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Research Article

THE CIRCULATION IN EXPERIMENTAL NEUROGENIC HYPERTENSION [1]

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Experimental neurogenic hypertension has been successfully produced in the dog by resection or bilateral denervation of the carotid sinus with section of the aortic depressor nerves (1). There is at present general agreement that this type of hypertension persists for months and even years, though the levels of arterial pressure fluctuate widely in any given animal. In this respect, it differs from experimental renal hypertension which is characterized by a more constant elevation of the blood pressure (2); it resembles, however, the pre-hypertensive phase of essential hypertension during which the blood pressure is labile and hypertensive levels alternate with normal ones (3). Few reports have appeared in the literature on the circulation of unanesthetized animals with chronic neurogenic hypertension. The present paper is therefore concerned with the study of systemic hemodynamic alterations, including cardiac output, blood pressure, and the total peripheral resistance, and with an investigation of the renal and peripheral circulatory changes occurring in experimental neurogenic hypertension.

It has been found that, following denervation of the carotid sinus in the dog, the heart rate increased from an average of 100 beats to 240 beats per minute (4). Few observations have been published on the cardiac output of chronic hypertensive dogs. Using the Fick principle, one worker obtained an increase in the minute volume (5). Applying the same methods, others observed a rapid rise in the minute volume which was revealed by a decrease in the CO_2 difference between arterial and mixed venous blood (6). Using the cardiometer, however, the same investigators noticed a smaller heart volume following the clamping of the carotid arteries (6).

Data on the splanchnic and peripheral circulation of animals with chronic neurogenic hypertension are not available. In anesthetized dogs with acutely denervated carotid sinuses, an increase was found in the arterial inflow to the hind limb (6), accompanied by vasoconstriction in the kidney, the spleen, and the intestine (7). No pressure changes occurred in the vena cava during the acute hypertensive phase (7).

METHODS

All experiments were performed over a period of from 5 to 11 months on a total of 6 unanesthetized female dogs. The animals were kept on a daily diet of 500 grams of Purina dog chow, fortified by 5000 units of Vitamin A, 200 units of Vitamin D, and 10 grams of Brewer's yeast. The dogs were made hypertensive according to the method previously described (8). The cardiac output was determined by the Fick principle which involves the measurement of the oxygen content of arterial and mixed venous blood as well as of the total oxygen consumption. The latter was obtained by connecting the muzzle of the animal to a waterless Sanborn metabolism machine with the help of a rubber mask (9). Four minutes following the onset of oxygen inhalation, the mixed venous blood was collected from the right ventricle by means of a catheter threaded through a 9-gauge needle which was inserted into the external jugular vein. The use of the needle made extensive exposure of the vein unnecessary. It also permitted repeated determinations within a short period of time. In every instance, an effort was made to insert the tip of the catheter into the ventricle rather than the auricle, as auricular blood of the dog is not fully mixed (10). The correct position of the catheter was determined by fluoroscopic examination. Clot formation in the catheter was prevented by a saline drip set to flow at a rate of 2.5 ml. per minute. The withdrawal of mixed venous blood was preceded by the removal of 7 ml. of a blood-saline mixture in order to avoid dilution of the sample; 10 ml. of mixed venous blood were then collected under oil. One minute later, an equal amount of arterial blood was removed under oil from the femoral artery. The blood oxygen was determined by the manometric method (11). For the measurement of right auricular pressure, the catheter was slightly withdrawn until its tip was within the auricular cavity. The zero point for the venous pressure was found by fluoroscopic determination of the position of the catheter tip. The coefficient of oxygen utilization was calculated by the formula:

$$\frac{\text{Difference in arterial-venous } O_2 \text{ content}}{\text{Arterial } O_2 \text{ content}} \times 100.$$

The effective renal plasma flow was determined by

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means of the clearance of p-aminohippuric acid (12). The renal blood flow was derived by use of the formula:

$$\frac{\text{CpAH}}{100 - \text{hematocrit percentage}} \times 100.$$

The creatinine clearance was used to measure glomerular filtration (13). The filtrate fraction which expresses the percentage of water filtered from the plasma flowing through the kidneys, was calculated according to the formula:

$$\frac{\text{Filtration rate}}{\text{Effective renal plasma flow}} \times 100.$$

As a rule, 3 urine periods, lasting 10 to 15 minutes each, were found sufficient for the determination of the renal clearances. The renal fraction which expresses the percentage of the cardiac output perfusing the kidneys in a minute's time was obtained with the formula:

$$\frac{\text{Renal blood flow in liters per min.}}{\text{Cardiac output in liters per min.}} \times 100.$$

