Pulsatile AC of the left VLM has been postulated to have a neurogenic origin in a subset of patients with essential hypertension. Both autopsy and MRI studies have shown a higher than normal incidence of AC of the VLM in patients with essential hypertension. We have previously shown an association between sympathetically mediated hypertension (elevated serum norepinephrine) and neuroimaging evidence of AC in the ROS region of the VLM. Pulsatile AC of other neural structures has been established as the source of syndromes such as trigeminal neuralgia and hemifacial spasms. Surgically elevating the artery from the nerve, or microvascular decompression, will often relieve the symptoms. Pulsatile AC of the VLM has also been suggested to be the cause of the hypertension in a subset of patients with essential hypertension. In animals, a network of subpial neuronal aggregates in the VLM has been shown to control cardiovascular functions. Although histochemically similar, neurons have been identified in the retro-olivary sulcus (ROS) of the human VLM, but their function is unclear.

Methods. The authors recorded cardiovascular responses to electrical stimulation at various locations along the VLM surface, including the ROS, in patients who were undergoing posterior fossa surgery for trigeminal neuralgia. This vasomotor mapping of the medullary surface was performed using a bipolar electrode, with stimulation parameters ranging from 5- to 30-second trains (20–100 Hz), constant current (1.5–5 mA), and 0.1-msec pulse durations. Heart rate (HR) and blood pressure (BP) were recorded continuously from baseline (10 seconds before the stimulus) up to 1 minute poststimulus. In 6 patients, 17 stimulation responses in BP and HR were recorded.

Results. The frequency threshold for any cardiovascular response was 20 Hz; the stimulation intensity threshold ranged from 1.5 to 3 mA. In the first patient, all stimulation responses were significantly different from sham recordings (which consisted of electrodes placed without stimulations). Repeated stimulations in the lower ROS produced similar responses in 3 other patients. Two additional patients had similar responses to single stimulations in the lower ROS. Olive stimulation produced no response (control). Hypotensive and/or bradycardic responses were consistently followed by a reflex hypertensive response. Slight right/left differences were noted. No patient suffered short- or long-term effects from this stimulation.

Conclusions. This stimulation technique for vasomotor mapping of the human VLM was safe and reproducible. Neuronal aggregates near the surface of the human ROS may be important in cardiovascular regulation. This method of vasomotor mapping with measures of responses in sympathetic tone (microneurography) should yield additional data for understanding the neuronal network that controls cardiovascular functions in the human VLM. Further studies in which a concentric bipolar electrode is used to generate this type of vasomotor map should also increase understanding of the pathophysiological mechanisms of neurogenically mediated hypertension, and assist in the design of studies to prove the hypothesis that it is caused by pulsatile AC of the VLM.

Key Words • essential hypertension • human medullary stimulation • arterial compression • ventrolateral medulla • functional neurosurgery
Human medullary vasomotor mapping

of essential hypertension. The hypothesis is that the pulsatile AC abnormally elevates central sympathetic outflow to produce hypertension.

Microvascular decompression of the VLM, however, has not relieved hypertension in all cases. Similarly, in several MRI studies similar rates of vascular compression of VLM were reported in normotensive and hypertensive patients. One explanation for these observations is the lack of definition of the hypertension type in these patients; whether it is neurogenically mediated (sympathetic dependent) or not. Another explanation is a lack of definition of the exact location of AC along the VLM in previous studies. In fact, in imaging studies, the medullary location of the sympathoexcitatory and inhibitory neuronal groups has not been established in humans. In animals, a network of sympathoexcitatory (rostral VLM) and inhibitory (caudal VLM) neuronal aggregates has been shown to lie close to the surface of the VLM bilaterally. These 2 sets of neurons are integral in the baroreflex control of BP, and have afferent input from the nucleus solitarius as well as from several other CNS locations. Histochemical investigation of human medulla at autopsy has shown neuronal aggregates close to the surface of the ROS region that are chemically similar to the C-1 catecholamine-synthesizing neurons in animals.

However, the physiological importance of these neuronal aggregates in the control of BP has only been inferred from animal studies. To confirm the topographic location of these aggregates and their role in vasomotor control in humans, we electrically stimulated the VLM surface in consenting patients undergoing posterior fossa surgery.

Methods

All patients irrespective of the history of hypertension were included in this study. The patients were allowed to take their baseline antihypertensive medication before the surgery. After the surgical exposure of the brainstem surface for microvascular decompression of the trigeminal nerve root (for the treatment of trigeminal neuralgia), the ipsilateral VLM surface was visualized for the study. All patients enrolled in this study signed an additional study consent (approved by the internal review board at the Medical University of South Carolina) to have VLM stimulation performed at the time of their planned treatment procedure. Although no additional bone was removed during exposure, the stimulation increased the operating time by 15–30 minutes. Both of these issues were communicated to patients while obtaining an informed consent for enrollment in the study.

