Neurogenic Hypertension: Etiology and Surgical Treatment

I. Observations in 53 Patients

PETER J. JANNETTA, M.D., RICARDO SEGAL, M.D., SIDNEY K. WOLFSON, JR., M.D.

Although an extensive literature exists concerning essential arterial hypertension, the primary etiology has been unclear. Arterial compression of the left lateral medulla oblongata by looping arteries of the base of the brain was seen incidently in 51 of 53 hypertensive patients who underwent left retromastoid craniectomy and microvascular decompression for unrelated cranial nerve dysfunctions. Such compression was not noted in normotensive patients. Treatment by vascular decompression of the medulla was performed in 42 of the 53 patients. Relief in the hypertension was seen in 32 of the patients and improvement in four. Arteriosclerosis and arterial ectasia contribute to arterial elongation and looping. If pulsatile compression of the left lateral medulla occurs, hypertension may develop as a consequence of an imbalance in the neural control systems that normally regulate blood pressure. The hypertension may further contribute to arterial elongation, providing a vicious circle of pathophysiologic changes.

From the Department of Neurological Surgery, University of Pittsburgh School of Medicine, and Presbyterian-University Hospital, Pittsburgh, Pennsylvania

IDIOPATHIC ARTERIAL HYPERTENSION, termed "essential" or "neurogenic," is a common generalized cardiovascular syndrome comprised of a sequence of pathophysiologic changes and accommodations. These may include alterations in cardiac output, stroke volume, baroreceptor sensitivity, peripheral resistance, subsequent failure of the heart, and various complications dependent upon organ failure and neurologic and/or cardiac catastrophies. It is estimated that ten per cent of the population in the United States are hypertensive. The literature concerning essential hypertension is vague about the etiology of the disease.

Based on clinical microsurgical observations, we formed a hypothesis concerning the etiology of neurogenic hypertension elaborating upon observations in 53 patients and developed a subhuman primate model that mimics essential hypertension in the human. This hypothesis concerns vascular abnormalities affecting the left vagal nerve and the lateral medulla. In this paper, we describe observations that led us to make prospective observations in patients and report the findings and results in our patient population. In a companion paper, we describe the chronic model in a subhuman primate (baboon) and present physiologic data obtained in this model.

The hypothesis of vascular compression at the level of the medulla as a cause of hypertension emerged from observations that we made in operations for cranial nerve dysfunction using microvascular decompression techniques. Sunderland demonstrated in anatomical studies of elderly cadaver brains without clinical correlation that arteriosclerosis and ectasia, as part of the aging process, cause abnormal vascular contacts with neural tissue at the base of the brain.[1] The first microvascular decompression (MVD) of a cranial nerve (in a patient with hemifacial spasm) was performed on June 1, 1966.[2] Since that time, we have performed retromastoid craniectomy (RMC) and MVD in more than 700 patients with trigeminal neuralgia, 450 with hemifacial spasm, 70 with tinnitus and/or vertigo, 17 with glossopharyngeal neuralgia, and more than 300 patients with various other cranial nerve problems due to vascular compression. Operative findings, results, and complications in the first 800 patients have been reported in various publications.[2-13] Other investigators have verified these findings.[14-18]

In 1973 we operated on a 55-year-old woman with glossopharyngeal neuralgia who suffered a right cerebral hemispheric hypertensive stroke 2 hours after an uneventful microvascular decompression of the glossopharyngeal-vagal complex. The patient died three days later. Another 1973 patient, a 41-year-old man, had severe

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Correspondence and reprint requests: Peter J. Jannetta, M. D., Department of Neurosurgery, University of Pittsburgh, School of Medicine, Pittsburgh, PA 15261.

