Detection of Myocardial Ischemia by Regional Dysfunction During and After Rapid Pacing in Conscious Dogs

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SUMMARY The effects of increased heart rate (HR) on regional myocardial function and circumflex coronary artery blood flow (CBF) were examined in the conscious dog before and during coronary artery stenosis. Regional myocardial function (ultrasonic crystals) was determined during graded elevations of HR and after pacing. Before coronary stenosis (implanted hydraulic cuff), both control segment and a segment to be rendered ischemic showed similar responses to increased HR, with increases in CBF and no significant change of coronary flow pattern. During coronary stenosis, which reduced resting CBF to 75% of control, percent shortening (%AL) in the control segment did not change significantly, end-diastolic length in the ischemic segment increased and %AL decreased in proportion to the increase in HR; holosystolic elongation occurred at 180 beats/min, accompanied by a slight decrease of CBF, and the flow pattern changed to an elevated systolic/diastolic ratio. After the cessation of pacing without coronary stenosis, potentiation of %AL and peak segment velocity were observed for several beats. Upon stopping pacing with coronary stenosis, there was early potentiation of %AL and velocity, but the ischemic segment then became very depressed at five seconds post pacing, gradually returning to 90% of control %AL after only five minutes. These data indicate that regional depression of myocardial function during and after stress testing by pacing-induced increases in HR is a sensitive indicator of coronary artery narrowing, even in the absence of dysfunction at rest.

CHANGES IN THE ELECTROCARDIOGRAM, left ventricular pressures, angiocardiographic features, and in the radarkymogram, induced by rapid cardiac pacing, have been used clinically for the detection of coronary artery disease. With the latter two techniques, temporary abnormalities in segmental contraction patterns of the left ventricle have been observed during the pacing period. Such pacing stress is considered to increase the heart's regional oxygen requirements beyond the coronary reserve, and thereby allows delineation of myocardial regions that may be subject to ischemia during normal activities. The availability of reliable methods for determining regional myocardial function under a variety of conditions should help to provide a more complete understanding of the responses of various areas of the heart to this form of stress. Therefore, this experimental study was designed to define the effects of increased heart rate on regional left ventricular function in the conscious dog under normal conditions and after a degree of coronary stenosis was produced, which resulted in normal or only mildly reduced regional myocardial shortening before cardiac pacing.

Methods

Six adult mongrel dogs weighing 26–39 kg were anesthetized with sodium pentobarbital (30 mg/kg I.V.) and ventilated with a Harvard respirator. During a sterile operation, a left thoracotomy was performed in the fifth intercostal space. A micromanometer (Konigsberg P-22) was inserted through the apex of the left ventricle and two pairs of ultrasonic dimension gauges were implanted subendocardially, one in a control area and the other in an area to be made ischemic. A Doppler flow probe with 10 MHz transducers was placed around the circumflex coronary artery, and a hydraulic occluder made from polyvinyl tubing was positioned just distal to it. Pacing electrodes were sutured to the left atrial appendage and the right ventricle to allow pacing. The hydraulic occluder tubing and wires from the instruments were tunneled dorsally to the base of the neck.

The experiments were performed at least 10 days postoperatively in the conscious state when the animals had recovered. Before coronary constriction, the heart was paced at rates from 100–190 beats/min using stepwise increments of 30 beats/min to establish baseline regional myocardial responses. The total pacing time was four minutes. Coronary blood flow was determined in all dogs after the pacing response had stabilized about 30 seconds following the initiation of each higher pacing rate. After pacing was stopped, measurements of hemodynamic variables and regional myocardial function were continued over the next five minutes. The coronary artery was then gradually made stenotic at the highest pacing rate by inflating the hydraulic cuff with water (fig. 1), using a power driven syringe. When regional dysfunction appeared, as indicated by reduced shortening of the ischemic segment, pacing was stopped, leaving the stenosis constant (fig. 1). After waiting 10 minutes to confirm a stable state, stepwise increments in the pacing rate were carried out in exactly the same manner as during the control pacing period.