The blood flow through the fore-limb was measured with a metal plethysmograph, insulated with asbestos. In principle, the method of Lewis and Grant was followed (14). Volume changes were recorded on a smoked drum with a water manometer. This consisted of capillary tubing forming a writing point at one end and fused at the lower end to a hollow glass bulb which was made to float inside a piece of glass tubing of only slightly larger diameter (1.0 cm.), rising and falling with any change in the water level. This apparatus had the advantage over other volume recorders because of its ease of manufacture and its greater durability. The plethysmograph was heated by resistance coils surrounding the metal frame. All determinations were made at a constant temperature of 38° C. For the occlusion of the venous flow, a small blood pressure cuff, 3 inches wide, was inflated to a pressure of from 40 to 50 mm. Hg. At the end of each determination, the inflow curves were standardized by repeated injections of 2 ml. of water into one of the rubber tubes connected to the plethysmograph. Arterial blood pressures were recorded with the Hamilton manometer (15), which permitted accurate measurements of the systolic and diastolic blood pressures and of the heart rate. Mean pressures were calculated by planimetric integration of the area under the pressure curve.

Simultaneous determinations of the cardiac output and the mean blood pressure permitted calculations of the total peripheral resistance according to the formula:

$$\frac{\text{Mean pressure} \times 1332}{\text{Cardiac output per second}} \quad (16).$$

This formula expresses the loss of pressure head in the circulatory system in absolute units, one unit representing 1 dyne cm.$^{-5}$ per second. As the total resistance measured the resistance to flow through the entire vascular tree, its variations from the normal control did not permit localization of occurring changes. Consequently, the resistance to blood flow in the renal vessels, and in those of the limb, were calculated separately by means of the formula:

$$\frac{\text{Mean pressure} \times 1332}{\text{Renal blood flow or limb blood flow per second}}$$

Prior to the sectioning of the depressor fibers, a series of 2 to 5 control experiments was performed on each animal until constant values were obtained. During this control period, all determinations were carried out without interruption in 3 to 4 hours. This procedure permitted close correlation of the cardiac output and mean blood pressure with the circulation in the kidney and the fore-limb.

After the buffer nerves were sectioned, however, the blood pressure of some of the animals remained constant at significantly high levels for only 20 to 40 minutes before falling as much as 40 mm. Hg. Consequently, long tests could not be carried out during the hypertensive phase. Despite this difficulty, adequate results were obtained by determining the blood pressure along with either the cardiac output, the renal clearances, or the blood flow through the limb, inasmuch as each of these values could be determined during the period of constant elevation of the blood pressure. During the period of observation, the dogs were lying quietly on the table. As all the animals were well trained, local anesthesia was used only prior to the introduction of the needle into the jugular vein.

EXPERIMENTAL

Experiments on the cardiac output and the total peripheral resistance

Changes in the cardiac output were followed in a series of 6 animals, and are summarized in Tables I and II. In every instance, the minute volume rose 30 to 50 per cent following section of the depressor fibers. This change was associated with the high oxygen content of the mixed venous blood, resulting in a decrease of the arteriovenous oxygen difference. Similar observations have been made in animals with chronic neurogenic hypertension (5), and in acute experiments (6). In 4 animals, the oxygen consumption increased an average of 30 ml. of oxygen per minute. As previously observed by a number of investigators, the heart rate rose an average of 85 beats per minute in the hypertensive dogs (4). As a result of this tachycardia, the cardiac output increased, while the systolic discharge did not change from its control values. The utilization of oxygen declined in every instance following the establishment of neurogenic hypertension (Figure 1). The decrease in both arteriovenous oxygen difference and oxygen utilization was the result of the increased circulatory rate. As seen in Tables I and II, the total peripheral resistance rose sig-

