Clinical characteristics and long-term survival of patients with variant angina

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ABSTRACT We studied 109 consecutive patients with variant angina who underwent cardiac catheterization over an 11 year period. All patients were followed for at least 6 months or until death, and 46 patients (22 treated medically and 24 treated surgically) were followed for 5 years or more. Of the 62 patients initially treated medically, 14 had nonfatal myocardial infarctions (12 within 1 month of catheterization) and 12 died (six within 6 months). Survival probabilities at 1, 3, and 5 years were 0.88, 0.84, and 0.77, respectively. Of the 48 surgically treated patients (including four patients initially treated medically and one initially treated with coronary angioplasty), four had nonfatal infarctions (three in the perioperative period) and three died (all in the perioperative period). The survival probability in these patients at 1 year was 0.94 and remained unchanged at 3 and 5 years. Only one nonfatal infarction and no deaths have occurred in the group of surgically treated patients subsequent to hospital discharge. Three additional patients were treated with coronary angioplasty. The single most important prognostic factor in medically treated patients was the presence or absence of fixed obstructive coronary artery disease. Infarction-free survival probabilities at 1 and 3 years in the 23 patients without significant coronary artery disease were 1.0 and 0.89, compared with 0.51 and 0.46 in the 39 patients with significant coronary disease. Analysis by the Cox model showed that variant angina patients had a higher probability of death and nonfatal infarction than did those with nonvariant angina coronary disease if other important prognostic variables were held constant. The major independent prognostic variables for medically treated patients with variant angina were similar to those that were important in medically treated patients with coronary disease who did not have variant angina. Finally, we examined how well variant angina patients with and without significant (≥75%) coronary artery disease could be distinguished from each other with the use of noninvasive baseline characteristics. Although these two groups did have different distributions of some variables, neither univariable nor multivariable techniques were accurate enough to supplant cardiac catheterization for identifying variant angina patients without significant disease.
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ONLY 2% to 3% of patients with chest pain undergoing cardiac catheterization at large referral centers have Prinzmetal's variant angina.[1-2] Even centers with a research interest in the disorder have a reported experience amounting to 200 patients or less per institution.[3] Much of the published literature on variant angina deals with its clinical, angiographic, and therapeutic features; other aspects have been less completely studied. For example, relatively few reports describe the prognosis for these patients. In two reports dealing with the long-term prognosis for medically treated patients with variant angina a high rate of death and nonfatal myocardial infarction during the first 3 to 6 months of follow-up was observed.[4-6] In surgically treated patients the risk of nonfatal infarction or death has been low among those surviving the perioperative period.[7-9] Important predictors of prognosis in variant angina have not been clearly identified, although the presence of significant coronary artery disease does appear to be associated with a poorer prognosis in

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medically treated patients.[4–6] Because of the small numbers of patients available for study, it has not previously been feasible to identify the important independent variables associated with survival with the use of multivariable methods (e.g., the Cox regression model). Finally, it remains unclear whether groups of patients with and without significant fixed coronary obstructive disease can be distinguished on the basis of clinical information obtained noninvasively. Consequently, many authorities currently recommend that all patients with variant angina undergo diagnostic cardiac catheterization.[10–12]

In this report, we study three specific aspects of variant angina. First, we describe the long-term clinical outcomes in 109 consecutive patients. Second, we examine the important variables associated with prognosis in this population. Finally, we examine the problem of predicting the presence or absence of significant coronary disease in this population with the use of noninvasively obtained clinical characteristics.

Methods

Study patients. The study group was drawn from all patients undergoing cardiac catheterization for suspected coronary artery disease at Duke University Medical Center between January 1972 and December 1982. Patients with valvular or congenital heart disease, except those with mitral regurgitation secondary to coronary artery disease, were excluded. Specific criteria for entry into the study were: (1) history of chest discomfort at rest (2) accompanied, on at least one occasion, by transient ST segment elevation occurring either spontaneously or after intravenous ergonovine and (3) no evidence of acute myocardial infarction after the pain. Of the 6281 patients eligible for the study, 109 (2%) met the specific entry criteria and form the basis of this report.

