Neurogenic Hypertension: Etiology and Surgical Treatment

II. Observations in an Experimental Nonhuman Primate Model

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In a companion paper (Ann Surg 1985; 201(3):391–398), clinical data which suggest that neurogenic hypertension may be caused by arterial compression of the left medulla oblongata was presented. A chronic pathophysiologic animal model of neurogenic hypertension using a substitute for arterial pulsation, the neurovascular compression simulator (NCS), was developed. This paper presents data that demonstrate how development of hypertension in a nonhuman primate baboon (5 subject animals, 5 control animals) can be caused by the NCS, and the blood pressure can subsequently return to normal following cessation of NCS activity. These experiments show that pulsatile compression of the left ventrolateral medulla oblongata results in cardiovascular changes consistent with the sequence found in human neurogenic hypertension. Arteriosclerosis and arterial ectasia in the human contribute to arterial elongation and looping at the base of the brain. An arterial loop, by causing pulsatile compression of neural structures, elicits an increase in blood pressure initiated by an increase in cardiac output. This may be due to interference with the autonomic control of the heart and/or by alteration of the relative capacitance of the vascular system.

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CLINICAL OBSERVATIONS STRONGLY SUGGEST that neurogenic hypertension may be associated with arterial compression of the left lateral medulla oblongata and that the blood pressure is normalized after microvascular decompression of this area of the medulla oblongata.[1,2]

The development of scientific syllogisms by clinical observation is limited by the fact that such observation provides only *post hoc* reasoning. It was obvious to us early on that an experimental animal model was needed to fulfill the criteria of the Henle-Koch postulates for the proof of causation of chronic disease.[3] Therefore, in keeping with these criteria, we attempted to develop an animal model to study the mechanism involved. Acute studies of pulsatile compression of the ventrolateral medulla and entry zone of the ninth and tenth cranial nerves on the left side in the cat demonstrated the induction of an increased stroke volume and cardiac output, but did not show statistically significant changes in blood pressure.[4,5] However, these acute experiments were restricted to a few hours, and the animals were anesthetized. The next step was to study a similar manipulation of the nervous system in a chronic, progressive, nonhuman primate model. This paper describes the hemodynamic changes investigated in this model.

The animals were chronically implanted with a self-contained neurovascular compression simulator (NCS) that applies pulsatile pressure on the ventrolateral medulla and the entry zone of the ninth and tenth cranial nerves on the left side. We observed the development of arterial hypertension after inflation of the pulsating balloon pressing on the medulla, and we observed how the blood pressure decreased by cessation of the pulsatile compression on the brain stem.

The NCS, which we have described in a recent publication,[6] consists of a double balloon catheter, a connecting tube, and an injection port, all fabricated of polyurethane and silicone rubber. The larger balloon is placed in the descending thoracic aorta, and the smaller balloon is placed in the cerebellopontine angle beside the left lateral medulla oblongata anterior to the ninth and tenth cranial nerves. The system is filled with saline. With each systole, the rise in intraaortic pressure causes a pressure wave to propagate from the intraaortic balloon. The smaller cephalic balloon, in turn, pulsates against the adjacent nervous structures (Fig. 1). This functions as an artificial artery pulsating in synchrony with the heart.

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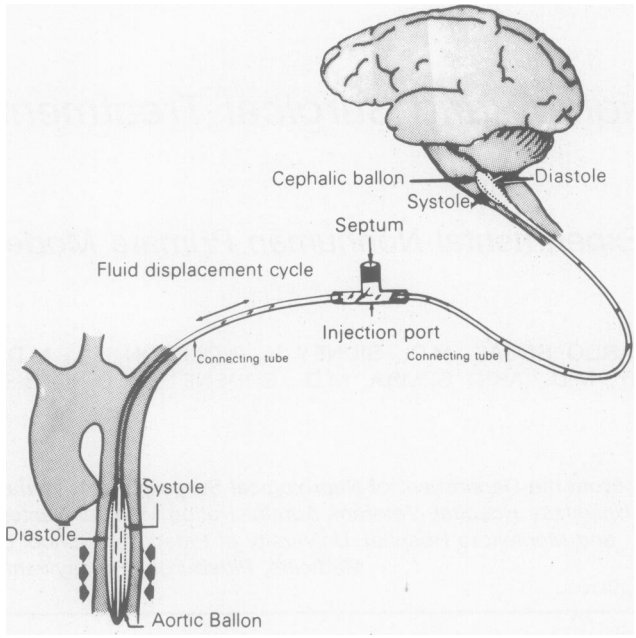

FIG. 1. Schematic drawing of neurovascular compression simulator (NCS). The anatomical structures are represented in reduced scale compared to the NCS to fit into the illustration.

Experiments were carried out in 10 adult male baboons (Papio Cynocephalus/Anubis) weighing 7.4 to 9.5 kg. The baboons were divided into two groups of five animals each. In both groups, hemodynamic parameters were monitored at baseline and again after implantation of the larger balloon of the NCS in the aorta, but with the smaller balloon placed in the subcutaneous tissue of the posterior cervical region. Next, in Group 1 (experimental), the smaller distal balloon was implanted intracranially and the NCS inflated so as to pulsate. Lastly, the system was deflated *in situ.* In Group 2 (control), the balloon was implanted adjacent to the brain stem but not inflated and, thus, not pulsating.

