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Regional patterns of cardiac sympathetic denervation in patients with type 2 diabetes mellitus and it's relationship to autonomic dysfunction

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Abstract

Objective: In this study we evaluated regional myocardial blood flow (MBF) and left ventricular (LV) sympathetic innervation using positron emission tomography (PET) and its relationship to standard autonomic function tests (AFT).

Methods: We studied 12 diabetic patients (7M, 5F) (mean age 62±8), and 5 healthy controls (2M, 3F) (mean age 59±10). All patients underwent AFT and cardiac PET imaging with oxygen-15 labeled water to measure myocardial blood flow (MBF) and carbon –11 hydroxyephedrine (HED) to assess presynaptic cardiac sympathetic nerves. HED images were read semi-quantitatively (summed score 4 segment/4 point model) and quantitatively (3-compartment model) to quantify cardiac HED density and flux (B-max). Single compartment model was used for MBF quantification.

Results: All 5 controls had normal MBF, homogeneous uptake of HED, no regional difference in B-max and normal AFT. All 12 diabetic patients had normal MBF, 5 had homogeneous uptake of HED and 7 had heterogeneous uptake. The average HED defects summed score in diabetic patients was 9 in apical, 15 in basal lateral, 11 in distal lateral and 0 in septal region. In heterogeneous group there was a significant difference in B-max between the septal and lateral wall regions (24±12 vs.18 ± 10). On AFT all 12 diabetic patients had normal resting heart rate, RR and normal postural heart rate variability but 6/12 had postural hypotension. All 6 of these patients had heterogeneous HED uptake.

Conclusions: Diabetic patients exhibited LV sympathetic dysfunction predominantly in the lateral wall region and only postural hypotension was significantly correlated with it.

Keywords: Myocardial blood flow, cardiac sympathetic innervation, positron emission tomography, diabetes mellitus, carbon-11 hydroxyephederine

Introduction

The incidence and prevalence of diabetes mellitus (DM) are increasing. Type 2 DM is the most common form and accounts for 97% of cases worldwide. In 2005, approximately 20.8 million US adults (7%) had DM (14.6 million diagnosed and 6.2 million undiagnosed) as determined by elevated fasting glucose levels (>126mg/dl). Approximately 54 million people in United States have impaired fasting glucose levels (100-125 mg/dl). About 20% to 40% of diabetics also have abnormal autonomic function on clinical testing, even when DM is first diagnosed [1-3].

Cardiac autonomic neuropathy is associated with increased morbidity and mortality and has been linked to the occurrence of sudden death. Diabetic patients with autonomic dysfunction, particularly sympathetic involvement as evidenced by postural hypotension, have a poor clinical prognosis with a high 5-year mortality rate, approaching 50% in one series. [4-6]. The determination of the presence of cardiac autonomic neuropathy (CAN) is based on a battery of autonomic function tests. A consensus conference in 1992 recommended that three tests (heart rate variability, Valsalva maneuver, and postural blood pressure testing) be used for longitudinal testing of the cardiovascular autonomic system [1]. These autonomic function tests have been validated as clinical tools for diagnosing diabetic autonomic dysfunction. Proposed mechanisms of neuronal damage include metabolic abnormalities, neuronal ischemia, and immune mediated injury [5,8,9].

Scintigraphic assessment of cardiac sympathetic integrity is possible with the use of radiolabeled analogues of norepinephrine, which are actively taken up by the presympathetic nerve terminals of the heart. Single photon imaging using radiolabeled ^{123}I-metaiodobenzylguanidine (MIBG) and positron emission tomography (PET) using carbon-11 hydroxyephedrine (HED) for evaluating cardiac sympathetic nerve function have been reported [10,20]. HED has been shown to have a regionally homogeneous distribution in all the myocardial segments of the left ventricle in healthy individuals [10]. The objective of this study was to quantify global and regional cardiac HED uptake in patients newly diagnosed with Type 2 DM, and to determine whether there is a correlation between cardiac HED uptake, myocardial perfusion and autonomic dysfunction as assessed with physiologic testing. HED uptake was assessed quantitatively using a

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Table 1. Clinical Characteristics.