Baseline data collection. The computerized information system used in this study has been described previously.[13] Baseline information was collected prospectively at the time of cardiac catheterization. The variables examined in the present study consisted of multiple descriptors of the history, physical examination results, chest x-ray, electrocardiogram, and results of cardiac catheterization.[14] Decisions about therapy were made by the individual physicians in conjunction with their patients. Of the 109 patients with variant angina, 62 were initially treated medically, four underwent percutaneous transluminal coronary angioplasty (PTCA), and 43 underwent coronary artery bypass graft (CABG) surgery. Four medically treated and one PTCA patient subsequently underwent surgical therapy, all but one within 6 months of catheterization.

Follow-up. Follow-up information was obtained at 6 months and 1 year after cardiac catheterization or CABG and annually thereafter, as reported previously, and was 99% complete.[14] Standard electrocardiographic and enzyme criteria were used for diagnosis of myocardial infarction during follow-up, as described previously.[15] A myocardial infarction was classified as nonfatal if the patient survived to hospital discharge.

Cardiac catheterization. Biplane or single-plane left ventriculography was performed in all patients. Left ventricular ejection fraction was calculated when technically feasible (85% of patients) by the modified area-length method.[16] Coronary angiograms were obtained in multiple left anterior oblique and right anterior oblique projections. Results were reviewed by two or three senior angiographers in conference on the day of catheterization. Significant fixed obstructive coronary disease was defined as 75% or greater narrowing of the luminal diameter of a major coronary artery.[17] Since 1977, patients found to have normal coronary arteries or insignificant (≤50%) coronary obstructive disease have been considered for provocative ergonovine testing at the discretion of the senior angiographer. A positive ergonovine test was defined as the production of reversible coronary artery narrowing resulting in 75% or more stenosis of the luminal diameter. Patients receiving a total of 0.30 mg ergonovine without significant coronary spasm were considered to have a negative test result. Due to our limited use of ergonovine before 1979, only half of the 24 patients without significant coronary disease underwent ergonovine testing. In nine patients (75%) the test produced significant coronary artery spasm; for five of these patients the test provided the only documentation of ST segment elevation with chest pain.

Data analysis. Survival was analyzed separately for medical and surgical patients. Kaplan-Meier life-table estimates of survival and of infarction-free survival were used to summarize the follow-up experience of these patients.[18] Survival rates were not calculated when fewer than 15 patients remained to be followed during an interval. Follow-up time was calculated from the date of initial cardiac catheterization for medical patients and the date of operation for surgical patients. The outcome events considered were cardiovascular death and total cardiac events (defined as cardiovascular death or nonfatal myocardial infarction). Patients who were initially treated medically and then underwent surgery were included in the medical group until the time of surgery and then data on their medical follow-up was censored (withdrawn alive). The follow-up times of patients who died of noncardiovascular causes were censored at the time of death. Four patients were initially treated with PTCA. One of these patients subsequently underwent surgical therapy and is counted as a surgical patient from that time. Data from the other three have been excluded from both medical and surgical follow-up calculations.

To identify potentially important prognostic variables in the medically treated group, the individual effect of certain variables on survival and infarction-free survival was evaluated with the use of the likelihood ratio chi-square test with the Cox regression model.[19] Variables selected for examination included: significant coronary disease, frequency of angina, progressive angina, preinfarction angina, ejection fraction, age, sex, and anterior ST segment elevation with pain. This analysis was done only to identify variables that were strongly associated with survival. Because of the small number of patients with events and the consequent risk of a type II error, no inferences were drawn if a variable failed to achieve a .05 significance level.

We previously demonstrated that variant angina was a significant independent risk factor for both nonfatal myocardial infarction and cardiovascular death in our overall medically treated coronary disease population.[15] In this study we extended these findings by testing the hypothesis that the important independent prognostic variables in patients with medically treated variant angina were not significantly different from those important in our larger coronary disease population. This approach was taken because direct development of multivariable prognostic models was felt to be inadvisable due to the small sample size.

As described elsewhere,[14–15] we previously developed Cox proportional hazards regression models for predicting the probability of survival and infarction-free survival in medically treated patients with coronary disease. These models contained clinical and invasive descriptors including: chest pain course

and frequency, congestive heart failure, peripheral vascular disease, ejection fraction, left ventricular end-diastolic pressure, amount of significant coronary artery disease, electrocardiographic conduction disturbances, sex, and presence of variant angina. In the present analysis, these original model variables and their respective weights were combined to form a linear score that was then used as a single initial variable in new Cox models. To assess whether the weight assigned to each variable in the linear score was appropriate for the medically treated variant angina population, each variable except presence of variant angina was added into the new models in a stepwise fashion. Chi-square score statistics[19–20] were then used to test the added prognostic importance of each variable after adjusting for the linear score. This process provided a statistical test for the adequacy of the weights in the linear score as applied to the variant angina population. We also tested whether independent prognostic information was provided by the presence of anterior ST segment elevation with pain. Predictive ability of the model was evaluated by comparing the mean predicted survival probability for each interval of follow-up with the observed survival experience.

