Myocardial Function in Coronary Artery Disease Determined by Atrial Pacing

By Joseph W. Linhart, M.D.

SUMMARY
Right atrial pacing was performed in 21 patients with and 10 patients without coronary artery disease (CAD). The values for the control (C) and maximum paced (P) heart rate were similar in all patients. During pacing cardiac output did not change, and mean arterial pressure remained constant except for a slight increase during pacing-induced angina pectoris in 11 patients with CAD. Left ventricular end-diastolic pressure (LVEDP) decreased in the normal subjects (C = 9 ± 1, P = 3 ± 1 SEM mm Hg) and in all 10 patients with CAD who did not develop angina (C = 15 ± 3, P = 5 ± 1 mm Hg). In 11 patients with CAD, developing angina, LVEDP did not decrease before pain occurred (C = 9 ± 1, P = 9 ± 2 mm Hg) and increased during induced angina (P = 14 ± 3 mm Hg). Pacing ventricular function curves (VFC) relating induced changes in LVEDP and stroke work were abnormal in five of 10 patients with CAD and without induced angina when compared to the normal subjects. In patients developing angina, pacing VFC were normal in five of 10 before pain and then became abnormal in four of these five when angina occurred.

Atrial pacing may be used to evaluate ventricular function and may demonstrate abnormalities in patients with CAD even in the absence of pacing-induced angina. Angina pectoris is usually associated with an overall decrease in myocardial function.

Additional Indexing Words:
Angina pectoris  Left ventricular end-diastolic pressure  Left ventriculography
Ventricular function curve

Several methods are available to stress a patient with coronary artery disease so that myocardial performance can be assessed.1–5 Recently, atrial pacing has been used extensively since the hemodynamic and metabolic accompaniments of muscular exercise are eliminated.6–12 When pacing has induced angina, the angina is usually associated with significant hemodynamic changes implying abnormal myocardial function, although increases in left ventricular filling pressures are less than those induced by exercise. Since abnormal myocardial function may influence the feasibility and the assessment of the results of coronary arterial surgical procedures,13–16 it is also important to ascertain the myocardial status in such patients in the absence of angina.

In a previous communication from this laboratory, the use of atrial pacing to construct ventricular function curves using induced changes in stroke work and left ventricular end-diastolic pressure (LVEDP) was described.17 This technique was shown to be capable of characterizing left ventricular function, and it permitted a separation of normal and abnormal responses. This report describes the use of that technique in patients with coronary artery disease and demonstrates that abnormalities in myocardial function can be uncovered, not only during angina, but also in the absence of chest pain.
Methods

Thirty-one patients, all in sinus rhythm, 10 without coronary artery disease (nine male, one female) and 21 with severe coronary artery disease (20 male, one female) were studied in the postabsorptive state under light sedation by pentobarbital. Each patient was informed regarding the nature and technique of the investigation. In each instance, cardiac catheterization studies were indicated for diagnosis or for evaluation before or after operation.

Under local anesthesia with lidocaine, a needle was placed in the left femoral artery, and a cutdown was performed in the right antecubital area. By standard techniques, one catheter was placed in the pulmonary artery through an antecubital vein and another in the left ventricle (LV) retrograde from the brachial artery. A bipolar electrode catheter was positioned in the right atrium. The pressures were recorded by fluid-filled systems on an Electronics for Medicine DR 8 recorder, through Statham P23Db strain gauges. The midchest position served as the zero reference point. Mean pressures were determined electronically. LVEDP was recorded on a high sensitivity scale and measured where the downslope of the left ventricular (LV) a wave coincided with the initial upstroke of the LV pressure. This usually occurred near the peak of the R wave of the electrocardiogram, or approximately 0.05 sec after the Q wave. LVEDP was averaged over two respiratory cycles or approximately 10 beats. After control arterial and intracardiac pressure measurements, heart rate was gradually increased by right atrial pacing beginning at a rate 5–10 beats/min above the control level. Lead II of the electrocardiogram was continuously monitored. Subsequent rate increases were in increments of approximately 10 beats/min with hemodynamic measurements recorded after a 2-min period at the particular heart rate. Cardiac output was determined by the dye-dilution method during the control period, at an intermediate heart rate of 100–110 beats/min and at the maximum pacing rate. The highest pacing rate was determined individually for each patient and depended upon his response. Pacing rates suitable to obtain a significant change in LVEDP (reduction to a value close to zero when the control LVEDP was normal and a pacing LVEDP within the normal range when the control value was elevated) were chosen. In a patient in whom the LVEDP rises during pacing, the level reached will depend upon the clinical status. If the subject is asymptomatic, then a change from normal to abnormal levels is considered to be significant. If chest pain, dyspnea, etc., occur as heart rate is increased, hemodynamic measurements are made at that level, and then appropriate action is taken to relieve the symptoms. True angina pectoris was considered to be present when the patient’s chest discomfort had the usual characteristics and was similar to that occurring in the patient during exertion. This was distinguished from the feeling of discomfort in the chest that patients sometimes experience during pacing by careful questioning and familiarity with the patient’s clinical syndrome. In two patients (one normal and one with coronary artery disease), the development of Wenckebach-type second degree A-V block fixed the upper limit of the pacing rate to that which still permitted 1:1 atrioventricular conduction. However, at least one, and occasionally two, sets of data were obtained after angina was induced in patients with coronary artery disease. From the control and pacing hemodynamic information, ventricular function curves were constructed relating the induced changes in LVEDP and stroke work. Stroke work (in gram-meters) was calculated from the formula:

