Since the introduction of permanent pacing, the preferred site for ventricular stimulation has been almost exclusively the right ventricular apex, because this site provides excellent lead stability and low capture thresholds. However, such pacing results in an asynchronous ventricular contraction, associated with a deterioration in left ventricular systolic and diastolic function indexes.\textsuperscript{1,2} Pacing from the right ventricular outflow tract mimics the normal ventricular activation sequence, decreases the degree of pacing-induced asynchrony, and may produce less deterioration in left ventricular performance.\textsuperscript{3} However, there are no detailed hemodynamic data in humans with regard to atrioventricular dual-chamber sequential pacing (DDD) from the two sites. The purpose of our study was to compare the acute hemodynamic status during short-term DDD pacing from the apex vs the outflow tract of the right ventricle in patients with no structural heart disease.

**Materials and Methods**

Participants in our study were screened among patients referred for diagnostic cardiac catheterization and electrophysiological study. The aim of our study was to compare left ventricular hemodynamics during short-term atrioventricular sequential pacing from the right ventricular apex and from the outflow tract of the right ventricle.

**Study objectives:** Pacing-induced asynchrony may deteriorate left ventricular function; however, limited data exists in humans. The aim of our study was to compare left ventricular hemodynamics during short-term atrioventricular sequential pacing from the right ventricular apex and from the outflow tract of the right ventricle.

**Design:** Three 5-min pacing intervals were applied in a random order, at a rate of 15 beats/min above the resting sinus rate. Atrioventricular sequential pacing from the two sites was compared with atrial pacing. During each pacing mode, left ventricular pressure was recorded, and cardiac output was calculated using Doppler echocardiography.

**Setting:** Cardiac catheterization laboratory.

**Patients:** Twenty patients (18 male, mean age 62 ± 11 years) without structural heart disease were studied.

**Results:** During atrial pacing, maximum negative first derivative of pressure (dp/dt) was 1,535 ± 228 mm Hg/s; during pacing from the apex it decreased to 1,221 ± 294 mm Hg/s (p = 0.0001), but was not significantly different during pacing from the outflow tract (1,431 ± 435 mm Hg/s, p > 0.05). Isovolumic relaxation time constant (\(\tau\)) during atrial pacing was 39.7 ± 11.9 ms; during pacing from the apex, it increased to 47.9 ± 14.0 (p = 0.001), but was not significantly different during pacing from the outflow tract (42.5 ± 11.2, p > 0.05). Peak systolic pressure decreased significantly during atrioventricular sequential pacing from either site; however, it did not differ between the two sites. No differences in end-diastolic pressure, maximum positive dp/dt, or cardiac output could be demonstrated.

**Conclusion:** In patients with no structural heart disease, short-term right ventricular outflow tract pacing is associated with more favorable diastolic function, compared to right ventricular apical pacing.

(CHEST 2000; 117:60–64)

**Key words:** apex; diastolic function; hemodynamics; outflow tract; pacing

**Abbreviations:** AAI = atrial pacing; DDD = atrioventricular dual-chamber sequential pacing; dp/dt = first derivative of pressure; SP = peak systolic pressure; \(\tau\) = isovolumic relaxation time constant

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**From the 2nd Department of Cardiology, Onassis Cardiac Surgery Center, Athens, Greece. Manuscript received December 23, 1998; revision accepted July 15, 1999. Correspondence to: Theofilos M. Kolettis, MD, Onassis Cardiac Surgery Center, 356 Syngrou Ave, 176 74 Kallithea, Athens, Greece; e-mail: elbee@ath.forthnet.gr**
ologic study. Those with normal left ventricular function, normal 12-lead ECG, and absence of significant ischemia on thallium exercise scintigraphy were considered eligible for the study. All medications were discontinued 24 h before the study. Informed consent was obtained before entry into the study, and the protocol was approved by the Hospital Ethics Committee.

All patients underwent contrast left ventriculography, coronary arteriography, and electrophysiologic study, as clinically indicated. All studies were performed in the fasting, postabsorptive state, without the use of premedication. A standard percutaneous Seldinger technique was used to gain access to the femoral vein and artery. Patients with no significant coronary artery disease were enrolled in the study. For purposes of this study, “significant coronary artery disease” was defined as (1) any degree of stenosis in the left main stem, or (2) stenosis > 50% in diameter in any other coronary vessel.

