Muscle Sympathetic Nerve Activity in Renovascular Hypertension and Primary Aldosteronism

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Previous studies, including our own, have demonstrated that muscle sympathetic nerve activity (MSNA) is increased in patients with essential hypertension compared with normotensive subjects. However, the features of sympathetic nerve activity are still unknown in secondary hypertension. We examined MSNA in eight patients with renovascular hypertension and in 11 patients with primary aldosteronism. Twenty patients with essential hypertension and 20 normotensive subjects who were age-matched to the patients with renovascular hypertension and those with primary aldosteronism were also studied. The MSNA of a bundle of the tibial nerve was recorded by microneurography in supine subjects and expressed as both burst rate (bursts/min) and burst incidence (bursts/100 heart beats). Plasma renin activity and the plasma concentration of angiotensin II and aldosterone were also measured. MSNA was increased in the patients with renovascular hypertension compared with the patients with primary aldosteronism and those with essential hypertension and the normotensive subjects (p<0.01 for each). MSNA was decreased in the patients with primary aldosteronism compared with those with essential hypertension (p<0.01), and it was smaller than in the normotensive subjects (p<0.1). Furthermore, MSNA, plasma renin activity, and the plasma concentration of angiotensin II decreased significantly in five patients with renovascular hypertension 4–10 days after successful percutaneous renal angioplasty. Thus, the changes in MSNA seem to characterize the pathophysiology of renovascular hypertension and primary aldosteronism. Activation of the renin-angiotensin system may be involved in the increase in the central outflow of sympathetic nerve activity, thus exacerbating hypertension in patients with renovascular hypertension. (Hypertension 1991;17:1057–1062)

Neurogenic mechanisms have often been implicated in the pathogenesis of hypertension. Although the plasma concentration of norepinephrine has been used as a rough index of overall sympathetic nerve activity, its pathophysiological implications need careful evaluation since the plasma concentration of norepinephrine is determined by many factors, such as the reuptake and metabolic degradation of norepinephrine and its spillover from the nerve endings. Accordingly, we have investigated sympathetic tone by directly recording the muscle sympathetic nerve activity (MSNA) contained in a bundle of the tibial nerve using a microneurographic technique in the conscious human. Our previous studies have demonstrated that the baroreflex control of sympathetic nerve activity is impaired and that there is a consequent increase in MSNA in patients with borderline or essential hypertension compared with normotensive subjects. These results suggest a role of the sympathetic nervous system in the development and maintenance of high blood pressure in essential hypertension (EH). However, the role of sympathetic nervous activity in secondary hypertension remains controversial.

It is well known that angiotensin II (Ang II) can affect the plasma norepinephrine concentration by increasing the synthesis or release of norepinephrine or by blocking its neuronal uptake. Furthermore, Ang II may stimulate sympathetic nervous discharges by acting on the central nervous system or the sympathetic ganglia. However, the relation of the sympathetic nervous system to blood pressure elevation in secondary hypertension or the interaction between sympathetic nerve activity and the renin-angiotensin system remains unclear. Thus, the present study investigates MSNA in two common forms...
of secondary hypertension, renovascular hypertension (RVH) and primary aldosteronism (PA), which contrast one another with respect to the activity of the renin-angiotensin system, and it compares the MSNA in these patients with the MSNA in patients with essential hypertension and in normotensive subjects. Furthermore, the changes in MSNA in patients with RVH who underwent successful renal angioplasty are also examined.

Methods

Subjects

Eight patients, 16–58 years old, with RVH and 11 patients, 27–52 years old, with PA caused by a solitary aldosteronoma were studied. Twenty patients, 18–57 years old, with EH and 20 normotensive subjects, 23–58 years old, were also studied for comparison. All participants were hospitalized and placed on a diet containing about 7 g of sodium chloride per day. Diagnosis was based on thorough examinations, including radiological and endocrinologic studies in addition to hematologic and biochemical studies. When the presence of significant renal artery stenosis was confirmed by renal arteriography and a definite difference in plasma renin activity (PRA) between the renal vein blood samples was obtained from both kidneys, the patients were diagnosed as having RVH. The diagnosis of PA was based on the demonstration of increased production of aldosterone despite low PRA levels and the existence of adrenal adenomas by adrenal phlebography or adrenal scintigraphy. All of the PA patients were free from serious cardiovascular complications, and many of them underwent surgery thereafter. Accordingly, the presence of adrenal aldosteronomas was confirmed by histological examinations.

