Left Ventricular Remodeling and Heart Failure in Diabetic Patients Treated With Primary Angioplasty for Acute Myocardial Infarction

Nazario Carrabba, MD; Renato Valenti, MD; Guido Parodi, MD; Giovanni M. Santoro, MD; David Antoniucci, MD

Background—Diabetes mellitus has been recognized as a strong predictor of heart failure (HF) in patients with acute myocardial infarction (AMI). However, considerable controversy exists regarding the pathogenetic mechanisms of HF after AMI in diabetic patients. We hypothesized that the increased incidence of HF in diabetic patients was associated with a greater propensity for left ventricular (LV) remodeling.

Methods and Results—A series of 325 patients (42 diabetics) with AMI successfully treated with primary angioplasty underwent serial 2D echocardiography from admission to 1 and 6 months and 6-month angiography. No significant difference was found between diabetics and nondiabetics regarding baseline clinical, angiographic, and echocardiographic characteristics, as well as 6-month restenosis and reocclusion rates. At 6 months, a similar incidence of LV remodeling was observed in diabetics and nondiabetics (33% versus 25%; P=0.234), with similar patterns of changes in LV volumes and LV global and regional systolic function. At 5 years, the incidence of HF was higher in the diabetics (43% versus 20%, P=0.001). Diabetes was found to be an independent predictor of HF at 5 years (hazard ratio, 1.8; P=0.0366). However, LV remodeling was predictive of HF in the nondiabetics (P=0.023) but not in the diabetics (P=0.123). In a subgroup of patients, higher LV chamber stiffness (as assessed by echocardiography) was detected in the diabetics with HF.

Conclusions—The more frequent progression to HF in the diabetics after AMI is not explained by a greater propensity for LV remodeling. Other factors, such as diastolic dysfunction, may play a role.

Key Words: diabetes mellitus ■ heart failure ■ remodeling ■ myocardial infarction ■ angioplasty
Data Analysis

Complete M-mode and 2D echocardiographic examinations were performed using commercially available imaging systems (Aloka model SSD-830; HP SONOS model 5500; 2.5 and 3.5-MHz transducers). 2D echocardiographic images were transferred to the hard disk of a Tomtec P90 analysis system and digitized. LV volumes and LV ejection fractions (LV EF) were then calculated by the modified Simpson’s rule algorithm. The mean values of 3 measurements of the technically best cardiac cycles were taken from each examination. Intraobserver and interobserver variability values in the evaluation of end-systolic and end-diastolic volumes (ESV and EDV) have been reported to be <5% in our laboratory, indicating the good reproducibility of the measurements. To evaluate regional systolic function, the left ventricle was divided according to a 16-segment model. For each segment, wall motion was scored from 1 (normal) to 4 (dyskinetic). Anterior and inferior infarct zones were constructed, and an infarct zone wall motion score index (IZ WMSI) was derived for baseline and follow-up 2D echocardiograms. In a subset of patients, the E and A waves and the E-wave deceleration time (DT) were measured from the mitral inflow Doppler echocardiograms to evaluate diastolic function. Moreover, the ratio of the transmitral E-wave velocity to E/Ea (E/Ea) was calculated by the modified Simpson’s rule algorithm. The mean values of 3 measurements of the technically best cardiac cycles were taken from each examination. Intraobserver and interobserver variability values in the evaluation of end-systolic and end-diastolic volumes (ESV and EDV) have been reported to be <5% in our laboratory, indicating the good reproducibility of the measurements.

Definitions and Outcome Measures

The study population was divided into 2 groups according to the presence or absence of diabetes mellitus. Patients were classified as having diabetes if it was documented on medical reports or if patients were taking oral hypoglycemic agents or insulin at the time of admission to the study. Restenosis was defined as a ≥50% diameter stenosis of the culprit lesion at follow-up angiograms. On the basis of repeated measurements in individual patients and on the upper 95% confidence limit of the intraobserver variability in the laboratory, an increase in end-diastolic volume index >20% was considered LV remodeling. LV restrictive filling pattern was recognized in the presence of DT ≤130 ms. The diagnosis of HF was based on either hospitalization for HF or presence of at least 2 of the following criteria at follow-up visit: dyspnea, bibasilar pulmonary rales, third heart sound, or radiographic evidence of pulmonary congestion. For patients who died, the last evaluation of HF at follow-up was considered for analysis.

