Pacing-Induced Changes in Stroke Volume in the Evaluation of Myocardial Function

By Joseph W. Linhart, M.D.

SUMMARY
For characterization of left ventricular function using changes in heart rate, we performed right atrial pacing in 16 patients during right and left heart catheterizations. Hemodynamic data was obtained before pacing (B), during pacing (D), and immediately after (A) the sudden interruption of pacing, for assessment of the consequences of rapid changes in stroke volume. In 10 patients with normal left ventricular function, as heart rate (HR) changed from 81 ± 4 SEM (B) to 125 ± 6 (D) to 77 ± 5 beats/min (A), left ventricular end-diastolic pressure (LVEDP), from 8 ± 1 (B) to 3 ± 1 (D) to 9 ± 0.5 mm Hg (A), and stroke volume, from 74 ± 9 (B) to 46 ± 4 (D) to 77 ± 9 ml/beat (A), changed linearly. No change occurred in cardiac output (5.7 ± 0.5 liters/min) or in arterial pressure. In six patients with myocardial disease, HR changed similarly (from 86 ± 5 (B) to 126 ± 8 (D) to 90 ± 3 beats/min (A)), but LVEDP, cardiac output (CO), and stroke volume (SV) values were significantly different in comparison to the corresponding values for the subjects with normal function (LVEDP was 21 ± 3 (B), 8 ± 2 (D), and 25 ± 3 mm Hg (A), P = 0.001; CO was 4.1 ± 0.5 liters/min (B, D, and A), P = 0.01; SV was 48 ± 4 (B), 32 ± 5 (D), and 47 ± 4 ml/beat (A), P = 0.02). When pacing ventricular function curves were constructed relating left ventricle stroke work (SW) to LVEDP, normal patients exhibited a steep curve, while those with myopathies had flat responses. When the change (Δ) in SW was related to ΔLVEDP (ΔSW/ΔLVEDP), the value for normal subjects was 5.6 ± 1, and that for patients with myopathies, 0.6 ± 2 (P = 0.001). Atrial pacing may be used for characterization of left ventricular function, and permits a separation of normal and abnormal responses.

Additional Indexing Words:
Atrial pacing Frank-Starling mechanism Myocardial disease
Left ventricular end-diastolic pressure Ventricular function curve Bowditch effect

Atrial pacing has become not only a standard technique for the treatment of selected atrial and ventricular arrhythmias, but also a valuable research tool in the study of the electrocardiographic, hemodynamic, and metabolic influences of an increase in heart rate in the normal and the abnormal heart.1-12 These investigations have adequately demonstrated the relative ease and safety of the atrial pacing method. Since atrial pacing is used so frequently in the cardiac laboratory, a consideration of its usefulness for routine assessment of ventricular function was indicated.

An increase in heart rate itself tends to enhance myocardial performance in the animal and in isolated muscle preparation, and an increase in the velocity of myocardial fiber shortening, with little change in total force development, has also accompanied increased heart rates in human studies.13-17 However,
this enhancement of intrinsic ventricular function may be masked in most clinical hemodynamic studies by a decrease in the booster pump action of the left atrium and, possibly, by alterations in the level of autonomic nervous system activity.\textsuperscript{1, 17} Therefore, previous clinical studies have shown little or no change in the gross external hemodynamic performance of the heart.\textsuperscript{1-3, 18} Since standard measurements of ventricular function (cardiac index, the relationship between stroke volume and work and left ventricular end-diastolic pressure (LVEDP), arterial pressure, etc.) are usually unaltered by atrial pacing alone, this method and its known effects upon stroke volume and LVEDP, could be used for construction of pacing ventricular function curves. Since heart rate is altered by atrial pacing, the relationship between LVEDP and stroke work will be referred to as a pacing ventricular function curve since the “classic” curves are determined at a constant heart rate.\textsuperscript{19} Furthermore, an increase in heart rate and any resulting effect upon the myocardium would be common to all patients, and should not significantly influence the comparison between them.

In this study, an atrial pacing stress test was devised which clearly separated patients considered to have normal, from those considered to have abnormal ventricular function. In addition to the usual hemodynamic information, the effects of a rapid change in stroke volume were also determined through the sudden interruption of atrial pacing. The results of this study form the substance of this report.

**Methods**

Sixteen patients, 14 male and two female, ranging in age from 27 to 60 years (mean, 47 years), were studied in the post-absorptive state under light pentobarbital sedation. Each patient was informed regarding the nature and technique of the investigation. In each instance, cardiac catheterization studies were indicated for diagnosis, or for pre- or postoperative evaluation.