Because of the small number of follow-up events, no attempt was made to identify important prognostic variables in the surgical group. Furthermore, an evaluation of the effect of therapy on prognosis was not attempted because of the large number of imbalances in baseline characteristics between the medically and surgically treated patients and the small number of patients in each group.

The distribution of baseline characteristics in patients with and without significant coronary disease was compared with either the chi-square test or the Fisher exact test for discrete variables and the Wilcoxon two-sample rank-sum test for continuous variables.

Because of the small number of subjects in the population, it was not considered feasible to develop a multivariable model for predicting the probability of significant coronary disease in patients with variant angina. Instead, we approached the problem by using the same indirect analysis strategy described above for prognostic modeling. As described elsewhere,[21] we have developed and validated a logistic regression model for predicting the probability of significant coronary artery disease in patients with chest discomfort. The model contains nine noninvasive descriptors: type of chest pain, previous myocardial infarction, electrocardiographic ST-T changes, age, sex, and certain cardiovascular risk factors. We applied this model to the 109 patients with variant angina to determine how well it characterized this specific group. The appropriateness of the diagnostic weight assigned to each variable was assessed as described above. We also tested whether independent predictive information was provided by the presence of effort angina, progressive or preinfarction angina, or anterior lead ST segment elevation with pain.

The model was then used to predict the probability of significant coronary artery disease for each of the 109 patients with variant angina. Two components of the model's predictive accuracy were examined: reliability and discrimination. "Reliability" is a measure of the agreement between the model's predictions in selected patient subgroups and the observed prevalence of disease in those subgroups. The predictive reliability of the model in the variant angina population was evaluated by ordering the model's predictions from highest to lowest and grouping them into four quartiles of equal size. The mean probability of coronary artery disease for each quartile was then calculated, and the results were compared with the mean prevalence of disease in the same quartile. "Discrimination" is a measure of the model's ability to generate two separate populations of predictions: a low set of predictions for patients without significant disease and a high set for those with disease. The discrimination of the model was evaluated by comparing the model predictions for patients with variant angina with and without significant coronary artery disease.

Results

Prognosis for medically treated patients. In the group of 62 medically treated patients, 14 had nonfatal myocardial infarctions during follow-up. Nine of the 14 infarctions (64%) occurred between the time of catheterization and hospital discharge and another three occurred within 1 month of discharge. Thus, 86% of nonfatal infarctions occurred within 1 month of catheterization. None of these patients had normal coronary arteries, but one had "insignificant" fixed obstructive disease. Over half had a duration of anginal symptoms before catheterization of 1 month or less. Sixty-four percent had preinfarction angina and the remainder had progressive angina.

Deaths were less concentrated in the immediate postcatheterization period, but six of 12 (50%) occurred within the first 6 months of follow-up. Half of the deaths were sudden, three were due to congestive heart failure, and two were due to fatal myocardial infarction. One patient had a cardiac arrest during catheterization and was successfully resuscitated, but he subsequently developed evidence of a large cerebral infarct and died 8 days later. Two of the three deaths attributed to congestive heart failure occurred after a documented nonfatal myocardial infarction and the third occurred after a probable nonfatal myocardial infarction. Preinfarction angina was common (58%); the remainder had a progressive anginal course. No patient who died had normal coronary arteries, but two patients had "insignificant" coronary obstructive disease. Five patients had three-vessel disease and two also had disease of their left main coronary arteries.

Survival in the 62 patients initially treated medically is shown in figure 1. For the whole group, survival probabilities at 1, 3, and 5 years were 0.88, 0.84, and 0.77, respectively. The most important single predictor of survival was the number of coronary arteries with significant obstructive disease ($p = .003$). Survival probabilities at 1 and 3 years for the 23 patients with normal coronary arteries or angiographically insignificant coronary disease were 1.0 and 0.94 compared with 0.80 and 0.76 for the 39 patients with one or more diseased vessels. The other important predictor of survival, besides coronary disease, was chest pain frequency ($p = .04$). A low ejection fraction fell just short of being a significant predictor ($p = .07$), probably because of the small sample size.