Recordings were made during each experiment on a multi-channel recorder and also on a magnetic tape for subsequent analysis. The signals from the two
Pairs of ultrasonic length gauges and the left ventricular pressure were recorded simultaneously. Instantaneous coronary blood flow velocity was obtained by a zero-cross counter, and the average flow was also recorded using an averaging filter. Calibration of the Doppler flow velocity recording was conducted by injecting signals of known frequency into the zero-cross counter, and flow velocity was then calculated from the Doppler equation.\textsuperscript{6,7} The micromanometer was calibrated before implantation against a mercury manometer, and before and after the study the micromanometer was calibrated electrically against known voltages.\textsuperscript{6,7} Segment dimensions were calibrated as described previously.\textsuperscript{6,7} Derivatives such as dP/dt and dL/dt, were obtained using an active differentiating circuit with high frequency cutoff set for 700 Hz. A triangular wave signal with a known slope was substituted for the pressure and dimension signals to calibrate dP/dt and dL/dt. Heart rate was measured using a cardiotachometer. End-diastolic and end-systolic segment lengths were identified on the recordings, and these dimension values were normalized by dividing the observed lengths by the control end-diastolic segment length and multiplying by ten.\textsuperscript{6,7} In four of six dogs, we also recorded the lead II ECG, but significant ST segment changes were not observed during and after pacing.

The high level of vagal tone usually observed in conscious, resting dogs often precluded rapid atrial pacing, and therefore in four animals right ventricular pacing was necessary to provide a high ventricular rate; atrial pacing was possible in two dogs. The pacing sites were not changed during studies in any one dog, and the same pacing procedure was used before and during coronary stenosis. During ventricular pacing, the length wave form was slightly different during the isovolumetric phase (fig. 2, control tracing) but extent of shortening was not discernibly different from that with sinus rhythm, and the general trend of segmental response with regard to percent shortening was similar whether atrial or ventricular pacing was applied. Therefore, the control and paced data were compiled and analyzed together. Comparison of dP/dt between the resting and paced state was not made because of the ventricular pacing used in four of the six dogs.

All values were expressed as mean ± SEM. Regression lines were analyzed with a least squares method using an EAI computer. Calculations by a program for analysis of variance with repeated measures factors were made using an XDS SIGMA-3 computer. The statistical significance of differences before and during coronary stenosis was tested by the F ratio with a conservative method because variances were not homogeneous between groups,\textsuperscript{11} and the time course was analyzed at six points: control, maximum heart rate, and at five seconds, 30 seconds, one minute and five minutes after cessation of pacing. Statistical analysis of the time course of the post pacing period was conducted by a single factor analysis of variance with repeated measures over time.\textsuperscript{11} The level of statistical significance used was $P < 0.05$.

**Results**

**Observations During Cardiac Pacing Without and With Coronary Constriction.**

**Left Ventricular Pressures (table I)**

Left ventricular systolic pressures remained unchanged during pacing compared to the control state.
and were not statistically different between control runs and pacing runs during coronary artery stenosis. The left ventricular end-diastolic pressures also did not change significantly during pacing, tending to drop from the control state during pacing both without and with coronary stenosis (fig. 2); they tended to be slightly higher during coronary stenosis, but this difference was not statistically significant. Peak positive dP/dt during coronary stenosis was slightly depressed, but not significantly so, compared to the same pacing rates before coronary stenosis.

Regional Myocardial Function (table 2)

A series of tracings showing control and ischemic segment function during the control state in the presence of coronary stenosis and at two pacing rates is shown in figure 2. The control segment maintained active shortening with only slight reduction of end-diastolic length as heart rate increased. In contrast, ischemic segment shortening, which was slightly decreased before pacing, decreased further with increased heart rate until at the highest heart rate the shortening was near zero. End-diastolic length increased and an early systolic elongation developed as heart rate was increased.

Figure 3 summarizes the responses of control and ischemic segments to increased heart rate during normal perfusion and during coronary constriction in six dogs (fig. 3). The control segment responses to pacing were the same after coronary stenosis as those before stenosis, indicating that the function of this normally perfused segment was not modified directly or indirectly as the function of the ischemic segment deteriorated. The responses of the segments to be rendered ischemic were similar to those of the control segments, prior to stenosis. Following coronary stenosis at rest, in the ischemic segments the percent shortening decreased to 73% of control (P < 0.01) and end-diastolic length increased slightly (table 2). As the pacing rate was increased, the end-diastolic length remained slightly above the control pacing level, but the percent shortening decreased progressively to below zero at the highest heart rate (fig. 3, r = 0.99).

