Impact of Diastolic Dysfunction on the Development of Heart Failure in Diabetic Patients After Acute Myocardial Infarction

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Background—Diabetes is often associated with an abnormal diastolic function. However, there are no data regarding the contribution of diastolic dysfunction to the development of heart failure (HF) in diabetic patients after acute myocardial infarction.

Methods and Results—A total of 1513 patients with acute myocardial infarction (417 diabetic) underwent echocardiographic examination during the index hospitalization. Severe diastolic dysfunction was defined as a restrictive filling pattern (RFP) based on E/A ratio >1.5 or deceleration time <130 ms. The primary end points of the study were readmission for HF and all-cause mortality. The frequency of RFP was higher in patients with diabetes (20 versus 14%; \( P = 0.005 \)). During a median follow-up of 17 months (range, 8 to 39 months), 52 (12.5%) and 62 (5.7%) HF events occurred in patients with and without diabetes, respectively (\( P < 0.001 \)). There was a significant interaction between diabetes and RFP (\( P = 0.04 \)) such that HF events among diabetic patients occurred mainly in those with RFP. The adjusted hazard ratio for HF was 2.77 (95%, CI 1.41 to 5.46) in diabetic patients with RFP and 1.21 (95% CI, 0.75 to 1.55) in diabetic patients without RFP. A borderline interaction (\( P = 0.059 \)) was present with regard to mortality (adjusted hazard ratio, 3.39 [95% CI, 1.57 to 7.34] versus 1.61 [95% CI, 1.04 to 2.51] in diabetic patients with and without RFP, respectively).

Conclusion—Severe diastolic dysfunction is more common among diabetic patients after acute myocardial infarction and portends adverse outcome. HF and mortality in diabetic patients occur predominantly in those with concomitant RFP. (Circ Heart Fail. 2010;3:125-131.)

Key Words: diabetes mellitus ■ diastole ■ echocardiography ■ heart failure ■ myocardial infarction

Epidemiological and clinical studies have shown that diabetes mellitus is a major risk factor for the development of heart failure (HF).1 Diabetes contributes to the HF epidemic both as a risk factor for coronary artery disease and through other less well-understood mechanisms that directly alter myocardial function.2,3 Among patients with chronic HF, patients with diabetes have worse long-term outcomes than their nondiabetic counterparts regardless of the underlying etiology. Diabetes increases the risk for HF hospitalizations and death in patients with reduced or preserved systolic function4 and in patients who are hospitalized for decompensated HF.5

HF is a common and ominous complication in patient with diabetes who sustained an acute myocardial infarction (AMI). HF and cardiogenic shock are more common and more severe in diabetic individuals than would be predicted from the size of the infarct.6–9 In the Diabetes Insulin Glucose in Acute Myocardial Infarction study of myocardial infarction in patients with diabetes, HF was the most common cause of mortality, accounting for 66% of deaths in the year after the first infarction.10 The mechanisms underlying the increased incidence of HF in patients with diabetes and AMI remain poorly understood.6

The increase in the clinical manifestations of HF may occur in the face of a modest decrease in left ventricular systolic function. Therefore, it has been suggested that preexisting subclinical impairment of left ventricular diastolic function contributes to the development of HF in diabetic patients after AMI.6,7 However, there is no information with regard to the prevalence and clinical consequences of diastolic dysfunction in diabetic patients with AMI.

Therefore, in this study, we sought to determine the contribution of diastolic dysfunction to the development of HF in diabetic patients after AMI. To this aim, we used a
prospective database\(^1\) that provided an opportunity to study the associations between diabetes and HF in the setting of recent AMI, accounting for left ventricular systolic and diastolic function. We present, herein, data that support the hypothesis that in patients with diabetes and AMI, diastolic dysfunction is a major determinant of HF and mortality.

**Methods**

**Patients**

The study cohort consisted of patients enrolled in a prospective observational study designed to determine predictors of postinfarction HF. All patients presenting to the intensive coronary care unit with AMI were eligible for entry into the study if they had a diagnosis of AMI according to the American College of Cardiology criteria.\(^2\) The investigational review committee on human research approved the study protocol.

**Echocardiographic Examination**

Echocardiography was performed during hospital stay after a median of 2 days from admission (interquartile range 1 to 3 days). Analysis of diastolic function, left ventricular function, and presence and degree of mitral regurgitation was carried out by 1 of 7 experienced noninvasive cardiologists (Y.A., S.R., D.M., J.L., D.A., S.C., and S.D.) without the knowledge of the patient outcome. Patients with technically limited Doppler echocardiograms and patients with atrial fibrillation, sinus tachycardia or/and first-degree AV block resulting in partial fusion of the E and A velocities, ventricular pacing, and other arrhythmias (eg, atrial flutter) were excluded. In addition, to avoid the effects of mitral regurgitation on E wave velocity and other Doppler parameters of filling pressures,\(^13\) we excluded patients with moderate or severe mitral regurgitation, mitral stenosis, or prothetic mitral valves.

