Left Ventricular Remodeling and Ventricular Arrhythmias After Myocardial Infarction

Martin St John Sutton, FRCP; Douglas Lee, MD, PhD; Jean Lucien Rouleau, MD; Steven Goldman, MD; Ted Plappert, CVT; Eugene Braunwald, MD; Marc A. Pfeffer, MD, PhD

Background—The relation between left ventricular (LV) remodeling and ventricular arrhythmias after myocardial infarction is poorly documented. We investigated the relations between LV size, hypertrophy, and function and ventricular arrhythmias in 263 patients from the Survival and Ventricular Enlargement (SAVE) study, using quantitative 2D echocardiography and ambulatory ECG monitoring after myocardial infarction.

Methods and Results—Transthoracic 2D echocardiograms and arrhythmia monitoring were performed at baseline (mean, 11 days) and 1 and 2 years after infarction. LV size, short-axis muscle (mass) area (LVMA), and function were quantified from 2D echocardiograms. The prevalence of ventricular tachycardia (VT) and frequent ventricular ectopy (premature ventricular contractions [PVCs] >10/h) was assessed from ambulatory ECG. VT and PVCs >10/h occurred in 20% and 29% of patients at baseline, in 22% and 35% at 1 year and 23% and 39% at 2 years, respectively. VT and PVCs >10/h at baseline and 1 and 2 years were significantly related to LV size, LVMA, and function. Furthermore, changes in LV size and function from baseline to 2 years predicted both VT and PVCs >10/h. The study was underpowered to detect treatment effect of ACE inhibitors and β-adrenergic receptor blockers but did not alter the relations between ventricular arrhythmias, LV size, and function.

Conclusions—Quantitative echocardiographic assessment of LV size, LVMA, and function and changes in these measurements over time predict ventricular arrhythmias after infarction. Altered LV architecture and function during postinfarction LV remodeling provide an important substrate for triggering high-grade ventricular arrhythmias. (Circulation. 2003;107:2577-2582.)

Key Words: remodeling ▪ arrhythmia ▪ myocardial infarction ▪ echocardiography

Left ventricular (LV) remodeling after myocardial infarction is characterized by progressive dilation, hypertrophy, distortion of cavity shape, and deterioration in contractile function.1–4 Progressive LV dilation results from an imbalance between distending forces and the ability of the extracellular matrix to maintain the tensile strength of the infarct zone.5 Patients with more extensive LV remodeling are at greater risk for cardiovascular fatalities, including sudden death attributable to arrhythmias.6–8 Although ventricular arrhythmias are common in patients with LV dysfunction and congestive heart failure,9,10 the relation between LV remodeling and ventricular arrhythmias after acute myocardial infarction has not been explored systematically.11 Ventricular tachycardia is believed to be due to anisotropic reentry, consequent on slowed impulse propagation velocities through myocardium partially replaced by fibrosis,10,12–14 which typifies postinfarct remodeling myocardium. In addition, activation of plasma neurohormones after infarction15 provides a potential electrophysiological substrate for triggering ventricular arrhythmias.16 ACE inhibitor therapy has been associated with reduced incidence of sudden death after myocardial infarction17,18 and was used in half of this study population. Attenuation of LV remodeling, hypertrophy, and myocardial fibrosis by ACE inhibitor therapy19 may be a plausible mechanism for the reported favorable effect on ventricular arrhythmias after infarction.17,18

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The major aim of this study was to examine the relation between LV remodeling, specifically LV dilation, hypertrophy, and function and their changes over time on ventricular arrhythmias in patients after myocardial infarction with LV dysfunction followed up for a minimum of 2 years. A subsidiary aim was to determine whether ACE inhibitor

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Dr Pfeffer receives honoraria and/or educational research grants or serves as a consultant for Bristol-Myers Squibb. The Brigham and Women’s Hospital has been awarded a patent regarding the use of inhibitors of the renin-angiotensin system in selected survivors of myocardial infarction. Dr Pfeffer is among the co-inventors. The licensing agreement with Abbott and Novartis is not linked to sales.

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therapy or β-adrenergic receptor blockade was protective against ventricular arrhythmias.

Methods

The Survival and Ventricular Enlargement (SAVE) trial was a randomized, double-blind study designed to assess the effect of captopril versus placebo on survival in patients with acute myocardial infarction and left ventricular dysfunction (LV ejection fraction <40%). The echocardiographic substudy consisted of 512 patients. The Holter electrocardiographic substudy was conducted on 564 patients. Two hundred sixty-three patients participated in this prospective, combined echocardiographic and Holter study with evaluations at baseline (11±3 days) and 1 year and 2 years after infarction. The baseline demographics of these 263 patients (mean age, 60±11; 219 men) were representative of the overall SAVE population (Table 1).

