Hemodynamic Accompaniments of Angina
A Comparison During Angina Induced by Exercise and by Atrial Pacing


SUMMARY
The hemodynamic responses of nine patients with severe coronary artery disease were studied during the precipitation of angina by both supine exercise and increasing rates of atrial pacing. Tension-time index and the first derivative of left ventricular pressure pulse (LV dp/dt) at the onset of angina were significantly higher (P < 0.01) in each patient when angina was induced by exercise than when angina was provoked by atrial pacing. Heart rate, in contrast, was significantly greater (P < 0.05) when angina was precipitated by atrial pacing. Left ventricular end-diastolic pressure (LVEDP) was abnormally elevated in each patient when angina occurred during supine exercise, whereas LVEDP was normal in all patients at the onset of angina provoked by atrial pacing. On the basis of these results it appears that the hemodynamic accompaniments of angina depend to a large extent on the particular circumstances leading to the development of angina. Tension-time index, LV dp/dt, and heart rate are major determinants of myocardial oxygen consumption, and the interrelationships between the determinants of myocardial oxygen consumption are complicated. Thus, changes in any one of these determinants after a therapeutic intervention must be viewed in relation to possible changes in the others.

Additional Indexing Words:
Tension-time index  Left ventricular end-diastolic pressure  Left ventricular dp/dt
Heart rate  Coronary artery disease

Although myocardial revascularization procedures have been performed in a large number of patients for the treatment of angina pectoris caused by coronary artery disease, the results of such treatment have not been adequately documented. Because a high percentage of such patients improve on placebo medication alone,1 reliable symptomatic assessment is extremely difficult.

Attempts have been made to define the cardiac status of patients with coronary artery disease more objectively, and one approach has been to measure several hemodynamic parameters at a time when angina has been provoked by either exercise2-4 or atrial pacing.5 These studies have shown that in a given patient angina induced by atrial pacing occurs at a constant and reproducible heart rate and tension-time index,6 and furthermore, that the tension-time index at the onset of angina is similar in an individual patient whether the angina is induced by exercise or atrial pacing.7 On the basis of such results it would appear that the heart rate necessary to provoke angina during pacing and the hemodynamic response of the left ventricle to pacing and exercise may provide a basis for the assessment of altered myocardial function following revascularization.

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The reproducibility of the hemodynamic changes accompanying the onset of angina is not well defined, however, when angina occurs under different circumstances. Such information would be of importance in interpreting the significance of alterations produced by any therapeutic intervention. Therefore, the present investigation was undertaken to examine and compare several hemodynamic indices measured at the onset of angina when angina was provoked by two different methods in the same patient.

**Methods**

Nine men, aged 42 to 58 years, were studied. All were potential candidates for myocardial revascularization because of severe angina pectoris. Seven patients had a history of previous myocardial infarction, and the diagnosis of coronary artery disease was confirmed by coronary arteriography in all. Clinical signs or symptoms of congestive heart failure were not present in any patient at the time of study, but two patients had symptoms of heart failure in the past.

Studies were performed in the fasting state. Each patient was premedicated with pentobarbital (100 mg, intramuscularly) 1 hour before the study. Right and left heart catheterizations were performed from the right antecubital vein and brachial artery. We measured left ventricular (LV) pressures through a no. 7 Courand catheter with Statham strain-gauge transducers (P23Db series) and took left ventricular end-diastolic pressure (LVEDP), recorded at high sensitivity, as the point at which the downslope of the a wave coincided with the upstroke of the LV pressure pulse. This point usually occurred approximately 0.05 sec after the Q wave of the electrocardiogram. The zero reference pressure was set at the midchested level. The first derivative of the LV pressure pulse (LV dp/dt) was determined by means of an R/C differentiating circuit (Electronics for Medicine, Inc.). Care was taken to obtain undamped pressure recordings so that dp/dt, derived from pressures obtained through a conventional end-hole catheter, would reasonably parallel measurements obtained by use of a catheter-tip transducer system. Cardiac output was determined by the indicator-dilution technic with injection of the indicator, indocyanine green, into the left ventricle. Exercise was performed in the supine position on a bicycle ergometer. During the pacing study, all measurements were made with the legs horizontal; during the exercise study, control and exercising values were obtained with the feet elevated and attached to the bicycle ergometer.