	Heterogeneous	Homogeneous	P value
Age (mean)	69 ± 8	75 ± 5	NS
Gender (male/female)	4/3	3/2	NS
Hypertension (%)	100	100	NS
Hyperlipidemia (%)	86	80	NS
Smoking History (%)	71	60	NS
Family History of CAD (%)	29	40	NS
Fasting Blood Glucose (mg/dl)	150 ± 49	158 ± 64	NS
Resting Heart Rate (beats/min)	68 ± 8	71 ± 14	NS
Hemoglobin A1C (%)	7.7 ± 0.6	8.5 ± 1.6	NS

All values are presented as mean ± SD.

3-compartment model that yielded a value for presynaptic receptor density (B_{max}).

Methods

We studied a total of 17 subjects: 12 patients with uncontrolled type 2 DM (based on 1997 ADA criteria), 5 males and 7 females, with a mean age of 62 ± 8 years and 5 non-diabetic controls, 2 male and 3 female subjects, with a mean age of 59 ± 10. (**Table 1**). Investigators were blinded to the DM and control groups.

Patients were excluded if they had pre-existing CAD, congestive heart failure, previous cerebrovascular event, non-diabetic autonomic neuropathy secondary to Parkinson's disease, Shy-Drager syndrome, ethanol use, renal disease (serum creatinine > 1.5 mg/dl), hepatic disease; body mass index > 45 k/m^2, breast feeding or pregnant patients. Women of child bearing potential were required to have a negative urine pregnancy test on the morning of the study prior to PET scans. Patients taking medications known to interfere with neuronal uptake of norepinephrine analogue (tricyclic antidepressants, monoamine oxidase inhibitors, beta-blockers) abstained from such substances for at least 2 weeks before all studies.

Autonomic function testing

All study subjects were tested for cardiovascular autonomic neuropathy utilizing a set of standardized autonomic function tests. For six hours before the autonomic function tests, the subject was asked to avoid food, alcohol, caffeine containing drinks, smoking and insulin. For parasympathetic, testing heart rate variability was measured with deep breathing lying supine at a rate of 6 breaths/min and recorded for 2 minutes on a continuous EKG tracing. Maximal and minimal RR intervals during each respiratory cycle were recorded and the mean value for respiratory cycles was calculated in beats/min. For sympathetic testing, the postural change in systolic blood pressure was measured. The subject's blood pressure was recorded after lying supine for 10 minutes in a quiet room and measured again after standing for 1 minute. For combined parasympathetic and sympathetic testing, resting heart rate was calculated in beats/min as a mean value obtained over 5 minutes after 20 minutes of supine rest. The Valsalva maneuver was performed against a pressure of 40 mmHg for 15 seconds and the ratio of the longest RR interval after the maneuver to the shortest RR interval during the maneuver was calculated. Investigators were blinded to autonomic function test results.

PET imaging

On a separate day after autonomic testing, patients underwent PET scans after an overnight fast. PET images were acquired on Siemens ECAT Accel high-resolution PET scanner (CTI Siemens, Knoxville, Tenn). All images were corrected for scatter and measured photon attenuation. Oxygen-15 labeled water (0.3-0.4 mCi/Kg) was administered by an intravenous bolus and a 5-minute dynamic scan was obtained for the assessment of myocardial perfusion. After decay of radioactivity to background levels, carbon-11 HED (10-20 mCi) was injected intravenously over 30 seconds. A dynamic 60-minute scan for HED uptake was then performed.

Image reconstruction was performed using iterative reconstruction and a Hann filter. Multiple transverse slices of the heart were obtained and standardized regions of interest are placed on the septum, apex and lateral myocardium. In addition, a region of interest in the basal left ventricular blood pool was monitored for input function. Myocardial perfusion in ml/g/min was assessed using a single compartment model by a standard mathematical approach developed and validated in our laboratory [**11**]. B_{max} was obtained in the same regions of interest using a 3-compartment model (**Figure 1**). We applied this formula to calculate $B_{max}/K_d = (K_1 \times k_3)/(k_2 \times k_4)$ [**12**].

