Ventricular Remodeling Does Not Accompany the Development of Heart Failure in Diabetic Patients After Myocardial Infarction

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Background—Diabetic patients are at increased risk for heart failure (HF) and other adverse events after myocardial infarction (MI). Left ventricular (LV) enlargement after MI is also associated with the same increased risk. We used data from the Survival and Ventricular Enlargement (SAVE) echocardiographic substudy to test the hypothesis that diabetes was associated with increased LV enlargement after MI.

Methods and Results—Four hundred twelve nondiabetic and 100 diabetic patients underwent echocardiographic assessment at baseline and 3 months, 1 year, and 2 years after MI. HF developed in 30% of diabetic and 17% of nondiabetic patients during follow-up ($P<0.001$). Baseline LV diastolic size, ejection fraction, and infarct segment length were similar between diabetic and nondiabetic patients. Diabetic patients demonstrated less LV enlargement between baseline and 2 years than nondiabetic patients (0.9±11.1 cm$^2$ versus 3.8±10.9 cm$^2$, $P=0.047$). In patients who developed HF, LV diastolic dilatation (10.0±12.4 cm$^2$ versus 3.7±13.1 cm$^2$, $P=0.06$) and systolic dilatation (4.6±11.8 versus 0.91±12.1, $P=0.017$) were greater in nondiabetic than in diabetic patients. LV dilatation between baseline and 2 years was a predictor of HF in nondiabetic patients, but not in diabetic patients, even after excluding patients with recurrent MI and adjusting for history of hypertension, prior MI, age, treatment group, and smoking. Diabetes modified the relationship between ventricular enlargement and the risk of HF ($P=0.011$).

Conclusions—The increased incidence of HF after MI in diabetic patients is not explained by a greater propensity for LV remodeling. (Circulation. 2002;106:1251-1255.)

Key Words: diabetes mellitus ■ heart failure ■ remodeling ■ myocardial infarction

Patients with diabetes are at increased risk for the development of cardiovascular diseases and death from cardiovascular causes. In addition, diabetes is associated with a variety of cardiac alterations, including left ventricular (LV) hypertrophy and reduced systolic and diastolic function. After myocardial infarction (MI), diabetic patients are at increased risk for adverse events, including death, recurrent MI, and heart failure (HF). LV remodeling—as indicated by LV enlargement—is also associated with an increased risk of the same adverse events after MI. Remodeling after MI is a heterogeneous process and is influenced by a variety of factors, including infarct size, coronary reperfusion, and ACE inhibitor therapy, and has been thought to represent an important component in the progression to HF in patients after MI. We studied patients enrolled in the Survival and Ventricular Enlargement (SAVE) study to test the hypothesis that the increased incidence of HF in diabetic patients after MI was associated with a greater propensity for LV enlargement or remodeling.

Methods

Patients

The Survival And Ventricular Enlargement (SAVE) trial enrolled 2231 patients with LV dysfunction (ejection fraction ≤40%) after MI and randomized these patients to receive either captopril or placebo. Patients enrolled in the echocardiographic substudy (n=512) underwent two-dimensional echocardiography at a mean of 11.1±3.2 days after MI (baseline) and again at 3 months, 1 year (n=426), and 2 years after MI (n=387). Echocardiograms from baseline, 1 year, and 2 years were analyzed in all patients; echocardiograms at 3 months were only analyzed in patients who died before the subsequent study. The demographics of the echocardiographic participants were similar to the overall study group. Diabetic patients comprised 22% of the entire study cohort and 19.5% of the echocardiographic cohort at baseline (n=512), as assessed at the...
TABLE 1. Baseline Characteristics of Diabetic and Nondiabetic Patients