TABLE I

Circulatory changes following sectioning of the moderator nerves

Dog No. 2 S.A. = 0.367 sq. m.	Date of experiment	Mean blood pressure	O_2 intake	Minute volume	Cardiac index	Pulse rate	Systolic discharge	Arterial O_2 content	O_2 A-V difference	Coefficient of O_2 utilization	Intra-auricular pressure	Blood flow in limb	Renal function				Resistances		
													Filtration rate	Blood flow	Filtrate fraction	Renal fraction	Limb	Renal	Peripheral
		mm. Hg	*ml. per min.*		*liters per min. per sq. m.*		*ml. per beat*	*volumes per cent*	*ml. per liter blood*	*per cent*	*cm. H_2O*	*ml. per 100 ml. per min.*	*ml. per min.*				*dynes cm.$^{-5}$ sec.*		
	9-23-43	126	210	2330	3.31	120	19.5	22.2	90	40.0									4320
	9-24-43	126				120							59.1	381	0.342	15.7		26,400	
	10- 1-43	115	214	2440	3.18	120	20.2	22.5	88	38.8	+5.4								3760
	10-14-43	115										4.0	85.8	542	0.348	22.4	2,553,000	16,850	
	12- 6-43	119	175	2500	3.26	136	20.9	18.4	70	33.5	+3.1	5.7					1,660,000		3810
	1- 5-44	146				150													
	1-20-44 1-26-44	Operations																	
	1-27-44	160				152													
	1-28-44	210				188													
	1-29-44	190	212	3710	4.84	180	20.3	26.0	57	21.9		6.8	79.6	550	0.317	14.5	2,230,000	25,500	4100
	2-11-44	192				195							46.9	346	0.300	9.14		44,300	
	2-22-44	154				190						11.6					1,061,000		
	2-23-44	172	185	3780	4.94	180	20.5	26.0	49	18.5	+5.1								3640
	3-10-44	183				165							55.2	327	0.331	8.60		44,700	
	3-15-44	185				170						17.3					856,000		
	3-16-44	186	195	4020	5.25	140	28.7	26.7	49	18.2	+3.1								
	4-11-44	179				195							53.1	383	0.290	10.10		37,400	3700
	4-12-44	185				160						11.5					1,310,000		
	4-13-44	185	220	3670	4.78	195	18.9	28.3	60	21.2	+5.1								4030
	7-12-44	160				150						14.2	62.7	300	0.305	7.92	900,000	42,700	
	7-13-44	175	197	5500	7.17	210	26.2	25.6	36	13.9	+6.3								2550

TABLE II

Representing the arithmetic means of data obtained before and after sectioning of the moderator nerves

Dog	Before operation							After operation						
	Mean blood pressure	Minute volume	Pulse rate	O_2 A-V difference	Limb blood flow	Resistance		Mean blood pressure	Minute volume	Pulse rate	O_2 A-V difference	Limb blood flow	Resistance	
						Renal	Peripheral						Renal	Peripheral
	mm. Hg	*ml. per min.*		*ml. per liter blood*	*ml. per 100 ml. per min.*	*dynes cm.$^{-5}$ sec.*		*mm. Hg*	*ml. per min.*		*ml. per liter blood*	*ml. per 100 ml. per min.*	*dynes cm.$^{-5}$ sec.*	
3	129	3513	122	61	3.9	15,000	3133	184	4913	172	41	11.8	27,000	3190
5	105	3133	122	56	6.6	32,300	2710	182	4360	169	46	15.6	48,300	3666
7	127	3340	141	63	5.0	24,800	2663	184	4603	185	55	13.5	45,500	3433
16	134	3578	105	52	4.1	21,900	3078	188	5300	183	37		39,300	3020
17	153	4750	110	44	5.9	26,800	2560	189	7050	191	36	7.5	31,800	2210

nificantly in only 2 animals (No. 7 and No. 5), but remained constant in the rest of the dogs (Nos. 1, 2, 3, 17). It has been mentioned above that the total peripheral resistance measured the resistance to flow throughout the entire organism. Therefore, its values furnished no information concerning the localization of vascular changes which took place following the section of the buffer nerves.

In every instance, the measurement of the cardiac output was followed by a determination of the auricular pressure. As seen in Table I, no change in the intra-auricular pressure occurred subsequent to the development of hypertension. In experiments on anesthetized animals, it was found that the pressure in the inferior vena cava remained at its control level (7). This observation suggested that the static volume in the veins during hypertension was the same as that existing during the control period.

