Impact of Diabetes on Cardiac Sympathetic Innervation in Patients With Heart Failure

A ^{123}I meta-iodobenzylguanidine (^{123}I MIBG) scintigraphic study

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OBJECTIVE—Impaired parasympathetic and sympathetic nervous system activity have been demonstrated in patients with diabetes mellitus (DM) and correlated with worse prognosis. Few data are available on the effect of DM on cardiac neuropathy in heart failure (HF). The aim of the current study was to assess cardiac sympathetic activity in HF patients with and without DM.

RESEARCH DESIGN AND METHODS—Patients with severe HF (n = 75), with (n = 37) and without DM (n = 38), and 14 diabetic patients with normal cardiac function underwent ^{123}I meta-iodobenzylguanidine scintigraphy from which early and late heart-to-mediastinum (H/M) ratios were calculated. Clinical, echocardiographic, and biochemical data were measured.

RESULTS—DM compared with non-DM patients showed significantly lower early (1.65 ± 0.21 vs. 1.75 ± 0.21; $P < 0.05$) and late H/M ratios (1.46 ± 0.22 vs. 1.58 ± 0.24; $P < 0.03$). Early and late H/M were significantly higher in DM patients without HF (2.22 ± 0.35 and 1.99 ± 0.24, respectively) than HF patients with ($P < 0.0001$) and without ($P < 0.0001$) DM. In HF patients, an inverse correlation between early or late H/M ratio and hemoglobin A_{1c} (HbA_{1c}) (Pearson = −0.473, P = 0.001; Pearson = −0.382, P = 0.001, respectively) was observed. In DM, in multivariate analysis, HbA_{1c} and ejection fraction remained significant predictors of early H/M; HbA_{1c} remained the only significant predictor of late H/M. No correlation between early or late H/M and HbA_{1c} was found in non-DM patients.

CONCLUSIONS—Diabetic patients with HF show lower cardiac sympathetic activity than HF patients not having DM or than DM patients with a similar degree of autonomic dysfunction not having HF. HbA_{1c} correlated with the degree of reduction in cardiac sympathetic activity.

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Heart failure (HF) is a leading cause of morbidity and mortality worldwide and is characterized by sympathetic nervous system hyperactivity that significantly worsens prognosis (1–8). Cardiac adrenergic nerve activity has been assessed by ^{123}I meta-iodobenzylguanidine (^{123}I MIBG) imaging (9) and, as demonstrated by the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) study (10), the heart-to-mediastinum (H/M) ratio is an independent predictor of HF progression, arrhythmic cardiac events, and cardiac death. Reduced ^{123}I MIBG uptake, likely due to diabetic neuropathy, has also been demonstrated in patients with diabetes mellitus (DM) without HF and correlated with worse prognosis (11,12). DM is common in HF patients with a prevalence range from 10 to 30% (13) and adversely influences long-term morbidity and mortality of symptomatic and asymptomatic HF patients (14,15). In diabetic HF patients enrolled in the ADMIRE-HF trial, it has been recently demonstrated that the combination of DM and reduced ^{123}I MIBG cardiac uptake is an independent predictor of HF progression (16). Yet, the distinct impact of DM on cardiac ^{123}I MIBG uptake in patients with HF has not been largely investigated, and no previous studies have assessed cardiac innervation in matched HF patients with and without DM. Therefore, the aim of this study was to evaluate ^{123}I MIBG uptake in matched DM and non-DM patients with severe systolic HF.

RESEARCH DESIGN AND METHODS

Population and study protocol

We enrolled 37 consecutive patients with systolic HF and type 2 DM and 38 HF patients without DM referring to the outpatient clinic for HF at the University of Naples Federico II. To be included in the study, patients needed to fulfill the following criteria: left ventricular ejection fraction (LVEF) ≤40% and dilated