The hypertensive patients had never been treated or had not been given any antihypertensive drugs for at least 1 week before the study, except for two patients with RVH and one with PA, who were administered short-acting calcium antagonists until 48 hours before the study began. Participants were asked to refrain from smoking, drinking coffee, and taking sedatives for at least 14 hours before study onset. The study protocol was approved by the Committee for Clinical Research Trials, Second Department of Internal Medicine, Yokohama City University. Informed consent was obtained from each subject after the purpose and procedures of the study had been fully explained.

Study Protocol

The study was performed on subjects lying supine on a table. Brachial blood pressure was measured continuously using an automated sphygmomanometer (CBM 2000, Colin Medical, Komaki, Japan). Heart rate was also monitored electrocardiographically. Thirty to 40 minutes after insertion of an electrode into a nerve bundle of the tibial nerve for recording the MSNA, venous blood samples were obtained from the antecubital vein to measure PRA, plasma Ang II, and plasma aldosterone concentration (PAC). Recording of the MSNA was carried out for 30–60 minutes. When MSNA, blood pressure, and heart rate stabilized, the baseline MSNA was sampled for 15–30 minutes.

Five of the eight RVH patients underwent percutaneous transluminal renal angioplasty, which was performed using a regular balloon catheter (OMG 7.0R, Cook Inc., Bloomington, Ind.). A definite reduction in blood pressure was observed in all of the treated patients. The same protocol for recording MSNA was repeated 4–10 days after the successful angioplasty.

Recording of MSNA

The recording of MSNA was carried out in the same way as previously described. Briefly, a tungsten microelectrode 200 μm in shaft diameter with an uninsulated tapered tip of 1–5 μm (25-05-1, Frederick Haer & Co., Brunswick, Me.) was inserted through the skin into a bundle of muscle nerve fibers of the tibial nerve at the popliteal fossa. The criteria for acceptable recordings were as follows: 1) Weak electrical stimulation of the tibial nerve via the electrode elicited involuntary muscle contraction but not paresthesia. 2) Tapping or stretching of the muscle and tendon supplied by the fascicle of the tibial nerve that was being monitored elicited different mechanoreceptor discharges, whereas stroking of the skin in the distribution of the tibial nerve did not evoke afferent discharges. 3) The spike revealed characteristic pulse-synchronous spontaneous discharges during phases II and III of a Valsalva's maneuver. 4) The spike potential was markedly diminished by ganglion blockade with trimethaphan. If the recording showed instability or a poor signal-to-noise ratio, then it was discarded.

The intensity of MSNA was assessed by counting the number of sympathetic bursts. Two blinded observers collected the data by listening to the characteristic sounds of sympathetic bursts projected from a loudspeaker. Both burst rate (bursts/min) and burst incidence (bursts/100 heart beats) were calculated.

Measurement of Plasma Renin Activity, Angiotensin II, and Plasma Aldosterone Concentration

Venous blood samples obtained from the antecubital vein were placed into prechilled tubes containing ethylenediaminetetraacetic acid disodium (1 mg/ml). Samples were immediately centrifuged at 4°C, and stored at −80°C until use. PRA, Ang II, and PAC were determined by radioimmunoassay (New England Nuclear, Boston, Mass.).

Statistics

Data are expressed as mean±SEM and were analyzed by analysis of variance. For F ratios significant at 0.05 or less, Duncan's multiple range test was applied to determine the significance of the differences between given pairs of means. The data ob-
TABLE 1. Age, Systolic and Diastolic Blood Pressure, Heart Rate, Plasma Renin Activity, Plasma Angiotensin II, and Plasma Aldosterone Concentration in Patients With Renovascular Hypertension, Primary Aldosteronism, and Essential Hypertension and in Normotensive Subjects

