Angiographic and histopathologic correlations. Diaq Radiol 113: 581, 1974

Many studies have documented the relationship between frequency and complexity of premature ventricular contractions (PVC) and the risk of subsequent sudden death in patients with coronary artery disease.1–4 The presence of both multivessel disease4 and abnormal left ventricular contraction (LVC)6 has been associated with increased risk of both sudden and nonsudden death. Cardiac catheterization data from patients resuscitated from ventricular fibrillation have revealed a high incidence of three vessel disease and abnormalities of left ventricular wall motion.7 From this center, Margolis et al. studied a cohort of 536 patients who had angiographically demonstrated coronary artery disease (CAD), and correlated survival with clinical, angiographic and hemodynamic variables.8 Patients who died, either suddenly or nonsuddenly, had a much higher prevalence of

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**Relationships among Ventricular Arrhythmias, Coronary Artery Disease, and Angiographic and Electrocardiographic Indicators of Myocardial Fibrosis**

**ROBERT M. CALIFF, M.D., JOHN M. BURKS, M.D., VICTOR S. BEHAR, M.D., JAMES R. MARGOLIS, M.D., AND GALEN S. WAGNER, M.D.**

**SUMMARY** This study was performed to determine the relationships among angiographic, hemodynamic, clinical, and electrocardiographic data and premature ventricular contractions (PVCs). Arrhythmias were analyzed by 24 hour Holter monitor in 244 patients evaluated for chest pain by coronary angiography and left ventriculography. Using a categorical linear model, the presence of myocardial fibrosis as indicated by both abnormal left ventricular contraction (LVC) and abnormal initial QRS on electrocardiogram was found to be the only independent predictor of both frequent and complex ventricular arrhythmias ($P < .0001$). All other descriptors, including the number of diseased vessels ($\geq 75\%$ obstruction), were dependent upon abnormal LVC in their association with PVCs. When the right anterior oblique view of the left ventriculogram was divided into nine segments to allow automated quantitative analysis of LVC, the prevalence of frequent PVCs was directly related to the number of abnormally contracting segments. Of patients with 0 abnormal segments, $11\%$ had $\geq 2$ PVC/hr, in contrast to $44\%$, $73\%$ and $100\%$ of patients with 1–3, 4–6, and 7–9 abnormal wall segments, respectively ($P < 0.01$). A similar quantitative relationship was found between premature ventricular contractions and abnormal initial forces indicating previous myocardial infarction on the electrocardiogram.
three vessel disease and left ventricular contraction abnormalities than the survivors.

It is important to determine whether baseline ventricular arrhythmias, number of diseased vessels, and abnormalities of LVC are independent predictors of sudden death, or interrelated characterizations of the terminal phase of an illness which may conclude either gradually or suddenly. The purpose of this study was to clarify these relationships and to determine whether noninvasive descriptors might be equally predictive of the presence of either frequent or complex premature ventricular contractions.

Methods

The study population was drawn from all patients evaluated for suspected coronary artery disease at Duke University Medical Center between August 1975 and January 1977. All underwent left ventriculography and coronary arteriography. Patients with rheumatic heart disease, congenital heart disease or mitral prolapse were excluded. Two hundred forty-four of the 928 patients meeting these criteria underwent 24 hour Holter monitoring on the day following cardiac catheterization. During the monitoring period, all patients were ambulatory in the hospital environment as their symptoms permitted. These 244 patients were selected solely on the basis of available monitoring equipment, and without knowledge of catheterization findings. A comparison of baseline characteristics including age, sex, catheterization findings and severity of clinical symptoms by New York Heart Association classification revealed no significant differences between the group monitored and the group not monitored. The mean age of the patients, 75% of whom were male, was 48 years with a range of 21 to 72 years. A complete medical history and physical examination were obtained on all patients. In addition, all patients had a standard 12 lead electrocardiogram (ECG).