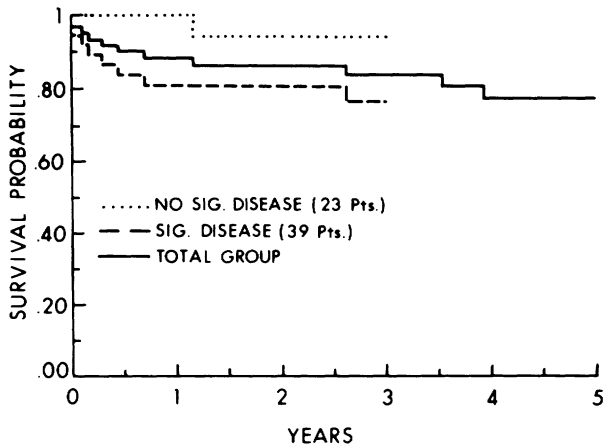

FIGURE 1. Survival of 62 medically treated patients as a group and according to the presence or absence of significant coronary artery disease (sig. disease).

Figure 2 shows the infarction-free survival probabilities for the whole group and for the group subdivided according to the presence or absence of significant coronary artery disease. For all the patients, infarction-free survival probabilities at 1, 3, and 5 years were 0.70, 0.63, and 0.60. There was a pronounced difference in infarction-free survival probabilities between the subgroup without significant disease and that with one or more diseased vessels ($p = .0007$). For the patients without disease, infarction-free survival probabilities at 1 and 3 years were 1.0 and 0.89 compared with 0.51 and 0.46 for the patients with significant disease. Other factors separately associated with a lower probability of survival without infarction were preinfarction angina ($p = .009$), male sex ($p = .02$), and a higher frequency of chest pain ($p = .02$).

Surgically treated patients. In the group of 48 variant angina patients that underwent CABG there were three deaths and four nonfatal myocardial infarctions (figure 3). One of the three patients that died had left main coronary artery disease. A second patient had three-vessel disease and a 50% left main lesion. Two deaths occurred intraoperatively and the third occurred on the seventh postoperative day. Two of the four patients who had nonfatal infarctions had three-vessel coronary disease. Only one patient had a nonfatal myocardial infarction after hospital discharge.

The baseline characteristics of the medically treated patients with significant coronary disease and the surgically treated patients are shown in table 1. The surgically treated patients tended to have a shorter anginal course and more preinfarction angina. The medical group had slightly more congestive heart failure and more of the patients in this group had low ejection fractions. In the surgical group 71% of patients had two- or three-vessel coronary disease compared with 44% in the medical group.

Prediction of prognosis for medically treated patients. Using the Cox model, we found that the important independent predictors of prognosis, including descriptors of coronary anatomy, anginal course, and left ventricular function, were not significantly different in medically treated patients with variant angina and those with coronary disease without variant angina. The variable describing the location of ST segment elevation with pain failed to add independent prognostic information. Figures 4 and 5 compare the observed survival and event-free experiences of the patients with variant angina with Cox model estimates of the mean probabilities of survival and infarction-free survival at each interval of follow-up. Model predictions in both categories closely approximated the observed survival rates, indicating that the models are accurate estimators of prognosis in this specific population.

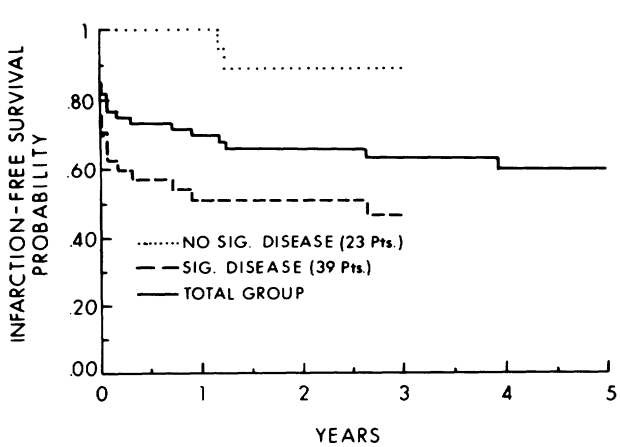

FIGURE 2. Infarction-free survival of 62 medically treated patients as a group and according to the presence or absence of significant coronary artery disease (sig. disease).

