Effect of Rate on Left Ventricular Volumes and Ejection Fraction During Chronic Ventricular Pacing

KENNETH A. NARAHARA, M.D., AND M. LOUIS BLEETTEL, P.A.

SUMMARY  Resting left ventricular (LV) function was evaluated in 22 patients with permanent ventricular pacemakers. LV ejection fraction and volume indexes were determined by gated blood pool scintigraphy at ventricular pacing rates of 50–100 beats/min. In patients with a normal heart size, increases in pacing rates resulted in significant linear decreases in stroke volume index and ejection fraction. However, end-systolic volume index and cardiac index did not change. Patients with cardiomegaly appeared to respond differently. End-diastolic volume index decreased significantly as the pacing rate was increased from 50 to 100 beats/min. Ejection fraction was significantly reduced only at pacing rates of 90 and 100 beats/min. Mean cardiac index was highest at ventricular pacing rates of 70–90 beats/min. Increases in cardiac index, achieved by increasing the pacing rate, were maintained over a 4.3-month follow-up. Patients with underlying sinus rhythm had a 27% increase in cardiac output in association with an increase in ejection fraction from 55% to 62% when sinus rhythm was compared to ventricular pacing at a rate of 60 beats/min.

These data suggest that patients with cardiomegaly have a narrow range of optimal pacing rates at rest.

PROGRAMMABLE PACEMAKERS are widely available. Pacing rate and other pacemaker functions can be altered easily and noninvasively. Investigations of the role of pacing rate on cardiac function have produced varying results. Many investigations\textsuperscript{1–4} suggest that patients will have little or no change in cardiac output when the ventricular pacing rate is altered. However, Sowton\textsuperscript{5} and Samet et al.\textsuperscript{6} reported marked increases in cardiac output when pacing rate is increased in selected patients. In addition, there are occasional reports of patients with congestive heart failure and severe bradycardia who have responded favorably to ventricular pacing.\textsuperscript{7, 8}

The cardiac response to changes in pacing rate may be related to the degree of cardiac compensation.\textsuperscript{5, 6} However, few data are available regarding left ventricular ejection fraction or ventricular volumes during alterations in ventricular pacing rate. This study was undertaken to evaluate resting left ventricular function in patients with chronically implanted ventricular pacemakers and to define alterations that might be produced by changes in pacing rate.
Materials and Methods

Twenty-two male patients with a diagnosis of complete atrioventricular block were enrolled in the study. All patients had ventricular inhibited, rate-adjustable pacemakers (Medtronic Inc. models 5994, 5995, 5984 and 5985). The mean duration of ventricular pacing was 5.2 years (range 1–9 years). Nineteen patients had transvenous pacing leads implanted in the right ventricular apex and three had left ventricular epicardial leads. The patients were 48–78 years old and had a variety of underlying cardiac disorders (table 1).

Patients were initially categorized as having a normal heart size or an abnormal heart size. An abnormal heart size was defined as a cardiothoracic ratio greater than 0.50.

Seventeen of the patients had no intrinsic cardiac activity at a pacing rate of 50 beats/min. Further testing of these patients revealed that none had an unpaced cardiac rhythm during exercise stress. During the course of the investigation, five of the patients with a prior diagnosis of complete atrioventricular block were noted to have an underlying sinus bradycardia with ventricular rates of 52–60 beats/min.

Study Design

Each patient gave informed consent. Gated blood pool scintigraphy was performed and left ventricular ejection fraction and volume indexes were determined at ventricular rates of 50, 60, 70, 80, 90 and 100 beats/min. The five patients with an underlying sinus bradycardia mechanism were studied while in sinus rhythm as well as at ventricular pacing rates of 60, 70, 80, 90, and 100 beats/min. One of the five patients had a sinus rate of 60 beats/min. In this patient, the lowest ventricular pacing rate resulting in 100% capture was 61 beats/min. Acquisition of scintillation data required 5–10 minutes at each pacing rate. Cuff blood pressure recordings were obtained at the end of each scintigraphic collection period. At least 10 minutes were allowed between a change in pacing rate and the commencement of scintigraphic data acquisition.