Experimental Methods

General

In the first phase of the project, four continuously chair-restrained baboons were studied with continuous monitoring of hemodynamic parameters through indwelling intravascular lines. Of these animals, one belonged to Group 1 and three to Group 2.

In the second phase, six baboons were studied unrestrained with intermittent monitoring of blood pressure, heart rate, and cardiac output. Of these animals, four belonged to Group 1 and two to Group 2.

The Neurovascular Compression Simulator

The NCS used in these studies consisted of four parts (Fig. 1): an intraaortic balloon, a smaller balloon for placement in the cephalic subarachnoid space, connecting tubing, and an injection port. The aortic balloon was an enclosed cylindrical bag, 5 mm in diameter and 8 cm long. It was fabricated using polyurethane (Cardiothane 51 Copolymer® and Cardiomat-610® Polymer, Kontron Cardiovascular, Inc., Everett, MA) and silicone rubber.[3] A perforated Cardiothane tube impregnated in barium ran the length of the interior of the large balloon. The small balloon, of the same materials, was a flattened ovoid 2 by 3 mm in cross section and 1 cm long, attached to the tubing only at the proximal aspect. The tube connecting the large balloon was 12 cm long. Both were 2 mm in outside diameter. The tubes were joined by a T-port containing a silicone rubber septum for inflation and monitoring purposes. The entire NCS was sterilized using a cold ethylene cycle.

Intraballoon pressure was monitored through a 26-gauge needle penetrating the injection port and connected to a transducer. The physical properties of the NCS were tested both *in vitro* and *in vivo,* and a pressure-volume study was carried out to characterize the performance of the NCS. A pulse duplicator system (incorporating a Pulsatile Pump, Model 1401, Harvard Apparatus Co., Inc., Millis, MA) was used for the *in vitro* test where both static and pulsatile pressures were applied.

Implantation

The baboons were anesthetized with endotracheal halothane after IM ketamine hydrochloride induction. A closed system with a Harvard respirator was used. Blood gases were monitored and the respirator was adjusted to keep PCO_2, pH, and arterial PO_2 within physiologic limits. An intravenous infusion of 0.45% NaCl with 5% dextrose was given for fluid replacement. Blood pressure and electrocardiogram were recorded using a research recorder monitor. The animals were placed in the supine decubitus position with the left forelimb abducted. The larger balloon was introduced through an axillary incision into the intrathoracic aorta through a small incision in the axillary artery using fluoroscopic guidance. The arteriotomy was closed around the connecting tube with a 6-0 silk-pursestring suture. The remaining tubing, T-port, and small balloon were tunneled subcutaneously cephalad and buried subcutaneously in the posterior cervical region. The port was tapped with a 26-gauge needle to obtain an *in vivo* pressure-volume (PV) curve. The pressure inside the device was measured with a Statham transducer (Statham Instruments Division, Gould Inc., Oxnard, CA) while fractions of 0.1 ml of saline were injected until total filling (1.0 ml) was reached. When the NCS was inflated to the plateau of the PV curve (0.6 ml), the polygraph recording from the port reproduced with fidelity the

pressure wave from the abdominal aorta. The small balloon was introduced into a plethismograph, and its synchronous pulsations were recorded in terms of volume changes averaging 6 to 7 μL. When fully inflated, the volume of the small balloon was 38 μL.

The intracranial balloon was implanted 1 week or more later. The baboons were anesthetized and placed in the right lateral decubitus position. A left retromastoid vertical incision was made exposing the subcutaneous balloon, the occipital bone, and the posterior arch of the first cervical vertebra. The rim of the foramen magnum on the left side was removed, a left retromastoid craniectomy was performed, and the atlanto-occipital membrane was divided. Using microneurosurgical techniques, the arachnoid was dissected between the floor of the posterior fossa and the spinal accessory nerve after cutting the first dentate ligament. The dissection was extended superiorly so the balloon could be easily inserted adjacent to the brain stem, lateral to the inferior olive, and under the axillae of the ninth and tenth cranial nerves. The wounds were irrigated with antibiotic solution and closed. The animals were extubated and allowed to stabilize.

Continuous Recording of Blood Pressure, Heart Rate, and Electrocardiogram

For continuous monitoring, the baboons were trained to sit in the restraining chair. In each of four baboons, the tip of a silicone rubber catheter was placed in the right atrium *via* the femoral vein, and a polyvinylchloride catheter was placed in the common iliac artery *via* the femoral artery. The distal end of each catheter was tunneled subcutaneously to the posterior lumbar region. The arterial catheters were kept open by a continuous flush (3 ml per hour) of normal saline solution (4 units/ml) containing heparin using a C.F.S. Intraflo (Sorenson Research Inc., Salt Lake City, UT) and connected to a Statham® transducer. The pressure signals were amplified and displayed on an E-for-M Physiograph (Electronics for Medicine, Inc., White Plains, NY). The peak of the arterial pulse triggered a cardiotachometer and the heart rate was simultaneously recorded. A three-lead electrocardiogram also was recorded. The venous line was kept open by daily flushing of the catheter with normal saline containing 1000 USP heparin per ml.

Cardiac Output

Cardiac output was recorded intermittently in the unanesthetized chair-restrained baboons by thermodilution technique requiring the additional insertion of an indwelling thermistor line. A Thermodilution Cardiac Output Meter (Model 72-9, Columbus Instrument Co., Columbus, OH) was used for these measurements.

