

# Impact of Type 2 Diabetes Mellitus on Sympathetic Neural Mechanisms in Hypertension

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**Background**—Essential hypertension (EHT) is a major cardiovascular risk factor, and the additional presence of type 2 diabetes mellitus (DM2) increases this risk. However, although the sympathetic nerve hyperactivity of EHT is known to play a role in cardiovascular risk, the level of sympathetic nerve activity is known neither in DM2 nor in hypertensive type 2 diabetic patients (EHT+DM2). Therefore, we planned to quantify the vasoconstrictor sympathetic nerve activity in patients with EHT+DM2 and with DM2 relative to that in matched groups with EHT and normal blood pressure (NT).

**Methods and Results**—In 68 closely matched subjects with EHT+DM2 (n=17), DM2 (n=17), EHT (n=17), and NT (n=17), we measured resting muscle sympathetic nerve activity as the mean frequency of multiunit bursts (MSNA) and of single units (s-MSNA) with defined vasoconstrictor properties. The s-MSNA in EHT+DM2 ( $97 \pm 3.8$  impulses/100 beats) was greater (at least  $P < 0.001$ ) than in EHT ( $69 \pm 3.4$  impulses/100 beats) and DM2 ( $78 \pm 4.1$  impulses/100 beats), and all these were significantly greater (at least  $P < 0.01$ ) than in NT ( $53 \pm 3.3$  impulses/100 beats) despite similar age and body mass index. The MSNA followed a similar trend. In addition, the level of insulin was also raised in EHT+DM2 ( $20.4 \pm 3.6$   $\mu\text{U/mL}$ ) and DM2 ( $18.1 \pm 3.1$   $\mu\text{U/mL}$ ; at least  $P < 0.05$ ) compared with HT or NT.

**Conclusions**—Patients with EHT+DM2, EHT, or DM2 had central sympathetic hyperactivity, although plasma insulin levels were raised only in EHT+DM2 and DM2. The combination of EHT and DM2 resulted in the greatest sympathetic hyperactivity and level of plasma insulin, and this hyperactivity could constitute a mechanism for the increased risks of this condition. (*Circulation*. 2003;108:3097-3101.)

**Key Words:** nervous system, sympathetic ■ hypertension ■ diabetes mellitus

Sympathetic hyperactivity is known to occur in essential hypertension (EHT)<sup>1-4</sup> and has been reported to be involved in its pathogenesis and ensuing cardiovascular risks.<sup>5,6</sup> Type 2 diabetes mellitus (DM2) commonly coexists with EHT, and the presence of EHT and DM2 (EHT+DM2) is known to multiply these risks further,<sup>7,8</sup> to the extent that the World Health Organization and the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommend screening for DM2 in all patients with EHT.<sup>9,10</sup> Despite these 2 points, very little is known about the level of sympathetic output in EHT+DM2 or in DM2 alone. Increases in sympathetic output in EHT+DM2 or in DM2 alone have not been confirmed in studies measuring indirect indices such as noradrenaline plasma levels.<sup>11-14</sup>

The present investigation was therefore designed to determine whether or not the magnitude of central sympathetic output in EHT+DM2 is greater than that in EHT alone, to quantify this output in DM2 alone, and to examine any contribution of DM2 to the sympathetic hyperactivity in

combined EHT+DM2. For this purpose, we directly measured the resting mean frequency of central sympathetic nerve output to the periphery in age-, body weight-, and arterial pressure-matched groups of patients with treated EHT+DM2, EHT alone, or DM2 alone and a normal control group (NT).

