

Organic Coronary Stenosis in Prinzmetal's Variant Angina

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Abstract

Functional factors are known to precipitate ischemic episodes at rest in variant angina, but the role of fixed coronary lesions is still debated. The prevalence, extent, severity and prognostic implications of organic coronary stenoses in variant angina were evaluated in 162 patients with transient ST segment elevation documented during hospitalization. Seventy-eight patients had normal coronary arteries or single-vessel coronary lesions (group 1) and 84 patients had multivessel coronary stenoses (group 2). Both groups were followed up for 82 ± 41 months.

Angiographically normal coronary arteries were observed in only 11 patients (7%). In 59 patients with single-vessel coronary stenoses, the internal luminal diameter was reduced by $51 \pm 12\%$. There were 20 deaths (16 from cardiac causes) during the 5-year follow-up. Kaplan-Meier survival analysis revealed a significantly lower 5-year survival rate in group 2 (80.1%) compared to group 1 (94.6%, $p=0.006$ by Mantel-Haenszel test). If only cardiac causes of death were considered, the 5-year survival rate was still lower in group 2 (84.0%) than in group 1 (97.1%, $p=0.004$). Considering both revascularized patients and those treated medically for the entire duration of the follow-up, the survival rate was significantly lower in group 2 than in group 1. Finally, the extent of coronary lesions was an independent predictor of survival by Cox multivariate regression analysis.

Organic coronary stenoses are frequent in patients with variant angina and are important for the long-term prognosis.

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Key Words

Angina pectoris, Coronary vasospasm, Atherosclerosis, Prognosis

INTRODUCTION

Prinzmetal's angina is a variant form of angina in which the pain occurs with the subject at rest or during ordinary activity and the ST segment during pain is transiently and often remarkably elevated¹⁾. Temporary increased tonus of a large narrowed coronary artery was suggested by Prinzmetal as the cause of attacks in this variant of angina. With the

advent of coronary arteriography it soon became apparent that the syndrome was caused by a sudden, transient reduction in coronary blood supply^{2,3)}. The underlying coronary disease, however, could vary from a subtotal occlusion to a very mild stenosis and, in some patients, to angiographically normal coronary arteries²⁻⁴⁾. Thus, although the consensus is that functional factors precipitate the attacks of variant angina¹⁻⁷⁾, the role of organic coronary le-

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sions in Prinzmetal's angina is still debated. In a large series of patients with variant angina, the extent and severity of underlying coronary artery disease appeared to be the most important factor influencing long-term outcome⁴. In contrast, the presence of severe coronary stenosis in at least one coronary vessel was not associated with an increased incidence of myocardial infarction or death in the first 9 years after diagnosis in another group of 80 patients⁸. In addition, silent ischemia was shown to be a marker for early unfavorable outcome in unstable angina⁹ and the occurrence of long lasting episodes of ST segment elevation was identified as the most important predictor of unfavorable short-term outcome in variant angina¹⁰. Finally, the clinical status of the disease (which typically shows warning and waxing phases) was considered to be the most important predictor of adverse outcome by Severi *et al*¹¹.

This study was undertaken to evaluate the prevalence, extent, severity and prognostic implications of fixed, organic coronary stenoses in patients with Prinzmetal's variant angina.

SUBJECTS AND METHODS

Subjects

Patients selection

Starting in 1982, a digital archive of patients admitted to our Institute was set up and several parameters were prospectively recorded for each patient. This study is based on the observation of patients with Prinzmetal's variant angina admitted between 1984 and 1993. Inclusion criteria for the study were: 1) the documentation of one or more episodes of ST segment elevation (≥ 0.2 mV at 0.08 sec after the J point) during hospitalization, with or without chest pain, and 2) the reversibility of electrocardiographic changes. Exclusion criteria were: early post-infarction angina, no coronary arteriography and the presence of a left main stenosis. ST-T segment changes were collected by either electrocardiographic monitoring in the coronary care unit or a 12-lead electrocardiogram recorded during chest pain. According to the study criteria, a total of 162 patients was selected. The mean age was 55 ± 8 years, range 36–73 years. The majority of patients (91%) were male.