To evaluate the stability of rate-induced changes in left ventricular function, the pacing rate was programmed from 70 beats/min to rates of 80 or 90 beats/ min in six patients. These patients were restudied scintigraphically an average of 4.3 months afterwards to evaluate serial changes in left ventricular function.

Scintigraphic Studies

The scintigraphic studies were obtained using in vivo labeled red blood cells. Unlabeled stannous pyrophosphate (Phosphotel, Squibb) was administered intravenously. Thirty minutes later, 25 mCi of technetium-99m sodium pertechnetate were administered. Scintigraphic data collection was performed with a mobile gamma camera (Ohio Nuclear Sigma 420) equipped with high-resolution, parallel-hole collimator interfaced to a dedicated computer system (Ohio Nuclear VIP 450). The cardiac cycle was divided into 32 equal segments and approximately 180,000 counts/frame were collected. Left ventricular volumes were calculated by the method of Dehmer et al.,9 with an operator-chosen background around the left ventricle. Left ventricular isotope activity was related to isotope activity per milliliter of peripheral venous blood and converted to volumes by a regression equation after correction for isotope decay.

Radionuclide ventriculography in this laboratory was compared with contrast ventriculography using the single-plane Kennedy regression equation.10 A comparison of 24 patients not included in this study demonstrated that the correlation coefficient for the ejection fraction between contrast and radionuclide left ventriculography was 0.95 (S.E. = 2.7 ejection fraction percentage points). The correlation coefficient for

### Table 1. Clinical Data

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Pacing (years)</th>
<th>Diagnosis</th>
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</thead>
<tbody>
<tr>
<td>Normal heart size</td>
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<tr>
<td>1</td>
<td>65</td>
<td>4</td>
<td>Idiopathic conduction system disease</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>8</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>3</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>1</td>
<td>Idiopathic conduction system disease, hypertension</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>4</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
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<td>63</td>
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</tr>
<tr>
<td>8</td>
<td>48</td>
<td>5</td>
<td>Idiopathic conduction system disease, hypertension</td>
</tr>
<tr>
<td>9</td>
<td>73</td>
<td>9</td>
<td>Idiopathic conduction system disease</td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>8</td>
<td>Post aortic valve replacement for aortic stenosis</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>73</td>
<td>7</td>
<td>Idiopathic conduction system disease, compensated CHF, normal coronary arteries</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>9</td>
<td>Idiopathic conduction system disease, compensated CHF</td>
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<td>62</td>
<td>8</td>
<td>Post aortic valve replacement for aortic insufficiency, compensated CHF, normal coronary arteries</td>
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<tr>
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<td>Coronary artery disease, prior myocardial infarction, compensated CHF</td>
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<td>4</td>
<td>Idiopathic conduction system disease, congestive cardiomyopathy, normal coronary arteries</td>
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<td>7</td>
<td>66</td>
<td>1</td>
<td>Idiopathic conduction system disease, hypertension</td>
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<tr>
<td>Underlying sinus rhythm</td>
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<td></td>
<td></td>
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<td>1</td>
<td>66</td>
<td>4</td>
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<td>72</td>
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</tbody>
</table>

Abbreviation: CHF = congestive heart failure.
left ventricular volumes between contrast angiography and radionuclide ventriculography was 0.94 (see = 16.3 ml over a volume range of 20–378 ml). At least two radionuclide ventriculograms were performed at the same pacing rate on the same day in 15 patients. For example, if a patient initially had a pacing rate of 70 beats/min, an initial study at a pacing rate of 70 beats/min was performed. After other pacing rates had been tested, another study was performed at a rate of 70 beats/min. The standard error of the estimate for the ejection fraction when the two studies at the same rate were compared was 2.1 ejection fraction percentage points. The standard error of the estimate for end-systolic and end-diastolic volumes was 10.7 ml when the two scintigraphic studies were compared.

**Statistical Methods**

Left ventricular ejection fraction and volume indexes, systolic blood pressure and double product were evaluated in each patient group. These variables were evaluated using Duncan’s multiple-range test for variable response. A Student-Newman-Keul test was then applied, and a p value < 0.05 was considered statistically significant.1 All values are mean ± SEM.