Baroreflex Response

Baroreflex sensitivity was tested in the unanesthetized baboon by plotting the RR intervals of the electrocardiogram against the increase of arterial pressure induced by intravenous injection of phenylephrine (bolus injection of 150 μg).

Transcutaneous Doppler Systolic Pressure Monitoring

Intermittent monitoring of blood pressure and heart rate was performed in six non-chair-restrained baboons. These parameters were measured daily by a transcutaneous Doppler technique. The baboon was sedated with ketamine hydrochloride, 10 mg/kg. The baboon was removed from his cage five minutes following injection. Blood pressure from the radial or humeral artery was then measured by the Doppler systolic method: ten separate measurements were made over a 15-minute period.

Preparation and Collection of Pathologic Material

The baboon tissue was fixed *in situ* by intraaortic gravity perfusion of normal saline solution followed by 2% paraformaldehyde. For this, the animal was anesthetized with halothane. After removal from the cranium, the brain was fixed in large volumes of paraformaldehyde for a minimum period of 2 weeks with several changes of fluid before brain stem sections were obtained. Both control and experimental tissues were obtained using the same procedure. Heart, kidney, and samples of the arterial tree and veins were also recovered and prepared for light and electron microscopy. Five transverse sections of equal thickness were cut on the major axis of the left ventricle, and the width of the left ventricular wall was measured.

Light Microscopy

Following fixation of the brain in paraformaldehyde, 5-mm thick horizontal sections of the brain stem were obtained and processed for paraffin embedding. Tissue sections were made and stained with hematoxylin and eosin. Sections for examination of the area of entry zone of the ninth and tenth cranial nerves and brain stem were obtained in all of the animals for light microscopy.

Statistical Analysis

Paired t-tests were used to compare the values of BP, HR, CO, and SV of the baseline period (pre-NCS implantation) with the values of the aortic balloon in place and the cephalic balloon extracranial, and both balloons in place but uninflated. This was done in both restrained and unrestrained animals. Factorial analysis

TABLE 1. *Hemodynamic Sequence in Five Baboons (Group 1) Showing The Development of Hypertension with Implantation of Inflated Pulsatile Intracranial Balloon**

Parameter	Test Period: Baseline N = 5	Aortic Implantation of NCS† N = 5	Aortic and Cephalic Implantation of NCS Inflated N = 5	After Deflation N = 2‡
Systolic pressure (torr)	127 ± 9	131 ± 4	169 ± 18§	143 ± 11
Heart rate (beats/min)	117 ± 25	117 ± 18	120 ± 19	105 ± 11
Cardiac output (L/min)	1.34 ± 0.48	1.38 ± 0.20	2.03 ± 1.00‖	
Stroke volume (ml)	10.1 ± 3.0	12 ± 2	16 ± 7	

* Values are mean ± standard deviation.

† NCS = neurovascular compression simulator.

‡ Of the five animals in column three, two died during the hypertensive phase; one as a result of an acute hypoglycemic episode (unexplained) and the other presumably as a result of cardiac insufficiency. A third animal was lost to study because of malfunction of NCS; therefore, only two are listed in column 4.

§ $p = 0.01$.

‖ These measurements were made at the same time of maximal CO (6 to 9 days postinflation).

of variance was used to test for differences among periods in both restrained and unrestrained animals. This was done separately for values adjusted (by subtraction) for baseline levels and for unadjusted values of NCS-implanted animals with cephalic balloon intracranial, both noninflated and inflated. Paired t-tests were used to compare the hemodynamic values of periods in both group 1 (experimental) and group 2 (control) animals. The thickness of the lateral wall of the left ventricle for each animal was measured and divided by the cube root of the body weight. That adjustment reflects the fact that width is a one-dimensional measure and weight is a three-dimensional measure. These adjusted widths were compared between group 1 and group 2 using a Student's t-test (two-tailed). Significance was considered to be $p < 0.05$.

Prolonged chair restraint of four baboons did not induce significant changes of the measured parameters. Implantation of the inflated aortic nonpulsatile balloon, as well as of the cephalic balloon intracranially noninflated, did not alter the hemodynamic baseline. Our experience with continuous chair restraint resulted in several, not unexpected, problems. These included chronic infection, anemia, and difficulties with arterial and venous catheters. The difficulties were such that, in the early part of this study, only one of four animals was carried through the entire protocol. Because of these problems, intermittent recording of systolic blood pressure by a transcutaneous Doppler technique, as well as the recording of other hemodynamic variables, were carried out for up to 1 year in animals that were not chair restrained. The data collected again showed no change in cardiovascular parameters before the NCS was inflated intracranially.

Analysis of the data collected for both restrained and unrestrained baboons, including all periods of measurement, did not reveal significant differences attributable to restraint *versus* no restraint or to the method of measurement. Accordingly, we believe that it is proper to compare the data collected from experimental (group 1) with control (group 2) animals without regard to monitoring methodology.

Results

The five animals of Group 1 developed significant ($p = 0.01$) arterial hypertension with the implantation of the pulsatile intracranial balloon. Hemodynamic changes in these animals are summarized in Table 1.