Early (E) and late (A) transmural velocities of the mitral inflow, their ratio, and the E-wave deceleration time were measured from the apical window using pulsed-wave Doppler with the sample volume placed at the tips of the mitral leaflets during diastole. Previous studies in patients after AMI used several definitions for restrictive filling pattern (RFP).\(^14\)–\(^19\) In the absence of universal criteria for RFP, we chose to use criteria that are consistent with most previous studies. Therefore, RFP was defined as the presence of E/A wave ratio of >1.5 or an E-wave deceleration time of <130 ms.\(^14\)\(^15\)

The severity of mitral regurgitation was determined, as previously described.\(^11\) Left ventricular ejection fraction (LVEF) was visually estimated and classified as normal (\(\geq 55\%\), mildly reduced (45% to 54%), moderately reduced (30% to 44%), or severely reduced (<30%).\(^20\) Preserved left ventricular systolic function was defined as LVEF >45% as suggested by the European Study Group on Diastolic Heart Failure\(^21\) and in large clinical trials.\(^22\)

**Definition of Diabetes**

Patients were considered as having diabetes if they had been previously informed of the diagnosis by a physician or were taking oral antihyperglycemic agents, insulin, or receiving dietary therapy. Patients without previously diagnosed diabetes who required initiation of antihyperglycemic therapy during hospital stay were also considered to have diabetes.

**Study End Points**

The primary end points of the study were (1) development of HF analyzed by time to first event and (2) all-cause mortality.\(^23\) HF was defined as readmission to hospital for the management of HF (defined by the presence of new symptoms of paroxysmal nocturnal dyspnea, orthopnea, or edema with 1 or more concurrent signs, including ventricular gallop rhythm, jugular venous distention, bilateral posttussive rales in at least the lower third of the lung fields, elevated venous pressure, or pulmonary venous congestion on radiograph with interstitial or alveolar edema).

After hospital discharge, clinical end point information was acquired by reviewing the national death registry and by reviewing the hospital records for major clinical events if the patient had been rehospitalized. To confirm the diagnosis of HF, all hospital records were abstracted. Data were collected on the course and care of the patient during the hospital stay, including admission notes, consultation notes, discharge summaries, and pertinent laboratory data. Three physicians (D.A., A.M., and D.M.) independently reviewed all records and adjudicated the occurrence of events. The majority rule was applied in case of disagreement.

**Statistical Analysis**

Data are expressed as mean±SD. The baseline characteristics and echocardiographic parameters of the study groups were compared using unpaired t test for continuous variables and by the χ² test for categorical variables.

Survival curves were constructed using the Kaplan–Meier method, and comparisons were made using the log-rank test. Multivariable Cox proportional hazards modeling was used to determine the relationship between diabetes, RFP, and admission for the treatment of HF. Known predictors of the development of HF in survivors of myocardial infarction\(^11\)\(^24\) were forced into the model: age, LVEF (stratified as normal, mildly reduced, moderately reduced, or severely reduced),\(^20\) baseline heart rate, Killip class at admission, hypertension, diabetes, previous infarction mild mitral regurgitation, and RFP. In addition, other potential predictors were considered (gender, serum creatinine, anterior infarction, ST-elevation infarction, and coronary revascularization) if they demonstrated an association with HF on univariate analysis (P<0.1). Because recurrent myocardial infarction greatly increases the risk for HF,\(^24\) all survival analyses were performed censoring the data to the time of recurrent infarction.

Cox proportional hazard modeling was also performed to determine the relationship between diabetes, RFP, and mortality. Clinical and echocardiographic variables thought to have clinical importance\(^25\) (age, gender, baseline creatinine, previous infarction, history of hypertension, diabetes, smoking status, anterior infarction, ST-elevation infarction, Killip class, reperfusion therapy, coronary revascularization, mild mitral regurgitation, and LVEF) were included in a stepwise multivariable model.

