Hemodynamic Consequences
of Pacing-Induced Changes in Heart Rate
in Valvular Aortic Stenosis

By Joseph W. Linhart, M.D.

SUMMARY
Atrial pacing was performed in 10 patients with various degrees of aortic valvular stenosis (AVS) and the hemodynamics were compared to eight normal subjects. Similar maximum heart rates (135 ± 6/min) in each group resulted in no significant complications or symptoms and no changes in cardiac output or transvalvular pressure difference while stroke work (SW) and volume and left ventricular end-diastolic pressure (LVEDP) declined. A postpacing overshoot in LVEDP (control, 14 ± 2; postpacing, 25 ± 3 mm Hg, P = 0.01) which occurred in the cases of AVS probably reflects a decrease in myocardial compliance. Pacing ventricular function curves relating induced changes in SW and LVEDP were generally steeper in patients with AVS than in the normal subjects and were definitely abnormal in three of the former. Pulsus alternans induced in two patients was associated with abnormal myocardial function while the control LVEDP level was not a good indication of the functional response of the myocardium.

Atrial pacing appears to be beneficial in the preoperative evaluation of the patient with AVS when exercise stress may be dangerous because of the possibilities of inducing arrhythmias, syncope, and sudden death. It permits precisely controlled evaluation for preoperative and postoperative comparison.

Additional Indexing Words:
Left ventricular end-diastolic pressure Myocardial compliance Pulsus alternans
Left ventricular angiography Myocardial hypertrophy Tachycardia

Atrial pacing has found wide application therapeutically and as an investigative technic in the study of the electrocardiographic, hemodynamic, and metabolic consequences of an increase in heart rate in the normal and the abnormal heart.1-5 In addition, since atrial pacing induces changes in stroke volume, stroke work, and left ventricular end-diastolic pressure, it has been used to characterize myocardial function through pacing ventricular function curves.6-8 Since the status of the left ventricular myocardium may be extremely important, especially with regard to surgical morbidity and mortality, a safe analysis of this parameter is also needed in patients with valvular aortic stenosis.9 Although exercise stress has been extensively used to determine the status of the myocardium in other forms of heart disease10,11 and occasionally also used in aortic stenosis,12,13 it is dangerous in the latter since syncope, arrhythmias, and sudden death may occur.14-16 With this in mind, the present studies were carried out to determine the effects of atrial pacing-induced changes in heart rate on the hemodynamics of patients with aortic stenosis and to evaluate the usefulness of atrial pacing as a determinant of myocardial function.
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Methods

This study includes eight (seven males) relatively normal patients (mean age, 43 years; range, 30 to 68) who were evaluated for chest pain but who had no coronary artery disease, and 10 (seven males) with various degrees of essentially pure aortic valvular obstruction (mean age, 50; range 25 to 62), one of whom also had coronary artery disease. The latter group included three patients who were studied after the insertion of a Starr-Edwards aortic valve prosthesis for aortic stenosis. Each patient was informed concerning the nature and technic of the investigation. In each instance, cardiac catheterization was indicated for diagnosis or for preoperative or postoperative evaluation.

Light pentobarbital sedation and local anesthesia with lidocaine were induced. A needle then was placed in the left femoral artery (LFA) and a cutdown was performed in the right antecubital area. With standard technics, one catheter was placed in the pulmonary artery (PA) through an antecubital vein and another in the left ventricle (LV) retrograde from the brachial artery in those subjects without aortic valve disease. In patients with aortic stenosis, the left ventricle was entered from the left atrium, by the percutaneous Brockenbrough transseptal method, and the retrograde catheter was left in the aorta. A bipolar-electrode catheter was positioned in the right atrium. All pressures were recorded through fluid-filled systems on a recorder (Electronics for Medicine DR8) through Statham P 23 Db strain gauges. The midchest position served as the zero reference point and mean pressures were determined electronically. Electrocardiographic lead II was continuously monitored. LVEDP was recorded on a high-sensitivity scale and measured where the downslope of the left ventricular 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. At rapid pacing rates, the time relationship between the Q wave or R wave and the LVEDP, at the control rate, was used as the reference to measure LVEDP. The mean pressure difference across the aortic valve was determined by planimetric integration from simultaneously made tracings of aortic or femoral artery pressure or both and left ventricular pressure for five cardiac cycles.

