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PATHOGENESIS AND MAINTENANCE OF HYPERTENSION PRODUCED BY
AORTIC BARORECEPTOR DEAFFERENTATION IN THE RAT

By

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A DISSERTATION

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ABSTRACT

Pathogenesis and Maintenance of Hypertension Produced by Aortic Baroreceptor Deafferentation in the Rat

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There are conflicting reports about the effects of baroreceptor deafferentation in conscious animals. The present project was designed to examine, in conscious neurogenic hypertensive rats, a number of factors generally thought to be important in the pathogenesis and maintenance of experimental hypertension. Aortic baroreceptor deafferentation (ABD) was chosen as the method to produce hypertension, as previous work in rats indicated that this procedure produces chronic hypertension.

The absolute level, variability and pattern of blood pressure changes after ABD were assessed using a variety of pressure measuring techniques.

The gain of the baroreflex was estimated and compared to the blood pressure levels in ABD rats to see if the degree of deafferentation was related to the degree of hypertension produced by ABD.

Pulsed Doppler and electromagnetic flowmetry were used to investigate the whole body hemodynamic response in acute ABD hypertension.

The neural control of heart rate following ABD was assessed by pharmacological methods.

Interventions which interfered with sympathetic nervous system function were used to assess the role of this system in the genesis and maintenance of ABD hypertension.

The pathophysiology of ABD hypertension was studied at various times post-operatively.

The effect of ABD on body fluid volumes was examined using indicator dilution techniques.

The role of the kidneys in ABD hypertension was assessed by measuring fluid and electrolyte handling before and after provocative interventions.

The role of vasopressin in ABD hypertension was examined in one study by performing ABD in rats whose vasopressin levels were held constant.

The results of these studies indicate that acute ABD hypertension is characterized by sympathetic vasoconstriction.

Interference with factors that might prevent a pressure diuresis following ABD resulted in only a transient diuresis and no mitigation of hypertension.

ABD produced a mild, chronic (up to one year), labile hypertension (in most animals) associated with some signs of pathological changes usually associated with clinical hypertension. Increased sympathetic nervous system activity was the major factor responsible for chronic ABD hypertension. However, volume factors and 'structural' changes in the vasculature appeared to contribute to the elevated blood pressure levels observed in chronic ABD rats.

DEDICATION

This dissertation is dedicated to:

Mr. and Mrs. P. Werber

Janice Werber

Gregory Fink

Ed Meyer

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INTRODUCTION

The studies of Hering and Cyon established the existence and basic functions of the carotid sinus and aortic depressor nerves (Heymans and Neil, 1958). It was found that stimulation of the central end of these nerves caused systemic hypotension and bradycardia. Crossed circulation studies showed that hypertension in the isolated carotid sinus caused systemic hypotension, while local hypotension caused systemic hypertension (Heymans and Neil, 1958).

These observations led Hering to cut the carotid sinus and aortic depressor nerves in the dog in the hope of producing chronic hypertension. He was unsuccessful. However, Hering's students, Koch and Mies (1929) were successful in producing chronic hypertension in rabbits following sino-aortic deafferentation (SAD).

Conflicting reports on the efficacy of SAD as a method of producing chronic hypertension have been reported in the literature for over 50 years (Scher, 1981). The numerous failures to produce hypertension and the general lack of serious cardiovascular sequelae in chronic SAD animals (Heymans and Neil, 1958; Liard, 1980) has resulted in limited acceptance (Grollman, 1954) of this procedure as a model of hypertension.

The work in this thesis was performed on aortic baroreceptor deafferented (ABD) rats. Since there is little work on this particular

model, this introduction will review work on the pathogenesis and maintenance of hypertension following various baroreceptor deafferentation procedures. Studies on other forms of neurogenic hypertension will be reviewed only where directly relevant or information on baroreceptor deafferented animals is unavailable.

Anesthesia affects the circulation (Smith and Hutchins, 1980; see Gross et al., 1981 for brief review) and baroreflex functions (Krasney, 1971; Katz et al., 1967; Kirchheim, 1976). Since most of the work in this thesis was performed on unanesthetized animals, the following review will not include studies on anesthetized animals, unless directly relevant or if comparable studies on unanesthetized animals cannot or have not been performed.

Definitions

Certain terms often have an unclear meaning. This is particularly true in the study of conscious versus anesthetized animals. In this introduction acute will describe studies in conscious animals from zero up to about 72 hours after recovery from operation; chronic will describe studies performed on conscious animals after the acute phase; acute anesthetized will describe studies which assess the effects of baroreceptor deafferentation immediately after nerve section; chronic anesthetized will describe experiments performed on anesthetized animals which had been allowed to recover for a day or more after baroreceptor deafferentation.

Patel et al. (1981) have reported that section of the cervical sympathetic chains and aortic nerves in the rat produces hypertension.

abbreviate this procedure as ADN. For the sake of clarity, their
will be considered an ABD.

Animals receiving a constant infusion of saline at a rate of
approximately 40 ml per day and not allowed access to drinking water
referred to as fluid replete rats.

Characteristics of Blood Pressure After SAD

Blood pressure level and its variability following SAD has been
thoroughly studied. The following sections will review these studies
in order to establish the basic patterns seen after SAD.

Blood Pressure Level. The level of blood pressure reached at
various times after SAD has been the subject of much debate for over
years. There is no debate that there is an acute increase in blood
pressure immediately following SAD in anesthetized (Levy et al.,
Charlier and Philippot, 1947; Thomas, 1944; McCall and Gebber,
Cowley et al., 1973; Barman and Gebber, 1978) and unanesthetized
(et al., 1969; Strait, 1977; Olmsted et al., 1966) animals.
Blood pressure declines towards normal about 30 minutes after SAD in
anesthetized animals (Levy et al., 1955; Charlier and Philippot, 1947;
McCall and Gebber, 1976; Cowley et al., 1973; Barman and Gebber, 1978;
Strait, 1977).

There is no simple explanation of this return to normal. Barman
and Gebber (1978) and Strait (1977) have observed that sympathetic
nervous activity is still elevated while blood pressure is normal 30
minutes after SAD. The phenomenon of vascular escape from sympathetic
stimulation (see Ross, 1971 for review) may partially explain
the decline in blood pressure in the presence of increased sympathetic

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nerve activity. In addition, the decline in plasma volume after SAD (Yun et al., 1976) may also contribute to this decline.

The level of blood pressure after this normalization period is the most disputed aspect of SAD animals. Many investigators, using a variety of pressure measurement techniques, have reported that blood pressure remains at normal levels over the first few days after SAD, then rises to a variable degree (Korner, 1965; Somova, 1970; Imbs et al., 1968; Thomas, 1944; Schafer, 1944; Cowley et al., 1973). In contrast, some investigators do not see such a delay (Krieger, 1970; Ferrario et al., 1969; Alexander and DeQuattro, 1974a; Alexander, 1979). The reason for this discrepancy is unknown.

Some investigators (see Heymans and Neil, 1958 for review) have reported a transient hypertension in conscious animals following SAD. However, most investigators report that SAD produces chronic hypertension in dogs (Grimson, 1941; Nowak, 1940; Dammin et al., 1956; Thomas, 1944; Ferrario et al., 1969; Ito and Scher, 1981; Grimson et al., 1944; McRitchie et al., 1976; Krasney et al., 1973; Schafer, 1944), rabbits (Koch and Mies, 1929; Chalmers et al., 1965; Korner, 1965; Berthelot et al., 1981; Alexander and DeQuattro, 1974b; Chalmers et al., 1967a,b; Blombery and Korner, 1979; Chalmers and Reid, 1972), cats (Kremer and Wright, 1932; Kumazawa et al., 1969) and rats (Krieger et al., 1979; Somova, 1970; Chalmers et al., 1979; Masson et al., 1966; Junquiera and Krieger, 1976; Jones and Hallback, 1978; Krieger, 1964, 1967; Imbs et al., 1968). Some investigators (Krieger, 1964; Dammin et al., 1956; Koch and Mies, 1929) have followed the course of SAD-induced hypertension for a significant fraction of an animal's

lifespan and concluded that SAD induces permanent hypertension.

However, all of these studies lacked a sham-operated control group.

Many investigators (Boyd and McCullagh, 1937; Alexander and DeCuir, 1966; Green et al., 1935; Cowley and DeClue, 1976; Cowley et al., 1974; Cowley and Guyton, 1975; Krasney et al., 1974; Liard et al., 1974; Krasney, 1971; Norman et al., 1981; Baccelli et al., 1976, 1980) have found that SAD does not produce chronic hypertension. Cowley et al. (1973) and Norman et al. (1981) attribute this negative result to the method of blood pressure recording. These investigators contend that only continuous blood pressure monitoring for 24 hours a day can give the 'true' blood pressure level of a SAD animal. They feel that all other methods of blood pressure measurement will yield inaccurate results in SAD animals. To date, no one has demonstrated that SAD produces chronic hypertension (as judged by an average difference between groups of greater than 10 mmHg) using the continuous recording technique recommended by Cowley et al. (1973) and Norman et al. (1981).

The justification for the use of the rigorous blood pressure measuring techniques advocated by Cowley et al. (1973) and Norman et al. (1981) is their contention that the mean resting blood pressure of SAD animals is actually normal but these animals exhibit exaggerated pressor and depressor responses to environmental stimuli. Casual observations by Cowley et al. (1973) and Ferrario et al. (1969) substantiate this contention.

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These casual observations do not answer the critical question: are the reports of hypertension following SAD an artifact of the blood pressure measuring technique? If one accepts 24 hour continuous recording as the 'gold standard' against which other methods are to be judged, then one can examine the question just posed by comparing the blood pressure measured by 24 hour recording to other techniques. The only experiment of this kind has been performed by Norman et al. (1981). They found that SAD rats were normotensive when measured by 24 hour recording, but hypertensive when the animals were placed in a restrainer used for indirect blood pressure determination. This result shows that SAD-induced hypertension may be an artifact of the recording technique. However, it is necessary to compare other blood pressure measurement techniques to that of 24 hour recording before judging the accuracy of the other techniques in determining the 'true' blood pressure level in SAD animals.