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TABLE 1. *Primary Problem*

	Number
Trigeminal neuralgia (TN)	13
Hemifacial spasm (HFS)	26
Glossopharyngeal neuralgia (GPN)	4
Atypical trigeminal neuralgia (ATN)	2
Bell's palsy	1
Spasmodic torticollis	1
Multiple cranial nerve symptoms*	6
Total	53

* Multiple cranial nerve dysfunction (TN and HFS, TN and GPN, ATN and anesthesia dolorosa, HFS and vertigo, HFS and ipsilateral hearing loss), one each.

hypertension (up to 220/110) following a microvascular decompression for left glossopharyngeal neuralgia. His hypertension was controlled by medication and lasted for 7 days.[8,9] The experience with these two patients directed our attention to the effect of pulsatile vascular compression of the lateral medulla and the vagal nerve on the possible cause of hypertension, and on the basis of these experiences we found it likely that such vascular abnormalities could cause hyperactive autonomic dysfunction in the cardiac central system of the medulla and affect the left vagus nerve. Vascular compression of the left medulla and vagal nerve could thereby be a factor in the development of neurogenic hypertension. It was not clear from these early observations whether it was a vascular compression of the adjacent brain stem where many cardiovascular control centers are located or whether it was compression of the vagus nerve that was the common cause of this autonomic dysfunction. In 1975, we began to make serial observations in normotensive and hypertensive patients who underwent RMC and MVD for other cranial nerve vascular compression syndromes,[8,9,11,13] and we began to develop an animal model in which we could study the effect of pulsatile compression on cranial nerve (CN) X and the medulla.

TABLE 2. *Offending Artery (All Left-Sided)**

Artery	Total
Vertebral (normal)	14
Vertebral, ectatic or severely arteriosclerotic	5
Vertebral and PICA*	8
PICA† or branches thereof	23
Superior cerebellar	1
Vertebral and basilar, ectatic	1
PICA† and AICA‡	1
Total	53

* Questionable compression in two patients (see text).
† PICA = Posterior inferior cerebellar artery.
‡ AICA = Anterior inferior cerebellar artery.

Patient Selection and Operative Methods

Observations were made in 53 serial hypertensive patients and 50 normotensive patients who underwent left RMC and MVD and 25 normotensive and seven hypertensive patients who underwent right RMC and MVD for cranial nerve vascular syndromes. We analyzed the 53 hypertensive patients in detail and will cite pertinent data regarding the other groups when indicated. The hypertensive group ranged in age from 31 to 74 years at the time of operation (mean, 57.3 years). The most common problem for which the patients were operated upon was hemifacial spasm, with trigeminal neuralgia second. The primary diagnoses of the 53 hypertensive patients are tabulated in Table 1. The years of operations are as follows: 1975 (1); 1976 (1); 1977 (5); 1978 (7); 1979 (12); 1980 (9); 1981 (9); and 1982* (9) (total = 53). Details of operative technique have been previously published.[5,6,12] All hypertensive patients had been evaluated prior to admission and/or had undergone preoperative evaluation by internists at Presbyterian-University Hospital to rule out other causes of high blood pressure. All were given the diagnosis of "essential" or "neurogenic" hypertension. When the risks and benefits of operation were discussed, the patients were apprised of the evidence regarding hypertension. All agreed to undergo exploration of the lateral medulla oblongata. Our technique of obtaining informed consent met the criteria of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[19]

At operation, after microvascular decompression (MVD) of the symptomatic nerve, the cerebellum was elevated gently from CN IX and X with the nerves exposed to the brain stem in order to visualize the vascular compression of the brain stem clearly. Microvascular decompression of the lateral brain stem was attempted if this could be performed easily, rapidly, and safely. The artery (Table 2) was mobilized away from the brain stem, and held away with an implant of plastic sponge, muscle, or multiple soft rolled pieces of shredded Teflon® felt. This was attempted in 42 of the 53 patients with varying degrees of success. The quality of the vascular decompression was evaluated for adequacy by the operating surgeon (PJJ) at the time of operation (Tables 3 and 4).

The postoperative blood pressure data are presented as follows: "Normal" means under 135/85. "Improved" means more than a 20-mm drop in both systolic and diastolic pressures. Preoperative blood pressure measurements are mean daily pressures when possible. Many of the patients were on large doses of strong medications,

* Six months.

