Atrial fibrillation (AF) is one of the most common arrhythmias, but prophylactic drug treatment to prevent AF has limited effectiveness. Recently, bi-atrial (BiA) pacing has been suggested as an alternative therapy for preventing the recurrence of AF (1–10).

There are, however, few reports on the hemodynamic effects of BiA pacing, and the results that exist are controversial (11,12). We hypothesized that simultaneous and early activation of both atria by BiA pacing could improve atrial pressure and cardiac hemodynamics variables. The present study was designed to evaluate the acute cardiac hemodynamic effects of BiA atrioventricular (AV) sequential pacing with optimal AV delays in comparison with high right atrial (HRA) pacing and coronary sinus (CS) pacing.

METHODS

Patient population. The study protocol was approved by the institutional ethical research committee. From February 2003 to March 2004, 20 consecutive patients (12 men and 8 women) with a mean age of 67 ± 12 years were enrolled at the time of clinically indicated electrophysiological studies for bradyarrhythmia or tachyarrhythmia. Written informed consent was obtained from all patients.

Study protocol. All patients underwent electrophysiological studies in the non-sedated state. All antiarrhythmic drugs were discontinued for at least five drug half-lives before testing. Two 6-F steerable, quadripolar electrode catheters with 2.5-mm inter-electrode spacing (Steerocath Dx, EP Technologies Inc., San Jose, California) were introduced percutaneously via the femoral vein and positioned in the right atrial appendage and right ventricular apex under fluoroscopic guidance. A 5-F decapolar catheter with 2-mm inter-electrode spacing (Torqr, Medtronic Inc., Minneapolis, Minnesota) was positioned into the CS. Programmed electrical stimulation was performed with a 2-ms pulse at twice the diastolic threshold, delivered from a...
**Abbreviation and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Acronym</th>
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<tbody>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
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<tr>
<td>AV</td>
<td>atrioventricular</td>
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<tr>
<td>A Vmax</td>
<td>peak velocity of the atrial filling wave</td>
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<tr>
<td>BiA</td>
<td>bi-atrial</td>
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<tr>
<td>CS</td>
<td>coronary sinus</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<tr>
<td>E Vmax</td>
<td>peak velocity of the early filling wave</td>
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<tr>
<td>HRA</td>
<td>high right atrial or atrium</td>
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<tr>
<td>Max CD</td>
<td>maximal interatrial conduction delay</td>
</tr>
<tr>
<td>PCWP</td>
<td>pulmonary capillary wedge pressure</td>
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<tr>
<td>S-A peak</td>
<td>the interval from the atrial pacing spike on the ECG to the peak of the atrial filling wave</td>
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<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
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<tr>
<td>TVI</td>
<td>mitral flow time velocity integral</td>
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programmable stimulator (SEC-3120, Nihon Koden, Tokyo, Japan). Left atrial pacing was performed from the left lateral site of the CS. Bipolar pacing was performed from the HRA and CS, respectively, simultaneously from both (BiA), and from the right ventricular apex. The 12-lead electrocardiogram (ECG) and intracardiac electrograms (HRA, CS, BiA, and the right ventricular apex) were monitored and recorded on a computer-based digital amplifier/recorder system with disk storage (Cardiolab system, Prucka Engineering, Houston, Texas). In all patients, HRA, CS, and BiA pacing were randomly performed with optimal AV delays at 80 and 100 beats/min. All data were collected during AV pacing after 5-min AV sequential pacing with optimal AV delays from the three pacing sites at both pacing rates. The pacer was turned off after collecting data from each site. The next pacing protocol was performed after checking, 5 to 10 min later with a Swan-Ganz catheter, that the hemodynamics had returned to baseline.

**Transthoracic echocardiography.** For all patients, transthoracic echocardiography was performed with two-dimensional and pulsed wave Doppler ultrasound (Sequoia, Siemens, Solna, Sweden) with simultaneous monitoring of ECGs and heart sounds. All Doppler examinations of transmitral flow were performed with patients in the supine position. The apical four-chamber view was used with the sample volume between the tips of the mitral leaflet during diastole. Optimization of AV delays was performed at each pacing site and pacing rate. We defined the optimal AV delay as the time when the end of the atrial filling (A)-wave on the transmitral flow coincided with the onset of the first heart sound; this was determined with simultaneous heart sound monitoring (Fig. 1). The following measurements were made by a single investigator who was blind to the pacing sites. P-wave onset was defined as the first atrial deflection from the isoelectric line, and offset was the return of the atrial signal to baseline. Maximal P-wave duration was compared among the three pacing sites in all patients.