In baboon 524, 3 days after the pulsatile compression was initiated by inflation of the NCS, the cardiac output, stroke volume, and blood pressure started to rise with a slight decrease in the heart rate (Fig. 2). The cardiac output increased by 36%. At the eighth day, the cardiac output and stroke volume returned to normal values coincident with a dramatic rise in peripheral resistance (63% increase) while maintaining the hypertension. No decrease in baroreceptor sensitivity was observed after implantation of the NCS, both inside the aorta and intracranially. Baroreceptor sensitivity actually increased (average slope before hypertension = 0.27 ± 0.04 and during hypertension = 0.39 ± 0.08) (Fig. 3). This baboon died suddenly after 3 weeks of persistent and progressive hypertension, presumably of cardiac insufficiency.

In baboon 491 (Fig. 4), the blood pressure started to rise together with a slight bradycardia 7 days after onset of pulsatile compression. The hypertension became progressively higher (42% increase) until the NCS was deflated after 30 days. A gradual return of the blood pressure to normal values through another 30 days then was observed.

In baboon 573, blood pressure rose by 14% 3 days after the pulsatile intracranial balloon was in place (Fig. 5). The intracranial balloon slipped out of position on

day 8, and the blood pressure returned to control levels. When the balloon was replaced, the blood pressure again rose. However, in the second operative procedure, the dorsal aspect of the pons on the left side was injured. The baboon developed a mild left hemiparesis with left central facial weakness and was sacrificed on the 27th day after the initial insertion of the intracranial balloon.

In baboon 585, blood pressure increased by 23% 2 days after NCS implantation (Fig. 6). NCS deflation 1 week later led to a return of blood pressure to normal values. Reinflation caused hypertension.

In baboon 589, blood pressure increased by 27% 2 days after NCS implantation, while the cardiac output increased by 20% (Fig. 7). The baroreflex sensitivity actually increased with the development of the hypertension (average slope before hypertension 0.18 ± 0.06 and during hypertension 0.53 ± 0.21).

In the five animals in Group 2, with intracranially implanted but deflated nonpulsatile NCS for periods ranging from 3 weeks to 2 years, no hemodynamic changes were observed (Table 2).

Seven of the baboons have been autopsied while another two remain alive. The autopsy of a 10th baboon (control) is not included in the study because a specimen suitable for study was not obtained. Three of the hypertensive baboons (Group 1) had a maximal left ventricular wall thickness of 12.45 ± 2.8 mm, compared with 7.4 ± 0.9 mm of four control (Group 2) baboons. The mean ratio between the thickness of the left ventricular wall and the cube root of body weight for the hypertensive animals (Group 1) was 5.8 ± 1.06, compared with 3.73 ± 0.52 for the normotensive animals (Group 2) (Fig. 8). The difference is significant ($p = 0.01$) and indicates concentric hypertrophy of the left ventricle in the hypertensive animals. There was no clot in the aorta in any animal. A slight depression on the ventrolateral surface of the medulla, indicating the proper intended placement of the intracranial balloon, was found in all baboons. No intrinsic lesion was seen in sections of the medulla. A hemorrhagic lesion on the dorsal aspect of the pons on the left side was found in baboon 573.

Discussion

The experimental evidence reported here indicates that hypertension can be the result of neurovascular compression of the brain stem. While these observations were made in an experimental primate model, the results described, along with the clinical observations also alluded to, have led us to speculate that some cases of what has been termed "essential hypertension" may, in fact, be the result of a similar mechanism. Because of our clinical experience, we believe that such neurovascular compression is a common entity.

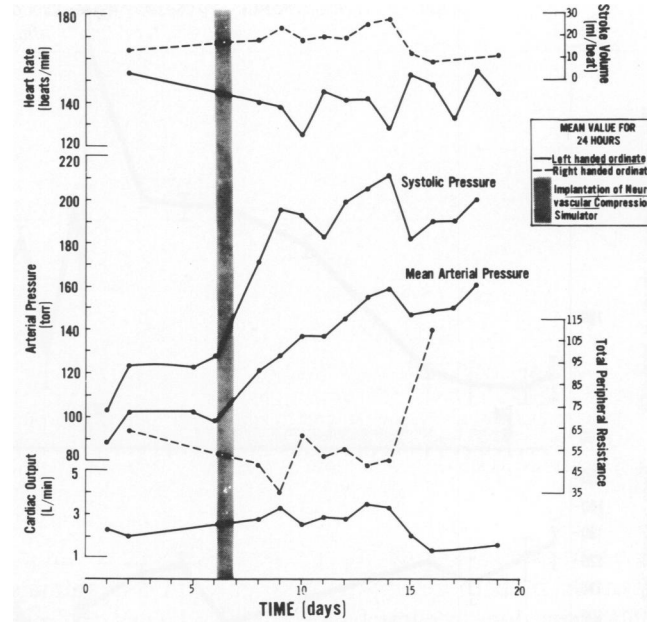

FIG. 2. Hemodynamics in baboon 524. This animal did not have the neurovascular compression simulator deflated period because he died during hypertensive period.