**Results**

In patients with cardiomegaly by conventional chest x-ray, end-diastolic volume index at a pacing rate of 50 beats/min was substantially above the upper limits of normal, with a mean of 149 ± 21.3 ml/m². End-diastolic volume index fell significantly at each incremental increase in pacing rate (fig. 1), and at a pacing rate of 100 beats/min, had fallen to 112 ± 17.4 ml/m². In contrast, patients with a normal-sized heart on conventional chest x-ray had an end-diastolic volume index of 81 ± 5.3 ml/m² at a pacing rate of 50 beats/min (range 54–97 ml/m²) (fig. 2). Although there was a trend toward decreasing end-diastolic volume index with increasing pacing rate, the increments that reached statistical significance were at pacing rates of 70 and 90 beats/min. Pacing rates of 70 and 90 beats/min yielded progressively smaller end-diastolic volume indexes than rates of 50 and 60 beats/min. Values at pacing rates of 80 and 100 beats/min were not significantly different from those at 90 beats/min.

End-systolic volume index was not significantly altered by changes in ventricular pacing rate in either group of patients. End-systolic volume index was 94 ± 22.8 ml/m² in the patients with cardiomegaly and fell to 79 ± 18.2 ml/m² at a pacing rate of 100 beats/min. This decrease was not significant at any point in the pacing range. Similarly, end-systolic volume index in the patients with a normal heart size was 35 ± 2.4 ml/m² at a pacing rate of 50 beats/min and fell only slightly, to 33 ± 2.2 ml/m², at a pacing rate of 100 beats/min.

Since end-systolic volume index was essentially unchanged in both groups and end-diastolic volume index tended to decrease with increases in pacing rate,
stroke volume index fell in both groups. Stroke volume index in the patients with cardiomegaly was 55 ± 4.2 ml/m² at a pacing rate of 50 beats/min, and it fell significantly, to 33 ± 1.8 ml/m², at a pacing rate of 100 beats/min. The mean values of estimated stroke volume index at each of the six pacing rates were significantly different (p < 0.05) (fig. 3). Similar values, were recorded in patients with a normal heart size in whom stroke volume index was 46 ± 3.1 ml/m² at a pacing rate of 50 beats/min and decreased to 25 ± 1.8 ml/m² at a pacing rate of 100 beats/min. The values for stroke volume index at each of the six ventricular pacing rates in this group were also significantly different from each other (fig. 4).

Mean cardiac index in patients with cardiomegaly was 2.8 ± 0.2 l/min/m² at a pacing rate of 50 beats/min. There were small but statistically significant increases in cardiac index at ventricular pacing rates of both 60 and 70 beats/min (3.1 ± 0.2 and 3.3 ± 0.2 l/min/m², respectively). Cardiac indexes at pacing rates of 80 and 90 beats/min were not significantly different from those recorded at 70 beats/min. However, there was a small but significant decrease in cardiac index at a ventricular pacing rate of 100 beats/min (3.2 ± 0.2 l/min/m²). The mean value for cardiac index at a pacing rate of 100 was not significantly different from those at 50 and 60 beats/min.

The maximum cardiac index in this group of patients was recorded at a ventricular pacing rate of 70 beats/min in two patients, 80 beats/min in two, 90 beats/min in two and 100 beats/min in one patient. In comparing the highest cardiac indexes in these patients with the values at a ventricular pacing rate of 50 beats/min, the average increase was 0.8 ± 1.1 l/min/m² (27%). In contrast, changes in the ventricular pacing rate had no significant effect on estimated cardiac index in patients with a normal heart size.

The patients with cardiomegaly had their pacemakers programmed to the rate that provided the highest resting cardiac index. These patients were restudied an average of 4.3 months later. No significant changes were noted between values recorded during the initial study and the later study at the same rate.

