Relationship of Neurovascular Compression to Central Sympathetic Discharge and Essential Hypertension

Paul A. Smith, MB, ChB,* James F. M. Meaney, FRCR,† Lee N. Graham, MB, ChB,* John B. Stoker, BSc, MB, ChB,* Alan F. Mackintosh, MA, MD,* David A. S. G. Mary, MB, ChB, PhD,* Stephen G. Ball, MB, BCHIR, PhD*

Leeds, United Kingdom; and Dublin, Ireland

OBJECTIVES
We planned to examine the relationship between neurovascular compression (NVC) of the rostral ventrolateral medulla (RVLM) and the magnitude of central sympathetic hyperactivity in normal subjects and in patients with untreated and uncomplicated essential hypertension (EHT).

BACKGROUND
Previously it has not been possible to establish a definitive relationship between EHT and NVC of the RVLM, a location containing efferent sympathetic vasoconstrictor neurons. Furthermore, the relationship between NVC and magnitude of sympathetic nerve hyperactivity has not been adequately examined, despite the knowledge that hyperactivity varies according to EHT severity.

METHODS
In 83 subjects, we used magnetic resonance imaging to detect NVC and, independently, peroneal microneurography to quantify muscle sympathetic nerve activity (MSNA), expressed as the mean frequency of multi-unit discharge (m-MSNA) and of single units (s-MSNA). Subjects were classified according to arterial pressure values into groups with normal (NT) (n = 24) or high-normal (HN) (n = 14) arterial pressure and mild (EHT-1) (n = 26) or severe (EHT-2/3) (n = 19) EHT.

RESULTS
A significantly greater sympathetic activity was found in 23 subjects with NVC, compared with 60 subjects without NVC. The prevalence of NVC and the magnitude of sympathetic hyperactivity were greater in the EHT-1 group (p < 0.05) than in the other three groups. There was no significant difference in confounding variables between the groups. Although increased sympathetic activity was strongly predictive of NVC, this was not significantly related to baroreceptor sensitivity controlling the pulse interval (cardiac baroreceptor reflex sensitivity).

CONCLUSIONS
Neurovascular compression of the RVLM may cause central sympathetic activation in normal and hypertensive populations and therefore has significant implications regarding the pathogenesis of EHT. (J Am Coll Cardiol 2004;43:1453–8) © 2004 by the American College of Cardiology Foundation

Central sympathetic hyperactivity has long been implicated in the pathogenesis of essential hypertension (EHT) (1,2). Despite extensive research, the precise cause of this central sympathetic activation remains unclear. The rostral ventrolateral medulla (RVLM) is an area rich in central sympathetic neurons (3), and it has been proposed that neurovascular compression (NVC) of the left RVLM may lead to activation of these neurons and thereby EHT. There have been numerous reports on the association between NVC and hypertension (4,5), and a microsurgical approach to NVC has been employed to treat patients with intractable hypertension (6), albeit with inconclusive results. Despite this, there has been sparse and inadequate information on the relationship between NVC and the magnitude of central sympathetic output (7–11), as either indirect indexes of sympathetic activity have been used or the confounding effects of antihypertensive treatment have not been excluded. Furthermore, the complex relationship between arterial pressure level and sympathetic activity has not been taken into account. Previously, using the mean frequency of single units of muscle sympathetic nerve activity (s-MSNA), the magnitude of central sympathetic activity has been shown to vary according to the level of arterial pressure in untreated groups of normal and hypertensive subjects (12).

The present study was therefore planned to determine the relationship between NVC and the magnitude of central sympathetic vasoconstrictor nerve output to the skeletal muscle vascular bed. This was undertaken in populations with untreated and uncomplicated EHT and normotension, classified according to the Joint National Committee (JNC)-VI criteria (13).