## Methods

### Subjects

A total of 73 white subjects were examined. They included 18 patients with EHT+DM2, 19 with EHT, 18 with DM2 alone, and 18 normotensive controls (NT). All had similar occupational status and dietary habits, including a sodium intake of  $\approx 400$  mmol/d. All patients were screened by history and physical and laboratory examination. They were excluded if there was evidence of secondary hypertension, cardiac dysrhythmias, left ventricular hypertrophy, vascular disease, microalbuminuria, or chronic disease that may influence the autonomic nervous system, including peripheral or autonomic neuropathy. Screening for neuropathy included conventional neurological examination and previously established techniques,<sup>15,16</sup> in addition to the use of a standard 1- and 10-g Semmes-Weinstein monofilament on-off vibration. Absence of au-

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tonomic neuropathy was also confirmed by showing that the baroreceptor reflex sensitivity that controls the efferent vagal effect on heart rate, as derived from the Valsalva maneuver,<sup>17,18</sup> in EHT+DM2 ( $3 \pm 0.5$  ms/mm Hg) was similar ( $P > 0.05$ , ANOVA) to that in EHT ( $4 \pm 0.5$  ms/mm Hg) and was less (at least  $P < 0.01$ , ANOVA) than the similar values ( $P > 0.05$ , ANOVA) obtained in DM2 ( $6 \pm 0.5$  ms/mm Hg) and in NT ( $6 \pm 0.5$  ms/mm Hg). In addition, all subjects showed an increase in arterial pressure and sympathetic nerve activity during an initial screening isometric handgrip test. Left ventricular hypertrophy was excluded by 2D echocardiography, whereby none of the patients had posterior wall or interventricular septal thickness that exceeded 11 mm, as recommended by the American Society of Echocardiography.<sup>19</sup> Of the 73 patients examined, stable microneurographic data to obtain single-unit activity could not be obtained in 5. Complete data were therefore obtained from 17 patients with EHT+DM2, 17 patients with EHT, 17 patients with DM2, and 17 subjects with NT.

Patients with EHT+DM2 had their diabetes and hypertension diagnosed for a mean of  $22 \pm 5$  and  $25 \pm 6$  months, respectively, and their DM2 and EHT both well controlled at least over the preceding 6 months (mean hemoglobin [Hb] A1c of  $\leq 7.3 \pm 0.5\%$ ). The diagnosis of DM2 was confirmed as recommended by the American Diabetes Association.<sup>20</sup> Patients with EHT had established hypertension for a mean of  $20 \pm 4$  months, and this was not significantly different from that of the EHT+DM2 group ( $P > 0.5$ , unpaired *t* test). As with EHT+DM2, arterial pressure in the EHT group had also been well controlled at least over the preceding 6 months. Patients in the DM2 group were diagnosed  $24 \pm 6$  months previously, and their condition was well controlled at least over the preceding 6 months (mean Hb A1c of  $\leq 7.3 \pm 0.3\%$ ). The documented arterial pressure for all subjects was based on the average of at least 3 seated recordings taken on separate occasions. Fasting plasma insulin, glucose, and Hb A1c levels were obtained through a venous sample. Insulin was measured by solid-phase 2-site immunoassay (AutoDELFIA, PerkinElmer Life Sciences). The intra-assay variability was 2.1% to 3.7%. The interassay coefficient of variation was 3.3% to 3.8%. Blood glucose was measured by autoanalyzer (Roche/Hitachi GOD-PAP, Roche Diagnostics), with an intra-assay variability for glucose of 0.9%. Insulin resistance was assessed by the previously validated homeostasis model assessment (HOMA),<sup>21,22</sup> whereby the HOMA index of insulin resistance (HOMA-IR) = fasting glucose (mmol/L)  $\times$  fasting insulin ( $\mu$ U/mL)/22.5. The 4 groups were matched in terms of age, body weight, and body mass index. Also, patients who were entered into the investigation were receiving similar antihypertensive therapy and had similar levels of arterial pressure. Therapy in the EHT+DM2 and EHT groups respectively included ACE inhibitors (13 and 9 patients), angiotensin II receptor blockers (1 patient each), and  $\beta$ -blockers (5 and 7 patients). In addition, EHT+DM2 patients were receiving metformin ( $n=10$ ), gliclazide ( $n=4$ ), or combined therapy ( $n=1$ ). Therapy in DM2 patients included ACE inhibitors ( $n=9$ ), metformin ( $n=9$ ), gliclazide ( $n=3$ ), or combined therapy ( $n=2$ ). The investigation was performed with the approval of St. James's University Hospital Ethics Committee, and all subjects provided informed written consent.