<table>
<thead>
<tr>
<th></th>
<th>Entire Cohort (n=412)</th>
<th>Diabetic Patients (n=100)</th>
<th>P</th>
<th>Nondiabetic Patients (n=316)</th>
<th>Diabetic Patients (n=71)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.0±11.5</td>
<td>60.9±9.5</td>
<td>0.020</td>
<td>56.9±11.5</td>
<td>60.5±8.7</td>
<td>0.015</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>84</td>
<td>70</td>
<td>0.001</td>
<td>83</td>
<td>72</td>
<td>0.027</td>
</tr>
<tr>
<td>Killip class &gt;1, %</td>
<td>33</td>
<td>42</td>
<td>0.12</td>
<td>33</td>
<td>37</td>
<td>0.51</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>27.9</td>
<td>49.0</td>
<td>&lt;0.0001</td>
<td>25.6</td>
<td>46.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>111±14.3</td>
<td>116±17.0</td>
<td>0.001</td>
<td>110±13.4</td>
<td>115±16.0</td>
<td>0.006</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70±9</td>
<td>70±9</td>
<td>0.98</td>
<td>69±10</td>
<td>70±10</td>
<td>0.73</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>76±13</td>
<td>79±15</td>
<td>0.040</td>
<td>74±12</td>
<td>78±16</td>
<td>0.020</td>
</tr>
<tr>
<td>Active therapy, %</td>
<td>51</td>
<td>44</td>
<td>0.23</td>
<td>50</td>
<td>40.9</td>
<td>0.16</td>
</tr>
<tr>
<td>β-Blocker use at baseline, %</td>
<td>18.4</td>
<td>17.5</td>
<td>0.85</td>
<td>14.9</td>
<td>18.6</td>
<td>0.45</td>
</tr>
<tr>
<td>Diuretic use at baseline, %</td>
<td>17.4</td>
<td>30.5</td>
<td>0.004</td>
<td>12.7</td>
<td>21.7</td>
<td>0.054</td>
</tr>
<tr>
<td>Digitalis use at baseline, %</td>
<td>6.9</td>
<td>16.8</td>
<td>0.002</td>
<td>4.4</td>
<td>11.6</td>
<td>0.020</td>
</tr>
<tr>
<td>Combined diastolic area, cm²</td>
<td>71.3±12.5</td>
<td>70.5±12.8</td>
<td>0.58</td>
<td>69.8±11.4</td>
<td>69.0±13.1</td>
<td>0.60</td>
</tr>
<tr>
<td>Combined systolic area, cm²</td>
<td>51.4±12.3</td>
<td>51.6±12.7</td>
<td>0.88</td>
<td>49.7±10.7</td>
<td>49.6±12.9</td>
<td>0.97</td>
</tr>
<tr>
<td>Infarct segment length, %</td>
<td>34±11</td>
<td>33±13</td>
<td>0.39</td>
<td>33.0±10.4</td>
<td>36.0±12.6</td>
<td>0.094</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>35.4</td>
<td>34.7</td>
<td>0.42</td>
<td>31.8</td>
<td>31.1</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Clinical and Outcome Measures

The development of HF was defined as either hospitalization for HF (as indicated on a case-report form by the site investigator as being the primary reason for hospitalization) or a clinical diagnosis of HF determined by the patient’s physician to be of sufficient severity to require discontinuation of study medication and placement on open-label ACE inhibitor. Concomitant medication usage on follow-up was assessed by reviewing medication usage at each follow-up visit and determining the percentage of visits in which patients were taking various concomitant medications.

Results

HF developed in 30% of diabetic compared with 17% of nondiabetic patients (P<0.001) enrolled in the echo cohort, proportions that were similar in the entire study cohort. In patients who survived to the 2-year echocardiogram (n=387), HF developed in 29.6% of diabetic and 13.9% of nondiabetic patients (P=0.001). Diabetic patients were slightly older and more likely to be female (Table 1). Baseline systolic blood pressure and heart rate were slightly higher in diabetic patients. Whereas diuretic and digitalis use was higher in diabetic patients at baseline and on follow-up visits, use of β-blocker therapy was similar in both groups at baseline and during the follow-up period. Importantly, baseline echocardiographic determination of LV areas, infarct segment length, and ejection fractions showed no difference between diabetic and nondiabetic patients.

