Neurogenic Hypertension in the Rat

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■ Chronic neurogenic hypertension has been produced frequently by radical denervation of the sino-aortic pressoreceptor areas in dogs and rabbits. However, there is still some doubt concerning the exact mechanism which produces this elevation of blood pressure. Is an increase in peripheral resistance or an increase in cardiac output responsible, or are both involved?[1] In the dog the selective elimination of the aortic depressor fibers is impossible without destroying a significant number of efferent vagal fibers. This question received special study recently.[2] In the rabbit no such anatomical difficulty exists, but the great lability of the blood pressure and the technical problems involved in repeated pressure measurements have tended to prevent general use of rabbits in studies of neurogenic hypertension.[1]

Although the rat has been used in almost every type of study of experimental hypertension, chronic hypertension produced by sino-aortic denervation has not been described in this species. The reason may be that in the rat the aortic depressor fibers in the neck follow a different course than in the dog or the rabbit, as has been observed by Andrew,[3] McCubbin et al.,[4] and in this laboratory.[5] However, when these anatomical peculiarities were identified and the sino-aortic afferent fibers were cut, chronic neurogenic hypertension was obtained in the rat. The present paper describes observations on such hypertension over periods up to 12 months.

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Methods

Wistar rats of both sexes and weighing from 200 to 380 grams were used throughout the study. All surgical procedures were performed under low power magnification on ether-anesthetized rats which had received 0.5 mg atropine intraperitoneally prior to operation. A number of techniques were tried in the attempt to obtain a radical denervation of the sino-aortic depressor areas. Finally, one method was chosen on account of its effectiveness and simplicity. This will be described in some detail and referred to as the standard technique of denervation.

DENERVATIONS

In preparation for this standard denervation, animals were fixed in a supine position and an extensive (3 cm) midline incision was made in the neck, to expose the muscles and the neurovascular sheaths enclosing the common carotid arteries, the vagi, and the sympathetic trunks.[5] In a few rats a slender aortic nerve was found but usually the fibers from the aortic baroreceptors were closely associated with the sympathetic trunks. The vagus nerves seemed to be separate from these ascending afferent fibers. Therefore, the vagi and the carotid arteries were carefully freed from the sympathetic trunks and the neurovascular sheath. A strip (1 cm long) of this sheath and sympathetic trunk was resected on both sides. Usually small blood vessels were severed during this resection but bleeding was easily stopped by gentle compression. The baroreceptor fibers from the aorta, except those traveling with the recurrent laryngeal and superior laryngeal nerves, were thus severed. The fibers of the latter type were also interrupted by resection of the superior laryngeal nerves.

Denervation of the sinus was performed after the area of carotid bifurcation was widely exposed by separating the neck muscles (sternocleidomastoideus and omohyoideus). The carotid sinus and the afferent fibers therefrom were not identified individually but the bifurcation and all carotid branches were stripped of fibers and connective tissues. After the vessels were stripped they were painted with 10% phenol in ethanol. Perfusion experiments have shown that such dissection and treatment assures complete denervation.[6]

Bilateral sino-aortic denervation was normally performed in a one-stage operation lasting 30 to

40 minutes. During a three-day period after operation each rat received approximately 10,000 IU of penicillin daily.

MEASUREMENTS OF BLOOD PRESSURE

A tail plethysmographic method[7] was used to measure arterial pressure repeatedly in unanesthetized rats. They were placed in a rat-holder supplied with a heating unit to provide the necessary preheating. A rat was considered to be hypertensive when, in successive indirect readings, the blood pressure exceeded 135 mm Hg. The presence of hypertension was always confirmed by direct pressure measurement in the unanesthetized rat before sacrifice. This was accomplished by preliminary insertion of a closed 4-cm heparin-filled plastic cannula (PE50) into the femoral artery under ether anesthesia. Four to five hours later, after recovery from the anesthetic, femoral arterial pressure was recorded continuously by connecting this cannula through a 30-cm length of polyethylene tubing (PE90) to a Statham pressure transducer P23-AA and a multichannel recorder.* This method permitted recording not only pressures and heart rates of the quiet unrestrained rats but also indicated the effects of walking and other stimuli.

