Chronic Experimental Hypertension in Dogs after Constriction of Brachiocephalic and Left Subclavian Arteries

By Edward W. Hawthorne, M.D., Ph.D., and A. K. Mandal,* M.D.

Chronic hypertension of moderate to marked severity has been produced in dogs by bilateral carotid sinus area constriction with specially devised plastic clamps.1,2 Three possible mechanisms have been proposed to explain this type of experimental hypertension: (a) an alteration in cerebral hemodynamics, presumably leading to the liberation of an increase in total peripheral resistance;1,2,3 (b) a chronic absence of impulse traffic over the sinus nerves caused by the placement of the plastic clamps over the carotid sinus area;4,5 (c) a combination of the above proposals.

In dogs, adequate constriction of the common carotid arteries above the thyroid arteries leads to immediate development of a severe hypertension1,2,4 which persists for two to three weeks, followed by return of blood pressure to normotensive levels.1 The most likely explanation for this course of events is the rapid development of collateral circulation with adequate retrograde flow into the sinus areas.1,2,4 In the studies to be reported, an effort was made to avoid this problem of collateral circulation by simultaneously constricting the brachiocephalic and left subclavian arteries instead of the common carotids.

Studies are presented which show: (a) that chronic hypertension can be produced in dogs by simultaneous constriction of the brachiocephalic and left subclavian arteries; (b) the pattern and general nature of the hypertension produced; and (c) the changes in cardiac output and total peripheral resistance observed in this type of experimental hypertension.

Methods

Eighteen dogs, varying in age, sex, and weight, were used for these studies. Each dog was followed for a period of one or more months of normotension prior to simultaneous constriction of the brachiocephalic and the left subclavian arteries. Observation of each dog was continued after constriction for the extent of his survival.

Throughout the period of study, femoral intra-arterial pressure pulse tracings were recorded in the unanesthetized, lightly restrained animal, two or more times a week. On occasion, the right axillary intra-arterial pressure pulse and the femoral intra-arterial pressure were recorded. In five animals, bilateral carotid loops were constructed in the neck, and femoral and carotid artery pressure pulses were recorded before, during, and immediately after bilateral common carotid artery occlusion.

During the period of hypertension, satisfactory indicator dilution curves were obtained in five dogs, along with femoral artery pressure. For these studies, the dogs were anesthetized with sodium pentobarbital. Six normal dogs were also studied in this manner.

Technique of Simultaneous Brachiocephalic and Left Subclavian Artery Constriction

Figure 1 shows the brachiocephalic and left subclavian arteries arising from the arch of the aorta, the type of clamp used for the constriction, and its placement below the origins of the common carotid arteries from the brachiocephalic artery.

All surgical procedures were done under sterile conditions with sodium pentobarbital anesthesia (30 mg./kg. of body weight). A left thoracotomy was performed through the second or third interspace. The brachiocephalic and left subclavian arteries were identified and cleaned by separation of their surrounding sheath of tissue. Every effort was made to preserve nervous tissue passing to the arch of the aorta. A large Goldblatt-type clamp, made of aluminum and fitted with a lock

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nut on the adjustable screw, was placed around the left subclavian and brachiocephalic arteries to permit simultaneous constriction of both vessels. Controlled constriction was achieved by continuously observing the full wave and mean femoral arterial pressure pulse during the tightening of the clamp. When the blood pressure as measured in the femoral artery had risen at least 30 mm. Hg, the clamp was locked in position by means of the lock nut. Routine postoperative antibiotics and other therapy were given each dog.

**Measurement of Pressure**

The zero reference point for calibration of pressure transducers was always the level of the left atrium of the dog when restrained and lying on its back. Pressure pulses were recorded through a 20-gauge needle, fitted to a short length of lead tubing either to the PI side of a Sanborn differential pressure transducer (model 267B) or a Statham strain gauge (model P23AA). The gauges were connected to a Sanborn carrier preamplifier, from which calibrated records of the pressure pulse were obtained on the paper recorder of a Sanborn polyviso (model 150).