The significance of the nervous system in mediating and maintaining the blood pressure is well-recognized.[7,8] However, the possibility of a primary role of the nervous system in the development of hypertension has been questioned.[9] Although experimental models of neuro-

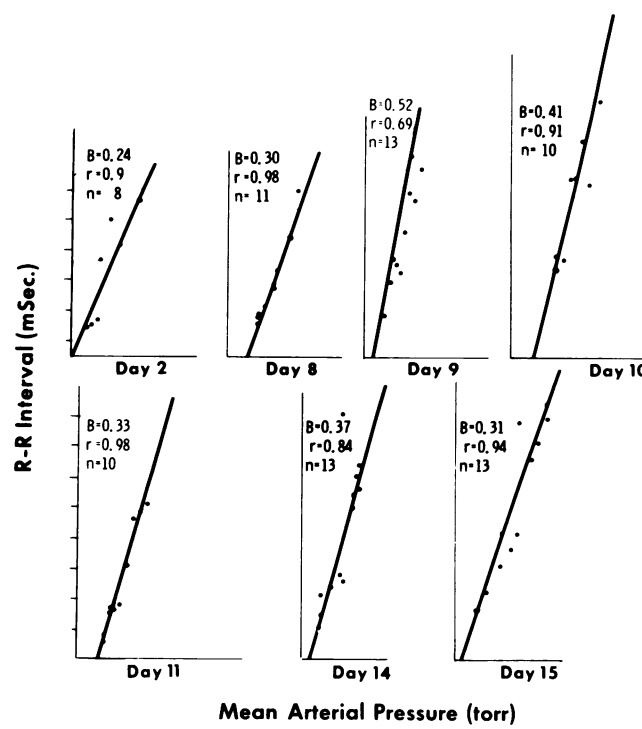

FIG. 3. Sequence of baroreflex sensitivity tests by intravenous injection of phenylephrine in baboon 524.

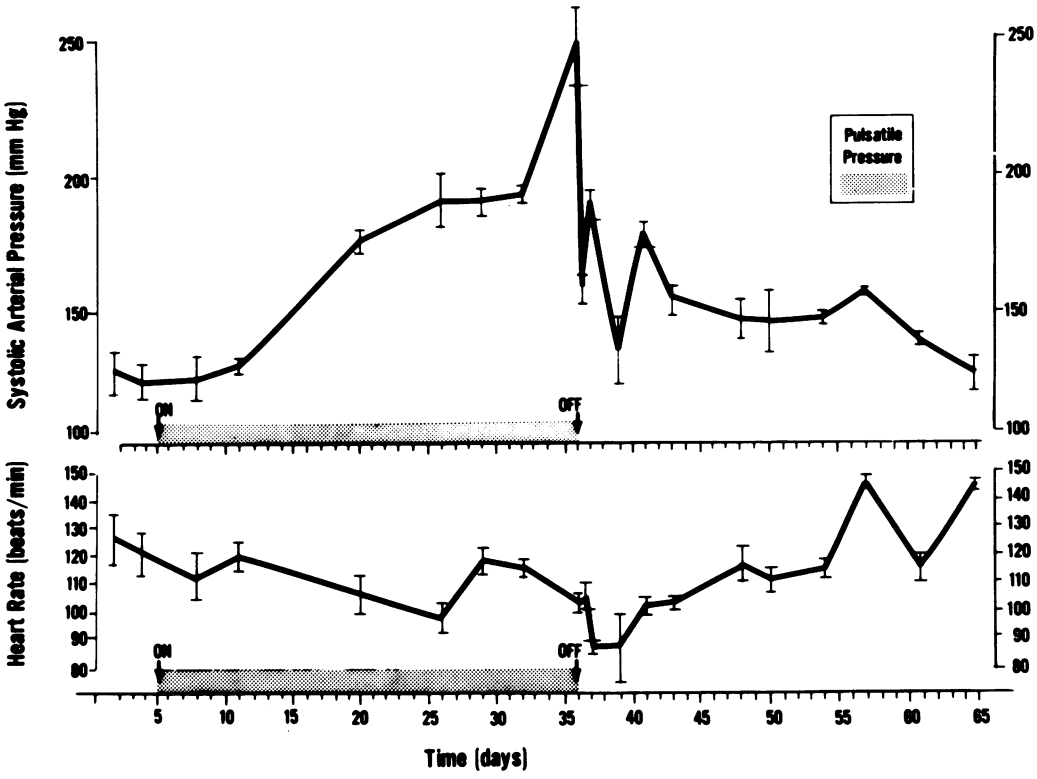

FIG. 4. Systolic blood pressure and heart rate information from baboon 491. The time of pulsatile neurovascular compression is indicated by the shaded bar.

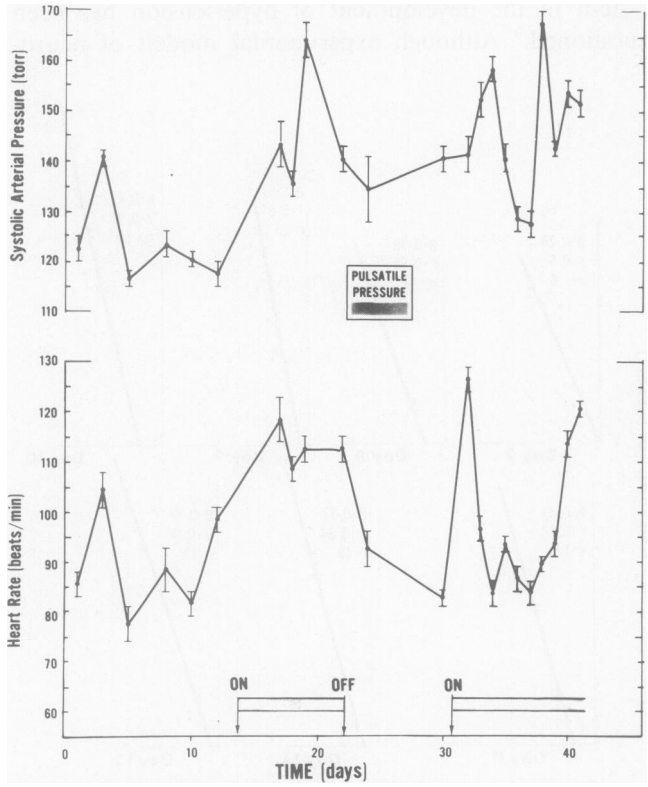

FIG. 5. Systolic blood pressure and heart rate information from baboon 573. The time of pulsatile neurovascular compression is indicated by the shaded bar.