METHODS
Subjects. The study involved a consecutive series of 95 untreated Caucasian subjects who were prospectively examined between 1999 and 2002. Twelve subjects were excluded because of either an inability to obtain stable microneuro-
Abbreviations and Acronyms

- BRS = baroreceptor reflex sensitivity
- EHT = essential hypertension
- EHT-1 = group classification for mild essential hypertension
- EHT-2/3 = group classification for severe essential hypertension
- HN = group classification for high-normal arterial pressure
- JNC = Joint National Committee
- m-MSNA = multi-unit muscle sympathetic nerve activity
- NT = group classification for normal arterial pressure
- NVC = neurovascular compression
- RVLM = rostral ventrolateral medulla
- s-MSNA = single-unit muscle sympathetic nerve activity

graphic data (n = 7), a failed magnetic resonance examination due to claustrophobia (n = 4), or poor magnetic resonance image quality (n = 1). Of the 83 subjects studied, 40 were women and 43 were men, ranging in age between 26 and 73 years. All subjects were screened by a history, physical examination, and laboratory study. Patients with complicated or secondary hypertension (including those with left ventricular hypertrophy) were excluded, as were those with arrhythmia or chronic disease, which may influence the autonomic nervous system. All subjects had similar dietary habits, in particular, a sodium intake of ~400 mmol/day. Each subject provided informed, written consent to be in the investigation, which was performed under the approval of the Leeds Health Authority Ethical Committee.

Values of arterial pressure were based on the average of at least three recordings taken in a seated position on separate occasions in the clinic setting, and this was used to classify groups according to JNC-VI criteria (13). Thus, subjects classified as NT had systolic and diastolic pressures of <130 and <85 mm Hg, respectively; those classified as HN had either systolic pressure of 130 to 139 mm Hg or diastolic pressure of 85 to 89 mm Hg; those classified as EHT-1 had systolic or diastolic pressure of 140 to 159 or 90 to 99 mm Hg, respectively; and those classified as EHT-2/3 had respective values of ≥160 or ≥100 mm Hg. Blood pressure (BP) status was confirmed using ambulatory BP monitoring (TRACKER NIBP2, Reynolds Medical Ltd., Hertford, United Kingdom).

Magnetic resonance imaging. Magnetic resonance imaging was performed using a 1.5-T Philips Gyroscan ACS-NT (Philips Medical Systems, Eindhoven, the Netherlands) with a standard head coil. Images were obtained using a three-dimensional, fast-field, gradient-echo, “time-of-flight” sequence (repetition time [TR] 30 ms, echo time [TE] 7 ms, flip angle 15°, scan matrix 256 × 192, field of view 220 × 150 mm, 64 × 0.8-mm-thick slices centered over the posterior fossa were generated) (14,15).

Source axial images were inspected for the presence or absence of blood vessel contact with the left ventrolateral medulla. The three-dimensional nature of the acquisition allowed the reviewer to reformat the anatomy in multiple planes and to identify the vessel responsible for compression by applying a maximum-intensity projection algorithm. Neurovascular compression was defined by the absence of “black” cerebrospinal fluid between the “white” of the blood vessel and the “grey” of the left-hand side of the medulla within 10 mm of the ponto-medullary junction (Fig. 1). All images were assessed by two reviewers, independently of other variables, and a consensus decision was reached as to the presence or absence of NVC.

Microneurography. The details of the microneurography protocol have been published previously (12,16). Briefly, studies were performed under similar conditions between
Table 1. Characteristics of the 83 Subjects Classified According to the Presence or Absence of Neurovascular Compression

<table>
<thead>
<tr>
<th>Variable</th>
<th>NVC (−)</th>
<th>NVC (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females (n)</td>
<td>34/26</td>
<td>9/14</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>49 ± 1.4</td>
<td>50 ± 2.5</td>
</tr>
<tr>
<td>Range</td>
<td>26–73</td>
<td>26–69</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 0.5</td>
<td>27 ± 0.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79 ± 1.8</td>
<td>80 ± 3.2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68 ± 1.4</td>
<td>67 ± 2.0</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>143 ± 2.4</td>
<td>148 ± 4.0</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>91 ± 1.7</td>
<td>92 ± 1.8</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>108 ± 1.6</td>
<td>111 ± 2.4</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SEM. There were no statistically significant differences in any variable between the two groups.

BMI = body mass index; BP = blood pressure; MAP = mean arterial pressure; NVC (+) and NVC (−) = with and without neurovascular compression, respectively.

