Vascular Compression of the Rostral Ventrolateral Medulla in Sympathetically Mediated Essential Hypertension

Digesh Gajjar, Brent Egan, Joel Curè, Philip Rust, Pamela VanTassel, Sunil J. Patel

Abstract—The pathophysiological factors of neurogenic or sympathetically mediated essential hypertension are unknown. Neurons close to the surface of the ventrolateral medulla (specifically, in the retro-olivary sulcus [ROS]) are integrally involved in the control of blood pressure by means of efferent connections to presympathetic neurons in the spinal cord. It is hypothesized that vascular contact with the ROS is pathogenically involved in neurogenically mediated hypertension. We evaluated that theory in 20 subjects with uncomplicated stage 1 to stage 2 essential hypertension (EHTN) (18 of whom completed the study). The baseline supine plasma norepinephrine level served as an index of central sympathetic outflow. The response of blood pressure to clonidine was used as a surrogate marker for neurogenically mediated hypertension. We also examined the relationship between those markers and evidence of anatomic abnormalities in the area of the ROS that was provided by magnetic resonance imaging. A vessel contacted the left ROS in 5 of the 18 subjects. Those 5 subjects had higher plasma norepinephrine concentrations than did the 13 subjects without this vascular contact (358±46 versus 76±43 pg/mL, P<0.001). These 5 subjects also exhibited a significant depressor response to clonidine that tended to be greater than that seen in the 13 subjects without vascular contact (−20.6±3.2 versus −13.6±9 mm Hg). Both race and baseline mean blood pressure had only an independent effect on the depressor response to clonidine. The findings are consistent with the theory that vascular contact with the left ROS may contribute to neurogenically mediated “essential” hypertension in some patients. (Hypertension. 2000;36:78-82.)

Key Words: hypertension, essential ■ norepinephrine ■ medulla oblongata ■ clonidine ■ sympathetic nervous system

The cause of essential hypertension (EHTN) remains unclear and is probably multifactorial. Centrally mediated hyperactivity of the sympathetic nervous system has been proposed as an “initiator” of early EHTN and may provide a major contribution to sustaining elevated blood pressure over the long term in some patients. Studies in animal models1–7 have confirmed the presence of sympatho-pressure over the long term in some patients. Studies in all the patients.12–15 We hypothesize that vascular compression to relieve such vascular contact with the VLM has not been uniformly effective in normalizing blood pressure in all the patients.12–15 We hypothesize that vascular compression of the ROS may have an important role in the pathogenesis of hypertension only in those clinically defined as having centrally or sympathetically maintained hypertension (neurogenic hypertension). Clinically, one method of defining neurogenic hypertension is to show elevated baseline levels of plasma norepinephrine and significant clonidine suppression of blood pressure.16 We present our findings in a group of 18 volunteers with EHTN in whom MRI of the posterior fossa and baseline measurements of plasma norepinephrine were obtained and in whom clonidine suppression testing was conducted.

Methods

The study protocol and consent form were reviewed and approved by our Institutional Review Board. Twenty subjects (age range, 18 to 75 years) with a history of uncomplicated stage 1 to stage 2 EHTN were enrolled in the study after they had signed the approved consent form. Criteria for inclusion included hypertensive volunteers with a history of blood pressure readings (obtained when the patients were receiving no treatment) that ranged from 140 to 179/90 to 109 mm Hg (ie, stage 1 to 2). Subjects with evidence for clinically significant cardiac or cerebrovascular disease and those with a history of more severe hypertension were excluded. Each patient provided a thorough history and underwent a physical examination, and medical information was obtained from his or her physician.

At the initial visit (during which the patient’s history was obtained and the physical examination was performed), blood pressure and heart rate were measured in triplicate with a standard mercury sphygmomanometer and an appropriately sized arm cuff after the...
patient had rested for 5 minutes in a seated position. All antihypertensive medications were then discontinued. Blood pressure was recorded with the patient seated every day by each patient and by a nurse on 2 separate occasions ~1 week apart for the next 2 weeks. Subjects with mean systolic and/or diastolic blood pressure readings in the range of 140 to 179/90 to 109 mm Hg were enrolled in the study and proceeded to the protocol described below.