cardiomyopathy in at least two consecutive echocardiographic evaluations, diagnosis of HF since at least 6 months, stable clinical conditions (New York Heart Association [NYHA] II–III), coronary angiography within 1 year from enrollment, and no acute coronary syndrome or angina in the 6 months before inclusion in the study. Ischemic cardiomyopathy was defined as ventricular dysfunction in myocardial regions subtended by significant (>70% diameter) coronary stenosis, with normal regional contractile function at echocardiography and/or invasive angiography in regions subtended by coronary arteries without significant stenosis. At the time of enrollment, all patients were on optimized medical therapy for HF treatment including the use of angiotensin-converting enzyme inhibitors or AT1 antagonists when not tolerated, β-blockers, loop diuretics, antialdosterone, and digitalis, when necessary, in addition to conventional drugs used for the treatment of cardiovascular risk factors and for secondary prevention of coronary heart disease. Fourteen type 2 DM patients with normal cardiac function were also included in the study. The diagnosis of DM was confirmed by clinical history or through the assessment of at least two determinations of fasting plasma glucose ≥126 mg/dL or a random plasma glucose test ≥200 mg/dL or with blood glucose levels ≥200 mg/dL 120 min after an oral glucose tolerance test performed with 75 g of glucose dissolved in water and confirmed by repeating the test on another day (17). On the same day, patients underwent clinical examination, venous blood sample collection, transthoracic echocardiography, and ^{123}I MIBG imaging. Demographic data, including age, sex, height, body weight, BMI, HF medications, NYHA class, tobacco use, hypertension, dyslipidemia, family history of coronary events, duration of DM, presence of comorbidities, and ischemic versus nonischemic HF etiology were also collected. A venous blood sample was collected in all patients to assess biochemical data, including hemoglobin A_{1c} (HbA_{1c}) and N-terminal pro-brain natriuretic peptide (NT-proBNP); serum creatinine levels were obtained to estimate glomerular filtration rate (GFR) and assess renal impairment, as previously described (18). Diabetic patients were also screened for the presence of diabetic neuropathy using the Michigan Neuropathy Screening Instrument examination (19,20). A standard transthoracic echocardiography was performed in all patients using a VIVID E9 ultrasound system (GE Healthcare) with second-harmonic capability and a 3.5-MHz probe. All measurements were performed according to the European Society of Cardiology Recommendations for Chamber Quantification (21). Left ventricular (LV) diameters were obtained in the M-mode view. Global and regional LV function was evaluated and LVEF was calculated from apical four- and two-chamber views using the Simpson biplane method (21). Wall motion score index (WMSI) was calculated to assess the extent of regional wall motion abnormalities. At the end of this initial evaluation, synaptic noradrenaline reuptake was assessed by ^{123}I MIBG scintigraphy. All patients gave written informed consent, and the local ethic committee approved the protocol.

^{123}I MIBG imaging procedures

After blockage of the thyroid gland with 300 mg perchlorate, an activity of 111 MBq ^{123}IMIBG (Mallinckrodt, Covidien) was administered over 1–2 min, and a 10-min planar anterior chest image was performed at 15 min ("early" image) and again at 3 h and 50 min ("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 (22). Two observers, blinded about patient status (i.e., diabetic or nondiabetic), analyzed ^{123}I MIBG studies (10,23). H/M ratios were calculated from the early and late images after drawing regions of interest over the entire heart and upper mediastinum (7 × 7 pixels). Care was taken to exclude lung or liver from the myocardial and large vessels and lung from the mediastinum region of interest. ^{123}I MIBG washout rate was calculated using the following formula: [(early heart counts/pixel – early mediastinum counts/pixel) – (late heart counts/pixel decay-corrected – late mediastinum counts/pixel decay-corrected)]/(early heart counts/pixel – early mediastinum counts/pixel).

