Left Ventricular Function During and After Right Ventricular Pacing

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OBJECTIVES
The aim of this research was to evaluate right ventricular pacing effects on left ventricular function.

BACKGROUND
Right ventricular pacing alters the ventricular activation sequence and reduces left ventricular ejection fraction (EF). It is unclear whether the observed reduction in EF can be completely attributed to the alteration in activation sequence.

METHODS
Twelve subjects (eight women), mean age 68 ± 12 years, with transvenous dual-chamber pacemakers, normal left ventricular function, and intact atrioventricular (AV) conduction were studied with serial-gated blood pool studies. Left ventricular EF was measured at a fixed rate after at least 1 week of atrial pacing only (baseline), during short-term (2 h) and mid-term (1 week) AV sequential pacing with a short AV delay, and after short- and mid-term AV pacing.

RESULTS
Baseline EF was 66.5 ± 4.5%. Short-term AV pacing resulted in a decrease in EF to 60.3 ± 5.2% (p < 0.0002). After one week of AV pacing, there was a further decline in EF to 52.9 ± 8.3% (p < 0.0001). After cessation of mid-term pacing, EF was 57.3 ± 5.9% (p < 0.0001 vs. baseline). A total of 2, 5, 8, and 24 h later, EF remained depressed (59% to 60%, p < 0.007). At 32 h, EF was 62.9 ± 7.6% (p < 0.11 compared with baseline).

CONCLUSIONS
The abnormal activation sequence resulting from right ventricular pacing accounts for only part of the reduction in EF as mid-term pacing is associated with a lower EF than short-term pacing, and EF remains depressed after cessation of AV pacing. Changes in ventricular function induced by right ventricular pacing may account for some of its associated adverse effects. (J Am Coll Cardiol 2004;44:1883–8) © 2004 by the American College of Cardiology Foundation

It is well known that acute right ventricular pacing (VP) alters the normal sequence of activation and may result in a reduction of the left ventricular ejection fraction (EF) (1–3). Recent clinical trials have highlighted the possibility that right VP may result in a higher incidence of congestive heart failure in patients with depressed left ventricular function (4,5). Although the mechanism for the higher incidence of congestive heart failure in these studies is likely linked to the right VP, it remains unclear whether the observed reduction in left ventricular EF can be completely attributed to the alteration in activation sequence. If this were the case, then the left ventricular EF would be expected to decrease with right VP and recover immediately with restoration of a normal activation sequence.

Cardiac memory describes the phenomenon of persistent alterations in T-wave morphology or repolarization when normal depolarization has been restored after extended periods of abnormal depolarization, such as right VP (6). The electrical or repolarization changes that occur as a result of right VP may take weeks to resolve even when the normal depolarization has been restored. Using echocardiographic techniques, we (7) previously demonstrated that the phenomenon of cardiac memory may also apply to diastolic function; that is, when normal depolarization has been restored after extended periods of abnormal depolarization, such as right VP, persistent abnormalities in filling and relaxation indexes of diastolic function can be demonstrated. The present study was undertaken with the hypothesis that cardiac memory may also apply to left ventricular systolic function. Specifically, we hypothesized that when normal depolarization has been restored after extended periods of abnormal depolarization, such as right VP, abnormalities in left ventricular EF may persist.

METHODS
Subjects. Subjects were recruited from the Pacemaker Follow-up Program at Northwestern Memorial Hospital. All subjects provided written, informed consent. The study was approved by the Northwestern University Institutional Review Board. To be eligible to participate, subjects had to have transvenous dual-chamber pacemakers, normal left ventricular function, sinus rhythm, and intact atrioventricul-
ular (AV) conduction. Right VP leads were positioned at or near the right ventricular apex. No subject had clinical or electrocardiographic evidence of ischemia. Exclusion criteria included significant arrhythmias, significant valvular heart disease, left ventricular systolic dysfunction, hypertrophic cardiomyopathy, prior coronary bypass or valve surgery, and second- or third-degree AV block.

