Original Articles

Effect of Peri-Infarct Pacing Early After Myocardial Infarction

Results of the Prevention of Myocardial Enlargement and Dilatation Post Myocardial Infarction Study

Eugene S. Chung, MD; Dan Dan, MD; Scott D. Solomon, MD; Alan J. Bank, MD; Joseph Pastore, PhD; Anand Iyer, PhD; Ronald D. Berger, MD, PhD; Jay O. Franklin, MD; Gregory Jones, MD; Christian Machado, MD; Craig M. Stolen, PhD

Background—Left ventricular (LV) remodeling has been attributed to the segmental loss of viable myocardium due to myocardial infarction (MI), which results in redistribution of cardiac workload, with increased regional wall stress in and around the infarct zone. Because ventricular pacing has been shown to reduce regional wall stress and workload in regions near the pacing site, this trial was designed to test whether chronic pacing near the infarct attenuates LV remodeling.

Methods and Results—Eighty patients with an anterior MI, peak creatine kinase >2000 mU/mL, ejection fraction ≤35%, wall motion abnormality (WMA) in >5 of 16 segments, and QRS <120 ms, were randomized to either control (implantable cardioverter-defibrillator [ICD]) or biventricular pacing with peri-infarct LV lead placement (cardiac resynchronization therapy [CRT]-D) arms between 2 and 14 days after the MI. The primary end point—change in LV end-diastolic volume (LVEDV) from baseline to 12 months—was not significantly different between the 2 groups (CRT, 10.6±27.7 mL; ICD, 11.2±31.2 mL; 2-sample t test P>0.05). In a hypothesis-generating secondary analysis, there was a sustained reduction in the WMA score at 12 months in paced patients (CRT, −0.16±0.28; ICD, −0.01±0.24, 2-sample t test P=0.03). No differences were found in the therapy-related event rate, hospitalizations, or mortality (all P>0.05).

Conclusions—Chronic pacing in the infarct region did not alter the primary end point of LV remodeling over 1 year.

Clinical Perspective on p 658

The severity of remodeling has been shown to be one of the major determinants of poor outcomes, including HF, hospitalization, and death. Ventricular remodeling has been attributed to the segmental loss of viable myocardium due to MI, which results in redistribution of cardiac workload, with increased regional wall stress in the susceptible infarct zone (IZ) and peri-infarct zone (PIZ). It is possible that a strategy to reduce regional wall stress in the IZ and PIZ early after an MI may be beneficial in attenuating chronic adverse remodeling.
Ventricular pacing has been shown to significantly reduce regional wall stress and workload near the pacing site. The preexcitation of a region through pacing causes the region of early activation to contract against a reduced afterload, thereby reducing the wall stress in that area, and distributes the local stress over a thicker surface. Using magnetic resonance-tagged imaging in dogs, it has been demonstrated that pacing can alter midwall fiber shortening with a redistribution of work, reducing workload by 50% at the pacing site and increasing workload by 50% at remote regions. The modulation of myocardial activation pattern may be used to chronically unload the IZ and the PIZ and can be accomplished using currently available biventricular pacing devices.

Results from animal studies suggest that pacing in the IZ or PIZ may reduce wall stress in the regions near the pacing site without a significant effect on global stroke work both acutely and chronically. In a swine model, electrical preexcitation applied to the IZ and PIZ for 60 days beginning immediately after left circumflex artery ligation reduced ventricular remodeling compared with no preexcitation.

The Prevention of Myocardial Enlargement and Dilation Post Myocardial Infarction Study (MENDMI) tested the hypothesis that preexcitation therapy using existing pacing technology delivered in the IZ or PIZ early post-MI can relieve regional stress and attenuate remodeling in patients with a large anterior infarct and systolic dysfunction.

Methods

Study Design

MENDMI was a prospective, randomized, patient-blinded feasibility study that enrolled patients with anterior MI who had a peak creatine kinase level >2000 mU/mL within the first 72 hours of presentation. Eligibility criteria included a QRS duration <120 ms measured by 12-lead ECG at any time after the most recent MI plus an ejection fraction (EF) <35% and abnormal wall motion in at least 5 of 16 possible segments measured 2 to 14 days after presentation. Eligible patients were randomized 1:1 in blocks of 4 stratified per center to therapy (cardiac resynchronization therapy [CRT]-D) or control (ICD) between 3 and 14 days of their presenting MI. Patients not meeting the EF or wall motion abnormality (WMA) criteria could be enrolled in open registry arms (Figure 1).

Exclusion criteria were permanent or persistent atrial tachyarrhythmia, cardiogenic shock, 2° or 3° heart block, marked renal dysfunction, coronary artery bypass grafting 30 days before or after enrollment, pregnancy, life expectancy of <6 months due to noncardiac causes, New York Heart Association (NYHA) class IV, placement on a heart transplantation list, or previous implantation with a pacemaker, ICD, or CRT device. All patients signed informed consents.

