Variant Angina with Angiographically Normal or Near-normal Coronary Arteries: A 10-year Experience

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Abstract

To determine clinical and laboratory characteristics and prognosis of consecutive Taiwanese patients presenting with variant angina and normal or near-normal coronary arteries. A total of 1,329 consecutive patients with acute coronary syndrome who underwent coronary angiography at out hospital were retrospectively screened and reviewed. Over a 10-year period at our hospital, variant angina developed in 14 patients who had normal or near-normal coronary arteries. Of the 14 patients included in the study, mean age 52 years, 10 patients were men and 9 of the 10 men were cigarette smokers. All but one patient developed chest pain between midnight and morning. Twelve patients whose blood tests for high-sensitivity C-reactive protein on the second day after admission had a mean level of 5.5 mg/L. The electrocardiographic location of transient ST-segment elevation was in the anterior leads in 8 patients, inferior leads in 3 and both anterior and inferior leads in 3. Spasm of left anterior descending artery was the most common finding in these cases. Three patients developed atrial fibrillation and 2 patients had atrioventricular block during variant angina. During a median follow-up period of 54 months, no patient expired, suffered a nonfatal infarction, or recurrent variant angina. One percent of patients with acute coronary syndrome had variant angina with normal or near-normal coronary arteries. The variant angina with normal or near-normal coronary arteries could be found in 2% of the patients with ST-segment elevation acute coronary syndrome. These patients had a good prognosis. (J Intern Med Taiwan 2010; 21: 79-89)

Key Words: Spasm, Variant angina, Inflammation

Introduction

Coronary vasospasm (CVsp) with transient ST-segment elevation can occur in diseased coronary arteries as Prinzmetal's variant angina; it may also occur in angiographically normal coronary arteries as so-called 'variant of the variant'. Subsequently, many investigators found that most CVsp are associated with ST-segment depression rather than ST-segment elevation on electrocardiography. Therefore, variant angina is only one aspect of the spectrum of coronary vasospastic myocardial ischemia. CVsp plays an important role in the pathogenesis not only of variant angina but also of ischemic heart disease, including effort angina, unstable angina, acute myocardial...
infarction, and sudden death\textsuperscript{19}. Recently, we found that CVsp-related acute coronary syndrome was more common than originally thought in Taiwan\textsuperscript{10-12}. Therefore, we hypothesized that the clinical and angiographic characteristics of Taiwanese patients with variant angina with normal or near-normal coronary arteries were similar to those reported previously\textsuperscript{13,14}. This first retrospective investigation in Taiwan was designed to describe their diagnostic procedures, clinical and laboratory characteristics, and prognoses.

Methods

1. Patients

Based on the catheterization laboratory database, all consecutive patients with acute coronary syndrome from August 1999 to July 2009 were screened for enrollment. The study inclusion criteria for variant angina with angiographically normal or near-normal coronary arteries were: 1) clinical status of unstable angina; 2) documented transient ST-segment elevation at rest; 3) creatine phosphokinase levels less than twice the normal value and creatine phosphokinase MB isoenzyme \( \leq 5\% \); 4) no evidence of fixed coronary artery stenosis \( \geq 25\% \) after intracoronary nitroglycerin administration; 5) no other (non-coronary) cardiac abnormalities. Unstable angina was defined as angina pectoris with at least one of following three features; 1) occurring at rest (or with minimal exertion) and lasting for more than 20 minutes (if not interrupted by nitroglycerin); 2) severe, frank pain of new onset within the past 1 month; and, 3) occurring in a crescendo pattern (i.e., becoming more severe, prolonged, or with increasing frequency). Exclusion criteria were: 1) refusal of patient to undergo cardiac catheterization; 2) severe symptomatic electrolyte imbalance; 3) decompensated heart failure with/without evidence of infiltrating cardiomyopathy; 4) severe coagulopathy; 5) severe anemia with hemoglobin <7.0 g/dL; 6) aortic valve endocarditis; 7) unexplained fever. The retrospective study protocol was approved by the institution's Human Research Committee (98-2181C).