Experiments on the renal circulation and the renal resistance

The rôle of the kidney in experimental neurogenic hypertension has been the subject of a series of investigations. Certain workers (17, 18) have noticed that, in sympathectomized animals with sectioned depressor fibers, arterial blood pressure decreased temporarily following renal denervation. Others (19), however, made the observation that bilateral nephrectomy failed to prevent the development of acute neurogenic hypertension. A series of 36 experiments was therefore performed in which the glomerular filtration rate and the renal blood flow were examined both before and after section of the depressor fibers. Following the operation, both the renal blood flow and the glomerular filtration rate fell in 2 animals, but remained constant in the rest of the dogs. Because the creatinine and p-aminohippuric acid clearances fell proportionately in these 2 instances, the filtrate fraction remained at its control level, indicating that there was constriction of the afferent arterioles (20) (Figure 2). In human subjects, similar changes of the filtration fraction during orthostatic vasoconstriction have been observed (21). Constriction of the afferent arterioles seen in the experiments described above distinguished the renal circulation in neurogenic hypertension from that of essential hypertension, in which the filtrate fraction rises due to efferent arteriolar spasm (3). Arteriolar constriction is further illustrated in Figure 2, which shows a 50 per cent rise in the renal resistance and a significant fall in the renal fraction. Similar results were obtained in the rest of the animals (Tables I and II).

The circulation through the fore-limb

The evidence presented in this paper furnished no proof that renal vasoconstriction was accompanied by arteriolar spasm in other regions of the splanchnic circulation. It has been shown by others, however, that acute neurogenic hypertension was followed by vasoconstriction in the intestine and the spleen (7). Hence the assumption might be ventured that neurogenic hypertension resulted in generalized constriction of the vessels supplied by the splanchnic nerves. It seemed of

