tubular LAD</td>
<td>mild inferoseptal hypokinesis</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>130 days after</td>
<td>45% LAD</td>
<td>moderate apical hypokinesis</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>210 days before</td>
<td>100% RCA; 30% LAD; 50% LCF on the same day</td>
<td>posterobasal akinesi</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100% RCA; 100% LAD; 50% first diagonal; 50% LCF</td>
<td>posterobasal akinesi</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100% RCA; 100% LAD; 50% first diagonal; 50% LCF; patents grafts to RCA and LAD</td>
<td>posterobasal hypokinesis; anterolateral hypokinesis</td>
<td>49</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: RCA = right coronary artery; LAD = left anterior descending coronary artery; LCF = left circumflex coronary artery.
angina on exertion and the intermediate syndrome or unstable angina are characterized by a definite increase in heart rate and blood pressure during the episodes of pain. Although similar changes were rarely seen in our patients, angina was mostly associated either with stable blood pressure and heart rate, or reduction in these two variables, suggesting that angina in our patients was precipitated by an acute regional reduction of coronary blood flow rather than by increased energy demands in myocardial zones with fixed perfusion. The history of resting angina in half of these patients and failure of intraaortic balloon to relieve symptoms further supports this speculation. Spasm of coronary vessels might have played a role in the pathogenesis of variant angina in these patients.

Spasm of normal or arteriosclerotic coronary vessels has been documented during spontaneous variant angina and transient myocardial perfusion defects have been demonstrated during spontaneous variant angina by thallium-201 scintigraphy. Since spasm did not occur during coronary arteriography in our patients, provocative tests for its induction might have confirmed the diagnosis of variant angina in this group. The experience of Heupler et al. suggests that the ergonovine maleate provocative test is safe and induced spasm in 10 of 11 patients with history of variant angina, and in none of six patients with previous myocardial infarction and minor coronary obstruction who did not have history of variant angina. Provocative tests therefore may be useful in discerning the patients with vasoreactive angina from the subjects with angina or myocardial infarction who have normal anatomy or mild coronary lesions. Two of these patients with variant angina suffered a myocardial infarction, one 4 years before and the other 10 months after a positive ergonovine test. Although provocative tests do have risks, they can be done safely following certain guidelines, and may contribute to the understanding of the role of vasospasm in the initiation and/or perpetuation of ischemic myocardial injury leading to necrosis.

The prognosis for patients with variant angina was previously considered grave, but more recent work has not corroborated this idea. Infarction was thought to occur frequently in patients with variant angina, but subsequent observations did not verify this concept. Despite frequent association in the literature of variant angina with myocardial infarction, there are no data temporally linking episodes of variant angina with proven myocardial necrosis. Thus, the notion that infarction can be precipitated by attacks of variant angina cannot be supported by existing data. In a limited number of cases, variant angina preceded or followed acute myocardial infarction. In two case reports, an association was implied between variant angina and myocardial infarction; but in one patient, infarcts preceded and followed spontaneous and provoked angina by several months, and in the other, details of the clinical course were not presented. Oliva et al. have lately produced documentation of normal or near-normal coronary vasculature within 12.5 hours of clinical onset of proven acute myocardial infarctions. Since these authors implicated coronary vasospasm in the pathogenesis of infarction in their patients, and a similar mechanism is believed to produce the syndrome of variant angina, a distinction should be made between their patients and ours. The 10 patients we describe suffered myocardial infarction in the midst of recurrent transient attacks of variant angina (presumably due to coronary spasm), interspersed with periods during which ECGs and clinical pictures were normal. In contrast, patients in Oliva's study who suffered acute myocardial infarction in the absence of coronary occlusions (probably due to spasm) showed sequential clinical and ECG features of conventional myocardial infarction.

Nontransmural myocardial infarctions in our patients resulted in persisting T-wave inversions in ECG leads which, both before and after infarction, showed ST-segment elevations during variant angina. Progressive increase in the amplitude of T-wave inversion after recurrent attacks of chest pain might have represented a cumulative effect of these attacks on the extent of myocardial ischemia. Shortly after variant angina, the ECG returns to normal, although T-wave inversions occasionally persist longer in the absence of enzymatic evidence of necrosis. Such occurrences may represent "micro-infarcts" which cannot be detected. Refinement of current or development of new diagnostic methods may clarify the nature of these persisting T-wave inversions. Complications, including extension of necrosis, were similar in our patients to the ones previously noted in patients with conventional myocardial infarctions. Variant angina did not recur after myocardial infarction, in the experience of previous workers, but in our study and in the work of others, angina occurred in a few patients shortly after the infarct and in the follow-up period.