Variability. It is well established that SAD animals have a very high degree of minute-to-minute lability of blood pressure (Green et al., 1935; Thomas and Warthin, 1940; Ferrario et al., 1969; Alpert and Thomas, 1943; Bing et al., 1945; Ito and Scher, 1981; Guazzi and Zanchetti, 1965; Jones and Hallbäck, 1978; Masson et al., 1966). It is because of this marked variability that Cowley et al. (1973) initiated the use of continuous blood pressure recording techniques in order to assess the blood pressure level in SAD dogs.

In summary, the occurrence of chronic hypertension following SAD is highly disrupted and may depend on the technique used to measure blood pressure. Some characteristics of blood pressure after SAD are

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agreed upon: 1) blood pressure rises immediately after nerve section, 2) while under anesthesia, the highly elevated blood pressure begins to decline, 3) the minute-to-minute variability of blood pressure in SAD animals is very high.

Characteristics of Blood Pressure After Aortic or Carotid Sinus Baroreceptor Deafferentation

The changes in blood pressure following section of just the aortic or carotid sinus baroreceptors have not received a great deal of attention. In rabbits (Alexander and DeCuir, 1963, 1970; Chalmers et al., 1967a; Blombery and Korner, 1979), ABD produces either a modest (Alexander and DeCuir, 1963; Chalmers et al., 1967a, Blombery and Korner, 1979) or no (Alexander and DeCuir, 1970) increase in blood pressure. In contrast, ABD in dogs (Ito and Scher, 1979; McRitchie et al., 1976) is more consistent in producing a mild chronic hypertension. Blood pressure levels following complete ABD may be close to those after SAD (compare Ito and Scher, 1979 to Ito and Scher, 1981). In rats, ABD also produces an acute hypertension similar to that seen after SAD (Krieger, 1970).

ABD also produces a mild chronic hypertension in rats. Using tail plethysmography, Krieger (1964) showed that ABD produced a sustained mild hypertension lasting about 13 weeks. Unfortunately, Krieger (1964) did not compare these two chronic ABD rats to a control group, but to the 'usual' blood pressure range seen in his laboratory. He concluded that ABD produced only a transient hypertension. Masson et al. (1966) observed that ABD produced a chronic hypertension in rats. The hypertension dissipated over a four week period. Kreher

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and Nitschkoff (1976) found that ABD rats had higher blood pressures than SAD rats over the first two weeks after operation. After this initial period the blood pressure levels were elevated (against an arbitrary reference) to the same degree in both ABD and SAD rats for 9 weeks. One group (Ciriello et al., 1980), using intra-arterial blood pressure measurement, has found that ABD produces a mild, chronic hypertension. This procedure was not associated with a latent period of normotension after ABD (Patel et al., 1981).

In summary, ABD produces a mild hypertension with no latent period in rats and dogs. In experiments where the blood pressure levels of ABD animals have been compared to those of SAD animals (Kreher and Nitschkoff, 1976; Krieger, 1970) the degree of hypertension in the two groups was comparable. It should be noted that most of the studies in rats (Patel et al., 1981; Kline et al., 1980; Masson et al., 1966; Kreher and Nitschkoff, 1976; Krieger, 1964) have used tail cuff plethysmography to determine blood pressure levels in chronic ABD rats. As mentioned earlier, Norman et al. (1981) has criticized the use of this blood pressure measuring technique in SAD rats. Thus, it is possible that the elevated pressures seen chronically after ABD in rats may be an artifact of the measurement technique. The observations of Ciriello et al. (1980), using intra-arterial pressure measurements, have yet to be confirmed.

Section of the carotid sinus baroreceptor nerves does not produce acute or chronic hypertension in the rat (Ciriello et al., 1980; Masson et al., 1966; Krieger, 1964, 1970). In dogs, it has been

reported that bilateral carotid sinus nerve section produces either a mild chronic hypertension (McRitchie *et al.*, 1976) or no increase (Ito and Scher, 1978) in blood pressure. Similar conflicting results have been reported for rabbits (Chalmers *et al.*, 1967a; Alexander and DeCuir, 1970). It can be concluded that carotid sinus nerve section does not produce chronic hypertension.

Relationship Between the Degree of Baroreceptor Deafferentation and the Degree of Hypertension

Over the last 50 years, many investigators (Grimson, 1941; Heymans and Neil, 1958; Koch and Mies, 1929; Ito and Scher, 1981) have speculated that the degree of hypertension varies directly with the extent of baroreceptor deafferentation. The first study to suggest this idea was that of Koch and Mies (1929). They found that vagotomy performed in sino-aortic deafferented rabbits raised pressure to a greater degree in the rabbits with the lowest pressures and least in the rabbits with the highest pressures. Statistical analysis of their published data shows that this correlation was significant ($P < 0.05$). However, the final pressures after SAD were taken in awake rabbits while the vagotomies were presumably performed under different conditions (otherwise, vagotomy would have been fatal; Heymans and Neil, 1958). Unfortunately, Koch and Mies (1929) gave no information as to the conditions under which the vagotomies were performed.

The next investigator to test the hypothesis was Nowak (1940). He found that vagotomy raised pressure significantly in dogs which had not developed hypertension following SAD. Nowak (1940) concluded that incomplete SAD was the reason for the lack of hypertension in these animals. Unfortunately, Nowak (1940) did not perform vagotomies in

the hypertensive dogs as a control. Without this control, the results are impossible to interpret.

The next study to address the hypothesis was that of Ito and Scher (1981). They found that some dogs had residual aortic baroreceptor activity following SAD performed by sectioning the baroreceptor nerves running through the neck. They demonstrated this residual activity by showing reflex bradycardia after acute hypertension in dogs pretreated with atropine. This residual activity was eliminated following injection of a local anesthetic into skin tubes containing the vagosympathetic trunks. After sectioning the remaining baroreceptor nerves by intra-thoracic stripping of the vagi, the blood pressure increased significantly. Unfortunately, Ito and Scher (1981) did not test for baroreceptor activity after this procedure. They also did not show if the animals with residual baroreflexes after cervical deafferentation had a greater rise in blood pressure than those cervical SADs that had complete suppression of baroreflex activity.

In summary, the hypothesis that the degree of deafferentation determines the degree of hypertension after SAD is unproven. Indeed, the observations of Ito and Scher (1979, 1981) would suggest that the degree of aortic baroreceptor deafferentation and not the degree of total baroreceptor deafferentation is more critical in determining the degree of hypertension after baroreceptor deafferentation.

Whole Body Hemodynamics of SAD Hypertension

Blood pressure can be expressed as the product of the time averaged volume of blood leaving the heart (cardiac output), and the

resistance that the blood vessels present to the blood (total peripheral resistance). In almost all cases of chronic clinical and experimental hypertension, the elevated blood pressure is characterized by an increased total peripheral resistance, and cardiac output is normal (Frohlich, 1977).

The fact that resistance is elevated in chronic hypertension does not necessarily mean that an increased resistance was the initiating event leading to the increased pressure. Guyton et al. (1981) have hypothesized that acute hypertension resulting from an increased cardiac output can lead to "whole body autoregulation" which would result in a chronic hypertension characterized by normal cardiac output and elevated total peripheral resistance. It is well established that autoregulatory increases in resistance occur in individual vascular beds (Liard, 1980). The sequence of events associated with this hypothesis does occur in experimental (Ferrario and Page, 1978) and clinical (Eich et al., 1966) hypertension. Therefore, it is important to examine the early hemodynamic events in any form of hypertension, since increased peripheral resistance in chronic hypertension could be a consequence of an initial increase in resistance or cardiac output.

It is particularly important to examine the initial hemodynamic events in hypertension induced by SAD. Granger and Guyton (1969) have shown that whole body autoregulation occurs within a few hours in the absence of the nervous system. More specifically, Liedtke et al. (1973) have shown that after SAD, whole body autoregulation occurs within minutes in the anesthetized dog. In contrast, Levy et al.

(1954) have shown that the cardiovascular system behaves as an iso-resistance system after acute SAD in anesthetized dogs. These observations suggest that an increase in total peripheral resistance triggered by whole body autoregulation could occur very rapidly following SAD.

Anesthetized Animals. The preceding discussion indicates the importance of monitoring cardiac output and total peripheral resistance in the earliest phases of SAD-induced hypertension, even during the operation. Charlier and Philippot (1947) were one of the first investigators to follow whole body hemodynamics following SAD. They found that acute hypertension produced in anesthetized dogs 9 minutes after SAD was the result of an increased cardiac output as total peripheral resistance was unchanged. At 34 minutes after SAD, the blood pressure had declined. A parallel fall in cardiac output was the basis for this decline. Total peripheral resistance was decreased by $3 \pm 7\%$ (mean $\pm$ SEM) 9 minutes after SAD and increased by $1 \pm 0.3\%$, 34 minutes after SAD, suggesting that whole body autoregulation as not occurring.

The results of Charlier and Philippot (1947) have been contradicted by recent studies. Levy et al. (1955), using the Fick technique as Charlier and Philippot did, found that cardiac output increased only slightly following SAD in the anesthetized dog. They found that total peripheral resistance increased significantly and paralleled the blood pressure changes.

Levy et al. (1955) could not adequately explain the difference between their results and those of Charlier and Philippot (1947).

Recently, the results of Levy et al. (1955) have been confirmed by Laubie and Schmitt (1979). Using thermodilution to measure cardiac output, these researchers found that cardiac output was normal 20 minutes after SAD, while blood pressure and total peripheral resistance were significantly elevated.

Conscious Animals. Changes in cardiac output immediately after SAD have been studied in conscious animals. These special methods of SAD may not be comparable to the usual surgical SAD, but produce results usually seen after SAD in the acute anesthetized animals.

Olmsted et al. (1966) produced acute SAD by manually occluding the carotid arteries in dogs with a prior ABD. They found that occlusion always increased blood pressure, but either cardiac output or total peripheral resistance increased. This variable response occurred between dogs but also upon repeated trials in the same dog.