TABLE 3. *Postoperative Results after Microvascular Decompression of Left Lateral Medulla Oblongata that Was Deemed Adequate at Operation in 36 Patients*

	Normal Blood Pressure (All Improved Over Preop)			Elevated Blood Pressure		
				Improved	No Change	Total
Med. Rx*	ō Rx	HCTZ†	Multiple Rx	↓↓ Rx	Same Rx	
Number	13	12	6	1	3	35
Preop Status	7-Multiple Rx 3-HCTZ 3-ō Rx	7-Multiple Rx 4-HCTZ but BP better 1-HCTZ no preop Rx	1-Same Rx 4-↓↓Rx			
Subtotal		31		1	3	35
Lost to follow-up		1 (Normal at last follow-up)				1
					Total	36

* Rx = Medical therapy.
† HCTZ = Hydrochlorothiazide.

so their pressures were not significant in the treated *vs.* untreated groups until the fifth to seventh postoperative day; blood pressure on the last 2 days of hospitalization are given. Blood pressure would frequently continue to fall with patients requiring progressively less medicine months after operation.

Results

Fifty-one of the 53 hypertensive patients had obvious compression of the left anterolateral medulla by arterial loops. In two of the 53 hypertensive patients, such compression was questionable, one located in the caudal pons and the other in the anterior medulla. These were called "negative" explorations, but the artery compressing the pons was decompressed (Table 3). The typical configuration of the compressing artery was almost always a loop, with the outside of the loop pressing into the medulla, usually between the inferior olive anteriorly and the CN IX and X posteriorly (Figs. 1, 2, and 3). The offending arterial loops are tabulated in Table 2. In only two of the normotensive patients, a branch of the posterior inferior cerebellar artery was adjacent to and perhaps slightly compressing the left anterolateral medulla. One of these was decompressed and the other was not. Both patients remain normotensive.

Of the 42 patients in whom vascular decompression of the left medulla was attempted, *significant* lowering in blood pressure to normal was obtained in 32 of 36

TABLE 4. *Postoperative Results in Six Patients after Microvascular Decompression of Left Lateral Medulla Oblongata that Was Deemed Inadequate by the Surgeon at Operation*

Normal Blood Pressure (All Improved Over Preop)			Elevated Blood Pressure		
			Improved	No Change	
ō Rx*	HCTZ†	Multiple Rx	Rx	Same Rx	Total
0	0	1‡	3	2	6

* Rx = medical therapy.
† HCTZ = Hydrochlorothiazide.
‡ Decreased Rx.

in whom the medullary MVD was deemed adequate at operation. The blood pressure remains *normal* at present in 31 patients, 13 without medication, 12 on diuretics alone, and six on medical combination therapy, four of them with smaller doses than before surgery. The 32nd patient, lost to follow-up, had normal blood pressure 6 months after surgery. Of the remaining four of the 36, blood pressure is *significantly* improved in one and unimproved in three (Table 3). In six of the 42 patients, the left medullary MVD was deemed inadequate at operation. Of these, two are unimproved, three are improved on combination therapy, and the blood pressure is normal in only one patient who takes combination therapy (Table 4). Of the 11 patients in whom the left medullary vascular compression was not treated at operation, the blood pressure was unchanged after surgery