$$\text{Stroke work} = \frac{(F \text{Am}) - \text{LVEDP} \times SV \times 1.36}{100}$$

where (F Am) is mean femoral arterial pressure and SV is stroke volume. In the classic function curves alterations in stroke volume are produced by varying venous return and holding the heart rate and other potential variables constant. In these studies, stroke volume is being decreased by increasing the heart rate rather than by increasing the stroke volume at a fixed heart rate. Therefore, these function curves will be referred to as pacing ventricular function curves, since they are produced by changes in heart rate and must be interpreted in relation to the control normal patient rather than to the classic description.

After the completion of the physiologic studies, left ventricular and coronary cineangiography was done. The technique used, the evaluation of these films, and the grading systems have been previously described.

On the basis of their clinical status and control hemodynamic and angiographic data, the patients could be divided into two groups as regards the presence or absence of coronary artery disease. The normal group included seven with no cardiac abnormalities at all (all class I), two with significant mitral stenosis and normal coronary arteries (class III because of their valve lesion but with normal left ventriculograms and LVEDP), and one following aortic valve replacement (class I). Twenty-one patients had definite coronary artery disease with clinical angina pectoris, or a documented history of a myocardial infarction, or both. Six of these patients had a history compatible with congestive heart failure and were taking a digitalis preparation. This
history was not obtained in those who were not taking digitalis. In each, the coronary atherosclerosis was extensive with occlusive lesions of two or three vessels of more than 50% of a vessel diameter.22 The patients with coronary artery disease could also be further subdivided into those who did and did not experience angina pectoris during pacing on the basis of the previously described characteristics.

Results

General Hemodynamic Observations

The control values for heart rate, mean femoral arterial pressure, and stroke volume were similar in the three groups of patients (table 1). In the patients with coronary artery disease (CAD) not subsequently experiencing angina, the control LVEDP was slightly higher than in those of the other groups, and the control values for cardiac output for both groups of patients with CAD were lower than those of patients with no CAD, but neither was statistically significant. Values for control stroke work were significantly lower in the patients with CAD and no angina than in the other groups. The significant differences among the three groups were as follows: mean femoral arterial pressure was higher in patients experiencing angina during pacing than in those with no angina during the highest paced heart rate; control stroke work was lower in the group with CAD and no angina than in the normal group; LVEDP was higher during pacing after angina occurred than during pacing in the other two groups; and LVEDP was higher in the group with angina during pacing before angina occurred than during pacing in the normal group.

It was possible to increase the heart rate to a similar level by atrial pacing in all patients not developing angina pectoris (124 ± 6 beats/min). The range of pacing heart rates in the normal subjects was 106–156 beats/min, while in the patients with CAD without angina it was 95–150 beats/min. The average upper pacing level in those experiencing angina was lower (110 ± 7 beats/min, range 93–138 beats/min), since further increases in heart rate were discontinued when definite pain developed. These differences are not statistically significant since the heart rate at which patients experience angina is quite variable and dependent upon many factors other than heart rate.9, 23, 24 During pacing, the cardiac outputs did not change, while stroke volume and stroke work decreased significantly (table 1). The mean femoral artery pressure was significantly higher during angina relative to the control value in that group of patients with coronary artery disease. LVEDP also decreased significantly in the