Assessment of cardiac autonomic neuropathy

Evaluation of autonomic neuropathy was performed as previously described (11,24). In particular, five tests were used: *1*) blood pressure change during standing up and *2*) during sustained handgrip and *3*) heart rate response to Valsalva maneuver, *4*) to standing up, and *5*) to deep breathing. Blood pressure response to standing up was evaluated through the difference of systolic blood pressure measured after 2 min of lying down and systolic blood pressure after standing up, whereas blood pressure response to 5 min of sustained handgrip at 30% of maximum voluntary contraction was evaluated through the difference of diastolic blood pressure assessed just before release of the handgrip and diastolic blood pressure measured before starting the maneuver. For heart rate responses, Valsalva maneuver was continued for 15 min at 40 mmHg, and then the ratio between the longest R wave–to–R wave (RR) interval soon after the release and the shortest RR during the maneuver was evaluated. Heart rate response to standing up was assessed as the ratio between the longest RR interval around the 30th beat and the shortest RR around the 15th beat (30:15 ratio), and finally heart rate changes to deep breathing were calculated through the mean of the differences of maximum and minimum heart rate of three consecutive deep breathings (six breaths per minute). A mean autonomic score was then calculated, referring to previously described normal, borderline, or abnormal values (24), and the presence of autonomic impairment was defined as an abnormal response to two or more of the five tests (11).

Statistical analysis

Data are expressed as mean ± SD. The Student *t* test was used for continuous variables. Correlation between variables was assessed by linear regression analysis, and variables that revealed a statistical significance in the univariate model were then included in a multivariate analysis. Categorical variables such as NYHA classification were analyzed by χ^2 test. All data were collected in an Excel database and analyzed by SPSS 20.0. Statistical significance was accepted at $P \leq 0.05$.

RESULTS

Patient characteristics

Mean age of the 75 patients with HF was 67.33 ± 9.6 years (84% male patients) with mean LVEF of 31.03 ± 7.15%. In 52 subjects (69.3%), HF was of ischemic etiology, and in 23 (30.7%), the etiology was an idiopathic dilated cardiomyopathy. All diabetic patients had a diagnosis of type 2 DM. No statistically significant differences between HF patients with and without DM were found for cardiovascular risk factors, demographic variables, comorbidities, LV systolic function, NYHA functional class, serum NT-proBNP levels, and

Table 1—*Baseline characteristics of HF patients with and without DM*

Characteristic	All	Patients with DM	Patients without DM	*P* value
Male sex % (*n*)	84 (63)	78.4 (29)	89.5 (34)	0.222
Age (years)	67.33 ± 9.6	68.46 ± 9.89	66.24 ± 9.301	0.319
LVEF (%)	31.03 ± 7.15	29.78 ± 6.63	32.24 ± 7.52	0.139
NYHA class II–III % (*n*)	38.7 (29) 58.8 (40)	32.4 (12) 67.6 (25)	44.7 (17) 55.3 (21)	0.154
Ischemic vs. nonischemic % (*n*)	69.3 (52)	73 (27)	65.8 (25)	0.618
NT-proBNP (ng/L)	1,475.08 ± 1,169.73	1,453.92 ± 1,131.36	1,495.68 ± 1,220	0.878
HbA_{1c} (%)	6.17 ± 0.74	6.61 ± 0.69	5.75 ± 0.49	0.0006
GFR (mL/min/1.73 m^2)	78.4 ± 32	77.3 ± 34.3	79.5 ± 30.1	0.788
DM duration (months)		62 ± 79		
Cardiovascular risk factors				
Familiar history of CAD % (*n*)	32 (24)	37.8 (14)	26.3 (10)	0.329
Hypertension % (*n*)	76 (57)	81.8 (30)	71.1 (27)	0.419
Smokers % (*n*)	69.3 (52)	64.9 (24)	73.7 (28)	0.460
Dyslipidemia % (*n*)	66.7 (50)	73 (27)	60.5 (23)	0.329
Comorbidities				
COPD % (*n*)	42.7 (32)	43.2 (16)	42.1 (16)	1.000
Chronic kidney disease % (*n*)	18.7 (14)	21.6 (8)	15.8 (6)	0.565
Peripheral artery disease % (*n*)	10.7 (8)	16.2 (6)	5.3 (2)	0.147
Atrial fibrillation % (*n*)	18.7 (14)	10.8 (4)	26.3 (10)	0.137
Therapy				
ACE inhibitors % (*n*)	53.3 (40)	59.5 (22)	47.4 (18)	0.357
AT1 blockers % (*n*)	24 (18)	18.9 (7)	28.9 (11)	0.419
β-Blockers % (*n*)	73.3 (55)	81.1 (30)	65.8 (25)	0.192
Carvedilol % (*n*)	53.3 (40)	59.4 (22)	47.3 (18)	1.000
Bisoprolol % (*n*)	20 (15)	21.6 (8)	18.4 (7)	1.000
Ca^{++} channel antagonists % (*n*)	6.7 (5)	8.1 (3)	5.3 (2)	0.674
Aldosterone antagonists % (*n*)	38.7 (29)	35.1 (13)	42.1 (16)	0.637
Loop diuretics % (*n*)	69.3 (52)	73 (27)	65.8 (25)	0.618
Antidiabetic therapy				
Diet % (*n*)		32.4 (12)		
Oral antidiabetic agents % (*n*)		51.4 (19)		
Insulin % (*n*)		5.4 (2)		
Oral agents+insulin % (*n*)		10.8 (4)		