Following control determinations of arterial and intracardiac pressure, the heart rate was gradually increased by right atrial pacing beginning at a rate 5 to 10 beats/min above the control level. Subsequent increases in rate were in increments of approximately 10 beats/min; hemodynamic measurements were 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 to 110/min and at the maximum pacing rate. The highest pacing rate was determined individually for each patient and depended upon his response. Pacing rates were never limited in any patient by the development of chest pain or dyspnea as angina pectoris was never induced in this study. Attempts were made to reach heart rates of approximately 140/min, but in two patients (one normal and one with aortic stenosis), the rate was limited by the development of Wenckebach-type second-degree A-V block.

In all patients we attempted to obtain significant changes 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) in order to construct “pacing ventricular function curves” relating pacing-induced changes in LVEDP to stroke work. The latter was calculated from the formula:

\[
\text{Stroke work} = \frac{(\text{LV} - \text{LVEDP}) \times \text{SV} \times 1.36}{100} = \text{g-m}
\]

where \( \text{LV} \) is the mean left ventricular pressure during ejection as determined planimetrically and \( \text{SV} \) is stroke volume.

These function curves have been referred to as “pacing ventricular function curves”\(^6^\) to distinguish them from the classic function curves. For the latter, heart rate and other potential variables are held constant, and alterations in stroke volume are produced by varying venous return\(^17\) whereas in our studies, stroke volume was decreased by increasing heart rate.\(^3^,4\) These pacing ventricular function curves should also be interpreted in relation to the pacing control curves for normal patient rather than to the classic curves\(^7,18\) as their shape appears to be more linear over a wide range of LVEDPs.\(^6^\)-\(^8^\) Absolute rather than index values are reported in this study in keeping with the classic type curves.\(^7\) When pulsus alternans was induced, an average value for the two types of beats was used.

In our studies no attempt was made to disclose the incidence or the cause for any myocardial abnormality in patients with aortic valvular stenosis; we sought only to determine whether or not atrial pacing might be useful in patient
Table 1

Hemodynamic Changes during Atrial Pacing

<table>
<thead>
<tr>
<th>State</th>
<th>HR</th>
<th>Art</th>
<th>LVEDP</th>
<th>CO</th>
<th>SV</th>
<th>SW</th>
<th>P-R</th>
<th>GRAD</th>
<th>PP LVEDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Con</td>
<td>78 ± 4</td>
<td>98 ± 5</td>
<td>9 ± 1</td>
<td>5.3 ± 0.4</td>
<td>69 ± 6</td>
<td>82 ± 6</td>
<td>0.16 ± 0.01</td>
<td>0</td>
</tr>
<tr>
<td>(8 patients)</td>
<td>Pace</td>
<td>134 ± 6*</td>
<td>100 ± 6</td>
<td>1 ± 1*</td>
<td>5.6 ± 0.5</td>
<td>63 ± 4*</td>
<td>56 ± 4*</td>
<td>0.24 ± 0.02*</td>
<td>0</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>Con</td>
<td>75 ± 5</td>
<td>102 ± 5</td>
<td>14 ± 2</td>
<td>4.2 ± 0.4</td>
<td>56 ± 6</td>
<td>108 ± 10</td>
<td>0.14 ± 0.01</td>
<td>40 ± 7</td>
</tr>
<tr>
<td>(10 patients)</td>
<td>Pace</td>
<td>135 ± 6*</td>
<td>107 ± 4</td>
<td>9 ± 3</td>
<td>4.2 ± 0.4</td>
<td>32 ± 3*</td>
<td>68 ± 9*</td>
<td>0.24 ± 0.01*</td>
<td>38 ± 7</td>
</tr>
</tbody>
</table>

*Significant differences between control and pacing values (P ≤ 0.05) within the same group.

Abbreviations: All values are mean ± standard error of the mean; Con = control measurements; Pace = measurements at highest paced heart rate; HR = heart rate in beats/min; Art = mean systemic arterial pressure in mm Hg; LVEDP = left ventricular end-diastolic pressure in mm Hg; CO = cardiac output in liters/min; SV = stroke volume in milliliters; SW = stroke work in g-m; P-R = P-R interval in seconds; GRAD = mean pressure difference across the aortic valve in mm Hg; PP LVEDP = postpacing LVEDP in first (1) and in an average of 10 beats (10).