The mechanism by which recurrent episodes of variant angina result in myocardial necrosis is unclear. Coronary artery spasm may be the stimulus initiating ischemic injury, although vasospasm could be the consequence of an initial ischemic injury occurring through some other mechanism. Platelet aggregates alone or in combination with coronary spasm could originate such ischemic injury. Intramyocardial spasm has followed myocardial ischemic injury in dogs subjected to transient coronary occlusion. Such spasm, occasionally spreading to epicardial vessels, could generate a vicious cycle perpetuating and extending the original ischemic injury. Between episodes of variant angina, our patients showed persisting T-wave inversions, which probably indicate continuing ischemia. Such ischemic regions could result in recurrent attacks of intramyocardial, or occasionally epicardial, spasm leading to necrosis. Vasospasm of microvasculature has also been shown to follow the development of experimental
cerebral infarction and has been inferred to contribute to the extension of cerebral infarcts in man.\textsuperscript{40, 41} Occurrence of infarction vs reversible ischemia could be due to differences in the frequency or duration of ischemic phases of a similar nature. Since data from these 10 patients are not contrasted with observations from patients with variant angina who did not develop acute myocardial infarction, this hypothesis cannot be tested. Duration of ischemic phases must relate to eventual development of necrosis. Kloner et al. showed that reperfusion after a 40-minute coronary occlusion did not damage the canine heart, but a 90-minute occlusion was followed by cell swelling and capillary damage of the subendocardium.\textsuperscript{42} Willerson et al. found reduced reflow and damage in the subendocardium after transient 2-hour coronary occlusion but not after shorter ischemic periods.\textsuperscript{43} These observations may explain the high prevalence of subendocardial myocardial infarction (70\%) in our patients and the only occasional development of acute myocardial infarction in patients who have attacks of variant angina. Cobb et al.\textsuperscript{44} found that 2-hour coronary occlusion in conscious dogs progressively reduced myocardial flow after reperfusion. Since the same workers noted that ischemic periods of 40 minutes did not result in damage, and since most of our patients had attacks of variant angina much shorter than the occlusive periods which produced permanent necrosis in dogs,\textsuperscript{44} further clarification is needed to explain the eventual development of myocardial infarction in our patients. The duration of ischemic periods in our patients could have been longer than clinically estimated. Resolution of ST-segment elevation with persistent T-wave inversions could have indicated continuing subendocardial ischemia. Also, therapy might have played a role in ameliorating, but not quite abolishing, myocardial ischemia.\textsuperscript{45} Atherosclerosis and species difference might also explain the apparently shorter ischemic periods required for development of myocardial necrosis in the clinical setting. Multiple short episodes of ischemia might have had a cumulative effect resulting in eventual necrosis. This was suggested by progressive deepening of T-wave inversions after recurrent episodes of variant angina.

Various explanations have been offered for the increase in coronary resistance caused by transient coronary occlusions. Rubio and Berne have implicated an impairment in synthesis of adenosine (a normally present coronary vasodilator) due to prolonged severe ischemia.\textsuperscript{46} Local tissue release of catecholamines, resulting in vasoconstriction, has also been implicated with varying response to adrenergic blockade.\textsuperscript{47} Intracellular edema responding to hypertonic mannitol\textsuperscript{48} and vascular damage\textsuperscript{49} are other mechanisms compromising the hyperemic response after transient coronary occlusions. There are no data on parameters which play a part in the transition from variant angina to acute myocardial infarction.

Nitrates and propranolol are the most frequently used drugs for management of patients with variant angina, and could probably prevent progression to myocardial infarction.\textsuperscript{12-16, 18} Propranolol has been found to be effective,\textsuperscript{46} ineffective,\textsuperscript{18} occasionally useful,\textsuperscript{19} and possibly harmful.\textsuperscript{43} Nitrates in various forms have aborted chest pain successfully and prevented recurrences.\textsuperscript{12, 13, 18} with occasional exceptions,\textsuperscript{6, 15} as was shown in our experience. For cases resistant to nitrates, nifedipine, either alone or in combination with nitrates, may be successful.\textsuperscript{15, 20} Nitrates at higher than ordinary doses\textsuperscript{49} or platelet deaggregants,\textsuperscript{34, 39} hypertonic mannitol,\textsuperscript{43} or other measures currently evaluated for containment of ischemic injury probably should be considered, especially with prolonged episodes of variant angina.

Surgery for intractable variant angina has been strongly advocated by some,\textsuperscript{6, 8} although others have recommended it with caution only for patients with severe coronary obstructions.\textsuperscript{12} Results of surgical therapy occasionally appear to be less optimal in patients with variant angina than in patients with conventional angina.\textsuperscript{47} Emergency surgery may be required for patients with variant angina and complicating myocardial infarction who are refractory to medical treatment, and with coronary anatomy that would permit surgery. Our patients who underwent surgery shortly after onset of infarction did not show extension of the original necrosis. It should be therefore presumed that resolution of chest pain was not related to intraoperative infarction. However, the detection rate of perioperative infarction improved when scintigraphy and MB-CK isoenzymes were used in addition to the ECG.\textsuperscript{35} Since our patients already had an infarction preoperatively, such diagnostic methods could not be utilized, and a small infarction therefore cannot be definitely excluded.

Surgery is probably the indicated mode of therapy for patients with variant angina with or without complicating myocardial infarction unresponsive to medical treatment. Coronary arteriography, however, before and after administration of nitroglycerin, should be performed to detect possible presence of spasm contributing to coronary occlusion. If such a functional component is the main contributor to coronary obstruction, surgery should not be considered, but high doses of nitrates and platelet antiaggregants should be administered.\textsuperscript{39, 48} A high rate of coronary spasm was recently detected by angiography shortly after the onset of chest pain in patients with conventional myocardial infarction.\textsuperscript{48} Patients with recurrent episodes of variant angina culminating in myocardial infarction may have even higher rates of coronary spasm, and should be considered for coronary arteriography early in the course of their illness. Such practice may result in the detection of coronary vasospasm and assessment of the effect of vasodilators, especially when angiography is done shortly after an episode of variant angina or during spontaneous occurrence of angina in the catheterization laboratory. Application of currently available drugs in higher doses (pending the availability of more effective agents) may arrest the process of myocardial
necrosis or prevent extension of myocardial infarction.

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