Data are expressed as mean ± 1 SD or as % (*n*) unless otherwise indicated. Mean follow-up times. CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease.

HF therapy, as shown in Table 1. Medical treatment of DM was as follows: 19 patients (51.4%) were on oral antidiabetic agents alone, 2 (5.4%) on insulin alone, 4 (10.8%) on oral drugs + insulin, and 12 (32.4%) on diet only. Mean HbA_{1c} was 6.61 ± 0.69% (49 mmol/mol), and 22 patients (59.5%) had an HbA_{1c} measurement ≥6.5%, whereas 11 subjects (29.7%) had an HbA_{1c} value >7%. Mean duration of DM was 62 ± 79 months. In 14 patients with DM without HF, mean age was 65.9 ± 8.8 years, mean DM duration was 58 ± 36 months, and mean HbA_{1c} was 7.5 ± 1.5% (58 mmol/mol).

^{123}I MIBG imaging

Early and late H/M ratios were significantly lower in patients with HF and DM compared with patients with HF without DM. In particular, DM patients showed a mean early H/M ratio of 1.65 ± 0.21 vs. 1.75 ± 0.21 in non-DM subjects ($P < 0.05$) and a mean late H/M ratio of 1.46 ± 0.22 vs. 1.58 ± 0.24 in non-DM subjects ($P < 0.03$). ^{123}I MIBG washout rate did not significantly differ between the two groups (38 ± 22 vs. 34 ± 22%; $P = 0.44$). Both early and late H/M were significantly higher in DM patients without HF (2.22 ± 0.35 and 1.99 ± 0.24, respectively) when compared with HF patients with ($P < 0.0001$) and without ($P < 0.0001$) DM.

Cardiac autonomic neuropathy

Mean autonomic score was 2.85 ± 0.80 in 20 patients with HF and DM and 3.06 ± 0.62 in 14 patients with DM without HF (P = NS). Autonomic impairment was found in all but 1 diabetic patient with HF and in 12 (86%) diabetic patients without HF. H/M ratios in 12 DM patients without HF with autonomic dysfunction were significantly higher compared with 19 DM patients with HF and with autonomic dysfunction (early H/M 2.24 ± 0.37 vs. 1.62 ± 0.16, respectively, $P < 0.0001$; late H/M 1.96 ± 0.24 vs. 1.42 ± 0.16, respectively, $P < 0.0001$). In the whole group of 34 DM patients evaluated for autonomic impairment, no correlation was found between autonomic score and both early and late H/M ratios ($r = -0.70$, $P = 0.723$ for early H/M; $r = -0.787$, $P = 0.340$ for late H/M). In addition, no correlation was found between mean autonomic score and HbA_{1c} ($r = -0.006$, $P = 0.977$).

Determinants of ^{123}I MIBG uptake in HF patients with and without DM

In the group of 75 patients with HF, in univariate analysis, early H/M ratio significantly correlated with age, LVEF, NYHA class, HF etiology, NT-proBNP, presence of DM, and HbA_{1c} (Table 2). In multivariate analysis, only HbA_{1c}

remained a significant predictor of early H/M ratio (Table 2).

In univariate analysis, late H/M ratio significantly correlated with the same variables associated with early H/M and, in addition, with GFR (Table 2). In multivariate analysis, only etiology of HF remained significantly associated with late H/M. Interestingly, when "presence of DM" was eliminated from the multivariate analysis, HbA_{1c}, in addition to HF etiology, remained significantly correlated with H/M ratio, surely because HbA_{1c} acted as a surrogate for DM.