## General Protocol

Hemodynamic, microneurographic, and autonomic measurements in the 4 groups were obtained in an identical manner during each session. The details of the protocol regarding most of the 4 groups of data have been published previously.<sup>4,23</sup> In brief, all investigations were performed under similar conditions between the hours of 9 AM and 12 PM to avoid circadian autonomic variation. Subjects were asked to have had a light breakfast and to empty their bladder before commencing the study. They were requested to avoid nicotine and caffeine products for 12 hours and alcohol and strenuous exercise for 24 hours before investigation. During each session, subjects were studied in the semisupine position. Measurements were made in a darkened laboratory in which the temperature was always between 22°C and 24°C. Resting blood pressure was measured from the arm with a mercury sphygmomanometer. Changes in heart rate and

arterial pressure were monitored and recorded by standard ECG and a Finapres device, and blood flow to the muscle of the left calf was obtained with standard mercury-in-silastic strain-gauge plethysmography.

## Microneurography

Postganglionic muscle sympathetic nerve activity (MSNA) was recorded from the right peroneal nerve as described previously.<sup>4,23</sup> The neural signal was amplified ( $\times 50\,000$ ), and for the purpose of generating bursts representing multiunit discharge, the signal was filtered (bandwidth of 700 to 2000 Hz) and integrated (time constant 0.1 second). The output of action potentials and bursts from this assembly was passed to a data-acquisition system, which digitized the action potentials at 12 000 samples/second and other data channels at 2000 samples/second (8 bits).

MSNA was differentiated from skin sympathetic activity and afferent activity by previously accepted criteria.<sup>24–26</sup> Single units (s-MSNA) in the raw action potential neurogram were obtained by adjusting the electrode position while using fast monitor sweep and an online storage oscilloscope to confirm the presence of a consistent action potential morphology, as described previously.<sup>4,23</sup> Only vasoconstrictor units were accepted and examined, the criteria of acceptance being appropriate responses to spontaneous changes in arterial blood pressure, the Valsalva maneuver, and isometric handgrip exercise. Simultaneous measurement of calf vascular resistance confirmed the vasoconstrictor function of the observed neural activity. During the Valsalva maneuver, sympathetic activity increased during the latter part of phase II and/or phase III and decreased during phase IV (corresponding to the decrease and increase of arterial pressure). Isometric handgrip exercise, performed with a dynamometer, produced a late increase in arterial blood pressure and sympathetic nerve activity.

An electronic discriminator was used objectively to count the spikes of s-MSNA, and this was quantified as the mean frequency of impulses/minute and also as impulses/100 cardiac beats to avoid any interference by the length of the cardiac cycle.<sup>27</sup> The bursts of MSNA were identified by inspection when the signal-to-noise ratio was  $>3$ , and they were quantified in a similar manner. The variability of measuring both s-MSNA and MSNA in this laboratory did not exceed 10%.<sup>4</sup> Calf vascular resistance was obtained from the product of mean arterial blood pressure on the mean of at least 3 measurements of calf blood flow.

## Statistics

One-way ANOVA with Newman-Keuls multiple posttest comparisons was used to compare data between the 4 groups. The least squares technique was used for assessing the linear relationship between variables. Values of  $P < 0.05$  were considered statistically significant and the data presented as mean  $\pm$  SEM.