Under local anesthesia with lidocaine, a needle was placed in the left femoral artery (LFA), and a cutdown was performed in the right antecubital area. With standard techniques, one catheter was placed in the pulmonary artery (PA) through an antecubital vein, and another in the left ventricle retrograde from the right brachial artery. Five patients also had transeptal left heart catheterization, percutaneously from the right femoral vein by the Brockenbrough technique. A bipolar electrode catheter was positioned in the right atrium. Control pressure measurements and the cardiac output were determined, the latter by the dye-dilution method with PA injections and LFA sampling. The pressures were recorded on an Electronics for Medicine DR8 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 down stroke 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 a period of two respiratory cycles, or approximately 10 beats. Stroke work (SW) was calculated from the formula

\[
SW = \frac{FAm - LVEDP \times SV \times 1.36}{100} = \text{g-m}
\]

where FAm is mean femoral artery pressure, and SV is stroke volume. The electrocardiogram (lead II only) was continuously monitored.

These measurements were repeated sequentially as the heart rate was gradually increased by right atrial pacing. Heart rate was increased in increments of approximately 10 beats/min, with hemodynamic measurements during pacing recorded after a 2-min period at the particular heart rate. The highest pacing rate was determined individually for each patient, and depended upon his response. No attempt was made to reach any particular level, but only to bring about a significant change in LVEDP. When the control LVEDP was normal (12 mm Hg or less), this meant a pacing value near zero. For an elevated control LVEDP, I arbitrarily tried to reach a pacing figure within the normal range. In a patient in whom the LVEDP rises during pacing, the level reached will depend upon his clinical status. If the patient is asymptomatic, then a change from normal to abnormal levels is considered significant. If chest pain or dyspnea, etc., occurs as heart rate is increased, hemodynamic measurements are made at whatever level has been reached, and then appropriate action is taken to relieve the symptoms. A pacing rate of over 100 was reached in all patients. Most patients were paced between 120 and 150 beats/min. In some patients Wenckebach-type of second degree atrioventricular block limited the pacing
Table 1
Hemodynamic Response to Atrial Pacing in Patients Considered to Have Normal and Abnormal Left Ventricular Function

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>LVEDP</th>
<th>FAM</th>
<th>CO</th>
<th>SV</th>
<th>SW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal LV (10 patients)</td>
<td></td>
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<tr>
<td>C</td>
<td>81 ± 4</td>
<td>8 ± 1</td>
<td>97 ± 4</td>
<td>5.7 ± 0.5</td>
<td>74 ± 9</td>
<td>86 ± 12</td>
</tr>
<tr>
<td>P</td>
<td>125 ± 6</td>
<td>3 ± 1</td>
<td>102 ± 4</td>
<td>5.7 ± 0.5</td>
<td>46 ± 4</td>
<td>61 ± 8</td>
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<tr>
<td>S</td>
<td>77 ± 5</td>
<td>9 ± 0.5</td>
<td>102 ± 4</td>
<td>5.6 ± 0.5</td>
<td>77 ± 9</td>
<td>92 ± 10</td>
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<tr>
<td>Abnormal LV (6 patients)</td>
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<tr>
<td>C</td>
<td>86 ± 5</td>
<td>21 ± 3</td>
<td>105 ± 5</td>
<td>4.1 ± 0.5</td>
<td>48 ± 4</td>
<td>55 ± 10</td>
</tr>
<tr>
<td>P</td>
<td>126 ± 8</td>
<td>8 ± 2</td>
<td>106 ± 6</td>
<td>3.9 ± 0.5</td>
<td>32 ± 5</td>
<td>46 ± 11</td>
</tr>
<tr>
<td>S</td>
<td>90 ± 6</td>
<td>25 ± 3</td>
<td>107 ± 6</td>
<td>4.2 ± 0.5</td>
<td>47 ± 4</td>
<td>52 ± 11</td>
</tr>
</tbody>
</table>

Abbreviations: C = control data; P = during atrial pacing; S = after sudden interruption of pacing; LV = left ventricular function; HR = heart rate in beats/min; LVEDP = left ventricular end-diastolic pressure in mm Hg; FAM = mean femoral artery pressure in mm Hg; CO = cardiac output in liters/min; SV = stroke volume in ml/beat; SW = stroke work in g-m/beat.