Determinants of ^{123}I MIBG uptake in HF patients with DM

In the group of HF patients with DM, in univariate analysis, early H/M ratio significantly correlated with LVEF, NT-proBNP, and HbA_{1c} (Table 2 and Fig. 1*A*). In multivariate analysis, LVEF and HbA_{1c} remained significantly associated with H/M (Table 2).

Late H/M ratio significantly correlated with age, LVEF, NT-proBNP, and HbA_{1c} (Table 2 and Fig. 1*B*). In multivariate analysis, only HbA_{1c} remained significantly associated with late H/M (Table 2).

Determinants of ^{123}I MIBG uptake in HF patients without DM

In the group of HF patients without DM, in univariate analysis, early H/M ratio significantly correlated with age, NYHA class, HF etiology, and NT-proBNP

Table 2—*Determinants of ^{123}I MIBG in all patients and in DM and non-DM patients*

	Early H/M				Late H/M			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	β	*P*	β	*P*	β	*P*	β	*P*
All patients								
Age	−0.337	0.003	−0.184	0.079	−0.424	0.000	−0.218	0.138
LVEF	0.360	0.001	0.092	0.506	0.398	0.000	0.070	0.619
NYHA class	−0.291	0.011	−0.088	0.399	−0.362	0.001	−0.184	0.083
Ischemic vs. nonischemic	0.281	0.015	0.094	0.365	0.377	0.001	0.233	0.040
NT-proBNP	−0.404	0.000	−0.193	0.158	−0.462	0.000	−0.235	0.098
WMSI	−0.229	0.179	—	—	−0.194	0.256	—	—
GFR	0.198	0.106	—	—	0.331	0.006	0.057	0.699
Diabetes	−0.227	0.050	0.086	0.475	−0.258	0.025	−0.067	0.580
HbA_{1c}	−0.473	0.001	−0.444	0.000	−0.382	0.001	−0.215	0.074
ACE-Is	0.128	0.274	—	—	0.124	0.288	—	—
ARBs	−0.044	0.706	—	—	−0.012	0.915	—	—
BBs	0.067	0.568	—	—	0.135	0.247	—	—
DM patients								
Age	−0.284	0.088	—	—	−0.369	0.025	−0.247	0.072
LVEF	0.578	0.000	0.396	0.010	0.446	0.006	0.237	0.195
NYHA class	−0.196	0.245	—	—	−0.266	0.112	—	—
Ischemic vs. nonischemic	0.149	0.379	—	—	0.267	0.110	—	—
NT-proBNP	−0.488	0.002	−0.034	0.818	−0.405	0.013	−0.025	0.890
WMSI	−0.334	0.206	—	—	−0.336	0.203	—	—
DM duration	−0.054	0.752	—	—	0.001	0.995	—	—
MNSI	0.109	0.521	—	—	0.170	0.316	—	—
GFR	0.218	0.224	—	—	0.297	0.093	—	—
HbA_{1c}	−0.697	0.000	−0.579	0.000	−0.579	0.000	−0.478	0.001
ACE-Is	0.153	0.367	—	—	0.093	0.586	—	—
ARBs	0.011	0.950	—	—	0.162	0.337	—	—
BBs	0.211	0.210	—	—	0.271	0.104	—	—
Antidiabetic therapy	−0.107	0.528	—	—	0.028	0.868	—	—
Non-DM patients								
Age	−0.359	0.027	−0.180	0.277	−0.452	0.004	−0.252	0.212
LVEF	0.125	0.456	—	—	0.315	0.054	—	—
NYHA class	−0.337	0.038	−0.202	0.217	−0.403	0.012	−0.210	0.161
Ischemic vs. nonischemic	0.385	0.017	0.240	0.152	0.454	0.004	0.254	0.104
NT-proBNP	−0.357	0.028	−0.158	0.350	−0.546	0.000	−0.329	0.039
WMSI	−0.334	0.206	—	—	−0.336	0.203	—	—
GFR	0.173	0.320	—	—	0.375	0.026	−0.022	0.916
HbA_{1c}	−0.075	0.653	—	—	0.034	0.841	—	—
ACE-Is	0.169	0.311	—	—	0.222	0.180	—	—
ARBs	−0.146	0.383	—	—	−0.200	0.230	—	—
BBs	0.030	0.858	—	—	0.130	0.435	—	—

ACE-I, ACE inhibitor; ARB, angiotensin II receptor blocker; BB, β-blocker; MNSI, Michigan Neuropathy Screening Instrument.