2. Clinical Data

Patients were assessed for cardiac risk factors, including cigarette smoking, diabetes mellitus, hypercholesterolemia, and hypertension. Current smoking was defined as having smoked a cigarette within 3 weeks of the cardiac catheterization. Diabetes mellitus was defined as dietary treatment and/or medical therapy; hypertension was defined as receiving the appropriate medical therapy or blood pressure of \( >140/90 \) mmHg. Hypercholesterolemia was defined as serum total cholesterol \( >200 \) mg/dL.

3. Laboratory Analysis

Blood specimens for measurement of routine blood tests and high-sensitivity C-reactive protein (hs-CRP) were collected on the second day after admission, after overnight fasting. Plasma hs-CRP was measured in duplicate by enzyme-linked immunosorbent assay on the basis of purified protein and polyclonal anti-CRP antibodies (IMMULITE hs-CRP; Diagnostic Products Corp., Los Angeles, California). The lower limit of this assay was 0.10 mg/L, and the coefficients of variation were \( \leq 5\% \) at 0.20 mg/L of CRP.

4. Coronary Angiography and Intracoronary Methylergonovine Testing

Coronary angiography was performed within 3 days of admission. With the exception of sublingual nitroglycerin, all antispastic agents (calcium antagonists and/or isosorbide dinitrate) were withdrawn for at least 24 hours before coronary angiography in patients suspected to have CVsp. The left ventricular ejection fraction was calculated using Simpson's method. Quantitative coronary angiography with an edge-detection algorithm was performed using Judkin's technique and a Philips digital angiography system (Philips Integris BH
3000; Philips, Bast, Netherlands). Selective left and right coronary angiography were performed in multiple axial and hemi-axial projections. An independent cardiologist interpreted all coronary angiograms. Significant coronary artery stenosis was defined as >50% diameter reduction in lumen caliber after administration of intracoronary nitroglycerin (50-200 µ g). A near-normal coronary angiogram was defined as <25% stenosis of the luminal diameter after administration of intracoronary nitroglycerin. Intracoronary methylergonovine (Methergin; Novartis, Basel, Switzerland) provocation testing was performed in succession if no significant coronary stenosis was demonstrated. The absolute contraindications to intracoronary methylergonovine testing included pregnancy, severe hypertension (systolic blood pressure >180 mmHg), moderate to severe aortic stenosis, high-grade left main stenosis, severe left ventricular dysfunction, and uncontrolled ventricular arrhythmia. Methylergonovine was administered stepwise (1, 5, 10, 30 µ g) first into the right coronary artery, and subsequently into the left coronary artery. Provocation testing for CVsp was considered positive where there was a >70% reduction in luminal diameter compared to post intracoronary nitroglycerin and it was associated with angina and/or ST depression or elevation change. After CVsp diagnosis, the intracoronary methylergonovine administration was stopped with intracoronary nitroglycerin 50-200 µ g (Millisrol; G. Pohl-Boskamp, Hohenlockstedt, Germany). The reversal of coronary artery diameter further confirmed the CVsp diagnosis. Spontaneous CVsp was defined as relief of >70% luminal diameter after intracoronary nitroglycerin administration (50-200 µ g).

5. Patient Follow-up

Follow-up data were obtained from hospital records, telephone interviews, and patients' regular visits to staff physicians at the outpatient clinic. The types of medication administered during outpatient follow-up were recorded. Events were defined as death, nonfatal myocardial infarction, and recurrent angina. Causes of death were further classified as cardiac or noncardiac.

Results

1. Demographic and Clinical Laboratory Data

Of the 1,329 patients who underwent coronary angiography for acute coronary syndrome between August 1999 to July 2009, 696 patients were ST-segment elevation acute coronary syndrome. In 1,329 patients, 339 patients (25.5%) were reported as having no significant coronary artery stenosis. All of these 339 patients underwent intracoronary methylergonovine testing immediately after coronary angiography. Methylergonovine testing elicited CVsp in 198 patients of the 339 patients (58%). Of the 198 patients, 14 patients (7%) with transient ST-elevation unstable angina had no fixed significant coronary artery disease corresponding to the electrocardiographic leads with transient ST-elevation. In other words, 1% patient with acute coronary syndrome (14 in 1329) had variant angina with normal or near-normal coronary arteries. The variant angina with normal or near-normal coronary arteries could be found in 2% of the patients with ST-segment elevation acute coronary syndrome (14 in 696).