Table 2. Characteristics of the 83 Subjects Classified According to the Level of Arterial Pressure and Criteria of JNC-VI (13)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal BP (NT)</th>
<th>High-Normal BP (HN)</th>
<th>Mild Hypertension (EHT-1)</th>
<th>Severe Hypertension (EHT-2/3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females (n)</td>
<td>11/13</td>
<td>8/6</td>
<td>12/14</td>
<td>12/7</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>46 ± 2.5</td>
<td>49 ± 2.7</td>
<td>49 ± 2.1</td>
<td>52 ± 2.7</td>
</tr>
<tr>
<td>Range</td>
<td>26–68</td>
<td>33–64</td>
<td>26–73</td>
<td>26–69</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26 ± 0.8</td>
<td>27 ± 0.8</td>
<td>27 ± 0.8</td>
<td>28 ± 1.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 ± 2.5</td>
<td>82 ± 3.7</td>
<td>79 ± 2.9</td>
<td>83 ± 3.7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65 ± 1.9</td>
<td>66 ± 3.0</td>
<td>67 ± 1.9</td>
<td>74 ± 2.6*</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>125 ± 1.0</td>
<td>136 ± 1.0</td>
<td>149 ± 1.1</td>
<td>170 ± 3.2†</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>80 ± 0.8</td>
<td>85 ± 1.2</td>
<td>95 ± 0.8</td>
<td>101 ± 1.3†</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>95 ± 1.0</td>
<td>102 ± 0.9</td>
<td>113 ± 0.9</td>
<td>124 ± 1.5†</td>
</tr>
</tbody>
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*p < 0.05 and †p < 0.001 by analysis of variance. Data are presented as the mean value ± SEM.

EHT-1 = group classification for mild essential hypertension; EHT-2/3 = group classification for severe essential hypertension; HN = group classification for high-normal arterial pressure; NT = group classification for normal arterial pressure; Other abbreviations as in Table 1.

STATEMENT OF THE PROBLEM

The relationship between systolic blood pressure and heart rate may be a result of the interplay of sympathetic neural mechanisms (12). The present study was designed to test the hypothesis that sympathetic neural outflow to peripheral vasculature, as quantitated by post-ganglionic neural activity, is increased during the Valsalva maneuver in hypertensive compared to normotensive subjects. The study also compared the results obtained in hypertensive subjects with and without the presence of neurovascular compression (NVC), as previously described (12,16).

METHODS

Subjects

Table 1. Characteristics of the 83 Subjects Classified According to the Presence or Absence of Neurovascular Compression

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Data are presented as the mean value ± SEM. There were no statistically significant differences in any variable between the two groups.

BMI = body mass index; BP = blood pressure; MAP = mean arterial pressure; NVC (+) and NVC (−) = with and without neurovascular compression, respectively.

RESULTS

The characteristics of the 83 subjects examined are shown in Table 1, according to the presence or absence of NVC, and in Table 2, according to the level of arterial pressure, classified using JNC-VI criteria (13), as this is known to be accompanied by different sympathetic activity levels (12). There were no statistically significant differences in age, gender, body weight, and mass index between any of the
groups. As expected, the average indexes of arterial BP were significantly different between the four groups, and, as previously reported (20), the heart rate was slightly higher in the EHT-2/3 group (Table 2).

**Presence or absence of NVC.** When all of the patients were considered regardless of arterial pressure level, NVC was found in 23 (28%) of the 83 subjects examined (Table 1). Those with NVC had significantly greater s-MSNA (by 16%) and MSNA (by 14%) than those without (Fig. 2A), although both groups had a similar value of cardiac BRS (Fig. 2B). Both s-MSNA (p < 0.03) and MSNA (p < 0.04) were predictive of NVC.

Within the hypertensive groups, 15 patients with NVC were closely matched for age, body mass index, body weight, and arterial pressure level with 15 patients without NVC. The magnitude of s-MSNA (72 ± 3.5 vs. 57 ± 2.1 impulses/100 beats) and MSNA (62 ± 3.1 vs. 51 ± 2.1 bursts/100 beats) was 26% and 21% greater, respectively (at least p < 0.01) in the group with NVC. Also, there were no significant differences in cardiac BRS (3.8 ± 0.6 vs. 3.2 ± 0.5 ms/mm Hg).