**Study protocol.** Figure 1 is a schematic illustration of the study protocol. The study was designed to assess the effect of short-term (2 h) and mid-term (1 week) VP on left ventricular systolic function during and after cessation of VP. Ventricular function was assessed by gated blood pool studies. All studies were done at a fixed atrial paced rate of 80 beats/min, either with intact AV conduction or with VP as indicated (short AV delay of 100 ms). Thus, ventricular pacing throughout refers to dual chamber, AV sequential (DDD) pacing with a short AV delay. At each evaluation, an electrocardiogram (ECG) and blood pressure were also obtained. In addition, as VP has been shown to affect myocardial catecholamine levels and sympathetic nerve activity (8,9), morning plasma catecholamine levels were obtained on each day of this study. The study was conducted in the clinical research center of Northwestern Memorial Hospital.

On the initial visit (day 0), the pacemaker was programmed so that normal AV conduction would occur. In 11 subjects, the pacemaker was programmed to atrial pacing (AAI) mode; in one subject with carotid sinus hypersensitivity, it was programmed to the DDD mode with a long AV delay. In this subject, after one week of pacing in this mode, pacemaker interrogation demonstrated <3% VP. Baseline studies were performed after at least one week of AAI (day 7) to allow for normal AV conduction. All studies were done at a rate of 80 beats/min. Short-term ventricular pacing (STVP) studies were performed after 2 h of DDD pacing with short AV delay (100 ms) to ensure 100% VP. Ventricular capture during this period was confirmed on the ECG, and the number of sensed and paced events was retrieved from the pacemaker event counters (>99% VP). After the 2-h STVP evaluation, pacemakers were reprogrammed to AAI mode, and the subjects were immediately restudied. Upon completion of the day 7 studies, subjects were sent home with the pacemaker programmed to the DDD mode with a short AV delay (100 ms) to ensure 100% VP. Subjects returned for evaluation after at least one week of VP. Pacemaker interrogation confirmed >99% VP in all subjects. Subjects were then studied during mid-term ventricular pacing (MTVP). The pacemakers were then reprogrammed to AAI, and studies were performed immediately, 2, 5, 8, 24, and 32 h after cessation of MTVP.

**Gated cardiac blood pool imaging.** Standard multiple-gated acquisition scans were performed at rest in the supine position after the injection of 20 to 25 mCi of technetium-99m-labeled red blood cells on each of the three study days. Imaging was performed with a standard Anger camera (Siemens, Hoffman Estates, Illinois) equipped with a parallel-hole collimator oriented in a modified left anterior oblique projection to best isolate the left ventricle from surrounding structures. A sequence of cardiac images spanning the cardiac cycle was constructed from several hundred cardiac cycles by computer-based electrocardiographic gating. The ECG was monitored continuously to ensure appropriate gating of the QRS complex. Data were acquired at a frame rate of 32 frames per R-R interval (approximately 23 ms/frame). All studies were performed at a fixed heart rate (80 beats/min).

Left ventricular regions of interest were manually drawn in systole and diastole. Global left ventricular EF was calculated from a background-corrected time-activity curve according to the formula:

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\text{left ventricular EF} = \frac{\text{end-diastolic count} - \text{end-systolic count}}{\text{end-diastolic count}}
\]

**Electrocardiography.** Standard 12-lead ECGs (50 mm/s) were acquired. QRS duration was measured at baseline and during both short-term and MTVP.

**Catecholamines.** Plasma epinephrine and norepinephrine levels were measured on the morning of day 7 (baseline value with intact AV conduction), one week later during MTVP (day 14), and one day after the cessation of MTVP. Blood samples were drawn in the morning before the subject had risen from bed from an indwelling intravenous catheter.

Blood samples were collected in heparinized tubes and placed on ice. After centrifugation at 4°C at 3,000 rpm for 15 min, 2 ml of plasma was transferred to a tube containing
4 mg of reduced glutathione as a preservative and stored at −70°C for subsequent analysis. Catecholamine levels in plasma were assayed by liquid chromatography with electrochemical detection. The method combines liquid/liquid extraction of catecholamines from plasma with reversed-phase chromatography incorporating a cation-exchange reagent (Plasma Catecholamine Kit; Bioanalytical Systems, Inc., West Lafayette, Indiana) (10,11) and has been used in previous studies (12).