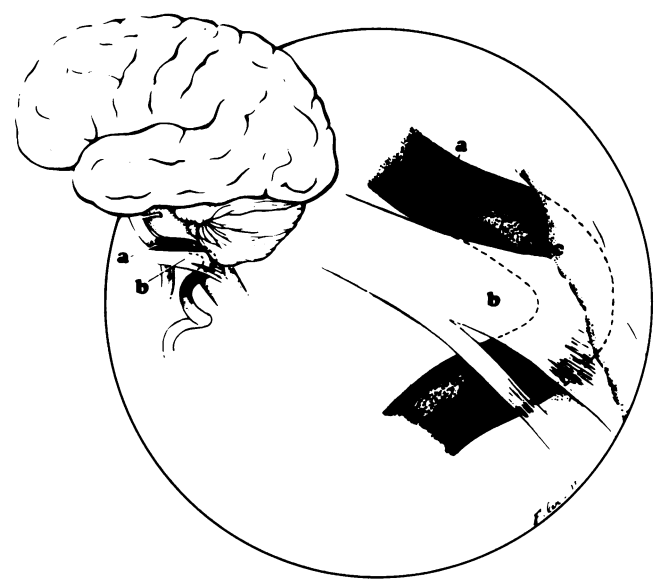

FIG. 1. Semidiagrammatic representation of vascular compression of left anterolateral medulla oblongata by vertebral artery loop in "essential" or "neurogenic" hypertension. Note that the loop protrudes medially anterior to the ninth and tenth cranial nerves. The loop, which may be of a smaller artery, may be located posterior to these nerves or run between fascicles of the nerves. (a) vertebral artery; (b) left glossopharyngeal-vagal nerve complex; (c) medulla oblongata posterior to root entry zone of cranial nerves IX and X.

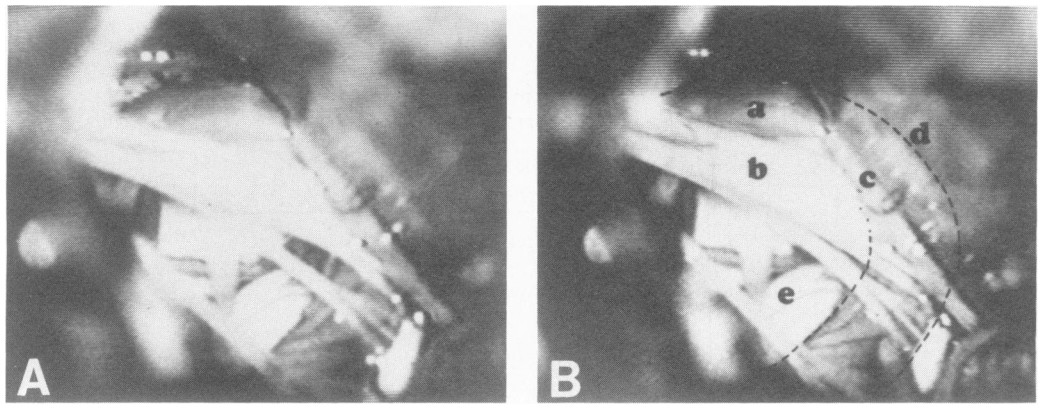

FIG. 2. Vascular compression of left anterolateral medulla oblongata by loop of vertebral artery. Microsurgical exposure of cerebellopontine angle *via* retromastoid craniectomy in 36-year-old woman. Photograph from videotape, 16× magnification, untouched (A) and retouched (B). Dotted line shows course of vertebral artery loop. (a) distal segment of vertebral artery; (b) left glossopharyngeal-vagal complex; (c) medulla oblongata posterior to root entry zone of cranial nerves IX and X; (d) retractor on cerebellum; (e) inferior olive.

in ten.† The blood pressure remains unchanged in the seven hypertensive patients operated upon on the right side, and in the 75 normotensive patients operated upon on either side.

Pre- and postoperative blood pressure measurements in the 42 patients who underwent MVD of the left lateral medulla oblongata are tabulated in Tables 3 and 4. Diastolic blood pressure (DBP) ranges are collated and analyzed in Tables 5 through 7. The improvement in DBP is statistically significant based on the McNemar test for change ($\chi^2 = 25.03$, df = 1, p = 0.01). It is highly unlikely that chance can account for the distribution of patients reflecting change in blood pressure class in the observed partition of 27.0 (Table 6). There is statistical evidence for association between the proportion of patients whose DBP is normal and their operative procedure ($\chi^2 = 26.537$, p = 0.01). Comparison of groups 2 and 3 is not statistically significant (Fisher's exact, p = 0.6571, df = 1) because of the small size of samples (Table 7).

