Influence of Diabetes Mellitus on Prognostic Utility of Imaging of Myocardial Sympathetic Innervation in Heart Failure Patients

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Background—Patients with diabetes mellitus have accelerated progression of heart failure and often have impaired cardiac sympathetic innervation. The present study examines the implications for heart failure progression of cardiac sympathetic denervation, assessed by I-123 metaiodobenzylguanidine imaging, in diabetic compared with nondiabetic subjects.

Methods and Results—We evaluated 343 diabetic and 618 nondiabetic subjects with New York Heart Association class II or III heart failure and a left ventricular ejection fraction ≤35% over a median follow-up of 17 months. A multivariable Cox proportional hazards model was used to examine the influence of clinical variables, b-type natriuretic peptide, plasma norepinephrine, left ventricular ejection fraction, and I-123 metaiodobenzylguanidine imaging parameters on time to a heart failure event. The late heart-to-mediastinum (H/M) ratio and the interaction term of diabetes mellitus with the prospectively selected late H/M ratio ≤1.6 were independent predictors of heart failure progression, providing incremental prognostic information beyond that available from all other variables. In diabetic subjects, late H/M ratio ≤1.6 was associated with a 2.99-fold greater 2-year rate of heart failure progression (33.5%) than late H/M ratio >1.6 (11.2% event rate).

Conclusions—The combination of diabetes mellitus and I-123 metaiodobenzylguanidine H/M ratio is an independent predictor of heart failure progression, confirming the high risk of diabetic subjects with impaired cardiac sympathetic nerve function.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00126438 and NCT00126425.

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Key Words: radionuclide imaging □ heart failure □ prognosis □ diabetes mellitus □ nervous system, sympathetic

Heart failure is the leading cause for hospitalization in the United States Medicare population.1 Heart failure mortality is particularly high in patients with diabetes mellitus.2 A major predictor of survival in patients with heart failure is the activity of the adrenergic nervous system as reflected by circulating levels of norepinephrine and cardiac sympathetic nerve activity.3 One method to assess cardiac adrenergic activity is imaging with the radiotracer iodine-123 metaiodobenzylguanidine (MIBG), which is taken up into presynaptic cardiac sympathetic nerves by the norepinephrine uptake-1 transporter. Numerous studies have demonstrated that I-123 MIBG activity in the myocardium is an independent predictor of survival in patients with heart failure.4-6 Nevertheless, reduced myocardial I-123 MIBG activity may also be seen in diabetic patients without evidence of underlying heart disease.7 Reduced cardiac I-123 MIBG activity in diabetic subjects could reflect either cardiac autonomic dysfunction alone or downregulation of the norepinephrine uptake-1 transporter and depletion of presynaptic sympathetic nerve vesicle norepinephrine as a result of progressive heart failure.8,9

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In the prospective, international ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study of patients with New York Heart Association (NYHA) class II or III heart failure and reduced left ventricular ejection fraction (LVEF) ≤35%, the heart-to-mediastinum activity ratio (H/M) at 3 hours and 50 minutes after injection of I-123 MIBG was independently predictive of heart failure progression.
progression, arrhythmic cardiac events, and cardiac death. The purpose of the present study was to assess whether cardiac sympathetic innervation, assessed by I-123 MIBG imaging, is predictive of heart failure progression in diabetic subjects.

**Methods**

The present study is an analysis of the 343 patients with diabetes mellitus in comparison to the 618 nondiabetic subjects in ADMIRE-HF. The design and primary results of ADMIRE-HF have been described previously. The presence of diabetes was determined by clinical history. Diabetes was reported as type 1 in 29 subjects and type 2 in 314 subjects. Medical treatment of diabetes was as follows: oral agents alone: 157 subjects (46%); insulin alone: 85 (25%); oral agents + insulin: 45 (13%); other: 4 (1%); and diet only: 52 (15%). The protocol specified measurement of hemoglobin A1c for all diabetic subjects, and adequate blood samples were obtained in 323 (94%); 253 of 323 diabetic subjects (78%) had a Hgb A1c value ≥ 6.5% and 199 (62%) had a Hgb A1c measurement > 7.0%. Each study participant completed an informed consent statement approved by their local institutional review board or ethics committee.