**Measurement of Cardiac Output and Total Peripheral Resistance**

Indicator-dilution curves were obtained using indocyanine-green as the indicator. The dye was detected with a Gilford (model 103) IR Cavette densitometer, through which the blood was drawn by a Harvard Instrument constant withdrawal pump (model 600-960). Femoral blood pressure before and after dye dilution was measured using a Statham P23AA connected to a Sanborn 350-1100AS carrier preamplifier. The outputs from the cavette densitometer and the carrier preamplifier were recorded on a Sanborn 2 channel recorder (model 320). The recording, calibration and analysis of these curves were consistent with accepted techniques.

The total peripheral resistance was calculated by the formula:

\[ \text{TPR} \text{ dynes sec./cm.}^2 = \frac{\text{MAP} \times 1328}{\text{CI} \text{ cc./sec./M}^2} \]

where MAP represents the mean femoral arterial pressure in millimeters of mercury, 1328 the conversion factor and CI the cardiac index in cc. per second per square meter of body surface area.

**Phenoxybenzamine Test**

Phenoxybenzamine (Dibenzyline) was given intravenously (2 mg./Kg.) to the normotensive and hypertensive dogs. Pressure pulse tracings were taken immediately preceding the injection and at 1/2, 1, 3, 4, and 24 hours after injection.

**Carotid Loops**

At varying times in normal dogs, and in five or six dogs with hypertension for more than three months, both common carotid arteries were explanted in a tube of skin low in the neck. Pressure pulses were recorded in these both from the right axillary artery and a common carotid to compare the mean pressures obtained from the two sites.

**Results**

Ten dogs survived the operation for a period of at least two months. Five dogs died suddenly between two and four weeks after constriction as a result of rupture of the brachiocephalic artery at the site of the clamp. Three dogs died from various postoperative complications within 72 hours after the operation. All dogs surviving more than 72 hours developed an immediate rise of mean blood pressure of 30 to 40 mm. Hg which persisted in all but one dog (dog 6) at this or a reduced level throughout the period of observation.
Pressure data on the 10 dogs surviving surgery by at least two months are given in table 1. The average preoperative mean femoral artery pressure was 127 ± 3.8 (S.D.) mm Hg. During the third month of hypertension in seven of these dogs (excluding dogs 4, 9, 10) the average mean femoral pressure was 168 ± 19 (S.D.) mm Hg. Thus an average rise in pressure of 41 mm Hg was observed three months after constriction of the brachiocephalic and left subclavian arteries among a group of seven dogs.

Figure 2 illustrates the changes in heart rate and diastolic pressure which were observed most commonly following brachiocephalic and left subclavian artery constriction.

Heart rate was initially increased in all dogs after constriction but generally returned to normal limits within a month.

Comparison of Pressures Above and Below the Constriction

Pressure pulses were taken from the right axillary and one common carotid artery in the dogs with carotid loops. The mean arterial pressure and pulse pressure were found to be the same in these two areas. Table 1 records the right axillary and femoral artery mean arterial pressures and pulse pressures taken in dogs at various times after hypertension had developed. At each time of measurement, the pulse pressures were clearly reduced below the normotensive level of each dog. In three of the dogs (dogs 3, 4, and 5), the mean right axillary pressure was either equal to, or above, the normotensive level. Measure-

<table>
<thead>
<tr>
<th>Dog no</th>
<th>Normotension Mean P.P.</th>
<th>Mean P.P. after constriction Axillary Mean P.P.</th>
<th>Femoral Mean P.P.</th>
<th>Difference in mean P.P.</th>
<th>Average rise in pressure (mean)</th>
<th>Duration of hypertension (months)</th>
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<tr>
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<td>140 100</td>
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<td>178 120</td>
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<td>4 120 24</td>
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*Returned to normotension after 4 months.
†Died of rupture of brachiocephalic artery.
TABLE 2
Cardiac Output and Total Peripheral Resistance

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>CI liters/min/m²</th>
<th>SVI cc./beat/m²</th>
<th>TPR X 10⁻⁴ dynes sec./cm⁻⁵</th>
<th>Duration of hypertension (months)</th>
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<td>18.5</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>3.1</td>
<td>18.2</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.7</td>
<td>17.3</td>
<td>4.1</td>
<td></td>
</tr>
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</table>

*Previously hypertensive for 4 months.