Arterial pressures were recorded continuously by the direct method and simultaneously measured indirectly by plethysmograph in several rats with different grades of hypertension for the purpose of comparison (table 1). Directly recorded femoral systolic pressures were 57 ± 10 mm Hg greater than the values obtained by tail plethysmography. These results are similar to those obtained by Shuler et al.[8] using a tail pressure cuff of equal size (3 cm). The plethysmographic pressures though 10 to 20 mm Hg lower, approximated the mean pressure values obtained by direct recording from normotensive and hypertensive rats.

TABLE 1

Comparison Between Direct and Indirect Pressure Measurements

Rat no.*	Blood pressure in mm Hg			
	Direct femoral			Tail pleth.
	Systolic	Diastolic	Mean	
1	148	96	118	105
2	169	103	129	105
3	173	103	128	110
4	170	110	134	117
5	170	117	138	130
6	185	123	148	135
7	183	123	147	140
8	192	123	152	140
9	210	139	167	145
10	200	138	163	150
11	216	144	171	150
12	225	135	171	155
13	218	140	172	155
14	215	144	170	160
15	220	146	175	162
16	254	147	186	175
17	243	166	195	180

* Numbers 1 to 4 control rats, numbers 5 to 17 neurogenic hypertensive rats.

Results

EFFECTS OF DIFFERENT TECHNIQUES USED TO DENERVATE THE SINO-AORTIC AREAS

Bilateral Carotid Resection

No rat survived the resection of both carotid bifurcations done in a one-stage operation. Results described elsewhere[6] have already shown that the rats used in this laboratory do not tolerate acute occlusion of both common carotids. In confirmation of this finding five rats whose common carotid arteries were ligated under ether anesthesia with only minor surgical trauma, died within a few hours after operation. They presented evidence of cerebral ischemia, i.e., unconsciousness, convulsions, etc. A few rats survived when the carotid bifurcations were resected in a two-stage operation (10 days apart). One of them (R-1 in fig. 1) developed a hypertension that had not receded after a full year. In this rat the superior laryngeal nerves remained intact as did the aortic depressor fibers which may have reached the brain in those nerves. In this animal only the depressor fibers within the sympathetic trunk had been eliminated. Other rats subjected to this same operation failed to develop chronic hypertension.

Unilateral Resection of the Carotid Bifurcation and Contralateral Carotid Stripping

This procedure was well tolerated even when performed in one-stage operations done simultaneously with aortic denervation. One of the rats (R-2 in fig. 1) presented one of the highest blood pressures ever observed in chronic neurogenic hypertension. Femoral arterial pressure measured (mercury manometer) at the end of the one-year period of observation, with no anesthesia, was 185 mm

* E & M Instrument Company Inc., Houston, Texas.