Initial screening evaluation included laboratory tests (biochemistry, hematology, and urinalysis), a medical history, a limited physical examination, vital signs, oxygen saturation, height and body weight, and a 12-lead ECG. Demographic data collected included age, sex, heart failure medications used, NYHA class, tobacco use, hypertension, and ischemic versus nonischemic heart failure etiology. The following were performed to assess cardiac functional status: NYHA heart failure classification, echocardiography, plasma b-type natriuretic peptide (BNP), and norepinephrine levels.

**Radionuclide Imaging Procedures**

An activity of 370 MBq (10 mCi ± 10%)123I-MIBG (AdreView, GE Healthcare, Princeton, NJ) was administered over 1 to 2 minutes and a 10-minute planar anterior chest image was performed at 15 minutes ("early" image), and again at three hours and 5 minutes ("late" image). Imaging was performed with low-energy/high resolution collimators, and the camera peaked at 159 keV with a symmetrical 20% energy window. The images were acquired and stored in a 128×128 matrix.

**Image Data Analysis**

123I-MIBG studies were analyzed at an independent Imaging Core Laboratory using methods described previously. H/M ratios were calculated from the early and late images. I-123 MIBG washout rate was calculated using the following formula: [(early heart counts/pixel − early mediastinum counts/pixel)/(late heart decay−corrected counts/pixel − late mediastinum decay−corrected counts/pixel)]/ [(early heart counts/pixel − early mediastinum counts/pixel)].

**Clinical Follow-Up**

In-person follow-up visits and telephone contacts were alternated every 6 weeks after 123I-MIBG administration for up to 24 months. Data including current NYHA class and details of any interval hospitalizations or change in clinical condition were conveyed to an independent end point adjudication committee composed of cardiologists with expertise in the diagnosis and treatment of heart failure. Heart Failure Progression was defined as an increase from NYHA class I or II to NYHA class III or IV. All decisions regarding the date of first heart failure progression events were made by consensus of the members of the adjudication committee who reviewed the clinical data.

**Data Analysis**

Demographic data were compared between diabetic and nondiabetic subjects using the Fisher exact test for categorical variables and the Student t test for continuous variables. Cox proportional hazards models were used to assess the relative hazard at time t associated with individual and groups of test variables. For assessment of the H/M ratio in the Cox models, the study subjects were either classified into 2 groups, based on H/M ratio < 1.6 and H/M ratio ≥ 1.6, or the H/M ratio was treated as a continuous variable. The choice of the H/M ratio of 1.6 for the binary population division was prespecified based on an analysis of published data on control subjects with this value representing the mean minus 2 standard deviations (mean, 2.2; standard deviation, 0.3; n = 202).

A univariable Cox proportional hazards model was fitted to the time to a heart failure progression event. Right censored times were used if an event had not occurred at or before the last contact with the subject. Any subject who had a noncardiac death was censored as of the date of death. Any subject for whom contact could not be made for a period of 6 months after the last contact was categorized as "lost to follow-up" and considered censored at the time of the last contact. Time to heart failure progression was compared between heart failure subjects with diabetes and heart failure subjects without diabetes, using a multiparameter Cox proportional hazards model. The incremental value of variables predictive of time to heart failure progression was further analyzed by a forward addition Cox proportional hazards analysis in 5 steps. Step 1 included the following clinical variables: use of β-blockers; use of an aldosterone inhibitor; use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; diagnosis of hypertension; diagnosis of diabetes mellitus; ischemic versus nonischemic heart failure etiology; use of one or more lipid-lowering drugs; past or present tobacco use; age; history of dyslipidemia; sex; race; NYHA class; and body mass index. Step 2 variables were BNP and norepinephrine. The step 3 variable was LVEF. Step 4 variables were the continuous early H/M ratio, late H/M ratio, and I-123 MIBG washout. For step 5, an interaction variable was created combining the binary late H/M ratio with the presence or absence of diabetes mellitus (ie, the binary interaction term $I = DM$ [diabetes mellitus] + H/M < 1.60; 0 = all others). The interaction of the binary H/M ratio and the variable ischemic versus nonischemic etiology of heart failure was also tested.