All but one patient (patient 14) had initial treatments (oxygen, aspirin, and sublingual nitroglycerin) for ST-elevation acute coronary syndrome at emergency department. Patient 14 was found incidentally to have transient ST-elevation by 24 hrs Holter electrocardiography at ordinary medical ward. The characteristics of the patients are listed in the Table. The age range was 38-73 years, with a mean age of 52 years. Ten patients were men and 9 of 10 men were cigarette smokers, which was the most common cardiac risk factor in this study. None of these patients had abused cocaine. Their
Table 1. Characteristics of 14 patients with variant angina

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yrs)/sex</th>
<th>Month/year</th>
<th>Time of angina</th>
<th>Risk factors</th>
<th>Troponin-I (ng/mL) &lt;br&gt;first</th>
<th>Troponin-I (ng/mL) &lt;br&gt;6 hrs later</th>
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<tbody>
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<td>12.5</td>
<td>NA</td>
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<tr>
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<tr>
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<table>
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<th>hs-CRP (mg/L)</th>
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<th>Spastic coronary artery</th>
<th>LV EF (%)</th>
<th>Medications at discharge</th>
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<td>A, C, N</td>
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<td>LAD</td>
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<td>A, ACEI, C, N, St</td>
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<td>LAD &amp; Lx</td>
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<td>A, C, N</td>
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<td>V₁,₂, I, aV₇</td>
<td>LAD</td>
<td>75</td>
<td>C</td>
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</table>

A, aspirin; ACEI, angiotensin-converting enzyme inhibitor; C, calcium antagonist; ECG, electrocardiographic; EF, ejection fraction; H, hypertension; L, hypercholesterolemia; LAD, left anterior descending artery; LV, left ventricular; Lx, left circumflex artery; N, nitrates; NA, not available; RCA, right coronary artery; S, cigarette smoking; St, statin; — = nil.

*The upper reference limit of troponin-I for patients 1-6 is <2.0 ng/mL and for patients 7-14 is <0.5 ng/mL.

chest pain occurred in all months except March and April. All but one patient (patient 7) developed chest pain between midnight and morning (22:00 to 10:00). Four (patients 2, 4, 6, and 8) of 13 patients had elevated troponin-I levels, which is consistent with possible CVSp-related myocardial necrosis, rather than acute myocardial infarction. Twelve patients had hs-CRP measurements with a mean level of 5.5 mg/L (range, 0.65-23.7 mg/L), which are higher than that of the healthy population.

2. Electrocardiographic and Coronary Angiographic Findings

The electrocardiographic location of transient ST-segment elevation was in the anterior leads in eight patients, inferior leads in three, and both anterior and inferior leads in three.
Fig. 1. Electrocardiograms and coronary angiograms for patient 6. The male patient developed ST-segment elevation in leads V_{2,3,}, I, and aV_{L}, with reciprocal changes in the inferior leads on admission to the emergency department (A). Normal electrocardiogram noted later (B). Subsequent coronary angiography with intracoronary methylergonovine testing revealed segmental spasm in the mid-portion of left anterior descending artery (C, arrow), which was relieved after intracoronary nitroglycerin administration (D).

Fig. 2. Twenty-four-hour Holter electrocardiographic results for patient 14 showed atrial fibrillation with ST-segment elevation in precordial, I, and aV_{L} leads at 3:49 am (A) and these electrocardiographic changes resolved 2 minutes later (B). The same electrocardiographic changes occurred at 6:28 am (C) and resolved 2 minutes later (D). Coronary angiography with intracoronary methylergonovine testing showed focal spasm in the mid-portion of the left anterior descending artery (E, arrow), with relief after intracoronary nitroglycerin administration (F).

Fig. 3. Baseline electrocardiogram on admission (A) showed sinus rhythm and Mobitz type 1 secondary degree atroventricular block, with ST-segment elevation in the inferior leads. These changes resolved at the follow-up electrocardiogram (B). Coronary angiography showed total spasm in the distal portion of right coronary artery following intracoronary methylergonovine administration (C, arrow), and it resolved after intracoronary nitroglycerin administration (D).