Discussion

The results of this study strongly suggest that certain forms of hypertension are caused by pulsatile compression of the left lateral medulla oblongata by arteries of the base of the skull and that the hypertension can be relieved by decompression of the lateral medulla oblongata. We suggest that compression of the left lateral medulla oblongata and root entry zone (REZ) of CN IX and CN X may affect several parts of the neurogenic control system for BP and cause such a neural imbalance.

The possibility that a disorder within the central nervous system can lead to hypertension in experimental animals has been studied by many investigators. Reis[20,21] has termed this a central neural-imbalance hypothesis. The nervous system has a significant role in the mediation of the blood pressure.[8,22] Yet, the function of the nervous system in the development of hypertension has been questionable.[23] A number of animal models of hypertension have been developed utilizing manipulation of the central nervous system,[24] but persistent hypertension has been difficult to produce. The hypertension produced in these experimental models cause severe hypertension of acute onset, frequently lethal, or mild chronic hypertension which is labile. A great deal of important information regarding mechanisms of hypertension has been provided by these experimental models, but they do not reflect the pattern or sequence of changes in the human condition. Primary neurological diseases are rarely the cause of hypertension in man.[25]

Due to the complexity of the control system for blood pressure and the fact that it involves many feedback loops with mutual interactions at different levels, it is difficult to predict the result of abnormal function of one part of the system. Compensation is likely to occur in other systems that may take over the function of systems that are impaired.

Neurogenic control of blood pressure is mainly mediated *via* two systems: the carotid baroreceptors, the afferents of which travel in CN IX to the nucleus tractus

† Changes in arterial blood pressure in hypertensive patients in whom the left medulla was evaluated for presence of arterial compression but microvascular decompression was *not* performed (See Table 3 for comparison): improved BP (1);‡ no improvement (8); dead (2) (total = 11).

‡ One patient was improved, although he remains on medication in smaller dosage and prior impotence is gone. Two patients, both of whom were well-controlled before surgery, remain well-controlled after surgery. In review of the videotape of the operation in the patient who improved, it is our impression that the medulla was decompressed inadvertently when the artery was mobilized to treat hemifacial spasm.