A separate Cox proportional hazards analysis was performed in which only the variables found to be significant in the stepwise Cox proportional hazards analysis were entered into the model. The purpose of this analysis was to rank each independent variable on the basis of its contribution to the final global $X^2$ value.

### Table 1. Comparison of Baseline Characteristics for Diabetic and Nondiabetic Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subjects With Diabetes (n=343)</th>
<th>Subjects Without Diabetes (n=618)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td>80.5</td>
<td>79.9</td>
<td>0.867</td>
</tr>
<tr>
<td>Age, y</td>
<td>63.6±10.7</td>
<td>61.7±12.4</td>
<td>0.017</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>26.8±6.3</td>
<td>27.3±6.0</td>
<td>0.225</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, %</td>
<td>93.6</td>
<td>94.2</td>
<td>0.778</td>
</tr>
<tr>
<td>β-Blocker, %</td>
<td>89.5</td>
<td>93.4</td>
<td>0.047</td>
</tr>
<tr>
<td>Aldosterone antagonist, %</td>
<td>32.1</td>
<td>42.7</td>
<td>0.001</td>
</tr>
<tr>
<td>NYHA class II, III, %</td>
<td>62.1, 37.9</td>
<td>83.8, 16.2</td>
<td>0.000</td>
</tr>
<tr>
<td>Etiology: Ischemic vs nonischemic, %</td>
<td>74.3, 25.7</td>
<td>61.6, 38.4</td>
<td>0.000</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>57.1</td>
<td>56.8</td>
<td>0.946</td>
</tr>
<tr>
<td>Smoker (past or present), %</td>
<td>58.3</td>
<td>74.3</td>
<td>0.000</td>
</tr>
<tr>
<td>BNP, ng/L (n=926)</td>
<td>266.3±394.5</td>
<td>244.4±374.3</td>
<td>0.404</td>
</tr>
<tr>
<td>Plasma norepinephrine, pg/mL (n=910)</td>
<td>629.2±427.9</td>
<td>629.7±355.6</td>
<td>0.978</td>
</tr>
<tr>
<td>Early H/M ratio</td>
<td>1.53±0.20</td>
<td>1.58±0.22</td>
<td>0.001</td>
</tr>
<tr>
<td>Late H/M ratio</td>
<td>1.40±0.19</td>
<td>1.47±0.20</td>
<td>0.000</td>
</tr>
<tr>
<td>Washout, %</td>
<td>40.62±17.03</td>
<td>35.76±17.38</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. Mean follow-up times. Diabetic subjects: 485.8±204.9 days; nondiabetic subjects: 493.3±204.7 days (P=NS).
For all proportional hazards analyses, a probability value <0.05 was required for inclusion of final variables in the models. Significance level for all other statistical tests was also set at $P<0.05$.

Results

Compared with nondiabetic subjects, the 343 subjects with diabetes were older, had a higher prevalence of ischemic heart disease, had less use of $\beta$-blockers and aldosterone antagonists, and had more severe heart failure, with more than twice as large a proportion being NYHA class III (Table 1). The mean early and late I-123 MIBG H/M values were significantly lower in diabetic compared with nondiabetic subjects. There were no significant differences in the mean early or late I-123 MIBG H/M ratios among diabetic subjects receiving insulin only ($n=85$; late H/M ratio, $1.37\pm0.21$), those treated with an oral hypoglycemic agent only ($n=157$; late H/M ratio, $1.40\pm0.19$), those treated with insulin and an oral agent ($n=45$; late H/M ratio, $1.42\pm0.17$), subjects treated without diabetic medication ($n=52$; late H/M ratio, $1.41\pm0.17$), and those treated by other means ($n=4$; late H/M ratio, $1.36\pm0.17$). There was no relationship between Hgb A1c levels and H/M ratios. There was no significant difference between diabetic and nondiabetic subjects in terms of sex, LVEF, hypertension, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, BNP, or plasma norepinephrine levels.

During a median follow-up of 17 months, 163 of the 961 study subjects (17.0%) had a heart failure progression event. Heart failure progression occurred in 74 of 343 diabetic subjects (21.6%) compared with 89 of 618 nondiabetic subjects (14.4%, $P=0.005$).