We assessed whether the effect of diabetes on HF and death varied according to RFP status using traditional interaction testing and stratified analyses. The existence of an interaction was formally evaluated with the use of a Cox regression model incorporating terms for the main effect of diabetes, the main effect of RFP, and the interaction between diabetes and RFP. The impact of concomitant RFP on the risk of HF and death was analyzed in subgroups of patients with preserved LVEF (\(>45\%\)) and reduced LVEF (\(<45\%\)).\(^21\) Two-sided, 95% likelihood ratio CI were constructed, and an α level of 0.05 was used to declare statistical significance of the interaction term. Statistical analyses were performed using the SPSS statistical software version 15.0 (SPSS Inc, Chicago, Ill).

**Handling of Missing Data**

Of the 2398 patients initially enrolled in the study, 562 (23.7%) had missing data on diastolic function for various reasons including conditions for which interpretation of diastolic function is unreliable; these patients were not included in the analyses. To estimate the influence of missing diastolic function information, the primary analyses were replicated using the maximum likelihood expectation maximization method (which estimates conditional means for missing values, given the observed values of the other covariates) to impute the missing E/A ratio and deceleration time data. These analyses showed no substantive differences, which suggests that any bias because of incomplete diastolic function data were minimal. Therefore, only the analyses from nonimputed data are presented.

**Results**

Between January 2000 and June 2008, 2398 patients were recruited into the study. Patients were excluded due to mitral
valve disease (n=227; moderate or severe mitral regurgitation, mitral stenosis, or mitral prosthesis) and atrial fibrillation (n=96). Inadequate quality of the echocardiogram, missing diastolic function data, and other conditions for which interpretation of diastolic function is unreliable resulted in the exclusion of 562 additional patients. The study population consisted of the 1513 remaining patients of whom 417 were diabetic.

Compared with participants for whom diastolic function was available, patients with missing diastolic function data were older (62±13 versus 60±13; P=0.002), had higher creatinine levels (1.2±0.7 versus 1.0±0.5 mg/dL; P<0.001), were more likely to have tachycardia at admission (12% versus 6%; P<0.001), to present with Killip class >1 (31% versus 17%, P<0.001), and to have reduced LVEF (48% versus 35%; P<0.001); they were less likely to undergo percutaneous revascularization (41% versus 49%; P<0.001) and were similarly likely to have diabetes (29% versus 28%, P=0.65). Among the patients with missing diastolic function, readmission for HF was similar to that of patients with complete data (P=0.59), but mortality was higher (P=0.001).

The clinical characteristics of patients with available diastolic function data according to diabetes status are shown in Table 1. Patients with diabetes were more likely to be older and females, had higher baseline creatinine, and were more likely to have had a previous myocardial infarction and a history of hypertension and smoking; they presented with higher heart rates and higher Killip class.

The overall prevalence of RFP was 15.5% with higher rates of RFP among diabetic patients (Table 1). Patients with diabetes had lower LVEF and higher rates of mild mitral valve regurgitation. They were less likely to receive percutaneous revascularization and more likely to undergo coronary bypass surgery. There was less use of antiplatelet agents and greater use of angiotensin-converting enzyme inhibitors in patients with diabetes.

### Diabetes, RFP, and HF

The median duration of follow-up after hospital discharge was 17 months (range, 8 to 39 months). During the follow-up period, 135 patients (8.9%) were readmitted for the treatment of HF. Of these, 114 patients were admitted for HF without a preceding recurrent infarction, with 52 (12.5%) and 62 (5.7%) events occurring in patients with and without diabetes, respectively (P<0.001).

The results of univariable and multivariable Cox model examining the relationship between clinical and echocardiographic variables and risk of HF is shown in Table 2. After multivariable adjustments, both diabetes and RFP were independent predictors of subsequent HF, together with age, Killip class >1, moderately and severely reduced LVEF, and mild mitral regurgitation (Table 2).

Kaplan–Meier plots according to RFP and diabetes status showed a markedly increased risk for HF in diabetic patients with RFP (Figure 1). Likelihood ratio tests demonstrated a significant interaction between diabetes and RFP with respect to readmission for HF in the adjusted Cox model (P=0.04), such that the increased risk for HF among diabetic patients occurred predominantly in patients with concomitant RFP.

### Diabetes, RFP, and Mortality

During the follow-up period, 117 patients (7.7%) died, with 58 (13.9%) and 59 (5.4%) deaths occurring in patients with and without diabetes, respectively (P<0.0001). In a multivariable Cox proportional hazards model, diabetes and RFP were independently associated with an increased adjusted risk for mortality (Table 3). There was a borderline-significant interaction between diabetes and RFP with regard to the mortality end point (Figures 2 and 3; P=0.059). Stratified analyses revealed that in patients with RFP, the adjusted HR...
for mortality associated with diabetes was 3.39. In contrast, for patients without RFP, the adjusted HR for mortality in patients with diabetes was only 1.61.