Data Analysis

Continuous 24 hour electrocardiographic recordings were obtained with a 2 channel Model 425 Avionics Holter recorder. Modified bipolar chest leads V1 and V6 were used. An Avionics Model 660 Dynamic Electroscanner with an Avionics Model 662A Arrhythmia Computer was employed for analysis of the recordings. An R wave triggered sound system and oscilloscopic display of the two channel cardiogram and R-R intervals were provided by the electroscanner. The arrhythmia computer was set for each recording to identify prematurity and differing QRS width and amplitude to count automatically the frequency of PVCs. (PVC = premature QRS complex greater than or equal to 120 msec. Clear atrial premature contractions with aberrancy were excluded.) The recordings were analyzed by a technician, and when possible, each abnormal cycle was printed out for review by a cardiologist. When more than 10 PVCs per hour were present, a representative five minute hand count from each hour was compared to the arrhythmia computer count. When the two were consistent, the computer count was used. Otherwise, all counting was done by hand.

Tallies were made of the number of PVCs in each hour, and the average number of PVCs per hour (PVC/H) was calculated. Thus an average of ≥2 PVC/H was ≥48 PVC on the 24 hour tape. Complex ventricular arrhythmias included ventricular tachycardia (3 or more consecutive PVCs), pairs (2 consecutive PVCs), bigeminy (alternating PVCs and sinus beats) or multiformity (PVCs with different QRS configuration).

In the ECG analysis Q waves were defined as initial downward deflections of .03 seconds duration or longer. "Minimal R waves" considered present were in leads V1-4 when initial QRS deflection was positive but ≤.01 mV in amplitude and did not exceed 20 msec duration. Congestive heart failure was classified by the standard New York Heart Association classification. Records of enzyme changes or ECG changes were required for documentation of previous myocardial infarctions. The historical and clinical variables along with the catheterization data and arrhythmia analysis were entered into a previously described data bank.

Single plane coronary cineangiography and biplane left ventriculography were performed on all subjects. Results were reviewed by at least three senior angiographers on the day of catheterization. Significant coronary artery disease was defined as 75% or greater stenosis of a major coronary artery. Localized areas of abnormal left ventricular contraction were qualitatively categorized as asynery, dyskinesia, or akinesia according to criteria reported by Herman et al.

A quantitative analysis of ventricular wall motion was obtained using the hemiangular wall motion analysis technique previously described by Ideker, Behar and co-workers. In this technique the end-diastolic and end-systolic ventricular outlines in the right anterior oblique position were traced with a sonic digitizer pen that was interfaced with a PDP 11/45 computer. The program determined the longitudinal axis from the apex to the midpoint of the aortic valve for both the diastolic and systolic images, and constructed four evenly spaced axes perpendicular to these lines. The percentage change from end diastole to end systole for each of the

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Distribution of average number of PVCs per hour among 244 patients who had 24 hour Holter monitoring. The mean PVC/H was 23, but the median was less than 1.
eight hemiaxes and the apex then was calculated by the computer according to the equation:

\[
\text{Percent shortening} = \frac{\text{end diastolic length} - \text{end systolic length}}{\text{end diastolic length}} \times 100
\]

A value within 2 standard deviations from the mean value for that segment (obtained from a series of 58 normal patients) was considered normal. Thirty unselected ventriculograms of patients who were qualitatively considered to have normal LVC were analyzed quantitatively. Since none of these ventriculograms had any abnormal segments, the remainder which were considered to be qualitatively normal were assumed to be quantitatively normal as well. Ninety-three of the 117 qualitatively abnormal ventriculograms were technically suitable for the quantitative analysis.

Statistical analysis of the data was performed using the chi-square test and the categorical linear model

\(^{14}\) where applicable. This model allows determination of the independent predictive power of a number of variables, and also whether there is interaction between variables.

### Results

Of the 244 patients monitored, 169 had PVCs. The average number of PVCs per hour (PVC/H) was 22.9 with a range of 0 to 1697 (fig. 1). Seventy percent of the patients averaged < 2 PVC/H and the median PVC/H was less than 1.0. At least one complex ventricular arrhythmia occurred in 82 patients (34%). Ventricular tachycardia was found in 13 patients, bigeminy in 47 patients, pairs in 33 patients, and multifornitv in 64 patients. Complex ventricular arrhythmias occurred in 14% of patients with <2 PVC/H, in 76% with 2-9 PVC/H and in 85% with >9 PVC/H.