**Cardiac hemodynamic measurements.** The Swan-Ganz catheter was advanced from the femoral vein. Systolic blood pressure (SBP), cardiac output (CO), and pulmonary capillary wedge pressure (PCWP) were measured in the baseline state and after 5-min AV sequential pacing with optimal AV delays from the three pacing sites at both pacing rates. These parameters were averaged from triplicate measurements by a single investigator who was blind to the pacing sites. We compared these parameters among the three pacing sites in all patients.

**Interatrial conduction delay.** At HRA, following eight beats of drive pacing at a basic cycle length of 500 ms, a programmed extrasystole was delivered at progressively decreasing coupling intervals in steps of 10 ms until the effective refractory period of the atrium was reached. S1 and A1 refer to the driving stimulus and atrial electrogram, respectively, of a basic drive beat, and S2 and A2 refer to the stimulus artifact and the atrial electrogram, respectively, of the induced extrasystole. Interatrial conduction delay was calculated as the time interval between the atrial response at the distal CS (A1A2) and the stimulus coupling interval (S1S2) at HRA, that is, A1A2 – S1S2 (13). The maximal

![Figure 1](image1.png)

**Figure 1.** The optimization of the atrioventricular (AV) delay. We defined the optimal AV delay as the time when the end of the atrial filling wave (A) on the transmitral flow coincided with the onset of the first heart sound (S1), using simultaneous heart sound monitoring. **Dotted line** indicates the onset of the first heart sound. E = the early filling wave; S2 = the second heart sound.
interatrial conduction delay (max CD) was then determined (Fig. 3).

Intra- and inter-observer variability. Measurements of P-wave duration and the echocardiographic parameters were assessed for intra- and inter-observer variability. Intra-observer variability was determined from triplicate measurements, and inter-observer variability was determined from measurements by three observers.

Statistics. All data were presented as the mean ± standard deviation. All data from different pacing sites were tested with repeated-measures analysis of variance (ANOVA). If ANOVA was significant, paired values were compared by Scheffé test. Inter- and intra-observer variability were assessed by nested ANOVA. Linear regression analyses were performed to show the relationships between the cardiac hemodynamic variables, echocardiographic measurements, and interatrial conduction delay; differences between regression lines were determined with analysis of covariance. For all comparisons, a p value of <0.05 was considered significant.

RESULTS

Patient data. The clinical characteristics of the twenty patients enrolled in this study are summarized in Table 1. Three patients had paroxysmal supraventricular tachycardia, seven had ventricular tachyarrhythmia, five had sick sinus syndrome, and five had complete AV block. After defining that the prolonged P-wave duration at baseline was >120 ms, we found that 70% of all patients had a P-wave duration of this duration. Five of these patients (25%) had a history of paroxysmal AF. In three patients, the atrial rate at baseline was over 80 beats/min; therefore, in these individuals, AV sequential pacing was performed at only 100 beats/min. In the remaining 17 patients, AV sequential pacing from all pacing sites at both pacing rates was successfully performed. In all patients, no fusions between the intrinsic ventricular activation and the activation from the ventricular pacing site were found during any AV sequential pacing.

Maximal P-wave duration. Compared with at baseline, only BiA pacing significantly reduced maximal P-wave...
Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Men/women</th>
<th>Age (yrs)</th>
<th>Associated arrhythmias</th>
<th>Paroxysmal supraventricular tachycardia without structural heart disease</th>
<th>Ventricular tachyarrhythmias</th>
<th>Complete atrioventricular block</th>
<th>Without structural heart disease</th>
<th>History of paroxysmal atrial fibrillation</th>
<th>Left ventricular ejection fraction (%)</th>
<th>CO (l/min)</th>
<th>PCWP (mm Hg)</th>
<th>P-wave duration (ms)</th>
<th>Heart rate at baseline (beats/min)</th>
<th>PCWP (mm Hg)</th>
<th>CO (l/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12/8</td>
<td>67 ± 12</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>24</td>
<td>55 ± 13</td>
<td>3.51 ± 0.73</td>
<td>10 ± 5</td>
<td>128 ± 17</td>
<td>64 ± 12</td>
<td>10 ± 5</td>
<td>3.51 ± 0.73</td>
</tr>
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</table>

CO = cardiac output; PCWP = pulmonary capillary wedge pressure.

duration (p < 0.001; Tables 1 and 2). Among the three pacing sites, P-wave duration during BiA pacing was the shortest at both pacing rates; the differences between BiA and HRA pacing, and BiA and CS pacing, were significant (p < 0.001; Fig. 4A).