In addition to quantitative analyses, PET images were also assessed visually. For each study subject, the transaxial images obtained from PET scan were visually inspected and a score assigned to the HED uptake in each of the four regions of interest, the basal lateral wall, distal lateral wall, septum and apex. Scores were given based on the following scale: 0=Normal tracer uptake, 1=Mild reduction, 2=Moderate reduction, 3=Severe reduction or absent tracer activity. Summed score was based on 4 segment/4 point model. For each myocardial segment, the scores of all the diabetic patients were summated. Higher scores were consistent with more severe reduction of tracer uptake. Participants with a score of $\geq$2 were defined as heterogeneous and participants with a score of less than 2 were defined as homogeneous.

Autonomic function tests and PET imaging were conducted by separate investigators and technicians. The cardiologists reading the PET scans were blinded to the results of the autonomic function tests and vice versa.

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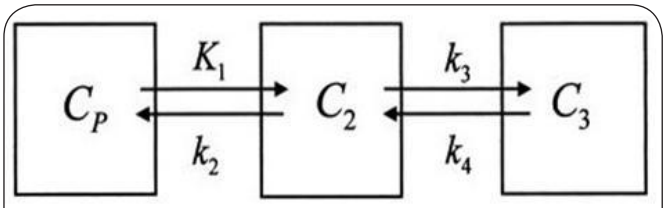

Bmax/Kd = (K1 x k3)/(k2 x k4)

Figure 1. Three compartment model used to quantify cardiac HED density and flux.
Cp = plasma activity, K1 = transfer constant from plasma to tissue for receptor-containing and reference tissues, respectively (ml/g/min), k2 = transfer constant from tissue to plasma for receptor-containing tissues (per minute), k3, k4 = transfer constants between second and third compartments (per minute). K3 = (1/V2) kon Bmax and k4=koff.
Bmax (RATIO OF RECEPTOR DENSITY TO BINDING CONSTANT (Kd)

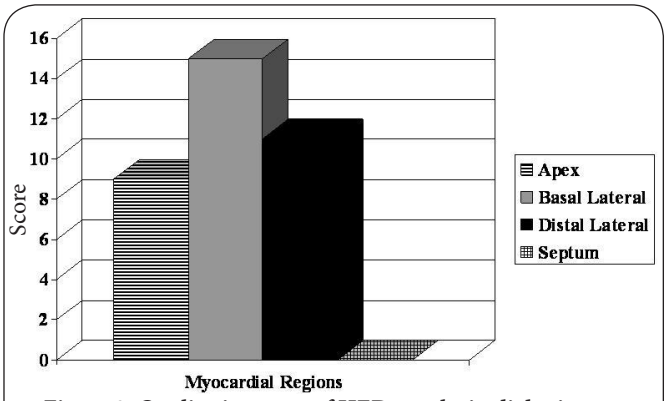

Figure 2. Qualitative score of HED uptake in diabetics.
Qualitative score (visual assessment) for left ventricular HED uptake in diabetics by 4segment/4point model.
Segments: Basal lateral, Distal lateral, Apical, Septal.
Severity Score (point): 0=Normal, 1=Mild reduction, 2=Moderate reduction, 3=Severe reduction or absent tracer activity.

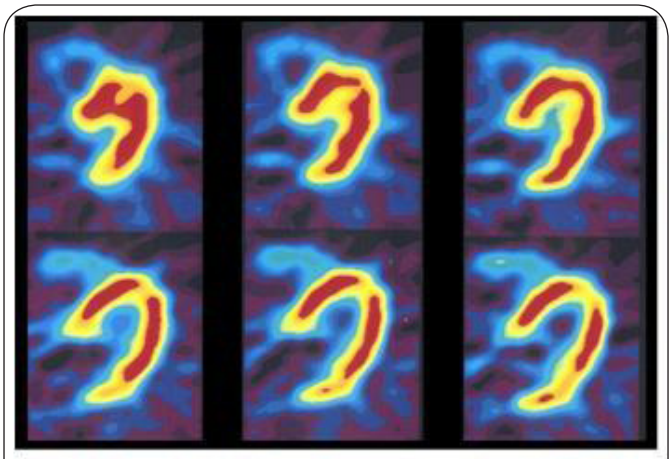

Figure 3. Mid-left ventricular trans-axial images of C-11 HED uptake in a diabetic patient without autonomic dysfunction.
In this figure, the septum is to the upper left, apex to the upper right, lateral wall to the lower right, and the discontinuity to the lower left represents the mitral valve plane.