Tension-time index (mm Hg sec/min) was calculated as the product of heart rate, ejection time, and the mean ventricular pressure during ejection (mean ventricular pressure was measured by planimetric integration of the ventricular pressure pulse during ejection). The LV stroke work index (LVSWI) was computed as follows:

\[
\text{LVSWI} \ (\text{g-m/m}^2) = \frac{\text{LVSP} - \text{LVEDP}}{\text{SVI}} \times 0.136
\]

Where LVSP is the mean LV systolic pressure during ejection and SVI is the stroke volume index.

The pacing study was performed in a manner similar to that described by Sowton and associates. After positioning a bipolar pacing catheter in the right atrium, we began pacing at a rate of 5 to 10 beats/min above the resting heart rate and increased the rate by 5 to 10 beats/min until angina occurred. Hemodynamic measurements were made after pacing at each rate for 1 min and at the onset of angina. As soon as the measurements during angina were completed, pacing was discontinued, and angina disappeared in all of the patients within 2 min. After a 10-min interval the pacing procedure was repeated in each patient to ascertain the reproducibility of the technic. We began the exercise study after a 15-min rest period. Hemodynamic measurements were made after each minute of exercise and immediately after the onset of angina. The statistical significance of differences was evaluated by the paired t-test.

**Results**

In seven of the nine patients angina occurred both during atrial pacing and exercise. The hemodynamic findings in these seven patients are summarized in table 1. In the remaining two patients angina was readily provoked by exercise but did not occur during atrial pacing. In one of these two, marked pulsus alternans necessitated discontinuing the pacing study after a rate of 143 had been reached. In the other, pain did not occur when the rate was increased up to 153/min; beyond this point it became difficult to maintain pacing control. These latter two patients are omitted from all subsequent analyses.

**Tension-Time Index**

The tension-time index (TTI) did not change significantly during pacing; however, during exercise it rose significantly \((P < 0.01)\) from control levels to the onset of angina (fig.
### Table 1