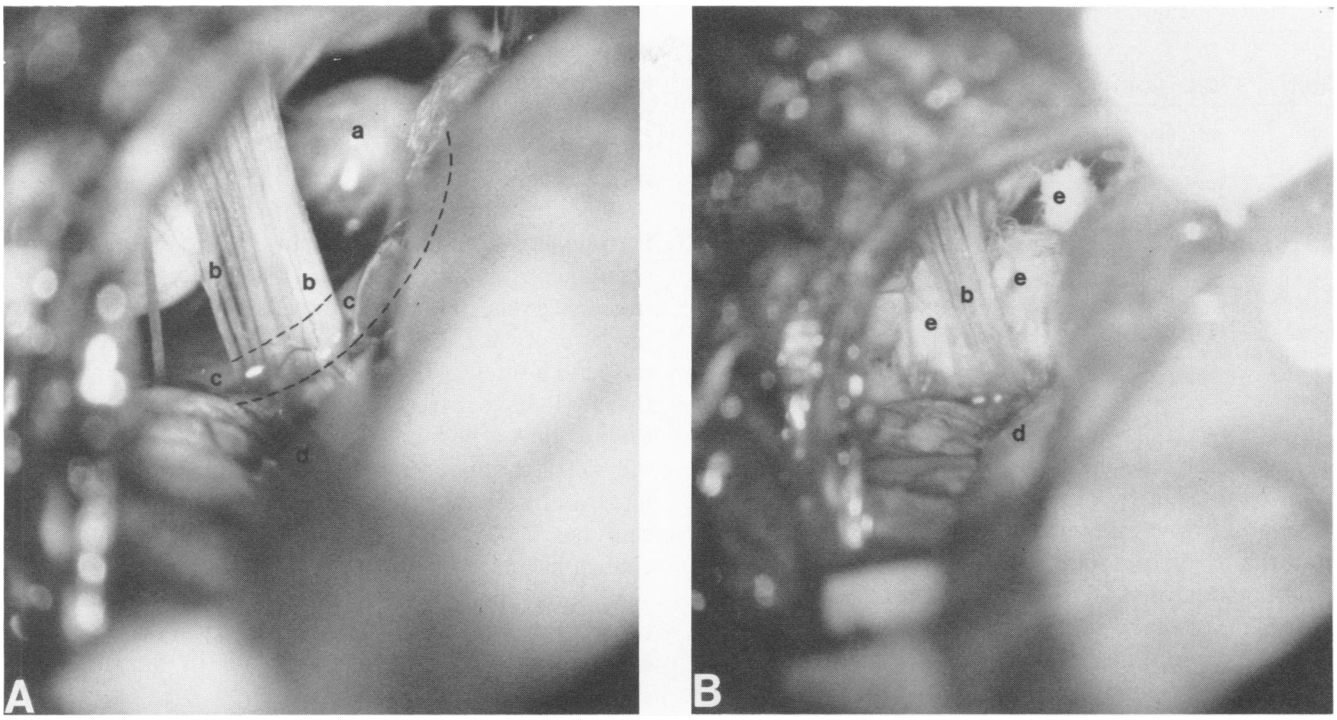

FIG. 3. Vascular compression of left anterolateral medulla oblongata by arterial loop in a 48-year-old man. Same exposure as Figure 2. Photographs from 35 mm color slides: A, 16×; B, 10× magnification. (a) vertebral artery; (b) left glossopharyngeal-vagal complex; (c) posterior inferior cerebellar artery loop impacting medulla oblongata anterior to IX-X (Dotted line shows course of loop); (d) retractor on cerebellum; (e) implant.

solitarious (NTS) and baroreceptors in the aorta *via* CN X. Connections *via* the descending sympathetic nervous system reach the effector organs (smooth muscle) to control peripheral resistance. The other system is the cardiac vagal afferents that also reach the NTS and can control BP probably mainly through sympathetic efferents to control peripheral resistance. This system is much less studied but it is likely to play an important role in the control of BP.[26] These two systems, the arterial baroreceptors and the cardiac vagal afferents, are assumed to converge to the same neuron pool within the brain stem vasomotor center.

Interruption of the baroreceptor afferents causes initial increase in BP but the long-term effect consists mainly of larger fluctuation in BP rather than hypertension. There is a large species difference, although some have reported sustained increase in BP as a result of interruption of arterial baroreceptor input.

Cardiac vagal afferents have a complex influence on circulation. Mainly, they are volume sensors and in that capacity they regulate blood volume *via* the kidneys. The majority of the fibers belong to the C-fiber group.[27,28] The afferent pathway of the Bezold-Jarisch reflex travels in the left vagus nerve.[29]

The C-fiber cardiac afferents are mainly responding to atrial distention.[28,36] Left ventricular receptors give rise to both medullated and nonmedullated fibers that respond to ventricular (systolic) pressure, but also to ventricular distention (left ventricular and diastolic pressure.[28]

It has been demonstrated by electrical stimulation that these cardiac vagal afferents can induce both pressor

TABLE 5. *Diastolic Blood Pressure (DBP)**

Range (mm)	Preop DBP	Late Hospital DBP	Late Follow-up DBP†
70–79	0	6	4
80–89	4	27	26
90–99	19	7	8
100–120	19	2	3
Totals	42	42	41†

*Early and late DBP after microvascular decompression of left anterolateral medulla oblongata in 42 patients.

† One patient lost to follow-up.

TABLE 6. *Distribution of Patients According to Preoperative and Postoperative Diastolic Blood Pressure (DBP) Changes**

No Change in Preop and Postop DBP Class		14
Postop DBP	Preop DBP	0
Postop DBP	Preop DBP	27

* Forty-one patients who underwent microvascular decompression of left medulla. One patient, lost to follow-up, not included.