The study protocol was approved by the Institutional Review Board of Columbia University Medical Center as well as by the Radioactive Drug Research Committee and the Joint Radiation Safety Committee of the University.

Statistical analysis
Data are presented as mean ± SD. HED data was correlated with each autonomic function test using the Spearman's coefficient for non-parametric variables. Tests for significant associations were conducted using a two-tailed student's t-test. Statistical significance was defined as a p value less than 0.05.

Results
Regional myocardial C-11 HED uptake
In all the study participants, C-11 HED uptake was measured separately for the four segments of the left ventricle (basal lateral wall, distal lateral wall, apex, and septum). The tracer uptake was evaluated by both visual and quantitative analyses. The diabetic patients were subdivided into 2 groups – Patients with heterogeneous HED uptake, and patients with homogeneous HED uptake.

Visual assessment of tracer distribution
Scores from all four LV segments showed homogeneous HED uptake in 5 diabetic patients, moderate to severe reduction of lateral wall tracer uptake in 6 patients with or without additional apical defects and isolated severely reduced uptake only in the apical region of one patient. The average score for the 6 patients with defects in the basal lateral LV wall was 2.5 ± 0.8 and the distal lateral region having a score of 1.8 ± 1.1. Basal lateral tracer uptake was reduced in all 6 patients and 5 out of 6 also had reduced tracer uptake in distal lateral region. Apical uptake was reduced in 3 patients and their average score was 1.5 ± 1.6. Tracer uptake was normal in the septum of all the diabetic patients; therefore, the summated score was 0. The differences in the regional myocardial scores in the diabetic patients are illustrated in **Figure 2**. All five non-diabetic control subjects had normal tracer uptake in all four LV regions. **Figure 3** shows the PET images of a diabetic patient with normal HED uptake in all the myocardial regions. **Figure 4** shows PET images of a diabetic patient with severely reduced HED uptake in the basal lateral segment and moderately decreased HED uptake in the distal lateral segment.

Quantitative analysis of C-11 HED uptake
In the heterogeneous HED group, the mean B_{max} in the lateral wall was significantly lower than that in the septum (18±10 vs. 24±12 P= 0.05) despite equal blood flow. The mean B_{max} in the apical region was not significantly different from the B_{max} measured in either the lateral wall or the septum. In

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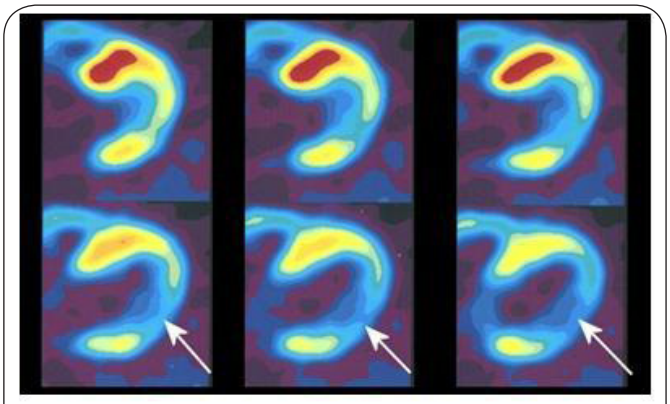

Figure 4. Mid-ventricular trans-axial images from a patient with DM and autonomic dysfunction.
There is severely decreased HED uptake in the basal lateral segment and moderately decreased HED uptake in the distal lateral segment.