Two-year echocardiograms were performed in 387 patients, 316 nondiabetic and 71 diabetic (Table 2). LV diastolic area increased to a greater extent in nondiabetic than in diabetic patients over 2 years (Table 2; P=0.047). Ejection fraction remained similar in the diabetic and nondiabetic groups at 2 years.

The 65 patients who developed HF at any time during follow-up demonstrated increased diastolic enlargement (Table 2). Diastolic LV enlargement was greater in nondiabetic patients who developed HF (n=44) compared with diabetic patients (n=21) who developed HF (10.1±12.4 versus 3.7±13.1, P=0.062). Changes in systolic enlargement paralleled changes in diastolic enlargement, with significantly greater systolic enlargement in nondiabetic compared with diabetic patients (12.5±13.4 versus 4.4±13.7, P=0.027).

Whereas ejection fraction at 2 years was significantly reduced in patients who developed HF compared with patients who did not develop HF (27.0±8.5% versus 36.0±10.3%, P<0.0001), the ejection fraction among diabetic patients who...
developed HF was higher than in nondiabetic patients who developed HF (31.2±10.1% versus 25.1±7.0%, \(P=0.007\)).

To determine whether dilatation represented an important intermediate in the development of HF, we assessed the relationship between dilatation during the first 2 years of MI and the subsequent risk of developing HF. During follow-up, 37 patients developed HF within the first 2 years and 28 patients developed HF subsequently. Nondiabetic and diabetic patients who subsequently developed HF were similar with respect to baseline ventricular size (73.6±11.4 cm\(^2\) versus 68.0±16.9 cm\(^2\), respectively, \(P=0.32\)). Nondiabetic patients who developed HF after 2 years demonstrated an 11.0±12.4 cm\(^2\) increase in diastolic cavity area over the first 2 years compared with a -2.9±13.2 cm\(^2\) decrease in cavity area in diabetic patients (Figure; \(P=0.018\)). In a Cox proportional hazards analysis, dilatation by 2 years was predictive of subsequent HF in the nondiabetic group (\(P=0.001\)) but not in the diabetic group (\(P=0.85\), even after adjusting for history of hypertension, prior myocardial infarction, age, treatment group, and history of smoking, diuretic, and digoxin use and after excluding patients with recurrent myocardial infarction before the development of HF. The development of HF was modified by the presence of diabetes, with a significant interaction between diabetes and ventricular enlargement in the development of subsequent HF (\(P=0.011\)).

To clarify the effect of diastolic function and LV compliance in this population, we assessed E/A ratios and average wall thickness in diabetic compared with nondiabetic patients at baseline, 1-year, and 2-year echocardiograms. E/A ratios were slightly higher in diabetic patients only at baseline (1.46±0.81 versus 1.23±0.63, \(P=0.037\)), whereas absolute E/A ratios were similar at subsequent examinations. The proportions of diabetic and nondiabetic patients in each of 3 E/A ratio categories were similar at all time points. Diabetic patients, but not nondiabetic patients, in the highest E/A category (E/A >1.5) were more likely to develop HF (OR, 6.9; 95% CI, 2.1 to 22.5). Wall thickness, similar between the 2 groups at baseline (diabetic, 1.20±0.16 cm versus nondiabetic, 1.17±0.15 cm, \(P=0.10\)), was minimally increased in diabetic patients at 1 year (1.20±0.15 versus 1.15±0.15, \(P=0.019\)) and 2 years (1.21±0.19 versus 1.17±0.15, \(P=0.04\)).

Because mortality before the second-year echo was higher in diabetic than in nondiabetic patients (27% versus 18%), we assessed the effect of survivor bias on our results by comparing LV area on the last available echocardiographic study (3-month or 1-year echocardiograms) in patients who died or did not have the 2-year follow-up study. In the small number of patients who did not have the 2-year echocardiogram, there were no differences between those who were diabetic and nondiabetic in the degree of ventricular dilatation from baseline to each of these time points (Table 3), arguing against increased dilatation in diabetic patients who did not have the 2-year echocardiogram.