A silver-tipped, flexible bipolar electrode was customized and approved by the internal review board to stimulate the surface of the VLM. The electrode was stabilized by fixing it to the head holder that is normally used to fix the patient’s head to the operating table. The electrode was then lowered onto various locations on the surface of the ipsilateral VLM. After stimulations in the first 2 patients, it was established that the frequency threshold for response was 20 Hz, so subsequent patients were all stimulated at a frequency of 100 Hz (Fig. 1). Each location was given 30-second stimulation trains (100 Hz) with 0.1-msec pulse durations, 1.5-mA constant current pulses (some patients required 3.0 mA for response). One patient was given a 5-second stimulus at a site within the ROS noted to have a large depressor response to a 30-second stimulus. The stimulation and recording of cardiovascular responses were done by nonblinded but independent investigators. The BP and HR were recorded continuously starting at baseline (10 seconds before the stimulus), throughout the period of stimulation, for up to 1 minute after the stimulus. In several cases, stimulations were repeated in each location with the same parameters. Each stimulation was begun after baseline BP remained stable (± 5 mm Hg) for at least 1 minute. Seventeen stimulation responses were recorded in 6 patients.

Inhalation anesthetic agents (isoflurane and sevoflurane) were administered to the patients and were maintained at a stable dose during the stimulation and recording session. All stimulations were performed only when the physiological parameters were stable and there was no clinical need for vasoactive agents. All parameters of stimulation were recorded, as was the location of the stimulation.

Results

Four of the 6 patients had a diagnosed history of hypertension. Two of these patients were taking angiotensin receptor blockers: 1 took an angiotensin-converting enzyme inhibitor, the other a calcium channel blocker. Table 1 shows 4 “sham” (electrode placed, no stimulation) and 4 stimulation responses recorded during the stimulation period in Case A from the lower one-third of the ROS. All stimulation responses were significantly different from sham recordings. Repeat stimulations (same parameters) produced similar responses. Repeated stimulations in the ROS produced consistent similar responses in 3 other patients. Two additional patients had similar responses to single stimulations in the ROS.

Hypotensive and/or bradycardic responses during stimulation were followed in each case by a reflex hypertensive response. Responses in BP were seen only with stimulation along specific regions of the ROS. Pressor responses were observed consistently in all cases with stimulation of the inferior one-third of the ROS. Patients who had right-sided stimulations had responses similar to the ones from left-sided stimulations. Olive stimulation produced no response in BP or HR in any patient.

Most pressor responses were preceded by an initial depressor response (Fig. 2 left). This was noted to be immediate, and peaked at approximately 10–15 seconds into the stimulation period. The rise in BP often occurred before the stimulus was stopped. The depressor response was dependent on stimulus intensity. In the single patient who had 1 responsive site with a 5-second stimulus, there was a smaller, but visible, depressor response (Fig. 2 right). These depressor and/or pressor responses were consistently reproduced with stimulation of the inferior ROS.

No short- or long-term (follow-up 1–3 months) effects of these stimulations were observed. The BP returned to normal within 3 minutes after the end of each stimulation.

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in all patients. The maximum poststimulation elevation of MAP noted in this study was 20 mm Hg. All patients maintained normal BP up to 1 month after surgery.

Discussion

This preliminary information demonstrates the feasibility and safety of our stimulation technique. The frequency threshold of 20 Hz may be due to the fact that the response is generated through a polysynaptic efferent system, as is the case in the sympathetic (vegetative) system (Fig. 3). Activation of smooth muscle does, in fact, require bursts of high-frequency stimulation of its efferent sympathetic nerves.\(^{22}\)

We speculate that the simultaneous depressor response, HR, and BP during stimulation may actually be a “blockage” of the sympathoexcitatory pathways, with a poststimulus rise in BP a reflex response to the hypotension. As expected in a vegetative system, the smaller periods of stimulation seem to produce low-amplitude responses.

The percent rise in MAP in animal studies was often in the range of 50%–100%, whereas our responses were never more than 20% over baseline with stimulations.\(^{12,26}\) Reasons for these differences may include our use of bipolar electrodes, with stimulations close to the threshold. Neuronal recruitment may be much smaller than that achieved in significantly above-threshold, monopolar stimulation responses observed in animal studies. This may also explain the delay in response we observed compared with animal studies. The sympatholytic effects of the anesthetic agents (fentanyl and isoflurane) used may be the reason for the low-amplitude responses.\(^{4,5,11,27}\) Finally, higher responses would be considered unsafe in these anesthetized patients.