Cardiac hemodynamic measurements. Concerning CO and PCWP, there was no significant difference between HRA and CS pacing (p = 0.36 and p = 0.44, respectively; Table 2). When analyzed by individual groups, BiA pacing resulted in the most significant improvement in CO and PCWP among the three pacing sites at both pacing rates (p < 0.01 for BiA vs. HRA or CS pacing; Figs. 4B and 4C). Concerning SBP, there was no significant difference between HRA and CS pacing (p = 0.92). When analyzed by individual groups, BiA pacing resulted in the most significant improvement in SBP among the three pacing sites at both pacing rates (p < 0.01 for BiA vs. HRA or CS pacing; Table 2, Fig. 4D). Concerning CO, PCWP, and SBP, there were no significant differences between the two pacing rates (p = 0.41, p = 0.52, and p = 0.87, respectively).

Transesophageal echocardiography. At a pacing rate of 80 beats/min, we were able to detect discrete E and A waves at all pacing sites, and different Doppler transmural flow patterns among the three pacing sites were found (Fig. 2B). The transmural flow pattern at 100 beats/min, however, indicated a single fusion wave consisting of E and A waves at all pacing sites. Therefore, we measured E Vmax, A Vmax, and S/A peak only at 80 beats/min.

Bi-atrial pacing most significantly tended to increase E Vmax. There was a significant difference between BiA and HRA pacing (p < 0.05), but there was no significant difference between BiA and CS pacing (p = 0.74; Table 2, Fig. 5A).

Among the three pacing sites, BiA pacing most significantly increased A Vmax (p < 0.01 for BiA vs. HRA or CS pacing; Table 2, Fig. 5B). There was no significant difference in A Vmax between HRA and CS pacing (p = 0.56).

Bi-atrial pacing also gave the most significant increase in TVI (p < 0.01 for BiA vs. HRA or CS pacing; Table 2, Fig. 5C). There was no significant difference in TVI between HRA and CS pacing (p = 0.48). The TVI was significantly higher at 80 beats/min than at 100 beats/min (7.41 ± 1.09 cm and 7.90 ± 1.07 cm, respectively; p < 0.01).

The S/A peak during CS and BiA pacing was significantly shorter than that during HRA pacing (p < 0.01; Table 2, Fig. 5D); however, there was no significant difference between CS and BiA pacing (p = 0.06).

At both pacing rates, the optimal AV delay was significantly shorter during CS and BiA pacing than during HRA pacing (p < 0.01; Table 2, Fig. 5E), although there was no significant difference between CS and BiA pacing (p = 0.40).

There were no significant differences in inter- and intra-observer variability.

Comparison between patients with and without a history of AF. We examined the differences between patients with and without a history of AF. P-wave durations in these patients were 131 and 127 ms, respectively, which were not significantly different (p = 0.52). There were also no significant differences in the hemodynamic benefits of BiA pacing between the two groups.

Relationship between interatrial conduction delay and the cardiac hemodynamic variables. The interatrial conduction delay elicited by a single extrasystole at HRA pacing could be evaluated in all the patients. The mean max CD was 49.9 ± 30.1 ms.

The max CD was correlated with the improvements in the hemodynamic variables when pacing site was changed from HRA or CS pacing to BiA pacing. For ΔS-A peak, ΔA Vmax, ΔCO and ΔTVI, r = 0.54 and r = 0.57, r = 0.58 and r = 0.56, r = 0.51 and r = 0.51, and r = 0.59 and r = 0.56, respectively, p < 0.05 (Fig. 6). P-wave duration during sinus rhythm was weakly correlated with ΔS-A peak, ΔA Vmax.