A sample size estimate of 50 complete data sets for the randomized groups was based on a 2-sample Student t test with 80% power and a difference in left ventricular (LV) end-diastolic volume (EDV) means of 20 mL and SD of 25 mL. Based on this estimate, the MENDMI study was approved by the Food and Drug Administration on April 14, 2005, to enroll 60 randomized patients, with a total patient ceiling of 90. To offset attrition, a protocol revision was approved by the Food and Drug Administration on January 10, 2007, that added 20 patients to the randomized arms, thus bringing the randomized patient number to 80 (total 110). The study was closed to further enrollment on March 13, 2008, after filling the randomized arms. The study was conducted under the approval of the investigational review boards of the 29 participating centers (see online supplement).

Therapy

All patients randomized to the control arm received either a single- or a dual-chamber ICD (Ventak Prizm or Vitality; Guidant/Boston Scientific; St Paul, Minn) 3 to 14 days after their MI. All right ventricular (RV) leads were placed in the apical region. The specified programming mode and lower rate limit for the control group (ICD) was VVI-40.

All patients in the therapy group received a Guidant CRT-D system (Contak Renewal and Livian). The right atrial lead position was determined by the implanting physician. All RV leads were placed in the apical region. Using a transvenous approach, the LV leads were placed near the infarct border, as determined by echocardiography. Based on venous anatomy, the leads were preferentially
placed in a lateral vein (anterior branch recommended) or if a suitable lateral vein was not available, in an anterior vein (superior and basal to the MI location). The LV lead could not be placed in the PIZ apical or inferior to the MI but could be in the infarct as long as acceptable pace and sense parameters were obtained. Placement on the posterior wall or any other region remote from the infarct area was not allowed. Lead positions were documented with drawings and with fluoroscopic and radiographic images. This documentation was then analyzed by 3 core laboratory physicians, and the lead locations were assigned to specific segments of a 16-segment LV model.

The specified CRT programming mode and lower rate limit for the therapy group was VDD-40 or DDD-40. The AV delays were programmed to 70% of the intrinsic AV interval measured by device intracardiac signals. The AV delay programming was checked at each follow-up and adjusted if necessary. All remaining device programming was left to the discretion of the physician.

### Testing Procedures

Although the reading of the initial echocardiogram to determine eligibility for enrollment (EF and WMA) was performed locally at each site before enrollment, all echocardiographic data used in the end point analysis, including the enrollment data, were generated at a core center (St Paul Heart Clinic, St Paul, Minn) by a single technician and overread by a board-certified cardiologist. The studies were blinded to each patient’s therapy assignment and reviewed in random order. All end point assessments were made with pacing turned on and turned off for at least 5 minutes. The echocardiographic measurements were made using GE EchoPAC 7.0.0 (GE Vingmed Ultrasound; Milwaukee, Wis) whenever possible or ProSolv CV Analyzer 3.0 software (ProSolv Cardiovascular; Indianapolis, Ind). Volumes were calculated using the Simpson method of discs from standard apical 4-chamber (A4C) and 2-chamber (A2C) views. Biplane LV volumes were calculated as well. WMA scores were assessed in a 16-segment model as described by the standards of the American Society of Echocardiography. Each segment was scored as follows: 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. Global scores were calculated by dividing the total score by the number of analyzable segments. Regional scores were calculated by averaging the WMA in an individual segment with each of its adjacent segments. Five percent of the echocardiograms were randomly selected for variability assessment.

At each follow-up visit, device programming, spontaneous arrhythmia episodes, and lead measurement data were collected. NYHA functional classification and MacNew quality-of-life questionnaires \(^*\) were obtained at predischarge and at each additional follow-up visit. Participating centers were asked to submit an adverse event for either an arrhythmia or an inappropriate therapy whenever antiarrhythmia therapy was delivered.

### Data Analysis

The primary end point was 12-month change in LVEDV. The specific method of echocardiography measurement was not prespecified (ie, biplane, A4C, A2C); thus, all views are presented. Effectiveness also was assessed by change in EF, WMA, NYHA class, and quality of life. In this protocol, safety was assessed using the prespecified therapy-related event-free rate that included LV lead dislodgement, postimplantation LV lead repositioning, permanent failure to deliver biventricular pacing, ventricular tachyarrhythmia, hospitalization due to cardiac causes, and all-cause mortality. The study was not powered to detect differences in therapy-related event-free rates, hospitalizations, or mortality. Prospectively defined reasons for patient exclusion from end point analysis included ventricular pacing >5% of the time or upgrade to a CRT device in the control arm or permanent loss of capture for a patient in the therapy arm.