**Statistical analysis.** Data are reported as mean values ± 1 SD. Time-dependent changes were assessed with repeated measures analysis of variance. Post-hoc pairwise comparisons were done with t tests. A p value <0.05 was considered significant.

**RESULTS**

Twelve subjects, mean age 68 ± 12 years, were studied. There were eight women and four men. The indication for cardiac pacing was sick sinus syndrome in 11 subjects, and carotid sinus hypersensitivity in one subject. A total of four subjects were receiving beta-blocker therapy, one was taking an angiotensin-converting enzyme inhibitor, and one was receiving antiarrhythmic drug therapy. There were no alterations in medication regimens during the study period.

During each measurement of left ventricular EF, heart rate was 80 beats/min. Baseline systolic blood pressure was 137 ± 25 mm Hg with no significant change in systolic blood pressure throughout the study protocol.

**Effects of STVP on left ventricular EF.** The baseline left ventricular EF after at least one week of AAI with normal AV conduction was 66.5 ± 4.5%. All subjects had a normal baseline left ventricular EF (>55%). Short-term VP for 2 h resulted in a decrease in left ventricular EF to 60.3 ± 5.2% (p < 0.0002). Immediately after discontinuing DDD pacing, there was no significant change in left ventricular EF compared with STVP (58.2 ± 4.8%). However, it was significantly reduced compared with the baseline study (p < 0.0001). The QRS duration during STVP was 168 ± 16 ms versus 90 ± 16 ms at baseline (p < 0.0003).

**Effects of MTVP on left ventricular EF.** After one week of VP, there was a significant decline in left ventricular function compared with baseline. The left ventricular EF decreased from 66.5 ± 4.5% to 52.9 ± 8.3% (p < 0.0001). Furthermore, the left ventricular EF during MTVP was significantly lower than the left ventricular EF during STVP (p < 0.0008). Figure 2 demonstrates the left ventricular EF for each subject at baseline, during STVP, and during MTVP. A decline in EF between the STVP and MTVP studies was observed in 10 of the 12 subjects. The QRS duration during MTVP was 167 ± 16 ms, which was significantly prolonged compared with baseline (p < 0.0003), but similar to the QRS duration during STVP.

**Recovery of left ventricular function after cessation of VVI.** Figure 3 demonstrates individual data for left ventricular EF at baseline, during MTVP, and immediately after cessation of MTVP. An immediate increase in EF after cessation of MTVP occurred in 9 of 12 subjects. However, all subjects had a lower left ventricular EF immediately after cessation of VP, when the depolarization sequence had been restored to normal, than at the baseline evaluation.

The time-dependent changes in left ventricular EF due to MTVP and after cessation of MTVP were significant (p < 0.0001). Immediately after cessation of MTVP, left ventricular EF was 57.3 ± 5.9%. This was significantly reduced compared with the baseline EF (p < 0.0001). However, it was significantly improved compared with MTVP (p < 0.05). Figure 4 demonstrates the sequential measurements of left ventricular EF during MTVP and after cessation of MTVP. At 2, 5, 8, and 24 h after cessation of MTVP, left

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**Figure 2.** Plot of individual values of left ventricular ejection fraction obtained at the baseline evaluation after at least one week of atrial pacing with normal atrioventricular conduction (BASE), during short-term (after 2 h) ventricular pacing (STVP), and during mid-term (after at least one week) ventricular pacing (MTVP).

**Figure 3.** Plot of individual values of left ventricular ejection fraction obtained at the baseline evaluation after at least one week of atrial pacing with normal atrioventricular conduction (BASE), during mid-term (after at least one week) ventricular pacing (MTVP), and immediately after cessation of MTVP (immediately post-MTVP).
ventricular EF remained depressed (between 59% to 60%) compared with baseline AAI (59.2 ± 6.2%, p < 0.001; 59.5 ± 6.5%, p < 0.002; 58.8 ± 8.0%, p < 0.004; 59.8 ± 6.9%, p < 0.007, respectively). At 32 h after cessation of MTVP, the left ventricular EF was 62.9 ± 7.6% (p < 0.11 compared with baseline, p < 0.02 compared with the EF immediately after cessation of ventricular pacing).