**Summary of Hemodynamic Findings in Seven Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Study</th>
<th>Left ventricular pressure (mm Hg)</th>
<th>Ejection period (sec)</th>
<th>Heart rate (beats/min)</th>
<th>Tension-time index (mm Hg sec/min)</th>
<th>LV peak dp/dt (mm Hg/sec)</th>
<th>Total diastolic time (sec/min)</th>
<th>Cardiac index (L/min/m²)</th>
<th>Stroke work index (g·m/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.H.</td>
<td>Pacing</td>
<td>110/12 115/6</td>
<td>0.22 0.15</td>
<td>96 169</td>
<td>2240 2840</td>
<td>1120 1510</td>
<td>38.9 34.6</td>
<td>2.84 2.95</td>
<td>37.3 25.2</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>130/26 142/40</td>
<td>0.23 0.21</td>
<td>106 137</td>
<td>2710 3600</td>
<td>1230 1680</td>
<td>35.6 31.2</td>
<td>2.28 3.31</td>
<td>31.5 29.6</td>
</tr>
<tr>
<td>J.K.</td>
<td>Pacing</td>
<td>123/8 130/9</td>
<td>0.25 0.23</td>
<td>78 101</td>
<td>2130 2810</td>
<td>2160 2900</td>
<td>40.5 36.8</td>
<td>2.67 2.39</td>
<td>47.0 36.0</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>124/8 142/17</td>
<td>0.26 0.25</td>
<td>81 98</td>
<td>2430 3020</td>
<td>2430 3290</td>
<td>38.9 35.5</td>
<td>2.58 3.11</td>
<td>50.6 50.0</td>
</tr>
<tr>
<td>A.C.</td>
<td>Pacing</td>
<td>110/8 109/8</td>
<td>0.27 0.19</td>
<td>85 121</td>
<td>2360 2250</td>
<td>1790 1380</td>
<td>37.0 37.0</td>
<td>— —</td>
<td>— —</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>128/18 134/38</td>
<td>0.31 0.27</td>
<td>81 103</td>
<td>2540 3370</td>
<td>2240 2520</td>
<td>34.9 32.2</td>
<td>3.18 3.79</td>
<td>44.3 41.3</td>
</tr>
<tr>
<td>A.D.</td>
<td>Pacing</td>
<td>155/16 155/8</td>
<td>0.32 0.24</td>
<td>67 110</td>
<td>2790 3640</td>
<td>1840 2450</td>
<td>38.6 33.6</td>
<td>— 3.76</td>
<td>— 60.4</td>
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<tr>
<td></td>
<td>Exercise</td>
<td>140/16 180/28</td>
<td>0.34 0.27</td>
<td>67 102</td>
<td>2960 4380</td>
<td>2180 3500</td>
<td>37.2 32.5</td>
<td>3.14 3.12</td>
<td>72.7 54.5</td>
</tr>
<tr>
<td>W.S.</td>
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<td>116/8 124/9</td>
<td>0.20 0.18</td>
<td>80 110</td>
<td>1600 2220</td>
<td>2360 2600</td>
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<td>2.70 2.50</td>
<td>44.1 31.8</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>140/12 170/16</td>
<td>0.22 0.22</td>
<td>85 105</td>
<td>2520 3420</td>
<td>2600 3760</td>
<td>41.3 36.9</td>
<td>2.59 3.95</td>
<td>51.0 67.5</td>
</tr>
<tr>
<td>C.K.</td>
<td>Pacing</td>
<td>108/6 94/6</td>
<td>0.25 0.17</td>
<td>94 154</td>
<td>2340 2390</td>
<td>1340 1420</td>
<td>36.5 33.8</td>
<td>3.24 1.95</td>
<td>44.1 14.6</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>139/22 124/36</td>
<td>0.29 0.27</td>
<td>86 115</td>
<td>3000 3200</td>
<td>1600 2000</td>
<td>35.1 29.0</td>
<td>2.77 3.35</td>
<td>44.7 26.9</td>
</tr>
<tr>
<td>E.O.</td>
<td>Pacing</td>
<td>140/17 117/7</td>
<td>0.32 0.15</td>
<td>71 154</td>
<td>2840 2700</td>
<td>1450 1450</td>
<td>37.3 36.9</td>
<td>2.75 2.40</td>
<td>56.9 45.1</td>
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<tr>
<td></td>
<td>Exercise</td>
<td>135/17 148/20</td>
<td>0.32 0.29</td>
<td>66 94</td>
<td>2560 3080</td>
<td>1540 2200</td>
<td>38.9 32.7</td>
<td>2.90 4.14</td>
<td>62.1 70.1</td>
</tr>
<tr>
<td>Mean</td>
<td>Pacing</td>
<td>11* 8*</td>
<td>0.26 0.19</td>
<td>82 131</td>
<td>2340 2600</td>
<td>1720 1960</td>
<td>38.9 36.1</td>
<td>2.84 2.44</td>
<td>45.9 30.5</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>17* 28*</td>
<td>0.28 0.25</td>
<td>82 108</td>
<td>2690 3520</td>
<td>1990 2710</td>
<td>37.4 32.9</td>
<td>2.79 3.71</td>
<td>48.0 50.0</td>
</tr>
<tr>
<td>Mean difference†</td>
<td></td>
<td>20 0.07 24 830 750 3.3 1.27 19.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>±1 Standard error of the mean</td>
<td></td>
<td>±0.02 ±8 ±124 ±150 ±0.6 ±0.24 ±5.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.01 &lt;0.05 &lt;0.01 &lt;0.01 &lt;0.01 &lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C = control values; A = values at onset of angina.

* Left ventricular end-diastolic pressure.

† Mean difference refers to the paired comparisons of pacing and exercise data at the point of angina.
Hemodynamic accompaniments of angina. Control values are shown on the left of each panel, and those obtained at the onset of angina on the right. Each value represents the average of the seven patients.

In each patient the TTI at which angina occurred was significantly higher ($P < 0.01$) during exercise than during atrial pacing (fig. 2A).

Peak Left Ventricular dp/dt

The change in peak LV dp/dt during the pacing study was not significant, but during exercise there was a significant ($P < 0.01$) increase from control values to the appearance of angina (fig. 1). Peak LV dp/dt at the onset of angina induced by exercise was significantly higher than when angina was induced by pacing ($P < 0.01$, fig. 2C).