Pacing Protocol

One electrode catheter was positioned in the right atrium and one in the right ventricle. Three pacing modes were applied: atrial pacing, DDD with ventricular pacing from the right ventricular apex, and DDD with ventricular pacing from the right ventricular outflow tract; the order was chosen randomly. Pacing was performed with a DDD temporary pulse generator (model 5346; Medtronic, Inc; Minneapolis, MN). During outflow tract pacing, the electrode was placed high in the outflow tract, almost to the pulmonary valve, and was pulled back until the tip pointed in a lateral direction on a posteroanterior fluoroscopic projection, as previously described. The position was confirmed in the right and left anterior oblique projections. After fine manipulations of the ventricular electrode, the pacing site producing the shortest QRS-complex duration was chosen as the final outflow tract pacing site. We have previously reported on this electrode positioning procedure in detail. To avoid fusion beats, atrioventricular delay was set at 60% of the intrinsic PR interval. The pacing rate was 15 beats/min higher than the resting sinus rate. QRS-complex duration was averaged from hard copy recordings (at paper speed of 100 mm/s) using hand-held calipers. Measurements were performed at baseline and during each pacing sequence. QRS-complex duration was averaged from three consecutive complexes in the lead with the widest QRS complex.

Pressure Recordings

Left ventricular pressure was recorded during the last 30 s of each pacing protocol, using a high-fidelity, micromanometer-tipped pressure catheter (Millar Instruments; Houston, TX). All measurements were performed using a custom-made software program, and recordings were stored on a hard disk. This program, which allows accurate measurements of multiple variables on a beat-to-beat basis, has been described previously. Variables were measured during atrial pacing (AAI) and during DDD pacing from the two sites. To express steady-state values during the last 30 s of each pacing protocol, data were averaged from beats 10, 20, 30, 40, and 50.

Variables

The following hemodynamic variables were measured: left ventricular peak systolic pressure (SP), left ventricular end-diastolic pressure, maximum positive and maximum negative first derivative of pressure (dp/dt). Isovolumic relaxation time constant (τ) was calculated using a zero asymptote from peak negative rate of decrease of left ventricular pressure over time (dp/dt) to 5 mm Hg above the previous left ventricular end-diastolic pressure. Cardiac Output Measurements

At the end of each pacing protocol, cardiac output was measured using Doppler echocardiography. This method was favored over the Fick or thermodilution techniques because the Doppler technique is practical, reproducible, and accurate. The equipment used was the Sonos 2500 (Hewlett-Packard; Andover, MA) with a 3.5-MHz transducer. Measurements were performed using standard techniques. In brief, the highest audio signal and the sharpest outline with the maximal envelope were used to assess blood flow velocities in the ascending aorta from the apical five-chamber view. Measurements were performed off-line using a computer-assisted digitization system. The area under the Doppler flow velocity curve was determined by digitizing the signal from baseline to baseline. An average of three consecutive cycles was taken. Cardiac output was calculated as the systolic velocity integral times the aortic root area, times heart rate. The aortic root area was measured using the parasternal long-axis view. Heart rate was measured using two consecutive spikes on the ECG. All measurements were blindly performed by two experienced echocardiographers (DT and JAP).

QRS-complex Duration

QRS-complex duration was measured from hard copy recordings (at paper speed of 100 mm/s) using hand-held calipers. Measurements were performed at baseline and during each pacing protocol. QRS-complex duration was averaged from three consecutive complexes in the lead with the widest QRS complex.

Statistics

Differences in variables were compared using the analysis of variance for repeated measures (split plot design), utilizing the Statistica statistical software (version 5, 1997 edition; StatSoft; Tulsa, OK). Post hoc analysis was performed using Tukey’s multiple comparisons test. Values are expressed as mean ± SD. Statistical significance was defined at an α level of 0.05. Percent changes from atrial pacing were calculated for DDD pacing from the two sites and were compared using the Student’s paired t test.

RESULTS

Twenty patients (18 were male, 2 were female) with a mean age of 62 ± 11 years and a mean ejection fraction of 62 ± 5% were included in the study. Mean heart rate during pacing was 84 ± 7 beats/min.

Left Ventricular Pressure Data: Left ventricular end-diastolic pressure and maximum positive dp/dt were comparable between the three pacing protocols. Significant variance was found for maximum negative dp/dt, τ, and for peak systolic pressure (Table 1). Compared to AAI pacing, maximum negative dp/dt decreased significantly during pacing from the apex (p = 0.0001), but was not statistically significantly different during pacing from the outflow tract (p > 0.05). When DDD pacing from the two sites was compared, maximum negative dp/dt was significantly higher during outflow tract, compared with apical pacing (p = 0.004). τ increased significantly during pacing from the apex (p = 0.01), but
was not statistically significantly different during pacing from the outflow tract. When DDD pacing from the two sites was compared, \( t \) was significantly lower during outflow tract, compared with apical pacing \( (p = 0.036) \).