Patients with three vessel disease averaged 38.9 PVC/H compared to 7.3 PVC/H for patients with two vessel disease, 5.5 PVC/H for patients with one vessel disease and 16.4 PVC/H for patients with no significant CAD (table 1). A higher percentage of patients with ≥2 PVC/H and with at least one of the complex arrhythmias also was found in the group with three vessel CAD than in the other groups. No significant difference was found among patients with two vessel disease, one vessel disease, or no CAD with respect to any of the arrhythmia categories. Therefore, when only the number of diseased vessels was considered, patients with three vessel CAD had a significantly higher frequency of ventricular arrhythmias than the remainder of the population.

However, when the patients were subdivided into those with any abnormality of LVC at cardiac catheterization and those with normal LVC, the relationship between PVCs and the number of diseased vessels was found to be dependent upon abnormalities of LVC. Within each group with an equal number of diseased vessels, those with abnormal LVC had a larger number of ventricular arrhythmias (table 2). The widest differences were found in the three vessel disease category, in which 57% of those with abnormal LVC had ≥2 PVC/H, whereas only 13% with normal LVC had ≥2 PVC/H. Among patients with normal LVC, there was no relationship between ventricular arrhythmias and the number of diseased vessels.

These data were analyzed using the categorical linear model

\(^{14}\) to determine whether the number of diseased vessels and abnormalities of LVC were independent predictors of ventricular arrhythmias. When LVC was controlled the number of diseased vessels had no independent importance in predicting increased frequency of either ≥2 PVC/H or complex ventricular arrhythmias. However, the presence of abnormal LVC was a highly significant independent predictor (P < 0.0001). Therefore, ventricular arrhythmias in pa-

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**Table 1. Relationship between Extent of CAD and Ventricular Arrhythmias**

<table>
<thead>
<tr>
<th>No. of diseased vessels</th>
<th>0 (N = 66)</th>
<th>1 (N = 40)</th>
<th>2 (N = 35)</th>
<th>3 (N = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average PVC/H (P &lt; .05)*</td>
<td>16</td>
<td>6</td>
<td>7</td>
<td>39</td>
</tr>
<tr>
<td>Percent with complex arrhythmias (P &lt; .01)*</td>
<td>15% (10)</td>
<td>23% (9)</td>
<td>23% (8)</td>
<td>44% (45)</td>
</tr>
<tr>
<td>Percent with ≥ 2 PVC/H (P &lt; .01)*</td>
<td>24% (10)</td>
<td>30% (12)</td>
<td>20% (7)</td>
<td>46% (47)</td>
</tr>
</tbody>
</table>

*P value denotes significant difference between 3 vessel disease and any other category.

**Table 2. Relationships among Extent of CAD, Abnormal LVC and Ventricular Arrhythmias**

<table>
<thead>
<tr>
<th>Number of diseased vessels</th>
<th>0 (N = 66)</th>
<th>1 (N = 40)</th>
<th>2 (N = 35)</th>
<th>3 (N = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal LVC</td>
<td>7.3</td>
<td>4.3</td>
<td>3.2</td>
<td>0.9</td>
</tr>
<tr>
<td>(N = 60)</td>
<td>(N = 23)</td>
<td>(N = 13)</td>
<td>(N = 31)</td>
<td></td>
</tr>
<tr>
<td>Abnormal LVC</td>
<td>107.0</td>
<td>7.1</td>
<td>9.5</td>
<td>55.3</td>
</tr>
<tr>
<td>(N = 6)</td>
<td>(N = 17)</td>
<td>(N = 22)</td>
<td>(N = 72)</td>
<td></td>
</tr>
</tbody>
</table>

*Percent of patients with ≥ 2 PVC/H

| Normal LVC                | 12% (7/60) | 13% (3/23) | 8% (1/13)  | 13% (4/31) |
| Abnormal LVC              | 50% (3/6)  | 35% (6/17) | 32% (7/22) | 57% (41/72) |