Table 1

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>FA (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>CO (liters/min)</th>
<th>SV (ml)</th>
<th>SW (g·m)</th>
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<tr>
<td>Normal response (10 patients)</td>
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<tr>
<td>Control</td>
<td>80 ± 4</td>
<td>96 ± 4</td>
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<td>5.4 ± 0.4</td>
<td>67 ± 5</td>
<td>76 ± 5</td>
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<tr>
<td>Pace</td>
<td>124 ± 6*</td>
<td>101 ± 4</td>
<td>3 ± 1*</td>
<td>5.4 ± 0.4</td>
<td>44 ± 3*</td>
<td>56 ± 3*</td>
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<td>Coronary artery disease: no angina (10 patients)</td>
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<tr>
<td>Control</td>
<td>76 ± 4</td>
<td>92 ± 4</td>
<td>15 ± 3</td>
<td>4.4 ± 0.4</td>
<td>58 ± 3</td>
<td>61 ± 5</td>
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<tr>
<td>Pace</td>
<td>124 ± 6*</td>
<td>97 ± 4</td>
<td>5 ± 1*</td>
<td>4.5 ± 0.3</td>
<td>37 ± 4*</td>
<td>46 ± 4*</td>
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<td>Coronary artery disease: angina (11 patients)</td>
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<tr>
<td>Control</td>
<td>74 ± 3</td>
<td>96 ± 4</td>
<td>9 ± 1</td>
<td>4.5 ± 0.2</td>
<td>63 ± 4</td>
<td>74 ± 5</td>
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<tr>
<td>Pace PTA</td>
<td>107 ± 6*</td>
<td>102 ± 4</td>
<td>9 ± 2</td>
<td>4.7 ± 0.3</td>
<td>46 ± 5*</td>
<td>58 ± 5*</td>
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<tr>
<td>Pace angina</td>
<td>110 ± 7*</td>
<td>109 ± 3*</td>
<td>14 ± 3</td>
<td>5.0 ± 0.4</td>
<td>47 ± 4*</td>
<td>61 ± 5</td>
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Abbreviations: HR = heart rate; FA = femoral artery mean pressure; LVEDP = left ventricular end-diastolic pressure; CO = cardiac output; SV = stroke volume; SW = stroke work; Pace = the values during the highest paced heart rate; Pace PTA = values during pacing prior to the development of angina; Pace angina = values during pacing after angina has occurred.

*Significant differences between control and pacing values (P < 0.05) within the same group of patients.
stroke work is associated with small changes in LVEDP.25 The responses in this group are compared to those of the patients with coronary artery disease in figures 2-4.

Figure 2 represents the values for patients with CAD who did not experience anginal pain during atrial pacing. Five of these curves are normal and five are considered to be abnormal, since little or no change in stroke work occurred relative to their induced changes in LVEDP. All five patients whose control LVEDP were normal had normal VFC, and all five having elevated control LVEDP had abnormal curves.

Figure 3 demonstrates the ventricular function curves in 10 of the 11 patients who subsequently developed angina in whom sufficient data are available prior to chest pain. Five of these curves are normal and five, abnormal. Both patients with elevated normal subjects, and in the patients with coronary artery disease and no angina, but remained essentially unchanged in those patients subsequently experiencing angina. The LVEDP was significantly higher, at a similar heart rate, during angina pectoris than in the normal subjects or in patients with CAD who had no chest pain (table 1). The LVEDP decreased with pacing in all patients in the latter two groups. In patients developing angina LVEDP, as compared to the control state, increased in seven, decreased in two, and was unchanged in two. Since LVEDP usually decreases with atrial pacing, a lack of change probably indicates an abnormal response.6-9

Pacing Ventricular Function Curves

Figure 1 demonstrates the pacing ventricular function curves (VFC) in the normal group. All are normal, since a large increase in
LVEDP had abnormal curves, and, in addition, three of eight patients with normal control LVEDP also had abnormal ventricular function. When the information from figures 2 and 3 is combined 10 of 20 patients with coronary artery disease had abnormal ventricular function by the criteria mentioned above, disclosed by atrial pacing, in the absence of chest pain.