Resting left ventricular ejection fraction in the patients with cardiomegaly was depressed (average 43 ± 6.7%). The only significant changes in ejection fraction in this group occurred when ventricular pacing rates of 90 and 100 beats/min were programmed. The left ventricular ejection fraction at a rate of 90 beats/min was 38 ± 6.3%, significantly less than the ejection fraction at a rate of 80 beats/min and less. The ejection fraction at 100 beats/min fell further, to 35 ± 5.7%, which was also significantly less than that at 90 beats/min and less. In patients with a normal heart size, the left ventricular ejection fraction fell significantly with each 10-beat increase in pacing rate.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Ejection fraction (EF) and volume indexes in patients with a normal heart size. Symbols and abbreviations are as in figure 1. Significant decreases in end-diastolic volume are noted at pacing rates of 70 and 90 beats/min. Significant decreases in EF are noted with each increase in ventricular pacing rate, but cardiac index (CI) and end-systolic volume index are unchanged.
Patients with Intrinsic Sinus Rhythm

Five patients were noted to have sinus rhythm despite a diagnosis of complete atrioventricular block. Their average sinus rate was 55 ± 2 beats/min (range 52–60 beats/min). All had a normal heart size.

Estimated end-diastolic volume index with the patient in sinus rhythm was 95 ± 10.3 ml/m², which fell significantly, to 81 ± 9.7 ml/m², when ventricular pacing was initiated at a rate of 60 beats/min (fig. 5). End-diastolic volume index at a pacing rate of 100 beats/min was significantly less (66 ± 6.5 ml/m²) than the value recorded at a pacing rate of 80 beats/min. There were no significant changes in estimated end-systolic volume index when the patients were in sinus rhythm or at any of the pacing rates from 60 to 100 beats/min. Stroke volume index in sinus rhythm was 56 ± 5.3 ml/m² (fig. 6). This fell to 43 ± 5.0 ml/m² at a pacing rate of 60 beats/min (p < 0.05). Increasing pacing rates further to 70 and 80 beats/min had no effect on stroke volume index. However, at a pacing rate of 90 beats/min, stroke volume index decreased to 33 ± 2.4 ml/m² (p < 0.05) and decreased further, to 29 ± 1.9 ml/m² (p < 0.05), when the pacing rate was increased to 100 beats/min.

Cardiac index was 3.1 ± 0.3 l/min/m² when pa-
Patients were in sinus rhythm and fell significantly, to \( 2.6 \pm 0.3 \text{ ml/m}^2 \), when pacing at 60 beats/min was instituted (fig. 6). Cardiac index was unchanged at pacing rates of 70 and 80 beats/min; however, pacing at 90 beats/min resulted in an estimated cardiac index of \( 3.0 \pm 0.2 \text{ l/min/m}^2 \), which was significantly higher than that at a ventricular rate of 60 beats/min.

Ventricular pacing decreased the ejection fraction from 62 \( \pm 1.6\% \) in sinus rhythm to 55 \( \pm 1.2\% \) when ventricular pacing at a rate of 60 beats/min was initiated. A ventricular pacing rate of 100 beats/min further decreased ejection fraction to 48 \( \pm 2.5\% \), which was significantly less than that at a pacing rate of 80 beats/min (54 \( \pm 2.2\% \)).

**Discussion**

Ventricular pacemakers are often used to treat chronic or intermittent bradyarrhythmias. The widespread availability of rate-programmable pacemakers provides the possibility of optimizing ventricular pacing rate for arrhythmia control, the preservation of sinus rhythm in patients with rare episodes of bradyarrhythmia, and potential increases in cardiac output. Resolution or improvement of congestive heart failure has been reported when patients with complete atrioventricular block were paced from the ventricle at rates of 50–75 beats/min. In addition, studies performed by Samet and co-workers\(^4\) and Sowton\(^5\) indicate that acute increases in ventricular pacing rate from 50 to 125 beats/min may be associated with an incremental increase in resting cardiac output in selected patients. This investigation demonstrates that changes in ventricular pacing rate can alter values of resting left ventricular function, which may be clinically significant.