genic hypertension are available, it has been difficult to produce persistent hemodynamic changes by manipulating the central nervous system. These experimental models, from which we have learned much, cause acute lethal hypertension, acute hypertension which abates, or chronic mild, labile hypertension.[10,11] This is in contrast to the human condition, which is rarely of acute onset, but usually mild and labile, slowly progressive, and subsequently fixed. Primary neurological diseases have been implicated only rarely as a primary cause of high blood pressure in man.[12]

In view of the above, we believe that neurovascular compression may be a cause of essential hypertension. While the evidence at hand falls short of establishing this, the clinical result is highly suggestive, and the animal experiments provide the basis for further controlled studies.

For over 80 years, it has been known that arterial hypertension may result from a generalized increase in intracranial pressure.[13] Ischemia of the brain stem, as well as localized pressure or distortion, reproduces the same phenomenon.[14] Recently, Reis and co-workers have added much to a better understanding of the mechanisms involved.[8,15] However, while the above is true for the acute situation, still unanswered is the question of whether chronic arterial hypertension may result from chronic pressure, distortion, or ischemia of

the brain stem. In our model it would seem unlikely that the hypertension could have resulted from a static mass effect when we recognize the extremely small volume (38 μL) of the 2-by-3-mm diameter cephalic balloon and its relatively large distance from the floor of the fourth ventricle.

Chronic, sustained hypertension has been difficult to elicit by interfering with the baroreceptor reflexes peripherally.[11] Bilateral central denervation of the baroreflex has been shown to cause chronic hypertension in cats.[12] However, we do not have evidence that the unilateral manipulation to which we subjected the baboons in our experimental model depressed the baroreflexes.

Hypertension may result from an increase in cardiac output, an increase in peripheral resistance, or a decreased relative capacitance of the vascular bed. The initiation of hypertension in our model appear to be mediated by an increase in cardiac output rather than by an increase in peripheral resistance. This is not surprising because it has been observed in other experimental models of neurogenic and renal hypertension.[16]

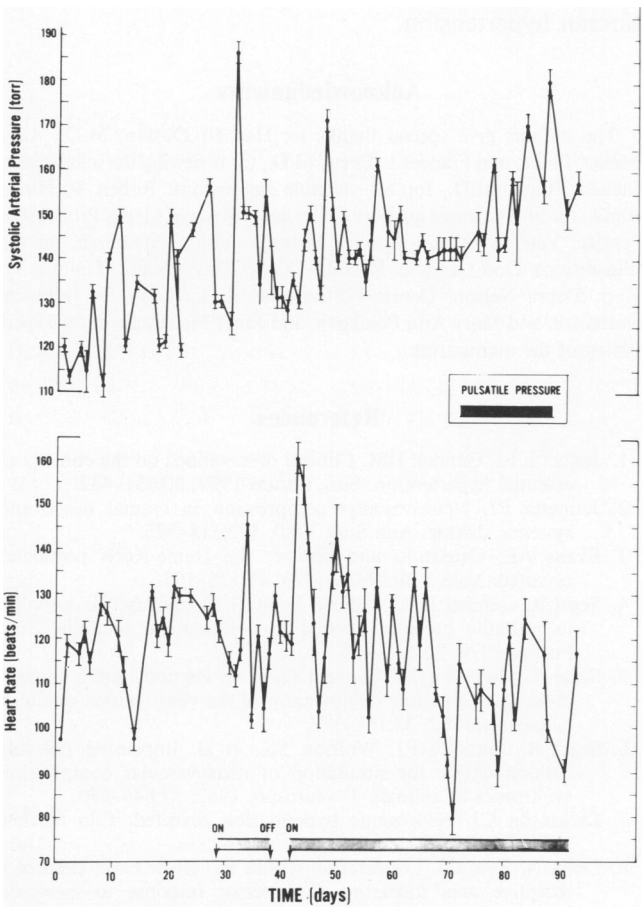

FIG. 6. Systolic blood pressure and heart rate information from baboon 585. The time of pulsatile neurovascular compression is indicated by the shaded bar.