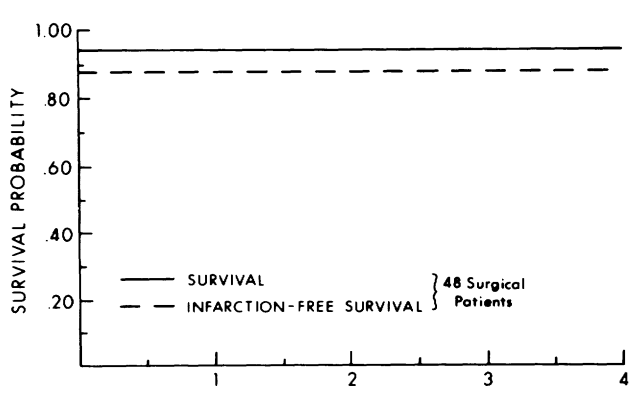

FIGURE 3. Survival and infarction-free survival experience of 48 surgically treated patients with variant angina.

TABLE 1
Baseline characteristics of medically treated patients with significant coronary disease (n = 39) and surgically treated patients (n = 48)

Characteristic	Medical group (%)	Surgical group (%)
Male	82	83
Age ≤50 years	36	42
Historical features		
Duration of angina ≤6 weeks	33	48
Progressive angina	72	85
Preinfarction angina	51	75
Exertional angina	62	50
Nocturnal angina	54	33
Previous myocardial infarction	21	33
CHF (NYHA class ≥2)	8	2
History of syncope or ventricular tachycardia	10	19
Anterior ST segment elevation	33	58
Catheterization features		
Ejection fraction <40%	18	14
Normal LV contraction	54	44
Left main coronary artery disease	5	2
LVEDP >18 torr	10	13
No. of vessels with ≥75% stenosis		
1	56	27
2	26	40
3	18	31
Surgery within 1 week of catheterization	—	77

CHF = congestive heart failure; NYHA = New York Heart Association; LV = left ventricular; LVEDP = left ventricular end diastolic pressure.

Prediction of significant coronary artery disease. Table 2 lists the baseline characteristics of the 85 patients with variant angina and significant coronary disease and the 24 patients without significant coronary disease. In the group with significant disease there was more men ($p = .007$) and the members tended to be older ($p = .05$). Approximately 80% of patients presented with an acceleration of their anginal pain pattern. However, patients with significant coronary disease were much more likely to present with preinfarction angina ($p = .001$). Also, diagnostic Q waves were seen on precatheterization electrocardiograms more frequently in the subjects with significant coronary disease ($p = .04$).

The important predictors of the probability of significant coronary disease in variant angina were not significantly different from those previously identified in our larger coronary disease population. After adjustment for multiple comparisons,[22] none of the additional variables tested (i.e., progressive angina, preinfarction angina, effort angina, anterior ST segment elevation with pain) added independent predictive information.

The reliability of the model is demonstrated in table 3, which compares the model probability estimates with observed prevalence of coronary disease in the variant angina population. Overall, the mean model prediction of the probability of significant coronary disease was close to the mean observed prevalence. The model was very reliable when it predicted a high probability of disease (quartiles 2 to 4), but was less reliable when it predicted a low probability of disease (quartile 1).

The ability of the model to distinguish between patients with variant angina with and without significant coronary disease is demonstrated in figure 6. The median prediction for the patients without significant disease was 0.52 and that for the patients with disease was 0.89. Only 4% of patients without coronary disease received a model prediction of 0.10 or less. In contrast, 49% of patients with disease received a predic-