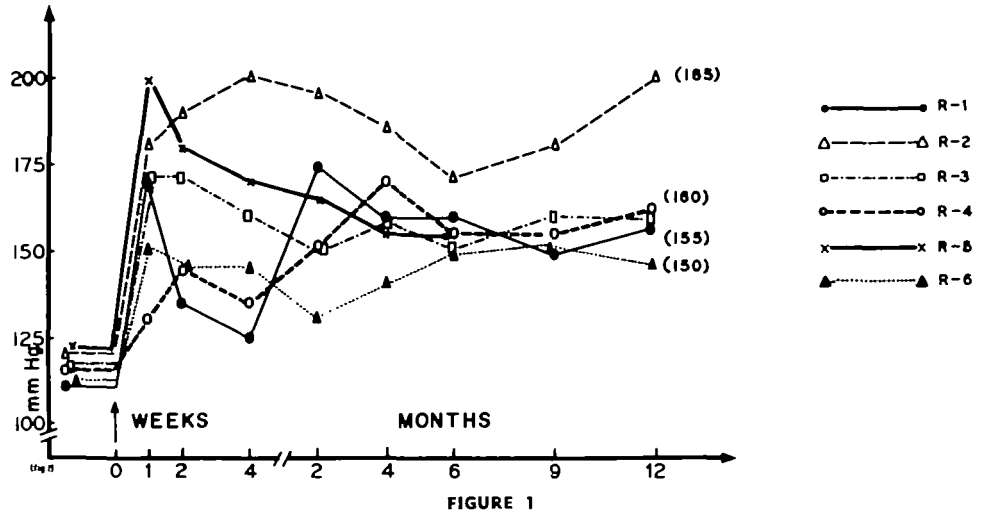

FIGURE 1

Neurogenic hypertension produced by different denervation procedures. R-1: Resection of both carotid bifurcations and cervical sympathetic-depressor trunks (C S-D T). R- 2: Unilateral resection of the carotid bifurcation and contralateral carotid stripping plus resection of the C S-D T. R-3 and R-4: Standard technique of denervation. R-5 and R-6: Standard technique except that the superior laryngeal nerves were left intact. In parentheses are the mean femoral pressures (mm Hg) obtained at the end of the observation period in unrestrained quiet rats.

Hg. In 13 normal rats under similar conditions mean arterial pressure averaged only 112 mm Hg (range 100 to 123 mm Hg). It must be emphasized that this rat was one of those having intact laryngeal nerves.

Importance of Depressor Fibers Present in Superior Laryngeal Nerves

As shown in another study[5] the contingent of aortic depressor fibers which accompany the superior laryngeal nerve is usually large. However, as described above, a few rats became hypertensive even when the superior laryngeal nerve remained intact. To assess the importance of eliminating this nerve, two groups of rats were submitted to the same sino-aortic denervation except that in one group the superior laryngeal nerves were cut and in the other group they were left intact. During the first month after operation eight out of nine rats of the first group were hypertensive, whereas only five of the eight rats with intact superior laryngeal nerves developed mild hypertension. The pressures (mean ± SD) of the former group at the first, second, and fourth weeks were 172 ± 20, 167 ± 17, and 149 ± 18 whereas those of the latter group were respectively 145 ± 17, 133 ± 17, and 134 ± 14. Results from two of the rats (R-5 and R-6) that had intact superior laryngeal nerves and that developed chronic hypertension are shown in figure 1 with results from two other rats (R-3 and R-4) in which these nerves were cut. This figure illustrates the possibility of obtaining neurogenic hypertension in some rats without cutting the superior laryngeal nerves. However, when these nerves were also cut (as in the standard technique) the number of rats which became hypertensive was greater and, in addition, the grades of hypertension obtained were more severe.

Isolated Denervation of Aortic and Sinus Areas

All 10 rats subjected to bilateral denervation of the aortic baroreceptor area (cervical neurovascular sheath as well as superior laryngeal nerve) presented some degree of transitory hypertension. The observed pressures were highest usually before the fifth week, and declined to normotensive levels thereafter. At the end of the sixteenth week, when the sinuses of these rats were denervated, six were already normotensive while the other four presented a mild hypertension (140 to 155 mm Hg). After the second operation