All values are ± SEM.

rate to that which still permitted 1:1 atrioventricular conduction. After pressure and cardiac output values were recorded, at the highest paced heart rate, continuous recordings were accomplished during, and after the abrupt cessation of atrial pacing. A determination of cardiac output was repeated immediately with the abrupt termination of pacing. This output is unfortunately not instantaneous, but was accomplished within 20–30 sec of pacing interruption. No significant change occurred in pressure levels during this interval. The pressure levels reported are those obtained by averaging the values for the first 10 beats following the interruption of pacing.

Following the completion of the physiologic studies, left ventricular and coronary cineangiography were carried out. The techniques used, the evaluation of these films, and the grading systems have been previously described.20, 21

On the basis of their clinical status and control hemodynamic and angiographic data, the patients were divided into two groups with regard to left ventricular function. Those considered to have normal myocardial function, at the time of catheterization, had no symptomatology or physical findings suggesting a reduction in left ventricular reserve. Their intracardiac pressures and cardiac index were normal, and they demonstrated normal left ventricular contractility on angiography. This group included four patients with no cardiac abnormalities at all (all class I), two with coronary artery disease (both had angina with no symptoms of congestive heart failure), and normal left ventriculograms and LVEDP, two with mitral stenosis (class III, due to the valve lesion, with normal left ventriculograms and LVEDP), one postoperative from aortic valve replacement for aortic insufficiency (class I), and one who had recovered from a previous episode of suspected viral myocarditis (class I).

The patients considered to have a decrease in myocardial function were all class III, and had signs and symptoms reflecting pulmonary congestion and left ventricular enlargement.22 In addition, one of the patients with coronary artery disease had angina pectoris. They had an elevated LVEDP at rest (five of six), reduced cardiac index, and evidence of a significant decrease in left ventricular contractility on angiography. Three patients had an idiopathic myocardiopathy, two had coronary artery disease, and one had severe myxedema. All were taking maintenance doses of digitalis.

Results
General Hemodynamic Considerations (Table 1)

Patients with normal left ventricular function by the standard criteria had lower LVEDP (8 ± 1 mm Hg SEM vs. 21 ± 3; \( P = 0.001 \)), with higher cardiac output (5.7 ± 0.5 liters/min vs. 4.1 ± 0.5; \( P = 0.01 \)), stroke volume (74 ± 9 ml/beat vs. 48 ± 4; \( P = 0.02 \)), and stroke work (86 ± 12 g-m/beat vs. 55 ± 10; \( P = 0.05 \)), than the patients with abnormal left ventricular function. There was no difference noted as regards control heart rate (81 ± 4 beats/min vs. 86 ± 5), or mean femoral artery pressure (97 ± 4 mm Hg vs. 105 ± 5).
Atrial pacing resulted in the same average upper pacing rate in the two groups (normal LV function 125 ± 6, abnormal LV function 126 ± 8), while no changes occurred in FAm or in cardiac output within the two groups (table 1). Stroke volume and stroke work decreased with atrial pacing as did LVEDP (table 1). Although LVEDP decreased significantly for both groups (P = 0.01), the pacing LVEDP—at the same paced heart rate in both groups—was lower for those with normal left ventricular function (3 ± 1 mm Hg vs. 8 ± 2; P = 0.05).

The PR interval increased with atrial pacing, in the normal patients from 0.18 ± 0.01 sec in the control state to 0.25 ± 0.01 sec. In those patients with abnormal ventricular function, it increased from 0.17 ± 0.01 sec to 0.25 ± 0.02 sec. There was no significant difference between these values for PR interval.

**Abrupt Termination of Atrial Pacing**

Following the abrupt termination of atrial pacing, sinus rhythm was quickly established in all patients at a rate similar to the control value. The mean heart rate after pacing in those with abnormal left ventricles was higher than in the normals (90 ± 6 beats/min vs. 77 ± 5; P = 0.1). However, this difference is not statistically significant. This may reflect the number of patients studied. Stroke volume and stroke work values returned to their control levels (table 1), while femoral artery pressure and cardiac output levels continued to remain stable. The LVEDP quickly returned to control values for both groups, with no significant “overshoots” between control and post-pacing values occurring for either group (table 1).

**Left Ventricular Function**

Three-point pacing ventricular function curves were constructed relating stroke work and LVEDP, with the data obtained in the control state, during atrial pacing (the highest paced rate), and following the abrupt termination of atrial pacing.