**Plasma catecholamine levels.** The baseline epinephrine and norepinephrine levels were 1.30 ± 1.14 and 2.08 ± 1.21 pmol/ml. After one week of AV pacing with a short AV delay, the epinephrine and norepinephrine levels were 1.54 ± 1.26 and 1.86 ± 0.58 pmol/ml. A total of 24 h after cessation of MTVP, the epinephrine and norepinephrine levels were 1.47 ± 0.87 and 2.34 ± 1.20 pmol/ml. There were no significant changes in plasma catecholamine levels.

**DISCUSSION**

Our findings suggest that abnormal activation sequence accounts for only part of the reduction in global left ventricular EF associated with prolonged right VP. The abnormal activation sequence cannot completely explain the observed reduction because:

1) There was further reduction in left ventricular EF associated with MTVP compared with STVP despite having the same abnormal activation sequence in both types of studies;

2) Ejection fraction did not completely recover immediately after cessation of either short-term or MTVP despite normalization of activation sequence;

3) Ejection fraction was significantly depressed compared with baseline for at least 24 h after cessation of MTVP despite restoration of a normal activation sequence.

The effects of short-term versus MTVP on left ventricular EF and the recovery of left ventricular function after cessation of right VP have not been previously evaluated. It is noteworthy that only 2 h of VP (short-term) led to persistent reduction in left ventricular EF after restoration of a normal activation pattern. There was a gradual recovery in EF after cessation of MTVP. By 32 h after cessation of pacing, the EF was approaching its baseline values.

**Effects of VVI on left ventricular EF.** Several studies of STVP have demonstrated that even AV synchronous pacing is associated with a statistically significant reduction in left ventricular EF compared with AAI pacing (1–5). In those studies, left ventricular EF and cardiac output as determined by echocardiography, radionuclide studies, and cardiac catheterization were higher in the AAI mode than in the DDD mode, likely because of the preservation of the normal ventricular activation pattern with AAI pacing. Boucher et al. (13) reported no significant change in EF with VP, though 11 of 13 subjects with normal EFs did have a decline in EF with VP. The present study confirms that VP, even in AV sequential paced mode, results in a reduction in EF.

Nielsen et al. (14) randomized patients with sick sinus syndrome to either DDD or AAI for two years. In the AAI group, the left ventricular EF at baseline was 62% and remained unchanged after two years (61%), whereas, in the DDD group, the left ventricular EF decreased from 61% at baseline to 56% after two years of pacing (p = 0.013). The present study confirms that prolonged VP is associated with a reduction in left ventricular EF. Furthermore, left ventricular EF is reduced to a greater extent after MTVP than with STVP.

**Potential mechanisms of the effect of right VP on left ventricular function.** In addition to the potential role of an altered sequence of activation, there are several other pathophysiologic alterations that have been described to occur in the setting of VP that could contribute to or result from the observed decline in EF with VP. Ventricular pacing affects myocardial perfusion (14–16). Nielsen et al. (14) found that VP reduced inferior, septal, and global mean myocardial blood flow compared with the effects of temporary AAI pacing in the same subjects.

Lee et al. (8) studied 16 dogs with iatrogenic complete AV block and found that cardiac tissue norepinephrine levels were significantly increased in the ventricular paced group compared with controls. Although no change in plasma catecholamines were noted in this study, it remains possible that testing peripheral catecholamine levels is not sensitive enough to detect changes in myocardial catecholamine levels or small changes in sympathetic nerve activity. Heightened sympathetic activity would likely be secondary to the decline in EF, rather than the primary cause.

Karpawich et al. (17), in a histopathologic study on the effects of epicardial permanent right VP on canine hearts, found evidence of myofibrillar cellular disarray, dystrophic calcifications, prominent subendocardial Purkinje cells, and an increase in variable-sized, disorganized mitochondria.
another study (18), pacing for three months from the right ventricular apex in dogs with iatrogenic complete AV block caused myofibrillar disarray in 9 of 12 dogs in the paced group and none in the control group.