Two-dimensional echocardiograms of the LV short axis were recorded from the left parasternal region at 3 levels: mitral valve and high and mid papillary muscle levels. The LV long axis was imaged from the apex in the 4-chamber, apical long-axis, and/or apical 2-chamber view. Echocardiographic images were digitized to obtain LV cavity areas at end-diastole and end-systole. LV size was defined as the sum of the average short-axis and the average long-axis cavity areas at end-diastole and end-systole, as described previously. LV function was assessed as the percent change in cavity area from end-diastole to end-systole divided by LV end-diastolic area. Epicardial and endocardial borders of the LV short axis images at high papillary muscle level were digitized to obtain LV myocardial areas (LVMA) at end-diastole. We used LVMA because distortion of LV shape and regional variation in wall thickness from myocardial infarction precluded calculation of LV mass, based on algorithms that assumed fixed cavity geometry and uniform wall thickness. These echocardiographic measurements were repeated at 1 and 2 years after infarction.

Twenty-four-hour Holter ambulatory ECG monitoring was recorded at baseline and 1 and 2 years. The mean time between echocardiograms and Holter monitoring was 11.1±3.4 days for the 3 studies. Holter recordings were analyzed with the use of commercially available software for detection of ventricular arrhythmias. Ventricular arrhythmias were defined as >10 premature ventricular contractions per hour (PVCs >10/h) and ventricular tachycardia (VT) as ≥3 consecutive ventricular contractions with a ventricular rate >100 beats/min.

Statistical Methods

The echocardiographic and arrhythmia assessments were performed in a double-blinded manner. We assessed the relations between ventricular arrhythmias (PVCs >10/h) and VT and echocardiographic measurements of LV size at end-diastole and end-systole, LVMA, and percent change in cavity area using logistic regression analysis for the whole study population and for the two treatment groups at baseline and 1 and 2 years after infarction. We illustrated these relations by dividing the study population into quintiles for each echocardiographic measurement. Logistic regression analysis was also used to assess the relation between ventricular arrhythmias (VT, PVCs) as the outcome variables and change in LV size, mass, and function from baseline to 1 and 2 years as the predictor variables.

The multivariate analysis included all risk factors with probability values of \( P < 0.15 \) in a backward stepwise logistic regression model. To determine the potential mechanism by which ACE inhibitor therapy or β-adrenergic receptor blockers affect ventricular arrhythmias, the interaction between risk factors and ACE inhibitor therapy with captopril was included in the model. The fit of the final model was assessed by the Hosmer-Lemeshow statistic. All tests were 2-sided, and probability values <0.05 were considered significant. All analyses were performed with the use of SAS software, release 6.12 (SAS Institute Inc).

Results

Demographics

Baseline demographics including sex, history of previous infarction, hypertension, diabetes, ejection fraction by radio-nuclide ventriculography, use of thrombolytic therapy, β-adrenergic receptor blockers, and antiarrhythmic agents and echocardiographic measurements of LV size, LVMA, and function were similar in the treatment groups and representative of the SAVE population (Table 1).

Prevalence of Ventricular Arrhythmias

PVCs >10/h occurred in 76 of 263 (29%) patients at baseline, 73 of 211 (35%) patients at 1 year, and 72 of 183 (39%) patients at 2 years (\( P = 0.067 \)). VT occurred in 53 of 263 (20%) patients at baseline, 46 of 211 (22%) at 1 year, and 42 of 183 (23%) at 2 years (\( P = 0.228 \)).

LV Size and Ventricular Arrhythmias

There were significant relations between LV end-diastolic size and PVCs >10/h (\( P < 0.0001 \)) at baseline and between LV end-systolic size and PVCs >10/h at baseline (\( P < 0.0001 \)). Relations between LV size and PVCs >10/h

### Table 1. Baseline Demographics and Echocardiographic Variables in the Total Study Population and in the Placebo and Captopril Treatment Groups