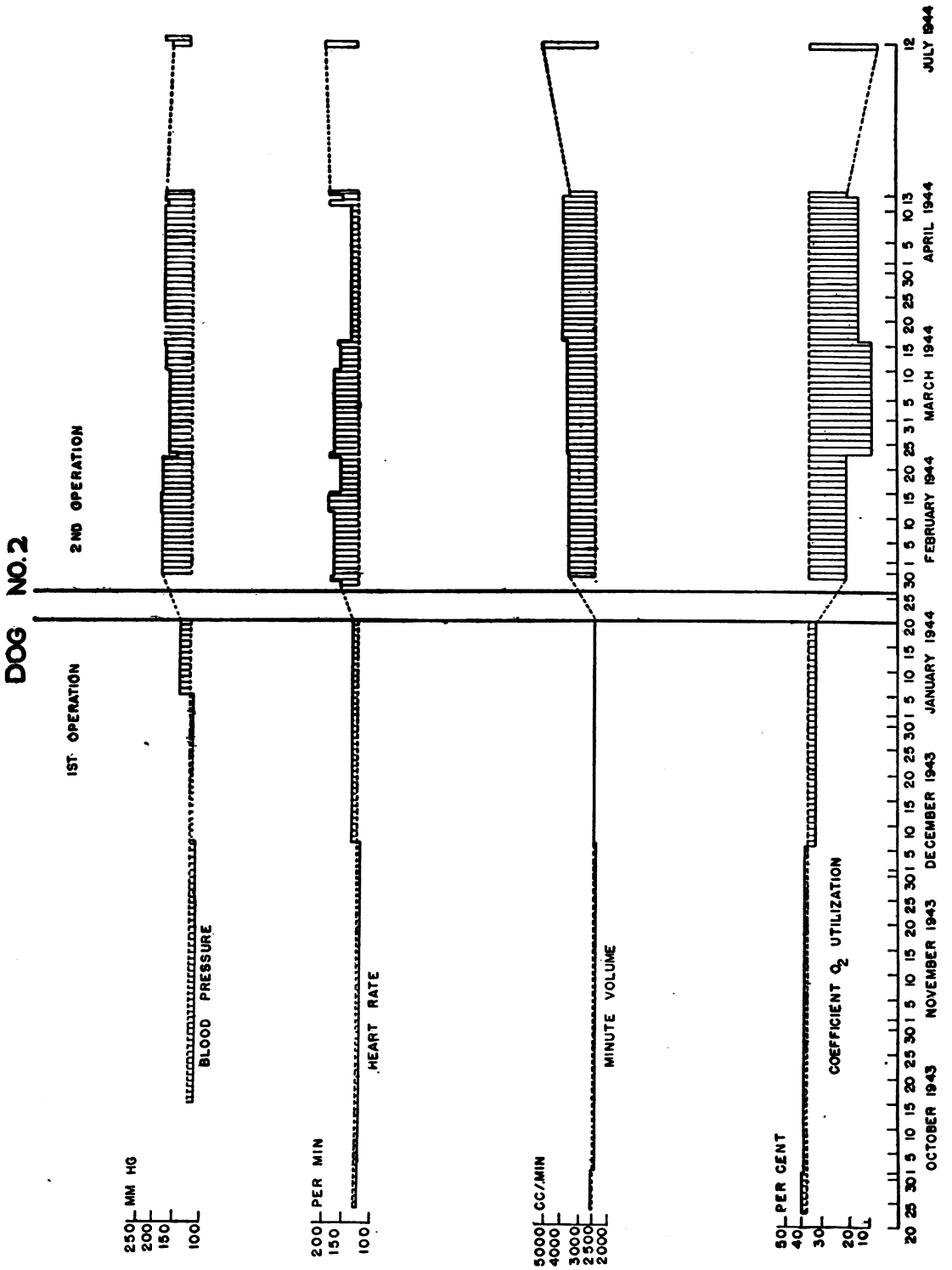

FIG. 1. ILLUSTRATES THE DEVELOPMENT OF NEUROGENIC HYPERTENSION FOLLOWED BY AN INCREASE IN THE HEART RATE AND THE MINUTE VOLUME. SIMULTANEOUSLY THE UTILIZATION OF OXYGEN DECREASES