Diabetes, RFP, and LVEF

To study the effect of diastolic dysfunction and diabetes in relation to the presence of left ventricular systolic dysfunction, additional analyses were performed after dividing the study population into 8 groups based on diabetes status, RFP, and presence of preserved (≥45%) or reduced LVEF. The adjusted HRs for the combined end point of HF and death in these 8 groups are shown in Figure 4.

The impact of concomitant RFP on the risk of HF and death (Figure 4) was evident in diabetic patients with preserved LVEF (≥45%) and reduced LVEF (<45%). The adjusted hazard ratio for HF and death in diabetic patients with RFP and preserved LVEF was higher than that of diabetic patient without RFP and preserved LVEF and similar to that of diabetic patients without RFP but with systolic dysfunction. Diabetic patients with combined diastolic and systolic dysfunction were at highest risk with a striking increase in the risk for HF and death.

Discussion

In this study, we sought to determine the prevalence and clinical consequences of RFP in diabetic patients after AMI. The prevalence of severe diastolic dysfunction was higher among diabetic patients after AMI. Diabetes remained a strong and independent predictor of HF and mortality after adjustment for established clinical predictors of adverse outcome among patients with AMI. However, the association between diabetes and clinical outcomes depended on the presence of RFP. The increase in mortality and HF events among diabetic patients occurred predominantly in those with concomitant RFP. The impact of RFP on the clinical outcome of diabetic patients was robust irrespective of whether LVEF was preserved or reduced.

Diastolic Dysfunction in Diabetes

Diabetes is associated with a variety of cardiac alterations that affect both systolic and diastolic function and result from complex and multifactorial mechanisms. Several ultrastructural changes have been described in the myocardium of diabetic patients, including myocellular triglyceride accumulation, increased deposition of collagen type III, myocardial

Table 2. Unadjusted and Adjusted Cox Proportional Hazards Model for Admission for Heart Failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>P</td>
</tr>
<tr>
<td>Age (per 10 y)</td>
<td>1.83</td>
<td>1.56 to 2.14</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.39</td>
<td>1.65 to 3.45</td>
</tr>
<tr>
<td>Killip class &gt;1</td>
<td>6.57</td>
<td>4.54 to 9.40</td>
</tr>
<tr>
<td>Mild mitral regurgitation</td>
<td>4.49</td>
<td>2.91 to 6.91</td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.0 (referent)</td>
<td>...</td>
</tr>
<tr>
<td>Mildly reduced</td>
<td>1.66</td>
<td>0.9 to 3.08</td>
</tr>
<tr>
<td>Moderately reduced</td>
<td>4.18</td>
<td>2.41 to 7.25</td>
</tr>
<tr>
<td>Severely reduced</td>
<td>8.52</td>
<td>4.71 to 15.40</td>
</tr>
<tr>
<td>RFP</td>
<td>3.13</td>
<td>2.12 to 4.0</td>
</tr>
</tbody>
</table>

The final model adjusted for age, gender, previous infarction, history of hypertension, diabetes, anterior infarction, ST-elevation infarction, coronary revascularization, Killip class on admission, mild mitral regurgitation, left ventricular ejection fraction, and restrictive filling pattern.

Figure 1. Kaplan–Meier plot showing the crude cumulative incidence of admission for the treatment of HF according to the presence of diabetes and RFP. P values are for the overall comparison among the groups using the log-rank test.
fibrosis and collagen glycation and cross-linking, leading to greater left ventricular mass and impaired contractility.2,3,27–29 Many studies have shown that patients with diabetes manifest diminished left ventricular compliance in the presence of preserved left ventricular systolic function. Diastolic abnormalities as defined by comprehensive Doppler techniques have been documented in both type 1 and type 2 diabetes, and occur in 27% to 75% of diabetic patients.30–33 However, the alterations in diastolic function among diabetic patients have been documented in asymptomatic individuals,30–33 and their long-term consequences or potential to progress to symptomatic HF remains unknown.

**Diastolic Dysfunction and Postinfarction HF**

Although diabetes is associated with increased risk for developing acute coronary events, in the postinfarction period, patients with diabetes also have a higher subsequent risk of developing HF.6–8 The markedly increased adjusted risk of HF and death associated with diabetes beyond the acute phase of coronary events is poorly understood.34 Several studies have shown that measures of infarct size and left ventricular function,7,8 or alterations in postinfarction left ventricular remodeling35 do not explain the increased propensity of diabetic patients to develop HF.