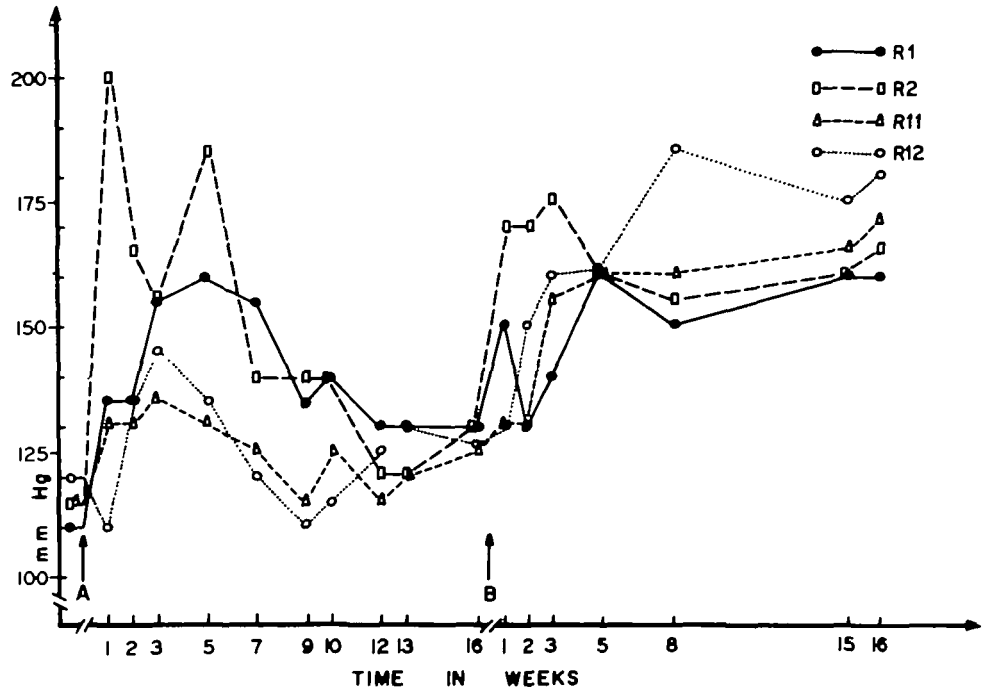

FIGURE 2

Arterial pressures following aortic or carotid denervation only. R1 and R2: Pressures after (A) aortic and (B) carotid denervation. R11 and R12: Pressures after (A) carotid and (B) aortic denervation.

all seven of the rats that survived developed chronic hypertension (fig. 2).

Isolated denervation of the carotid sinus produced no great changes of pressure in the seven rats studied. Denervation of the aortic baroreceptor area performed at the sixteenth week was followed by chronic elevation of pressure in the six rats that survived (fig. 2).

RESULTS OBTAINED BY USING THE STANDARD TECHNIQUE OF DENERVATION

Approximately 70% of the 98 male and 42 female rats subjected to this operation survived and were observed up to 30 days. Death occurred at operation in many instances or within a few days thereafter owing to serious respiratory difficulties.

The First Ten Weeks After Denervation

Weekly measurements in 24 males and 24 females showed that all rats presented blood pressures higher than 135 mm Hg (tail plethysmography) during this time. As shown in table 2 the mean values for the groups remained relatively constant and were almost the same for males and females. In a few rats the blood pressure was measured as early as the first, third, and fifth days after denervation. Some had elevated pressures even on the first day but in others this happened only on the third to fifth days. Usually, however, at the end of the first week the rats already presented the largest increases in blood pressure as is shown in figure 3. Further studies are necessary to describe more completely the initial changes of pressure after sinoaortic denervation in the rat. The latent period for the appearance of neurogenic hypertension which has been consistently observed in the dog and rabbit[9] was not evident in the present study of the rat.

Lasting Effect of Denervation

Of the 15 males with neurogenic hypertension, although observed up to 14 months, only two returned to normotension. The mean values of elevated blood pressure for the entire group were very stable (table 3).

TABLE 2

Changes of Blood Pressure During the First Ten Weeks After Sino-aortic Denervation. Tail Plethysmographic Readings in mm Hg (means ± SD). Standard Technique of Denervation

Number and sex	Time in weeks									
	0	1	2	3	4	5	6	7	8	10
24 Males	118 ± 3	153 ± 13	156 ± 15	155 ± 14	158 ± 16	158 ± 8	161 ± 10	158 ± 7		158 ± 14
24 Females	118 ± 3	166 ± 15	164 ± 14	157 ± 17	155 ± 19	154 ± 13	154 ± 16	157 ± 17	151 ± 15	157 ± 17

TABLE 3

Arterial Blood Pressures (mm Hg, means ± SD) First Twelve Months After Denervation. Averages Include Measurements from Animals that Eventually Returned to Normotensive State

Number and sex	Time in months								
	0	1	2	3	4	5	7	9	12
15 Males	117 ± 3	155 ± 13	149 ± 11	157 ± 17	152 ± 13	151 ± 15	148 ± 13	144 ± 15	152 ± 18
16 Females	118 ± 3	152 ± 18	152 ± 16	154 ± 11	150 ± 15	148 ± 13	153 ± 12	139 ± 10	139 ± 15

TABLE 4

Effect of Bilateral Adrenal Demedullation on the Blood Pressure (mm Hg, average ± SD) of Twelve Neurogenic Hypertensive Rats Six Months After Development of Hypertension and of Bilateral Adrenalectomy on Pressure of Six Rats Denervated Thirty Days Before

No.	Days before					Days after				
	5	4	3	2	1	1	2	3	4	5
12	157 ± 12	155 ± 17	150 ± 9	162 ± 10	158 ± 7	164 ± 12	160 ± 15	167 ± 19	162 ± 14	169 ± 12
6	—	—	159 ± 14	158 ± 10	148 ± 5	151 ± 17	140 ± 13	151 ± 8	157 ± 12	—