### Table 1. Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control</th>
<th>Therapy</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55±10 (34–83)</td>
<td>58±11 (40–86)</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>Male sex</td>
<td>26 (68)</td>
<td>38</td>
<td>34 (81)</td>
<td>42</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173±14 (127–196)</td>
<td>174±9 (150–188)</td>
<td>35</td>
<td>41</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85±21 (39–127)</td>
<td>84±19 (45–141)</td>
<td>25</td>
<td>33</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.6±5.0 (22.3–39.1)</td>
<td>27.3±5.3 (18.9–45.9)</td>
<td>25</td>
<td>33</td>
</tr>
<tr>
<td>History of diabetes*</td>
<td>4 (11)</td>
<td>2 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown/unreported</td>
<td>34 (89)</td>
<td>40 (95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>I</td>
<td>6 (16)</td>
<td>7 (17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>13 (34)</td>
<td>12 (29)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>13 (34)</td>
<td>16 (38)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>6 (16)</td>
<td>7 (17)</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>Pre-MI/enrollment</td>
<td>9 (27)</td>
<td>10 (31)</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Predischarge</td>
<td>14 (41)</td>
<td>16 (50)</td>
<td>34</td>
</tr>
<tr>
<td>Max 12-lead ECG QRS duration</td>
<td>91±18 (40–160)</td>
<td>86±12 (57–116)</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>Resting heart rate</td>
<td>84±15 (55–122)</td>
<td>80±15 (56–120)</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>113±16 (74–152)</td>
<td>110±16 (84–148)</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70±11 (45–96)</td>
<td>70±12 (50–98)</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>Enrollment LVEF, %</td>
<td>29.2±6.3 (13–35)</td>
<td>27.6±5.8 (15–35)</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>Time from presentation to implantation, d</td>
<td>8±3 (3–14)</td>
<td>8±3 (3–16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
<td>7</td>
<td>0.56</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean±SD (range) or n (%), unless otherwise indicated.

*Before protocol revision 4.0 on December 5, 2005, diabetes had been an exclusion criterion.
Statistical comparisons between groups were made using 2-sample \( t \) tests. Regression models that accounted for baseline covariates were not used for these analyses. If the distribution of the outcome failed to meet the normality assumption, as determined by the Shapiro-Wilk test for normality, medians also were presented, and Wilcoxon sign rank tests were used to make statistical comparisons. Statistical significance of changes from baseline in continuous outcomes within the randomization arms was determined with 1-sample \( t \) tests. Categorical measures and outcomes were summarized using counts and percentages, and any statistical comparisons were made using Fisher exact test.

**Results**

Eighty patients were randomized in a 1:1 ratio to control (ICD) or therapy (CRT-D) arms (Figure 1). Thirty-five of the 38 patients randomized to the control arm received either a single-chamber (n = 23) or dual-chamber (n = 12) ICD between 72 hours and 14 days after MI. Two control patients withdrew participation before implantation, and 1 patient was found not to meet inclusion criteria after randomization but before implantation. One control patient was lost to follow-up. For the control patients, all of the lifetime ventricular pacing percentages were <2%, and no patients received an upgrade to a CRT device.

Thirty-eight of 42 patients in the therapy arm received a CRT-D system implantation between 72 hours and 14 days after MI, and 1 patient received the implant at 16 days. One patient withdrew before implantation, and in 2 patients, the LV leads could not be placed. Seven patients in the therapy arm were excluded due to loss to follow-up or loss of capture, including 5 with LV lead dislodgements and 1 with LV pacing turned off due to diaphragmatic stimulation that could not be alleviated through programming (Figure 1). A lateral vein approach was used 41% (16/39) of the time, and an anterior vein approach was used 53% (21/39) of the time. For 1 patient, the “posterior vein” was used, and for another, a “high anterolateral” vein approach was used. When the final lead positions were compared with the regions of baseline WMA, we found that a lead (LV or RV) was consistently placed in (31/38) or adjacent to (7/38) the segment representing the region of highest WMA.