*Percent of patients having at least one complex ventricular arrhythmia

| Normal LVC                | 20% (12/60) | 22% (5/23) | 8% (1/13)  | 19% (6/31) |
| Abnormal LVC              | 67% (4/6)   | 41% (7/17) | 27% (6/22) | 57% (41/72) |
patients with CAD were directly related to the presence of abnormal LVC. The number of diseased vessels was a predictor of PVCs only because patients with three vessel CAD are more likely to have abnormal LVC. Although the relationship between ventricular arrhythmias and abnormal LVC can be demonstrated using all three descriptors of arrhythmias, the discontinuous variable of the number of patients with >X PVC/H is the most helpful for consideration of individual patients. It is important to determine the frequency of PVC/H which best differentiates between levels observed at random in the population and levels associated with abnormalities in LVC. Any frequency of PVC/H yielded a significant division by chi-square at P < 0.01 (table 3). A relatively low frequency (≥2 PVC/H) provided optimal separation of quantities of PVCs associated with abnormal LVC. Only 12% of patients with normal LVC, as opposed to 49% of patients with abnormal LVC had ≥2 PVC/H (sensitivity = 49%). As the population was divided according to increasingly frequent PVCs the chi-square value became lower. At a more conventional separation point such as ≥20 PVC/H, the group included only 20.5% of patients with abnormal LVC, while only a few patients with normal LVC had been eliminated. If the descriptor ≥2 PVC/H was used, complex arrhythmias could add little to the analysis, since 71% of patients with complex arrhythmias had ≥2 PVC/H. Of all 72 patients with ≥2 PVC/H, 57 (79%) had abnormal LVC (specificity = 79%). Of the 58 patients with complex arrhythmias in addition to ≥2 PVC/H, an identical percentage (79%) had abnormal LVC. Of 24 patients with complex arrhythmias and <2 PVC/H, only 12 (50%) had abnormal LVC.

Using the quantitative wall motion analysis, a strong relationship was found between the number of abnormally contracting segments and the prevalence of ≥2 PVC/H (table 4). Of the patients with no abnormally contracting segments, 11% had ≥2 PVC/H compared to 44% of patients with 1–3 abnormally contracting segments, 73% with 4–6 abnormal segments, and 100% with 7–9 abnormal segments (P < 0.01). Therefore, there was a direct relationship between the presence of ventricular arrhythmias and the extent of left ventricular contraction abnormality.

Figure 2 shows the correlation between the quantities of ventricular premature beats and contraction abnormality. Although there was not a linear relationship between PVC frequency and the number of abnormally contracting segments, a trend toward greater frequencies of PVCs was found in those with greater amounts of contraction abnormality. Eighty-four percent of patients with no abnormally contracting segments had <1 PVC/H. Among patients with 1–3 abnormally contracting segments 45% had <1 PVC/H. Eighty-five percent of patients with 4–6 abnormally contracting segments had ≥1 PVC/H and 87% of patients with 7–9 abnormally contracting segments had >9 PVC/H. Although generally greater frequencies of PVCs were found in patients with more abnormally contracting wall segments, all patients with frequent PVCs did not have markedly abnormal ventricles. Of 34 patients with >9 PVC/H, 29% had normal LVC, 19% had 1–3 abnormally contracting segments, 32% had 4–6 abnormally contracting segments, and 21% had >9 abnormally contracting segments.

The relationship between the invasively obtained parameters of systemic arteriovenous oxygen difference (A-VO₂D), cardiac index (CI), left ventricular end-diastolic pressure (LVEDP), and mitral insufficiency were studied to determine whether these were independently associated with PVCs. Patients with abnormal hemodynamic values had a much higher prevalence of ≥2 PVC/H (table 5). However, of the 15 patients with abnormal parameters but normal LVC, only two had ≥2 PVC/H. Thus there was no association independent of abnormality of LVC.

An extensive analysis of clinical findings revealed that only a history of congestive heart failure or prior myocardial infarction, presence of cardiomegaly on chest X-ray (table 5) or previous infarction on ECG (table 6) were significantly associated with ≥2 PVC/H. None of these variables was associated with ventricular arrhythmias independently of contraction abnormalities. Small numbers of patients with congestive heart failure precluded statistical analysis of the quantitative degree of heart failure. Although there was a significant association between cardiomegaly on chest X-ray and ventricular arrhythmias, only 16 of the 57 patients with abnormal contraction had cardiomegaly. Therefore this is a specific but very insensitive variable. The number of previous myocardial infarctions by history was quantitated. There was a stepwise relationship between the number of previous infarcts and the prevalence of ≥2 PVC/H (P < 0.01) which was dependent on the presence of abnormal LVC (table 6).