Coronary Blood Flow Velocities During Cardiac Pacing (fig. 3, lower panel)

In the absence of coronary stenosis, with increases of heart rate the mean flow increased (r = 0.95), and the flow pattern, as represented by the ratio of systolic to diastolic velocity (0.28 ± 0.02 at rest) was maintained relatively constant. When the coronary artery was stenosed to produce 75% of control flow at rest, the mean flow did not increase during pacing, and in three dogs it decreased by an average of 16 ± 1% from resting state at higher pacing rates (fig. 3). In the presence of coronary stenosis, the systolic to diastolic velocity ratio rose progressively from 0.76 ± 0.20 at rest to 0.89 ± 0.13 at a heart rate of 180/min (r = 0.99).

Observations After Cardiac Pacing With and Without Coronary Constriction

Hemodynamic variables were not significantly different in the post pacing period with and without coronary stenosis (table 1).

Regional myocardial function in the ischemic area improved initially, then deteriorated after pacing was stopped in the presence of coronary stenosis. This phenomenon is illustrated by the tracings in figure 4, which shows a brief 30 second pacing period followed by the recovery phase. Similar trends were also
Table 1. Left Ventricular Pressures in Response to Cardiac Pacing

<table>
<thead>
<tr>
<th></th>
<th>Pacing step</th>
<th>1st beat</th>
<th>5 sec</th>
<th>30 sec</th>
<th>1 min</th>
<th>5 min</th>
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<tbody>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
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<tr>
<td>C</td>
<td>84 ± 6</td>
<td>107 ± 4</td>
<td>137 ± 5</td>
<td>159 ± 5</td>
<td>190 ± 7</td>
<td>96 ± 2</td>
</tr>
<tr>
<td>S</td>
<td>87 ± 7</td>
<td>107 ± 4</td>
<td>130 ± 3</td>
<td>160 ± 6</td>
<td>184 ± 7</td>
<td>102 ± 7</td>
</tr>
<tr>
<td>LVSP mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C</td>
<td>113 ± 3</td>
<td>114 ± 4</td>
<td>116 ± 4</td>
<td>117 ± 5</td>
<td>115 ± 4</td>
<td>112 ± 5</td>
</tr>
<tr>
<td>S</td>
<td>113 ± 4</td>
<td>113 ± 5</td>
<td>111 ± 5</td>
<td>116 ± 5</td>
<td>114 ± 6</td>
<td>115 ± 3</td>
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<td>LVEDP mm Hg</td>
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<td></td>
<td></td>
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<tr>
<td>C</td>
<td>9 ± 1</td>
<td>6 ± 1</td>
<td>6 ± 1</td>
<td>5 ± 1</td>
<td>7 ± 1</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>S</td>
<td>10 ± 1</td>
<td>8 ± 1</td>
<td>6 ± 1</td>
<td>6 ± 1</td>
<td>6 ± 1</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>LVdP/dt mm Hg/sec</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>C</td>
<td>3003 ± 248</td>
<td>3007 ± 381</td>
<td>2784 ± 402</td>
<td>2882 ± 382</td>
<td>2708 ± 457</td>
<td>3706 ± 253</td>
</tr>
<tr>
<td>S</td>
<td>2736 ± 189</td>
<td>2489 ± 271</td>
<td>2355 ± 317</td>
<td>2360 ± 283</td>
<td>2487 ± 265</td>
<td>3190 ± 295</td>
</tr>
</tbody>
</table>

Abbreviations: C = before coronary stenosis; S = during coronary stenosis; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure. All data are shown as mean ± SEM.