**Effects of VP on postpacing left ventricular EF.** Any of the mechanisms described above may be implicated in the postpacing depression of the EF. Ventricular pacing is also known to cause secondary changes in repolarization after cessation of pacing, a phenomenon known as cardiac memory (6). Recent investigation into this phenomenon has identified specific ion channels that are modified as a result of VP, such as the calcium-insensitive transient outward current ($I_{to}$) (19) and the L-type calcium current (20). Furthermore, it has been shown that administration of the protein synthesis inhibitor cycloheximide before pacing markedly and reproducibly attenuates the evolution of cardiac memory (21). These data suggest that VP induces changes in cardiac ion channel function that persist when pacing is stopped, manifest as cardiac memory. Spragg et al. (22) provided further evidence that altered activation sequence may induce regional changes in protein expression that may have adverse effects on ventricular function in a canine tachycardia-induced heart failure model.

**Study limitations.** The present study focused on determination of global left ventricular EF during and after periods of right VP. We have previously shown using echocardiographic techniques that diastolic function abnormalities may also persist after cessation of right VP (7). Further studies will need to address the interdependence of these diastolic and systolic functional abnormalities. In addition, regional analysis of diastolic and systolic function in relation to pacing site may be useful in assessing the optimal sites for VP (i.e., those that have the least negative effect on regional and global diastolic and systolic function). Finally, this study utilized a very short AV delay to guarantee 100% VP. It is possible that some of the noted abnormalities could be related to this “unphysiologic” AV delay.

**Implications.** A Danish randomized clinical trial of 225 patients with sick sinus syndrome showed that AAI pacing is associated with significantly lower death rates, atrial fibrillation, thromboembolic complications, and heart failure (23) than VVI pacing. Yet, three large-scale North American trials (Pacemaker Selection in the Elderly [PASE], Canadian Trial Of Physiologic Pacing [CTOPP], Mode Selection Trial [MOST]), including 3,891 patients, demonstrated no difference in mortality between DDD and VVI pacing, with only minimal differences in outcomes between the treatment groups (24–26). The main difference between the North American and the Danish trials is the use of DDD (AV) pacing in the former and AAI pacing in the latter as the physiologic pacing treatment arm. It is interesting to note that patients with DDD pacemakers are very frequently paced in the ventricle, despite programming “long” AV delays and underlying intact AV conduction (27). It is, therefore, plausible that the benefit of AAI over VVI pacing is due to the absence of VP rather than the presence of AV synchrony, as DDD pacing preserves the latter but not the former.

The potential deleterious effects of right VP were recently highlighted in several recent reports in which an increased incidence of symptomatic congestive heart failure was noted in patients who were exposed to VP. In the Multicenter Automatic Defibrillator Implantation II trial (MADIT II) (4), the incidence of new or worsened heart failure was 14.9% in the control group versus 19.9% in those implanted with a device ($p = 0.09$). It is plausible that the increased heart failure was due to “inadvertent” right VP that might occur in patients with an implantable defibrillator. Supporting this concept, Saad et al. (28) recently reported worsening symptoms of congestive heart failure in 44% of those patients who received an implantable defibrillator and were exposed to right VP compared with 5% of those not exposed to VP ($p < 0.01$). In MOST (29), the cumulative percent of VP obtained from stored pacemaker data was a strong predictor of heart failure hospitalizations. Finally, the Dual Chamber and VVI Implantable Defibrillator trial (DAVID) (5) demonstrated that patients undergoing defibrillator implantation who do not also have indications for antibradycardia pacing had a higher incidence of the combined end point of mortality and first hospitalization for heart failure when their devices were programmed to dual-chamber rate-responsive pacing rather than ventricular back-up pacing at 40 beats/min. This adverse outcome was felt to be related to right VVI that was observed in the dual-chamber pacing group.

**Conclusions.** Right VP appears to have a modest depressant effect on left ventricular function due to underlying changes in intrinsic myocardial contractile properties. Further work is necessary to identify the underlying pathophysiologic changes responsible for the decline in left ventricular function. Concerted efforts should be made to maintain the normal activation sequence, when possible, in patients with pacemakers. Further work is necessary to define the optimal pacing site in patients who do require VP.

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