DDD pacing from either site was associated with a significant drop in peak systolic pressure, but peak systolic pressure was not statistically significantly different between the two sites. The percent changes from atrial pacing for all variables are shown in Figure 1.

No significant differences in cardiac output were found between pacing from the two sites. Compared with pacing from the apex, QRS-complex duration was consistently shorter during pacing from the right ventricular outflow tract (Table 1).

**Discussion**

The hemodynamic consequences of ectopic cardiac stimulation were first described by Wiggers in 1925.\(^1\) He believed that “a certain orderliness in the mode of contraction may be necessary in order to produce a maximal effect on intraventricular pressure.” Ventricular contraction and relaxation are both impaired, and this impairment may be proportional to the left ventricular mass, which is activated by intraventricular conduction, as opposed to normal His-Purkinje conduction.\(^1\)\(^,\)\(^2\) However, these observations remained clinically irrelevant, because the right ventricular apex has been regarded as the “only” pacing site for many decades. Recently, pacing from the right ventricular outflow tract proved to be safe and feasible in regard to pacing and sensing thresholds.\(^3\) Thus, the interest in alternative pacing sites resurfaced.

Several experimental animal studies have indicated that, during pacing, a hemodynamic impairment occurs that is proportional to the degree of the pacing-induced wall motion asynchrony.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\)\(^,\)\(^4\)\(^,\)\(^5\) Burkhoff et al\(^1\) paced isolated canine hearts at various sites, including the left ventricular apex, the left ventricular free wall, and the right ventricular free wall. Peak left ventricular pressure varied significantly between sites, being higher with shorter QRS complexes. In a similar experimental setting, pacing from the right ventricular lateral wall was associated with a significant decrease in maximum positive and negative \( dp/dt \), compared with left ventricular apical pacing.\(^4\) Mabo et al\(^1\) showed that mean BP fell with right ventricular apical pacing but remained stable with pacing from the His-Purkinje bundle.

The results from the animal studies\(^1\)\(^,\)\(^2\)\(^,\)\(^3\)\(^,\)\(^1\)\(^,\)\(^2\)\(^,\)\(^3\)\(^,\)\(^4\)\(^,\)\(^5\) indicate that, during pacing, ventricular performance deteriorates in proportion to the extent of induced ventricular asynchrony. Our study tested the hypothesis that, compared to pacing from the apex, pacing from the outflow tract may be associated with more favorable left ventricular hemodynamics.

Giudici et al\(^1\) examined right ventricular outflow tract pacing acutely in 89 patients, and they noted a significant benefit in cardiac output measured by Doppler echocardiography. Similarly, de Cock et al\(^1\) studied 17 patients and reported a higher cardiac output.

### Table 1—Hemodynamic Data\(^*\)

<table>
<thead>
<tr>
<th>Variables</th>
<th>AAI</th>
<th>DDD Apex</th>
<th>DDD OT</th>
<th>F Value</th>
<th>Overall p Value</th>
<th>Post hoc p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP, mm Hg</td>
<td>146 ± 12</td>
<td>128 ± 19(^†)</td>
<td>136 ± 27(^†)</td>
<td>10.0</td>
<td>0.0003</td>
<td>0.11</td>
</tr>
<tr>
<td>EDP, mm Hg</td>
<td>13.5 ± 4.0</td>
<td>13.3 ± 1.3</td>
<td>12.8 ± 2.4</td>
<td>0.3</td>
<td>NS</td>
<td>N/A</td>
</tr>
<tr>
<td>+dp/dt, mm Hg, s</td>
<td>1482 ± 298</td>
<td>1396 ± 276</td>
<td>1495 ± 506</td>
<td>1.1</td>
<td>NS</td>
<td>N/A</td>
</tr>
<tr>
<td>−dp/dt, mm Hg, s</td>
<td>1533 ± 228</td>
<td>1221 ± 294(^†)</td>
<td>1431 ± 435</td>
<td>13.5</td>
<td>0.000037</td>
<td>0.004</td>
</tr>
<tr>
<td>( \tau )</td>
<td>39.7 ± 11.9</td>
<td>47.9 ± 14.0(^†)</td>
<td>42.5 ± 11.2</td>
<td>8.0</td>
<td>0.0011</td>
<td>0.036</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>6.02 ± 1.05</td>
<td>5.71 ± 1.12</td>
<td>5.87 ± 1.33</td>
<td>0.3</td>
<td>NS</td>
<td>N/A</td>
</tr>
<tr>
<td>QRS complex, ms</td>
<td>82 ± 6</td>
<td>150 ± 5</td>
<td>144 ± 5</td>
<td>1.320</td>
<td>&lt;0.00001</td>
<td>0.0017</td>
</tr>
</tbody>
</table>