The VFC from the patients experiencing angina pectoris are shown in figure 4. The values include those for the control, or pacing, or both prior to chest pain and for at least one pacing level after the development of angina. Nine of 11 curves are abnormal in comparison to the values depicted in figure 1. In two patients, large changes in stroke work were associated with relatively smaller changes in LVEDP, and their curves compare favorably with those in figure 1. In one of these patients (the upper right-hand corner of figure 4) his "normal" VFC was associated with an increase in cardiac output from 5.4-7.2 liters/min, which is also indicative of no concomitant depression in myocardial function.

**Angiographic Correlations**

Coronary arteriography disclosed no significant differences between the extent of coronary artery disease in those who did or did not experience chest pain. All had significant disease of two or three vessels.

The left ventriculogram was normal in all those patients without coronary artery disease who had normal pacing ventricular function curves. No gross or localized defects were present. In those subjects with CAD who did not have angina, the LV cineangiogram was considered abnormal in all five patients whose
angiograms disclosed a generalized or significant localized decrease in myocardial contractility. Only one of the five patients whose pacing VFC were normal also had an abnormal LV angiogram. In those with CAD experiencing angina, the pacing VFC prior to angina were compared to their angiographic findings. The LV angiogram was abnormal in four of five patients who had an abnormal response to atrial pacing. That one patient also had a normal LVEDP. In two of five with normal pacing response, the LV angiogram disclosed definite localized functional abnormalities. Both of those patients with the abnormal LV angiogram had abnormal pacing VFC when angina occurred. A good correlation between myocardial function determined angiographically and by the pacing VFC was noted in 16 of 21 patients with CAD.

**Clinical Correlations**

All seven essentially normal subjects of the 10 without CAD had no symptoms (except for atypical chest pain), and each patient’s pacing VFC was normal. The two patients with mitral stenosis had symptoms referable to their valvular lesion, but hemodynamically and angiographically the LV functioned normally. The patient whose aortic valve had been replaced was studied 1 year later; he had returned to work with no symptoms. His heart size was essentially normal. The pacing VFC were normal in the latter three patients.

In six of the 21 patients with CAD, a history of congestive heart failure could be elicited. In five of these patients, who developed angina, the pacing VFC were abnormal. The sixth patient did not develop angina with pacing, and the pacing VFC was normal. In the 15 patients with no history of congestive heart failure, the pacing VFC were normal in nine and abnormal in six.

**P-R Interval Changes**

Since the P-R interval increases with atrial pacing, this might disturb the relationship between atrial and ventricular contractions and adversely influence left ventricular function.26-29 There were, however, no significant differences between the control and pacing P-R intervals for the normal subjects and those with coronary artery disease (normal subjects, control P-R interval = 0.17 ± 0.01 sec, pacing = 0.25 ± 0.01 sec; patients with CAD, control P-R interval = 0.15 ± 0.02 sec, pacing = 0.24 ± 0.02 sec).

**Discussion**

An increase in heart rate tends to enhance myocardial performance in certain animal and isolated muscle preparations, but this effect appears to be masked in clinical hemodynamic studies.29-35 The reason for this is unknown, but it has been theorized that there may be a decrease in the booster pump action of the left atrium and possibly, also, alterations in the level of activity of the autonomic nervous system.34-35 Since no definite change in intrinsic contractility can be identified, atrial pacing has been used to construct ventricular function curves based upon its known effects upon stroke volume and work and LVEDP.7, 9, 30, 36, 37 One must recall, however, that the “classic” ventricular function curves are produced by alterations in venous return and, thereby, changes in ventricular filling pressure and volume and myocardial fiber stretch.19 In those curves heart rate is held constant, and attempts are made to control or minimize other variables, including reflex autonomic changes. During atrial pacing, on the other hand, stroke volume and LVEDP are being decreased by increases in heart rate and, in addition, prolongation of the P-R interval occurs.26, 27 Since atrial pacing may still influence intrinsic myocardial function, there are changes in the relationship between atrial and ventricular contractions, and the method of obtaining stroke volume and LVEDP changes differs from the “classic” examples; these curves will be referred to as pacing ventricular function curves. It is, therefore, necessary to compare patients at similar heart rates and P-R intervals so that the effects of increases in heart rate will be common to all patients. In addition we must compare the pacing responses of the patients under study to control normal patients rather than directly to the “classic” curves.
In this study changes in heart rate were similar in all patients, and the control level and changes in P-R interval with pacing were the same. The P-R interval with pacing (0.24-0.25 sec) remained within the optimal range for an effective atrial contribution to ventricular contraction, but since the optimal P-R interval is inversely related to heart rate and is more important in patients with depressed myocardial function, a small effect cannot be discounted.