These electrocardiographic ST-segment changes were relieved spontaneously or by nitrates. Of the 14 patients, 13 underwent intracoronary methylergonovine testing immediately after diagnostic coronary angiography (only patient 13 did not). All patients had angiographically normal or near-normal coronary arteries with corresponding CVsp as follows: patients 1, 2, 5, 6 (Figure 1), 8, 10, and 14 (Figure 2) had provocative spasm of the left anterior descending artery; patients 4, 7 (Figure 3), 9, and 12 had spasm of the right coronary artery; patient 11 had spasm of both the left anterior descending artery and the left circumflex artery; patient 3 had spasm of the right coronary artery and the left circumflex artery; patient 13 had spontaneous left anterior descending artery spasm. No significant arrhythmias were noted during the methylergonovine testing. All patients had adequate left ventricular contractile function with no evidence of ventricular wall motion abnormality.

Two patients (3 and 7) developed atroventricular block during hospitalization, preceded...
by ST-elevation and chest pain. Patient 3 developed variant angina complicated by complete atrioventricular block and cardiogenic shock (blood pressure of 66/35 mmHg), which were reversed by intravenous fluids. Patient 7 (Figure 3) developed Mobitz type I secondary degree atrioventricular block which was reversed by intravenous nitroglycerin. Three patients (3, 11, and 12) developed ST-segment changes in different leads during admission which were relieved after sublingual nitrate. Patients 3, 4, and 14 (Figure 2) developed variant angina associated with paroxysmal atrial fibrillation which was relieved spontaneously or after sublingual nitroglycerin.

3. Treatment and Prognosis

Calcium antagonists were prescribed to all patients. During a median follow-up of 54 months (range, 1-119 months), five patients (1, 4, 8, 9, and 11) had recurrent ischemic chest pain (without transient ST-segment elevation) that developed due to irregular medication use and continued cigarette smoking (patients 1, 9, and 11). The recurrences of ischemic chest pain without transient ST-segment elevation were soon relieved after resumption of previous medications. No recurrent variant angina, myocardial infarction, or cardiac death occurred during the follow-up period.

Discussion

This observational study had three potentially important findings. Firstly, 1% of patients with acute coronary syndrome had variant angina with normal or near-normal coronary arteries. Secondly, the variant angina with normal or near-normal coronary arteries could be found in 2% of the patients with ST-segment elevation acute coronary syndrome. Thirdly, these patients had a good prognosis.

Selzer et al\textsuperscript{13} first suggested that patients with variant angina and normal coronary angiograms had a benign course, which was confirmed by other studies\textsuperscript{14,18}. In our study, we found that our patients' characteristics (age, time of angina, risk factor, site of ST-segment elevation, and prognosis) were similar to those reported by Japanese authors\textsuperscript{18-20}, with the gender distribution closer to a French study\textsuperscript{21}. Interestingly, we found elevated hs-CRP levels in patients with variant angina and normal or near-normal coronary angiograms. In the past, an increase of CRP was noted in patients with acute myocardial infarction\textsuperscript{22} and unstable angina\textsuperscript{23}. Recently, we found that hs-CRP was elevated in patients with active CVsp\textsuperscript{24,25}, which was confirmed by other investigators\textsuperscript{25,26}. The median level of hs-CRP was similar to that of unstable angina\textsuperscript{27}, suggesting the same acute inflammatory changes exist in unstable angina and variant angina, irrespective of angiographically normal coronary arteries or significant fixed coronary artery stenosis. In addition, previous studies using histologic or intravascular ultrasound evaluation of coronary plaques or arteries in patients who had variant angina reported evidence of intimal injury, such as neointimal hyperplasia with infiltration by inflammatory cells\textsuperscript{27,28}. Furthermore, coronary vasospastic angina patients who had no evidence of arterial narrowing on angiography had diffuse intimal thickening on intracoronary ultrasound scanning\textsuperscript{29}. These findings suggest that inflammatory changes occur in spastic coronary arteries though no obvious narrowing is found on coronary angiography.