**Clonidine Suppression Test**
Subjects reported to the General Clinical Research Center in the morning after an overnight fast beginning at 10:00 pm. Each subject was asked to lie comfortably supine on a bed during the entire period of testing. An intravenous catheter was placed and was flushed periodically with heparinized saline to maintain patency. One hour later, baseline blood pressure was recorded in triplicate by means of a random-zero sphygmomanometer. Heart rate was measured, and an electrocardiogram was performed. Blood was drawn for use in determining baseline plasma norepinephrine concentration. After the baseline measurements had been completed, clonidine (0.3 mg) was administered orally. Blood pressure and heart rate were recorded hourly for the next 3 hours. The heparinized cannula was then removed, an appointment for a posterior fossa MRI was provided, and the subject was discharged from the General Clinical Research Center. Supine and standing blood pressure and pulse rate were recorded before each subject was discharged. None of the subjects experienced orthostatic hypotension caused by clonidine.

**MRI Scan**
Magnified high-resolution T1-weighted 3D spoiled GRASS images were obtained to provide precise anatomic details of the relationship between the surface of the medulla and any vessels in the surrounding cisterns. A record was made of the name and location (left or right) of each vessel and its position (touching [T] or not touching [NT]) with respect to the medullary surface. The specific area of interest was the ROS just anterior to the root entry zone of the glossopharyngeal and vagus nerves. Two neuroradiologists (J.C. and P.V.) independently reported their findings with regard to each subject’s MRI scan. After 3 months, each neuroradiologist was asked to reread the MRI scans in random order. They were unaware of the previous readings and were not informed of the clonidine suppression test results. In addition, another author (S.J.P.), who was also unaware of clonidine suppression test results, independently reviewed the MRI scans.

**Biochemical Measurements**
Plasma norepinephrine was measured by high-performance liquid chromatography separation and electrochemical detection. The sensitivity of the assay was 5 pg/mL.

**Data Analysis**
The most important analysis was that of the presence or absence of vascular contact with the ROS as possibly correlating with the baseline plasma norepinephrine concentration. The age, gender, race, mean blood pressure, and depressor response to clonidine were evaluated as the modifiers of such a relationship. Multiple regressions were therefore planned, with plasma norepinephrine as the dependent variable. The same technique was also applied with clonidine depressor response as the dependent variable.

| TABLE 1. MRI Readings for Vascular Contact With the ROS (n=18) |
|---------------------|-----------------|-----------------|-----------------|
| Patient | Neuroradiologist, J.C. | Neuroradiologist, P.V. | S.J.P. |
|JC | T | T | T |
|KG | T | T | T |
|MG | T | T | T |
|RG | T | T | T |
|MW | NT | T-Rt | T |
|EO | NT | T-Rt | T |
|HG | NT | NT | NT |
|HY | NT | NT | NT |
|JR | NT | NT | NT |
|KC | NT | T-Rt | NT |
|LM | NT | NT | NT |
|MSa | NT | NT | NT |
|MSe | NT | NT | NT |
|PD | T-Rt | NT | NT |
|RM | NT | NT | NT |
|SD | NT | NT | T |
|CPy | NT | T-Rt | NT |
|OM | NT | NT | NT |
|LM | NT | NT | NT |

T indicates touching vessel (left); NT, no touching vessel; and T-Rt, touching vessel (right).

**Results**
Eighteen subjects with hypertension completed the clonidine suppression test and underwent MRI. Two subjects withdrew from the study before the clonidine suppression testing, including a woman who became symptomatic after discontinuing antihypertensive medications. Table 1 summarizes the 5 independent MRI readings from each of the 3 investigators. Vascular contact of the ROS was considered to occur only in those subjects in whom this was a consistent interpretation in all MRI readings. Only 5 of 18 subjects fulfilled these criteria (Figure 1A); this is shown in the last column of Table 2. All 5 of those subjects exhibited vessel contact on the left. The remaining 13 patients were judged not to have a vessel touching the ROS (Figure 1B). None of the 18 subjects had a consistent vascular anomaly of the right ROS. The 5 subjects with vascular contact demonstrated a baseline plasma norepinephrine level $>300$ pg/mL ($358 \pm 46$ pg/mL) (Figure 2). The plasma baseline norepinephrine concentration was significantly lower in the 13 subjects who did not have vascular contact along the ROS ($76 \pm 43$ pg/mL, $P<0.0001$). This difference was not significantly affected by baseline mean blood pressure, the depressor response to clonidine, or race. The 95% confidence interval for the difference in plasma norepinephrine concentration by vascular contact was (233 331).
The clonidine depressor response tended to be greater in the 5 subjects with vascular contact (−20.6±3.2 mm Hg) compared with that observed in the 13 subjects without contact (−13.6±9.3 mm Hg). However, the difference between the 2 groups was not statistically significant. The overall depressor response (−15.6 mm Hg) was significantly affected by baseline mean blood pressure ($P=0.0003$) and race ($P=0.0021$). The estimation regression is depressor response $=13.755 + 0.431 \times$ (blood pressure $−8.674 \times$ race), where for the latter, 1 denotes “white” and 2 denotes “black,” with the conditional standard error $=4.8$ mm Hg.