Statistical Analysis

Continuous data are expressed as mean±SD. Baseline data were compared by means of the χ² test for categorical variables and unpaired t test for continuous variables. ANOVA with the Tukey post hoc test was used to analyze repeated measures of LV EF, IZ WMSI, and LV volumes. Univariate and multivariate regression analyses were performed to identify variables that were independently correlated with LV remodeling at 6 months. Clinical, angiographic, and echocardiographic variables that were significant in univariate analysis, as well as those known to affect LV remodeling, in addition to diabetes, were entered into the multivariate models. The multivariate Cox proportional-hazards regression model was used to identify independent predictors of HF at 5 years. In addition to diabetes and 6-month LV dilation, clinical, angiographic, and echocardiographic variables that were significant in univariate analyses were included in the Cox model. An interaction term combining diabetes and LV dilation was used to determine whether diabetes altered the relationship between LV remodeling and HF. A value of P<0.05 was considered statistically significant. Statistical analysis was performed with Statistica 4.5 for Windows and SPSS 8.0 for Windows.

Results

Clinical Characteristics and Medical Treatment

Diabetes mellitus was present in 42 (13%) of the 325 patients. Of these, 32 (77%) were treated with oral hypoglycemic agents and 10 (23%) with insulin. Similar baseline characteristics were observed in patients with and without diabetes (Table 1). Interestingly, the time from symptom onset to balloon and the enzymatic infarct size, measured as peak creatine kinase, were similar between the 2 groups. Diabetics showed a greater incidence of anterior location of AMI, although the difference was not significant.

Angiographic Results

Diabetic patients had more frequently, but not significantly so, multivessel disease. Similar rates of Rentrop grade 2 to 3 collateral flow and chronic occlusion were found in the 2 groups of patients. There was no significant difference in the use of stents between diabetics and nondiabetics. Coronary angiography was repeated in 311 of the 317 eligible patients 6 months after the index infarction. Overall, restenosis/reocclusion rates were not significantly different between diabetics and nondiabetics (37% versus 27%, P=0.182). Reocclusion was more frequent in diabetic patients, although the difference was not significant (10% versus 5%, P=0.222).

Changes in LV Regional and Global Function and Volumes

At baseline, LV EF was lower, albeit not significantly so, in diabetics than in nondiabetics, whereas a similar IZ WMSI was found in the 2 groups (LV EF, 40.4±9.5% versus 43.1±9.8%, P=0.11; IZ WMSI, 2.32±0.43 versus 2.28±0.47, P=0.94, respectively). According to ANOVA, throughout the study period, a significant progressive improvement in LV EF was observed in both groups of patients (Figure, A). Comparison between groups by ANOVA revealed a similar improvement in LV EF at 1 and 6 months (Figure, A). Similarly, the IZ WMSI showed a similar improvement in both groups of patients (Figure, B).

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LV ESV and EDV were higher, albeit not significantly so, in the diabetics than in the nondiabetics at baseline (LV ESV, 77.1 ± 23.7 mL versus 70.6 ± 27 mL, P = 0.20; LV EDV, 128.1 ± 28 mL versus 123.5 ± 35 mL, P = 0.82, respectively). LV ESV decreased progressively from baseline to 6 months in both groups, without any difference between the 2 groups at each time point (Figure, C). LV EDV increased progressively in both groups, and at 6 months, in the nondiabetics, it was significantly higher than the baseline value. No significant difference was found between the 2 groups at each time point (Figure, D). From baseline to 6 months, LV diastolic enlargement was quantitatively similar in the diabetics (4.1 ± 35 mL) and in the nondiabetics (5.8 ± 37.8 mL) (P = 0.783), and no significant difference was found in the incidence of LV remodeling (33% versus 25%; P = 0.234, respectively).