Figure 1 represents the values for those subjects considered to have normal left ventricular function by the usual clinical criteria (see Methods). Each of these pacing curves is considered to have a normal configuration, with a relatively large change in stroke work accompanying small changes in LVEDP. The LVEDP levels remained within normal levels (12 mm Hg or less) following pacing, except for one patient whose post-pacing level was 18 mm Hg. His curve had a normal shape, however.
PACING-INDUCED CHANGES IN STROKE VOLUME

(normal subjects $5.2 \pm 1$ ml/mm Hg vs. $0.9 \pm 0.2$ for patients with abnormal LV function; $P = 0.001$).

Discussion

The ventricular function curve relating end-diastolic volume or filling pressure (preload) to the external work performed by the heart (stroke work or volume) has generally been used when characterizing the pumping action of the heart. As end-diastolic volume and, therefore, end-diastolic fiber length in-

Figure 2

Pacing ventricular function curves for patients having abnormal LV function by standard criteria. These curves are flat in type (large changes in LVEDP associated with little or no change in stroke work), and considered to be abnormal. The pacing, control, and post-pacing points are similar to those in figure 1.

Figure 2 illustrates the pacing LV function curves, similarly constructed, in the six patients with abnormal myocardial function. These curves are all flat or descending in type, and indicate small changes in stroke work with large changes in LVEDP. Except for their pacing points, the LVEDP is always within the abnormal range.

Figure 3 illustrates the relationships between changes in stroke work and LVEDP in a different way. When the change in stroke work is divided by the change in LVEDP between the paced and post-pacing values, a significant difference is found between the two groups of patients. $\Delta SW/\Delta LVEDP$ for normal subjects is $5.6 \pm 1$ g-m/mm Hg; for the patients with abnormal LV function, it is $0.6 \pm 0.2$ ($P = 0.001$). A similar difference between groups is found when the change in stroke volume relative to LVEDP is compared

An index, $\Delta SW/\Delta LVEDP$, relating change in stroke work ($\Delta SW$) and change in LVEDP ($\Delta LVEDP$) values between the pacing and immediate post-pacing states. Horizontal heavy bars represent mean values, while the small thin horizontal lines indicate one standard error of the mean.

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crease up to a certain limit, the normal heart responds by a significant enhancement in its force of contraction (Frank-Starling mechanism).26-35 This is represented on the ventricular function curve by a large increase in stroke volume or work relative to small changes in end-diastolic volume or pressure. A change in initial fiber length, such as is caused by changes in heart rate (pacing) or afterload (angiotensin or methoxamine infusion),36 will shift the ventricular response to various points on the same curve, indicating that intrinsic contractility has remained constant. Sarnoff has shown, however, that the ventricle has a family of ventricular function curves (VFC), and that the response may be shifted from one curve to another by enhancement or depression of myocardial contractility.19 An increase in contractility is indicated by a shift of the VFC upward and to the left of the control state; a depression of function is indicated by a shift downward and to the right.

In this study, I used atrial pacing to alter LVEDP and stroke work in order to produce pacing ventricular function curves for comparison of patients with abnormal and normal LV function by standard hemodynamic and angiographic criteria. Although the Bowditch effect57 on myocardial contractility may be involved with this method, previous pacing studies have shown little influence on myocardial performance using the parameters as set forth in this investigation.1-3,18 Although it cannot be ascertained for sure, the heart rate values for the normal and abnormal subjects were similar, and, therefore, the influence of heart rate, on both groups, if present, should have been similar. Afterload was also similar in the two groups, and did not change during or after the pacing studies (table 1). The PR interval increases with atrial pacing, and it is conceivable that this factor might disturb the relationship between atrial and ventricular contractions and adversely influence left ventricular function.17,38-40 In this study, the control PR intervals and the increases with atrial pacing were similar in the two groups and, therefore, should have had similar effects on the atrioventricular relationship. The PR interval with pacing (0.25 sec) remained within the optimal range for an effective atrial contribution to ventricular contraction,41,42 but, since the optimal PR interval is inversely related to heart rate,43 and is more important in patients with depressed myocardial function,41 a small effect can not be discounted.

As atrial pacing was performed, there was a decrease in LVEDP in both the normal and abnormal ventricle, even though it was significantly elevated in the latter. There is a significant decrease in heart size with atrial pacing44 associated with a reduction in stroke volume and work, and, according to the Frank-Starling mechanism, this would account for the decrease in LVEDP. The latter was still significantly higher, at the same paced heart rate, in the abnormal ventricle, in keeping with its reduced contractility and larger volume noted on angiography. It is apparent from this and other studies that atrial pacing will reduce LVEDP in subjects with abnormal ventricles, and will shift the patient to a lower level on the same function curve.45-48

On the other hand, in some patients with coronary artery disease, atrial pacing will result in myocardial ischemia, and may produce an elevation of the LVEDP and a definitely abnormal ventricular function curve.47,49 The patient may even shift from one VFC to another when atrial pacing and nitroglycerin are employed. In other patients with coronary artery disease, atrial pacing has resulted in an increase in LVEDP with no shift in the VFC; this, and other evidence suggests that the increase in LVEDP is due to a decrease in myocardial compliance18 (Linhart, J. W., unpublished observations).