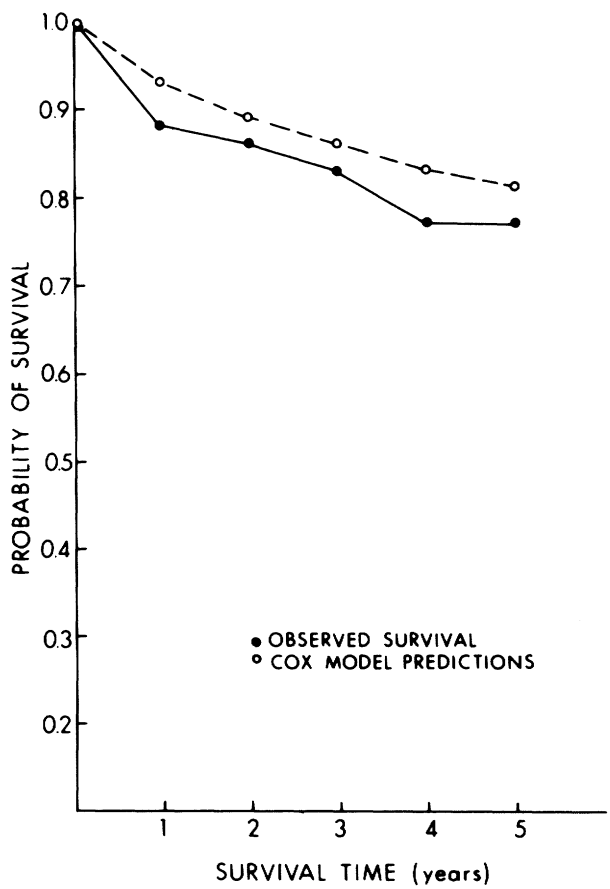

FIGURE 4. Comparison of observed survival experience (Kaplan-Meier estimates) and Cox model survival predictions for 62 medically treated patients.

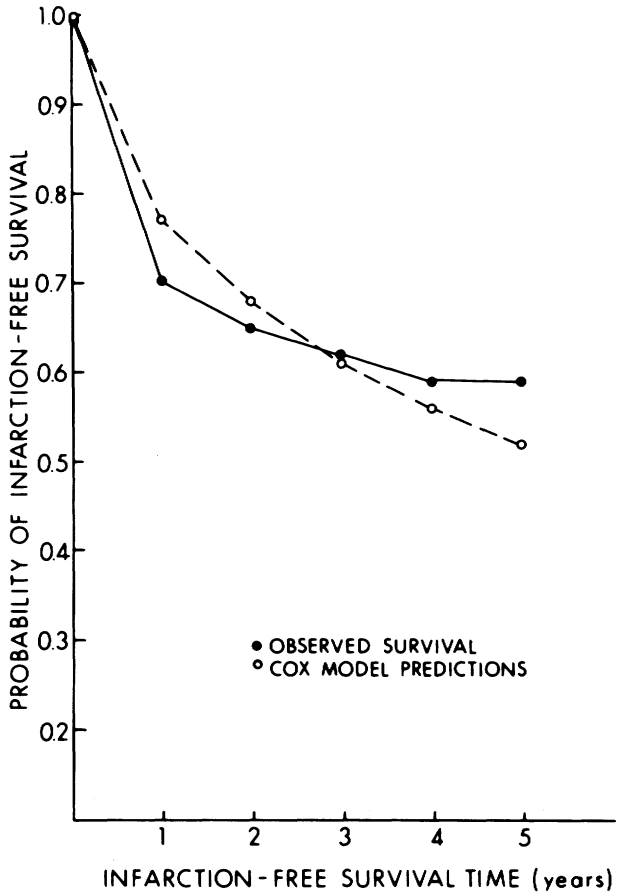

FIGURE 5. Comparison of observed infarction-free survival experience (Kaplan-Meier estimates) and Cox model predictions of infarction-free survival for 62 medically treated patients.

tion of 0.90 or greater. Thus, the model failed to achieve enough discriminating power in this population to allow accurate identification of the majority of patients without significant coronary artery disease.

Discussion

The survival characteristics of our 62 medically treated patients are similar to those reported by Severi et al.[4] and Waters et al.[6] Eighty-six percent of nonfatal myocardial infarctions in our population occurred within 1 month of catheterization. In the group studied by Severi et al., 87% of nonfatal infarctions occurred within 1 month of hospital admission. Waters et al. observed 91% of nonfatal infarctions during the first 3 months of follow-up. In our series, 50% of deaths occurred during the first 6 months after catheterization compared with the 42% before hospital discharge reported by Severi et al. and the 57% during the first 3 months of follow-up reported by Waters et al. These reports document that the patient with variant angina is at highest risk of both nonfatal myocardial infarction and death in the first 3 to 6 months after being referred to a tertiary care center for evaluation.