**Relation Between Diabetes and LV Remodeling**

To evaluate the independent contribution of diabetes to LV dilation, stepwise multiple regression analysis was performed. Table 1 presents the baseline clinical, echocardiographic, and angiographic characteristics of study patients.

<table>
<thead>
<tr>
<th></th>
<th>All (n=325)</th>
<th>Diabetic Group (n=42)</th>
<th>Nondiabetic Group (n=283)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.5 ± 10.8</td>
<td>62 ± 11</td>
<td>61 ± 11</td>
<td>0.70</td>
</tr>
<tr>
<td>Male</td>
<td>260 (80)</td>
<td>30 (71)</td>
<td>230 (81)</td>
<td>0.14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>111 (34)</td>
<td>17 (40)</td>
<td>94 (33)</td>
<td>0.35</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>93 (29)</td>
<td>12 (29)</td>
<td>81 (29)</td>
<td>0.96</td>
</tr>
<tr>
<td>Smoker</td>
<td>149 (43)</td>
<td>14 (33)</td>
<td>135 (48)</td>
<td>0.08</td>
</tr>
<tr>
<td>Previous angina</td>
<td>29 (9)</td>
<td>3 (7)</td>
<td>26 (9)</td>
<td>0.66</td>
</tr>
<tr>
<td>Previous MI</td>
<td>28 (9)</td>
<td>4 (9)</td>
<td>24 (8)</td>
<td>0.84</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>3 (1)</td>
<td>1 (2.4)</td>
<td>2 (1)</td>
<td>0.29</td>
</tr>
<tr>
<td>Symptom to balloon time, min</td>
<td>204±100</td>
<td>196±84</td>
<td>204±102</td>
<td>0.28</td>
</tr>
<tr>
<td>Peak CK, U/L</td>
<td>2804±2149</td>
<td>3016±2030</td>
<td>2814±2168</td>
<td>0.73</td>
</tr>
<tr>
<td>IZ WMSI</td>
<td>2.28±0.46</td>
<td>2.32±0.43</td>
<td>2.28±0.47</td>
<td>0.94</td>
</tr>
<tr>
<td>EF, %</td>
<td>42.7±9.8</td>
<td>40.4±9.5</td>
<td>43.1±9.8</td>
<td>0.11</td>
</tr>
<tr>
<td>LV EDV, mL</td>
<td>124.1±34</td>
<td>128.1±28</td>
<td>123.5±35</td>
<td>0.82</td>
</tr>
<tr>
<td>LV ESV, mL</td>
<td>71.4±27</td>
<td>77.1±23.7</td>
<td>70.6±27</td>
<td>0.20</td>
</tr>
<tr>
<td>Anterior MI</td>
<td>177 (54)</td>
<td>126 (69)</td>
<td>151 (53)</td>
<td>0.056</td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td>152 (47)</td>
<td>24 (57)</td>
<td>128 (45)</td>
<td>0.149</td>
</tr>
<tr>
<td>Collaterals (grade ≥2)</td>
<td>54 (17)</td>
<td>4 (10)</td>
<td>50 (18)</td>
<td>0.186</td>
</tr>
<tr>
<td>Chronic occlusion</td>
<td>28 (9)</td>
<td>6 (14)</td>
<td>22 (8)</td>
<td>0.160</td>
</tr>
<tr>
<td>Stent</td>
<td>189 (58)</td>
<td>25 (60)</td>
<td>164 (58)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± SD or numbers (%) of patients. CK indicates serum creatine kinase; CAD, coronary artery disease. Other abbreviations as in text.