**Baseline Characteristics**

The baseline characteristics for the therapy and control groups are summarized in Table 1. No significant differences were noted between the 2 groups (Table 1). All but 1 patient had a blockage in the left anterior descending artery, and the resulting infarcts were all anterior, anteroseptal, or anterolateral in location. Revascularization characteristics were also similar between the 2 groups (Table 2). Six patients in each randomized group had a history of MI (15% total), and 1 patient in each group had a history of HF. Center-reported EF on enrollment was 29 ± 6% and 28 ± 6% for the control and therapy arms, respectively (Table 1); however, when the same echocardiography studies were analyzed by the core laboratory, the average enrollment EF values for the control and therapy arms were 38 ± 8% and 38 ± 7%, respectively (Table 3). There was similar pharmacological therapy in both groups. At postimplantation discharge, 94% of patients in each group were receiving \( \beta \)-blocker therapy, and 94% of control and 88% of therapy patients were receiving angioten-

<table>
<thead>
<tr>
<th>Table 2. Revascularization Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Median time from symptoms to presentation, h:min</td>
</tr>
<tr>
<td>Range, h</td>
</tr>
<tr>
<td>Median time from symptoms to revascularization, h:min</td>
</tr>
<tr>
<td>Range, h</td>
</tr>
<tr>
<td>Revascularization</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>PTCA/PCI</td>
</tr>
<tr>
<td>Thrombolytics</td>
</tr>
<tr>
<td>Both</td>
</tr>
<tr>
<td>Stents used during revascularization</td>
</tr>
<tr>
<td>DES stent</td>
</tr>
<tr>
<td>Bare-metal stent</td>
</tr>
<tr>
<td>DES and bare-metal stent</td>
</tr>
<tr>
<td>Peak CK, mU/L</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
</tr>
</tbody>
</table>

Data are presented as \( n \) (%), unless otherwise indicated. CK indicates creatine kinase; DES, drug-eluting stent; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty.

sin-converting enzyme inhibitors or angiotensin-II receptor blockers. At 12 months, 94% of control and 100% of therapy patients were on \( \beta \)-blocker therapy, whereas 84% of control and 94% of therapy patients were on angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers.

**Efficacy**

The effect of peri-infarct preexcitation pacing on the primary end point—change in LVEDV from baseline to 12 months—was measured using the biplane method of disks (modified Simpson method) and in the single-plane A4C and A2C views. There were no statistically significant differences between the therapy and control groups in the degree of change in LVEDV (Figure 2), LV end-systolic volume (ESV), or EF from baseline to 12 months (Table 3). The intraobserver and interobserver variability for each view is presented in Table 4.

Using WMA as an exploratory and hypothesis-generating marker of post-MI LV dysfunction, we found a greater reduction in the prespecified global WMA score at 12 months in the therapy patients compared to controls (–2.49, 2.70 versus 0.40, 2.49; \( P = 0.03 \)) (Figure 3A) that was maintained when pacing was turned off (pacing off, –0.22, 0.29; 2-sample \( t \) test versus ICD \( P = 0.003 \)). There was also a reduction in the total number of segments with abnormal wall motion (ie, WMA score ≥ 2) in the therapy arm compared with controls (–1.20, 2.70 versus 0.40, 2.49; \( P = 0.02 \)) (Figure 3B). This difference also was maintained with pacing turned off (pacing off, –1.83, 2.81; 2-sample \( t \) test versus ICD \( P = 0.002 \)).
event-free rates in the CRT-D and ICD arms were 14.3% and 57.9%; Fisher exact

composite therapy-related event-free rate (CRT, 47.6%; ICD, 0.9; therapy group, 5.2

global MacNew heart disease quality-of-life score at 1 month

function). No unanticipated adverse events occurred and no

adverse event that resulted in death, serious injury, correction

similarity between CRT-D and ICD

When the LV lead-related events were excluded, the adverse

lead-related adverse events classified as complications (ie, an

peptide (ICD, 309 to 105 pg/mL; CRT, 426 to 114 pg/mL).

follow-up measurements. No significant differences were

ADC

LVEDV 23 131±42 0.3±32.8 25 111±30 12.4±36.3 0.24 25 111±30 8.3±29.2 0.38

LVEF 23 37±8 -0.2±8.3 25 37±8 4.0±8.0 0.08 25 37±8 2.8±8.2 0.21

Multiple

WMA Score 30 1.72±0.21 -0.01±0.24 30 1.77±0.23 -0.22±0.29 0.003 30 1.73±0.23 -0.16±0.28 0.03

Segment with WMA 30 8.03±2.54 0.40±2.49 30 8.13±2.21 -1.83±2.80 0.002 30 7.83±2.13 -1.20±2.70 0.02

Data are presented as mean±SD, unless otherwise indicated.

*ICD versus CRT-OFF.
†ICD versus CRT-ON.
‡CRT-OFF versus CRT-ON.
§P<0.05; paired t test enrollment versus 12 months.
¶P<0.001; paired t test enrollment versus 12 months.
||P<0.01; paired t test enrollment versus 12 months.

At 12 months, NYHA functional class improved or re-

remained unchanged in 21 (66%) patients in the control group

compared to 24 (77%) in the therapy group (P=0.30).