Since variant angina is a presentation of ST-elevation acute coronary syndrome, the diagnosis and initial management procedures must adhere to the guidelines proposed by American Heart Association in 2005\textsuperscript{30}. Initial general therapies for acute coronary syndrome include immediate oxygen therapy, continuous cardiac monitoring, establishment of intravenous access, and medications of aspirin, nitroglycerin, and/or morphine. If a normalized ST-segment was noted after the above
general therapies, the diagnosis of variant angina was possibly made and reperfusion therapy would be unnecessary. However, spontaneous resolution of a loose obstructing thrombus is not rarely seen in patients with acute coronary syndrome, could also present similar clinical features. Therefore, we may not diagnose variant angina even if transient ST-segment elevation disappeared soon. If there is a persistent ST-segment elevation, then reperfusion therapies would be necessary according to the facilities available in emergency room. The next diagnostic step for a transient ST-segment elevation would be coronary angiography as this the only certain method to distinguish between patients who have severe fixed multivessel disease or only angiographically normal or near-normal coronary arteries. This differential diagnosis is important as the treatment strategies proposed for variant angina with severe, fixed multivessel disease (e.g., aspirin, clopidogrel, nitrates, angiotensin-converting enzyme inhibitor, and/or percutaneous coronary intervention) or only angiographically normal or near-normal coronary arteries (e.g., calcium antagonists and/or nitrates) are different. Because there are some patients with CVsp who are refractory to the conventional medications and who may suffer from lethal arrhythmias or sudden death, and because percutaneous coronary intervention is not the right answer to the problem of CVsp, it is important for every emergency room or ward doctor to be alert to the presence of CVsp, a dynamic coronary artery stenosis, which may be silent and lethal.

The diagnosis of CVsp is not necessarily easy. Strictly speaking, the diagnosis of CVsp must be made on the basis of coronary angiographic findings during the attack. It is not possible to perform coronary angiography during the attack in every patient and there is no need for this. Theoretically, the intracoronary methylergonovine provocative CVsp in patients with variant angina can reproduce the same electrocardiographic findings as the clinical electrocardiogram. However, it is not definitely necessary to reproduce the same electrocardiogram in catheterization laboratory as the reproduced ST-segment elevation means one more episode of transmural myocardial ischemia. Therefore, in patients with ST-segment elevation during episodes of chest pain and a normal coronary angiogram, provocative tests are usually not definitely necessary, because ample clinical evidence is present to confirm the diagnosis of CVsp. On the other hand, pharmacologic assessment of CVsp is recommended in patients with recurrent episodes of apparent ischemic chest pain at rest and found to have a normal or mildly abnormal coronary angiogram and there have been no clinical observations substantiating the diagnosis of variant angina, i.e., ST-segment elevation during pain.

Although the provocation tests for CVsp by intracoronary ergonovine or methylergonovine are usually safe, rare complications may occur. These include various arrhythmias, hypertension, hypotension, abdominal cramps, nausea, vomiting, and other non-specific complications. Considering that intracoronary nitroglycerin is sometimes the only effective means to relieve a CVsp, methylergonovine test in a catheterization laboratory is safer than in any other place. The intracoronary route is preferable in hypertensive patients and affords the opportunity to evaluate the left and right coronary arteries separately. Small dosing increments of 5 to 10 μg are used, with a total dose not to exceed 50 μg. As patient safety is always the first priority, we must very familiar with the contraindications to methylergonovine. Absolute contraindications to methylergonovine include pregnancy, severe hypertension, severe left ventricular dysfunction, moderate to severe aortic stenosis and high-grade left main coronary stenosis. Relative contraindications include uncontrolled angina, uncontrolled ventricular arrhythmia, recent
myocardial infarction and advanced coronary disease. As in our present study, some investigators suggested that only patients with normal coronary arteries or mild to moderate lesions should be submitted to provocation test because CVsp is not required to explain the clinical symptoms for patients with severe atherosclerotic stenosis (≥80%)35,36,40-42. In these severe atherosclerotic stenosis patients, however, repeat coronary angiography of the stenotic vessel after the intracoronary administration of 100-1000 µg of nitroglycerin to exclude the possibility that spontaneous focal vasospasm is contributing to the appearance of severe atherosclerotic stenosis45. Thus, we should not stop considering the diagnosis of coronary vasospastic angina including variant angina and abandon any attempt to confirm the diagnosis and perhaps manage symptoms more appropriately45. However, an appropriate preparation in catheterization laboratory is highly recommended49.