Since PVCs were not independently related to either the number of diseased vessels or hemodynamic parameters, and contraction abnormalities may indicate previous infarction, a detailed analysis of the QRS complex on ECG was performed. Forty-one percent of patients with ECG evidence of infarction had ≥2 PVC/H, whereas only 14% of patients without ECG findings had ≥2 PVC/H. The relationship was quantitative in that the prevalence of ≥2 PVC/H was proportional to the number of leads with Q waves or minimal R waves (table 7).

A comparison of the relationships between both LV contraction abnormalities and QRS changes on ECG and the prevalence of ventricular arrhythmias is presented in table 8. Prevalence of ≥2 PVC/H was 36% (5 of 14) when abnor-
mal initial forces were not accompanied by an abnormal contraction pattern and 19% (8 of 41) when the contraction abnormality occurred in the absence of any QRS change. When both of the abnormal variables were present the prevalence was 54%. Overall, 41% of patients with positive ECG criteria for infarction had ≥ 2 PVC/H, whereas 49% of patients with abnormal LVC by ventriculography had ≥ 2 PVC/H. This difference was not statistically significant. When more than three leads showed abnormal initial forces, however, 71% of the patients had ≥ 2 PVC/H. Thus, both abnormal initial forces and wall motion abnormality correlated in a quantitative fashion with the presence of ≥ 2 PVC/H.

Because the use of cardiac drugs was not controlled in this study, an analysis of the association between drug therapy and PVCs was performed. No relationship was found between the prevalence of ≥ 2 PVC/H and diuretic or propranolol therapy. However, patients on digitalis therapy with abnormal LVC had a high prevalence of ≥ 2 PVC/H (81.5%) while patients with normal LVC not on digitalis therapy had a low prevalence of ≥ 2 PVC/H (13.0%) (table 9). An intermediate prevalence was found in the group with abnormal LVC not on digitalis therapy (39.3%). Patients with abnormal LVC on digitalis had a greater number of abnormally contracting wall segments (average 4.8) than those with abnormal LVC not on digitalis (average 2.6). None of the 11 patients with normal LVC who were on digitalis therapy had an average of even 1 PVC/H.

Although most patients with frequent PVCs had abnormal LVC, a subgroup of 15 patients had normal LVC and ≥ 2 PVC/H. Nine of these 15 had > 9 PVC/H. Of these nine patients, four had CAD (one with three vessel disease, one with two vessel disease and two with one vessel disease). These four patients represented only 6% of the total of 67 with CAD and normal LVC. Five had totally normal coronary arteries. One of the five patients had severe emphysema, but the other four were discharged from the hospital without any demonstrable etiology for their PVCs. Another interesting subgroup were the three patients with no CAD and normal LVC who averaged > 100 PVC/H.

### Table 5. Relationship between Ventriculographic Hemodynamic and Clinical Parameters and Premature Ventricular Contractions