## Results

The data from the 4 groups of EHT+DM2, EHT, DM2, and NT subjects are shown in Table 1. The groups were well matched for age, body weight, body mass index, and gender ( $\chi^2=0.01$ ;  $P > 0.90$ ). There were no statistically significant differences between the groups in heart rate. Also, there were no significant differences in indices of arterial pressure between the 4 groups, although as expected, EHT+DM2 and EHT patients had slightly higher systolic arterial pressure than DM2 and NT subjects. However, as previously shown in populations with hypertension or normal arterial pressure,<sup>4</sup> there was no significant correlation within any of the 4 groups between any of the measures of sympathetic nerve activity and the 3 indices of arterial pressure ( $0.18 < \Gamma < 0.36$ ; at least  $P > 0.07$ ). The measures of sympathetic activity showed a significant correlation to age in each of the 4 groups ( $0.55 < \Gamma < 0.86$ ; at least  $P < 0.02$ ), as has been reported previously.<sup>4,25</sup>

TABLE 1. Details of the 4 Groups

Variable	EHT+DM2 (1)	EHT (2)	DM2 (3)	NT (4)	P			
					1 vs 2	1 vs 3	2 vs 4	3 vs 4
No. of patients (females)	17 (7)	17 (7)	17 (6)	17 (8)	...	...	...	...
Age, y	57±2.1	57±2.2	54±2.5	56±1.9	>0.05	>0.05	>0.05	>0.05
BMI, kg/m <sup>2</sup>	31±0.7	30±1.0	30±1.0	28±0.9	>0.05	>0.05	>0.05	>0.05
Weight, kg	87±3.9	84±2.8	88±3.9	81±2.9	>0.05	>0.05	>0.05	>0.05
Heart rate, bpm	71±3.4	63±2.1	70±1.7	67±1.2	>0.05	>0.05	>0.05	>0.05
Mean ABP, mm Hg	101±2.1	103±2.3	97±1.2	99±1.0	>0.05	>0.05	>0.05	>0.05
Systolic ABP, mm Hg*	144±3.2	141±3.1	135±2.0	132±1.9	>0.05	<0.05	>0.05	>0.05
Diastolic ABP, mm Hg	80±1.9	83±2.1	78±1.3	82±0.8	>0.05	>0.05	>0.05	>0.05

BMI indicates body mass index; ABP, arterial blood pressure. Data are mean±SEM.

\* $P<0.01$ ; 1-way ANOVA for all groups. Significant differences between groups (Newman-Keuls) are shown in left 4 columns.

All measures of the mean frequency of sympathetic nerve activity of s-MSNA and MSNA per minute and per 100 beats were significantly greater in EHT+DM2 than in EHT and DM2, and the activity in these 3 groups was significantly greater than in NT (Table 2; Figures 1 and 2). Compared with the NT control group, s-MSNA hyperactivity of EHT+DM2 was approximately twice as large, EHT was ≈33% greater, and DM2 was ≈50% greater. Similar differences, although of lesser magnitude (respectively, 67%, 33%, and 50%), were seen with respect to MSNA in the hypertensive and diabetic groups compared with normal controls.

Levels of plasma insulin and glucose for the 4 groups are shown in Table 2. Plasma insulin and glucose levels were greater in the 2 diabetic groups (respectively by ≈240% and 104% in EHT+DM2 and 202% and 98% in DM2) than in NT controls. Similarly, HOMA-IR was greater in EHT+DM2 and DM2 than in the EHT and NT groups.

## Discussion

Our findings have reconfirmed the previously reported existence of sympathetic hyperactivity in EHT relative to NT,<sup>1-4</sup> and this occurred in the absence of raised plasma insulin levels. The findings have also provided novel evidence that patients with DM2 had sympathetic hyperactivity and that sympathetic neural discharge to the periphery was even greater in EHT+DM2 patients.