Strait (1977) produced SAD in the conscious cat by performing a surgical ABD and injecting lidocaine into the carotid sinuses. The degree of SAD achieved by this method was determined by finding no reflex bradycardia or reduction of local constriction after phenylephrine. In animals that became hypertensive after SAD, total peripheral resistance increased while cardiac output did not change. Control animals consisted of cats that did not become hypertensive after SAD. There were no changes in resistance or output in these animals.

In dogs (Ferrario et al., 1969) and rats (Krieger et al., 1979) studied soon after recovery from the usual surgical SAD, an increase in resistance is found. In the rat (Krieger et al., 1979) cardiac

output was reduced, but slightly elevated in the dog (Ferrario et al., 1969). Unfortunately, neither of these two studies used a sham-operated control group.

In contrast, Alexander and DeQuattro (1974), studying rabbits, have reported that cardiac output is increased over the first 40 hours after SAD, while resistance is near normal. Other investigators (DeQuattro and Alexander, 1974; Korner and White, 1966; Chalmers et al., 1965; Korner, 1965) have also seen elevated cardiac output and normal total peripheral resistance in the rabbit a few days after SAD.

Alexander and DeQuattro (1974) also observed that elevated total peripheral resistance replaced elevated cardiac output as the predominant hemodynamic basis of hypertension after the acute phase of SAD. These observations suggest that whole body autoregulation may have occurred in those rabbits. In contrast, Korner (1965) found that cardiac output did not decrease in the chronic (1 week after SAD) phase of SAD.

The study by Krieger et al. (1979), mentioned above, is the only study examining the whole body hemodynamic response to SAD in the rat. In acute hypertension in rats following lesions of the nucleus of the tractus solitarii (NTS), cardiac output decreases (Doba and Reis, 1973). In hypertension produced in rats following bilateral lesions of the anterior hypothalamus, there is an increase in total peripheral resistance (Nathan and Reis, 1975; Suarez et al., 1981), and either a decrease (Nathan and Reis, 1975) or slight increase (Suarez et al., 1981) in cardiac output. Unfortunately, in rats, hypertension produced by these brain lesions is lethal within hours.

These studies indicate that there is an inconsistent hemodynamic pattern after SAD. The rat may present a consistent response as total peripheral resistance increases following different forms of neurogenic hypertension. One study (Alexander and DeQuattro, 1974) suggested that whole body autoregulation could have occurred after SAD. In support of this possibility, Liard et al. (1975) found evidence that whole body autoregulation might occur in hypertension produced by stellate ganglion stimulation. However, Liard et al. (1975) also found that acute hypertension produced by stellate ganglion stimulation could occur even after blocking the increase in cardiac output which normally occurred right after the start of stimulation. This observation indicates that the sequence of events accompanying whole body autoregulation may occur after SAD, but there may not be a cause and effect relationship between the initial increased output and chronic increase in resistance.

Changes in Heart Rate Following Baroreceptor Deafferentation

An increased heart rate is almost always found after total or partial baroreceptor deafferentation. In the dog, most investigators (McCubbin and Page, 1951; McRitchie et al., 1976; Blombery and Korner, 1979; Cowley et al., 1973, 1974; Krasney et al., 1973; Ito and Scher, 1981; Laubie and Schmitt, 1979; Cowley and Guyton, 1975) find that heart rate is chronically elevated after SAD. The same is true in the rabbit (Alexander and DeCuir, 1970; Chalmers et al., 1967a,b; Chalmers and Reid, 1972; Reid et al., 1973; Koch and Mies, 1929), rat (Krieger, 1964; Alexander et al., 1980; Chalmers et al., 1979; Jones and

Hallböck, 1978) and cat (Baccellì et al., 1976, 1980). In contrast, normal heart rate following SAD has been reported in the dog (Krasney et al., 1974), rabbit (Chalmers et al., 1965) and rat (Norman et al., 1981). Norman et al. (1981) have suggested that 24 hour continuous recording of heart rate may uncover a normal heart rate after SAD. However, Cowley and Guyton (1975), using that technique, have observed elevated heart rates in chronic SAD dogs. The rare reports of normal heart rate after SAD may be due to random chance.

The chronotropic response to ABD or carotid sinus nerve section (CSD) has rarely been studied, but tachycardia (at least transiently) is the usual finding (Blombery and Korner, 1979; Chalmers et al., 1967a; Alexander and DeCuir, 1970; Patel et al., 1981; McRitchie et al., 1976).

The neural mechanism of the heart rate changes after SAD has been infrequently investigated. McCubbin and Page (1951) found that removal of the stellate ganglion in chronic SAD dogs nearly normalized heart rate, suggesting that increased sympathetic drive to the heart played an important role in the tachycardia associated with SAD. Unfortunately, McCubbin and Page (1951) did not observe the effects of stellate ganglionectomy in normal dogs.

Alexander and DeCuir (1970) found that neither propranolol or atropine alone would normalize heart rate in chronic SAD rabbits, but combined treatment did normalize heart rate. These results suggest that increased sympathetic activity and vagal withdrawal were responsible for the tachycardia associated with SAD.

Blombery and Korner (1979) found that atropine alone in chronic SAD, ABD and CSD rabbits normalized heart rate, suggesting that vagal withdrawal alone was responsible for the increased heart rate following barodeafferentation. In contrast, Chalmers et al. (1965) found that beta blockade with propranolol normalized heart rate in SAD rabbits. This result suggests that SAD-induced tachycardia is solely a consequence of increased sympathetic drive to the heart.

In summary, SAD appears to produce a permanent, and partial deafferentation a transient, tachycardia. The mechanism involved in this tachycardia has been studied infrequently, and conclusions about the role of vagal withdrawal and sympathetic activation have been conflicting.

The Role of the Sympathetic Nervous System in Hypertension Produced by Baroreceptor Deafferentation

It is generally agreed that hypotension causes a reflex sympathetic activation, and hypertension a reflex sympathetic depression (Aars and Akre, 1971). These changes in sympathetic nervous activity, mediated through changes in baroreceptor nerve activity, are thought to be part of a negative feedback system to maintain the blood pressure around a set level. These observations suggest that baroreceptor deafferentation should increase blood pressure via a reflex activation of the sympathetic nervous system.

Barman and Gebber (1978) and Strait (1977) have found that blood pressure and sympathetic nerve activity both increase immediately after SAD, but blood pressure returns to normal while sympathetic activity remains elevated. These observations indicate that while one might expect SAD-induced hypertension in the conscious animal to be

the result of increased sympathetic nerve activity persistent hypertension does not necessarily occur during increased sympathetic nerve activity.

Acute Baroreceptor Deafferentation-induced Hypertension. Recent biochemical studies (Patel et al., 1981; DeQuattro and Alexander, 1974; Alexander et al., 1976, 1980) indicate that sympathetic activity is increased in acute hypertension caused by baroreceptor deafferentation. These studies, however, do not demonstrate that the increased nerve activity is the cause of the elevated blood pressure. The demonstration that acute SAD hypertension could be normalized or blocked by interfering with the actions of the sympathetic nervous system are necessary in order to conclude that baroreceptor deafferentation-induced hypertension is caused by increased sympathetic nerve activity.

Such experiments have been performed. Heymans and Bouckaert (1935) found that prior surgical sympathectomy prevented hypertension after SAD. There were a number of shortcomings to this experiment. First, few animals were used. Second, the effects of sham SAD surgery performed on sympathectomized animals was not examined. If blood pressure fell significantly following such sham surgery, one could conclude that some factor other than the sympathetic nervous system was important in the development of SAD hypertension. Thirdly, positive controls were lacking. This control would consist of producing hypertension in sympathectomized animals by a non-neurogenic method (e.g., renal hypertension). This would show that the sympathectomy did not induce a general depression of vascular reactivity to pressor stimuli.

Heymans and Bouckaert (1935) recognized these limitations. They claimed that total sympathectomy did not lower blood pressure, and that renal hypertension could be produced in sympathectomized animals (Freeman and Page, 1937; Alpert et al., 1937; Verney and Vogt, 1938; Heymans et al., 1937). They did not address the problem of the reaction of sympathectomized dogs to sham SAD.

Studies by Grimson (1940, 1941) support the findings of Heymans and Bouckaert (1935). Grimson performed SAD 2 to 4 weeks after surgical sympathectomy, and found that blood pressure did not change after the SAD. Unfortunately, Grimson's (1940, 1941) studies lacked the same controls that Heymans and Bouckaert (1935) lacked.

These are the only studies that show that inactivation of the sympathetic nervous system could prevent acute hypertension caused by SAD. A report by Beckaert (1953) that bilateral adrenalectomy prevented acute SAD hypertension has not been confirmed (Hermann et al., 1959; Jourdan and Collet, 1951). Hermann et al. (1959) has pointed out that Beckaert (1953) used insufficient adrenocortical hormone replacement therapy. This explanation may account for Beckaert's (1953) inability to obtain hypertension and the high mortality rate after SAD.

Doba and Reis (1974) showed that inactivation of the sympathetic nervous system prevented hypertension after NTS lesion, a model that may be similar to SAD hypertension (Laubie and Schmitt, 1979).

Chronic (more than 1 day duration) Hypertension Following Baroreceptor Deafferentation. Numerous studies (Grimson, 1940, 1941;

Heymans and Bouckaert, 1935) have shown that total surgical sympathectomy reverses chronic hypertension produced by SAD. Unfortunately, sympathectomy was not performed on sham-SAD operated rats. Since sympathectomy in normal dogs lowers blood pressure (Grimson, 1940), it is not known if sympathectomy would have produced identical blood pressure levels in sham-operated or SAD dogs. Thus, these experiments are not decisive proof that increased sympathetic activity is the sole cause of chronic SAD hypertension.

Numerous investigations (Bing and Thomas, 1945; Moss and Wakerlin, 1950; Page and McCubbin, 1952; Chalmers et al., 1965; Touw et al., 1979) have shown that drugs interfering with sympathetic outflow and its vasoconstrictive effects are effective in normalizing the elevated blood pressure associated with baroreceptor deafferentation. These results indicate that increased sympathetic nerve activity is the most important factor in the maintenance of hypertension following baroreceptor deafferentation.