TABLE 7. *Neurogenic Hypertension**

Group	Operation	Number	DBP Normal	DBP Elevated
1	Adequate MVD	35†	31	4
2	Inadequate MVD	6	1	5
3	No MVD	9‡	1	8

* Analysis of Diastolic Blood Pressure (DBP) in 50 hypertensive patients comparing adequate, inadequate, or no microvascular decompression (MVD) of left lateral medulla oblongata.

† One patient lost to follow-up.

‡ Two patients dead.

and depressor reflexes.[27,30,31] These reflexes are counteracted by arterial baroreceptor action and the effect of stimulation of vagal afferents is augmented when input from the baroreceptors is eliminated.

Elimination of vagal afferents (cardiopulmonary input) by cooling of the vagus nerve in the absence of arterial baroreceptor input causes a rise in BP, tachycardia, and constricts resistance vessels in skeletal muscles, intestines, and kidneys, as well as constricts splanchnic capacitance vessels.[31,33] It was concluded that cardiopulmonary vagal afferents inhibit central vasomotor nerves that are controlling sympathetic outflow to resistance and capacitance vessels. The cardiopulmonary vagal C-fiber afferents thus have a tonic inhibitory effect on vasomotor sympathetic efferents and interact with the baroreceptor reflex in a complex way. Distention of the atrium is generally vasodepressive through C-fibers and distention is excitatory through activation of medullated fibers. These results have been obtained from the nonprimate frequently with the animal under general anesthesia. There may be reason to believe that the situation may be different in man, but there seems little doubt that these cardiopulmonary receptors can have a stronger effect on muscular vascular resistance in man.[28] If cross-compression of the vagal nerve affects the function of the vagal afferent, there seem to be several ways now that can influence the regulation of blood pressure.

Effects on more central structures of the neural pathways that regulate blood pressure can cause hypertension. Thus, chronic lesions in NTS in cats produce a chronically abnormal BP control but not a hypertension similar to that in man, although the mean BP is elevated and tachycardia is present.[34] Lesions in NTS also exaggerate BP variations due to environmental stimuli (mediated through the hypothalamus).

An increased activity of the sympathetic nervous system controlling mainly peripheral resistance has, for a long time, been regarded central in the pathogenesis of essential hypertension. Such hyperactivity may be caused by many factors such as mechanical compression of the root entry zone (REZ) of CN X in a similar way as it has been shown for other cranial nerves. It may also be the result of a loss of suppression (or inhibition) resulting from a loss of input from arterial baroreceptors or, maybe more likely, a loss of vagal afferents originating in the heart or lungs.

It is interesting to note that there is a difference in the pressure sensitivity of the atrial C-fiber receptors in spontaneous hypertensive rats (SHR) compared to normotensive rats. SHR have a mean threshold of left atrial pressure of 10.2 + 0.6 mmHg, whereas normotensive rats have a threshold of 5.4 + 0.5 mmHg.[25] This indicates that SHR have a resetting of the left atrial C-fibers and there is thus a possibility that a decreased sensitivity of the (left) cardiopulmonary vagal afferents may be a factor in hypertension. But it may also be that hypertension has caused this decrease in sensitivity (*e.g.*, by change in the mechanical properties of the heart walls).

It may therefore be hypothesized that vascular compression of the REZ of the vagus nerve causes hypertension by causing a decrease in sensitivity of cardiopulmonary C-fiber afferents.

Certain results indicate that stimulation of the low-threshold myelinated afferent fibers from the heart have a vasopressor effect. It is likely that an arterial loop compressing the REZ of CN X or the brain stem in the region of the medullary vasomotor integration center (NTS) through a long-term compression on these fibers where they enter the medulla (REZ of CN X) may cause hyperactivity in these fibers, which may result in an imbalance between the various control systems involved in keeping BP within its normal limits. Knowledge about the normal function of these fibers is sparse, and there may be species differences that render the results of animal experiments of less value in understanding the function of the system in man.