<table>
<thead>
<tr>
<th>Venticulographic</th>
<th>Percentage of the 72 patients with ≥ 2 PVC/H having the parameter</th>
<th>Percentage of the 172 patients with &lt; 2 PVC/H having the parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Abnormal LVC</td>
<td>79% (57)</td>
<td>19% (33)</td>
</tr>
<tr>
<td>*Mitra1 insufficieny</td>
<td>11% (8)</td>
<td>2% (4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemodynamic</th>
<th>Percentage of the 72 patients with ≥ 2 PVC/H having the parameter</th>
<th>Percentage of the 172 patients with &lt; 2 PVC/H having the parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>*AVO2D &gt; 5.5 vol %</td>
<td>22% (16)</td>
<td>6% (10)</td>
</tr>
<tr>
<td>*CI &lt; 2500 cc/min</td>
<td>22% (16)</td>
<td>8% (13)</td>
</tr>
<tr>
<td>*LVEDP &gt; 18 mm Hg</td>
<td>22% (16)</td>
<td>1% (1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Historical</th>
<th>Percentage of the 72 patients with ≥ 2 PVC/H having the parameter</th>
<th>Percentage of the 172 patients with &lt; 2 PVC/H having the parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60</td>
<td>12% (9)</td>
<td>8% (14)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36% (26)</td>
<td>37% (64)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8% (6)</td>
<td>7% (12)</td>
</tr>
<tr>
<td>Obesity</td>
<td>47% (34)</td>
<td>52% (89)</td>
</tr>
<tr>
<td>Smoking</td>
<td>75% (54)</td>
<td>65% (111)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>38% (27)</td>
<td>32% (55)</td>
</tr>
<tr>
<td>*Congestive heart failure</td>
<td>16% (12)</td>
<td>3% (5)</td>
</tr>
<tr>
<td>*Myocardial infarction</td>
<td>41% (30)</td>
<td>14% (24)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical findings</th>
<th>Percentage of the 72 patients with ≥ 2 PVC/H having the parameter</th>
<th>Percentage of the 172 patients with &lt; 2 PVC/H having the parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular gallop</td>
<td>9% (6)</td>
<td>4% (7)</td>
</tr>
<tr>
<td>Systolic blood pressure &gt;140</td>
<td>19% (14)</td>
<td>17% (29)</td>
</tr>
<tr>
<td>Diastolic blood pressure &gt;90</td>
<td>10% (7)</td>
<td>19% (33)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiographic</th>
<th>Percentage of the 72 patients with ≥ 2 PVC/H having the parameter</th>
<th>Percentage of the 172 patients with &lt; 2 PVC/H having the parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Cardiomegaly on chest X-ray</td>
<td>22% (16)</td>
<td>3% (5)</td>
</tr>
</tbody>
</table>

*P < 0.01.

### Table 6. Relationship between History of Previous Myocardial Infarction and Premature Ventricular Contractions

<table>
<thead>
<tr>
<th></th>
<th>No previous MI</th>
<th>One previous MI</th>
<th>&gt; 1 previous MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal LVC</td>
<td>11%*</td>
<td>25%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>(12/110)</td>
<td>(3/12)</td>
<td>(0/3)</td>
</tr>
<tr>
<td>Abnormal LVC</td>
<td>27%</td>
<td>50%</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>(7/27)</td>
<td>(28/52)</td>
<td>(21/29)</td>
</tr>
</tbody>
</table>

*% of patients in category with ≥ 2 PVC/H.
Each of these patients had a diffusely hypokinetic left ventricle presumed secondary to cardiomyopathy. Therefore, from a cohort of 244 patients monitored, a group of four could be found with very frequent PVCs not associated with any apparent cardiac abnormality.

**Discussion**

The data from this study are in agreement with several recently reported concepts concerning the prevalence of ventricular arrhythmias. They are present in the majority of patients monitored: 62% of 301 patients,16 83% of 124 patients17 and 69% of 244 patients in the present study. In approximately half of the patients with PVCs, however, the frequency is low. Ninety-six of 176 averaged less than one per 1000 complexes,18 and in the present study 91 of 169 averaged less than two per hour. Complex ventricular arrhythmias occur most commonly among patients who also have frequent PVCs: among 94% of patients with > 30 PVCs in one hour,18 100% of patients with > 30 PVCs in one hour,17 76% of patients with 2–9 PVC/H, and 85% of patients with > 9 PVC/H in the present study.

It is unclear from the literature whether PVC frequency is related to CAD alone, ventricular asynergy, or to the combination of these two variables. Sharma et al. studied 64 patients admitted for the investigation of chest pain.18 They found that the frequency of PVCs was related to the presence of ventricular asynergy but not to the extent of coronary disease without asynergy. However, Amsterdam et al. reported in abstract form that frequent or complex ventricular arrhythmias occurred with greater frequency in patients with significant CAD than in those with normal coronary arteries, but were not related to the presence of ventricular asynergy.18 Calvert, Gorlin and Lown recently reported that ventricular arrhythmias were directly related to both the number of diseased coronary vessels and the extent of left ventricular dysfunction, but did not attempt to determine the relative importance of these two variables.18 Schulze found similar results in a group of 38 patients studied 10–24 days after myocardial infarction, but also did not separate the effects of coronary disease from wall motion abnormality.20

Our data clearly illustrate that in this population the frequency of PVCs is related to the presence of abnormal LVC. The association with the extent of CAD exists only in that severe CAD frequently results in abnormal LVC. This point was demonstrated clearly using the categorical linear model. The extent of CAD alone had no independent predictive power for LVC frequency, but abnormal LVC was highly significant.