The present investigation was designed to avoid the confounding effects of left ventricular hypertrophy, race, age,

body weight, time of day, dietary sodium intake, large meal and visceral distension, alcohol, nicotine, and exercise on sympathetic nerve activity.<sup>23,28-36</sup> These criteria were satisfied by closely matching the study and control groups and by using the same protocol for all subjects. In addition, the result of antihypertensive therapy in EHT+DM2 and EHT patients led to comparable arterial pressure levels between the 4 groups. Although there was no correlation between sympathetic nerve activity and arterial pressure indices, the latter may be confounded by the severity of hypertension,<sup>4,23</sup> which was avoided in the present study. Furthermore, the 4 groups were well matched in terms of heart rate, and the findings were not affected by measuring the frequency of nerve activity over 1 minute or over 100 cardiac beats.

The above matching between groups was achieved while accepting that there must be differences between the hypertensive and diabetic groups and normal controls in terms of giving antihypertensive and antidiabetic therapy. Nevertheless, the antihypertensive therapy was similar between the EHT+DM2 and EHT groups. In the context of hypertensive patients, it has been shown that chronic administration of ACE inhibitors does not affect MSNA levels,<sup>37</sup> whereas  $\beta$ -blocking agents may have no effect on MSNA or may decrease it.<sup>38</sup> Analysis of data in patients who did not take  $\beta$ -blocking agents did not affect our findings of a greater sympathetic nerve hyperactivity in EHT+DM2 than in EHT. Patients in the EHT+DM2 and DM2 groups also received antidiabetic therapy comprising mainly metformin, the effect

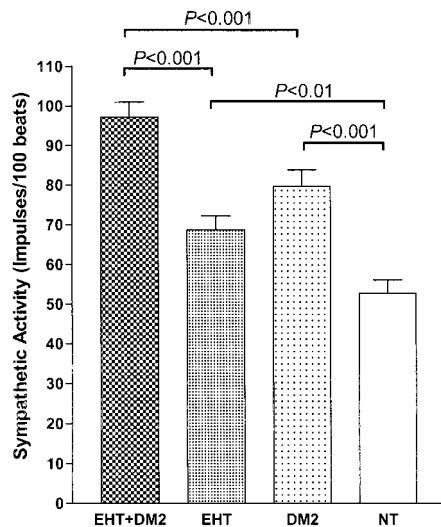
TABLE 2. Findings in the 4 Groups

Variable	EHT+DM2 (1)	EHT (2)	DM2 (3)	NT (4)	P			
					1 vs 2	1 vs 3	2 vs 4	3 vs 4
s-MSNA, impulses/100 b*	97±3.8	69±3.4	78±4.1	53±3.3	<0.001	<0.001	<0.01	<0.001
s-MSNA, impulses/min*	67±3.6	44±2.0	54±2.4	35±1.9	<0.001	<0.001	<0.05	<0.001
MSNA, bursts/100 b*	77±3.0	60±3.0	67±3.3	47±2.7	<0.001	<0.05	<0.01	<0.001
MSNA, bursts/min*	53±2.6	38±1.6	46±1.7	31±1.6	<0.001	<0.05	<0.01	<0.001
Fasting insulin, $\mu$ U/mL	20.4±3.6	7.2±1.8	18.1±3.1	6.0±1.3	<0.05	>0.05	>0.05	<0.05
Fasting glucose, mmol/L	10.2±0.9	5.5±0.2	9.9±0.9	5.0±0.2	<0.001	>0.05	>0.05	<0.001
HOMA-IR, U	9.1±1.8	1.9±0.6	7.9±1.4	1.4±0.3	<0.01	>0.05	>0.05	<0.05

Data are mean±SEM. MSNA and s-MSNA are expressed per 100 cardiac beats (100 b) and per minute.

\* $P<0.0001$ ; 1-way ANOVA for all groups. Between-group analyses (Newman-Keuls) are shown in left 4 columns.