In our population, 93% of nonfatal infarctions and 83% of deaths during follow-up occurred in patients with significant coronary disease. The remainder of the events occurred in patients with insignificant (≤50%) fixed disease, and none of the 10 patients with completely normal coronary arteries had a follow-up event. Severi et al. reported that 97% of nonfatal infarctions and 92% of deaths in their study were in patients with significant (≥50%) coronary disease. In the series of Waters et al., 73% of myocardial infarc-

TABLE 2

Baseline characteristics of 109 patients with variant angina grouped according to the presence (n = 85) or absence (n = 24) of significant fixed coronary disease

Characteristic	Significant coronary disease (%)	No significant coronary disease (%)
Male	81	54
Age ≤50 years	39	67
Historical features		
Duration of angina ≤6 weeks	42	38
Progressive angina	85	75
Preinfarction angina	66	29
Exertional angina	55	54
Nocturnal angina	43	50
Previous myocardial infarction	26	13
CHF (NYHA class ≥2)	5	4
β-Blocker therapy on admission	50	48
History of hypertension	45	33
History of diabetes	9	0
History of smoking	87	75
History of syncope	4	4
History of cardiac arrest or ventricular tachycardia	15	29
Laboratory findings		
Cardiomegaly on chest x-ray film	11	0
Diagnostic Q waves on electrocardiogram	25	4
Anterior ST segment elevation	57	37
Nonspecific ST-T wave changes on electrocardiogram	74	67
No. of vessels with ≥75% stenosis in total group (n = 109)		
0	22%	
1	33%	
2	25%	
3	20%	
Left main coronary artery disease	3%	

CHF = congestive heart failure; NYHA = New York Heart Association.

TABLE 3

Comparison of logistic regression model predictions of the probability of significant coronary artery disease vs observed prevalence of disease in 109 patients with variant angina (results for the entire population and for the population divided into four quartiles based on probability of significant disease)

	Predicted	Observed[A]	n
Overall	0.73	0.78 ± 0.08	109
Quartile 1	0.36	0.56 ± 0.19	27
Quartile 2	0.68	0.70 ± 0.18	27
Quartile 3	0.89	0.93 ± 0.10	27
Quartile 4	0.98	0.93 ± 0.10	28

[A]Values are ±2 SEs.

tions and 93% of deaths occurred in subjects with significant fixed obstructive disease.

The 10 patients in our series with arteriographically normal coronary arteries did not experience any follow-up events. Nevertheless, there is evidence that such patients are not completely free of the risk of cardiac events.[23–25] No center has yet accumulated enough experience to determine if they differ prognostically from patients with "insignificant" disease. The risk of cardiac events during follow-up does appear to increase with the amount of coronary disease present.

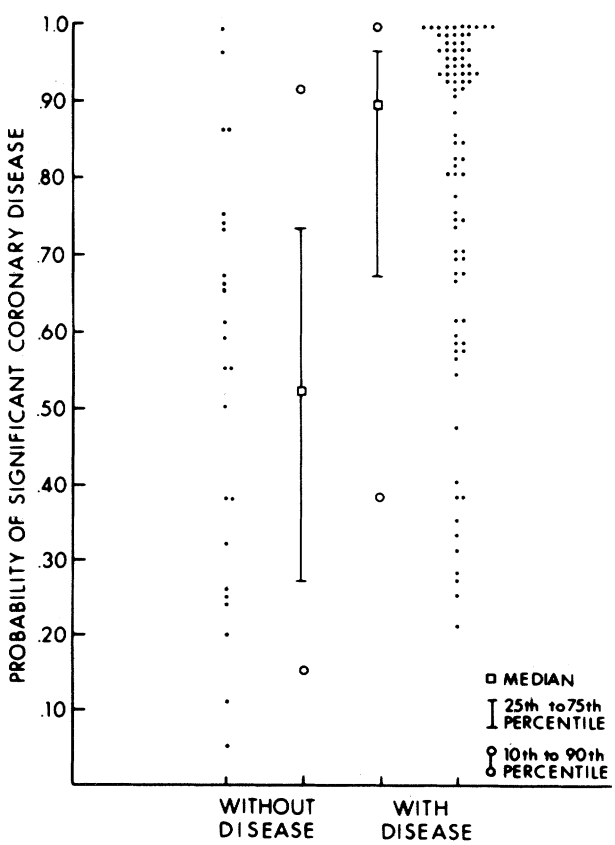

FIGURE 6. Probability of significant coronary artery disease predicted by logistic model for patients with and without significant coronary disease.

In our series of medical patients, six of seven subjects with three-vessel disease, seven of 10 with two-vessel disease, and seven of 22 with one-vessel disease suffered myocardial infarctions or died during follow-up. This trend is also evident in the other larger series.[4, 6] However, no published series to date has included enough patients in each of the five categories of coronary disease (i.e., normal, "insignificant", one-, two-, and three-vessel disease) to accurately compare the effects of gradations in severity of disease on survival probabilities.