The PVC frequency that is most often associated with abnormalities of LVC is a variable that has not been investigated previously. Our data showed that the frequency of PVCs that best separated patients with normal LVC from those with abnormal ventricles was the presence of ≥ 2 PVC/H and that the use of higher PVC frequencies did not separate the groups as well. It should be emphasized, however, that although a rate of ≥ 2 PVC/H separated patients with normal and abnormal LVC, it is not a sensitive indicator of abnormal LVC, since it detected only 57 of 117 (49%) such patients. On the other hand, this rate was found to be more specific since 57 of 72 patients (79%) with ≥ 2 PVC/H had abnormal LVC.

In general, patients with abnormal hemodynamic descriptors were more likely to have ≥ 2 PVC/H than patients with normal hemodynamics. However, in the small group of 15 patients with one or more abnormal hemodynamic values but normal LVC, only two had ≥ 2 PVC/H. This suggests that discrete areas of wall motion abnormality are necessary for the development of PVCs and not merely the presence of an increased hemodynamic load on the left ventricle.

Hinkle21 reported an association between the frequency of PVCs and various coronary risk factors. The significance of these risk factors in the absence of documented abnormalities of LVC has not been investigated. In the present study the only significant historical factors were a history of congestive heart failure or myocardial infarction. These conditions were significantly associated with the occurrence of PVCs, however, only if abnormal LVC was also present. Likewise, the only noninvasively determined clinical parameter which was associated significantly with PVCs (ECG of prior infarction) reflected the presence of abnormal LVC. Alternatively, PVCs may be associated with permanent myocardial damage rather than with dynamic

<table>
<thead>
<tr>
<th>Number of abnormally contracting wall segments</th>
<th>Number of ECG leads with abnormal initial forces</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1-3</td>
</tr>
<tr>
<td>1-3</td>
<td>4-6</td>
</tr>
<tr>
<td>7-9</td>
<td>7-10</td>
</tr>
</tbody>
</table>

*% indicates number of patients in this group having ≥ 3 PVC/H.
ischemia. Although digitalis therapy was associated with more frequent PVCs among patients with abnormal LVC, those on digitalis also had a greater number of abnormal wall segments. Our data therefore do not allow any conclusions about the effect of digitalis on PVCs in this population.

Both abnormal initial ECG forces and angiographic evidence of abnormal LVC have been associated with the presence of myocardial fibrosis at postmortem examination. Other data have demonstrated that abnormal initial forces on the vectorcardiogram accurately reflect angiographic abnormalities of LVC. Our data have shown a quantitative relationship between PVCs and both the ECG and ventriculographic manifestations of myocardial fibrosis. It therefore seems likely that in this population of largely stable patients with CAD, PVCs are related to the presence and extent of myocardial fibrosis. The plausibility of this hypothesis is strengthened by the findings of Fenoglio who demonstrated that subendocardial Purkinje fibers survive in areas adjacent to the fibrotic tissue in chronic infarcts and may be the site of initiation of ventricular arrhythmias.

During the late postinfarction period (10–24 days), PVCs have been shown to have independent prognostic importance. Schulze found that complicated PVCs among postinfarction patients were associated with greater extent of CAD and with greater impairment of left ventricular function. However, during follow-up the presence of complicated ventricular arrhythmias selected a group whose risk of sudden death exceeded that associated with low ejection fraction alone. Thirty-six of 81 patients had ejection fraction <40%; however, all eight sudden deaths occurred in the group of 26 patients who had both ejection fraction <40% and complicated ventricular arrhythmias. The projected one year mortality for these patients was 66%, as opposed to 31% among patients with ejection fraction <40% but no complicated ventricular arrhythmias. Similar data have been reported by Vismara.