Changes in EF (A), IZ WMSI (B), and LV volumes (C and D) during 6 months after AMI in patients with (solid line) and without (dashed line) diabetes (P<0.01 vs baseline, by ANOVA analysis).
TABLE 2. Predictors of LV Remodeling at Multivariate Analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak CK, U/L</td>
<td>1.42 (1.28–1.58)</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>LV EDV at baseline, mL</td>
<td>0.75 (0.68–0.83)</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>IZ WMSI at baseline</td>
<td>1.20 (1.08–1.34)</td>
<td>0.00078</td>
</tr>
<tr>
<td>Symptom to balloon time, min</td>
<td>1.11 (1.01–1.22)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1 and text.

formed. Variables used for analysis were age, diabetes, hypertension, hypercholesterolemia, infarct location, peak creatine kinase value, extent of coronary artery disease, presence of significant collateral circulation, chronic occlusion, symptom-to-balloon time and door-to-balloon time, mitral regurgitation, baseline IZ WMSI, LV EF, and LV volumes. For multiple regression analysis, factors showing a probability value of P<0.1 in univariate analysis were selected. Significant predictors of 6-month LV remodeling were peak creatine kinase (P<0.000001), LV EDV (P<0.000001), IZ WMSI (P=0.00078), and time to reperfusion (P=0.028), whereas diabetes was not a significant predictor (Table 2).

Long-Term Clinical Outcome and Relation Between Diabetes and HF

Follow-up data were collected for all but 4 patients. The mean length of follow-up was 56±17 months (range, 6 to 81 months). During follow-up, 36 patients (11%) died (4 diabetics; P=0.614 versus nondiabetics), 17 (5%) had nonfatal reinfarctions (3 diabetics, P=0.576 versus nondiabetics), and 54 (17%) underwent additional revascularization procedures (8 diabetics, P=0.218 versus nondiabetics). At 6 months, the incidence of HF was 24% (n=10) in the diabetics and 11% (n=30) in the nondiabetics (P=0.015). At 5 years, the rate of HF increased to 43% (n=18) in the diabetes and to 20% (n=57) in the nondiabetics (P=0.001). Among the 75 patients with HF, 14 were hospitalized for overt HF (3 diabetics, P=0.321 versus nondiabetics).

At multivariate Cox analysis, significant predictors of 5-year HF were age (P<0.0001), peak creatine kinase (P=0.0004), 6-month LV remodeling (P=0.0021), and diabetes (P=0.0366) (Table 3).

In Cox proportional-hazards analysis, 6-month LV remodeling was predictive of late HF in the nondiabetics (HR, 1.0083; 95% CI, 1.0011 to 1.0156; P=0.023) but not in the diabetics (HR, 1.0135; 95% CI, 0.996 to 1.03; P=0.123), even after adjustment for age, enzymatic infarct size, time to reperfusion, and multivessel disease. The development of HF was modified by the presence of diabetes, with a significant interaction between diabetes and LV dilation in the development of late HF (HR, 2.47; 95% CI, 1.16 to 5.27; P=0.018).

LV Diastolic Function

LV diastolic function was evaluated in 146 patients (21 diabetics). At baseline, we found similar E/A ratio in the diabetics and in the nondiabetics (0.93±0.46 versus 1.12±0.47, P=0.087), similar DT (169±240 vs 160.4±43.8 ms, P=0.390), and a similar rate of LV restrictive filling pattern (33% versus 36%, P=0.813). At 6 months, the results did not change, with similar E/A ratio in the diabetics and in the nondiabetics (0.94±0.49 versus 1.07±0.7, P=0.450), similar DT (204±43.7 versus 208±51.5 ms, P=0.755), and similar rate of LV restrictive filling pattern (17% versus 9%, P=0.302). At this time point, in patients without HF (n=111, 12 diabetics), similar E/A ratio (0.88±0.21 versus 1.06±0.66, P=0.350), DT (213±33.6 versus 202±50.7 ms, P=0.465), and LV restrictive filling pattern rate (0% versus 10%, P=0.248) were observed in the diabetics and the nondiabetics. On the contrary, in patients with HF (n=20, 6 diabetics), despite a similar E/A ratio in diabetes and nondiabetics (1.2±0.9 versus 1.1±1.0, P=0.83), a shorter DT (185±57.9 versus 240±46.5 ms, P=0.037), and a higher rate of LV restrictive filling pattern (50% versus 0%, P=0.0041) were observed in the diabetics. To clarify whether this LV inflow pattern was indicative of pseudonormalization, we measured the E/Ea ratio and the E/Ver ratio. Both indexes were higher in the diabetics (13.9±2 versus 8.2±1.8, P<0.0001; 1.6±0.7 versus 0.8±0.3 cm/s, P=0.0018, respectively), suggesting a higher LV chamber stiffness.