Table 2. Regional Myocardial Function in Response to Cardiac Pacing

<table>
<thead>
<tr>
<th></th>
<th>Pacing step</th>
<th>1st beat</th>
<th>5 sec</th>
<th>30 sec</th>
<th>1 min</th>
<th>5 min</th>
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<tbody>
<tr>
<td>EDL mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C</td>
<td>10</td>
<td>9.77 ± 0.05</td>
<td>9.67 ± 0.07</td>
<td>9.60 ± 0.09</td>
<td>9.55 ± 0.16</td>
<td>9.97 ± 0.08</td>
</tr>
<tr>
<td>S</td>
<td>10.22 ± 0.11</td>
<td>10.09 ± 0.11</td>
<td>10.01 ± 0.10</td>
<td>9.99 ± 0.11</td>
<td>9.91 ± 0.19</td>
<td>10.31 ± 0.16</td>
</tr>
<tr>
<td>Pc</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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</tr>
<tr>
<td>Ps</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>% shortening (EDL-ESL)/EDL-100</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>C</td>
<td>17.2 ± 1.5</td>
<td>16.4 ± 1.7</td>
<td>15.5 ± 1.7</td>
<td>13.9 ± 1.2</td>
<td>13.9 ± 1.2</td>
<td>20.9 ± 1.6</td>
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<tr>
<td>S</td>
<td>12.6 ± 1.8</td>
<td>10.6 ± 1.4</td>
<td>7.00 ± 0.84</td>
<td>1.46 ± 1.6</td>
<td>-1.32 ± 1.01</td>
<td>5.25 ± 1.62</td>
</tr>
<tr>
<td>Pc</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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</tr>
<tr>
<td>Ps</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>P</td>
<td>0.05</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Peak velocity (cm/sec)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1.58 ± 0.16</td>
<td>1.65 ± 0.16</td>
<td>1.58 ± 0.14</td>
<td>1.51 ± 0.12</td>
<td>1.51 ± 0.13</td>
<td>2.12 ± 0.19</td>
</tr>
<tr>
<td>S</td>
<td>1.24 ± 0.13</td>
<td>1.26 ± 0.13</td>
<td>1.09 ± 0.05</td>
<td>0.75 ± 0.14</td>
<td>0.58 ± 0.14</td>
<td>0.98 ± 0.14</td>
</tr>
<tr>
<td>Pc</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Ps</td>
<td>NS</td>
<td>NS</td>
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</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

All data are shown as mean ± SEM.
Statistical analyses of the trends in segment function during pacing were done by regression analysis.
Abbreviations: EDL = end-diastolic length; ESL = end-systolic length; C = before coronary stenosis; S = during coronary stenosis; Pc = comparison with resting state before coronary stenosis; Ps = comparison with resting state during coronary stenosis; P = comparison between C and S; NS = not significant.
**Figure 3.** A) Regional myocardial performance in two segments of the left ventricle with pacing before and during coronary stenosis. From top to bottom, end-diastolic length (EDL), and percent (%) segment active shortening (n = 6). Bars indicate standard errors. B) Average mean coronary blood velocities during cardiac pacing: n = 5. Bars indicate standard errors. Open circles = control and closed circles = during coronary stenosis.
REGIONAL DYSKINESIA INDUCED BY TACHYCARDIA/Tomoike et al.

LV PRESSURE  
mmHg

dP/dt  
mmHg/sec

CONTROL SEGMENT LENGTH  
mm

ISCHEMIC SEGMENT LENGTH  
mm

HEART RATE  
beats/min

**FIGURE 4.** Brief (30 sec) period of rapid ventricular pacing during coronary stenosis to illustrate post pacing depression of regional myocardial function. The right-hand panel shows the shortening patterns taken at rapid paper speed 3–5 sec after pacing, when the ischemic segment was markedly hypokinetic. LV = left ventricular.

**FIGURE 5.** Percentage changes in regional myocardial shortening expressed as percent segment shortening (%ΔL) (%ΔL control %ΔL · 100) at various times after pacing (resting state = 100%). Upper panel (stippled bars) shows average responses of segments to be rendered ischemic prior to coronary stenosis, and lower panel (cross-hatched bars) shows responses with coronary stenosis. C = control period prior to pacing, P = responses at maximum pacing rate. Arrow (off) = cessation of pacing. The first and second beats and subsequent responses are plotted. N = 6.
observed in the grouped data after the cessation of the stepwise pacing runs (table 2, fig. 5). The first beat after pacing was accompanied by a potentiation of dP/dt and an increase of segment shortening in both the control and ischemic segments, along with a marked increase of end-diastolic length (figs. 4 and 5, table 2). However, during the following five seconds to one minute, ischemic regional myocardial shortening became markedly depressed (fig. 5), requiring approximately five minutes to return to the prepacing control level (90% of control percent shortening at five minutes). Changes after post pacing in the control segments were not significant.

**Discussion**

Heart rate is one of the major determinants of myocardial oxygen consumption, and cardiac pacing provides an effective technique for increasing cardiac metabolic requirements in a repeatable manner. Therefore, we have used this approach to characterize the regional myocardial functional responses to graded increases of metabolic requirements under conditions of limited coronary flow reserve in order to characterize better the potential of cardiac pacing as a reliable stress test. Our results suggest that with partial coronary constriction, severe functional derangements can occur within an ischemic region both during and after cardiac pacing. These findings further support our previous proposal that regional myocardial shortening patterns provide a highly sensitive indicator of ischemia, and may prove useful for detecting latent coronary disease during pacing stress in man.