Within the normotensive groups (arterial pressure <140/90 mm Hg), eight subjects with NVC had greater s-MSNA (55 ± 6.3 vs. 40 ± 5.0 impulses/100 beats) and MSNA (50 ± 5.8 vs. 35 ± 5.7 bursts/100 beats) than eight subjects without NVC (at least p < 0.05), matched closely for age, body mass index, body weight, and arterial pressure level. Again, there were no significant differences in cardiac BRS (5.4 ± 1.1 vs. 5.0 ± 1.3 ms/mm Hg).

**Magnitude of sympathetic activity and arterial pressure level.** The prevalence of NVC in the four groups of patients is depicted according to the level of arterial pressure and its associated magnitude of sympathetic discharge (Fig. 3). As previously reported (12), s-MSNA was greater in the EHT-1 than in either the HN or EHT-2/3 group, greater in the HN than in the NT group, and greater in the EHT-2/3 than in the HN group. Also, MSNA was greater in the EHT-2/3 than in the HN and NT groups, but similar in magnitude in the EHT-1 and EHT-2/3 groups.

In these groups, the prevalence of NVC was greatest in the EHT-1 group and was higher in the HN than in the NT group, although only the former attained statistical significance (p < 0.05). Considering patients within the EHT-1 group, there was greater s-MSNA (76 ± 4.1 vs. 61 ± 1.8 impulses/100 beats) and MSNA (64 ± 3.8 vs. 57 ± 2.4 bursts/100 beats) values in those with NVC. Furthermore, the s-MSNA values relative to those of MSNA (obtained as the ratio of s-MSNA to MSNA in units of

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**Figure 2.** (A) Muscle sympathetic nerve activity (MSNA) (open bars) and (B) single-unit MSNA (s-MSNA) (solid bars) cardiac baroreceptor reflex sensitivity (BRS) in subjects with neurovascular compression, NVC (+), and without, NVC (−). The numbers in parentheses below the x-axis represent the number of subjects. Data are expressed as the mean (height of columns) ± SEM (bars). The unpaired t test was used to test for statistical significance (ns = not significant).

**Figure 3.** Sympathetic activity quantified per 100 cardiac beats in groups classified according to the level of arterial pressure. The numbers in parentheses below the x-axis represent the proportions and ratios of subjects with neurovascular compression. Analysis of variance with Newman-Keuls post-test comparisons was used to determine statistical significance. Compared with normal subjects (NT): *p < 0.05, †p < 0.01, ‡p < 0.001. Compared with high-normal arterial pressure subjects (HN): §p < 0.05, ¶p < 0.001. Compared with mild essential hypertension subjects (EHT-1): ●p < 0.05. EHT-2/3 = severe essential hypertension subjects; MSNA = muscle sympathetic nerve activity; s-MSNA = single-unit muscle sympathetic nerve activity.
impulses/burst) were greater in those with NVC (1.2 ± 0.07) than in those without (1.1 ± 0.02), although this did not attain statistical significance. Cardiac BRS was significantly (p < 0.05) depressed in the EHT-1 (2.9 ± 0.3 ms/mm Hg) and EHT-2/3 groups (2.5 ± 0.3 ms/mm Hg) relative to both the HN (5.4 ± 0.5 ms/mm Hg) and NT (5.7 ± 0.6 ms/mm Hg) groups.

DISCUSSION

Using the mean frequency of sympathetic discharge from single-unit and multi-unit burst recordings, this study has shown, for the first time, that a direct relationship exists between NVC of the RVLM and an increase in the level of central sympathetic discharge in both normal and hypertensive populations. This relationship occurred particularly in patients with mild hypertension in whom a higher prevalence of NVC and a greater magnitude of sympathetic nerve activity were found. These findings imply that NVC may be a cause for central sympathetic hyperactivity and thereby hypertension in some people.

To avoid confounding factors, we examined Caucasian subjects, as reported evidence suggests that race can affect the responses of MSNA (21). All studies were undertaken within the same environmental conditions and while avoiding the confounding effect of visceral distention (22,23). Considering all subjects in the present study, the groups were similar with respect to the confounding factors of age and gender (24), as well as body mass index (25). When subjects were classified according to JNC-VI criteria (13), the EHT-2/3 group had a higher heart rate than did the other three groups, as previously reported (20). As such, measures of sympathetic activity were expressed per 100 cardiac beats to avoid interference from the differing heart rates (17). In addition, when further analysis was undertaken using groups of normotensive or hypertensive subjects closely matched for age, body mass index, arterial pressure level, and heart rate, similar results were found with respect to the relationship between NVC and central sympathetic discharge.