**Patients with Normal Heart Size**

In patients with a normal heart size, defined from conventional chest x-ray, there were no significant differences in estimated cardiac index at any ventricular pacing rate from 50 to 100 beats/min. There were small, significant linear decreases in stroke volume index and ejection fraction with increasing pacing rates. These changes with increasing pacing rates may reflect decreased diastolic filling time. Alternatively, the decrease may represent a normal compensatory mechanism to maintain a stable cardiac index. End-systolic volume index, an important estimate of left ventricular contractile state,\(^6\) was unchanged at ventricular pacing rates of 50–100 beats/min.

**Patients with Enlarged Hearts**

In the patients with cardiomegaly, a different pattern emerged. Estimated cardiac index improved as ventricular pacing rates were increased from 50 to 60 and 70 beats/min. A further increase to 100 beats/min resulted in a decrease in cardiac index for the group. End-systolic volume index did not change significantly, although there appeared to be a downward trend as heart rate increased. End-diastolic volume index decreased with increasing pacing rate, and the absolute differences were greater than that in patients with a normal heart size. However, the percent changes in end-diastolic volume index were similar in both groups.

One interpretation of the data in this group of patients is that maximal resting cardiac index can be obtained from a specific ventricular pacing rate between 70 and 90 beats/min. In this range of heart rates, all but one patient demonstrated his peak cardiac index. Significant decreases in left ventricular ejection fraction occurred at pacing rates of 90 and 100 beats/min. Thus, the increases in pacing rate in the patients with cardiomegaly did not produce the same alterations in left ventricular function as in patients with normal hearts. The reduced cardiac index noted at rates of 50 and 60 beats/min could be interpreted to mean that low pacing rates in this patient population exposes an insufficient contractile reserve for maintenance of a stable cardiac index. Conversely, high pacing rates may also lead to a decreased cardiac index through insufficient diastolic filling time in an enlarged noncompliant ventricle. Increases in cardiac index associated with increased pacing rates appeared to be sustained for as long as 4 months.

**Patients with Sinus Rhythm**

Unexpectedly, five patients in this study had underlying sinus rhythm despite a previous diagnosis of complete atrioventricular block. The data presented are consistent with multiple studies that emphasize the importance of atrial contraction in augmenting stroke volume.\(^1\)–\(^3\),\(^13\) Their estimated end-systolic volume index was the same during sinus rhythm as during pacing at a rate of 60–100 beats/min. The major volume change noted in this group of patients was a marked increase in end-diastolic and stroke volumes during sinus rhythm. Atrial contraction during sinus rhythm at a rate of 51–60 beats/min resulted in a 27% increase in
cardiac index compared with ventricular pacing at a rate of 60 beats/min (with asynchronous atrial contractions).

Clinical Implications

Ventricular pacing in normal animals may result in either no change or a decrease in left ventricular contractility. Badke and co-workers noted a decrease in systolic shortening in the canine left ventricle when ventricular pacing was substituted for right atrial pacing. Others have reported similar results and suggest that the altered synchronization created by pacing results in a less efficient contraction. The data from our patients with a normal heart size indicate that global left ventricular function as measured by the ejection fraction is negatively affected by an increase in ventricular pacing rate. However, in these presumably more normal left ventricles, such decrements in ejection fraction were not associated with negative effects on end-systolic volume index or resting cardiac index, and may represent a normal physiologic response.

In patients with cardiomegaly, ventricular pacing and pacing rate may be more important. This group of patients had lower ejection fractions at all pacing rates than patients who had a normal heart size. Ventricular pacing at rates below 70 beats/min was associated with significantly lower cardiac indexes owing to an inability to increase stroke volume appropriately. To preserve resting cardiac index, optimal pacing rates appeared to be 70–90 beats/min. Neither the end-systolic volume index nor ejection fraction were significantly altered between pacing rates of 50 and 80 beats/min. Hence, diastolic filling time may be more critically rate-related in these patients. However, the number of patients with cardiomegaly examined in this study is small, and these findings must be confirmed in larger groups of patients.

Scintigraphic ejection fractions and volumes are independent of geometric considerations. Therefore, this technique may be ideally suited for evaluating the asynchronous left ventricular contraction that occurs in patients with pacemakers. In the patient with a marginal cardiac reserve, such studies may be useful for determining which rate is most applicable at rest.

Acknowledgment

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K A Narahara and M L Blettel

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