In contrast, biochemical studies (Alexander et al., 1980; Patel et al., 1981) indicate that sympathetic nerve activity is associated with acute but not chronic (after 1 month post-operatively) baroreceptor deafferentation-induced hypertension. The failure to find biochemical indices of increased sympathetic nerve activity in chronic neurogenic hypertension might be due to lack of sensitivity of the tests.

In summary, decisive experiments showing that acute hypertension after SAD is the result of increased sympathetic outflow have not been performed. Surgical extirpation of the sympathetic chains removes

afferent as well as efferent nerves. These afferent nerves may play an important role in cardiovascular control (Malliani et al., 1979; Ciriello and Calaresu, 1980; Brody, 1981). Also, these experiments do not differentiate between the role of the orthosympathetic nervous system and the adrenomedullary catecholamines in the pathogenesis of SAD hypertension.

That the sympathetic nervous system is important in the maintenance of SAD hypertension is well documented. However, 2-kidney one-clip Goldblatt renal hypertension may also be maintained but not initiated by increased sympathetic nervous system activity (Antonaccio et al., 1980). Thus, the factors responsible for the maintenance phase of hypertension may be different from those initiating the elevated blood pressure.

It is concluded that the hypothesis that elevated sympathetic nervous activity is responsible for hypertension immediately following SAD (after recovery from surgery) has been inadequately tested.

Pathological Findings in SAD Hypertension

Hypertension is associated with an increased risk of cardiovascular morbidity (Kannel, 1977). Typical pathologic findings include ventricular hypertrophy, stroke, heart failure, and damage to the blood vessels of the eye, brain and kidneys (Rojo-Ortega and Hatt, 1977; Brunner and Gavras, 1977; Kirkendall and Nottebohm, 1977).

Animal models of hypertension are also associated with increased cardiovascular morbidity (Rojo-Ortega, 1977; Brunner and Gavras, 1977; Okamoto, 1972).

The absence of such changes following SAD is often taken to indicate that these animals are not hypertensive (Grollman, 1935; Jones and Hallbäck, 1978; Liard, 1980). A survey of the literature on pathological changes in SAD hypertension would indicate that there are cardiovascular lesions following SAD. However, the experimental design of most of these studies is abysmal. Most investigators examined 4 or fewer animals (Grimson et al., 1939; Dammin et al., 1956; Hermann et al., 1959; Alpert and Thomas, 1943; Goormaghtigh, 1931; Hoerner et al., 1938), and/or did not examine sham-operated or any other type of control population (Grimson et al., 1939; Dammin et al., 1956; Krieger, 1964; Hermann et al., 1959; Alpert and Thomas, 1943; Goormaghtigh, 1931; Hoerner et al., 1938; Somova, 1970). None of the reports contained an explicit statement that the tissues were examined by someone who had no knowledge of which groups were hypertensive and which were controls. Despite these shortcomings, and in order to review some literature, the better studies will be reviewed. This leaves only a few reports.

Masson et al. (1966) did a thorough histological study in rats with SAD hypertension of 2 months duration. They found no pathological changes in the heart, kidney or mesentery. Masson et al. (1966) also found that heart and kidney weights were normal, although the variation in kidney weight was significantly increased in SAD's. As positive controls, significant pathological findings were seen following 2 months of DOCA-NaCl hypertension.

Krieger (1964) saw mild changes in the kidneys of rats one year after SAD. Controls were not examined in this study. Jones and Hallbäck (1978) saw no increase in the left ventricle weight to right ventricle weight ratio four months after SAD. In contrast, Somova (1970) found an extremely elevated heart weight to body weight ratio in chronic SAD rats. However, these values were much higher than those seen in the Japanese spontaneously hypertensive rat (Takatsu and Kashii, 1972). While there is no obvious basis for criticism of Somova's (1970) findings, they are hard to accept.

Two thorough histopathologic studies performed in rabbits (Kremer et al., 1973; Boyd and McCullagh, 1937) suggest that this species is sensitive to neurogenic hypertension. Kremer et al. (1933) found degenerative changes in the wall of the ascending aorta following SAD. They reported a very mild left ventricular hypertrophy and no changes in the kidney, adrenals, liver, spleen and skeletal muscle. These authors felt that the degree of the lesion seen was related to the duration of the hypertension. Unfortunately, they did not specify the time between SAD and examination of the tissues.

Boyd and McCullagh (1937) studied rabbits approximately 6 months after SAD. They found changes in the aortic wall similar to those seen by Kremer et al. (1933). Boyd and McCullagh (1937) also found no pathological changes in the parenchyma of the kidney, but did notice thickening of the renal arterioles. They also found a significant elevation of the left ventricle weight to right ventricle weight ratio.

DeQuattro et al. (1969) found significant cardiac hypertrophy in acute neurogenic hypertensive rabbits. Interestingly, they found that this increase was inversely related to cardiac norepinephrine content, but not related to the mean arterial blood pressure.

In summary, it appears that rabbits may be more prone to develop cardiovascular lesions in response to neurogenic hypertension than rats. Also, few of the well designed studies examined material from animals with hypertension of long (i.e., large fraction of the animal's lifespan) duration. Mandal et al. (1977) has found that the degree of pathologic lesions in the spontaneously hypertensive rat may be related to the duration of the hypertension. Since barodenervated animals are mildly hypertensive, it may be necessary to do more long-term histopathological studies in such animals.

It has been suggested that hypertension always leads to thickening of the arterioles (Jones and Hallbäck, 1978; Folkow and Hallbäck, 1973; Wolinsky, 1972; Click et al., 1977). Folkow and Hallbäck (1977) have demonstrated that such thickening ('structural changes') can be revealed by observing increased non-specific pressor vascular reactivity and higher resistance at maximal dilation of the vessels. Jones and Hallbäck (1978) saw no such changes in the isolated perfused hindlimb of rats 4 months after SAD.

In contrast, MacLean et al. (1980) have found biochemical but not functional evidence that there are structural changes in acute neurogenic hypertensive rabbits. Langer et al. (1975) have presented preliminary evidence showing increased vascular reactivity in the

isolated perfused mesenteric vascular bed in rats 6 months after SAD. They found that increased reactivity was of post-junctional origin, but did not examine resistance at maximal dilation. These results conflict with those of Jones and Hallbäck (1978). Further experiments along these lines are needed.

Body Fluid Volume Changes After SAD

It has been postulated that control of body fluids plays an important role in the pathogenesis and maintenance of hypertension (Tarazi, 1976; Guyton et al., 1981). The exact mechanisms by which fluid volumes are involved in the pathogenesis of hypertension are poorly understood (Tarazi, 1976). Guyton et al. (1981) have suggested that renal fluid retention may increase cardiac output and cause chronic hypertension following whole body autoregulation.

A number of investigators (Finnerty et al., 1958; Davis, 1963; Cohn, 1966; Baker, 1967) have shown that plasma volume decreases following sympathetic nerve stimulation or infusion of sympathomimetic drugs. Also, alpha-adrenergic blockade appears to cause fluid reabsorption at the capillary level (Nickerson and Hollenberg, 1967), suggesting that sympathetic withdrawal leads to fluid retention independent of renal effects. Thus, if there is sympathetic activation following SAD, one should expect a decrease in plasma volume. This decrease in plasma volume might have an antihypertensive effect (Guyton et al., 1974). However, it should be pointed out that the experiments listed above were short-term experiments, and their findings may not necessarily reflect the fluid volume response to chronic sympathetic activation.

The status of body fluid volumes following SAD has been examined by a number of investigators. Following SAD in anesthetized dogs, Levy et al. (1955) found that hematocrit increased. This might suggest that plasma volume decreased if there was no change in the amount of red cells in the circulation. Yun et al. (1976) also found that hematocrit increased immediately after SAD. These investigators did not measure plasma volume, but found that splenectomy did not prevent the increase in hematocrit following SAD. These data indicate that the increase in hematocrit following SAD in anesthetized animals is a result of decreased plasma volume.

If plasma volume decreases immediately following SAD, the decrease does not appear to be sustained. Most investigators have found that blood volume is normal in chronic SAD dogs (Cowley and Guyton, 1975; Cowley et al., 1973), rabbits (Chalmers et al., 1967c) and rats (Krieger, 1967). Schafer (1942) reported increased blood volume (due to increased red cells) in chronic SAD dogs. Unfortunately, Schafer (1942) only examined 2 dogs, no group averages were reported, and no statistics performed. Therefore, Schafer's (1942) results can be disregarded.

Plasma volume has been measured in very few studies of SAD animals. Plasma volume is normal in chronic SAD rats (Alexander, 1979; Alexander et al., 1980) and dogs (Schafer, 1942).

Alexander (1979) has reported that plasma volume (expressed as absolute volume) is reduced in acute SAD rats (published) and rabbits (mentioned as unpublished results). However, plasma volume expressed as a fraction of body weight was normal in these acute SAD rats. This

was the result of a significant decrease in body weight following SAD but not sham operation. Unfortunately, Alexander (1979) did not measure plasma volume in rats before and after a decline in body weight induced by dietary restriction as a control.

In summary, the majority of studies indicate that plasma volume is normal in chronic SAD animals. This might not be expected if sympathetic tone is chronically elevated in SAD animals, and if the fluid volume effects of acute sympathetic activation are the same as those of chronic activation. The relationship between blood pressure and plasma volume also has not been explored in SAD animals. In general, there is little known about volume changes in SAD animals, and nothing known in ABD or CSD animals.

The Role of the Kidneys in SAD Hypertension

The hydraulic, nervous and endocrine functions of the kidney have been implicated in the pathogenesis and maintenance of various forms of experimental hypertension. The role of the kidney in hypertension produced by baroreceptor deafferentation has also been studied. Glomerular filtration rate, renal blood flow and reabsorptive functions in chronic SAD animals are normal (Bing et al., 1945; Alpert and Thomas, 1943; Fontaine and Mandel, 1938; Alexander and DeQuattro, 1974a).