An increase of coronary flow during pacing in the normal coronary circulation has been described, and our data on circumflex coronary artery blood flow without coronary stenosis showed good accord with previous results derived both from clinical and animal studies. Autoregulation of the coronary circulation is substantial, and coronary blood flow remains constant until there is approximately 85% coronary stenosis, or a reduction of perfusion pressure to below 65 mm Hg. Although the grade of coronary stenosis is very difficult to quantify, evidence from this and previous investigations suggests that a peculiar response of coronary blood flow to pacing-induced increases in heart rate can occur during coronary stenosis or occlusion, i.e., reduction in coronary flow during tachycardia. For example, in one acute study in open-chested dogs, heart rate elevation by atrial pacing reduced subendocardial flow to below control in six of eight dogs, while increasing epicardial flow, but without significant reduction of total coronary blood flow in most animals; some dogs, however, showed a reduction of total flow. In patients with coronary heart disease, a reduction in coronary flow during pacing also was reported. In our study, the Doppler flowmeter at the origin of the circumflex coronary artery measured total blood flow rather than regional myocardial blood flow, and when the coronary artery was constricted, the average flow did not change during pacing; however, it decreased in three of the six dogs. The coronary flow pattern also showed relatively more flow during systole at higher pacing rates; this suggests a preferential regional flow redistribution to the epicardium, if the results obtained in conscious, normal dogs by Hess and Bache can also be applied to the setting of acute coronary stenosis. The limitation of diastolic time per minute in the presence of tachycardia undoubtedly plays a role in the coronary responses to tachycardia, but the mechanism of a further decrease in total coronary flow at high pacing rates in the presence of coronary stenosis is unclear; a limitation of flow by the ischemic region itself related to the severe dyskinesia, rather than by the site of stenosis, could provide an explanation for this phenomenon.

Regional myocardial function was measured in the inner layers of the left ventricular wall. Since subendocardial blood flow is reduced during pacing in the presence of coronary stenosis, as discussed above, contractile activity in this region may be more markedly affected by pacing than that in regions closer to the epicardium. Possible differences in myocardial fiber shortening across the wall during ischemia have not been studied systematically, although under normal conditions geometrical factors dictate that the percentage shortening of epicardial circumference is much less than that of the endocardial circumference. A few observations in our laboratory indicate that when regional dysfunction is detected by ultrasonic crystals placed in the subendocardium, it is also reflected by similar dysfunction in subepicardially-placed crystals. Our previous finding that subendocardial dysfunction is always associated with mirror-image dysfunctional changes in wall thickening characteristics in the same region further suggest that, perhaps in part because of tethering effects, a change in shortening pattern is evident across the entire wall. It is likely, however, that with pacing during coronary stenosis, relatively greater potential for contraction and tension development exist in the outer myocardial layers, and that the epicardial region contributes to isovolumetric tension development and, in ways that are yet to be quantified, to the overall pattern of the regional wall motion disorder. For example, it is possible that while severe transmural ischemia will be associated with a holosystolic bulge, subendocardial ischemia alone will result in hypokinesia of the entire wall in proportion to the severity and extent of the ischemia.

After pacing was stopped, all six dogs showed immediate improvement, rapidly followed by severe deterioration of ischemic segment shortening and peak shortening velocity. Several phenomena may be involved in this sequence. Initially, post stimulation potentiation improved shortening in both control and ischemic regions, but the rapid decay (time constant 0.7 sec) of post stimulation potentiation resulted in dissipation of this effect. During cardiac pacing, control segment end-diastolic length, reflecting overall heart size, was reduced (fig. 4), while that in ischemic segments fell less, but the positive in-
ototropic effect of post stimulation potentiation\(^4\) undoubtedly promoted enhancement of shortening in both regions on cessation of pacing. After this immediate effect had disappeared, there was a return of end-diastolic length of the control segments to normal, whereas the end-diastolic length of the ischemic region increased substantially (fig. 4), thereby producing an increase in systolic and diastolic wall tension in this area. We postulate that this effect of increased loading on the ischemic region, the loss of the positive effect of the force-frequency relation and, most importantly, the slow recovery from ischemia due to the sustained coronary stenosis all contributed to the marked and sustained deterioration in function which ensued (fig. 5). Whether elevation of wall stress after pacing could have further limited regional blood flow and contributed to this phenomenon, is not clear. Further studies with measurements of regional coronary blood flow may clarify this question.