Although there was a significant difference in the average
global MacNew heart disease quality-of-life score at 1 month

(control group, 4.5±1.1; therapy group, 5.2±0.9; P=0.01

[larger is better]), this difference was not sustained at follow-

up measurements. No significant differences were

found in median baseline to 12 months brain natriuretic

peptide (ICD, 309 to 105 pg/mL; CRT, 426 to 114 pg/mL).

Safety Analysis

No differences between randomized arms were found in the

composite therapy-related event-free rate (CRT, 47.6%; ICD, 57.9%; Fisher exact

P=0.38) (Table 5). The overall adverse event-free rates in the CRT-D and ICD arms were 14.3% and

26.3%, respectively (Fisher exact P=0.09); however, 26.2%

(11/42) of CRT-D patients had an LV lead-related adverse

event, whereas ICD patients did not receive an LV lead.

When the LV lead-related events were excluded, the adverse

event-free rates were very similar between CRT-D and ICD

patients (23.9% versus 26.3%, respectively; Fisher exact

P=0.80). Five (11.9%) of the CRT-D patients had LV

lead-related adverse events classified as complications (ie, an

adverse event that resulted in death, serious injury, correction

using invasive intervention, or permanent loss of device

function). No unanticipated adverse events occurred and no

deaths were classified by the Clinical Events Committee as

being related to the investigation or procedure. One therapy

patient was hospitalized after a failed ICD induction, and this

was the only hospitalization classified as related to the

investigation and procedure. The 12-month all-cause mortal-

ity rate for all the randomized patients was 2.5% (n=80;

average follow-up, 320±101 days; range, 1 to 542 days),

with 1 death in each of the randomized arms. One control

patient also received a heart transplantation. Six patients in

the control arm and 7 in the therapy arm received antiarrhyth-

mic therapy that included 1 therapy and 1 control patient who

received defibrillation for true episodes of ventricular fibril-

lation at 9 and 18 days post-MI, respectively, as well as 1

control patient who received antitachycardia pacing at 39

days. All patients receiving early antiarrhythmic therapy lived

to study completion.

Discussion

The main findings of MENNDM are that PIZ pacing did not

meet its primary end point of attenuating LVEDV dilation at

12 months. There were no significant differences in NYHA

functional class or quality of life between the 2 study arms,

and LV pacing early post-MI did not show evidence of major

negative consequences.

Clinical feasibility of PIZ pacing after MI (30 to 45 days)

was first demonstrated in the Ohio Pacing Post-infarction

Study (OPIS).19 In this observational pilot study of 18

patients, no deaths occurred, no patients receiving CRT-D

devices deteriorated in NYHA class, and therapy patients had

improved quality of life at 1 year (similar to controls). Although

1 patient had a lead dislodgement, no unanticipated

adverse events were reported. In addition, although not

Table 3. Echocardiography Changes From Enrollment to 12 Months

<table>
<thead>
<tr>
<th>View and Measurement</th>
<th>Control (ICD)</th>
<th>Therapy (CRT) Pacing Turned Off</th>
<th>Therapy (CRT) Pacing Turned On</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n Baseline 12-Mo Change</td>
<td>n Baseline 12-Mo Change</td>
<td>P*</td>
</tr>
<tr>
<td>Biplane</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV</td>
<td>30 124±35 11.2±31.2§</td>
<td>30 116±25 11.0±28.2§</td>
<td>0.98</td>
</tr>
<tr>
<td>LVEF</td>
<td>30 38±8 -0.6±8.3</td>
<td>30 38±7 1.9±7.0</td>
<td>0.21</td>
</tr>
<tr>
<td>A4C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV</td>
<td>23 131±42 23.7±44.3§</td>
<td>26 118±31 5.2±28.4</td>
<td>0.09</td>
</tr>
<tr>
<td>LVEF</td>
<td>23 38±8 -0.9±7.0</td>
<td>26 37±7 2.2±7.1</td>
<td>0.13</td>
</tr>
<tr>
<td>A2C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV</td>
<td>23 123±32 0.3±32.8</td>
<td>25 111±30 12.4±36.3</td>
<td>0.24</td>
</tr>
<tr>
<td>LVEF</td>
<td>23 37±8 -0.2±8.3</td>
<td>25 37±8 4.0±8.0</td>
<td>0.08</td>
</tr>
<tr>
<td>Multiple</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMA Score</td>
<td>30 1.72±0.21 -0.01±0.24</td>
<td>30 1.77±0.23 -0.22±0.29</td>
<td>0.003</td>
</tr>
<tr>
<td>Segment with WMA</td>
<td>30 8.03±2.54 0.40±2.49</td>
<td>30 8.13±2.21 -1.83±2.80</td>
<td>0.002</td>
</tr>
</tbody>
</table>
statistically powered, the CRT-D patients tended to have both smaller LVEDV and LVESV at 1 year.