Table 2. Comparison of Measurements Among the Three Pacing Sites

<table>
<thead>
<tr>
<th>Pacing</th>
<th>HRA</th>
<th>CS</th>
<th>BiA</th>
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<tbody>
<tr>
<td>P-wave duration (ms)</td>
<td>137 ± 19</td>
<td>137 ± 20</td>
<td>96 ± 10*†‡</td>
</tr>
<tr>
<td>E Vmax (cm/s)</td>
<td>37.6 ± 15.1</td>
<td>38.6 ± 16.9</td>
<td>41.0 ± 16.5§</td>
</tr>
<tr>
<td>A Vmax (cm/s)</td>
<td>67.1 ± 11.1</td>
<td>67.6 ± 11.7</td>
<td>71.6 ± 11.4*†</td>
</tr>
<tr>
<td>TVI (cm)</td>
<td>7.4 ± 1.5</td>
<td>7.6 ± 1.3</td>
<td>8.1 ± 1.3*†</td>
</tr>
<tr>
<td>S-A peak (ms)</td>
<td>184 ± 26</td>
<td>168 ± 18</td>
<td>162 ± 18*</td>
</tr>
<tr>
<td>Optimal AVD (ms)</td>
<td>144 ± 38</td>
<td>123 ± 30</td>
<td>119 ± 29*</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>151 ± 22</td>
<td>152 ± 23</td>
<td>160 ± 21*</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>3.76 ± 0.77</td>
<td>3.78 ± 0.77</td>
<td>3.98 ± 0.74*</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>9.6 ± 5.2</td>
<td>9.5 ± 4.9</td>
<td>8.5 ± 4.6*</td>
</tr>
</tbody>
</table>

*p < 0.001 vs. baseline; †p < 0.001 vs. HRA (high right atrial); ‡p < 0.001 vs. CS (coronary sinus); |p| < 0.01 vs. HRA; |p| < 0.01 vs. CS; |p| < 0.05 vs. HRA. Data presented are mean ± SD.

AVD = optimal atrioventricular delay; A Vmax = peak velocity of the atrial filling wave; BiA = bi-atrial; CO = cardiac output; E Vmax = peak velocity of the early filling wave; PCWP = pulmonary capillary wedge pressure; S-A peak = interval from atrial pacing spike to peak of A-wave; SBP = systolic blood pressure; TVI = mitral flow time velocity integral.

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ΔCO, and ΔTVI when pacing site was changed from HRA or CS pacing to BiA pacing. For ΔS-A peak, ΔA Vmax, ΔCO, and ΔTVI, r = 0.43 and r = 0.45, r = 0.43 and r = 0.46, r = 0.42 and r = 0.47, and r = 0.44 and r = 0.40, respectively; p < 0.05. We could find no significant correlation, however, between the conduction time from HRA to distal CS during sinus rhythm and the improvements in the hemodynamic variables. For ΔS-A peak, ΔA Vmax, ΔCO, and ΔTVI, r = 0.11 and r = 0.22, r = 0.08 and r = 0.18, r = 0.17 and r = 0.19, and r = 0.29 and r = 0.20, respectively; p > 0.05.

Figure 4. (A) Comparison of P-wave duration between baseline and the three pacing sites. P-wave duration is the shortest during bi-atrial (BiA) pacing. (B) Comparison of cardiac output (CO) between the three pacing sites at both pacing rates. The BiA pacing significantly produced the most increased CO. (C) Comparison of pulmonary capillary wedge pressure (PCWP) between the three pacing sites at both pacing rates. BiA pacing resulted in the most significant improvement. (D) Comparison of systolic blood pressure (SBP) between the three pacing sites at both pacing rates. BiA pacing significantly produced the most increased SBP. Solid line indicates data at 80 beats/min. Dotted line indicates data at 100 beats/min. Other abbreviations as in Figure 2.

Figure 5. (A) Comparison of E Vmax at a heart rate of 80 beats/min at the three pacing sites. The E Vmax was significantly larger during bi-atrial (BiA) pacing than during high right atrial (HRA) pacing; however, there was no significant difference between BiA and coronary sinus (CS) pacing. (B) Comparison of A Vmax at 80 beats/min between the three pacing sites; BiA pacing significantly produced the most increased A Vmax. (C) Comparison of TVI between the three pacing sites; BiA pacing significantly produced the most increased TVI. (D) Comparison of S-A peak at 80 beats/min between the three pacing sites; S-A peak was significantly the shorter during CS and BiA pacing than during HRA pacing, although there was no significant difference between BiA and CS pacing. (E) Comparison of the optimal AV delay between the three pacing sites. The optimal AV delay was significantly shorter during CS or BiA pacing than during HRA pacing; however, there was no significant difference between CS and BiA pacing. Solid line indicates data at 80 beats/min. Dotted line indicates data at 100 beats/min.
DISCUSSION

The findings of the present study indicate that BiA pacing with optimal AV delays yielded the most significant improvements in acute hemodynamics compared with HRA and CS pacing with optimal AV delays. It is obvious that optimal AV delays produce the best hemodynamic benefits during AV sequential pacing (14). In the present study, BiA pacing at both pacing rates produced the shortest P-wave duration, the largest improvements in SBP, CO, and PCWP, the greatest increase in A Vmax and TVI, and the earliest left atrial activation. These findings show that BiA pacing gives rise to the biggest improvement in atrial function and the largest reduction in intra-atrial pressure compared with HRA and CS pacing. Moreover, we showed that these improvements in hemodynamics were significantly correlated with interatrial conduction delay.