TABLE 1: Results of electrical stimulation study in Case A\(^*\)

<table>
<thead>
<tr>
<th>Stim No.</th>
<th>Max Change</th>
<th>Max Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (bpm)</td>
<td>Systolic BP (mm Hg)</td>
</tr>
<tr>
<td>1</td>
<td>−6</td>
<td>−10</td>
</tr>
<tr>
<td>2</td>
<td>−3</td>
<td>−8</td>
</tr>
<tr>
<td>3</td>
<td>−6</td>
<td>−7</td>
</tr>
<tr>
<td>4</td>
<td>−3</td>
<td>−9</td>
</tr>
<tr>
<td>sham</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>sham</td>
<td>1</td>
<td>−1</td>
</tr>
<tr>
<td>sham</td>
<td>−1</td>
<td>−2</td>
</tr>
<tr>
<td>sham</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>p values (stim vs sham)</td>
<td>0.008</td>
<td>0.000</td>
</tr>
</tbody>
</table>

\(^*\) bpm = beats per minute; Stim = stimulation.
These low-amplitude responses were reliable and likely responses from direct effects on some component of the medullary vasomotor system. This reliability of stimulation responses may help map relative differences in the pressor sensitivity among various areas of the VLM surface. Although our preliminary results do not reveal differences in responses between the left and right side, more data are desirable before any conclusions can be drawn. We have previously seen similar results in a study of 147 consecutive patients who underwent posterior fossa imaging for a variety of neurological ailments. We found that AC of the ROS was an independent predictor of history of hypertension, with 56% of the compressions being on the left and 44% on the right.32

Whether the observed cardiovascular responses are a result of direct stimulation of the C-1 neurons or a delayed or indirect response to inhibition through the lower VLM is unclear.2,31,37 Additional stimulation studies are being conducted with continuous records of cardiovascular parameters, including measures of sympathetic tone (muscle sympathetic nerve activity) performed using microneurography.7,16,22,33,38 The consistency of response to repeated stimulations at each site, and the lack of response to sham and olive stimulations confirm that these locations in the ROS are probably areas in which a portion of the vasomotor neuron network resides close to the surface in the human medulla. This could contribute to vulnerability to pulsatile stimulation effects by an artery touching or compressing the surface. To generate a map with the exact location of the inhibitory and excitatory neuronal aggregates, we are currently conducting stimulations with a grid that is referenced to the entry site of the 9th and 10th cranial nerve roots (Fig. 3). The latter will allow better comparisons between patients.

Conclusions

This technique of mapping the vasomotor areas of the human VLM proved to be safe and reproducible. Our preliminary results suggest that neuronal aggregates near the surface of certain aspects of the ROS may be important in cardiovascular regulation in humans. Direct recording of stimulation responses in the sympathetic tone with microneurography (muscle sympathetic nerve activity) should yield further data to enable better mapping of the VLM surface for cardiovascular control. Although this type of stimulation does not model the effects of pulsatile AC, it is expected that this type of vasomotor map could be used for imaging studies of the medulla in hypertensive patients, and could find more precise correlates of pulsatile AC and elevated sympathetic tone in these individuals.

Disclosure

This work was partly supported by National Institutes of Health/National Heart, Lung, and Blood Institute Grant No. 5 K23 HL067993-03. The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Fig. 2.** Graphs showing Δ MAP and Δ HR during and after stimulation of the inferior ROS in a 65-year-old woman. **Left:** A 30-second stimulation at 3 mA, with 0.1-msec pulses at 100 Hz. **Right:** A 5-second stimulation at 4.5 mA.

**Fig. 3.** A schematic depiction of the medullary surface in the region of the ROS. O. = olive.
Author contributions to the study and manuscript preparation include the following. Conception and design: Patel, Nicholas, Vera. Acquisition of data: Krishna, Patel, Welzig. Analysis and interpretation of data: Patel, Nicholas. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Patel. Statistical analysis: Nicholas. Administrative/technical/material support: Welzig. Study supervision: Vera.

Acknowledgments

The authors thank Dr. Schnellmann for valuable input during manuscript preparation and Ms. Vought for preparing the sketch of the medullary surface.

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Manuscript submitted June 6, 2011. Accepted March 28, 2012. Please include this information when citing this paper: published online April 27, 2012; DOI: 10.3171/2012.3.JNS11973. Address correspondence to: S. J. Patel, M.D., Department of Neuroscience, Medical University of South Carolina, Suite 428, 96 Jonathan Lucas Street, Charleston, South Carolina 29425. email: patels@musc.edu.