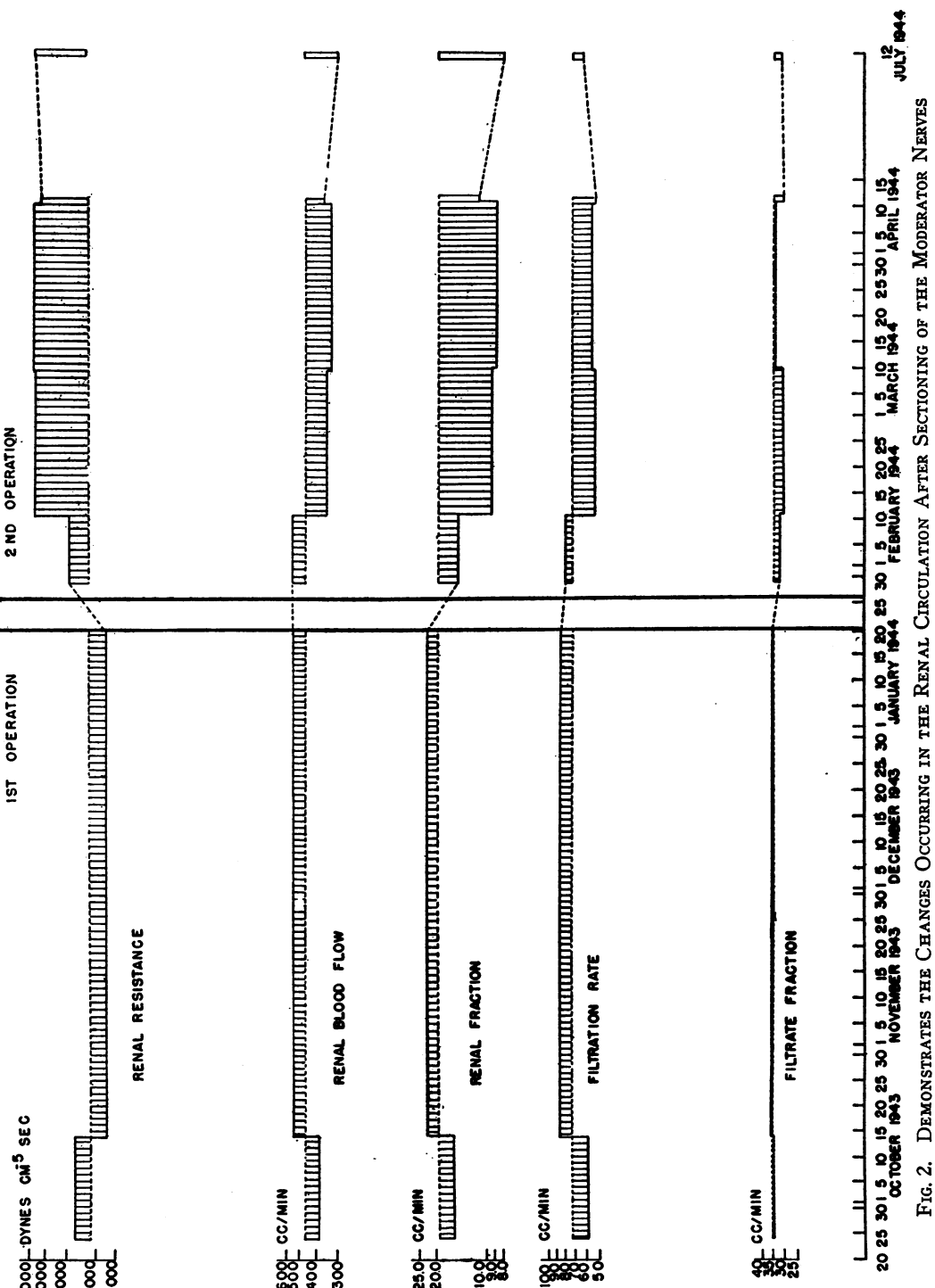

FIG. 2. DEMONSTRATES THE CHANGES OCCURRING IN THE RENAL CIRCULATION AFTER SECTIONING OF THE MODERATOR NERVES

As the renal blood flow and the glomerular filtration rate fall proportionally, the filtration fraction remains constant. The presence of renal vasoconstriction is indicated by a fall in renal fraction and a rise in the renal resistance.

importance, therefore, to study the blood flow through the limb in order to ascertain whether or not the increase in the minute volume reported above was to some measure accounted for by an acceleration of the blood flow through the vessels of the limbs.

Tables I and II show that the onset of hypertension was followed in 4 animals by a considerable rise in the blood flow through the forelimb, averaging 12 ml. per minute per 100 ml. of limb volume. This observation is illustrated in Figure 3, which demonstrates that the slope of the

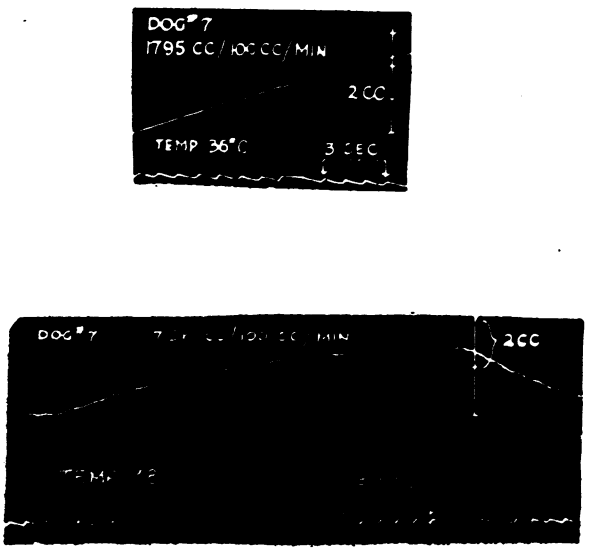

FIG. 3. SHOWS THE CURVES REPRESENTING ARTERIAL FLOW INTO THE FORE-LIMB OF A DOG

The blood flow through the fore-limb increases from 7.55 ml. to 17.95 ml. per 100 ml. of limb volume per minute after sectioning of the moderator nerves.

arterial inflow curve steepened after section of the depressor fibers. These findings are in agreement with other reports which show a significant increase in the blood flow through the femoral artery of anesthetized animals with acute carotid sinus hypertension (6).

The determinations of the vascular resistance in the limb furnished additional proof of an increase in the blood flow through the limb, the values falling an average of one million and a half absolute units (Figure 4). It was evident, therefore, that neurogenic hypertension was accompanied by an acceleration of the circulation through the extremity.

DISCUSSION

The foregoing experiments demonstrate that the production of neurogenic hypertension in unanesthetized dogs is followed by a decrease in the oxygen difference between arterial and right ventricular blood (Tables I and II), as well as, in 4 animals, by a slight rise in the oxygen consumption. Both these changes are the result of an increase in the minute volume which occurs in every instance. Similar results have been obtained by others (5, 6) in anesthetized dogs. Since the output per beat remains constant, even declining in some instances, the increase in cardiac output is dependent upon the increased heart rate. The fall in systolic discharge observed in several experiments may explain the finding of the last mentioned author that the cardiac volume decreases in some of his acutely hypertensive animals. The tachycardia which follows section of the depressor fibers permits the heart to cope with the increase in venous return and thus prevents a rise in the right auricular pressure. Increase in the circulatory rate precludes the extraction of large amounts of oxygen by the tissues and thus explains the decrease both in oxygen utilization and in arteriovenous oxygen difference. The values calculated for the total peripheral resistance vary from animal to animal, being elevated in 2 cases and showing no change in the remainder (Figure 4). This observation is of great significance, as it demonstrates that the hypertension produced by sectioning of the buffer nerves is almost entirely caused by a rise in the cardiac output.