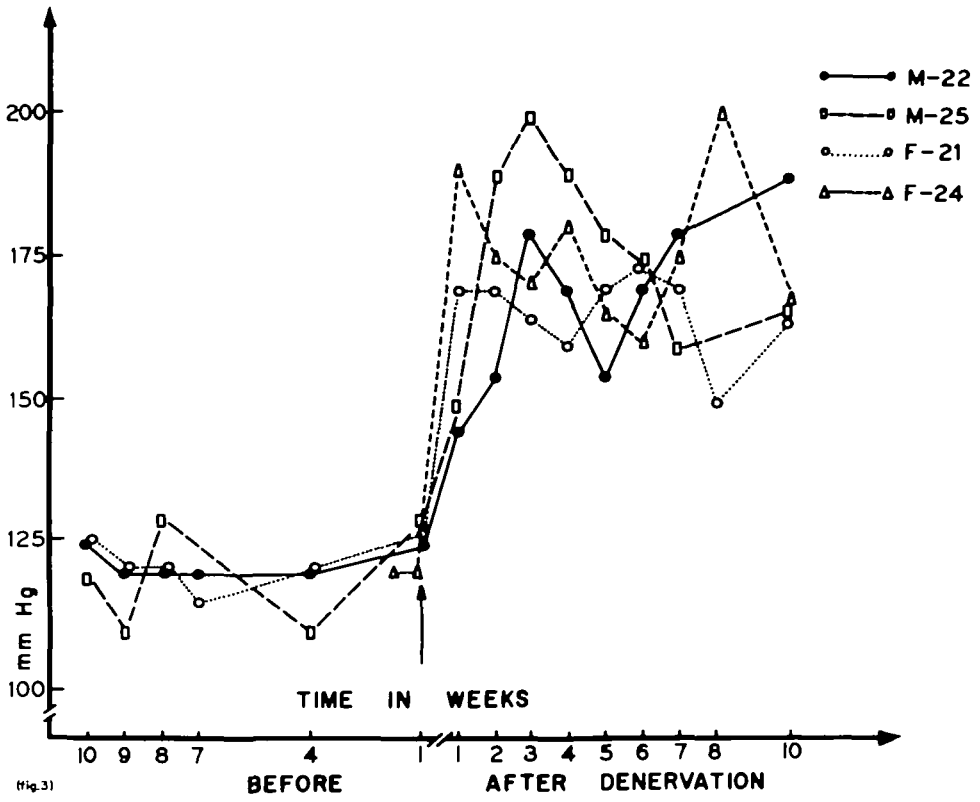

FIGURE 3

Elevation of blood pressure during the first ten weeks after denervation by standard technique. M-22 and M-25 male rats, F-21 and F-24 females.

More hypertensive females (6 out of 16) regained a normal blood pressure and this occurred usually after the third month of observation. The rats in which chronic neurogenic hypertension was only transitory were those which had shown only mild elevations of pressure.

Effect of Bilateral Adrenal Demedullation or Bilateral Adrenalectomy

These operations produced no changes in the blood pressure of the neurogenic hypertensive rats observed up to 60 days thereafter (first few days shown in table 4). The strain of rat used here needs extra NaCl only during the two first weeks after bilateral adrenalectomy; thereafter the accessory adrenals are already well developed and sustain the animals.

Direct Blood Pressure and Heart Rate Measurements

The mean femoral arterial pressure of 30 control unrestrained quiet rats was 117 ± 11 mm Hg (table 5). Under these conditions 139 mm Hg ($\bar{x} \pm 2\,SD$) was fixed as the upper limit of normality for mean blood pressure. All rats observed 20 and 40 days after denervation had mean pressures higher than that value. The same was true for 11 out of 12 rats six months after denervation and for 16 out of 22 observed more than a year after denervation. The mean values presented in table 5 are from only those rats considered hypertensive. This table shows that the increase of mean pressure was determined by an increase of systolic as well as of diastolic pressures. The increases of systolic pressure were approximately 25% greater than those of diastolic pressure, except for the group which was studied 20 days after denervation.