Results

Atrial pacing was uncomplicated in these patients as no arrhythmias or significant dyspnea or angina occurred. Although one patient had clinical angina, angiography revealed no significant coronary artery disease in any patient. The patients with chest pain, angina for angina pectoris was not induced by atrial pacing. In those with normal atrial and ventricular response to pacing, angina pectoris was not induced by atrial pacing. In those with normal atrial and ventricular response to pacing, angina pectoris was not induced by atrial pacing.
1). During pacing, no significant changes occurred in mean arterial pressure or cardiac output, while significant decreases in stroke volume and work and increases in P-R interval occurred in both groups. Transaortic valvular mean gradient did not change significantly with pacing, although small increases were noted in two patients and decreases in two patients (table 1, fig. 1).

**Left Ventricular End-Diastolic Pressure (LVEDP)**

LVEDP decreased to a greater extent and to a lower level in the normal patients than in those with AS during pacing (1 ± 1 vs 9 ± 3 mm Hg; *P = 0.02*). An increase in LVEDP occurred during pacing in two patients with aortic stenosis. In one it rose from 5 to 14 mm Hg and in the other from 9 to 24 mm Hg. Figure 2 illustrates the difference between the control LVEDP and the LVEDP in the first beat [1] and in an average of the first 10 beats [10] after sudden interruption of atrial pacing. In the normal group no postpacing overshoot in LVEDP was noted (control, 9 ± 1 mm Hg; postpacing [1], 8 ± 1 mm Hg; [10], 9 ± 1 mm Hg) while a significant increase in postpacing LVEDP was seen in those with AS (control, 14 ± 2; postpacing [1], 25 ± 3; [10], 25 ± 2 mm Hg; *P = 0.01*). A postpacing overshoot in LVEDP occurred in either the first beat or an average of 10 beats or in both in all eight patients with AS in whom this was measured. The patients with AS with normal pacing ventricular function curves (see below) had a larger change in stroke work per mm Hg change in LVEDP than did the normal group (9.4 ± 2.3 g-m vs 4.2 ± 1.0 g-m/mm Hg; *P = 0.05*).

**Pacing Ventricular Function Curves (Fig. 3)**

The normal subjects all have large changes in stroke work relative to changes in LVEDP which compare favorably to previously published data for the normal pacing ventricular function curves (VFC).\(^6,7\) Seven of 10 patients with aortic stenosis also have normal configurations in their pacing VFC and this
aortic stenosis tended to have higher levels of stroke work in the pacing VFC due to the increase in LV mean pressure secondary to the fixed obstruction and resistance at the aortic valve. The abnormal pacing VFC occurred in patients with high (143 g-m), intermediate (88 g-m), and low (56 g-m) control levels of stroke work and stroke volume. Two of the abnormal pacing VFCs occurred at normal stroke work levels. The mean gradients in these three patients were 81, 59, and 23 mm Hg, and their cardiac outputs were 5.7, 2.5, and 2.3 liters/min. Two also had normal control LVEDPs, and one had an elevated value. Two other patients with elevated control LVEDPs had normal pacing responses.

includes the three studied postoperatively. Three patients marked by the letter A in figure 3 have abnormal responses. This consisted of a flat VFC in two and a descending type of curve in one in which the highest level of LVEDP (14 mm Hg) is associated with less stroke work than the lowest level (5 mm Hg). Two of these patients developed pulsus alternans during atrial pacing. The patients with
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Angiography

The patients considered to be normal had no angiographic evidence of coronary artery or left ventricular disease. The three postoperative patients who all had normal control LVEDP and pacing VFC had no major coronary artery disease. Each had a mild increase in left ventricular volume with some mild residual myocardial hypertrophy. Angiographically, contractility was graded normal in one, and a mild generalized decrease was present in two. Aortography disclosed normal ball valve function with no evidence of perivalvular regurgitation.

The four preoperative patients with normal pacing VFC did not have any significant coronary artery disease. Left ventricular hypertrophy was noted in each patient; left ventricular chamber size was normal in three and slightly to moderately enlarged in size in one patient. Overall left ventricular contractility was considered on angiography to be normal in each patient.