Relationship of H/M Ratio to Heart Failure Progression

The mean late H/M ratio was significantly lower in diabetic subjects (Figure 1) with heart failure progression ($1.34\pm0.15$) compared with diabetic subjects without heart failure progression ($1.41\pm0.20$, $P=0.005$). As shown in Figure 2, there was no difference in time to heart failure progression between diabetics with late H/M ratio $\geq 1.6$ and nondiabetics with late H/M ratio $\geq 1.6$. In contrast, diabetic patients with late H/M ratio $<1.6$ had a higher rate of heart failure progression than nondiabetic patients with late H/M ratio $<1.6$.

Results of the stepwise multivariable Cox proportional hazards model, after sequentially entering clinical variables, BNP and norepinephrine, LVEF, I-123 MIBG variables, and interaction variables, are shown in Table 2. A final Cox model was then generated ranking the 6 variables independently associated with time to heart failure progression. The incremental contributions of these variables are shown in Table 3. When the DM*H/M interaction variable was included in the analysis, late H/M ratio retained its independent predictive value, but the presence of diabetes mellitus did not. Early H/M ratio and I-123 MIBG washout rate failed to retain independent or incremental value for prediction of heart failure progression when late H/M ratio was present in the model.

The relative risk for developing a heart failure event over 2 years is shown in Table 4. Diabetic subjects with an H/M ratio $<1.6$ had a 2.99-fold increase in risk for a heart failure event over 2 years compared with diabetic subjects with a H/M ratio $\geq 1.6$ ($P<0.001$).

Figure 3 and Figure 4 show the distributions of late H/M ratios for diabetic and nondiabetic subjects, respectively. For diabetic and nondiabetic subjects with a late H/M ratio $\geq 1.6$, heart failure progression was infrequent (negative predictive

Figure 1. Mean late I-123 MIBG H/M ratio in diabetic and nondiabetic patients, classified by the occurrence of heart failure (HF) progression. The mean late H/M ratio was significantly lower in both diabetic and nondiabetic patients who had progression of their NYHA class. Data are presented as the mean $\pm$ 1 standard deviation.

Figure 2. Time to heart failure progression by Kaplan-Meier analysis. For patients with a late H/M ratio $\geq 1.6$, there was no difference in time to heart failure progression between diabetic and nondiabetic subjects. Heart failure progression occurred significantly earlier in patients with a late H/M ratio $<1.6$, with the highest rate of progression in diabetic patients with a low late H/M ratio. DM indicates diabetes mellitus.
value, 88.6%). The large majority of both diabetic and nondiabetic subjects had late H/M ratio <1.6.

**Discussion**

The present analysis demonstrates that diabetic patients with NYHA class II or III heart failure and an LVEF \( \leq 35\% \) are nearly 3 times more likely to have heart failure progression over 2 years if cardiac sympathetic innervation is diminished. In a multivariable Cox model for prediction of time to heart failure progression, cardiac sympathetic denervation, assessed by the prospectively determined I-123 MIBG imaging H/M ratio <1.6, was an independent, incremental predictor in addition to BNP, LVEF, and NYHA class. Among patients with preserved cardiac sympathetic innervation (H/M ratio \( \geq 1.60 \)), presence of diabetes mellitus had no influence on risk for heart failure progression.

Diabetic autonomic neuropathy is present in 20% to 35% of non–insulin-dependent diabetic subjects and is associated with heart failure progression and increased mortality.\(^{12,13}\) The presence of autonomic neuropathy may promote heart failure progression in diabetic patients through a variety of pathways. A defective angina warning system resulting from autonomic dysfunction can interfere with identification of silent myocardial ischemia and infarction preventing application of effective therapies for ischemic heart disease.\(^{14}\) The result can be progressive left ventricular dysfunction. In diabetic patients with autonomic dysfunction, chronic elevation of circulating norepinephrine levels combined with reduced parasympathetic function results in tachycardia, which results in increased myocardial oxygen demand and may contribute to myocardial ischemia. Difficulty in controlling systemic blood pressure may result from orthostatic hypotension from autonomic impairment. In addition, activation of the renin/angiotensin system in diabetic patients with autonomic dysfunction worsens hypertension and can promote myocardial fibrosis.