The mean heart rate of control rats at the same moment when the blood pressure was

TABLE 5

Direct Femoral Arterial Pressures and Heart Rates of Control and Neurogenic Hypertensive Rats. Unanesthetized Unrestrained Quiet Animals

Rats	No.	Heart rate	Direct blood pressure		
			Systolic	Diastolic	Mean
		beats/min	mm Hg	mm Hg	mm Hg
Control	30	386 ± 53 *	148 ± 18 *	96 ± 9 *	117 ± 11 *
Denervated					
20 days	6	431 ± 26	184 ± 9	140 ± 9	157 ± 9
40 days	14	411 ± 43	217 ± 22	151 ± 17	177 ± 17
180 days	11	411 ± 66	202 ± 16	140 ± 6	164 ± 7
360 days	16	449 ± 41	191 ± 14	131 ± 13	155 ± 12

* ± = SD.

recorded was 386 ± 53 (SD) beats/minute with 492 ($\bar{x} \pm 2$ SD) as the upper rate limit. In spite of the finding that the average heart rate of the neurogenic hypertensive groups was slightly higher than that of the control group (table 5) the individual values for all these hypertensive rats were less than 492 beats/minute. However, when walking or when stimulated, the neurogenic hypertensive rats presented larger fluctuations of heart rate and blood pressure than did the normotensive animals. No strict correlation was observed in the neurogenic hypertensive rats between increases of blood pressure and elevations of heart rate. In figure 4 records are shown from two hypertensive animals (F-1 and F-2) which had heart rates of 350 and 360 whereas those of two control rats (F-3 and F-4) were respectively 440 and 470 beats/minute. In some hypertensive rats large fluctuations of pressure were observed in synchronism with respiratory movements (R-1, fig. 4). In unrestrained normal rats the respiratory movements were usually rapid and superficial, but the neurogenic hypertensive rats frequently exhibited a slower and deeper respiration. In some rats these respiratory movements were completely irregular, e.g., rat R-1 of figure 4 but in others they were still regular, as in rat R-2. Not all the denervated rats presented detectable alteration of respiration, e.g., rat R-3.

Chronic Tolerance to Denervation and Associated Microscopic Findings

Even those neurogenic hypertensive rats observed up to one year seemed to tolerate denervation and hypertension very well. At autopsy no gross vascular alterations were observed in the mesenteric areas. A usual microscopic finding * in the heart was myocardial hypertrophy and in the kidney a thickening of the basement membrane of the glomerular capsule. The degree of thickening seemed to be related to the duration of denervation, being more intense in those rats observed for a longer time. Rarely, and only in those rats hypertensive up to one year, a mild degree of arteriosclerosis in the kidney was also observed. These alterations in kidneys of rats with neurogenic hypertension are similar to those described in neurogenic hypertensive dogs.[10]

Discussion

The results presented here show that the rat is a suitable animal for studies of neurogenic hypertension. The one-stage operation described is technically simple and is a very effective method of producing a radical denervation of the sino-aortic baroreceptor areas; approximately 75% of the rats developed chronic hypertension. It is not necessary to destroy the efferent fibers of the cervical vagus trunk, and the increase of blood pressure in the rat is not accompanied by as marked a tachycardia as that which has been observed in dogs.[1, 9, 11–14]

Though it has been assumed that chronic neurogenic hypertension in the dog could

* Examined by W. A. Hadler, Department of Morphology.