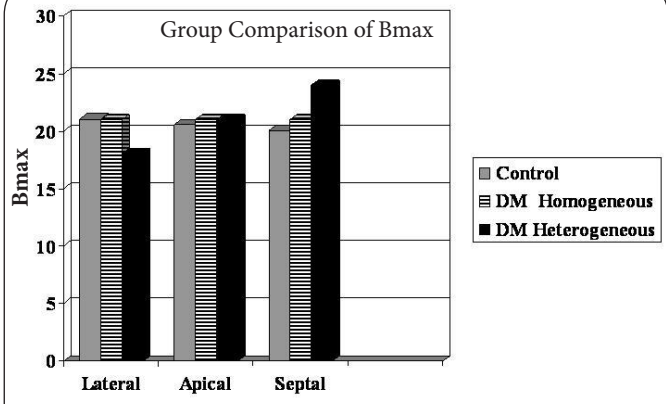

Figure 5. Comparison of Bmax in the 3 myocardial regions in diabetics.

the 5 patients with homogeneous HED uptake, there was no significant difference in B-max between the septal, apical or lateral wall.

In non-diabetic subjects, the mean B_{max} in septal, apical or lateral either wall was not significantly different from each other. **Figure 5** depicts the regional variations in B_{max} seen in diabetic patients, but not observed in the control group. When compared to the control subjects, the diabetic subjects were found to have lower mean B_{max} in the lateral wall and higher B_{max} in the septum, with a trend towards statistical significance. Visual assessments of the septal, apical and lateral walls were correlated with the mean B_{max} in these walls. There was a good correlation between the visual assessment and the quantitative analysis.

Regional myocardial perfusion

The blood flow measurements in the apex, lateral wall and the septum were not significantly different from each other in heterogeneous, homogeneous, or the control groups

Table 2. Myocardial blood flow.

	Lateral wall	Septum	Apex	Global
Diabetics with heterogeneous HED uptake	1.19 ± 0.36	1.26 ± 0.41	1.27 ± 0.41	1.24 ± 0.38
Diabetics with homogeneous HED uptake	1.22 ± 0.33	1.02 ± 0.35	1.40 ± 0.33	1.20 ± 0.33
Controls	1.04 ± 0.25	1.01 ± 0.22	1.06 ± 0.17	1.04 ± 0.19

All values are presented as mean blood flow in ml/g/min ± SD.

Table 3. Autonomic function test results.

	Diabetics with heterogeno HED uptake	Diabetics with homogenous HED uptake	Controls
Heart Rate at rest (beats/min)≥90*	70 ± 11	63 ± 10	59 ± 9.5
Heart Rate Variability (beats/min) ≤ 8*	8.0 ± 2.0	11± 1.2	12.0 ± 1.6
Systolic BP on Standing (mm Hg)≥20*	20 ± 6 *†	9 ± 4 †	8 ± 4*

All values are presented as mean ± SD
• Denotes criterion for abnormal test results
• *P<0.005
• † P<0.005

(**Table 2**). Comparing the heterogeneous HED uptake group with the homogeneous HED uptake group, no significant difference in myocardial blood flow was detected in any of the four LV segments. In patients with heterogeneous HED uptake, there was no significant difference in the blood flow among the four LV segments.

Clinical tests of autonomic dysfunction

There was no statistically significant difference noted in resting heart rate between the heterogeneous, group, homogeneous group and the controls There was also no statistically significant difference in heart rate variability among the three groups (**Table 3**). There was a statistically significant decrease in systolic blood pressure on standing (> 20 mm Hg) between heterogeneous group compared to the homogeneous group and between heterogeneous group compared to the controls but not between the homogeneous and control groups (**Table 3**).