Patients with prolonged electrocardiographic P-wave duration are thought to have interatrial conduction delay and atrial systolic dysynchrony (15). The present study showed that BiA pacing significantly produces the shortest S-A peak and the biggest increase in A Vmax and TVI, and CO. These improvements in hemodynamics were significantly correlated with interatrial conduction delay and were larger in the patients with longer interatrial conduction delay. These findings indicate that BiA pacing might result in interatrial resynchronization and hemodynamic improvements compared with HRA and CS pacing.

Reports on the hemodynamic effects of BiA pacing are very rare, and the available results are controversial. Levy et al. (11) studied the hemodynamic effects in only eight patients with overdrive single chamber atrial pacing by transthoracic echocardiography. They showed that BiA pacing significantly decreased the interval from the atrial pacing spike on the ECG to the peak of the A-wave, but that there were no significant changes in A Vmax, TVI, plasma atrial natriuretic peptide, and B-type natriuretic peptide. Alicja et al. (12) reported the acute effects of BiA pacing compared with HRA and CS pacing using Doppler transmitral flow on 12 patients with a history of drug refractory paroxysmal AF. After 5-min pacing, they showed that BiA pacing offered no better hemodynamic effect than HRA and CS pacing. In these studies, however, pacing was not performed with optimal AV delays, and the benefits of BiA pacing might have been underestimated. In the present study, we compared acute hemodynamics with HRA, CS, and BiA pacing with optimal AV delays, and using Swan-Ganz catheter and transthoracic echocardiography, showed that BiA pacing produced most improvement in the cardiac hemodynamic variables. Moreover, we indicated that the hemodynamic benefits of BiA pacing might be due to atrial resynchronization. To the best of our knowledge, this is the first report showing that atrial function and hemodynamic variables improvements were most prominent during BiA pacing with optimal AV delays compared with HRA and CS pacing with optimal AV delays, and that these benefits of BiA pacing were correlated with interatrial conduction delay.

Figure 6. Relation between interatrial conduction delay and the cardiac hemodynamic variables. The maximal interatrial conduction delay (Max CD) was correlated with the improvements in the hemodynamic variables when pacing site was changed from HRA or CS pacing to BiA pacing. For ΔS-A peak, ΔA Vmax, ΔCO, and ΔTVI, r = 0.54 and r = 0.57, r = 0.58 and r = 0.56, r = 0.51 and r = 0.51, and r = 0.59 and r = 0.56, respectively. ΔS-A peak (%) = (S-A peak [BiA] - S-A peak [HRA or CS]) / S-A peak (HRA or CS) × 100. ΔA Vmax (%) = (A Vmax [BiA] - A Vmax [HRA or CS]) / A Vmax (HRA or CS) × 100. ΔCO (%) = (CO [BiA] - CO [HRA or CS]) / CO (HRA or CS) × 100. ΔTVI (%) = (TVI [BiA] - TVI [HRA or CS]) / TVI (HRA or CS) × 100. Other abbreviations as in Figure 2.
Clinical implications. Bi-atrial pacing produces interatrial resynchronization and might be of use in pacing systems used to treat patients with congestive heart failure and intraventricular delay. Recently, cardiac resynchronization therapy by biventricular pacing has become an important therapy for patients with severe heart failure (16). In these patients, in addition to inter and intraventricular resynchronization, interatrial resynchronization and optimization of AV conduction might produce further improvements in hemodynamics. Bi-atrial AV sequential pacing with optimal AV delays might play an important role in the hemodynamic improvements in such patients and is a possible optional therapy for patients with severe heart failure.

Study limitations. The optimal site for CS pacing is the left lateral atrium. At first, we chose the most lateral site in the CS under fluoroscopy. When we occasionally failed to pace the left atrium from this site, we selected the nearest left lateral site neighboring the optimal site wherein we found large atrial and small ventricular potential. In all patients, AV sequential pacing from the left lateral or near lateral atrium was successfully performed.

Conclusions. Bi-atrial AV sequential pacing with optimal AV delays produced significant improvements in acute hemodynamics compared with single atrial AV sequential pacing with optimal AV delays. These benefits were correlated with interatrial conduction delay and might have been due to interatrial resynchronization. The acute hemodynamic benefits of BiA pacing might play a role in the treatment of heart failure.

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