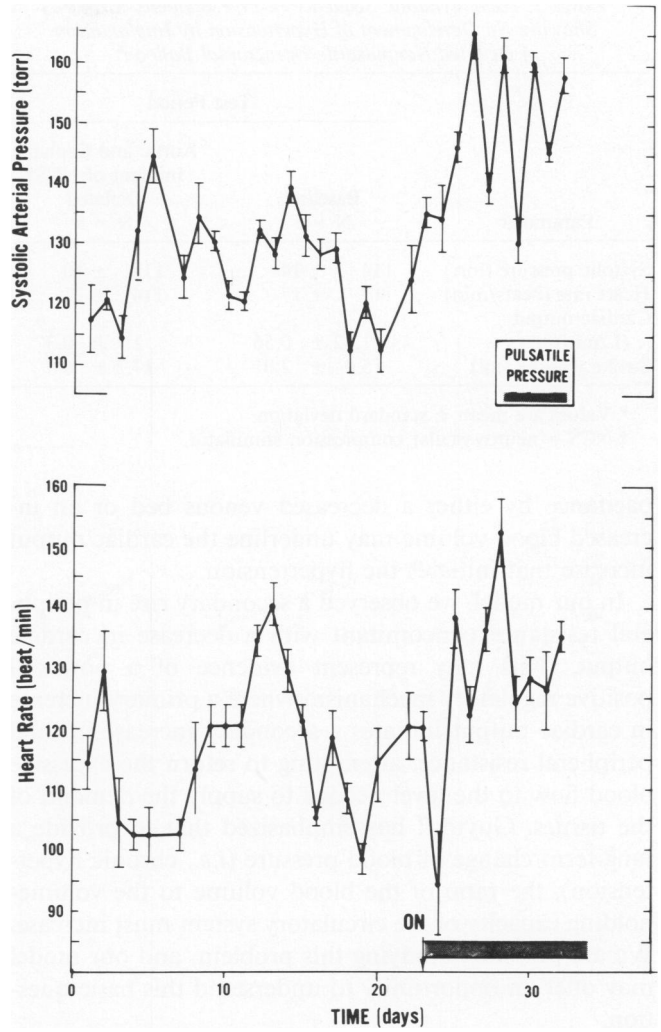

FIG. 7. Systolic blood pressure and heart rate information from baboon 589. The time of pulsatile neurovascular compression is indicated by the shaded bar.

However, in these models, the increase in cardiac output was usually accompanied by an increase in heart contractility. Since the pioneer studies of Peiss,[17] Manning and Peiss,[18] and Rosen,[19] we have known that electrical stimulation of the ventrolateral medulla may elicit positive inotropic effects. More recent studies have emphasized the presence in the ventrolateral medulla of important pathways related to cardiovascular control.[20–22] Also, a chemosensitive region had been described on the surface of the ventrolateral medulla, electrical stimulation of which also resulted not only in respiratory change but in a rise in blood pressure.[23] We do not know yet whether the pulsatile pressure applied by the NCS may induce or depress neuronal activity or fiber conduction on these neighboring structures to elicit positive inotropic effects.[5] We have not ruled out whether neurogenically-induced decrease of relative vascular ca-

TABLE 2. *Hemodynamic Sequence in Five Baboons (Group 2) Showing No Development of Hypertension by Implantation of Deflated Nonpulsatile Intracranial Balloon**

Parameter	Test Period: Baseline N = 5	Test Period: Aortic and Cephalic Implant of NCS† Deflated N = 5
Systolic pressure (torr)	114 ± 14	112 ± 10
Heart rate (beats/min)	117 ± 17	114 ± 21
Cardiac output (L/min)	1.82 ± 0.56	1.7 ± 0.3
Stroke volume (ml)	15.9 ± 7.0	17.2 ± 6.0

* Values are mean ± standard deviation.
† NCS = neurovascular compression stimulator.

pacitance by either a decreased venous bed or an increased blood volume may underline the cardiac output increase that initiates the hypertension.

In our model, we observed a secondary rise in peripheral resistance concomitant with a decrease in cardiac output. This may represent evidence of a powerful positive regulatory mechanism where a primary increase in cardiac output initiates a secondary increase in total peripheral resistance, attempting to return the excessive blood flow to the level needed to supply the demand of the tissues. Guyton[9] has emphasized that to provide a long-term change of blood pressure (*i.e.*, chronic hypertension), the ratio of the blood volume to the volume-holding capacity of the circulatory system must increase. We are presently studying this problem, and our model may offer an opportunity to understand this basic question.

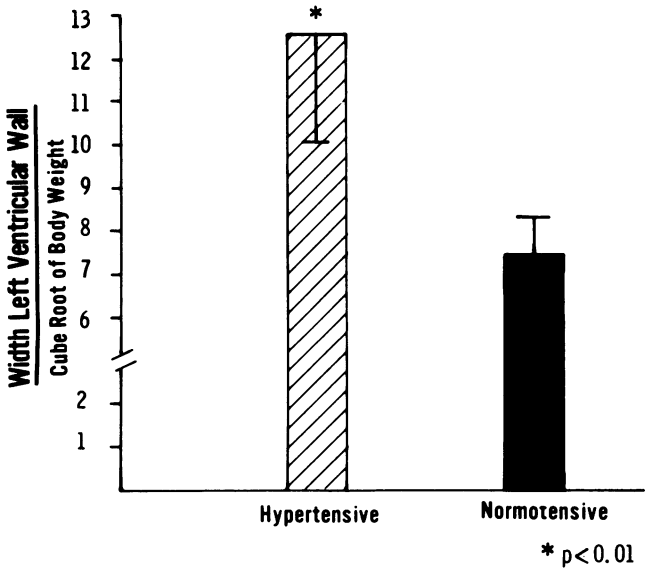

FIG. 8. Comparison of the weight-adjusted width of the left ventricular (control) animals. The values are mean ± SD from three and four baboons, respectively.

In contrast to the other cranial nerves, the laterality of autonomic control by the vagus nerves has been demonstrated both anatomically and physiologically.[24] Evidence showing asymmetry of cardiovascular function at the hypothalamic, medullary, spinal, and peripheral sympathetic nerve levels has been found by several authors.[25-29] Abnormality of neural control of the left ventricle caused by pulsatile compression of the left lateral medulla oblongata, as caused by arterial loops in man and by the NCS in the present study, would appear to allow or cause the heart to overwork, initiating the sequence that results in hypertension.