The results of this study indicate that diabetes-related changes in diastolic function markedly increase the risk of HF and death of diabetic patients who survive an AMI, regardless of their residual systolic function. In accordance with previous reports,7,8 this study demonstrates that HF develops more frequently in diabetic patients than in nondiabetic patients after AMI. The significant interaction between diabetes and RFP strongly suggests an independent link between diabetes, diastolic function, and clinical outcome. After adjustments for known risk factors for postinfarction HF,24 the most marked increase in the risk of HF conferred by diabetes was observed in diabetic patients with concomitant severe diastolic dysfunction. Thus, abnormal diastolic function is an important determinant of the progression to clinical HF among diabetic patients with AMI.

The borderline-significant interaction between diabetes and RFP with respect to mortality indicates that diastolic dysfunction also contributes to the increased mortality of diabetic patients after AMI,6 akin to the association between diastolic dysfunction and all-cause mortality in the general population.14 These findings suggest that assessment of diastolic function should become an important component of the echocardiographic examination in diabetic patients.

In-hospital and long-term mortality after AMI has declined over the years. However, despite the existence of treatments, which may benefit diabetic patients disproportionately, the relative hazard of mortality in diabetic patients has improved little compared with nondiabetic patients.34 The results of this study may explain these epidemiological observations, given that strong evidence for a beneficial effect of various therapies in patients with diastolic HF is still lacking.22

### Table 3. Unadjusted and Adjusted Cox Proportional Hazards Model for All-Cause Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>1.83</td>
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</tr>
<tr>
<td>Diabetes</td>
<td>2.39</td>
<td>1.65 to 3.45</td>
</tr>
<tr>
<td>Creatinine (per 1 mg/dL)</td>
<td>1.54</td>
<td>1.38 to 1.73</td>
</tr>
<tr>
<td>Heart rate &gt;100, bpm</td>
<td>2.25</td>
<td>1.38 to 1.73</td>
</tr>
<tr>
<td>LVEF</td>
<td>Normal 1.0 (referent)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Mildly reduced</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>Moderately reduced</td>
<td>2.52</td>
</tr>
<tr>
<td></td>
<td>Severely reduced</td>
<td>4.95</td>
</tr>
<tr>
<td>RFP</td>
<td>2.10</td>
<td>1.40 to 3.16</td>
</tr>
</tbody>
</table>

The final model adjusted for age, gender, previous infarction, history of hypertension, smoking, diabetes, anterior infarction, ST-elevation infarction, coronary revascularization, Killip class on admission, mild mitral regurgitation, left ventricular ejection fraction, and restrictive filling pattern.
Although the predominant diastolic abnormality during transient ischemia is an impairment in relaxation, the diastolic filling pattern may change during AMI, resulting in a RFP as a result of an increase in resistance to left ventricular filling or increased chamber stiffness. Depending on the patient population and echocardiographic criteria, the prevalence of RFP in previous studies ranged from 13% to 33%. The overall prevalence of RFP in this study was 15.5%. However, regardless of the definition used, the presence of RFP is a consistent powerful predictor of HF and death in the setting of AMI.

Changes in the composition of the myocardium in terms of increased collagen content during and after repair of the infarct zone and formation of a fibrous tissue scar can alter the mechanical properties of the myocardium after AMI and confer on the heart increased myocardial and chamber stiffness. These changes in left ventricular material properties, when superimposed on preexisting reduced compliance in the diabetic heart, may increase chamber stiffness and explain the higher prevalence of RFP among diabetic patients.

Study Limitations
This study used simple Doppler assessment of diastolic filling. Although a clear relationship between RFP and clinical outcomes was observed, the addition of more sophisticated diastolic parameters such as tissue Doppler and mitral flow propagation velocity may offer additional benefit, especially for identifying other diastolic filling patterns. However, RFP is the most validated predictor of HF and death after AMI.

Even though all of the patients included in this study underwent echocardiography during their hospital admission, a substantial number of eligible patients had missing diastolic function data because of either inadequate quality of the echocardiogram or associated conditions in which interpretation of diastolic function is unreliable. Therefore, the results of this study may not be applicable to all postinfarction patients. However, the relatively large study population allows for these results to be extended to a wide range of patients with AMI. Furthermore, analysis of missing data suggested that any selection biases in the results with regard to the interaction between diabetes and RFP are likely to be minimal.

Conclusion
This study demonstrates that RFP, a marker of severe diastolic dysfunction, is more common among diabetic patients after AMI. Diastolic dysfunction is an important determinant of clinical outcomes in diabetic patients after AMI, as the increase in HF and mortality in these patients occurs predominantly in those with concomitant RFP. Our findings suggest that assessment of diastolic function should become an important component of the echocardiographic examination in diabetic patients after AMI.

Disclosures
None.

References


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