### Discussion

Patients with diabetes are at increased risk for the development of atherosclerosis and the progression to end-stage heart disease. While initially at increased risk for developing MI, patients with diabetes have a higher subsequent risk of developing HF.\(^{14}\) In the SAVE echocardiographic cohort, baseline demographic and echocardiographic assessments did not explain the increased propensity to develop HF in diabetic patients. The results of this study suggest that although HF develops at twice the rate in diabetic than in nondiabetic patients after MI, and although the development of HF is associated with increased ventricular enlargement in both groups, the incidence and extent of LV enlargement are significantly less in the diabetic patient. Thus, the increased incidence of HF after MI in patients with diabetes cannot be explained by an increased propensity for LV enlargement.

### TABLE 2. Echocardiographic Features at Baseline and 2 Years in Nondiabetic and Diabetic Patients

<table>
<thead>
<tr>
<th>Feature</th>
<th>Nondiabetic Patients</th>
<th>Diabetic Patients</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Year diastolic area, cm(^2)</td>
<td>73.6±14.4</td>
<td>69.9±16.5</td>
<td>0.058</td>
</tr>
<tr>
<td>2-Year systolic area, cm(^2)</td>
<td>54.3±15.7</td>
<td>50.6±18.0</td>
<td>0.075</td>
</tr>
<tr>
<td>2-Year infarct perimeter, %</td>
<td>37±15</td>
<td>35±19</td>
<td>0.34</td>
</tr>
<tr>
<td>2-Year ejection fraction, %</td>
<td>34.0</td>
<td>36.9</td>
<td>0.038</td>
</tr>
<tr>
<td>LV diastolic enlargement from baseline to 2 y, cm(^2)</td>
<td>3.8±11.0</td>
<td>0.94±11.2</td>
<td>0.047</td>
</tr>
<tr>
<td>LV diastolic area at baseline in patients who developed HF, cm(^2)</td>
<td>78.5±16.6 (n=71)</td>
<td>74.2±2.3 (n=30)</td>
<td>0.20</td>
</tr>
<tr>
<td>LV diastolic area at baseline in patients who developed HF, cm(^2)</td>
<td>10.1±12.4 (n=44)</td>
<td>3.7±13.1 (n=21)</td>
<td>0.062</td>
</tr>
<tr>
<td>LV systolic area at baseline in patients who developed HF, cm(^2)</td>
<td>12.5±13.4 (n=44)</td>
<td>4.4±13.7 (n=21)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Relation between change in LV combined end-diastolic area between baseline and 2 years in nondiabetic and diabetic patients and development of HF after 2 years.
Diabetes is associated with a variety of ultrastructural changes in the myocardium. This so-called diabetic cardiomyopathy is characterized by increased myocardial fibrosis, LV hypertrophy, and increased collagen content. The increased collagen accumulation in the diabetic myocardium has been linked to alterations in both diastolic and systolic function. In addition, recent evidence suggests that both hyperglycemia and insulin resistance may contribute to adverse myocardial metabolism, resulting in abnormal systolic and diastolic function.

Although diabetes is well established to impact survival adversely after MI, there is relatively little known about the effects of diabetes on post-MI ventricular remodeling. Although remodeling is itself a complex process involving changes in ventricular size, shape, and mass, ventricular enlargement has been routinely used as a surrogate for changes that accompany active remodeling. One small study of 49 patients after MI suggested worsening of ventricular function and increased ventricular dilatation in diabetic compared with nondiabetic patients, whereas another study of 100 patients found no significant differences in the extent of ventricular enlargement after MI in diabetic compared with nondiabetic patients.

Our data suggest that after MI, diabetes was not associated with greater ventricular enlargement despite an increased incidence of HF. The observation that baseline infarct segment length and ejection fraction were similar in nondiabetic and diabetic patients suggests that the higher risk of HF in diabetic patients was not simply the result of larger infarcts. Likewise, recurrent myocardial infarction, more frequent in diabetic patients in our population, also did not account for the observed increased risk of HF in this group.