Autonomic dysfunction involving cardiac efferent sympathetic nerve transmission is an important determinant of coronary blood flow under conditions of increased sympathetic stimulation. In response to sympathetic activation by cold pressor stress, Di Carli et al\(^{15}\) showed a 31 ± 12% increase in myocardial blood flow with a 13% fall in coronary

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**Table 2.** Cox Proportional Hazards Model and Regression Coefficients for Time to Heart Failure Progression With Stepwise Insertion of Clinical and Historic Variables, Followed by Biochemical Variables, Followed by LVEF, Followed by MIBG Variables, Followed by Interaction Terms

<table>
<thead>
<tr>
<th>Step</th>
<th>Variables</th>
<th>Incremental ( \chi^2 )</th>
<th>( P ) Value</th>
<th>( \beta )</th>
<th>SE</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diabetes mellitus</td>
<td>0.433</td>
<td>0.159</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NYHA</td>
<td>0.498</td>
<td>0.182</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Etiology of heart failure</td>
<td>-0.366</td>
<td>0.160</td>
<td>0.022</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Summary of clinical variables</td>
<td>19.16</td>
<td>0.0003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>BNP</td>
<td>0.000630</td>
<td>0.000116</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Norepinephrine</td>
<td>0.000398</td>
<td>0.000179</td>
<td>0.026</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Summary of biochemical variables</td>
<td>27.73</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>LVEF</td>
<td>15.93</td>
<td>&lt;0.0001</td>
<td>-0.0497</td>
<td>0.0123</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4</td>
<td>H/M ratio (late)</td>
<td>-2.851</td>
<td>1.0685</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>H/M ratio (early)</td>
<td>1.882</td>
<td>0.882</td>
<td>0.033</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>H/M ratio (late and early)</td>
<td>9.84</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>DM*late H/M</td>
<td>4.55</td>
<td>&lt;0.0001</td>
<td>0.405</td>
<td>0.166</td>
<td>0.015</td>
</tr>
</tbody>
</table>

In step 1, the variables diabetes mellitus, NYHA, and etiology of heart failure were statistically significant at the \( P < 0.05 \) level. The remaining 11 clinical variables were not significant and are excluded from the table. The 3 key variables were adjusted for the variables that were removed in step 1.

Etiology of heart failure is ischemic versus nonischemic heart failure etiology. DM*late H/M is the interactive term diabetes mellitus with late H/M ratio; \( \beta \) is the regression coefficient; and SE is the standard error.

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**Table 3.** Ranking of Incremental \( \chi^2 \) Contribution to the Final Model for Heart Failure Progression Based on Those Variables Found to Be Significant in the Initial Stepwise Cox Proportional Hazards Analysis

<table>
<thead>
<tr>
<th>Rank</th>
<th>Variable</th>
<th>Incremental ( \chi^2 )</th>
<th>( \beta )</th>
<th>SE</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BNP</td>
<td>27.18</td>
<td>0.000746</td>
<td>0.000109</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2</td>
<td>LVEF</td>
<td>18.29</td>
<td>-0.0536</td>
<td>0.0123</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3</td>
<td>LateH/M</td>
<td>6.33</td>
<td>-1.069</td>
<td>0.434</td>
<td>0.014</td>
</tr>
<tr>
<td>4</td>
<td>DM*lateH/M</td>
<td>5.74</td>
<td>0.401</td>
<td>0.166</td>
<td>0.016</td>
</tr>
<tr>
<td>5</td>
<td>EarlyH/M</td>
<td>5.72</td>
<td>1.736</td>
<td>0.737</td>
<td>0.023</td>
</tr>
<tr>
<td>6</td>
<td>NYHA</td>
<td>4.30</td>
<td>0.396</td>
<td>0.184</td>
<td>0.032</td>
</tr>
</tbody>
</table>

DM*late H/M is the interactive term diabetes mellitus with late H/M ratio; \( \beta \) is the regression coefficient; and SE is the standard error.