Changes in Cardiac Output and Total Peripheral Resistance

Table 2 lists the pertinent findings from indicator dilution studies performed on five hypertensive and six normotensive animals, and on dog 6. The femoral intra-arterial pressure pulses in the hypertensive dogs were not significantly different during the determinations from their usual awake hypertensive levels. Heart rates in both the normotensive and hypertensive animals ranged between 150 and 170 per minute in the two groups and the means were not significantly different. The mean value for the cardiac index in the hypertensive animals was twice that for the normotensive control dogs. The total peripheral resistance of the hypertensive group was about 75 per cent of that for the normotensive animals, and the mean stroke-volume index for the hypertensive group was twice that of the control dogs. It appears, therefore, that the increased cardiac index of the hypertensive dogs was due primarily to an increase in stroke volume and not heart rate or a combination of the two.

Effects of Phenoxybenzamine (Dibenzylamine) on Blood Pressure

A hypotensive effect followed the intravenous administration of phenoxybenzamine in six hypertensive and six normotensive dogs. Figure 3 shows typical changes in diastolic pressure in these animals. The shaded area on the abscissa represents the range of diastolic pressure in all normotensive dogs. The figure illustrates that a temporary normotension was produced by the drug in the hypertensive animals.

Discussion

Our studies show that chronic hypertension develops in dogs following simultaneous brachiocephalic and left subclavian artery constriction. The finding that three of six dogs were chronically hypertensive at a time when the mean arterial pressure in the right axillary artery (cranial to the constriction) was the same as, or greater than, the normotensive level suggests that a chronic reduction in mean endosinal pressure did not exist in all of these animals. Mean pressure in the right axillary artery and in the common...
carotid artery just below the sinuses was found to be the same in several dogs with constriction of the brachiocephalic and subclavian arteries—not unexpected since both vessels are direct branches of the brachiocephalic artery. This observation, however, makes it difficult to argue that the hypertension was sustained by a chronic decrease in mean endosinal pressure, which in turn decreased the impulse traffic over the sinus nerves.

All hypertensive animals had a definite decrease in pulse pressure above the constriction. Ead, Green, and Neil showed that a decrease in endosinal pulse pressure is sufficient to decrease the impulse traffic over the sinus nerves. Ample evidence also exists to suggest that the latter can result in increased sympathetic activity leading to an increase in myocardial catecholamine concentration. This could produce an increase in the force of contraction and rate of the heart.

In the presence of a chronic decrease in pulse pressure and no decrease in mean endosinal pressure, one might assume that vagal tone need not be greatly decreased in these hypertensive animals and may well be the same as before constriction. Evidence exists to support the view that the increased vasoconstrictor activity which should follow a decrease in the impulse traffic over the sinus nerves may be counteracted in chronic studies by other baroreceptors, especially those connected to the aortic nerves. This may account, in part, for the modest level of hypertension that follows sinus nerve section in dogs.

The data presented suggests that the primary hemodynamic alteration in dogs with chronic hypertension after brachiocephalic and left subclavian artery constriction is an increase in cardiac output due to an augmented stroke volume with minor chronic changes in heart rate.

Crandall, McCorvey, Sukowski, and Walkerlin have previously shown that the effect of phenoxybenzamine on blood pressure seems to differentiate "buffer nerve" (or neurogenic) and "carotid sinus area" hypertension in dogs. They observed only temporary normotension in their carotid sinus area-constricted dogs as against temporary hypotension in dogs with neurogenic hypertension. Similarly, our studies showed only temporary normotension in all but one dog following phenoxybenzamine administration. The current view is that this potent sympathetic blocking agent has its effect at receptor sites in vascular smooth muscle but does not act on the receptor sites for norepinephrine in heart muscle. It is to be expected that animals whose hypertension is primarily due to an increase in stroke volume, as a result of an increase in cardiac catecholamine concentration, would not show as great a hypertensive response to this drug as completely debuffered animals. It seems that chronic hypertension following controlled constriction of the brachiocephalic and left subclavian arteries in dogs may be explained entirely on a neurogenic basis.