On the basis of both clinical and experimental data, we propose a scenario where arterial deterioration and lengthening with resultant pulsatile compression of the left lateral medulla oblongata causes pathophysiological effects in control of the heart, upsetting (as it were) the autonomic control of the blood pressure and causing arterial hypertension. This needs to be supported as larger numbers of patients and experiments come to observation. With respect to the experiments, examination of the other human observations in electrolyte balance, hormones, etc., needs to be compared with human hypertension.

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References

1. Jannetta PJ, Gendell HM. Clinical observations on the etiology of essential hypertension. Surg Forum 1979; 30:431–432.
2. Jannetta PJ. Neurovascular compression in cranial nerve and systemic disease. Ann Surg 1980; 192:518–525.
3. Evans AE. Causation and disease: the Henle-Koch postulates revisited. Yale J Biol Med 1976; 49:175–195.
4. Segal R, Gendell HM, Canfield D, et al. Cardiovascular response to pulsatile pressure applied to ventrolateral medulla. Surg Forum 1979; 30:433–435.
5. Segal R, Gendell HM, Canfield D, et al. Hemodynamic changes induced by pulsatile compression of the ventrolateral medulla. Angiology 1982; 33:161–172.
6. Segal R, Jannetta PJ, Wolfson SK, et al. Implanted pulsatile balloon device for simulation of neurovascular compression syndromes in animals. J Neurosurg 1982; 57:646–650.
7. Dickinson CJ. Neurogenic hypertension revisited. Clin Science 1981; 60:471–477.
8. Doba N, Reis DJ. Localization within the lower brain stem of a receptive area mediating the pressor response to increased intracranial pressure (the Cushing response). Brain Res 1972; 47:487–491.
9. Guyton AC. Arterial pressure and hypertension. *In* Circulatory physiology III. Philadelphia: WB Saunders Co, 1980; 1–9.

10. Reis DJ, Doba N. The central nervous system and neurogenic hypertension. Prog Cardiovasc Dis 1974; 17:51–71.
11. Nathan MA, Reis DJ. Chronic labile hypertension produced by lesions of the nucleus tractus solitari in the cat. Circ Res 1977; 40:72–81.
12. Magnus O, Koster M, van der Drift JHA. Cerebral mechanism and neurogenic hypertension in man, with special reference to baroreceptor control. *In* DeJong W, Provost AP, Shapiro AP, eds. Hypertension and brain mechanism, progress in brain research, vol 47. Amsterdam: Elsevier, 1977; 199–218.
13. Cushing H. Concerning a definitive regulatory mechanism of the vasomotor center which controls blood pressure during cerebral compression. Bull Johns Hopk Hosp 1901; 12:290–292.
14. Dickinson CJ. Neurogenic Hypertension. Oxford: Blackwell, 1965; 7–12.
15. Hoff JT, Reis DJ. Localization of regions mediating the Cushing response in CNS of cat. Arch Neurol 1970; 23:228–240.
16. Ferrario CM, Page IH. Current view concerning cardiac output in the genesis of experimental hypertension. Circ Res 1978; 43: 821–831.
17. Peiss CN. Cardiovascular responses to electrical stimulation of the brain stem. J Physiol 1958; 141:500–509.
18. Manning JM, Peiss CN. Cardiovascular response to electrical stimulation in the diencephalon. Am J Physiol 1960; 198:366–370.
19. Rosen A. Augmentation of cardiac contractile force and heart rate by medulla oblongata stimulation in the cat. Acta Physiol Scand 1961; 53:255–269.
20. Coote JM, MacLeod VH. Evidence for the involvement in the baroreceptor reflex of a descending inhibitory pathway. J Physiol 1974; 241:477–496.
21. Loewy AD, McKellar S. The neuroanatomical basis of central cardiovascular control. Federation Proc 1980; 39:2495–2503.
22. Loewy AD. Descending pathways to sympathetic and parasympathetic preganglionic neurons. J Autonom Nerv Sys 1981; 3: 265–275.
23. Trout CO, Loeschcke HH, Berndt J. Topography of the circulatory responses to electrical stimulation in the medulla oblongata. Pflugers Arch 1973; 339:185–201.
24. Stuesse SL. Origins of cardiac vagal preganglionic fibers: a retrograde transport study. Brain 1982; 236:15–25.
25. Randall WC, Rohse WG. The augmentor action of the sympathetic cardiac nerves. Circ Res 1956; 4:470–475.
26. Fang HW, Wang SC. Cardioaccelerator and cardioaugmentor points in hypothalamus of the dog. Am J Physiol 1962; 203: 147–150.
27. Henry JL, Calaresu FR. Excitatory and inhibitory inputs from medullary nuclei projecting to spinal cardioaccelerator neurons in the cat. Exp Brain Res 1974; 20:485–504.
28. Calaresu FR, Faiers AA, Mogenson GJ. Central neural regulation of heart and blood vessels in mammals. Prog Neurobiol 1975; 5:1–35.
29. Faden AI, Jacobs TP, Woods M, et al. Zona intermedia pressor sites in the cat spinal cord: right-left asymmetry. Exper Neurol 1978; 61:571–581.