In a previous report examining two hypertensive groups (11), it was found that the frequency of MSNA bursts was greater in the group with NVC. Unlike the present study, however, both groups were receiving antihypertensive therapy, and left ventricular hypertrophy was not excluded; both factors may affect MSNA bursts (26,27). The present study has gone further to show that NVC is closely related to sympathetic hyperactivity in both normal and hypertensive populations; previous reports have shown that sympathetic nerve activity is greater in mild than in more severe EHT and in normotensive subjects with a higher arterial pressure relative to those with optimal arterial pressure (12). In agreement with this, and further supporting the relationship between NVC and sympathetic hyperactivity, the prevalence of NVC was shown to vary according to the level of arterial pressure in this study. Also, the presence of NVC in normal subjects helps to refute the possibility that NVC might be due to tortuous, ectatic cerebral vessels resulting from chronic hypertension. Furthermore, the present study examined, for the first time, the mean frequency of single-unit activity (s-MSNA) in relation to NVC. In comparison to m-MSNA bursts, this is more likely to represent the central frequency of the sympathetic discharge supplying the periphery (12,18). In this respect, the group with mild hypertension (EHT-1) had relatively greater s-MSNA than MSNA values and also a greater prevalence of NVC, as compared with the other three groups. Finally, the relationship of NVC to sympathetic activation, but not to cardiac BRS levels, is also consistent with a central rather than peripheral reflex mechanism leading to sympathetic nerve hyperactivity. These factors further support a relationship between NVC and increased sympathetic output from the RVLM.

The present results may also provide an explanation for the inconsistent relationship between NVC, normotension, and hypertension reported in previous studies (28), as well as for the variable effects of microsurgical decompression of the RVLM on the level of arterial pressure in hypertensive patients (6). The present study showed that NVC is more likely to be present in hypertensive subjects with excessive central sympathetic hyperactivity and may occur more often in normal subjects with higher arterial pressure and sympathetic activity than in those with optimal levels of arterial pressure. These considerations suggest that a primary effect of NVC can only be adequately examined in relation to the magnitude of sympathetic activation, and this, in turn, is related to the various levels of arterial pressure values and severity of hypertension.

A further implication of this study is that NVC leads to sympathetic activation by a direct effect on the RVLM, rather than by attenuating the afferent baroreceptor reflex input, which is known to inhibit sympathetic discharge. In previous reports, there is evidence that pulsatile compression of the RVLM in dogs (29) and in a primate model (30) may increase vascular resistance and arterial pressure, thereby indicating an increased sympathetic output. In the current study, it was shown that NVC was significantly related to sympathetic activation and not to cardiac BRS. These considerations support the view that vascular contact with the RVLM may activate central sympathetic output rather than preventing the afferent inhibitory effect of the baroreflex mechanism (11).

Regardless of the exact mechanism of NVC-related sympathetic activation, our observations may be relevant to the understanding and management of EHT. The results support the concept of an important role for sympathetic hyperactivity in the pathogenesis of EHT (1,2). Furthermore, EHT-related sympathetic hyperactivity has been implicated in the development of target-organ damage (2,27). The greater prevalence of NVC in hypertensive and normal subjects with sympathetic activation, as shown in this study, would suggest that NVC may be indirectly
(through sympathetic hyperactivity) related to the pathogenesis and complications of EHT. In the present investigation, the group with severe hypertension had a lower level of sympathetic activity and NVC prevalence than did the mild hypertension group. This may have arisen because we excluded patients with treated and complicated hypertension in order to avoid their confounding effects on sympathetic output. It could also be argued that excessive sympathetic output in relation to NVC may lead to hypertension.

Acknowledgments
The authors thank Mr. J. Bannister and Mrs. J. Corrigan for their technical assistance.

Reprint requests and correspondence: Dr. Paul A. Smith, Cardio-Respiratory Unit, St. James’s University Hospital, Beckett Street, Leeds LS9 7TF, United Kingdom. E-mail: paulsmith.leeds@ukgateway.net.

REFERENCES