Group stratification

To evaluate the impact of coronary atherosclerosis on Prinzmetal's angina, the study population was

divided into two groups: group 1 consisted of 78 patients with either normal coronary arteries or single-vessel coronary lesions and group 2 consisted of 84 patients with multivessel coronary stenoses. The clinical characteristics of the two groups of patients are listed in **Table 1**.

Methods

Quantitative coronary angiography

All patients underwent coronary arteriography according to Judkins' technique¹². Quantitative analysis of stenosis severity was performed on 59 out of 67 patients with single-vessel coronary disease. Of the remaining eight patients with single-vessel lesions, five were excluded because of total coronary occlusion and three because of inadequate image quality. For each of the 59 patients studied the angiographic projection better delineating the coronary lesion was chosen, based on stenosis severity (the greatest), superimposition with other vessels (absent) and identification of an angiographically normal vessel up- or downstream of the stenosis. An end-diastolic still frame of the opacified stenotic vessel was digitized by computer for medical imaging (Mipron, Kontron, Germany) into a 512×512 pixel matrix with an 8 bit intensity range. Quantitative measurements were performed according to a semi-automatic program¹³ which identifies the edges of the vessel on the basis of changes in gray level intensity. From each patient the maximal percentage reduction in coronary diameter from the normal segment to the coronary lesion was measured.

Follow-up

The patients were followed up as outpatients. Those who did not come for periodic visits were interrogated by mail questionnaires. For patients who did not respond to the questionnaires, information about their vital status was collected by phone calls, questionnaires addressed to their family doctors or by interrogating the local demographic system. Follow-up information was available for all patients. The mean follow-up period was 82 ± 41 months.

Therapy

A total of 93 patients were treated medically for the 5-year follow-up while 69 patients underwent revascularization with either coronary angioplasty (30 patients) or bypass surgery (39 patients). Coronary angioplasty was more frequent among patients

Table 1 Clinical characteristics of patients

	Group 1	Group 2
Number	78	84
Age (yr)	53 ± 8	57 ± 7
Male gender	67 (86)	81 (96)
Family history	34 (44)	43 (51)
Cigarette smoking	62 (79)	63 (75)
Hypercholesterolemia	9 (12)	18 (21)
Hypertriglyceridemia	23 (29)	32 (38)
Diabetes mellitus	5 (6)	14 (17)
Obesity	6 (8)	17 (20)
Systemic hypertension	15 (19)	22 (26)
Previous myocardial infarction	13 (17)	44 (52)
Angina on effort	31 (40)	60 (71)
Angina at rest	76 (97)	78 (93)
Abnormal electrocardiogram	32 (41)	59 (70)
Positive exercise stress test	32 (41)	44 (52)
Abnormal echocardiogram	21 (27)	53 (63)
Angiographic ejection fraction (%)	66 ± 16	59 ± 17

(): %

with single vessel (19 patients) than in patients with multivessel coronary disease (11 patients) ($p=0.02$). Conversely, bypass surgery was more frequent among patients with multivessel (34 patients) than with single-vessel coronary disease (5 patients) ($p<0.01$). Calcium antagonists, nitrates, anti-platelet agents, and β blockers were prescribed in 97, 78, 47 and 4% of group 1 patients, respectively, and in 98, 86, 51 and 4% of group 2 patients, respectively ($p=NS$).

Statistical analysis

Comparisons between the two groups of patients were performed by using the χ^2 test for categorical variables. To calculate survival in the two groups of patients, life tables of survival were obtained by using the Kaplan-Meier method. The statistical significance of the difference between the 5-year survival for the two groups was evaluated by the Mantel-Haenszel test. The Cox proportional-hazards regression analysis (toward stepwise procedure) was used to investigate whether any variable was an independent predictor of survival, considering all causes of death. Variables selected for examination were age, gender, family history of coronary artery disease, cigarette smoking, hypercholesterolemia, hypertriglyceridemia, diabetes mellitus, obesity, hypertension, previous myocardial infarction, angina at rest, angina on effort or mixed, time from the onset of symptoms, baseline electrocardiogram