A clear separation between the abnormal and the normal ventricle was accomplished in this investigation by relating the changes induced by atrial pacing and its sudden interruption, in stroke work or volume to such changes in LVEDP. The pacing VFC in the normal subjects all showed large changes in stroke work accompanying small changes in LVEDP (fig. 1), distinctly normal responses. The patients considered to have depressed
myocardial function all had flat, abnormal curves exhibiting little or no change in stroke work as LVEDP was altered over a wide range of values (fig. 2).

An index, ΔSW/ΔLVEDP, relating these two variables between the pacing and immediate post-pacing states, also clearly separated the two groups, with no overlapping. An index value of over 2 g-m SW/mm Hg LVEDP was seen in patients who had normal function as judged by other criteria. Parker et al. have found a similar linear relationship between LVEDP and stroke volume in patients at several different pacing rates.45 They also found that a separation could be made between abnormally and normally functioning patients by relating the change in stroke volume to the change in filling pressure during atrial pacing. They did not present any post-pacing data.

Coincident with the sudden interruption of atrial pacing, the longer diastolic filling period results in the presentation of a sudden volume load to the left ventricle. This results in ventricular dilatation, increased fiber stretch, and, at least for the normal ventricle, an increase in the force of myocardial contraction. In both groups of patients, this resulted in the return of the LVEDP from its low, paced level back essentially to the control value. No “overshoot” in LVEDP, as is sometimes noted in patients with coronary artery disease46, 49 was seen in any of these patients. The LVEDP usually became stable within two to three beats after cessation of the pacing. Although there is probably a small increase in heart size above control values during the first few beats after pacing is stopped, accounting for a 2–3 mm higher LVEDP at this time, even the abnormal ventricles may have quickly resumed their control size, since stroke volume and LVEDP returned to pre-pacing values. However, this cannot be proven, since no measurements of heart size were made at that time. In some patients with coronary artery disease, the marked “overshoot” in LVEDP may represent a combination of myocardial failure and decreases in compliance.46, 49 Although one might find a difference in instantaneous flows between the normal and abnormal ventricle just after pacing is stopped, when cardiac output was measured within 20–30 sec following cessation of pacing, no change from control or pacing values was apparent. The abnormal ventricle accomplished much less work per unit change in volume and LVEDP, than the normal did when it was subjected to this sudden increase in stroke volume (figs. 1–3). Those subjects with a decrease in myocardial function also tended to have a higher heart rate after the interruption of pacing than the normals (90 ± 6 vs. 77 ± 5 beats/min). Although this difference was not statistically significant, there appeared to be a tendency for the abnormal ventricle to increase its rate as a compensatory mechanism to maintain cardiac output at the control level.

The pacing stress test, as performed in this study, proved to be devoid of any complications. No rhythm disturbances developed at any time, and all patients quickly returned to sinus rhythm after interruption of pacing. It can be performed easily and rapidly (in 10–15 min), and it permits the construction of a pacing ventricular function curve through rate changes alone, without changes in blood volume, exercise, or the infusion of drugs. Metabolic and autonomic nervous system influences are minimized. The patients remained free of symptoms during the stress of atrial pacing, except for one with coronary artery disease who developed angina pectoris at a rate of 150 beats/min. His pacing ventricular function curve was abnormal both prior to and after the development of ischemia, so the latter did not influence his VFC. His left ventriculogram also demonstrated a marked decrease in myocardial contractility.

A problem frequently encountered in patients with valvular heart disease is the separation of functional abnormalities due to the mechanical valvular defect from the disorder of myocardial function. Included in this series are two patients with severe mitral stenosis who had typical hemodynamic changes and were class III. During atrial
pacing, their left atrial and pulmonary artery pressures and diastolic gradient rose, while LVEDP decreased, and their pacing ventricular function curves were quite normal. Benchimol and Goldstein reported similar data, including three patients with mitral stenosis in whom a rise in LVEDP during pacing probably indicated abnormal myocardial function.50 Although more study is indicated, it appears as though atrial pacing may help identify patients with valvular disease (without insufficiency) with an associated decrease in myocardial function.

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