The following hypothesis is proposed: (a) a chronic decrease in endosinal pulse pressure results mainly in an increase in the catechol-
amine background of the heart; (b) in the chronic animal a decrease in pulse pressure with slight or no decrease in mean endosinal pressure permits the maintenance of a relatively normal vagal tone and evokes only a modest increase in pulse traffic over sympathetic vasoconstrictor fibers. This suggests that the carotid sinus area mechanoreceptors are designed so that they will respond to chronic decreases in pulse pressure by causing an increase in ventricular force of contraction and stroke volume. Their response to a reduction in mean and pulse pressure would lead to an increase in the force of contraction of the heart and an increase in peripheral resistance.

Summary
In summary, the studies suggest that:

(1) Simultaneous and controlled constriction of the brachiocephalic and left subclavian arteries resulted in chronic femoral hypertension in seven dogs.

(2) This hypertension is associated hemodynamically with an increase in cardiac index due mainly to an increased stroke volume.

(3) The suggestion is made that the initiating mechanism for this type of experimental hypertension is a chronic decrease in endosinal pulse pressure.

References
**Discussion**

**Dr. Kezdi:** Since our papers are quite similar in their approach, I would like to confirm Dr. Hawthorne's finding of hypertension following constriction of the common carotid arteries. In my experiments, constriction was made in some animals below the superior thyroid artery; in some, above. The major branches (external, internal carotid, occipital, etc.) were tied. Six dogs were observed two to six months before the kidney was wrapped. There was a significant increase in pressure from 127 mm. Hg mean to 142 mm. Hg. Later superimposed wrapping of one kidney further increased the pressure. The more modest increase in our experiments of carotid constriction alone as compared to that found by Dr. Hawthorne is probably due to the different location of the constriction. Dr. Hawthorne included more baroreceptor areas by placement of his clamp to a more proximal portion of the carotid artery.

**Dr. Hoppe:** What happened to the rest of the cerebral circulation of the dog? The dog has a fantastic ability to develop new blood vessels and restore circulation. What happened to the subclavian, for example, in these dogs?

**Dr. Hawthorne:** Since the left subclavian and the brachiocephalic arteries were constricted simultaneously, the only access for collaterals to the head would be through anterior spinal arteries through extremely small vessels, perhaps by way of the intercostals and the internal thoracic. I don't think this happens because the one dog in which normotension returned showed a definite loss of hair and weight and other signs which would suggest poor hypophyseal function. This was not mentioned in my presentation.

**Dr. Wakerlin:** I wonder, Dr. Hawthorne, if you had a chance to study the stroke volumes of these hypertensive dogs at intervals over a period of time. Is there a possibility that the stroke volume might return toward normal with the passage of time, with a compensatory increase in peripheral resistance?

**Dr. Hawthorne:** Indicator-dilution studies were made in some animals seven to nine months after the development of hypertension and in one dog, one month after hypertension. None of these data show an elevated peripheral resistance. The early hypertensives show what seems to be a clear reduction of peripheral resistance, presumably because of increased baroreceptor activity arising from sites other than the sinus.

**Dr. Tobian:** Pulse pressure is probably much more important than mean pressure in this effect on stroke volume, but in your dogs with a high stroke volume and a normal sinus pressure, if the stroke volume dropped at all, sinus pressure would drop. In other words, the only reason the mean pressure in the sinus is normal is that the stroke volume is high. If one measures a normal sinus pressure instead of an elevated stroke volume, it would become lower if the stroke volume were to be lowered. Might not mean pressure play some part in this, considering that at a normal cardiac output the mean pressure would probably be lowered?