Renal Nerves. Studies on the role of the renal nerves in SAD hypertension are conflicting. Braun and Samet (see Elaut, 1935) and Kline et al. (1980) found that prior renal denervation prevented baroreceptor deafferentation-induced hypertension.

In contrast, Nowak and Walker (1939) and Elaut (1935), each using one dog, found that renal denervation did not affect the course of acute SAD hypertension. Thomas (1941) found that bilateral nephrectomy did not prevent SAD hypertension. The reason for the conflict is unclear. Kline et al. (personal communication) could not explain their results based on the known functions of the renal efferent nerves.

Studies on chronic SAD animals are also conflicting. Braun and Samet (1935) found that renal denervation reduced blood pressure in chronic SAD dogs, while Elaut (1935) found the opposite result. Neither of these studies evaluated the effects of renal denervation on sham-operated dogs. More work in this area is indicated.

Angiotensin II. Angiotensin II (AII) is a highly potent pressor substance that has been implicated as a pathogenetic factor in 2-kidney renal hypertension (Carretero and Romero, 1977) and as an important determinant of the morbidity associated with human essential hypertension (Laragh, 1980).

The level of AII in the blood depends on the amount of renin secreted by the kidney (Freeman and Davis, 1977). Thus, plasma renin activity (PRA) is considered to be a measure of the amount of AII in the blood. The control of renin secretion, in turn, is controlled by a variety of factors (Freeman and Davis, 1977). One of the factors controlling renin release is renal sympathetic nerve activity. It is well documented that renal nerve stimulation can increase plasma renin activity (Freeman and Davis, 1977). Despite the fact that renal nerve

activity increases following SAD (Aars and Akre, 1971), few investigators have examined the role of AII in SAD hypertension.

Cowley and coworkers (Cowley et al., 1973; Cowley and Guyton, 1975; Liard et al., 1974) have made numerous measurements of PRA in SAD dogs. They have found that PRA is occasionally elevated, and in two of the studies noted above, there is a statistically significant increase in the variability of PRA in SAD dogs compared to controls. The possible significance of these findings have not been investigated since Cowley (1981) has contended that SAD does not cause chronic hypertension.

The studies described above examined only chronic animals. Yun et al. (1976) have demonstrated that PRA increases following SAD in anesthetized dogs if renal perfusion pressure was not allowed to rise. Since increased arterial pressure decreases PRA (Freeman and Davis, 1977), the results of Yun et al. (1976) cannot be directly extrapolated to other studies on SAD animals.

It has been reported that captopril treatment prevents ABD hypertension in rats (Kline and Mercer, 1980). Since captopril's major action is the prevention of AII formation (Antonaccio and Kerwin, 1981), Kline and Mercer's data indicates that ABD hypertension is in some way dependent on AII formation.

These studies indicate that AII may play a role in hypertension produced by baroreceptor deafferentation.

Renal Fluid Volume Control System. Guyton et al. (1981) have suggested that chronic hypertension can exist only if the renal

hydraulic control system is reset to operate around an elevated arterial pressure. According to this hypothesis, chronic SAD hypertension will not exist unless some factor causes the kidney to excrete normal amounts of fluid and sodium in the face of increased renal perfusion pressure.

There have been few studies examining the renal hydraulic system in SAD animals. Malmejac reported reduced (1934) and increased (1935) urine output immediately after baroreceptor deafferentation. Where urine output increased slightly (Malmejac, 1935), the renal nerves and adrenal catecholamines appeared to have a restraining influence on the diuresis. Cowley and Guyton (1975) found that saline-loaded SAD dogs became edematous (one even died), while control dogs were able to handle the volume load. These studies suggest that the renal fluid control system may not be functioning normally after SAD.

The Role of Vasopressin (ADH) in SAD Hypertension

The role of ADH in SAD hypertension is unknown. However, the following observations indicate that ADH may play a significant role in this model of hypertension.

ADH release is increased following bilateral section of the aortic depressor and vagus nerves in the anesthetized rabbit (Bond and Trank, 1972). The decreased plasma volume seen soon after SAD could act to increase release of ADH (Yun et al., 1976). These experiments suggest that ADH levels might increase after SAD.

There is increased pressor activity of ADH in SAD animals (Cowley et al., 1974; Liard, 1980) beyond the non-specific increase in pressor

reactivity to selected pharmacological agents following SAD (McRitchie et al., 1976). Elevated catecholamines increase the pressor response to ADH (see Cowley et al., 1974). These observations indicate that the blood pressure of barodenervated animals may have an increased ADH dependency even if plasma ADH is normal.

These observations suggest that ADH may play an important pressor role in hypertension produced by baroreceptor deafferentation. Further work in this area is indicated.

Summary

The factors involved in the pathogenesis and maintenance of hypertension following baroreceptor deafferentation are not as clear as Heymans and Neil (1958) would suggest.

The exclusive role of the sympathetic nervous system in the production of hypertension after SAD has not been decisively demonstrated. The neural basis of tachycardia in SAD animals is unclear. The whole body hemodynamic events following SAD appear to be highly variable. Important blood pressure controlling factors such as ADH, AII and the renal hydraulic system have received little attention. Finally, the very existence of chronic SAD hypertension has been questioned because of lack of pathological changes and failure to observe an elevated level of mean arterial pressure when pressure is monitored continuously over a few days.

STATEMENT OF PURPOSE

Because of the considerable confusion about the effects of baroreceptor deafferentation in conscious animals, the present project was designed to examine, in conscious neurogenic hypertensive rats, a number of factors generally thought to be important in the pathogenesis and maintenance of experimental hypertension. Aortic baroreceptor deafferentation was chosen as the method to produce hypertension, as previous work in rats (Masson et al., 1966; Krieger, 1964, 1970; Kreher and Nitschkoff, 1976) indicated that this procedure produced chronic hypertension.

The absolute level, variability and pattern of blood pressure changes were assessed by using a variety of pressure measuring techniques.

The gain of the baroreflex was estimated and compared to the blood pressure levels in ABD rats to see if the degree of deafferentation was related to the degree of hypertension produced by ABD.

Pulsed Doppler and electromagnetic flowmetry were used to investigate the whole body hemodynamic response in acute ABD hypertension.

The neural control of heart rate following ABD was assessed by pharmacological methods.

Interventions which interfered with sympathetic nervous system function were used to assess the role of this system in the genesis and maintenance of ABD hypertension.

Pathological studies in chronic ABD hypertension have been performed at various times after induction of hypertension.

The effect of ABD on body fluid volumes has been assessed using classical methods.

The role of the kidney in ABD hypertension has been assessed by measuring fluid and electrolyte handling before and after provocative interventions.

The role of ADH in ABD hypertension has been examined by performing ABD in rats in which ADH levels were held constant.

MATERIALS AND METHODS

General Methods

Animals. Male Sprague-Dawley rats (Spartan Farms, Haslett, MI) were used in almost all studies. Experiment 9 used homozygous Brattleboro rats (courtesy of Dr. J. Buggy, University of South Carolina); Experiments 8 and 9 used Long-Evans rats (Charles River, Inc.); Experiment 17 used spontaneously hypertensive (SHR) and Wistar-Kyoto rats (WKY) derived from the Okamoto strain (Charles River Laboratories, MA and University of Iowa, IA). Rats weighed 200-400 g at the commencement of study. The animals were kept in temperature controlled, light-cycled quarters. Food and water were available ad lib. Animals were housed in groups of 2-4 per cage. Following catheterization, use in metabolic studies, or when rats weighed more than 600 g, the animals were housed individually.

General Surgical Procedures. All major surgical procedures were performed while the rats were anesthetized with pentobarbital (50 mg/kg, i.p. or 30 mg/kg, i.v.). Atropine sulfate (1 mg/kg, i.p. or i.v.) was administered to reduce bronchial congestion. Animals allowed to recover from the procedures received 20,000 units of penicillin G and 25 mg of dihydrostreptomycin intramuscularly at the end of each operation. Ketamine hydrochloride (10 mg/kg, i.v.) or sodium

methohexital (10 mg/kg, i.v.) anesthesia was used for minor procedures.

Catheterization and Direct Blood Pressure and Heart Rate Measurement. Catheters, made of polyethylene or polyvinyl chloride, were placed in the abdominal aorta and vena cava, via the femoral artery and vein, respectively. When not in use, catheters were filled with a sterile saline solution containing heparin.

For recordings in conscious animals, the catheters were exteriorized at the back of the neck or the skull, and anchored with dental acrylic. Rats were allowed at least 24 hours to recover from these procedures before pressure measurements began.

When blood pressure was recorded while the rat was in a metabolism cage, the catheters exited through a flexible metal spring which was attached to a single-channel, plastic hydraulic swivel (Brown et al., 1976). This arrangement allowed the rat completely free movement, and also made possible continuous unrestricted access to the catheters.

Brief recording sessions were carried out in a quiet, lighted room between 8 a.m. and 5 p.m. Pressure readings were not made until the rat was sitting quietly in its cage (usually its home cage). The blood pressure reading was determined from the most stable part of the pressure tracing. When pressure was fairly unstable, a number of individual pressure readings were averaged to determine a representative pressure. Zero pressure level was determined before and after each session.

For continuous 24 hour/day pressure determinations, between 100 to 300 individual measurements were made and averaged for each hour or day to determine hourly or daily blood pressures, respectively. The individual values were also used to calculate the daily standard deviation of blood pressure for each rat. The catheters were kept patent by regular flushing or a slow infusion (4-20 ml/day) of a sterile saline solution containing heparin. Continuous recording sessions started at 10 a.m. Zero pressure level was checked once daily during continuous sessions. All pressure readings for the prior 24 hours were adjusted for baseline drift.

