Brainstem Compression as a Cause of Neurogenic Hypertension

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Introduction
More than 60 million people in the United States have hypertension, 95% of which is classified as primary or essential (i.e., it has no known or correctable cause). Black people are affected more often than white people. Among people younger than 50 years of age, men have a higher incidence of elevated blood pressure than women; however, after the age of 50 years, women are more commonly affected. The systemic effects of chronically elevated blood pressure are widespread and include renal, ophthalmic, cardiac, and peripheral vascular pathologies that can be life altering and life ending. Of patients with essential and secondary hypertension, 80% to 90% can achieve adequate control of their condition with single or multiple medications. This, however, leaves as many as 6 million people with elevated blood pressure and subsequent end-organ damage. There are also people who have treatable hypertension but have difficulty tolerating medication. This intolerance can manifest as electrolyte abnormalities, sexual dysfunction, insomnia, drowsiness, diarrhea, headache, and dizziness.

Historical and Anatomic Perspective
Arterial hypertension is defined as elevated arterial blood pressure. Because a distribution of blood pressures is seen throughout the population and because blood pressure varies in a single person over the course of a single day, any definition of “normal” blood pressure is limited. Nevertheless, it is accepted that a person has hypertension if he or she has 1) two or more diastolic blood pressure readings taken on separate occasions that average 90 mm Hg or more or 2) two or more systolic blood pressure readings taken on separate occasions that average more than 140 mm Hg. The causes of hypertension can be identified in some patients, but more than 95% of all cases of hypertension have no known cause and are labeled “essential.”

The autonomic nervous system is the catalyst for the development of essential hypertension. Elevated blood pressure is related to increased cardiac output, increased peripheral vascular resistance, or both. When essential hypertension first develops, cardiac output may be elevated and peripheral vascular resistance may be decreased. In established hypertension, cardiac output may actually decrease while vascular resistance increases. Autonomic activity is responsible for these alterations in cardiac output and peripheral vascular resistance secondary to sympathetic and parasympathetic imbalances.

Neurophysiologists have long been interested in the autonomic nervous system, its role in cardiac control, and the portions of the brain responsible for feedback control. In 1873, Dittmar transected a rabbit brainstem in a stepwise cranial-to-caudal direction and noticed that when he severed the pontomedullary junction, the rabbit’s blood pressure rapidly decreased. In 1974, Hokfelt et al. [1] identified epinephrine synthesizing C1 neurons in the reticular formation near the ventrolateral surface of the medulla. Ross et al. [2] designated these cells the nucleus rostralis ventrolateralis (ventrolateral nucleus). Stimulation of the C1 neurons with glutamate elevates blood pressure, whereas inhibition with γ-aminobutyric acid (GABA) reduces blood pressure.

Naraghi et al. [4] have provided an excellent summary of the current pathophysiologic theory behind neurogenic hypertension. The nucleus tractus solitarius (NTS) and, subsequently, the caudal nucleus solitarius receive input from the carotid nerve, which innervates the carotid body oxygen tension, detecting chemoreceptors and carotid sinus baroreceptors. Innervation to the NTS also comes from myocardial vagal c-fibers of the left atrium and ventricle stretch receptors. Of particular relevance to Jannetta's microvascular compression theory of essential hypertension is the fact that...
the majority of the afferent inputs from the myocardial receptors of the left ventricle and atrium to the NTS are conducted by low myelinated cardiac c-fibers of the left vagus nerve. In the normal state, the NTS has GABA projections to the C1 neurons, which inhibit C1 output. Efferent connections from C1 neurons in the rostral ventrolateral medulla project to and have an excitatory effect on the preganglionic sympathetic neurons of the intermediolateral cell column in the thoracic spinal cord. Excitation of the preganglionic sympathetic neurons results in an elevation of plasma catecholamine levels and elevated discharge of peripheral sympathetic fibers. In a similar mode, efferent connections of the C1 neurons to the hypothalamic paraventricular nucleus can effectively elevate plasma vasopressin (antidiuretic hormone) levels after stimulation. It is speculated that compression of the rostral ventrolateral medulla leads to decreased GABA output and increased inhibition of the C1 neurons. As a result of this hyperactive C1 neuron activity, antidiuretic hormone output, plasma catecholamine levels, and peripheral sympathetic tone all increase (Fig. 1).

Considering the neuroanatomy described above, Jannetta suggested that pulsatile arterial compression of the left rostral ventrolateral medulla near the root entry zones of cranial nerves 9 and 10 leads to deafferentation of the NTS. This, in turn, leads to decreased GABA output and increased C1 activity (Fig. 1). To test this theory, Segal et al. [5] produced an animal model for acute pulsatile compression of the ventrolateral medulla. By placing against the brainstem a balloon that inflated 120 times per minute to a diameter of 2 mm, the authors induced increased stroke volume and increased cardiac output in most animals over a 4-hour period of compression. In an attempt to develop a model of more chronic disease, Jannetta et al. [6] devised a balloon compression study in baboons. All animals that had balloon compression of the medulla developed systolic hypertension, increased cardiac output, and increased stroke volume. Animals with implanted, noninflating balloons did not develop autonomic changes. Marimoto et al. [7] performed similar studies in rats and showed increased sympathetic activity, arterial blood pressure, heart rate, and plasma epinephrine and norepinephrine levels.

Given the above neuroanatomy, theories, and research findings, numerous investigators have endeavored to use magnetic resonance imaging (MRI) to study people with essential hypertension in attempts to separate out those who have neurovascular compression of the left rostral ventrolateral medulla. Naraghi et al. [8] studied 24 patients with essential hypertension, 14 patients with renal hypertension, and 14 normal persons in a blinded, prospective manner. Twenty patients with essential hypertension had MRI evidence of left-sided neurovascular compression at the ventrolateral medulla. Two patients with renal hypertension and one normal participant had similar findings. Akimura et al. [9] also showed a higher incidence of left lateral brainstem vascular compression on MRI in patients with essential hypertension compared with normal controls and patients with secondary hypertension. Although this study was prospective, the authors did not indicate whether the radiologists were blinded to diagnosis before evaluation of the images. Mamata et al. [10] also studied MRI in controls, patients with essential hypertension, and patients with secondary hypertension. Patients with essential hypertension had a much higher incidence of vascular-induced brainstem compression.

1998 Publications

In 1998, Levy et al. [11••] published their results after studying microvascular decompression in 11 patients who received a diagnosis of medically intractable hypertension and 1 patient with severe autonomic dysfunction and mild hypertension. All patients had at least three preoperative blood pressure evaluations along with evaluation of medications. To be included in the study, patients had to be evaluated for pheochromocytoma and carcinoid and renal disease, when appropriate, and had to meet one of the following criteria: 1) systolic blood pressure greater than 180 mm Hg that did not respond to medical therapy, 2) blood pressure lability that did not respond to medical therapy and affected daily function, 3) systolic blood pressure greater than 160 that did not respond to medical therapy and was associated with debilitating autonomic dysreflexia, or 4) intolerable side effects from antihypertensive medications.

Preoperative imaging showed left medullary compression in four patients, dolichoectatic basilar arteries in two patients, and severe displacement of the vertebrobasilar