Discussion

About half (58%) of the diabetic patients in this study demonstrated regional variation in myocardial C-11 HED uptake with the majority of them showing reduced uptake in the lateral LV wall. These findings suggest destruction or dysfunction of sympathetic nerves preferentially in the lateral LV wall. Reduction of ^{11}C-HED uptake was more severe in the basal portion of the lateral LV wall than the distal LV wall and apex. Heterogeneity in MIBG uptake has been reported in diabetics in previous study. These studies have reported

a pattern of predominantly apical denervation and basal hyperinnervation [13]. Our findings show predominantly LV lateral wall sympathetic nerve destruction or dysfunction. There are major differences in our study and previous studies. All previous studies in diabetic patients have been with SPECT imaging using I-123 MIBG. This difference can be attributed to different isotopes, better resolution with PET imaging and the ability to do absolute quantification with PET imaging. To the best of our knowledge no other group has studied cardiac sympathetic nerve destruction or dysfunction in diabetic patients using ^{11}C-HED PET imaging.

Cardiovascular autonomic neuropathy has been implicated as an independent risk factor for increased cardiovascular mortality in patients with diabetes [14-16]. Although it is difficult to determine the independent effects of CAN on mortality because of the co-existence of coronary artery disease, predisposition to malignant arrhythmias is considered to be one of the mechanisms by which autonomic neuropathy may cause increased mortality independent of myocardial ischemia [17]. Literature suggests that regions of sympathetic hyperinnervation by acting as foci of electrical instability, may contribute to ventricular arrhythmias and sudden cardiac death [13]. Therefore, the abnormalities of sympathetic nerve structure/function found in our diabetic participants may have prognostic implications.

Abnormalities of cardiac sympathetic nerve structure/function observed in our PET studies correlated with abnormal tests of cardiovascular sympathetic function. Diabetic patients in this study with abnormalities of cardiac sympathetic nerve structure/function in PET images were noted to have postural hypotension consistent with decreased cardiovascular sympathetic reflexes. None of the diabetic patients with homogeneous HED uptake had postural hypotension.

Regional myocardial blood flow at rest was measured in all study subjects, to exclude decreased perfusion causing reduced tracer delivery and uptake. No significant difference was noted in the regional myocardial blood flow in diabetics, indicating that the decreased B_{max} in the lateral wall was a result of decreased HED uptake by sympathetic nerves rather than diminished regional blood flow. Compared with healthy controls, the global blood flow was found to be higher in diabetics, although the difference was not statistically significant. Similar findings on myocardial perfusion have been reported in previous studies on diabetic patients [18,19].

Abnormalities in sympathetic innervation have been seen on cardiac imaging in diabetic patients with normal cardiovascular reflex tests, suggesting direct cardiac imaging may be more sensitive in detecting CAN than indirect tests of autonomic function [20,21]. Most of the previously published studies have been conducted on patients with Type 1 diabetes. Our study is one of the few studies to evaluate the distribution of abnormalities of cardiac sympathetic nerve structure/function in patients with Type 2 diabetes. Limitations of our study include the small sample size, as well as the non-age matched control subjects. The younger controls do not however affect our results on the regional differences in sympathetic innervation observed in the diabetic subjects.

Nevertheless, our findings are interesting and suggest that abnormalities of cardiac sympathetic nerve structure and/or function are common in T2 DM and often are present before the usual autonomic screening tests become abnormal. It is interesting that, of the standard screening tests for cardiac autonomic neuropathy, only postural hypotension is associated with the regional changes in structure/function of cardiac sympathetic nerves detected by PET images using ^{11}C-HED as the imaging reagent. These striking findings should encourage additional studies of cardiac sympathetic nerves in a variety of pathologic states. By design, the present studies were kept simple by including patients with T2 DM of short duration and by excluding patients with known coronary heart disease.

Conclusion

We conclude that PET imaging with radiolabeled norepinephrine analogues *e.g.,* HED can be used to delineate abnormalities of cardiac sympathetic nerve structure/function in type 2 DM. We observed a pattern of sympathetic denervation in the lateral wall and hyperinnervation in the septum, which correlated with postural hypotension. Of the three standard autonomic function tests only postural hypotension was significantly correlated with cardiac sympathetic dysinnervation. Early detection of autonomic dysfunction on PET imaging would indicate need for more aggressive glucose control. Further studies are required to assess the prognostic value of this noninvasive modality in the diabetic population.

Competing interests

The authors declare that they have no competing interests.

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