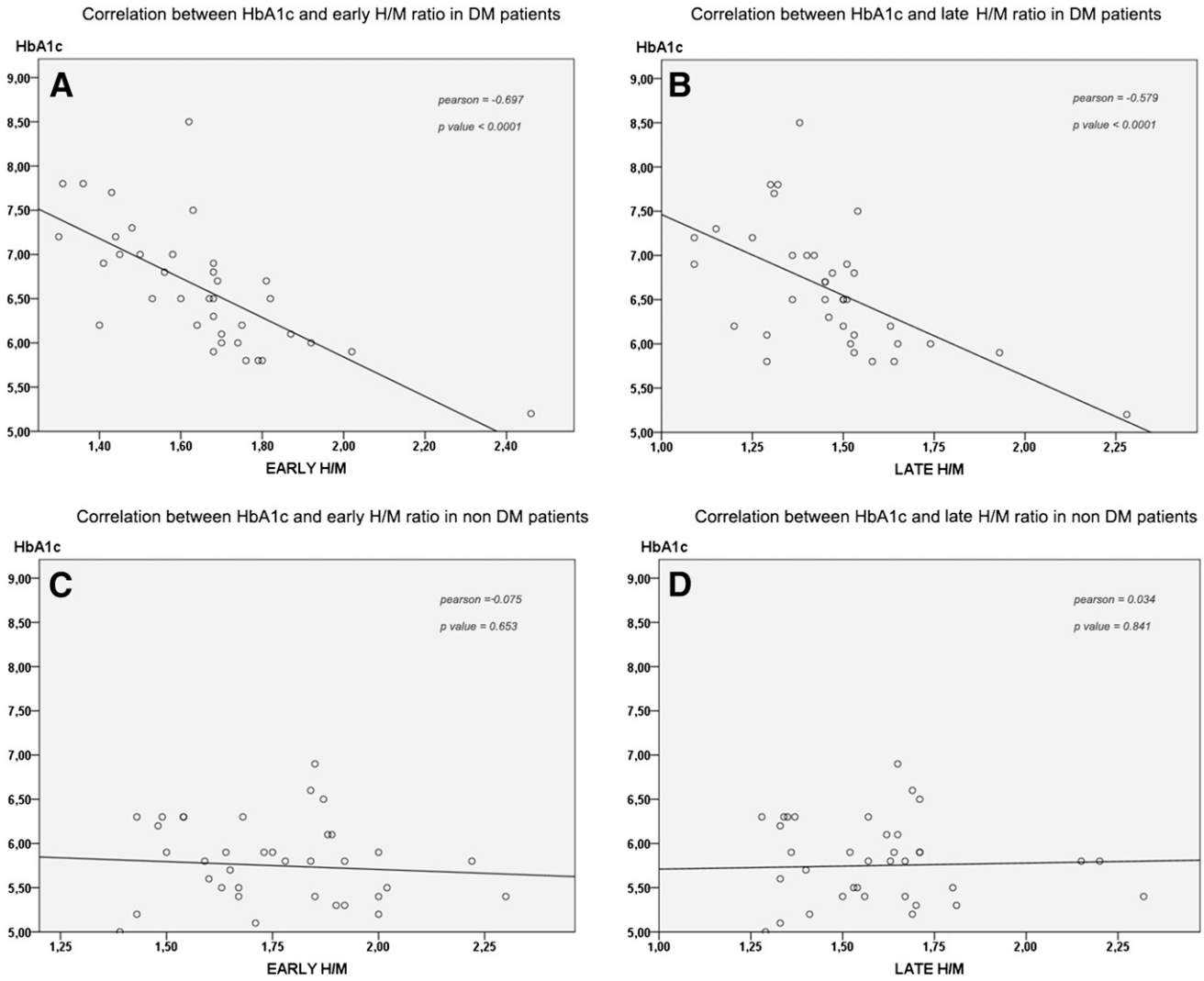

Figure 1—*Correlation between HbA_{1c} and early and late H/M ratio in HF patients with and without DM.* A*: Correlation between HbA_{1c} and early H/M ratio in DM patients.* B*: Correlation between HbA_{1c} and late H/M ratio in DM patients.* C*: Correlation between HbA_{1c} and early H/M ratio in non-DM patients.* D*: Correlation between HbA_{1c} and late H/M ratio in non-DM patients.*

(Table 2 and Fig. 1*C*). In multivariate analysis, none of these parameters remained a significant predictor of early H/M ratio (Table 2).

Late H/M ratio significantly correlated with the same variables associated with early H/M and, in addition, with GFR (Table 2 and Fig. 1*D*). In multivariate analysis, only NT-proBNP remained significantly associated with late H/M (Table 2).

CONCLUSIONS—The current study demonstrates that in DM patients with severe systolic HF, ^{123}I MIBG cardiac uptake is significantly impaired compared with matched HF patients without DM and with DM patients without HF. In addition, in HF patients, ^{123}I MIBG uptake significantly correlates with metabolic control of DM over the last 1–2 months, as indicated by the inverse association between H/M ratios and HbA_{1c} levels.

Previous studies

Impaired ^{123}I MIBG cardiac uptake was previously reported in DM patients without structural heart disease (12) and in DM patients with silent myocardial ischemia (11). In particular, Yufu et al. (12) recently demonstrated, in 108 subjects with type 2 DM but no cardiac diseases, that the ^{123}I MIBG washout rate predicts major adverse cardiac and cerebrovascular events. Moreover, Scholte et al. (25) reported that ^{123}I MIBG imaging was able to detect cardiac neuropathy in DM patients before the development of signs of cardiac autonomic imbalance, such as heart rate variability, and proposed that ^{123}I MIBG imaging may provide early prognostic information in these patients. Mechanisms of reduced cardiac ^{123}I MIBG uptake in DM patients