(normal or abnormal), baseline two-dimensional echo (normal or abnormal), extent of coronary lesions with greater than 50% diameter stenosis and angiographic left ventricular ejection fraction. Values of plasma cholesterol and triglyceride levels >240 and 200 mg/dl, respectively, were considered abnormal. Diabetes was defined by either anti-diabetic therapy or a fasting plasma glucose level of >140 mg/dl. Obesity was defined as a weight $\geq 20\%$ of the ideal weight by height, age and sex. Hypertension was defined as repeated values of blood pressure of ≥ 160 mmHg systolic or ≥ 95 mmHg diastolic. The stress test was considered to be positive for ischemia if either a depression of the ST segment ≥ 0.15 mV or an elevation of ≥ 0.2 mV, at 0.08 sec after the J point, occurred. A p value <0.05 was considered statistically significant.

RESULTS

Prevalence of coronary lesions

Coronary artery stenoses were detected in 151 of the 162 patients with Prinzmetal's variant angina (93%). Specifically, 41 patients (25%) showed stenoses of three major coronary vessels, 43 patients (27%) of two vessels, 67 patients (41%) of a single vessel, and only 11 patients (7%) showed absolutely normal coronary arteries.

Lesion severity

In the 59 patients with single-vessel coronary stenoses who underwent quantitative coronary angiography, the stenosis appeared to be severe, reducing the internal luminal diameter by $51 \pm 12\%$ (range 20–71%) (Fig. 1). The illustration also shows the histograms of the 11 patients with absolutely normal coronary arteries and of the five patients with total coronary occlusion.

Prognostic impact of the extent of coronary lesions

Considering overall mortality, there were 20 deaths during a 5-year follow-up. This also includes the mortality within 1 month of coronary surgery (three of 39 patients, 8%) and the mortality within 1 month of coronary angioplasty (one of 30 patients, 3%). Kaplan-Meier survival analysis revealed a significantly lower 5-year survival rate in patients with multivessel coronary lesions (80.1%) as compared with those with single-vessel lesions or normal coronary arteries (94.6%, $p=0.006$ by Mantel-

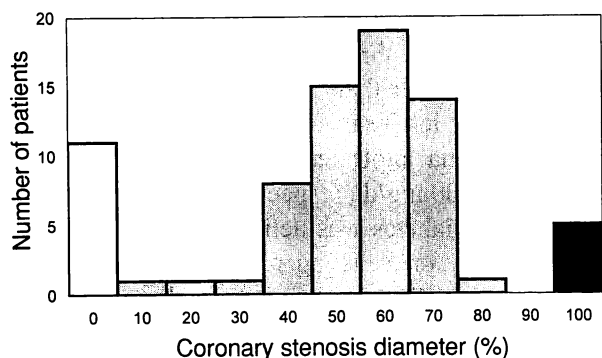


Fig. 1 Frequency distribution of coronary stenoses in patients with Prinzmetal's angina and single-vessel coronary lesions

Coronary stenoses (gray bars) are expressed as percentage luminal diameter reduction. Patients with normal coronary arteries (white bar) and those with total coronary occlusion (black bar) of a single vessel are also shown.

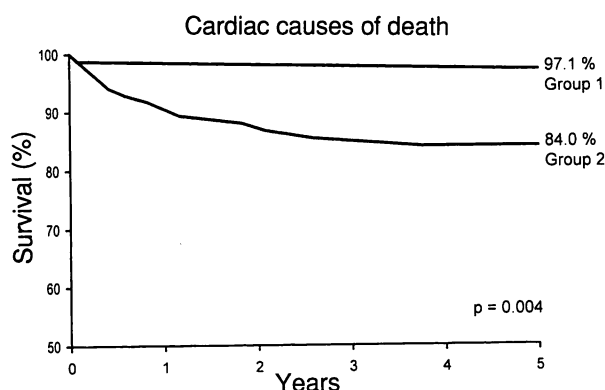


Fig. 2 Cumulative survival of patients with single-vessel coronary lesions or normal coronary arteries (group 1) and multivessel coronary stenoses (group 2), considering all causes of death

Haenszel test; **Fig. 2**). At the end of the 5-year follow-up, the overall mortality ratio between patients of groups 2 and 1 was 3.7. There were 16 cardiac deaths during follow-up. Again, the 5-year survival rate was lower in group 2 (84.0%) than in group 1 (97.1%, $p=0.004$; **Fig. 3**) at the end of the follow-up the cardiac mortality ratio between the two groups was 5.5.