Studies on the renal circulation of animals with neurogenic hypertension reveal a considerable degree of vasoconstriction. This is demonstrated by the observation that the renal blood flow remains constant or falls slightly, following the establishment of hypertension (Figure 2). Although renal ischemia is entirely absent or only slight, renal vasoconstriction is nevertheless present, as illustrated by a rise in renal resistance and a fall in renal fraction (Figure 2). According to the concept of Smith (20), the constriction is in the afferent arterioles, for the filtrate fraction remains unchanged. Consequently, the renal circulation in animals with neurogenic hypertension differs from that observed in essential hyperten-

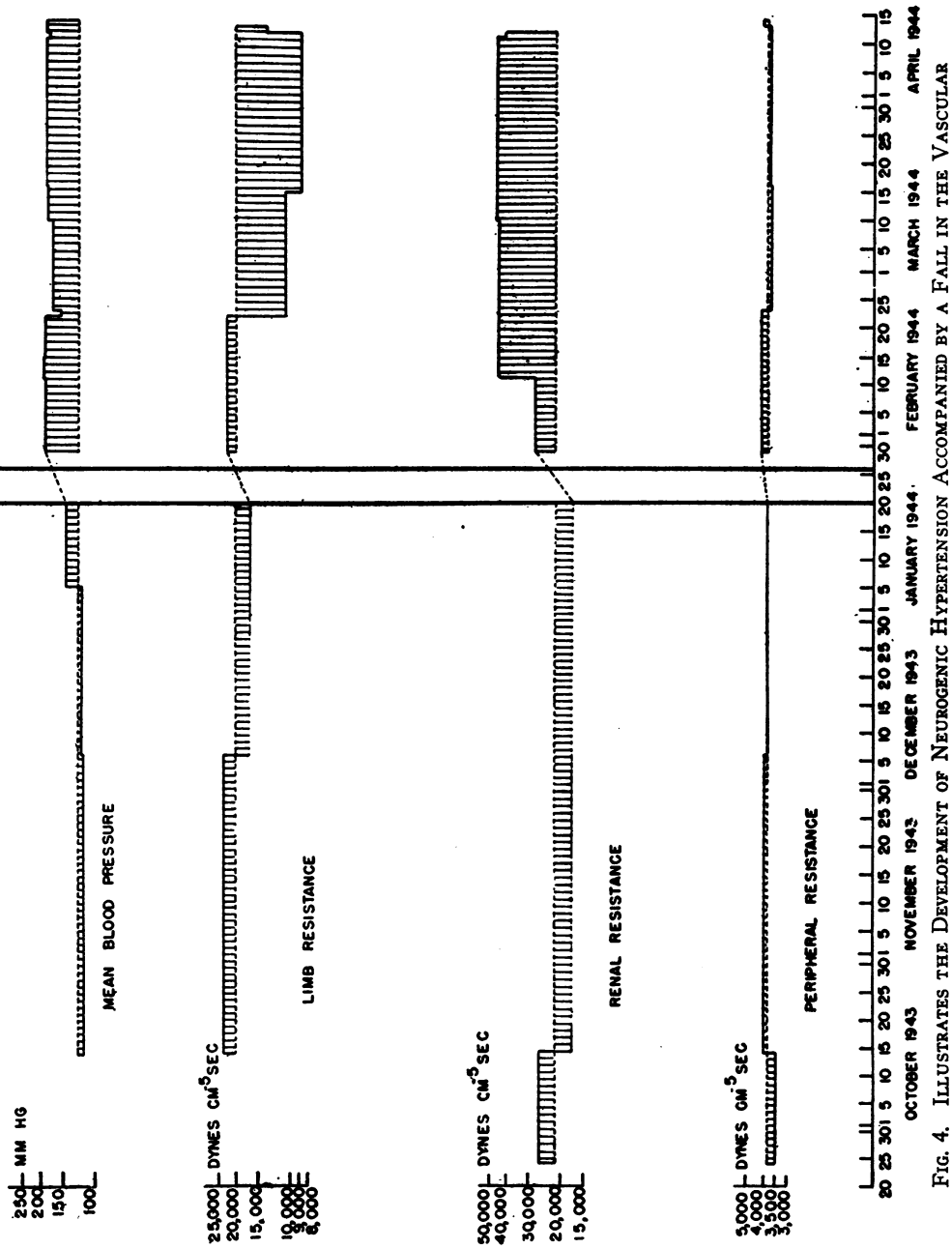

FIG. 4. ILLUSTRATES THE DEVELOPMENT OF NEUROGENIC HYPERTENSION ACCOMPANIED BY A FALL IN THE VASCULAR RESISTANCE THROUGH THE FORE-LIMB AND A RISE IN THE RENAL RESISTANCE

The total peripheral resistance does not change in this particular animal.

sion in which a rise of the filtrate fraction indicates participation of the efferent arterioles (4). It is probable that the changes in the renal circulation described above are mediated by the sympathetic nervous system. This conclusion is supported by the observation of Smith that afferent constriction is brought into play by orthostatic changes in man which are known to be the results of sympathetic discharges (21).