In OPIS, the patients were enrolled after 30 days and already had enlarged LV volumes. With MENDMI, it was hypothesized that an earlier PIZ pacing might prevent remodeling. To select patients with a high probability of remodeling, a number of recognized early predictors were used, including infarct location (anterior), magnitude of injury (high peak creatine kinase), poor systolic function (low EF), and extent of affected area (number of segments with WMA). However, the mean±SD biplane LVEDV remodeling response shown in the MENDMI patients (ICD, Δ11 mL±31 mL) was smaller than anticipated (Δ20 mL±25 mL) and may have reduced our ability to show an effect of preexcitation on this end point. Although pacing did not significantly prevent LV dilation at 1 year in MENDMI, in exploratory analysis there appeared to be a lasting benefit on global wall motion regardless of whether the pacing was on or off (Figure 3). In light of the negative primary findings, these findings also should be viewed with skepticism. There was a 5-minute delay between on and off measurements, and it is possible that the benefit may have dissipated with a longer delay. However, because WMA is a known post-MI risk factor for remodeling20,21 and mortality,22 it may be that with a longer follow-up, this theoretical benefit could be followed by an attenuation of deleterious remodeling.

It is possible that remodeling was not attenuated with PIZ pacing simply because this may not be an efficacious therapy to improve post-MI remodeling. It is also possible that the patients did not receive the intended preexcitation therapy. The recent work of Rademakers et al23 suggested that optimization of lead location, as well as AV and VV delay on a per-patient basis, may be necessary for optimal implementation of pacing therapies post-MI. Thus, although the device counters indicated a high percentage of LV pacing, the

<table>
<thead>
<tr>
<th>View and Measurement</th>
<th>Intraobserver</th>
<th>Interobserver</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>Biplane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>33</td>
<td>0.5±14.0</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>33</td>
<td>1.2±13.0</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>32</td>
<td>1.1±4.9</td>
</tr>
<tr>
<td>A4C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>33</td>
<td>1.4±14.6</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>33</td>
<td>0.1±12.4</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>30</td>
<td>0.9±5.4</td>
</tr>
<tr>
<td>A2C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>29</td>
<td>1.8±17.6</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>29</td>
<td>2.9±16.6</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>29</td>
<td>1.3±7.1</td>
</tr>
</tbody>
</table>
possibility of ineffective regional unloading due to fusion or pseudofusion with the tested therapy parameters cannot be ruled out.

There was a relatively low mortality rate (2.5%; 2/80 patients) at 1 year in MENDMI; however, the annual arrhythmic rate was 16% (13/80), which aligns with the event rates reported from trials like Multicenter Automatic Defibrillator Implantation Trial II (17% per year). Possible explanations for the low mortality include the high rates of revascularization, excellent care, and exclusion of early acute MI mortality (eg, in prehospital and in hospital mortality; MENDMI patients were enrolled at least 5–3 days after symptoms). In addition, the 3 patients who received defibrillation for true episodes of ventricular fibrillation before the 40 days post-MI may have been saved from death.

There was a nonstatistically significant trend for more adverse events and a lower composite therapy-related event-free rate in the therapy group that appears to be driven by LV lead issues. The control group did not receive LV leads, and the LV lead complication rate (11.9%) in the therapy group was not substantially higher than that found in other contemporary CRT trials, such as the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction trial (9.5%). In MENDMI, the implanting physicians were required to place the leads within 2 cm and were advised to use specific implantation routes. These implantation restrictions may have resulted in more-difficult lead placement and, hence, a slightly higher rate of related issues. Although these findings suggest that the placement of pacing leads near or in recent MIs may be feasible, it is worth pointing out that no adverse event rate is tolerable in the absence of therapy benefit and that the small trial size and short follow-up duration preclude a meaningful analysis of event rates.

Limitations
The present study had several limitations. First, although there were no noted baseline differences between the study groups, important determinants of LV remodeling, such as the success of revascularization (thrombolysis in myocardial infarction flow), the degree of target vessel restenosis, or occurrence of new coronary lesions during follow-up, were not assessed in this study and may have influenced the outcomes. Second, it is difficult to confirm that the patients received the intended preexcitation therapy; thus, it remains unclear whether regional unloading was insufficient in preventing post-MI remodeling. The large anterior MI inclusion criterion was designed to minimize the impact of lead placement because the RV and LV lead combination should “straddle” and preexcite an anterior infarct. Third, the use of echocardiography for LV volume measurements was not optimal given the inherent variability and technical pitfalls of the technique. However, this negative had to be balanced with

---

**Figure 3.** WMA. Average change in the wall motion score (A) and average change in the number of segments with a WMA (B) (hypokinetic, akinetic, or dyskinetic) are shown. Bars indicate the SEM. Although patients missing either preimplantation or 12-month echocardiographic images were excluded from the figure, patients with missing data at the interim follow-ups were included in A and B. For visual clarity, the CRT-OFF values are not shown. N indicates the number of patients at each follow-up. One-sample t test: #CRT \( P<0.05 \) versus preimplantation; ##CRT \( P<0.01 \) versus preimplantation; ###CRT \( P<0.001 \) versus preimplantation; *ICD \( P<0.05 \) versus preimplantation. Brackets indicate the \( P \) value for 2-sample t tests of the change in WMA score (A) or number of segments with WMA (B) from baseline for ICD versus CRT patients.