without structural heart diseases are not completely understood and are presumably different from the mechanisms of reduced ^{123}I MIBG uptake in HF patients with DM. Hyperinsulinemia exerts a sympathoexcitatory effect (26) that may lead to enhanced sympathetic tone and reduced ^{123}I MIBG uptake in early stages of DM, whereas cardiac sympathetic denervation, demonstrated at postmortem studies, would be responsible for reduced ^{123}I MIBG uptake in long-term diabetic patients with structural heart disease. However, few clinical data are available on the impact of DM on cardiac sympathetic activity in patients with HF. In fact, the only available data come from a recent

retrospective analysis of the ADMIRE-HF trial (16). In this analysis, Gerson et al. (16) compared 343 DM patients with 618 non-DM patients enrolled in the ADMIRE-HF study (10) and reported that HF patients with DM and ^{123}I MIBG H/M ratio <1.68 had about threefold increased risk of HF progression compared with HF patients without DM and with H/M ratio <1.68. It was also observed that DM patients in the ADMIRE-HF population showed significantly lower ^{123}I MIBG H/M ratios (either early or late H/M) compared with non-DM patients. At variance with our study, ^{123}I MIBG washout rate was also significantly higher in DM compared with non-DM patients. However, due to the retrospective design of that analysis, DM and non-DM patients were not matched for relevant characteristics that may have influenced the differences observed in ^{123}I MIBG parameters. In particular, DM patients had significantly worse clinical conditions and significantly less use of β-blockers and were significantly older than non-DM patients. Since it has been reported that β-blocker therapy restores ^{123}I MIBG uptake (27) and ^{123}I MIBG uptake impairment correlates with the degree of clinical deterioration, it is difficult to dissect from the data of the ADMIRE-HF trial the distinct influence of DM on cardiac ^{123}I MIBG uptake in HF patients.