The question whether vasoconstriction occurs in parts of the splanchnic circulation other than the kidney cannot be answered with certainty at the moment. If changes in the renal circulation follow those in other parts of the abdominal cavity, the assumption might be ventured that chronic neurogenic hypertension is accompanied by generalized splanchnic vasoconstriction. This conclusion is borne out by certain investigations which showed vasoconstriction in the intestine and spleen during the acute hypertensive phase (7).

The response of the vessels of the extremity to sectioning of the depressor fibers contrasts sharply with that of the renal arterioles: there is a rise in the blood flow through the fore-limb and a fall in the resistance in this extremity (Figure 4, Tables I and II). The above mentioned workers also describe an increased rate of flow through the femoral artery of anesthetized animals with acute neurogenic hypertension (6); they are of the opinion that this hyperemia is caused by the opening of arteriovenous shunts. On the basis of the results reported in this paper, it is impossible to conclude whether or not the peripheral hyperemia exists because of the opening of arteriovenous anastomoses, or by active arteriolar vasodilation.

The acceleration of the circulation through the limb furnishes additional evidence of increased sympathetic activity in neurogenic hypertension. Sympathetic vasodilation in the leg of the dog has been demonstrated successfully (22, 23). In man, other workers found that the subcutaneous injection of epinephrine was followed by marked vasoconstriction in the hand and foot, and by a definite increase in the blood flow through the forearm and calf (24). These investigators conclude that epinephrine causes vasoconstriction in the skin and active vasodilation in the muscle. It has been noticed in man that the intravenous injection of adrenalin produced a rise in muscle temperature and a fall in skin temperature (25). The difference in the reaction between the vessels of the skin and those of the muscles could explain the fact that in one animal (No. 17) the blood flow through the limb rose only slightly (Table II). In this dog, the large size of the leg permitted the inclusion of only relatively muscle-free paw in the plethysmograph.

The vascular dynamics of neurogenic hypertension differ in many respects from those observed in experimental renal hypertension. In Goldblatt hypertension, and in essential hypertension, the cardiac output is normal (26, 27), and the total peripheral resistance is increased (28). Other studies (29, 30) demonstrate that in essential hypertension the peripheral blood flow is not elevated despite the rise in systemic blood pressure. The renal circulation in essential hypertension is characterized by afferent arteriolar constriction which extends also to the efferent arterioles (4), in contrast to the afferent arteriolar constriction demonstrated in the experiments reported in this paper. In experimental renal hypertension and in hypertensive human subjects, the increase in blood pressure is the result of a generalized decrease in the arteriolar cross-sectional area. In neurogenic hypertension, however, it is due to an increase in the cardiac output which exists in conjunction with a shift in blood flow to the extremities.

SUMMARY

1. The hemodynamic alterations during chronic neurogenic hypertension were studied in 6 unanesthetized dogs.

2. Following the establishment of hypertension, the cardiac output rose, while the difference in the oxygen content between arterial and mixed venous blood, and the co-efficient of oxygen utilization, decreased. Since the heart rate increased, the systolic discharge and the right auricular pressure remained at their pre-hypertensive levels. The total resistance showed no change in 4 dogs, while it rose in the remainder of the animals.

3. The blood flow through the kidney and the glomerular filtration rate fell in 2 animals and remained constant in the rest. The decline in the renal fraction and the rise in the renal vascular resistance are evidence of renal arteriolar con-

striction. This takes place presumably in the afferent arterioles as the filtrate fraction remained constant.

4. The development of neurogenic hypertension was followed by a marked rise in the blood flow through the fore-limb and a fall of the vascular resistance through this extremity.

5. The changes described in this paper are compatible with increased sympathetic tone.

6. Differences in the vascular dynamics between neurogenic hypertension, experimental renal hypertension, and essential hypertension, are discussed.

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