Cox regression analysis

To determine whether organic coronary lesions were an independent predictor of survival, data were examined by Cox regression analysis. As shown in **Table 2**, several variables appeared to be predictors of survival by univariate analysis. However, multivariate analysis showed that only angiographic ejection fraction, hypertriglyceridemia and extent of coronary lesions were indepen-

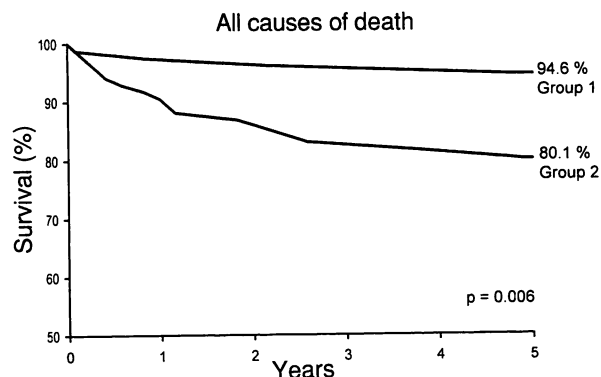


Fig. 3 Cumulative survival of patients with single-vessel coronary lesions or normal coronary arteries (group 1) and multivessel coronary stenoses (group 2), considering cardiac causes of death

Table 2 Variables predictive of survival by univariate Cox regression analysis

Variables	χ^2	p value
Left ventricular ejection fraction	25.96	0.000
Coronary artery disease	9.73	0.001
Hypertriglyceridemia	7.69	0.005
Angina at rest	4.84	0.027
Previous myocardial infarction	4.54	0.033
Duration of symptoms	4.27	0.038
Abnormal electrocardiogram	3.69	0.054

dent predictors of survival (**Table 3**).

Effects of treatment

Independent of the treatment, the mortality rate was significantly higher in group 2 than in group 1. Interrupting the follow-up at the time of coronary revascularization, Kaplan-Meier survival analysis showed a lower 5-year survival rate in group 2 (84.1%) than in group 1 (96.3%). Considering the revascularized patients, again, the 5-year survival rate was lower in group 2 (84.4%) than in group 1 (100%).

DISCUSSION

Prevalence and extent of coronary stenoses in variant angina

This study shows that organic coronary stenoses are frequent in patients with Prinzmetal's variant angina. In fact, angiographically detectable coronary lesions were observed in all patients but 11. The prevalence of absolutely normal coronary arter-

Table 3 Variables predictive of survival by multivariate Cox regression analysis

Variables	χ^2	p value	Risk ratio	Confidence	Interval
Left ventricular ejection fraction	25.96	0.000	1.0958	1.0586	1.1346
Hypertriglyceridemia	4.308	0.038	2.6519	1.0737	6.5498
Coronary artery disease	4.045	0.044	4.5213	1.4033	14.5664

ies might have been even lower if more accurate techniques were used. In fact, even angiographically normal coronary arteries of patients with variant angina can present with underlying atherosclerosis at autopsy¹⁴. More recently, intimal lesions, including intimal flap, intimal hemorrhage, thrombus and ulcer, were observed by angioscopy in four out of 10 patients with variant angina, who did not present angiographic lesions at the site of coronary artery spasm¹⁵.

The prevalence and extent of organic coronary lesions described in this study appear to be greater than those reported by Walling *et al.*⁴ and by Nakamura *et al.*¹⁶ in variant angina and similar to those previously described from our institution^{3,11}, but still lower than in patients with effort angina¹⁷⁻¹⁹.

Prognostic impact of coronary stenoses

Beside the known effects of impaired left ventricular function on long term prognosis of patients with coronary artery disease^{20,21}, this study shows that an anatomic factor (*i.e.*, the extent of coronary lesions) plays a major role in affecting the long-term prognosis of patients with variant angina. This observation is in agreement with the study of Walling *et al.*⁴ and at variance with the study by MacAlpin⁸.