Little information is available about the important prognostic factors in variant angina. Besides significant coronary disease, variables that have been associated with a poor prognosis include the presence of left ventricular wall motion abnormalities[4, 6] and the presence of spontaneous attacks of variant angina.[6] Waters et al.[5] have noted that although there are some differences in the baseline noninvasively and invasively determined characteristics of patients with and without follow-up events, none are prognostically powerful enough to be clinically useful when considered individually.

Using the Cox regression model, we tested the hypothesis that the important prognostic variables in medically treated patients with variant angina were not significantly different from those previously identified in our overall medically treated coronary disease population. We found that the effect of each variable (including number of vessels with significant coronary disease, chest pain course and frequency, and ejection fraction) on prognosis was not significantly different in patients with variant angina and those with coronary disease who did not have variant angina. The location of ST segment elevation with pain failed to add independent prognostic information to either model.

Figures 4 and 5 demonstrate that the Cox model predictions of survival and infarction-free survival were close to the observed rates. This finding provides evidence that the major independent prognostic variables are similar in coronary disease patients whether or not variant angina is present.

The fact that variant angina was found to be an important independent prognostic factor in our medically treated coronary disease population, as reported previously,[15] indicates that patients with variant angina have a significantly higher probability of death and nonfatal myocardial infarction during follow-up than do coronary disease patients who do not have variant angina, if other prognostic factors are held constant.

Our experience with surgically treated variant angina, which is one of the largest reported to date, shows

that patients surviving to hospital discharge have an excellent prognosis. With the exception of one nonfatal infarction, all events in this group occurred within 1 week of operation. Other recent series of surgically treated patients have noted a similar concentration of events around the time of operation with rare follow-up events thereafter.[7–9, 26] These results are in contrast to earlier reports that suggested a poor response to surgery in small groups of subjects.[1, 27] It should be emphasized that we have avoided making any direct comparison of prognosis in medically and surgically treated patients. Such an analysis would require that all important prognostic factors be accounted for before the effect of treatment on outcome coud be examined. As previously noted, our patient population was not large enough to permit us to do this.

Having identified the presence of coronary disease as the single most important prognostic variable in medically treated patients with variant angina, we sought to determine if there were specific noninvasive characteristics that could distinguish between patients with and without coronary disease. In previous studies[28–30] the variables most frequently associated with the absence of significant coronary disease have included female sex, absence of effort angina, and inferior lead ST segment elevation with pain. In our series, subjects without coronary disease were younger, more often female, more likely to have stable or progressive rather than preinfarction angina, and less likely to have diagnostic Q waves on their resting electrocardiograms. We did not find the prevalence of effort angina or inferior ST segment elevation with pain to be significantly different in the two groups. It is clear from the accumulated data, including that from our series, that there is no consistent single variable or small group of variables that permits clinical discrimination between these two disease states.

The failure to achieve adequate separation of patients by considering baseline characteristics one at a time or in small subgroups led us to postulate that our results could be improved by considering multiple characteristics simultaneously with a multivariable regression model. The model we used was fairly reliable in the variant angina population, particularly when it predicted a high probability of disease. Furthermore, it distinguished fairly well between groups with and without significant coronary disease. However, it still did not accomplish the clinical goal of accurately identifying individual patients with variant angina without significant disease. The implication of this result is that, at present, cardiac catheterization is required for accurate prognostic stratification of these patients.

Several clinical implications of our study are worth emphasizing. First, the presence of variant angina identifies coronary disease patients at an increased risk of nonfatal myocardial infarction and death. In most cases, the period of greatest risk is heralded by an acceleration of the tempo of the anginal pain pattern. Second, the risk of cardiac events in patients with variant angina is dramatically increased in the presence of significant coronary artery disease. Third, there does not appear to be any way, at present, to accurately identify patients with variant angina without significant coronary artery disease with the use of noninvasively determined characteristics. Thus, cardiac catheterization is required for accurate prognostic stratification of these patients. Finally, CABG appears to be associated with a low risk of follow-up events in variant angina patients with significant coronary disease. However, whether surgery is more effective than intensive medical therapy with calcium channel–blocking drugs as a prognosis-modifying intervention remains to be established.

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