<table>
<thead>
<tr>
<th>Baseline Demographic, Clinical, and Echo/Holter Variable</th>
<th>Echo/Holter All Patients (n=263)</th>
<th>Placebo Group (n=129)</th>
<th>Captopril Group (n=134)</th>
<th>Captopril vs Placebo P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60±11</td>
<td>59±11</td>
<td>60±10</td>
<td>0.283</td>
</tr>
<tr>
<td>Male patients, n (%)</td>
<td>219 (83)</td>
<td>102 (79)</td>
<td>117 (87)</td>
<td>0.073</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>82 (31)</td>
<td>44 (34)</td>
<td>38 (28)</td>
<td>0.314</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>47 (18)</td>
<td>23 (18)</td>
<td>24 (18)</td>
<td>0.986</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>86 (33)</td>
<td>38 (29)</td>
<td>48 (36)</td>
<td>0.271</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>31±7</td>
<td>31±7</td>
<td>31±6</td>
<td>0.618</td>
</tr>
<tr>
<td>Thrombolysis, n (%)</td>
<td>101 (38)</td>
<td>44 (34)</td>
<td>57 (43)</td>
<td>0.160</td>
</tr>
<tr>
<td>Average LV mass index</td>
<td>24.5±4.4</td>
<td>24.6±4.6</td>
<td>24.4±4.3</td>
<td>0.633</td>
</tr>
<tr>
<td>Combined axis cavity area (diastolic)</td>
<td>69.4±12.2</td>
<td>69.8±12.7</td>
<td>69.0±11.8</td>
<td>0.583</td>
</tr>
<tr>
<td>Combined axis cavity area (systolic)</td>
<td>49.6±11.8</td>
<td>50.2±12.2</td>
<td>48.9±11.4</td>
<td>0.370</td>
</tr>
<tr>
<td>Antiarrhythmic drug therapy, n (%)</td>
<td>26 (10)</td>
<td>10 (8)</td>
<td>16 (12)</td>
<td>0.255</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>37.6</td>
<td>35.7</td>
<td>39.6</td>
<td>0.515</td>
</tr>
</tbody>
</table>
were also demonstrated at 1 year ($P < 0.0012; P < 0.0002$) and 2 years after infarction ($P < 0.0002; P < 0.0001$), respectively. When the population was divided into quintiles by end-diastolic or end-systolic LV size, the prevalence of PVCs 10/h increased progressively from quintile 1 through 5 at baseline (Figure 1) and at 1 and 2 years after infarction (Figure 1).

There were significant relations between LV end-diastolic size and VT ($P < 0.013$) and between LV end-systolic size and VT ($P = 0.0017$) at baseline and at 1 year ($P = 0.0002; P < 0.0001$) and 2 years ($P < 0.0001; P < 0.0001$) after infarction. Quintile analysis demonstrated that the prevalence of VT increased with end-diastolic and end-systolic LV size at all time points.

**LVMA and Ventricular Arrhythmias**

Significant relations were demonstrated between LVMA and PVCs 10/h at baseline ($P = 0.0001$) and 1 year ($P = 0.0023$) and 2 years ($P = 0.038$). Similar relations were demonstrated between LVMA and VT at baseline ($P = 0.0011$) and 1 year ($P = 0.0030$) and 2 years ($P = 0.0468$) after infarction. When the patient cohort was divided into quintiles, PVCs 10/h and VT both increased progressively with LVMA after infarction (Figure 3).

**LV Function and Ventricular Arrhythmias**

LV function (% change in cavity area) was inversely related to PVCs 10/h ($P < 0.0001$) and VT ($P < 0.0001$) at baseline and at 1 year (both $P < 0.0001$) and 2 years (both $P < 0.0001$). When the study population was divided into quintiles by percent change in cavity area, the prevalence of PVCs 10/h and VT increased progressively with decreasing LV function at all time points after infarction (Figure 4).

**Multivariate Analysis of LV Size, Function, and Ventricular Arrhythmias**

When the echocardiographic measurements were considered together in a multivariate analysis, LV function (% change in cavity area) was most closely associated with PVCs 10/h and VT (both $P < 0.0001$ at baseline and at 1 and 2 years) (Table 2). LVMA was closely associated with PVCs 10/h and VT at baseline ($P < 0.001; P = 0.02$) and at 1 year ($P = 0.03$), whereas LV size was related to VT at 2 years after infarction ($P < 0.0001$) (Table 2). Adjusted odds ratios for variables significant on multivariate analysis are shown per 5-U increment for each measure (Table 2).