For all recordings, the diastolic (DBP) and systolic (SBP) pressures were monitored continuously on a Grass model 7 polygraph via a pressure transducer (Statham P23Db or Ailtech MS-10) which was connected to the arterial catheter via long flexible connecting tubing. For 24 hour continuous recording, the hydraulic swivel (Brown et al., 1976) was interposed between the catheter and transducer. Mean arterial pressure (MAP) was calculated according to the following formula: $MAP = (SBP + 2DBP)/3$. Transducers were calibrated regularly, and zero pressure was taken to be at the level of the rat's heart.

Heart rate (HR) was obtained when MAP was stable by using a high paper speed and counting pulses from the polygraph tracing.

Indirect Blood Pressure Measurements. Blood pressure was determined indirectly using tail cuff plethysmography with photoelectric pulse detection in restrained rats at an ambient temperature of 26°C.

Aortic Baroreceptor Deafferentation. The ABD was performed according to the method of Krieger (1964). Through a ventral neck incision, the superior laryngeal, cervical sympathetic, and aortic depressor nerves (where present) were sectioned bilaterally. Sham operation consisted of exposing the nerves without sectioning them.

Metabolic Studies. Rats were housed individually in metabolic cages (Acme Metal Products and Lab Products) for these studies. Daily determinations of the following variables were made: water intake, urine volume and, in studies 3-II and 7-I, food intake. Aliquots of urine were collected daily and assayed for sodium and potassium by flame photometry. The electrolyte concentrations were then used to calculate daily urinary electrolyte excretions.

Doppler Flowmetry and Cardiac Output Determinations in Conscious Rats. Pulsed Doppler flowprobes were constructed according to the method of Haywood et al. (1981). Briefly, the bared ends of two lengths of insulated, 36 gauge copper wire (Cooner Wire Co., Chatsworth, CA) were soldered to opposite sides of a one millimeter diameter, gold plated piezoelectric crystal (Valpey-Fisher, Hopkinton, MA). The crystal was then covered with degassed epoxy (Fibre-Glast Developments Corp., Dayton, OH). After the epoxy was hard, the free ends of the wires were passed through a small mold of silastic (Dow Corning, Midland, MI) tubing until the crystal was lodged in the mold. One-half of the mold was filled with liquid polyurethane foam (Fibre-Glast Development Corp., Dayton, OH) which was allowed to harden overnight. The molds were then mounted on 12 gauge metal tubing, and the mold-tubing combination was covered with silicone sealant to form a cuff.

The probe was removed from the tubing the next day and trimmed. Small pins (TRW Corp., Chicago, IL) were then soldered to the free ends of the wires and used as connectors.

The probes were placed on the ascending aorta following: 1) endotracheal intubation, 2) a right thoracotomy between the third and fourth ribs, and 3) isolation of the ascending aorta from surrounding tissue. Animals were artificially ventilated when the pleural cavity was open using a Harvard model 680 respirator. After probe implantation, the ribs and flank musculature were closed with silk suture and the probe leads were buried subcutaneously at the back of the neck.

All animals which underwent this procedure could not be used for study for the following reasons. Approximately 10% of the animals did not recover from the operation. Pulmonary congestion was noticed in these animals. About 50% of the rats died as a result of aortic rupture 2 to 4 days after the surgery. No animals died from this cause after this time period. Approximately 10% of the animals had non-functioning probes due to corrosion of the wires. About 5% of the animals were not used because of severe pleuritis or the probe coming off the vessel. Therefore, 25% of the animals which underwent flow probe implantation were studied. These animals were allowed to recover to their pre-implantation body weights before the probe leads were exteriorized and catheters implanted.

Cardiac output (minus coronary flow) was measured continuously in the conscious rat by connecting the probe leads to a directional pulsed Doppler unit (Department of Bioengineering, University of Iowa, Iowa City, IA) via lightweight wires. The phasic output of the

Doppler unit was connected to a Grass model 7 polygraph to obtain a written record of the signal. The zero flow level was set electronically by turning the Doppler output off. The sensitivity and range controls of the Doppler unit were adjusted to obtain a maximal Doppler shift and set the diastolic phase of the flow tracing as close as possible to the electronic zero.

Cardiac output (minus coronary flow) was recorded as kilohertz Doppler shift, stroke volume derived by dividing hertz Doppler shift by heart rate, and total peripheral resistance derived by dividing MAP by kilohertz Doppler shift.

Body Fluid Volume Determinations. Determinations of plasma volume (PV) and extracellular fluid volume (ECFV) were performed by determining the dilution of Evans Blue dye (Wang, 1959) 10 minutes after injection, and sodium thiocyanate (Gregersen and Stewart, 1939) 30 minutes after injection, respectively. A 0.6 ml control blood sample was drawn through the arterial catheter, and 0.2 ml of a solution containing 5 mg Evans Blue dye and 50 mg of sodium thiocyanate per ml was injected via a venous catheter. Additional 0.6 ml arterial blood samples were drawn at 10 and 30 minutes after indicator injection. For all blood samples, the plasma was separated from cells by centrifugation and frozen before assay. Evans Blue and thiocyanate concentrations in the plasma samples were determined spectrophotometrically from a standard curve.

Ventricular Hypertrophy. Ventricular hypertrophy was determined by removing the heart and dissecting atrial and ascending aorta tissue

from the ventricular tissue. Excess fluid was expelled from the ventricles by gently squeezing them. They then were air dried for five minutes before weighing. In one experiment the right (free wall) and left (plus septum) ventricles were separated and weighed. All tissue weights were normalized for body weight.

Adrenalectomy, Adrenal Demedullation and Renal Denervation.

Adrenalectomy (ADX) was performed through a flank incision after ligation of the vascular supply. Adrenal demedullation (AD-DEM) was performed by incising the adrenal cortex and then extruding the medulla by gentle pressure on the gland with smooth tip forceps. Animals were allowed one week to recover from this surgery. During recovery, adrenalectomized animals were given 1% saline to drink.

Renal denervation was performed by two methods. The first consisted of 1) retroperitoneal exposure of the kidney, 2) isolating the kidneys from surrounding fat and, 3) under magnification, stripping the ureter and vascular supply of all tissue. The other method consisted of 1) a laparotomy to expose the kidney, 2) isolating the kidneys from surrounding fat, 3) under magnification, stripping the ureter and vascular supply of all tissue, 4) painting the renal vessels with a 10% phenol solution and 5) biochemical confirmation (measuring renal catecholamine content) of the denervation at the end of the experiment (performed by Dr. R. Alper, Department of Pharmacology and Toxicology, Michigan State University).

Sham operation consisted of exposure of the appropriate organ.

Total Autonomic Blockade. Total autonomic blockade is here defined as combined administration of supramaximal doses of drugs

known to competitively block the muscarinic receptors of the parasympathetic neuroeffector junction (atropine), the beta receptors of the sympathetic neuroeffector junction (propranolol), and alpha receptors of the sympathetic neuroeffector junction (phentolamine). This combination leaves the entire animal without functional autonomic effectors. Since the heart is invested with only two types of functionally important autonomic receptor types--muscarinic receptors mediating vagal responses and beta-adrenergic receptors mediating sympathetic nerve responses--total cardiac autonomic blockade can be achieved with the combination of atropine and propranolol alone, leaving vascular sympathetic neuroeffectors (alpha-receptor mediated) intact.

The specific procedure for producing total autonomic blockade is as follows. Resting arterial pressure and heart rate are determined, then atropine (1 mg/kg), propranolol (1 mg/kg) and phentolamine (2 mg/kg) are administered intravenously in sequential order at 5-10 minute intervals, and arterial pressure and heart rate redetermined at least 5 minutes after each drug injection. In some experiments, the effect of saline vehicle (1 ml/kg, i.v.) was determined before the atropine was administered. The effectiveness of the blockade was assessed by examining the dose response curves of acetylcholine, isoproterenol and norepinephrine before and after blockade.

Twenty-four Hour Intravenous Infusions. The animals in these experiments were housed in metabolism cages. The rats were given food ad lib., and were administered a continuous (24 hr/day) intravenous

infusion of sterile saline (0.9% NaCl) up to a total volume of 40 ml/day, and had no access to water for drinking. For some experiments, measured amounts of drugs were dissolved in the saline. Syringes, placed in infusion pumps (model 975, Harvard Apparatus, Millis, MA), were connected to the venous catheters of the rats via long connecting tubing and a hydraulic swivel (Brown et al., 1976).

The term fluid replete refers to rats subjected to this procedure.

Isolated Vascular Bed Autoperfusion in Anesthetized Rats

Renal Autoperfusion. The left kidney of anesthetized rats was autoperfused via a free-flowing extracorporeal circuit as described by Fink and Brody (1978). This technique is illustrated in Figure 1. Briefly, an extracorporeal circuit was established between the left carotid artery and an abdominal aortic pouch from which the left renal artery was the only flow outlet. Blood flow in the circuit was measured with an extracorporeal flow transducer connected to a square-wave electromagnetic flowmeter (Carolina Medical Electronics, Inc., King, NC). Arterial pressure was measured from a tap in the extracorporeal line. MAP and blood flow were recorded continuously on a polygraph (Grass Instruments). Renal vascular resistance was calculated as arterial pressure (mmHg)/renal blood flow ($\text{ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$). Changes in renal vascular resistance to norepinephrine, angiotensin II and acetylcholine were assessed by injecting various doses of the drugs (in 10 μl volume) into a latex segment of the flow circuit just proximal to the kidney. The renal nerves were isolated near the aorta, crushed centrally, and placed over a bipolar stainless steel hook

Figure 1. Schematic representation of extracorporeal autoperfusion of the rat kidney. Shaded line indicates the approximate course of peri-arterial renal nerves.