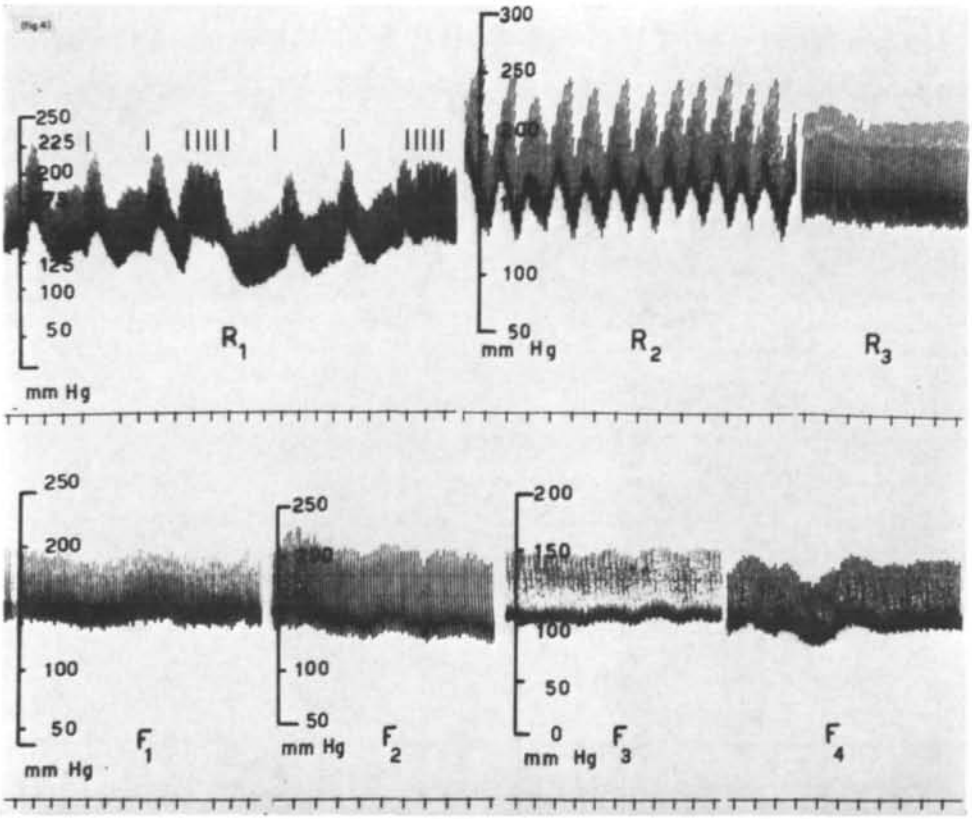

FIGURE 4

Direct recordings of femoral arterial pressures in unrestrained quiet rats. R_1: Large fluctuations of blood pressure in a hypertensive neurogenic rat in synchronism (upper bars) with irregular respiratory movements. R_2: Neurogenic hypertensive rat presenting slower, deeper, but still regular respiratory movements accompanied by simultaneous pressure fluctuations. R_3: Neurogenic hypertensive rat with no pressure oscillations (normal respiratory movements). F_1 and F_2: Neurogenic hypertensive rats with heart rates of 350 and 360 beats/minute, respectively. F_3 and F_4: Control normotensive rats with heart rates of 440 and 470 beats/minute, respectively. Time markings: One-second intervals.

be obtained only when both the sinus and the aortic baroreceptor areas are denervated,[1, 11] more recently a mild hypertension has been obtained by denervation of the carotid sinus only.[15–17] In the rats of the present study no appreciable changes of pressure were observed after pure sinus denervation, but the elimination of only the aortic depressor fibers produced a transitory hypertension. Further work is necessary to assess whether there is really a predominance of the aortic over the sinus depressor fibers in the regulation of blood pressure in the rat. An elevation of blood pressure for two months after pure denervation of the carotid sinus in the rat has been reported;[18] the lack of details, however, prevents comparison with the results presented here.

The ability of pure denervation without resection of the carotid bifurcation to produce chronic sinus denervation in the dog has been questioned in the past by Nowak[11] but denervation alone has been used successfully by Thomas.[9] By stripping the carotid bifurcation area in the rat, effective abolition of baroreceptor activity was obtained in acute experiments.[6] The observation in the present study that chronic neurogenic hypertension was obtained only when both the sinus and the aortic areas were denervated suggests that

permanent denervation can be produced by carotid stripping.

Since neurogenic hypertension in the dog is thought to be due to a hyperactivity of the sympathetic system,[19, 20] the possible role of hypersecretion of catecholamines from the adrenals has been investigated.[21, 22] The elimination of the adrenal medulla by adrenal demedullation or adrenalectomy produced no significant changes in the blood pressure of neurogenic hypertensive rats. This suggests that little or no hypertensive action can be attributed to the adrenal catecholamines. It has also been reported that the adrenal cortex plays no important role in the maintenance of elevated blood pressure in neurogenic hypertensive dogs.[23, 24] This is confirmed by our finding that no acute changes in pressure were observed after bilateral adrenalectomy in neurogenic hypertensive rats. However, the rapid development of accessory adrenal tissue after bilateral adrenalectomy in the rats used here impeded the study of the chronic effects of adrenal deprivation.