In previous studies, pacing ventricular function curves (VFC) have shown a clear separation between patients with normal and abnormal ventricular function determined by other criteria. The configuration of the pacing VFC was quite similar to the “classic” curves. Normal subjects had large changes in stroke work associated with small changes in LVEDP, while those with known myocardial dysfunction had flat curves with little change in stroke work as LVEDP was altered.

In this study 10 of 20 patients with severe coronary artery disease had abnormal pacing VFC in the absence of angina pectoris when compared to the normal response. This was true in five of 10 patients never experiencing angina during the study and in five of 10 patients who subsequently developed chest pain (figs. 2 and 3). Although it is possible that some of the former group had abnormal curves because they were in a “preanginal” state, the LVEDP decreased in all during pacing while it decreased in only two of 11 patients who developed angina pectoris. Although the hemodynamic response to angina is variable, at least some patients will have progressive increases in LVEDP prior to the occurrence of pain. Ventricular function curves were abnormal in nine of 11 patients during angina, including four of five patients whose VFC were normal prior to the occurrence of chest pain. This has been the most frequent finding during induced chest pain in other pacing studies. It is apparent that patients with coronary artery disease may have normal myocardial function even under mild stress, which then may become abnormal when significant ischemia is produced. Others, because of chronic ischemia and its effects or previous myocardial infarction, are always found to have abnormal myocardial function.

In patients with an elevated LVEDP and generalized poor myocardial contractility angiographically, the pacing VFC was always abnormal, indicating that except for some semiquantification of dysfunction the test was not essential for determination of myocardial function. However, two patients with localized abnormalities of contraction had normal pacing VFC. This probably indicates that their overall myocardial reserve is adequate, a fact that could not be ascertained without some form of stress. Although localized disorders of myocardial contraction may lead to heart failure, this is not true in all of these patients since compensation of the remaining myocardium may be adequate, even during stress. One additional patient with both normal LVEDP and left ventriculogram had abnormal myocardial function under stress, which also could not be ascertained from the routine procedures. This may be important clinically.

Since a good correlation frequently does not exist between the extent of coronary artery disease demonstrated angiographically and a patient’s electrocardiogram and myocardial integrity, some form of stress must be applied in order that myocardial performance might be evaluated. The relative ease of performance of this test (which requires only one additional pacing catheter than standard procedures) makes it an ideal method since it can separate not only those patients experiencing overt ischemia (angina), but also those without chest pain, from normal subjects. As performed in this laboratory abnormal myocardial function was disclosed in the absence of chest pain in half the patients with coronary artery disease. There is no doubt that overt myocardial ischemia will depress ventricular contractility concomitantly, but the status of the myocardium in the absence of clinical evidence of ischemia may be more important in regards to a patient’s morbidity, or mortality, or both, both medically and surgically. These results differ from
those of Khaja and associates, who found that when angina was not provoked, only exercise demonstrated abnormal ventricular function since the pacing response was indistinguishable from that of a normal group of patients. We have no explanation for this variance since we have found the test useful in other forms of myocardial dysfunction as well. All of our patients had severe coronary artery disease, and a difference in patient population may be a factor. The hemodynamic responses in coronary artery disease are so variable, however, that differences between small groups of patients may be more apparent than real.

In this regard further studies are underway to indicate the relationship between the exercise response and the pacing VFC. The pacing VFC is, however, easier to perform than exercise, and although it is associated with increases in myocardial minute work and oxygen consumption, it lacks the systemic metabolic and hemodynamic changes of exercise; heart rate changes may be precisely controlled and reproduced, and the semiquantitative nature of the data may permit comparisons both before and after operation. Additionally, atrial pacing has advantages over exercise stress when relative or absolute contraindications to exercise exist, as with recent myocardial infarction, heart failure, crippling arthritis, or a neuromuscular disorder.

This and other studies have clearly shown that the functional and hemodynamic changes associated with coronary artery disease and angina pectoris are quite variable despite similar anatomic lesions. The individual patient may function quite normally until angina occurs, at which time manifestations of myocardial decompensation are noted. Other patients have chronically depressed myocardial function that can only get worse with ischemia.

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