---

**Table 5. Therapy-Related Event-Free Rate**

<table>
<thead>
<tr>
<th></th>
<th>CRT-D (n=42)</th>
<th>ICD (n=38)</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pts With</strong></td>
<td><strong>Total</strong></td>
<td><strong>Event Free, %</strong></td>
<td><strong>Pts With</strong></td>
</tr>
<tr>
<td><strong>Events</strong></td>
<td><strong>Events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy-related events</td>
<td>22</td>
<td>29</td>
<td>47.6±20</td>
</tr>
<tr>
<td>Therapy delivery issues†</td>
<td>7</td>
<td>7</td>
<td>83.3±35</td>
</tr>
<tr>
<td>VT</td>
<td>3</td>
<td>3</td>
<td>92.9±39</td>
</tr>
<tr>
<td>Hospitalization, cardiac cause</td>
<td>15</td>
<td>18</td>
<td>64.3±27</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1</td>
<td>1</td>
<td>97.6±41</td>
</tr>
</tbody>
</table>

Data are presented as counts and mean±SD. VT indicates ventricular tachyarrhythmia.

*Fisher exact \( P \) value (CRT-D vs ICD event-free rate).

†LV lead dislodgement, postimplantation LV lead repositioning, or permanent failure to deliver biventricular pacing.
the advantages of universal access, relatively low cost, lack of radiation and contrast, and compatibility with implanted devices. The accuracy may have been enhanced with 3D echocardiography or the use of LV contrast, and ideally in the future, MRI may be used with compatible devices. Finally, because the primary end point of this study was not met, we must also be cautious about conclusions drawn from the subsequent WMA analysis. In this case, formal statistical determination of significance is not possible given that the primary end point was not positive and that these findings are merely exploratory and hypothesis generating. We must also be cautious when interpreting the safety measures because the small cohort sizes may have resulted in a lack of difference between the groups.

Conclusions
Chronic pacing in the infarct region did not alter the primary end point of LV remodeling over 1 year.

Acknowledgments
We thank all of the patients, investigators, research coordinators, and technicians who participated in the MENDMI. We also thank Laurie Vonderharr for assuring quality data collection and Lisa Thackery for statistical assistance.

Sources of Funding
This MENDMI study was supported by Boston Scientific Corporation.

Disclosures
Dr Chung has received research grants from Boston Scientific and Medtronic; has received fellowship support from Boston Scientific, Medtronic, and St Jude; has been on the speakers bureaus for Boston Scientific and Medtronic; and has served as consultant/advisory board member for Boston Scientific and Medtronic. Dr Solomon has received research grants from Boston Scientific and Medtronic, has been on the speakers bureaus for Boston Scientific and Medtronic, has received honoraria from Boston Scientific and Medtronic, and has served as consultant/advisory board member for Boston Scientific and Medtronic. Dr Pastore has ownership interest in and is employed by Boston Scientific. Dr Berger has received fellowship support from Boston Scientific, Medtronic, and St Jude; has served as expert witness for Boston Scientific and Medtronic; and has received fellowship support from Boston Scientific, Medtronic, and St Jude; has served as consultant/advisory board member for Boston Scientific and Medtronic. Dr Stolen has served on the speakers bureau for Sanofi and has received honoraria from Boston Scientific, Medtronic, and St Jude; has served as consultant/advisory board member for Boston Scientific and Medtronic; has received fellowship support from Boston Scientific, Medtronic, and St Jude; has served as consultant/advisory board member for Boston Scientific and Medtronic; has received research grants from Boston Scientific and Medtronic, and St Jude; has served as consultant/advisory board member for Boston Scientific and Medtronic. Dr Berger has received fellowship support from Boston Scientific, Medtronic, and St Jude; has served as expert witness for Boston Scientific and Medtronic; and has served as consultant/advisory board member for Boston Scientific and Medtronic. Dr Iyer has ownership interest in and is employed by Boston Scientific. Dr Pastore has ownership interest in and is employed by Boston Scientific. Dr Bank has served on the speakers bureaus for Boston Scientific and Medtronic, has received research grants from Boston Scientific and Medtronic, and has been on the speakers bureaus for Boston Scientific and Medtronic, has received honoraria from Boston Scientific and Medtronic, and has served as consultant/advisory board member for Boston Scientific and Medtronic. Dr Pastore has ownership interest in and is employed by Boston Scientific. Dr Berger has received fellowship support from Boston Scientific, Medtronic, and St Jude; has served as expert witness for Boston Scientific and Medtronic; and has served as consultant/advisory member for Boston Scientific. Dr Franklin has served on the speakers bureau for Medtronic, has received honoraria from Boston Scientific and Medtronic, and has ownership interest in Baylor Heart and Vascular Hospital. Dr Machado has received honoraria from Boston Scientific and Medtronic. Dr Stolen has served on the speakers bureau for Sanofi Aventis and has ownership in and is employed by Boston Scientific. Drs Dan and Jones report no conflicts.