Product of Peak Left Ventricular Pressure and Heart Rate

The average value of this index increased in a similar manner from control levels to the onset of angina, whether angina was precipitated by atrial pacing or exercise (fig. 1). No consistent differences were found in the product of peak LV pressure and heart rate at the onset of angina whether it was provoked by exercise or by atrial pacing (fig. 2B).

Figure 1

Tension-time index, product of peak left ventricular (LV) pressure and heart rate, and peak LV dp/dt at the onset of angina in seven patients. In each panel the closed circles represent the values obtained in individual patients when angina was induced by pacing (on the left) and by exercise (on the right).

Figure 2
five of the patients this index was similar at the onset of angina provoked by exercise or atrial pacing; in one patient it was much greater when angina occurred during exercise, and in one patient it was much higher when angina was provoked by atrial pacing.

**Left Ventricular End-Diastolic Pressure**

The average LVEDP with the feet down (control for the pacing study) was 11 mm Hg. In four of the seven patients the LVEDP increased when the legs were raised, so that the average control value for the exercise study was 17 mm Hg (table 1). From the onset of pacing to the appearance of angina LVEDP either remained the same or fell. In contrast LVEDP rose soon after the onset of exercise and tended to increase as exercise progressed. No further changes were noted when angina occurred. LVEDP at the onset of angina induced by exercise was greater than 15 mm Hg in each patient, while no patient had values above 10 mm Hg when angina was induced by pacing (fig. 3A). The mean difference at the onset of angina during pacing and exercise was statistically significant ($P < 0.01$). Examples of the response of LVEDP to exercise and to pacing are shown in figures 4 and 5.

**Heart Rate**

The heart rate necessary to provoke angina with atrial pacing ranged from 101 to 169 beats/min (average, 131). When pacing was repeated, angina recurred in each patient at a similar heart rate; the rates in the two studies differed by 0 to 7 beats/min (average, 3). When angina was provoked by exercise, the ventricular rate of each patient was significantly lower ($P < 0.05$), ranging from 94 to 137 beats/min (average, 108).

**Cardiac Output**

Cardiac output was not significantly altered by pacing, but during exercise it had increased by approximately 33% at the onset of angina (table 1). The mean difference between the cardiac outputs attained at the onset of angina during pacing and during exercise was statistically significant ($P < 0.01$).
Ejection Period
The ejection period consistently fell from control levels to the onset of angina both during pacing \((P < 0.01)\) and during exercise \((P < 0.02, \text{fig. 1})\). The decrease during pacing, however, was significantly greater \((P < 0.01)\), leading to a mean ejection period at the onset of angina during pacing of 0.19 sec in contrast to a mean of 0.25 sec during exercise (fig. 3C).

Discussion
In patients with coronary artery disease, angina pectoris is presumed to occur when myocardial oxygen requirements exceed the capacity of the diseased coronary arteries to supply sufficient oxygenated blood. Thus, if the maximal capacity to deliver oxygen is similar under various circumstances, angina would be expected to occur when a fairly constant level of myocardial oxygen requirements is exceeded.

The TTI, an index derived from the product of the integrated LV pressure pulse and heart rate, has been found to correlate with myocardial oxygen consumption \((\text{MVO}_2)\) under carefully controlled experimental conditions.\(^9\) Although it has been suggested that this, or similar indices, may provide a rough indication of the level of \(\text{MVO}_2\) at which myocardial ischemia occurs,\(^6,10\) the limitations of these indices as reflections of \(\text{MVO}_2\) have
HEMODYNAMIC ACCOMPANIMENTS OF ANGINA

Figure 5

Left ventricular pressure tracings obtained in patient H.H. during the pacing study (upper panel) and the exercise study (lower panel). With pacing the left ventricular end-diastolic pressure (arrow) fell and remained below the control level even during angina. When the feet were raised during the control period, left ventricular end-diastolic pressure increased. (Note the change in pressure scale.) It increased further when exercise began and continued to rise gradually. No distinct additional elevation occurred at the onset of angina. Ex = exercise; HR = heart rate.

been recognized. Factors other than intraventricular pressure and heart rate may independently alter MVO2; the major ones being myocardial wall tension (a factor dependent on both developed intraventricular pressure and ventricular volume) and the contractile state of the myocardium.11 The important influence of these factors on the relationship between TTI and MVO2 has been demonstrated in several studies. Thus, when the contractile state of the myocardium is altered by catecholamine infusion,8,12 exercise,13 or sympathetic nerve stimulation,14 pressure-time indices show no correlation with MVO2.