**Effect of Changes in LV Size and Function on Ventricular Arrhythmias**

There were significantly larger increases in both LV systolic and diastolic cavity areas in patients with increased frequency of PVCs 10/h at 2 years than in those without PVCs ($P < 0.05$) (Table 3). Similarly, patients with VT at 2 years had larger increases in systolic and diastolic cavity areas compared with patients without VT (both $P < 0.0001$), and they had greater reduction in LV function (% change in LV area; $P < 0.001$) (Table 3).
Effect of ACE Inhibitor Therapy and \( \beta \)-Blockers on Ventricular Arrhythmias

There was no evidence that ACE inhibitor therapy reduced ventricular ectopy or VT, although the power to detect an effect on VT at 1 year was only 50%. The prevalence of (PVCs \( \geq 10/h \)) in patients treated with ACE inhibitor therapy was similar to placebo at baseline (24% versus 34%, \( P=0.067 \)), at 1 year (31% versus 38%, \( P=0.33 \)), and at 2 years (45% versus 34%, \( P=0.129 \)). The prevalence of VT in the captopril-treated group was not different from the placebo group (17% versus 23%, \( P=0.218 \), at baseline; 17% versus 27%, \( P=0.064 \), at 1 year; and 19% versus 27%, \( P=0.209 \), at 2 years after infarction).

Antiarrhythmic drug (AAD) use at random assignment was not different between the placebo and captopril groups (10/129 versus 16/134; \( P=0.255 \)). There were 5 cardiovascular deaths in the AAD and 31 deaths in the non-AAD groups (19.2% versus 13.1%; \( P=0.39 \)). The use of AADs did not have a significant effect on the prevalence of PVCs or VT.

### TABLE 2. Multivariate Predictors of PVCs \( \geq 10/h \) and VT: Percent Change in LV Area, LVMA, and LV Diastolic Cavity Area as Odds Ratios With 95% Confidence Intervals

<table>
<thead>
<tr>
<th></th>
<th>PVCs ( \geq 10/h ) OR (95% CI), ( P )</th>
<th>VT OR (95% CI), ( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMA</td>
<td>1.96 (1.41, 2.78), ( P&lt;0.001 )</td>
<td>1.49 (1.06, 2.11), ( P&lt;0.05 )</td>
</tr>
<tr>
<td>Percent change in LV area</td>
<td>0.56 (0.42, 0.74), ( P&lt;0.001 )</td>
<td>0.61 (0.45, 0.81), ( P&lt;0.001 )</td>
</tr>
<tr>
<td>1 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMA</td>
<td>1.44 (1.06, 2.00), ( P&lt;0.05 )</td>
<td></td>
</tr>
<tr>
<td>Percent change in LV area</td>
<td>0.70 (0.56, 0.86), ( P=0.001 )</td>
<td>0.60 (0.46, 0.76), ( P&lt;0.001 )</td>
</tr>
<tr>
<td>2 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined axis cavity, diastolic</td>
<td>...</td>
<td>1.50 (1.29, 1.77), ( P&lt;0.001 )</td>
</tr>
<tr>
<td>Percent change in LV area</td>
<td>0.60 (0.49, 0.74), ( P&lt;0.001 )</td>
<td></td>
</tr>
</tbody>
</table>
not affect the relations between VT and LV size or function or between PVCs and LV size or function.

Thirty-seven percent of patients were taking β-adrenergic receptor blockers. With the use of the Cochran-Armitage trend test ($P = 0.528$), there was no difference between the proportion of patients taking β-blockers across the quintiles. Adjusting for baseline use of β-blocker therapy did not modify the prevalence of PVCs or VT.

**Discussion**

LV remodeling is associated with cavity dilation in approximately one third to one half of survivors of acute myocardial infarction with contractile dysfunction. Progressive LV dilation increases systolic and diastolic wall stresses, which activate cell surface mechanoreceptors that initiate intracellular signaling for myocyte hypertrophy and modulate the activity of matrix metalloproteinases, neurohormones, and local tropic factors. The extent of LV dilation after myocardial infarction is an important determinant of risk for major adverse cardiovascular events including ventricular arrhythmias, heart failure, and death.

Ventricular arrhythmias were frequent after infarction. VT occurred in 20% to 23% between baseline and 2 years. PVCs $>10/h$ increased from 29% at baseline to 39% at 2 years. We demonstrated significant relations between LV end-diastolic and end-systolic size and VT and between LV size and PVCs $>10/h$ early after infarction. Similar relations were present at 1 year and at 2 years after infarction. Division of the study population into quintiles by LV end-diastolic and end-systolic size showed a stepwise increase both in VT and PVCs $>10/h$ with increasing LV size up to 2 years after infarction (Figures 1 and 2). The important predictive value of echocardiographic measurements of LV size in patients after infarction has been reported for heart failure and recurrent infarction but not for ventricular arrhythmias.