The demonstrated relationship between graded elevations of heart rate and progressive decreases of regional segment shortening provides a firm experimental basis for systematic evaluation of latent coronary heart disease in man using such noninvasive techniques as high resolution echocardiography,\(^5\) or gated radionuclide angiography,\(^6\) for delineating wall motion abnormalities or changes in the ejection fraction during exercise stress.\(^7\) The fact that more severe changes occur after pacing may decrease technical difficulties compared to measurements during tachycardia and enhance the sensitivity of such methods for the detection of ischemia. The fact that a wide range of heart rates can be produced by right atrial pacing in man to produce ischemia has already been demonstrated,\(^1,4\) and it should be possible to study the effects of even higher rates by the use of right ventricular pacing with analysis of regional function in the postpacing period. Exercise stress also produces increases in myocardial metabolic demands and is often used in conjunction with the electrocardiogram in the detection of latent coronary heart disease.

Recently, we have also documented severe regional myocardial dysfunction in dogs during and after strenuous exercise in the presence of partial coronary artery stenosis.\(^8\) Thus, in man, comparable increases in heart rate can be achieved readily either by exercise or by pacing. The latter approach is readily controlled and may be considered a useful alternative mode of increasing cardiac metabolic requirements in the detection of limited coronary flow reserve.

**Acknowledgments**

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**References**

Coronary Arterial Spasm and Prinzmetal's Variant Form of Angina Induced by Hyperventilation and Tris-buffer Infusion

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SUMMARY Vigorous hyperventilation was induced for five minutes immediately after a five-minute infusion of 100 ml of Tris-buffer (pH 10) in nine patients with Prinzmetal's variant angina. In eight of the patients, chest pain with ischemic changes in the electrocardiogram occurred during this procedure or within five minutes after it ended. Coronary arterial spasm appeared after the procedure and disappeared after the administration of nitroglycerin in all four patients in whom coronary cineangiography was performed. This was evident both before and after the procedure and after sublingual administration of nitroglycerin (0.6 mg). The oral administration of 90 mg of diltiazem, a calcium antagonistic drug, two hours before, completely suppressed the attack induced by the procedure in all of the five patients who received this drug. We conclude that hyperventilation plus Tris-buffer infusion induces coronary arterial spasm and anginal attack in patients with Prinzmetal's variant angina and that diltiazem suppresses these reactions.

IT IS INCREASINGLY EVIDENT that coronary arterial spasm plays an important role in the pathogenesis of Prinzmetal's variant form of angina. However, the mechanism by which coronary arterial spasm occurs is unknown. Contraction of vascular smooth muscle depends quantitatively on the presence of calcium ions which are required for the activation of myofibrillar ATPase. Physiologically, a highly potent calcium antagonistic action is exerted by hydrogen ions which seem to compete with calcium ions for the same active sites both at the transmembrane calcium transport system and at the myofibrillar ATPase. Thus vasodilatation is produced by either calcium deficiency or an increased hydrogen ion concentration.

The present study examines whether coronary arterial spasm and anginal attack could be induced by hyperventilation and Tris-buffer infusion, which decrease hydrogen ion concentration, in patients with Prinzmetal's variant form of angina.

Materials and Methods

Nine patients with Prinzmetal's variant form of angina were studied. All the patients had recurring attacks of chest pain in association with ST segment elevation in the electrocardiogram more than five times a week at the time of the study. Their age, sex, electrocardiogram at rest and during attack, and coronary arteriograms are shown in table 1. None of the patients had received digitalis or diuretics, and all the medications were stopped at least three days before the study, except nitroglycerin, which was stopped at least two hours before the study.

Blood pressure, 12-lead electrocardiogram and arterial blood for pH and gas analysis were taken while patients were supine from 9:00 a.m. to 11:00 a.m. Patients then received a five-minute infusion of Tris-buffer 100 ml (pH 10). Immediately after, vigorous hyperventilation was performed for five minutes under the constant monitoring of blood pressure and electrocardiograph. Hyperventilation was stopped immediately when chest pain or ischemic changes in electrocardiogram occurred, at which time arterial blood for pH and gas analysis were taken again.

Electrocardiogram was recorded by the six-channel electrocardiograph (Mingraf 61) and blood pressure was taken with sphygmomanometer. Arterial blood pH and gas analysis were done by Corning 175 Automatic pH/Blood Gas System.

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