<table>
<thead>
<tr>
<th></th>
<th>RVH (n=8)</th>
<th>PA (n=11)</th>
<th>EH (n=20)</th>
<th>NT (n=20)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>39.4±5.6</td>
<td>39.5±2.3</td>
<td>39.7±2.7</td>
<td>39.3±2.6</td>
<td>0.003</td>
<td>0.997</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>180.0±5.2</td>
<td>166.2±3.4</td>
<td>159.5±4.5</td>
<td>124.4±2.0</td>
<td>37.925</td>
<td>2.0×10^-14</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>110.6±3.7</td>
<td>104.6±2.4</td>
<td>97.8±2.8</td>
<td>73.8±2.8</td>
<td>37.890</td>
<td>2.0×10^-13</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68.3±2.7</td>
<td>70.4±2.8</td>
<td>71.9±2.3</td>
<td>67.2±1.3</td>
<td>1.141</td>
<td>0.341</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>6.99±1.87</td>
<td>0.13±0.02</td>
<td>1.01±0.18</td>
<td>0.79±0.14</td>
<td>23.530</td>
<td>6.3×10^-10</td>
</tr>
<tr>
<td>Ang II* (pg/ml)</td>
<td>60.2±32.4</td>
<td>7.4±0.9</td>
<td>12.6±1.4</td>
<td>8.8±1.0</td>
<td>4.697</td>
<td>6.4×10^-7</td>
</tr>
<tr>
<td>PAC (ng/ml)</td>
<td>300.6±73.9</td>
<td>295.5±31.4</td>
<td>82.2±10.2</td>
<td>80.1±9.2</td>
<td>22.776</td>
<td>1.0×10^-9</td>
</tr>
</tbody>
</table>

Data are mean±SEM.

RVH, renovascular hypertension; PA, primary aldosteronism; EH, essential hypertension; NT, normotensive; BP, blood pressure; PRA, plasma renin activity; Ang II, plasma angiotensin II; PAC, plasma aldosterone concentration.

*Number of subjects undergoing Ang II measurement in each group: RVH, 7; PA, 8; EH, 17; and NT, 14.

Results

Main Clinical Characteristics in Hypertensive and Normotensive Subjects

Although age was not significantly different among the RVH, PA, and EH patients and the normotensive subjects, the differences in systolic and diastolic blood pressures were significant: Systolic and diastolic blood pressures were significantly higher in all of the hypertensive groups than in the normotensive group (p<0.01; Table 1). There was no significant difference in heart rate among the four groups (Table 1).

Both PRA and Ang II were significantly greater in the RVH patients compared with the PA and EH patients and the normotensive subjects (all p<0.01). In contrast, PRA was significantly smaller in the PA patients compared with the EH patients or the normotensive subjects (all p<0.01; Table 1). The difference in PAC between the patients with PA and those with RVH was not significant (Table 1).

MSNA in Patients With Renovascular Hypertension and in Those With Primary Aldosteronism

MSNA was significantly greater in the RVH patients compared with the PA and EH patients and the normotensive subjects (all p<0.01), whether it was expressed in terms of burst rate or burst incidence (Figure 1). In contrast MSNA, which was expressed as either unit, was significantly smaller in the PA patients than in the EH patients (p<0.01), and it tended to be smaller in the PA patients than in the normotensive subjects (p<0.01; Figure 1). The difference in MSNA, which was expressed as either unit, between the EH patients and the normotensive subjects was also significant (p<0.05; Figure 1).

Changes in MSNA, Plasma Renin Activity, and Angiotensin II After Successful Renal Angioplasty

In five patients with RVH, MSNA was reexamined 4–10 days after successful renal angioplasty. Both patients compared with the EH patients and the normotensive subjects (all p<0.01), while it was also significantly higher in the RVH patients than in the EH patients and the normotensive subjects (p<0.01; Table 1). The difference in PAC between the patients with PA and those with RVH was not significant (Table 1).