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**Table 4.** Relative Risk for Heart Failure Progression Over 2 Years Based on the Presence or Absence of Diabetes and Late H/M Ratio <1.6 Versus \( \geq 1.6 \)

<table>
<thead>
<tr>
<th>H/M</th>
<th>DM</th>
<th>No DM</th>
<th>Relative Risk (DM Versus No DM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>33.5*</td>
<td>23.0</td>
<td>1.46 (( P = 0.006 ))</td>
</tr>
<tr>
<td>High</td>
<td>11.2</td>
<td>14.0*</td>
<td>0.8 (( P = 0.653 ))</td>
</tr>
</tbody>
</table>

Relative risk 2.99 (\( P < 0.001 \)) 1.64 (\( P = 0.081 \)) …

*The relative risk for diabetic subjects with a low H/M ratio was 2.39-fold greater than for nondiabetic subjects with a high H/M ratio.

Event rates are not adjusted for the variables listed in Tables 2 and 3. HF indicates heart failure; DM, diabetes mellitus.
vascular resistance in diabetics without sympathetic nerve dysfunction compared to only a 14±10% increase in myocardial blood flow (P<0.001 versus diabetics without sympathetic nerve dysfunction) and a 5% increase in coronary resistance in diabetics with sympathetic nerve dysfunction. Stevens et al16 showed that diabetic autonomic neuropathy is associated with impaired regional myocardial blood flow and coronary flow reserve and suggested that this may form a substrate for sudden cardiac death. In addition to risk of arrhythmic events, impaired global and regional myocardial blood flow reserve associated with abnormal cardiac sympathetic innervation have been implicated in the presence of ischemia and disease progression in cardiomyopathy.17 Even in diabetic subjects without coronary artery disease, it has been shown that autonomic neuropathy is associated with abnormalities in left ventricular function in response to dynamic and isometric exercise.18,19

I-123 MIBG, as a result of its uptake into postganglionic, presynaptic nerves by the norepinephrine uptake-1 transporter, tracks cardiac sympathetic nerve activity.20 As a noninvasive measure of cardiac sympathetic nerve function, I-123 MIBG imaging provides a practical method to clarify the role of sympathetically mediated autonomic dysfunction in the etiology of heart failure progression and arrhythmic events in diabetic subjects. In nonhypertensive diabetic subjects, reduced cardiac sympathetic nerve function, manifested as decreased late H/M ratios, has been shown compared with control subjects.21 Assessment of the I-123 MIBG H/M ratio has several advantages for the study of patients with heart failure, including simplicity and reproducibility. The H/M ratio is based on a single anterior planar image that is easy to acquire on a conventional gamma camera. In addition, in the present study, there was excellent reproducibility of the H/M ratio as determined by 3 independent readers, similar to previous experience.
using this and similar methodologies. Variability in the H/M ratio on repeated studies separated by 3 months has been observed to be minimal in normal subjects.

The independent prognostic information provided by the I-123 MIBG late H/M ratio may assist in the selection of heart failure therapy for diabetic patients. For example, previous studies have found that in patients with nonischemic cardiomyopathy, the late H/M ratio provided better prediction of cardiac death or progression to cardiac transplantation compared with current routine testing using maximum oxygen consumption with exercise (VO2max). I-123 MIBG imaging may also have a role in monitoring response to heart failure therapy. Kasama et al have reported a significant improvement in echocardiographic left ventricular volumes and function as well as improvement in I-123 MIBG imaging measures with β-blocker treatment in patients with heart failure. Improvement in sympathetic nerve function has also been demonstrated with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone inhibitors. Measurement by I-123 MIBG imaging of response of cardiac sympathetic innervation to heart failure therapy may help guide drug treatment in selected diabetic patients with heart failure.