Previous experiments show that it is important that the compression on the REZ or the medulla is pulsatile. There are several conceivable reasons for this. One is that the damage from pressure or nerve tracts or cell bodies is greater when the pressure is pulsatile than when it is constant. Another explanation may be that the pulsatile pressure, in fact, acts as a stimulus to regions of the medulla of CN IX or CN X in which the natural activity is synchronized with the heart cycle and thereby interferes with control systems in which it is important that the input from receptors is synchronized with the cardiac cycle. There are results that indicate that this is the case for baroreceptors. It is important for the proper function of the BP control system that baroreceptor input occurs at a certain point of the cardiac cycle. If the pulsatile pressure from a blood vessel interferes with this input and shifts the activation within a cardiac cycle, the functioning of this control

system may be changed and may result in an elevation of BP. This would happen without any apparent damage to nerve tissue.

The primary cause of the arterial compression of the medulla is truly a concomitant of the aging process: arterial wall degeneration with arterial elongation and dilatation. The arteries at the base of the brain are subject to these changes and actually begin to loop about in their confined space. The looping arteries may or may not cause problems depending upon where they impinge. Also, with aging, the brain sags caudally, further exposing neural tissue to the looping arteries and bridging veins at the base. Hypertension itself, whatever the cause, augments elongation of arteries. This chronic, self-perpetuating process may correlate with progression of clinical hypertension due to medullary compression. A mild degree of arterial elongation and sag of the hindbrain may allow an arterial loop to pulsate against the left lateral medulla, causing mild disruption of central control of the left ventricle *via* the left vagus. The heart overworks. Mild, possibly labile, hypertension develops. This causes further arterial elongation which causes increased pulsatile compression of the medulla, increasing the hypertension.

Our results strongly suggest that it is the left side of the medulla that is sensitive to compression. We did not find lateral arterial compression in our hypertensive population operated upon on the right side, but have seen it mildly present in two normotensive patients on the left. One was treated by MVD. Both patients remain normotensive. This may be due to the fact that the autonomic distribution of the vagus nerves is asymmetrical. The left vagus nerve, in contrast to the symmetrically paired somatic and sensory function of all other cranial nerves with central innervation from both nuclei tracti solitarii, is the major control of the left heart. Pulsatile compression on the left medulla oblongata would appear to influence the nerve tracts leading to the left heart (afferent or efferent), and such influence may cause the heart to overwork early on either because of malfunction of the vagal afferents or because of change in the efferent inflow to the heart. This would explain the increased cardiac output and stroke volume seen in early labile or borderline hypertensives.

The results reported in this paper are supported by others. Kurze[16] observed relief of preoperative hypertension in a left-sided hemifacial spasm patient after MVD of the lateral medulla. Fein and Frishman recently described two hypertensive patients whose blood pressure gradually returned to normal after posterior circulation arterial bypass procedures for vertebral-basilar insufficiency.[35] In these patients, the posterior inferior cerebellar artery was mobilized from the glossopharyngeal-vagus nerve complex for purposes of performing the bypass. Whether relative ischemia of the medullary cardiovascular control nuclei or vascular compression was the causal factor is not known. These patients did not appear to have brain stem compression, or its presence or absence was not evaluated.

As pointed out above, the neurogenic control of BP is complex and incompletely known. Clinical observations alone are inadequate to prove that a given factor is causal of chronic disease.[36] We have, therefore, also performed animal experiments to study the effect of pulsatile pressure on the medulla, and in a companion paper (Jannetta PJ, Segal R, Wolfson SK, et al. Neurogenic hypertension: etiology and surgical treatment. Ann Surg 1985, in press), we describe our data in a chronic, progressive, experimental model in the subhuman primate of pulsatile compression of the left lateral medulla oblongata, utilizing the neurovascular compression stimulator.

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