Each of the three patients with abnormal pacing VFC had moderate to severe increases in left ventricular chamber size with significant myocardial hypertrophy. One had severe double-vessel coronary artery disease as well but no major coronary artery disease was noted in the other two patients.

Aortography in the preoperative patients disclosed no significant aortic regurgitation; only insignificant “puffs” of contrast material entered the outflow tract of the left ventricle as is frequently seen in patients with fixed valvular aortic stenosis.

Discussion

Most of the hemodynamic responses to graded atrial pacing in these patients with valvular aortic stenosis were similar directionally to those of the normal subject. 8-5 Although the resting magnitudes differed, similar changes in heart rate brought about no changes in peripheral arterial pressure, left ventricle-to-aorta pressure differences, or cardiac output while LVEDP, stroke volume, and stroke work declined. No untoward reactions occurred, and the technic seems harmless when applied in a fashion identical to that used in patients with myocardial and coronary artery disease. 6, 8

Certain differences from the normal response probably reflect changes in the left ventricular myocardium due to the chronic pressure load from the valvular stenosis and the resultant myocardial hypertrophy. Sudden interruption of atrial pacing resulted in large overshoots in LVEDP in all patients with aortic stenosis. This probably represents the effects of the sudden large volume upon a hypertrophied noncompliant ventricle which has a built-in resistance to normal filling. 25 Although the normal ventricle may undergo relatively large changes in volume with only small changes in LVEDP, a decrease in compliance is associated with large changes in pressure for volume increases similar to the normal chamber. 14 Similar changes have been seen with pacing interruption in patients with coronary artery disease and angina pectoris, and these have been attributed to decreases in compliance or myocardial failure or both. 6, 26-29 None of our patients developed angina, and only one had significant coronary artery disease on angiography, but two probably experienced cardiac failure during the stress of atrial pacing. These two patients had increases in LVEDPs from 5 to 14 and 9 to 24 mm Hg with reductions of 20 and 30%, respectively, in cardiac output. One developed pulsat alternans. They represent two of the patients having abnormal pacing ventricular function curves (fig. 3). The third patient reduced his LVEDP only minimally (32 to 29 mm Hg) with pacing, which is also an abnormal response. The changes in stroke volume relative to the change in LVEDP during pacing were greater in the patients with aortic stenosis than in the normal patients. This also may mirror a decrease in compliance as a ventricle operating on the steep portion of its pressure-volume curve would respond in this manner.

These responses are similar to those seen in patients with mitral stenosis except that, in the latter, transvalvular pressure differences increased significantly. In mitral stenosis, the...
pacing-induced reduction in diastolic filling period leads to an increase in left atrial and pulmonary venous pressures and like spontaneous tachycardia may lead to severe pulmonary congestion. The pressure difference usually does not change significantly with atrial pacing or exercise in aortic valvular stenosis, probably because the total systolic time per minute actually increases. Rapid pacing rates may be better tolerated by patients with aortic stenosis although some increase in left atrial pressure may occur since it even occurs in the normal subject. This seems to be related to the increase in P-R interval with atrial pacing and a superimposition of the a and v waves in the left atrial and pulmonary venous pressures. Although tachycardia may produce less pulmonary congestion in AVS, the induced increase in myocardial oxygen consumption could lead to myocardial ischemia, angina pectoris, and syncope. These latter symptoms did not occur in any of our patients.