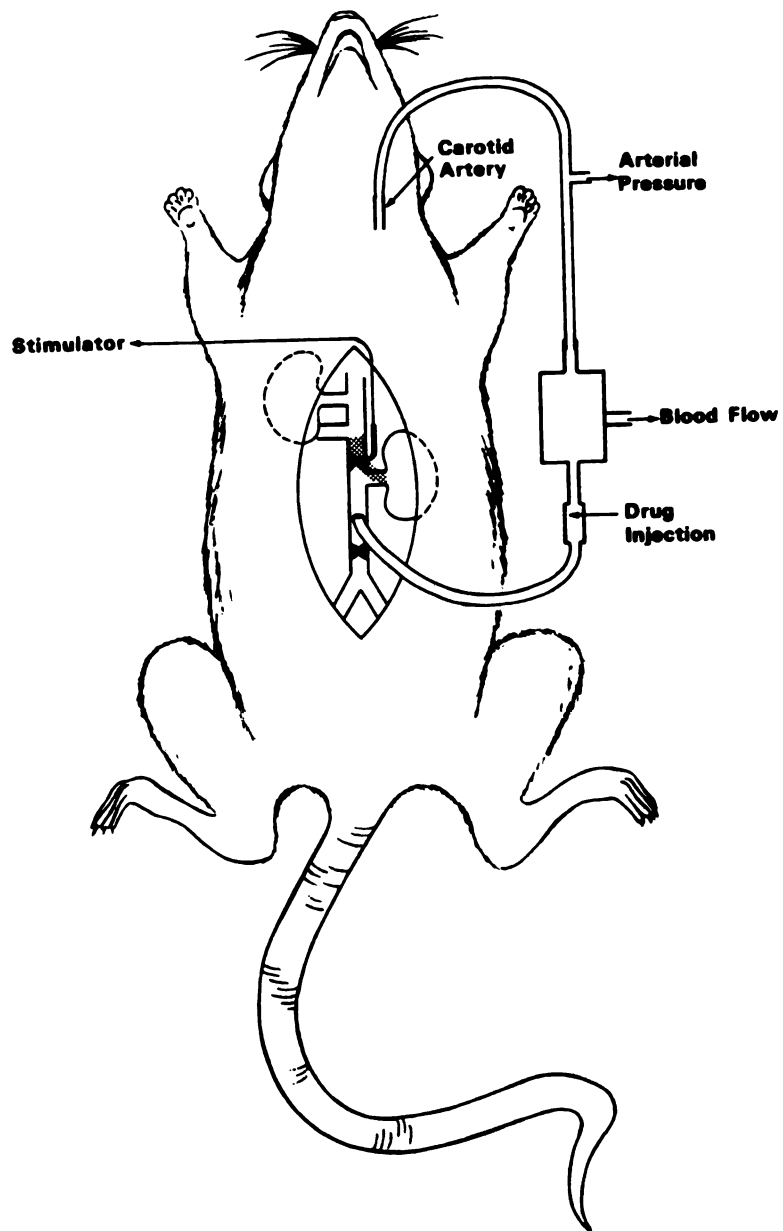


Figure 1

electrode for nerve stimulation. Bipolar square waves of supra-maximal current 0.5 ms in duration were applied through a stimulus isolation unit to the electrode at frequencies of 2, 4 and 6 Hz for 15 seconds, and peak changes in renal vascular resistance were determined. Responses were partially normalized by expressing changes as percent of control resistance, since in the kidney the magnitude of vascular response is directly proportional to resting vascular resistance (McNay and Kishimoto, 1969).

Hindquarter Autoperfusion. The preparation for perfusion of this procedure is illustrated in Figure 2, and is a modification of the technique of Fink and Brody (1978). The modification consists of directing flow from the carotid artery to the hindquarters via the abdominal aorta. The sympathetic chains near the lumbar artery are isolated, crushed centrally and placed on bipolar steel hook electrodes for nerve stimulation. The rest of the procedures are the same as those for renal autoperfusion, except the frequencies used for nerve stimulation are 0.5, 2, 4 and 16 Hz.

The experimental protocol for both procedures was as follows: 1) measurement of resting vascular resistance in the intact, innervated autoperfused vascular bed, 2) determination of resistance changes to acute sympathetic denervation following nerve crush, 3) measurement of vascular reactivity to nerve stimulation and vasoactive drugs, and 4) perfusion pressure was calculated by averaging 10-20 individual MAP determinations made during the drug injections.

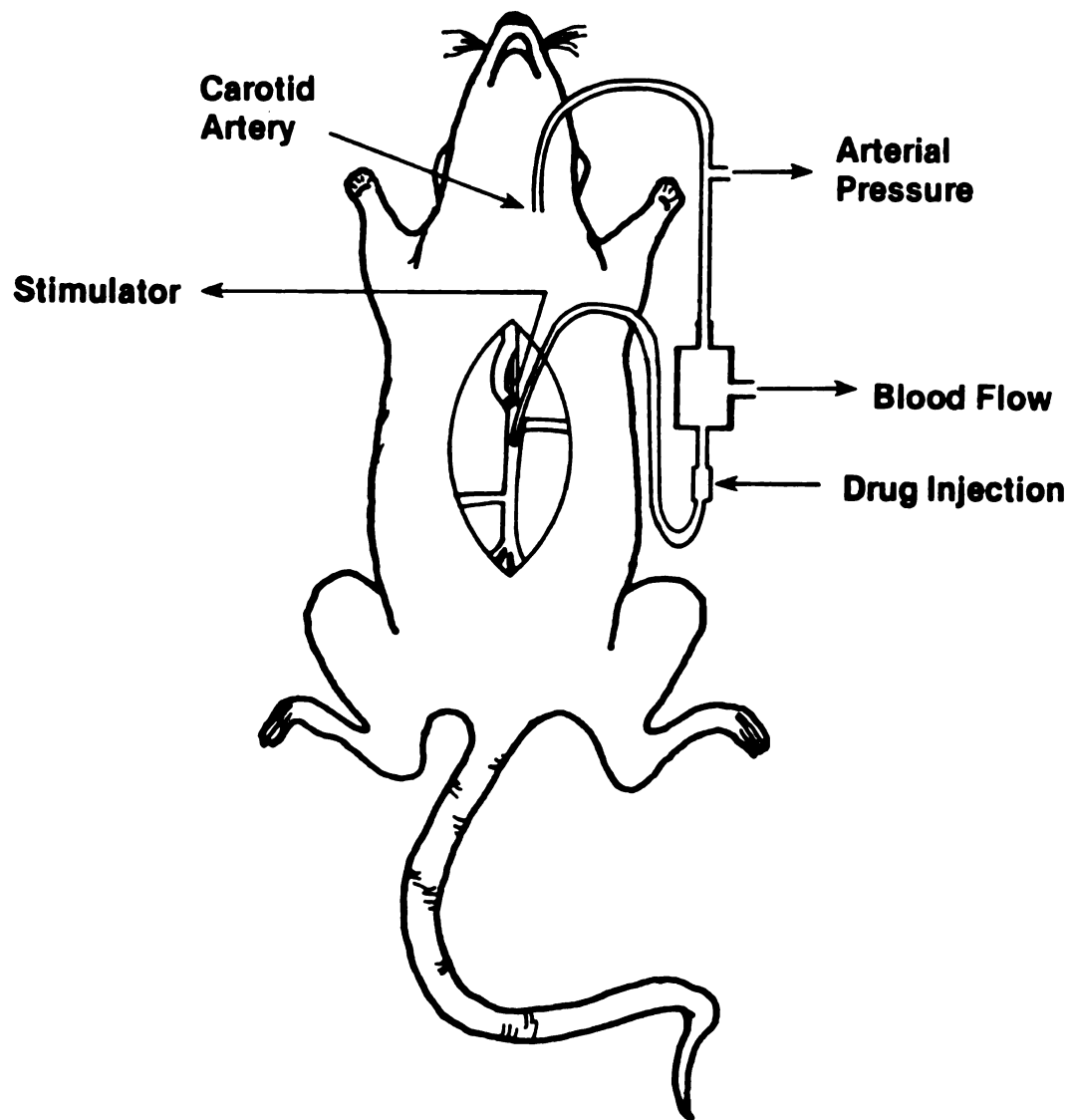


Figure 2. Schematic representation of extracorporeal autoperfusion of the rat hindquarters.

For renal autoperfusion, determination of a pressure-flow curve by progressive step-wise clamping of the extracorporeal flow circuit upstream from the pressure tap was carried out.

For hindquarter autoperfusion the following procedures were performed after determination of vascular reactivity: 1) vascular resistance at maximal vasodilation of the hindquarters was determined following maximally vasodilating (determined by observing no further dilation with higher doses) doses of papaverine hydrochloride, and 2) the ability of the hindquarter vascular bed to demonstrate reactive hyperemia was assessed. In addition, MAP immediately after carotid catheterization was recorded.

By determining vascular resistance at maximal vasodilation, the resting vascular resistance was divided into different components. These components and their method of determination is as follows (also see Figure 3): 1) the neurogenic component is the difference between the value for resting vascular resistance and the resistance 5 minutes after nerve crush, 2) the humoral-myogenic component is the difference between the value for vascular resistance 5 minutes after nerve crush and the resistance at maximal vasodilation, and 3) the structural component is the value for vascular resistance at maximal vasodilation.

Statistics. A variety of statistical methods appropriate for the individual experimental designs were used. The particular tests used will be indicated in the Results section, and can be found in any standard statistics text (e.g., Steel and Torrie, 1960). Data expressed in the body of the text is the mean plus or minus the standard error of the mean, with the number of animals tested in the group in

Figure 3. Method of determination of components of resistance for hindquarter autoperfusion studies. 1 - Significantly different level of vascular resistance. 2 - Significantly different component of vascular resistance (expressed in absolute units). %Significantly different component of vascular resistance (expressed as a percent of resting vascular resistance).