Similar discrepancies in the relationship between TTI and MVO2 also might be anticipated when angina is precipitated during such different physiological circumstances as atrial pacing and exercise. The contractile state of the myocardium, as estimated by peak LV dp/dt, and the ventricular volume, as reflected by LVEDP, were probably greater when angina was induced by exercise than when it occurred during pacing. Both of these factors by augmenting MVO2, would be expected to change the relationship between TTI and MVO2 during exercise-induced angina from
that which existed when angina was induced by pacing.

On the basis of these considerations, it was not surprising to find that angina occurred at different tension-time indices when provoked by exercise and pacing. However, the enhanced contractility and greater ventricular volume that appeared to be present during exercise as compared to pacing should have caused angina to occur at a lower TTI during exercise. The finding that angina appeared at a higher TTI during exercise is difficult to explain in the absence of other changes relating to myocardial oxygen delivery or oxygen needs. It is possible, for example, that exercise might produce a greater augmentation of coronary blood flow than atrial pacing, thereby allowing M\textsubscript{VO\textsubscript{2}} to increase to a greater extent before the occurrence of myocardial ischemia. This could not have occurred on the basis of differences in the time available for coronary filling, however, since total diastolic time per minute was greater during pacing than during exercise (table 1). Therefore, if exercise does provide a more potent stimulus than atrial pacing for increasing myocardial blood flow, the mechanism by which this is achieved is unknown.

The difficulties inherent in using a relatively simple index to estimate the level of M\textsubscript{VO\textsubscript{2}} that precipitates angina are illustrated by a comparison of the values of TTI and the product of peak LV pressure and heart rate, another index correlated with M\textsubscript{VO\textsubscript{2}}\textsuperscript{15} While TTI at the point of angina was consistently higher during exercise than pacing, the product of peak LV pressure and heart rate did not show any consistent differences.

One of the relatively common responses of patients with coronary artery disease is the elevation in LVEDP that occurs during exercise\textsuperscript{2-4} a finding confirmed by the present investigation. However, it is often not clear if this abnormal response represents LV failure, or results from a decrease in LV compliance. That the high end-diastolic pressures are at least in part the result of diminished left ventricular compliance is suggested by the following observations. First, the relatively minor increases in left ventricular volume that probably occur when the legs are elevated often resulted in large increases in LVEDP (table 1). Second, in one patient continuous recordings were made when atrial pacing was stopped shortly after the onset of angina (fig. 6). The beats occurring after termination of pacing demonstrated progressive increases in the R-R intervals and thus in diastolic filling time. Concomitant with these changes, stepwise increments in LVEDP appeared. The progressive increases in LVEDP most likely resulted from small increases in left ventricu-
lar end-diastolic volume, as would occur if the ventricle were functioning on a steep portion of its pressure-volume curve. These findings also demonstrate that very different values for LVEDP would have been obtained if measurements were made even two or three beats after pacing had been stopped.

Recent studies have suggested that atrial pacing is a valuable diagnostic test for coronary artery disease. In addition, the heart rate at which angina occurs during pacing has been proposed as a reliable index of the point at which myocardial ischemia occurs. While atrial pacing may prove to be of value in the evaluation of patients with coronary artery disease, its limitations are illustrated by the finding that two of the nine patients with severe coronary disease did not develop pain during atrial pacing although pain was readily provoked by exercise.

In conclusion, we have demonstrated that the hemodynamic accompaniments of angina are variable and depend upon the circumstances under which angina is precipitated. In addition, although TTI, peak LV pressure-heart rate product, and the heart rate at which angina occurs during atrial pacing may provide approximate indications of the level of MVO₂ necessary to provoke angina, the results of this study emphasize that the significance of any alteration in these indices following therapeutic interventions must be interpreted with caution.

References
Hemodynamic Accompaniments of Angina: A Comparison During Angina Induced by Exercise and by Atrial Pacing
KEVIN P. O'BRIEN, LAWRENCE M. HIGGS, D. LUKE GLANCY and STEPHEN E. EPSTEIN

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