References


---

**CLINICAL PERSPECTIVE**

Post-myocardial infarction, left ventricular dilation, and heart failure are major determinants of poor outcomes. During the early postinfarct phase (<1 month) in addition to timely revascularization, arrhythmia monitoring, antiplatelet and antilipid therapies, and neurohormonal modification, peri-infarct left ventricular pacing has been proposed as a method of attenuating the natural history of progression to heart failure. Animal studies and a preliminary clinical evaluation suggest potential benefit. In this randomized, multicenter pilot study, however, we found no clear salutary impact on left ventricular dilation with peri-infarct pacing at 12 months. Nonetheless, the therapy appeared safe, and there was a benefit noted in regional wall motion abnormalities. At this point, therefore, to further develop this line of therapy, a closer analysis of the data and refinement of the patient population, implantation technique, duration of follow-up, and end point are needed.
Effect of Peri-Infarct Pacing Early After Myocardial Infarction: Results of the Prevention of Myocardial Enlargement and Dilatation Post Myocardial Infarction Study

Circ Heart Fail. 2010;3:650-658; originally published online September 17, 2010;
doi: 10.1161/CIRCHEARTFAILURE.110.945881
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/3/6/650

Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2010/09/17/CIRCHEARTFAILURE.110.945881.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org/subscriptions/
Supplemental Material

MENDMI Investigators

D Dan, A Wickliffe, B Smith, C Kantipudi, T Deering, Piedmont Hospital; E Chung, E Schloss, M Gupta, S Menon, T Chow, Christ Hospital – Cincinnati; J Franklin, A Donsky, J Schussler, P Grayburn, R Stoler, Baylor University Medical Center – Dallas; C Machado, Providence Hospital: G Jones, A Rao, B Armstrong, D. Metzger, H Ladley, Wellmont Holston Valley Medical Center: R Augustini, E Daoud, J Hummel, R Weiss, S Kalbfleisch, Ohio State University Medical Center; S Compton, G Strobel, K Balaban, P Peterson, Alaska Heart Institute; A Leon, D Delurgio, F Mera, Emory Crawford Long Hospital; C Nydegger, K Rist, M Koslow, W Finneran, Reading Hospital and Medical Center; M Mollerus, G Litman, N Vanstrom, Saint Mary's Duluth Clinic; M Thompson, Carolina Heart Specialists; M Giudici, Genesis Medical Center; M Chisner, St. Joseph Hospital – Savannah; K Monahan, P Lelorier, Boston Medical Center; S Chough, M Nora, Good Samaritan Hospital - Downers Grove; D Mehta, M Kim, Mount Sinai Medical Center; G Greer, B Norris, Arkansas Cardiology; J Day, B Crandall, J Osborn, P Weiss, LDS Hospital; D Gohn, S Worley, T Sjapic, W Pilliam, Lancaster General Hospital; M Chang, Mercy General Hospital; S Bailin, A Chawla, D McAllister, L Iannone, M Ghali, M Tannenbaum, M Flemming, R Hoyt, W Johnson, Mercy Hospital Medical Center; V Gottipaty, J Beard, L Butterfiled, L Faulkner, M Foster, P Hall, P Zimmerman, Providence Hospital; A Strickberger, E. Platia, S O'Donoghue, Z Eldadah, Washington Hospital Center; R Mohama, Avera Heart Hospital, R John, B Hook, D Martin, F Parrella, G Michaud, Lahey Clinic Medical Center; E Powers, C Nielsen, L Sturdivant, M Gold, R Leman, Medical University of
South Carolina; B Crevey, A Yadav, J Miller, J Schutzman, J Szwed, M Das, Methodist Hospital of Indianapolis.

**Echocardiography Core Laboratory:**

St Paul Heart Clinic, St Paul, MN: Alan J. Bank and Kevin V. Burns.