FIGURE 1. Bar graphs showing muscle sympathetic nerve activity (MSNA) in patients with renovascular hypertension (RVH), primary aldosteronism (PA), and essential hypertension (EH), as well as in normotensive subjects (NT). Data were assessed by analysis of variance. Differences between groups were significant, whether MSNA was expressed as the burst rate (bursts/min) (left panel) or the burst incidence (bursts/100 heart beats) (right panel).
systolic and diastolic blood pressures decreased significantly following renal angioplasty, while heart rate did not change significantly (Table 2). PRA, Ang II, and PAC were reduced in all subjects after angioplasty, and the resulting average values were statistically significant (all \( p < 0.05 \); Table 2). MSNA was also decreased after the angioplasty in all of the patients (Figures 2 and 3), whether MSNA was expressed as the burst rate (\( p < 0.01 \)) or the burst incidence (\( p < 0.05 \)).

**Discussion**

We reported previously that MSNA at rest, which was assessed by the same method used in the present study, increased with advancing age in patients with EH and in normotensive controls and that the MSNA was significantly greater in the former than in the latter at any age level. Thus, sympathetic nerve activity plays a long-term role in the development and maintenance of blood pressure elevation in EH.\(^7\,8\) Although many pieces of evidence suggest the important role of the sympathetic nervous system not only in EH but also in some types of secondary hypertension, the clinical implication of sympathetic nerve activity in secondary hypertension remains controversial. Since it has been assumed that there is a close link between the sympathetic nervous system and the renin-angiotensin system, the present study focuses on the MSNA in RVH and PA, which contrast one another with respect to the activity of the renin-angiotensin system. For comparison, we also analyzed MSNA in patients with EH and in normotensive subjects who were of similar age to the RVH and PA patients (Table 1).

When we compared MSNA among these age-matched groups, the MSNA had increased significantly in the RVH group compared with the other groups (Figure 1). On the other hand, although blood pressure was comparable between the patients with PA and those with EH, MSNA tended to be smaller in the PA patients than in the normotensive subjects (Figure 1). In accordance with our previous study,\(^7\,8\) MSNA was significantly higher in patients with EH than in the normotensive subjects (Figure 1). Thus, despite comparable blood pressure levels, the MSNA moved in opposite directions in the RVH and PA patients, being increased in the former and decreased in the latter. Furthermore, we found that the reductions in blood pressure, PRA, and Ang II after successful renal angioplasty were accompanied by a significant reduction in MSNA in five patients with RVH (Figures 2 and 3). Accordingly, there is prob-

| TABLE 2. Systolic and Diastolic Blood Pressure, Heart Rate, Plasma Renin Activity, Plasma Angiotensin II, and Plasma Aldosterone Concentration Before and After Renal Angioplasty in Five Patients With Renovascular Hypertension* |
|---------------------------------|-----------------|-----------------|---|
| Systolic BP (mm Hg)            | Before          | After           | \( p \) |
|                                | 177.8±7.5       | 142.4±9.4       | 0.01 |
| Diastolic BP (mm Hg)           | 110.0±3.4       | 87.8±6.6        | 0.025 |
| Heart rate (beats/min)         | 70.0±3.0        | 68.8±1.5        | .. |
| PRA (ng/ml/hr)                 | 7.0±2.6         | 0.8±0.3         | 0.05 |
| Ang II (pg/ml)                 | 70.9±45.6       | 10.1±2.9        | 0.05 |
| PAC (ng/ml)                    | 299.6±106.8     | 75.5±38.1       | 0.05 |

BP, blood pressure; PRA, plasma renin activity, Ang II, plasma angiotensin II; PAC, plasma aldosterone concentration.

*Data are mean±SEM and were analyzed by the paired \( t \) test for systolic blood pressure, diastolic blood pressure, and heart rate. Skewed data for PRA, Ang II, and PAC were analyzed by the Wilcoxon signed rank test.

**FIGURE 2. Renal arteriogram from a 28-year-old woman with renovascular hypertension (RHV).** Arrow in upper left panel (before) indicates renal artery stenosis, which has been dilated by percutaneous transluminal renal angioplasty in upper right panel (after). After the successful angioplasty, muscle sympathetic nerve activity (MSNA) (shown as sympathetic bursts) was significantly reduced, accompanied by a significant reduction of blood pressure.
ably a close relation between the renin-angiotensin system and sympathetic nerve activity.