The neurogenic hypertensive rats usually presented larger fluctuations of pressure than those observed in normal rats when walking or when stimulated. Some unrestrained quiet denervated animals also showed wide oscillations in pressure synchronous with respiratory movements which in these animals were slower and larger than normal. The mechanical effects of respiration on blood pressure could account for these alterations, but oscillations of the central sympathetic output interconnected with activity of the respiratory center cannot be excluded. Wide fluctuations of arterial pressure correlated with Traube-Hering waves were seen in one neurogenic hypertensive dog.[9]

A close correlation between elevations of arterial pressure and of heart rate was described in neurogenic hypertensive dogs.[9, 25] An increased cardiac output was found to be the major cause of the elevated blood pressure in the denervated hypertensive dog.[26] However, hypertension still persisted in those dogs which had the sympathetic innervation to the heart eliminated,[20, 27] and more recently hypertension without tachycardia was observed in dogs after isolated denervation of the carotid sinus area.[15–17] In the present study of neurogenic hypertensive rats no positive correlation was observed between increases in pressure and increases in heart rate. The facts that these rats had intact all the efferent vagal fibers to the heart and that the heart rate in the rat is normally under almost maximal sympathetic tonus,[28, 29] may partially explain why the unrestrained quiet denervated rats exhibited hypertension accompanied by normal heart rate. It is suggested also that increased peripheral vasoconstriction may be the major cause of the hypertension because cardiac output, measured by a dye dilution method under light pentobarbital anesthesia, was usually normal in neurogenic hypertensive rats.[30]

Summary

Several techniques of radical denervation of the sino-aortic depressor areas were tried in order to produce a permanent neurogenic hypertension in the rat. The aortic depressor fibers were interrupted at the neck level by resecting the nerves which usually exhibit baroreceptor activity, namely, isolated aortic nerve, sympathetic, and laryngeal nerves. The carotid sinus was denervated by stripping the carotid bifurcation and painting with phenol. When the carotid bifurcation was resected bilaterally, in a one-stage operation, all rats showed symptoms of cerebral ischemia, dying shortly thereafter.

Isolated denervation of the aortic baroreceptors was followed by a transitory hypertension. No changes in pressure were observed when only the carotid sinuses were denervated. A few rats in which the usual baroreceptor pathways were interrupted, except the superior laryngeal nerve, developed chronic hypertension. Yet, to obtain consistently permanent hypertension it was necessary to include in the denervation every baroreceptor route.

A simple one-stage operation for complete sino-aortic baroreceptor denervation is described. This procedure was used in 140 rats

that were then studied for periods up to one year. All the operated animals presented some degree of hypertension. Blood pressure measurements made during the first week showed even then that the rats were hypertensive. This observation suggests that in the rat no latent period for the appearance of neurogenic hypertension is present. Hypertension was permanent in 75% of the rats observed up to one year; blood pressure returned to normal values in the remaining 25%, usually after the third month. Extirpation of the adrenal medulla had no effect on the evolution of the hypertension in the denervated rats.

Blood pressure was measured repeatedly in unanesthetized rats by tail plethysmography. Pressure values determined by this method, though 10 to 20 mm Hg lower, approximated the mean arterial pressure recorded directly from the femoral artery in normotensive and hypertensive rats. The hypertension in denervated rats included an increase of systolic as well as diastolic pressure. The heart rates of quiet hypertensive rats were within the normal range and, in general, no close correlation was observed between increases in blood pressure and elevations in heart rate. Normal rats have marked fluctuations in both pressure and heart rate when walking or when stimulated; these fluctuations were much greater in the neurogenic hypertensive animals. Moreover, the hypertensive rats showed large oscillations of blood pressure synchronous with respiratory movements particularly when the latter were slower and deeper than normal.

The rats seemed to tolerate both the denervation and the hypertension very well. Histological examination of tissues from hypertensive rats showed myocardial hypertrophy and a thickening of the basement membrane of the glomerular capsule. The severity of the latter abnormality was closely associated with the duration of the hypertension.

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