Several studies have demonstrated that the attacks of Prinzmetal's angina are precipitated by functional factors. In fact, the episodes of variant angina are not preceded by an increase in myocardial oxygen demand and are associated with a transient coronary obstruction leading to a primary reduction in regional blood supply³. The latter can be induced by several mechanisms, including coronary vasospasm²⁻⁵, mural thrombus^{6,7,15,22,23}, disruption of an atherosclerotic plaque^{24,25} or a combination of these. However, there is still the question of how organic factors so heavily influence the long-term prognosis of Prinzmetal's angina if anginal attacks are precipitated by functional factors. A possible explanation might be that the greater is the extent of

detectable coronary lesions, the greater is the probability of intimal injury, which is likely to be related to the pathogenesis of coronary artery spasm and thrombus.

Limitations of the study

Due to clinical instability, the exercise stress test was not performed in 19% of the patients. The angiographic ejection fraction was not available in 8% of the patients who did not undergo left ventriculography or showed frequent premature ventricular contractions during the study. The number of ischemic episodes was not considered among the predictors of prognosis, as well as the response to medical treatment. The mortality rate after revascularization appeared to be quite elevated, likely due to the combination of extensive anatomical damage with clinical instability. Finally, the results of this study cannot be transferred to patients with angina at rest and ST segment depression¹⁸.

Coronary atherosclerosis or transient ischemia at rest : Which is worst for prognosis?

The effect of myocardial ischemia at rest on the long-term prognosis of patients with effort angina was evaluated in a previous study¹⁹. Two groups of patients with exertional angina were studied : one group (483 patients) had ischemia only on effort and another (224 patients) both on effort and at rest. The two groups did not differ as to age, gender, coronary risk factors, baseline electrocardiogram, incidence of previous myocardial infarction, angiographic left ventricular dysfunction and extent of coronary lesions. Despite a similar prevalence of organic coronary stenoses, the 5-year survival rate was lower in patients with ischemia both on effort and at rest than in those with ischemia only on effort. The overall mortality was 1.95 times higher in patients with mixed ischemia than in those with effort ischemia, and cardiac mortality was 1.7 times higher in patients with mixed ischemia. Thus, transient ischemia at rest plays an independent role in the

prognosis, which quite doubles the mortality rate. The impact of organic coronary lesions in variant angina was evaluated in the present study. Transient ischemia at rest with ST segment elevation was documented in every patient. However, the overall mortality rate was 3.7 times higher in patients with multivessel coronary disease than in those with single-vessel coronary lesions or normal coronary

arteries, and cardiac mortality was 5.5 times higher. The comparison of these two studies, originating from the same institution, suggests that organic factors (coronary stenoses) are more important for the long-term prognosis of patients with angina pectoris than functional factors (reversible myocardial ischemia at rest).

要 約

Prinzmetal 異型狭心症における器質的冠動脈狭窄

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異型狭心症の安静時における虚血発作には機能的な要素が関与しているが、固定した冠動脈疾患の役割についてはまだ議論のあるところである。異型狭心症における器質的冠動脈狭窄の頻度、範囲、重篤度および予後的な意義を評価するために、入院中一過性にST上昇をきたした162例の患者を検討した。そのうち78例は正常冠動脈または一枝病変(第1群)、84例は多枝病変の例であった(第2群)。両群の追跡期間は82±41ヵ月である。

冠動脈造影上正常な例は11例(7%)にすぎなかった。一枝病変例の59例では、冠動脈内径は51±12%に減少していた。5年間の経過追跡中20例が死亡した(そのうち心臓死は16例)。Kaplan-Meier生存分析では、第1群の94.6%に比し、第2群での5年生存率は80.1%と明らかに低下していた($p=0.006$; Mantel-Haenszel テスト)。心臓死のみを取り上げても、5年生存率は第2群でなお低かった(84.0: 97.1%, $p=0.004$)。経過観察中、冠動脈再開通例や全期間を通じて薬剤投与を受けた例を考慮に入れても、第2群の生存率は第1群のそれよりも明らかに低かった。Coxの多変量回帰解析によると、冠動脈病変の広がりや程度が生存に対する独立した予測因子であった。

したがって、器質的冠動脈狭窄は異型狭心症例で頻繁にみられるものであり、長期予後を左右する役割を果たしている。

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