The results of our study seem to be consistent with those of the study that showed an increased urinary excretion of norepinephrine in RVH patients compared with hypertensive patients with normal renin activity. However, only a limited role of the sympathetic nervous system was suggested from a study that investigated two patients with RVH. In that study, it was concluded that the sympathetic nervous system might modulate only short-term blood pressure fluctuations since both blood pressure and PRA fell after nephrectomy, with plasma catecholamine levels being unaffected. However, it is possible that the stressful surgical intervention related to nephrectomy may have cancelled the decrease in plasma catecholamine levels accompanying a decrease in the activity of the renin-angiotensin system. In addition, despite the reduction in blood pressure, the plasma catecholamine levels of these two patients remained higher than normal after nephrectomy. Therefore, it does not seem reasonable to exclude the possibility that the sympathetic nervous system is involved in the maintenance of hypertension in human RVH.

Although the mechanism through which renal artery stenosis leads to increased sympathetic nerve activity is still uncertain, activation of the renin-angiotensin system and the subsequent elevation of circulating Ang II seem to be involved in the activation of the sympathetic nervous system. It is well known that Ang II can elevate peripheral sympathetic nerve activity by stimulating the central nervous system and the sympathetic ganglia. Furthermore, Luft et al have detected an elevation of basal splanchnic sympathetic nerve activity in conscious rats during prolonged Ang II infusion. However, Katholi et al suggested a key role of afferent renal nerves in activating the sympathetic nervous system and the maintenance of high blood pressure in two-kidney, one clip Goldblatt hypertension because renal denervation of the clipped kidney restored both plasma norepinephrine and blood pressure to their normal ranges, even though PRA was unchanged. Therefore, we may not be able to conclude that activation of the renin-angiotensin system simply accelerates MSNA, even if we find the concurrent reduction of both PRA and MSNA after renal angioplasty.

The sympathetic nervous system could be involved in various experimental models of hypertension; for example, steroid-salt hypertension has been reported to be accompanied by increased activity of the sympathetic nervous system. However, the present study demonstrates that in contrast to RVH patients, MSNA is decreased in PA patients (Figure 1). Similar findings have also been reported from both animal experiments and clinical studies. An elevation of blood pressure induced by long-term oral administration of metyrapone to dogs was associated with a decrease rather than an increase in plasma catecholamines. Furthermore, this elevation of blood pressure could not be prevented by agents that suppressed catecholamine release. It is postulated that mineralocorticoids elevate blood pressure mainly by increasing total peripheral resistance and vascular reactivity to catecholamines in humans, with a tendency to suppress circulating catecholamines. In addition, neither measurements of plasma catecholamine levels nor analysis of the cardiovascular responses to sympatholytic agents in patients with PA have afforded any evidence of enhanced peripheral sympathetic activity in mineralocorticoid-excess hypertension. These findings and our recent preliminary findings, which show an increase of MSNA after adrenalectomy in PA patients (unpublished observation from our laboratory), are in line with the results indicating that sympathetic nerve activity was rather suppressed in PA patients.

It has been indicated that RVH often has a high prevalence of malignant or accelerated hypertension compared with other types of hypertension. In contrast, it has been pointed out that the appearance of malignant or accelerated hypertension is relatively rare in PA. Thus, it seems possible that the renin-angiotensin system and the sympathetic nervous system, which are altered in opposite directions in RVH and PA, are involved in modulating the clinical characteristics of these two forms of secondary hypertension.

In summary, we found that MSNA was increased in patients with RVH, but decreased in those with malignant or accelerated hypertension.
PA compared with EH patients or normotensive subjects. MSNA, PRA, and Ang II were decreased after successful renal angioplasty in five patients with RVH. Thus, a close relation seems to exist between the sympathetic nervous system and the renin-angiotensin system, especially in RVH. These findings suggest that the sympathetic nervous system is involved in the pathophysiology of hypertension in which can be assessed by recording MSNA, may be partly responsible for the specific clinical features of some forms of hypertension.

References

Key Words • sympathetic nervous system • aldosterone • angiotensin II • plasma renin activity • renovascular hypertension • aldosteronism
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E Miyajima, Y Yamada, Y Yoshida, T Matsukawa, H Shionoiri, O Tochikubo and M Ishii

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