Ventricular tachycardia is believed to be due to anisotropic reentry, consequent on slowed impulse propagation velocities through myocardium partially replaced by fibrosis. The abnormal variability in impulse velocity and potential substrate for reentrant circuits may be facilitated in hearts undergoing progressive dilation in which there is dynamic imbalance between distending forces and the stretch-resistant extracellular collagen scaffold during postinfarction LV remodeling. This propensity may be amplified by elevated plasma levels of adrenergic neurohormones after infarction.

We demonstrated significant relations between LVMA, which we used as a surrogate for LV mass, and VT and between LVMA and frequent ventricular ectopy in the early postinfarction period. Similarly, relations between LVMA, VT, and frequent ectopy (PVCs $>10/h$) were present at 1 year and 2 years after infarction. In addition, there was a greater preponderance of ventricular arrhythmias in those with the largest LV mass. The relation between increased LV mass, ventricular ectopy, and adverse cardiovascular events was recognized initially in the Framingham study. Subsequently, LV hypertrophy caused by aortic stenosis, hypertension, and obstructive cardiomyopathy has been associated with ventricular arrhythmias. The mechanism for ventricular arrhythmias associated with increased LV mass is complex, but important etiologic factors include the combination of patchy subendocardial fibrosis, increased calcium-dependent slow inward current, altered kinetics of the outward potassium current, and altered repolarization time of hypertrophied myocardium.

There were significant inverse relations between LV function (% change in LV cavity area) and VT and between LV function and PVCs $>10/h$ in the early postinfarction period and at 1- and 2-year follow-up. The majority of ventricular arrhythmias occurred in patients in the lowest quintile for percent change in cavity area, with the most severe LV dysfunction at each time point studied. In patients with heart failure, ventricular arrhythmias are a common mode of death and predominate in patients with the most severe LV systolic dysfunction. Multivariate analysis identified LV function as the echocardiographic parameter most closely associated with ventricular arrhythmias.

There was a significantly greater increase in systolic and diastolic LV size from baseline to 2 years in patients with increased frequency of PVCs $>10/h$ at 2 years. In addition, patients with VT had significantly larger increases in LV systolic and diastolic cavity areas from baseline to 2 years compared with patients with no VT. Furthermore, there was a greater reduction in LV function (% change in LV area) in patients who had VT at 2 years (Table 3). Thus, the presence of ventricular arrhythmias was associated with progressive LV dilation and deteriorating function during postinfarction remodeling.

In this study, ACE inhibitor therapy did not have a detectable impact on the incidence of VT or PVCs $>10/h$ compared with placebo, concordant with several previous studies. This was not explained by any difference in use of antiarrhythmic agents among the treatment groups but probably reflected the small size of our patient cohort, which had only 50% power to detect an effect on VT at 1 year. A meta-analysis of several large postinfarction trials was required.
before a significant benefit of ACE inhibitor therapy on sudden arrhythmic death was demonstrated.17 Similarly, therapy with β-adrenergic receptor blockers, used in more than one third of our patients, had no significant effect on the prevalence of ventricular tachycardia or ventricular ectopic activity. However, since both of these agents have been shown to attenuate LV hypertrophy and remodeling, this favorable modification of ventricular structure and function may in the long term reduce the propensity for ventricular arrhythmias.

One potential limitation of our study is the absence of information describing the effect of LV shape on ventricular arrhythmias during postinfarction remodeling. Although LV size and function can be quantified in ventricles with abnormal regional wall motion, there is no consensus regarding the optimal descriptor of LV cavity shape. The most frequently used shape index, the ratio of LV short axis and long axis, is not representative of distorted postinfarction ventricles.

Our study, using serial quantitative echocardiography and ambulatory ECG monitoring, demonstrates striking relations between LV topography, function, and ventricular arrhythmias during ventricular remodeling for up to 2 years after infarction. This analysis of the long-term consequences of remodeling and arrhythmias cannot exclude survivor bias. In our prior work, patients undergoing the greatest remodeling are more likely to be nonsurvivors.19 However, we have constructed our data relating LV structure and function and changes therein to the propensity for arrhythmias at baseline and 1 year and 2 years and have found consistent relations in each evaluation. This study provides quantitative support for the concept that postinfarction LV remodeling is an important substrate for triggering ventricular arrhythmias.

Acknowledgments

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References

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