**Dr. Hawthorne:** I don't agree. We have shown that one can constrict the aorta above the left renal artery to a degree which decreases the pulse pressure without altering the mean pressure below the constriction. This results in the development of renal hypertension. Therefore, it is not surprising to us that a decreased pulse pressure may be present with a normal or elevated mean pressure. The other interesting thing is that in the intact awake animal and in the anesthetized animal, immediately upon constriction of the common carotid arteries, we have found that the cardiac output is not increased. This is something which occurs over a period of time. It seems reasonable to assume that the stroke volume increase comes some time after the change in pressure.

**Dr. Laragh:** What do you think the relationship of this type of hypertension is to that following coarctation of the aorta? Must we incriminate the sinuses as a mechanism when perhaps even renal or other factors are
involved whenever the flow from the major vessels is curtailed.

Dr. Hawthorne: We constricted the brachiocephalic arteries. The increase in pressure thus occasioned would tend to increase flow and pressure to the kidneys, so that I am not convinced a renal mechanism could be involved. I would rather say that here the sinus is in a place where it can check a decrease in pulse pressure before it can result in a subsequent renal hypertension. This is my view as to how the sinus mechanism fits into the mechanism of renal hypertension.

Dr. Laragh: You have clarified my anatomical misunderstanding. Have you actually measured the renal blood flow in these animals?

Dr. Hawthorne: No.

Dr. Neil: Dr. Lofving of Goteborg has a thesis, Acta Physiologica Suppl. 184, pub. Sept. 1961, which shows that this very technique which you are describing has very little effect in acute experiments on renal blood flow but quite a profound effect on muscle blood flow. Did you do any blood volume studies, blood sodium, etc.?

Dr. Hawthorne: No.

Dr. Hamilton: It is difficult for me to see how clamping of an artery supplying the carotid sinus can reduce pulse pressure without reducing flow and mean pressure—unless and until the procedure produces a systemic arterial hypertension that overcomes the added resistance and returns the endosinal pressure to a physiological figure. When this occurs, the baroreceptor is doing its job with no further needed changes in activity. The key parameter is the one most nearly normal when compensation reaches the steady state. Neurogenic hypertension clearly outlined in this presentation involves an increase in flow without the accompanying decrease in resistance usually seen in normal circulatory regulation. Instead of saying that the peripheral resistance is not involved, might we not better say that it is increased relatively if not absolutely?

Dr. Peterson: Isn’t there something different in the response to constriction of the brachiocephalic and cutting Hering’s nerve bilaterally? Has it not been found that elevation of blood pressure is not sustained for this long period, and thus there must be something different about the effect you describe than that it is simply due to the carotid sinus effect?

Dr. Hawthorne: One thing that struck me in Dr. Neil’s paper was that the subclavian also has mechanoreceptors. The major difference is that we have produced a physiological alteration in stretch on the baroreceptor, whereas in the other case a nerve has been cut. The major difference, I suppose, is the lack of significant collateral circulation development and that sites other than the carotid sinus area are inactivated by constricting the brachiocephalic and subclavian arteries.

Dr. Lee: Three comments this morning have intrigued me. One was a brief reference by Dr. Neil to the vasa vasorum and also others with regard to bringing the peripheral circulation into the picture and the effect of physiological levels of humors in the blood stream. We may be dealing with at least a dual mechanism in the carotid sinus. First is the acute phenomenon that reflects the influence of the blood within the lumen of the carotid sinus. However, every organ in the body also has its own blood supply. Perhaps some of the surgical procedures may alter to varying degrees the carotid sinus’ own blood “nourishment.” Blood-borne humoral materials might alter the effect of intraluminal changes on the wall by influencing the nature and response of the wall itself.

Dr. Hawthorne: We are concerned at the moment with the impulse traffic over the sinus nerves that is caused by these changes. Changes in the vessel wall or its nourishment again are things having to do with why the impulse traffic changes. The hypertensive response to constriction would begin with the decrease in pulse pressure in the sinus area under the hypothesis we suggested.
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