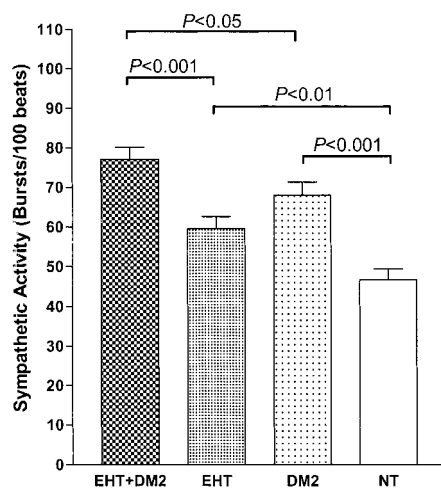




**Figure 1.** Resting mean frequency of s-MSNA in 4 groups of subjects (EHT+DM2, EHT, DM2, and NT), expressed as mean (height of columns) and SEM (bars). Significance values (*P*) refer to between-group comparisons (Newman-Keuls) after 1-way ANOVA.

of which on MSNA is unknown in the present patient population. However, it has previously been shown that metformin does not affect resting sympathetic nerve activity in insulin-resistant hypertensive patients.<sup>39</sup> Furthermore, despite the similar proportion of EHT+DM2 and DM2 patients who were receiving metformin, sympathetic hyperactivity was still greater in the former condition. Also, analysis of data in patients not taking metformin did not affect our findings of greater sympathetic nerve hyperactivity in EHT+DM2 than in DM2. Therefore, it is considered unlikely that these agents caused the sympathetic hyperactivity seen in EHT+DM2 and DM2.

Although the potential mechanisms that result in central activation or modulation of the sympathetic nervous system



**Figure 2.** Resting mean frequency of multiunit MSNA in 4 groups of subjects (EHT+DM2, EHT, DM2, and NT), expressed as mean (height of columns) and SEM (bars). Significance values (*P*) refer to between-group comparisons (Newman-Keuls) after 1-way ANOVA.

in EHT have been reported previously,<sup>4,6</sup> our new findings may suggest mechanisms for the observed sympathetic hyperactivity in DM2 and EHT+DM2. For instance, it is well known from research in humans and experimental animals that acute hyperinsulinemia increases sympathetic output, with the likely site of this activation being in the brain.<sup>40</sup> The present data have shown a remarkable association between hyperinsulinemia and sympathetic hyperactivity in that the 2 variables were increased in DM2 relative to NT and in EHT+DM2 relative to EHT. Furthermore, the present data show that the sympathetic hyperactivity in EHT+DM2 was approximately that found in DM2 in addition to that known to occur in EHT.<sup>1–4</sup> These considerations make it possible in the present patient population to suggest that the sympathetic nerve hyperactivity in DM2 may be related to increased plasma insulin levels and that this hyperactivity has contributed to the excessive sympathetic activation in EHT+DM2. These suggestions are supported by the present findings of no significant effects of confounding variables other than insulin; the sympathetic hyperactivity could not have arisen solely because of different age, body weight, arterial pressure, or heart rate.

The increased risk of cardiovascular complications in EHT+DM2 has been attributed to numerous mechanisms, including dyslipidemia, coagulation abnormalities, endothelial dysfunction, and chronic sympathetic nerve activation induced by the repeated occurrence of excessive hyperinsulinemia.<sup>7,8,14,41</sup> Although the present investigation was not designed to establish a role of augmented sympathetic drive, it is possible to argue that it may at least constitute a mechanism leading to the increased cardiovascular complications. Indeed, sympathetic hyperactivity has been proposed to lead to cardiovascular complications in some patients with EHT.<sup>3,6</sup> If such mechanisms are established, they may bring to light the importance of aiming antihypertensive treatments not only at the reduction of raised arterial pressure but also at the excessive sympathetic hyperactivity and its effects.

In summary, the present investigation has shown that the magnitude of peripheral sympathetic nerve hyperactivity in patients with EHT+DM2 was greater than that in patients with either EHT or DM2 alone. It is proposed that mechanisms related to hyperinsulinemia and hypertension combine to result in an excessive sympathetic hyperactivity, which could constitute one of the many mechanisms resulting in the greater cardiovascular complications reported in EHT+DM2.

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