Apart from the ADMIRE-HF data, no previous studies evaluated the impact of DM on cardiac ^{123}I MIBG uptake in patients with overt HF, whereas an influence of DM on ^{123}I MIBG uptake and an association with subclinical HF were previously observed (28,29). In fact, it was reported that DM patients with normal LV function at rest who developed contractile dysfunction during stress show more impaired ^{123}I MIBG uptake compared with patients with a normal response to stress (28,29).

A provocative observation of the current study is the inverse correlation between HbA_{1c} and either early or late H/M, observed in the whole population and in the subgroup of DM patients but not in non-DM patients. The strength of this association was supported by multivariate analysis that identified HbA_{1c} as the only significant predictor of late H/M ratio and as an independent predictor of early H/M ratio in the subgroup of DM patients. To our knowledge, this observation is novel and, indeed, no such correlation was found in the ADMIRE-HF population (10). However, consistent with our findings, in a previous study, Ziegler et al. (30) observed in a small series of 12 type 1 DM subjects followed up for 4 years that poor glycemic control, assessed by HbA_{1c}, represents a determinant of cardiac ^{123}I MIBG uptake impairment that might be prevented by normoglycemia. In our study, HbA_{1c} assessment and ^{123}I MIBG imaging were obtained in the same day, which may explain the lack of correlation observed in the ADMIRE-HF populations. Notably, MIBG uptake in diabetic and nondiabetic HF patients was significantly lower than that observed in diabetic patients with autonomic dysfunction and normal LV function, suggesting that autonomic dysfunction does not explain the impairment of MIBG uptake in HF diabetic patients. These previous observations and the findings of the current study suggest a potential working hypothesis for future mechanistic studies aimed at assessing whether glycation directly affects the process of noradrenaline reuptake at synaptic level.

Limitations

There are limitations of the study that need to be acknowledged. The first is the relatively small number of patients, which makes our findings preliminary and warranting further confirmation. However, the dispersion of data observed in the current study was of the same magnitude as that observed in the larger ADMIRE-HF population (16), as indicated by the similar coefficient of variations of H/M ratios in the two studies (data not shown). The small number of patients may have prevented differences in the use of β-blockers and ACE inhibitors between DM and non-DM patients with HF to reach statistical significance. However, both classes of drugs demonstrated to improve ^{123}I MIBG uptake (31). Thus, the higher percent of patients taking β-blockers and ACE inhibitors observed in the group of DM patients with HF may only have undermined the differences in H/M ratios observed in the current study. In addition, no influence of type of drug on MIBG uptake was found in univariate analysis. In the current study, ^{123}I MIBG uptake was evaluated from planar images, and, therefore, the value of single-photon emission computed tomography (SPECT) ^{123}I MIBG imaging, reported in previous studies (32), remains to be investigated. Likewise, although our findings were not influenced by wall motion score, lack of SPECT perfusion rest/stress data does not enable us to exclude the impact of myocardial necrosis or myocardial-inducible ischemia on our observations.

In patients affected by chronic, severe systolic HF, DM is associated with reduced cardiac ^{123}I MIBG uptake compared with non-DM patients and with DM patients without HF, and ^{123}I MIBG uptake independently correlates with glycemic control over the last 1–2 months. Additional pathophysiological studies are warranted to assess the biological relevance of these findings and their potential clinical implications for the management of diabetic HF patients.

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S.P. and G.R. conceived, designed, and executed the research project and wrote the first draft of the manuscript. G.P. designed and executed the research project and analyzed and interpreted data. T.P., M.T., and A.B. executed the research project and acquired scintigraphy data. G.S. analyzed data and performed statistical analysis. G.D.F. executed the research project and analyzed data. E.A. executed the research project and acquired data. R.F. executed the research project and performed autonomic neuropathy tests. L.P. executed the research project and performed autonomic neuropathy tests. F.S. executed the research project and performed laboratory analysis. G.G. executed the research project and reviewed and critiqued the manuscript. D.L., B.T., and A.C. reviewed and critiqued the manuscript. P.P.-F. conceived and designed the research project and reviewed and approved the final content of the manuscript. P.P.-F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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