Among patients with CAD who have not recently sustained an acute ischemic insult, the independent prognostic importance of PVCs is unclear. Hinkle showed that middle-aged men with >10 PVCs per 1,000 complexes had a ten-fold higher rate of coronary death over a 30 month period than did men with no PVCs. However, PVCs were usually associated with other overt manifestations of coronary disease, and there was no consideration of left ventricular function. Vismara followed 63 patients who had angiographically documented coronary disease for 30 months and compared many potential risk factors between survivors and patients who had sudden death. PVCs and ST-segment depression were significantly more frequent among those who died suddenly. Q waves on ECG were said to be similar in the two groups. In another study, survivors of out-of-hospital ventricular fibrillation had a 70% prevalence of left ventricular contraction abnormalities along with severe CAD, and those who suffered a second episode of fibrillation had even more severe contraction abnormalities. The data from the present study document that the prevalence of PVCs which occur outside of the setting of acute coronary insufficiency is independent of the number of diseased vessels, but is directly related to the extent of myocardial fibrosis as indicated by abnormal left ventricular contraction and confirmed by abnormal QRS forces on ECG.

Recently Lie et al. have provided the perspective for the importance of "warning arrhythmias" as predictors of ventricular fibrillation in acute myocardial infarction. Follow-up of patients in the current study will document the prognostic importance of chronically occurring warning ventricular arrhythmias in the presence of varying patterns of left ventricular contraction. This information will determine if the likelihood of sudden death is as dependent on the quantity of myocardial fibrosis as are the frequency of premature ventricular contractions and the likelihood of death due to myocardial failure.

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References

22. Savage RM, Wagner GS, Ideker RE, Podolsky SA, Hackel DB:
Effect of Nitroprusside on Regional Myocardial blood Flow in Coronary Artery Disease
Results in 25 Patients and Comparison with Nitroglycerin

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SUMMARY The effect of nitroprusside on regional myocardial specific blood flow (RMBF) was evaluated in 25 patients with the xenon-133 washout technique. Six patients were normal (group 1), six patients had coronary artery disease without collateral vessels (group 2), and thirteen patients had coronary artery disease with collateral vessels (group 3). In group 1, RMBF was unchanged following nitroprusside. RMBF decreased significantly in both group 2 and group 3, including seven patients in group 3 with high-grade collateral vessels. The results were compared to the effect of nitroglycerin in 31 patients previously studied using the same technique.

VASODILATOR THERAPY with nitroprusside and nitroglycerin has been shown to improve left ventricular performance in some patients with congestive heart failure due to ischemic heart disease. Although the effects on preload and afterload are different, both drugs reduce elevated left ventricular filling pressures and both (but especially nitroprusside) may improve cardiac output. Both drugs also decrease myocardial oxygen demand but only nitroglycerin has been shown to consistently reduce ischemic injury in patients with acute myocardial infarction. Reports of a beneficial effect of nitroprusside on indices of ischemia are limited, and it has been suggested that nitroprusside may actually increase ischemic injury in some patients by redistributing blood away from the ischemic area of myocardium. Thus, the present study was designed to evaluate the effects of nitroprusside on regional myocardial blood flow. The results are compared to the effect of nitroglycerin in similar patients reported in a previous study.

Materials and Methods

The study was performed in 25 patients undergoing cardiac catheterization for evaluation of chronic chest pain. Nineteen patients had coronary artery disease and six were normal. No attempt was made to alter the patients' chronic medical therapy and most were receiving propranolol at the time of the study. Informed consent was obtained in each case.

Standard left heart catheterization was performed in the fasting state after premedication with diazepam (10 mg p.o.). Pressures were measured through fluid-filled catheters connected to an external strain gauge transducer. Coronary angiography was performed using the femoral approach. Coronary angiograms were evaluated independently by two observers. Collateral vessels were graded according to their angiographic appearance. Thus, faint opacification of an artery distal to a stenotic lesion from several small collateral vessels was classified grade 1; moderate distal opacification from several small vessels, grade 2; dense opacification of the distal vessel from one large or several small collateral vessels, grade 3; dense opacification of the distal vessel from two large collateral vessels, grade 4. The vessels from which collaterals arose were also evaluated.
Relationships among ventricular arrhythmias, coronary artery disease, and angiographic and electrocardiographic indicators of myocardial fibrosis.

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