**Discussion**

The central nervous system plays an important role in the tonic and reflex control of the blood pressure by means of the sympathetic modulation of cardiovascular and renal function. Animal studies\(^1\)–\(^7\) have clearly defined the role of the sympathoexcitatory neurons of the RVLM and the inhibitory neurons of the caudal ventrolateral medulla in blood pressure regulation. The C1 group of adrenergic neurons in the RVLM has a major efferent pathway to the intermediolateral column of cells (preganglionic sympathetic neurons) in the spinal cord. In animals, electrical or chemical stimulation of the RVLM results in vasoconstriction and hypertension, and bilateral inhibition or chemical destruction of the RVLM results in hypotension.\(^1\)–\(^3\) In baboons, experimental pulsatile compression of the left VLM induced a hypertensive blood pressure response.\(^4\) Human postmortem studies have demonstrated that the C1 adrenergic neurons of the RVLM are within 1 mm from surface of the ROS.\(^8\) In patients undergoing posterior fossa surgery, we have found that bipolar electrical stimulation of the middle to inferior surface of the ROS consistently produces a response in blood pressure that is site and frequency specific. (S.J.P., unpublished data, 1999). In this study, interpretations of MRI scans were based on this blood pressure response map of the surface of VLM.

Only 27.5% of the subjects with hypertension were found to have vascular contact of the ROS in this study. This is much lower than the previously reported incidence of vascular compression along the VLM and may be a result of the stricter anatomic criteria of vascular contact that occurs only in the ROS. Another reason may be that only those in whom all 3 investigators reported vascular contact were considered to have it, which would eliminate any doubt about this finding. Finally, the small number of subjects in this study may account for some of the variation.

Arterial pulsatile compression may either directly stimulate the C1 neurons of the RVLM or disinhibit them via an effect on the caudal ventrolateral medulla, which results in elevation of central sympathetic outflow or tone. In such a group of hypertensives, sympathetic tone should show a positive association with vascular compression of the ROS. In fact, all 5 subjects with vascular contact along the left ROS, which is the presumed location of the C1 neurons, exhibited clinical evidence of neurogenic hypertension. The 5 “affected” patients had higher baseline plasma norepinephrine concentrations than those of the 13 subjects without vascular contact along the left ROS. In this study, the clonidine depressor response (sympathetic dependence of blood pressure) was
higher in the group that exhibited vascular contact. A larger number of subjects may prove this to be a significant finding.

We have demonstrated in this small group of hypertensive patients that those with vascular compression of the left ROS had elevated plasma norepinephrine concentrations. These findings are consistent with the hypothesis that vascular contact of the left ROS is etiologically related to neurogenic hypertension. The use of clinical criteria for neurogenic hypertension and improved MRI techniques may help to define such a specific group of patients who may benefit consistently from microvascular decompression.

The small number of subjects studied precludes us from making definitive statements about the specific cause of hypertension in these patients. Also, decubital blood represents a pooled sample with regard to the catecholamine level and may not accurately reflect the central sympathetic tone. However, the results provide a basis with which future studies could examine the relationship between MRI findings and more sensitive measures of central sympathetic outflow, such as microneurography, in a larger number of patients. These studies may help to substantiate our hypothesis of the pathogenesis of elevated blood pressure in patients with neurogenic “essential” hypertension.

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References


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