Although abnormalities of systolic function occur in people with diabetes, substantial evidence implicates diastolic dysfunction as a primary abnormality in these patients and a potential explanation for the alterations in ventricular remodeling that is observed. Diastolic abnormalities have been attributed to both increases in myocardial collagen content and to abnormalities of calcium handling and contribute to the increased risk for HF among diabetic patients in large epidemiologic studies.

In the present study, systolic function was similar in diabetic and nondiabetic patients at baseline and at 2 years, suggesting that progressive systolic dysfunction could not account for the increased incidence of HF. These findings are consistent with those of the GUSTO-I trial, in which early systolic function (up to day 7) was worse in diabetic patients despite a significantly higher mortality. In addition, a higher proportion of diabetic than nondiabetic patients had a history of hypertension or were receiving antihypertensive therapy at baseline, although these findings could not explain the decreased remodeling seen in diabetic patients. We also observed slightly greater LV wall thickness in diabetic patients on follow-up, which in the setting of decreased overall ventricular size may be associated with higher relative wall thickness and thus higher filling pressures. Furthermore, diabetic patients in the highest E/A ratio category—which may include patients with so-called “restrictive” filling—were more likely to develop HF, raising the possibility that restrictive physiology may be part of the diabetic cardiomyopathic process. Taken together, these data support a possible increased predisposition to diastolic dysfunction in the diabetic group.

LV enlargement occurs as a pathophysiologic adaptation to the loss of stroke volume after MI. Although the geometric changes that accompany active remodeling result in improved stroke volume, this adaptation is nevertheless associated with an increased risk of adverse events and death after MI. The finding that diabetic patients may develop HF with less enlargement than nondiabetic patients is contrary to the established notion that ventricular enlargement represents an intermediate step in the development of HF in all patients. These data suggest that the diabetic heart may be less capable of adapting to the loss of stroke volume by dilating than the nondiabetic heart and thus may be less able to restore stroke volume after MI. A decreased ability to remodel in the diabetic patient would likely be associated with increased filling pressures compared with a nondiabetic patient with the same degree of contractile loss. This hypothesis is supported by the finding that in a subset of the SAVE population, N-terminal proatrial natriuretic factor was higher in diabetic than in nondiabetic patients. Our data support the concept that the decreased extent and incidence of ventricular enlargement in diabetic patients may contribute to the greater propensity to develop symptomatic HF in this population.

The SAVE trial demonstrated that the ACE inhibitor captopril could reduce mortality and development of HF and attenuate ventricular enlargement in patients with LV dysfunction after MI. ACE inhibitors have been shown to be equally effective in diabetic and nondiabetic patients. In the present study, the relationship between diabetes and enlargement was comparable regardless of treatment assignment.

**Limitations**

Although the observation of decreased ventricular enlargement in the diabetic group was observed in both patients who survived and patients who died, it is possible that ventricular...
enlargement could have occurred as a preterminal event and could have been missed by an earlier echocardiogram. Likewise, although we excluded in our analysis patients who developed HF after recurrent MI, we cannot rigorously exclude the possibility that ischemia may have contributed to the development of HF in the diabetic patients. In addition, this was not a prespecified analysis, and the number of diabetics who developed HF in the echo substudy was relatively small; these results should therefore be confirmed prospectively among larger numbers of patients.

Conclusion
The results of this study suggest that after MI, patients with diabetes demonstrate less LV enlargement than patients without diabetes, and that diabetic patients who develop HF do so after less ventricular enlargement. These data suggest that diabetic patients may have a decreased capacity to remodel the left ventricle after MI and therefore develop HF that diabetic patients may have a decreased capacity to remodel the left ventricle after MI and therefore develop HF.

References
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Circulation. 2002;106:1251-1255; originally published online August 19, 2002; doi: 10.1161/01.CIR.0000032313.82552.E3
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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