There is a racial difference in the prevalence in CVsp between the Japanese and Caucasians44. Bertrand et al.45 reported that CVsp was provoked by ergonovine in 20% of patients with recent myocardial infarction and in 15% of patients who complained of chest pain in 1,089 consecutive patients undergoing coronary angiography. The recent investigation on the prevalence of CVsp in Japan showed that CVsp was documented in 40.9% of patients with angina pectoris who underwent coronary angiography46. Since we did not perform intracoronary methylergonovine provocative testing in patients with significant coronary artery stenosis, the prevalence of CVsp in Taiwanese could not be definitely obtained. In our previous report31, CVsp was documented in 57% of Taiwanese patients with acute coronary syndrome patients and no significant coronary artery stenosis, which is similar to a recent German report5. In this study, we found that CVsp was confirmed in 100% of patients with variant angina and in 54% of patients with non-ST-elevation unstable angina and no significant coronary artery stenosis.

The limitations of our study are: 1) we did not include 24-h Holter electrocardiography as a follow-up study, which means we might have missed some minor myocardial ischemic events; 2) despite a long enrollment period, the study population is too small to reach a definitive conclusion; 3) because our findings were obtained from a single hospital, our results might not be applicable to other hospitals; 4) the blood tests for hs-CRP were collected on the second day after admission which might be due to not only inflammation but also myocardial injury. As a result, we could not definitely conclude the causes of hs-CRP elevation; and 5) a lot of patients with acute chest pain present normal ST segment on their arrival to the emergency room even if they actually have variant angina, and are not hospitalized or studied in detail. Therefore, the incidence of variant angina is deemed much under-diagnosed.

In summary, inflammation was present in patients with variant angina and angiographically normal or near-normal coronary arteries, a specific form of acute ST-elevation acute coronary syndrome. The cause of variant angina and angiographically normal or near-normal coronary arteries was CVsp, a dynamic stenosis. Since most patients with CVsp present with ST-segment depression rather than ST-segment elevation, a high index of suspicion for CVsp-related acute coronary syndrome is important, as the treatment of choice will vary.

Conflict of Interest
None.

Declaration
Data for patient 3 was described, in part, in the International Journal of Cardiology 2007;117:37-44.

References
dynamically significant coronary artery disease. Int J Cardiol 2007; 117: 37-44.
變異型心絞痛併冠狀動脈攝影為正常
或幾近正常：十年的經驗

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摘要

為探討變異型心絞痛病患其臨床和實驗檢查的特徵及其預後，我們篩選於本院執行心導管檢查的連續1,329位急性冠心病病患，回溯分析變異型心絞痛病患併冠狀動脈攝影為正常或
幾近正常之病歷記錄及冠狀動脈攝影資料。這十年來共14位病患為變異型心絞痛病患併冠狀
動脈攝影為正常或幾近正常。其平均年齡為52歲；10位為男性而其中9位有抽煙。除了一位
病患外，大多數病患胸痛發生在半夜及早上。12位在住院第二天早上有抽血者，其高敏反應
C-反應蛋白質數據者其平均為5.5 mg/L。心電圖均呈現一過性ST波段升高，其中前壁導程有
8位、下壁導程有3位、同時前及下壁導程有3位。這些病例中以左前降枝冠狀動脈痙攣最常
見。於變異型心絞痛發病時，3位病患同時產生心房震顫，2位病患同時產生房室傳導阻滯。
在中位數54個月的追蹤中，無病患死亡、心肌梗塞、或復發變異型心絞痛。於追蹤期間有5
位病患因未抽煙或不規則服藥而有心絞痛發生。百分之之一的急性冠心病病患為變異型心絞痛
併冠狀動脈攝影為正常或幾近正常。變異型心絞痛併冠狀動脈攝影為正常或幾近正常佔ST波
段升高急性冠心病的2%。這些病人的預後是好的。