Although these hemodynamic changes in AVS are of academic interest, we were attempting to determine whether the induced hemodynamic changes could be helpful in the routine evaluation of the individual patient. Pacing ventricular function curves (VFC) relating induced changes in LVEDP and stroke work have been helpful in evaluating function in patients with coronary artery disease, cardiomyopathy, and mitral stenosis. The status of the myocardium may also be an important factor in AVS from the standpoint of both surgical mortality and long-term morbidity. Although muscular exercise is probably the most sensitive manner to stress and evaluate the myocardium, some other technic is needed because of the known hazards of exercise in AVS. Pacing VFCs from our patients with AVS are compared to those of a normal group of subjects in figure 3. Although the normal pacing VFC is more linear and steeper than the classic function curves, this effect is even more pronounced in AVS. This must be secondary to the previously discussed reduction in myocardial compliance in patients with AVS. This might limit the usefulness of the pacing VFC in AVS since the usual pacing-induced changes in stroke work and LVEDP in this condition tend to shift any curve toward a more normal contour. Two patients with normal pacing VFC did have a reduction in contractility as judged angiographically. This may represent a lack of sensitivity of the pacing test which is estimating overall myocardial function on the basis of the applied heart rate stress. More severe forms of stress might, therefore, uncover abnormalities in these patients. However, some of this pacing-angiographic disparity may be explained by the fact that both of these patients were studied after aortic valve replacement. Although patients having enlarged left ventricles, prior to surgery, may have some reduction in heart size postoperatively, the heart may not completely return to normal size even though the other parameters of function and clinical improvement are satisfactory. On the other hand, three of these postoperative curves were definitely abnormal, and in two patients actually represented further elevations of LVEDP with reduced stroke work. Each of these patients had large left ventricular cavities and poor contractions angiographically, and, therefore, good correlation was noted with the pacing VFC.

It is well known that increases in LVEDP do not necessarily indicate abnormal myocardial function or heart failure in patients with AVS. Four of our patients had elevations of LVEDP (above 12 mm Hg) and the pacing VFC was normal in two of them. Even though the contractile state of a segment of hypertrophied myocardium may be decreased, the large mass of the left ventricle may still permit normal responses to the stress imposed by the valvular lesion and increases in heart rate. The VFC was abnormal in one of six patients with normal control LVEDP.

Pulsus alternans, which is considered an indication of myocardial insufficiency, may be seen in 25 to 50% of patients with acquired aortic valvular stenosis. It is usually easier to discern in the left ventricular pressure tracing and is generally associated with more...
severe AVS with associated cardiomegaly, angina, and congestive heart failure. Although none of our patients had pulsus alternans during the control state, the added stress of atrial pacing precipitated it in two cases. Both had abnormal pacing VFCs, large left ventricular cavities, and poor myocardial contractions on angiography.

Atrial pacing leads to a prolongation of the P-R interval, and this might affect the myocardial response due to the elimination of the proper sequence of atrial and ventricular contractions. This enhanced ventricular filling subsequent to atrial contraction is important in AVS where ventricular filling is normally impeded by the hypertrophied myocardium. In this study, similar increases and maximum P-R-interval values were present for the normal patients and those with AVS whether their pacing VFCs were normal or abnormal. Since seven of 10 patients with AVS had even steeper VFCs than the normals, it is unlikely that the changes in P-R interval had any major influence on ventricular function as determined in this fashion.

On the basis of this series of patients atrial pacing may prove helpful in the preoperative assessment of the AVS patient with borderline changes in myocardial function, but additional studies are indicated to determine the proper role of atrial pacing in evaluation of the individual patient. The initial correlation with surgery has been good. Four of our preoperative patients have now undergone and survived aortic valve surgery. Two with normal pacing VFCs are clinically well with essentially normal heart sizes radiographically 4 to 6 months after operation. The other two, with abnormal pacing VFCs, have retained their preoperative cardiac enlargement and, although they are clinically improved, they are still in functional class II, 5 to 7 months after surgery. When myocardial contractility appeared angiographically to be perfectly normal or definitely abnormal, then pacing gave similar results and hence was not required for specific evaluation. These studies showed as expected, however, that LVEDP levels in AVS cannot be used as an indicator of the functional level of the myocardium, that pulsus alternans indicates abnormal myocardial function, and that mild angiographic contraction abnormalities may be associated with a normal pacing VFC. As in patients with coronary artery disease, the latter finding might also reflect a lack of sensitivity of the pacing VFC as compared to exercise. However, in all patients, pacing supplies semi-quantitative information regarding the status of the myocardium under precisely controlled reproducible conditions which may be used for preoperative and postoperative assessment when preoperative exercise is contraindicated and when noninvasive technics may be difficult to evaluate because of an absent second heart sound and altered carotid pulses. Pacing should also be more useful than an angiotensin infusion in studying AVS since it results in a decrease in stroke volume and work per beat rather than a further increase through enhanced peripheral resistance with the drug. Perloff and associates found that they were unable uniformly to distinguish mechanical from myocardial factors in AVS by angiotensin infusion since the maximal mechanical work was probably already being performed by the left ventricle and this precluded further increase after angiotensin.

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