The present study is the largest study of the prognostic power of I-123 MIBG imaging in diabetic patients to date. One limitation of the present analysis is that measures of myocardial ischemia were not available, so the role of ischemia in the progression of heart failure could not be compared with the contribution of sympathetic nerve dysfunction. Of note, however, the presence of ischemic compared with nonischemic etiology of heart failure was not an independent predictor of time to heart failure progression and did not alter the association of the I-123 MIBG late H/M ratio with heart failure events. Another limitation in the assessment of the contributions of I-123 MIBG imaging is the absence of quantitative data concerning the prognostic implications of regional heterogeneity of MIBG tracer distribution. In the previously reported summary of the ADMIRE-HF study, qualitative visual assessment of regional distribution of I-123 MIBG on single-photon emission computed tomography imaging was not independently associated with any of the outcome events. Therefore, the nonsignificant regional findings on I-123 MIBG single-photon emission computed tomography imaging were not reported in the present subanalysis of diabetic patients. It is possible that a quantitative assessment of regional I-123 MIBG distribution from single-photon emission computed tomography images may provide additional predictive information in patients with heart failure. Methods for quantitative assessment of regional distribution of I-123 MIBG activity are currently under development. The regional assessment of I-123 MIBG activity is complicated by the same global reduction in cardiac I-123 MIBG activity shown to have prognostic implications in the present analysis. Low regional myocardial I-123 MIBG counts make visual and quantitative assessment of regional tracer activity challenging.

A potentially confounding factor in the present analysis is the finding that the diabetic subjects had more advanced heart failure at the time of study entry (higher NYHA class) compared with nondiabetic subjects. This may reflect delayed detection of symptoms including angina in diabetics. It may also reflect the lower rate of use of β-blocking drugs and aldosterone inhibitors in the diabetic subjects. Treatment with β-blockers and aldosterone inhibitors did not provide independent prediction of heart failure progression in the present study.

In the present study, the interaction term DM*late H/M was an independent predictor of heart failure progression. Prospective validation of this term for prediction of heart failure progression in a separate study is needed. The present study is also limited by inadequate samples for analysis of BNP and norepinephrine levels in a small minority of subjects. Finally, although the median follow-up of subjects was 17 months, some patients had more limited follow-up of less than 1 year.

In the present study, a late H/M ratio ≥1.6 provided a negative predictive value of 88.6%, suggesting a low rate of heart failure progression in diabetic subjects with preserved sympathetic innervation. The large majority of diabetic and nondiabetic subjects had a late H/M ratio <1.6. The visible overlap in Figure 3 of diabetic subjects with H/M ratio <1.6 who did compared with those who did not have heart failure progression probably reflects the low overall incidence of heart failure progression over 2 years of follow-up. This appears to reinforce the observations from the Cox proportional hazards model that late H/M ratio provides incremental information for heart failure progression but provides greatest predictive accuracy in combination with BNP, LVEF, and diabetes with sympathetic impairment.

In conclusion, in this study of patients with heart failure, the presence of diabetes mellitus was associated with increased rate of heart failure progression, but only in those diabetics with scintigraphic evidence of cardiac sympathetic nerve impairment. Assessment of cardiac sympathetic nerve function with I-123 MIBG imaging identifies diabetic patients with increased risk for accelerated heart failure progression.

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CLINICAL PERSPECTIVE

Patients with diabetes mellitus have accelerated progression of heart failure (HF). The present study examines the implications for HF progression of cardiac sympathetic denervation, assessed by I-123 metaiodobenzylguanidine (MIBG) imaging. HF progression (defined as increase in New York Heart Association class) during a median follow-up of 17 months was examined in 343 diabetic and 618 nondiabetic subjects with New York Heart Association class II or III heart failure and a left ventricular ejection fraction $\leq 35\%$. By multivariable Cox proportional hazards model, the variables associated with time to an HF progression event were b-type natriuretic peptide, left ventricular ejection fraction, late I-123 MIBG heart-to-mediastinum (H/M) ratio, the interaction term diabetes mellitus with late H/M ratio, early H/M ratio, and New York Heart Association class. The presence of a late H/M ratio $<1.6$ was associated with a 2.99-fold increase in the risk of HF progression in diabetic subjects. Conversely, there was no difference in the risk of HF progression between diabetics and nondiabetics if the late H/M ratio was $\geq 1.6$, indicating relatively preserved cardiac sympathetic innervation. These findings indicate that cardiac sympathetic nerve dysfunction increases the risk of HF progression in patients with diabetes mellitus. Therefore, treatments designed to prevent or ameliorate cardiac sympathetic denervation in diabetic subjects (eg, $\beta$-adrenergic–blocking drugs) may provide additional benefit for prevention of HF progression beyond those therapies focused primarily on treatment of diabetes.
Influence of Diabetes Mellitus on Prognostic Utility of Imaging of Myocardial Sympathetic Innervation in Heart Failure Patients

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