*CO = cardiac output; +dp/dt = maximum positive \( dp/dt \); −dp/dt = maximum negative \( dp/dt \); EDP = end-diastolic pressure; OT = outflow tract; N/A = not applicable; NS = not significant.

\(^†\)\(^p < 0.05\) compared to AAI.

![Figure 1](http://example.com/figure1.png)

**Figure 1.** Diagram depicting mean percent changes (± SEM) from AAI for EDP, SP, +dp/dt, −dp/dt, and \( \tau \) (tau). See Table 1 for abbreviations.
index during pacing from the right ventricular outflow tract at three pacing rates (85 beats/min, 100 beats/min, and 120 beats/min). However, these studies had three significant limitations: (1) in both studies, only ventricular pacing was evaluated; (2) although the hemodynamic results of pacing-induced ventricular asynchrony may vary in different patient subgroups, inhomogeneous groups of patients were included, with an apparently wide range of left ventricular function and a variation of the severity of coronary artery disease; (3) in both studies, only cardiac output was compared, and detailed hemodynamic data were not reported.

We compared systolic and diastolic left ventricular function indexes during pacing from the two sites in a homogeneous group of patients, in patients with normal left ventricular function and absence of significant coronary artery disease. Furthermore, atrioventricular sequential pacing was examined. Such pacing is a more physiologic pacing mode, it results in substantial hemodynamic advantages, and it is widely used in the absence of atrial fibrillation.

Apical pacing is associated with an impairment in left ventricular relaxation. In the animal model, it has been shown that this impairment correlates with the degree of wall motion asynchrony. Compared with right ventricular apical pacing, outflow tract pacing may be associated with less ventricular asynchrony, resulting in higher positive and negative dp/dt, irrespective of the atrioventricular delay. In agreement with this concept, we report a lower τ and a higher peak negative dp/dt during outflow tract pacing, indicating more favorable left ventricular relaxation. This benefit could be attributed to shorter intraventricular conduction times during outflow tract pacing, evidenced by shorter QRS complexes. Previous studies have shown that indexes of isovolumic relaxation are independent of loading conditions, but are sensitive to pacing-induced changes in ventricular activation sequence. Our results confirm this notion, as comparable end-diastolic and peak systolic pressures were found during DDD pacing from the two sites.

In our study, we found no differences in cardiac output or in other systolic function indexes. Our results are in agreement with those of Buckingham et al., who compared the two ventricular pacing sites, in a study cohort very similar to ours; they reported no significant differences in cardiac output measured by Doppler echocardiography. In contrast, in patients with poor left ventricular function and low cardiac output, a pacing site that decreases pacing-induced asynchrony may be associated with a significant acute hemodynamic improvement.

Limitations of the Study

We believe that our study contributes to the ongoing research on the optimum ventricular pacing site. However, a few limitations may be apparent.

First, our study examined the effects of pacing site on ventricular hemodynamics at the resting, supine position and not at the upright position or during exertion.

Second, an important caveat needs to be made: the acute hemodynamic changes produced by short-term pacing do not necessarily predict the long-term hemodynamic status. A recent report failed to show any symptomatic improvement or any hemodynamic benefit after chronic (3 months) pacing from the right ventricular outflow tract, by comparison with apical pacing.

Third, our results probably apply to a minority of patients requiring permanent pacing, namely patients with normal left ventricular function and absence of coronary artery disease.

Clinical Implications

It appears that right ventricular outflow tract pacing results in less ventricular asynchrony because of the proximity of this pacing site with the His-Purkinje conduction system. In patients with normal left ventricular systolic function, such pacing seems to result in better indexes of left ventricular relaxation. Further studies are necessary, in order to examine whether the acute hemodynamic changes are sustained and whether these changes are translated into a symptomatic benefit and/or an improved outcome.

Conclusion

We conclude that in patients with structurally normal hearts short-term right ventricular outflow tract pacing is associated with more favorable left ventricular diastolic function compared with apical pacing.

References


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