Discussion

Diabetes and LV Remodeling

Conflicting results have been reported in previous small studies.13,14 Our data suggest that after AMI, diabetes is not an independent predictor of subsequent LV remodeling. Many of the factors known to influence LV remodeling, such as infarct size, anterior infarct location, baseline echocardiographic and angiographic characteristics, 6-month restenosis/reocclusion rate, and use of ACE inhibitors and β-blockers, were similar in diabetic and nondiabetic patients. According to these data, at 6 months, a similar incidence of LV remodeling was found in the 2 groups, with similar patterns of changes in LV global and regional systolic function and in LV volumes.

Diabetes and HF

At 5 years, a higher incidence of HF was observed in the diabetics. Diabetes was found to be an independent predictor of HF at 5 years. These findings are consistent with those of previous studies in which, despite similar20 or smaller21–23 enzymatic infarct size and similar LV systolic dysfunction,15,22 diabetics were more likely to develop HF than nondiabetics. However, LV remodeling at 6 months was found to be predictive of HF in the nondiabetics but
not in the diabetics. These findings confirm and highlight the missing link between progressive LV dilation and HF in diabetic patients with AMI. A potential explanation for these findings may imply a role for diastolic dysfunction. Although in the setting of AMI, the predominant diastolic abnormality is an impairment in relaxation, a restrictive filling pattern may be observed as the result of an increase in resistance to LV filling or in chamber stiffness. The abnormal LV relaxation or stiffness may improve over time. As myocardial healing progresses, the left ventricle may become more compliant and may dilate, inducing relevant changes in mitral flow velocities and a prolongation of DT. As in our study, a similar pattern of LV diastolic dysfunction was found at baseline in a subgroup of diabetics and nondiabetics. However, at 6 months, a lower prolongation in DT and a higher rate of restrictive pattern were observed in diabetic patients with HF compared with nondiabetic patients in the presence of similar LV remodeling. The evaluation of \( E/\varepsilon \) ratio and \( E/V_a \) ratio confirmed a higher LV chamber stiffness in the diabetics with HF. Thus, the persistence or development of diastolic dysfunction after the acute phase could contribute to the development of HF in diabetic patients.

**Study Limitations**

The present report may suffer from its relatively limited study population, which was restricted to patients who fulfilled predefined inclusion criteria. Therefore, our results cannot be directly extrapolated to other subgroup of patients, such as those treated with thrombolytic therapy or not receiving reperfusion treatment, or to patients who had overt HF or cardiogenic shock in the first week after AMI. Moreover, although similar rates of restenosis and reocclusion at 6 months were found in diabetics and nondiabetics, we cannot rigorously exclude the possibility that recurrent ischemia may have contributed to the development of HF in diabetics. In addition, we did not evaluate the impact of microvascular damage on LV remodeling and late HF. Finally, the impact of diastolic dysfunction on LV remodeling and HF after primary PCI should be evaluated prospectively in a larger sample of diabetics.

**Conclusions**

Diabetes does not seem to have a significant influence in the development of LV remodeling in patients with AMI successfully treated with primary PCI. More frequent progression to HF observed in diabetics may be related to other factors, such as diastolic dysfunction.

**Acknowledgment**

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**References**


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