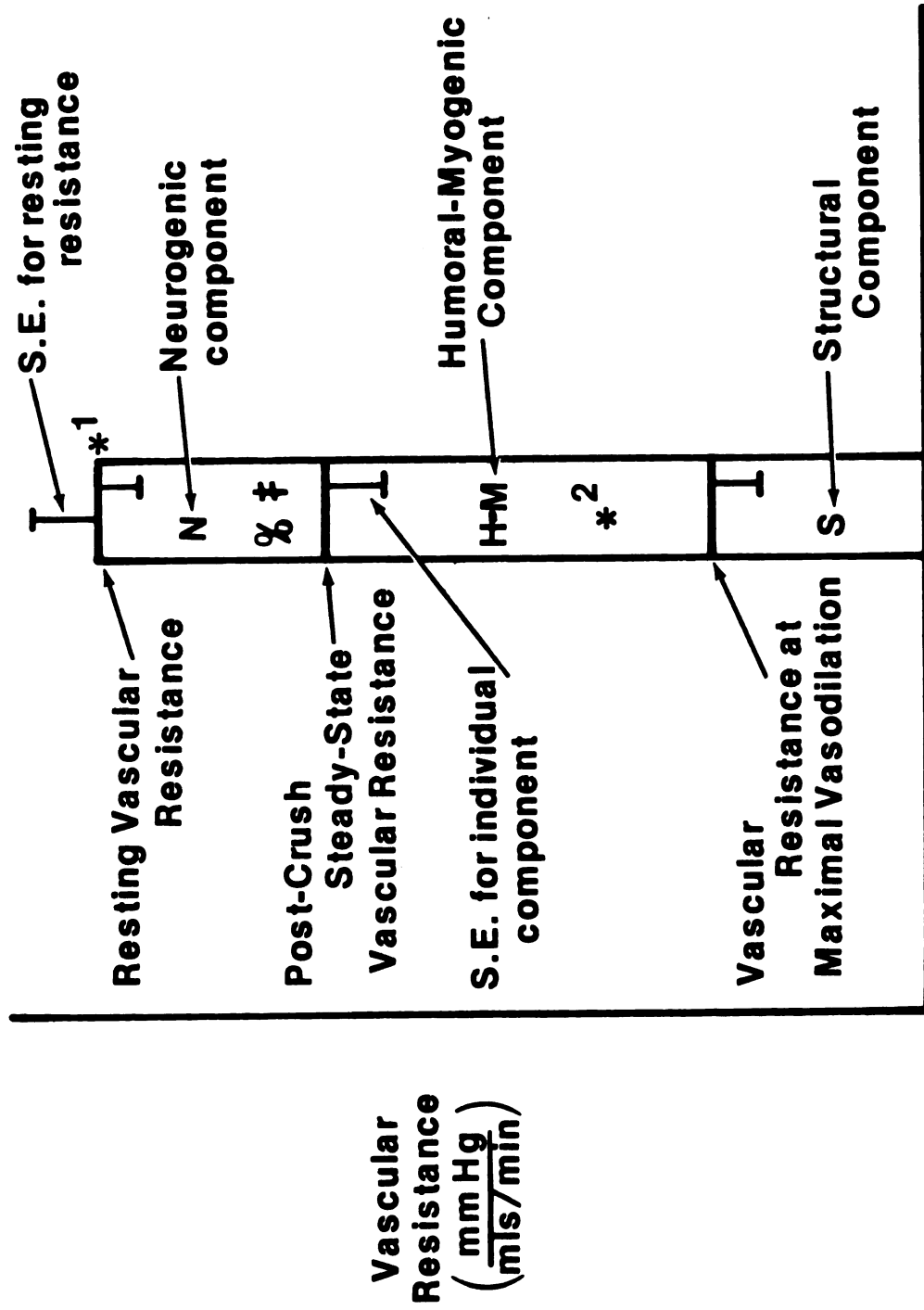


Figure 3

parentheses. Following an analysis of variance (ANOVA) the least significant difference (lsd) or Tukey's tests were used to compare individual means. In all tests, a probability level of less than 5% was the criterion used to reject the null hypothesis of equal means.

Exceptions. Deviations from any of the methods described above will be explicitly stated in the individual experimental protocol.

EXPERIMENTAL PROTOCOLS

Acute ABD Hypertension

Experiment 1. Hemodynamic Response to ABD in Anesthetized Rats

Seventeen rats were anesthetized and arterial and venous catheters were implanted as described. A short length of suture was placed around the nerves sectioned for an ABD. The trachea was cannulated, the rat paralyzed with gallamine (8 mg, i.v.) and artificially ventilated (model 680, Harvard Apparatus Co., Millis, MA). A thoracotomy was performed by cutting through the ribs just to the right of the sternum. An electromagnetic flow probe (Carolina Medical Electronics Inc., model EP-408, King, NC), previously calibrated in vitro, was placed on the ascending aorta to measure cardiac output (minus coronary flow). A snare around the aorta between the heart and probe was briefly closed to determine zero flow.

Cardiac output was recorded on a Grass model 7 polygraph by connecting the flowprobe to a flowmeter (model 301, Carolina Medical Electronics Inc., King, NC), which, in turn, was connected to the polygraph.

Control measurements of MAP and cardiac index (CI = ml/min/100 g body weight) were made after these parameters had stabilized after completion of surgery (approximately 15 minutes). Total peripheral resistance index (TPRI) was derived by dividing MAP by CI. The aortic baroreceptor nerves were cut rapidly and the peak change in MAP and the simultaneously occurring values for CI and TPRI were recorded. In addition, the pressor response 30 seconds after bilateral carotid occlusion (BLCO) was recorded before and after ABD as an indicator of successful aortic nerve section.

Six animals did not show an increase in blood pressure of more than 9 mmHg after ABD although the BLCO response was enhanced by nerve section. These animals were excluded from the results because it was decided to study only those rats with a clear increase in MAP immediately after ABD. Exclusion of these animals did not affect the final results.

Experiment 2. Continuous MAP Recording in Acute ABD Hypertension

Four rats were instrumented with arterial catheters and put in metabolism cages for 24 hr/day continuous measurement of blood pressure as previously described. After a one day recovery period, MAP was measured for 24 hours, ABD was performed, then MAP was measured for another 24 hours.

Experiment 3. Cardiovascular and Body Fluid Responses to ABD

This experiment consisted of two similar studies. The first (Study 3-I) was designed to examine cardiovascular and body fluid

changes caused by ABD, the other (Study 3-II) included measurements of electrolyte balance.

Rats were housed in metabolism cages throughout all studies. Daily metabolic measurements were performed throughout the study as described earlier. Study 3-II included daily measurements of food intake. After housing and two days before ABD or sham operations, all rats were instrumented with arterial catheters as described. Starting the next day, daily determinations of MAP and HR were begun as described, except that the rats were transferred to a large plastic cage for measurement.

Plasma sodium and potassium concentrations were determined before and after ABD or sham operation in some animals from Study 3-II. Approximately 1 ml of blood was withdrawn from each animal a few hours before, then 1 and 5 days after ABD or sham operation. Cells were separated by centrifugation, and the plasma frozen. Plasma sodium and potassium concentrations were determined by flame photometry (model IL 143, Instrumentation Laboratory, Watertown, MA).

In Study 3-I plasma volume and extracellular fluid volume were determined, as described, just before and 5 days after ABD or sham operation. Volumes were expressed as absolute values and as a fraction of body weight.

Two days after catheterization, and after all measurements for that day, animals were subjected to ABD or sham operation, as described. The experiment ended five days later.

Experiment 4. Effects of Total Autonomic Blockade in Acute ABD Hypertension

Fifteen rats were instrumented with arterial and venous catheters, as described, and a control MAP and HR were determined two days later. Ten rats then underwent ABD and five rats were sham-operated. The next day, control pressures were determined and all rats subjected to total autonomic blockade as described.

Experiment 5. Prevention of ABD Hypertension by Inactivation of the Sympathetic Nervous System

Five groups of 10 rats were studied: sham adrenalectomized, adrenalectomized (ADX), adrenal demedullectomized (AD-DEM), guanethidine (50 mg/kg, i.p.) treated (G), and combined adrenal demedullectomized with guanethidine (AD-DEM + G) treatment. Operations were performed as described in General Methods. Guanethidine treatment consisted of single daily injections given one hour after each MAP determination.

Following recovery, arterial catheters were implanted in the rats and daily recording of MAP and HR was initiated two days later, as described.

Daily pressure recordings for the first two days were averaged to give one control pressure for each rat. The rats then underwent ABD and the blood pressure readings on the next two days were averaged to give one post-operative reading per rat.

Experiment 6. Hemodynamic Basis of Acute ABD Hypertension

Twenty rats were instrumented with Doppler flowprobes and arterial catheters as described earlier. Cardiac output, heart rate and

stroke volume were determined daily, while MAP and total peripheral resistance were measured daily on two control days, and one and four or five days after ABD (9 rats) or sham operation (11 rats). In addition, all hemodynamic parameters were measured when the rats recovered from ABD or sham operation. Recovery was defined as the time when the animals showed spontaneous locomotor activity (approximately 3 hours after anesthetization).

Five of the twenty rats were additionally instrumented with venous catheters. The protocol outlined above was followed and, in addition, the rats underwent total autonomic blockade, as previously described, one day before, and one and five days after ABD (3 rats) or sham (2 rats) operation.

Experiment 7. The Role of the Renal Nerves in Acute ABD Hypertension

This experiment consisted of two similar metabolic studies, following the procedures for such studies as described in General Methods.

In study 7-I rats were accommodated to metabolism cages for one day. The rats then underwent renal denervation via a retroperitoneal approach or sham operation, as described. At the time of these operations arterial catheters were also implanted. Daily measurements of MAP and HR were started the day after these operations. The animals were transferred to large plastic cages during MAP and HR measurement.

After two control days, all rats were subjected to ABD, and the study ended five days later.

In study 7-II, 20 rats were renal denervated or sham-operated using an abdominal approach, then arterial and venous catheters implanted in the rats, which were then placed in metabolism cages. Metabolic parameters and MAP and HR (home cage) were measured daily throughout the study. The animals received a continuous infusion of saline, as described previously, throughout the study. Control measurements were made for two days, all animals were subjected to ABD, and the study ended five days later.

Experiment 8. Role of the Adrenal Glands in Acute ABD Hypertension

Fifteen Long-Evans rats were adrenalectomized and allowed to recover before study, as described. Arterial and venous catheters were implanted, the rats then placed in metabolism cages, and metabolic and cardiovascular (MAP and HR) parameters were determined daily, as described. The rats received a continuous infusion of saline, as previously described. In addition, the animals received 400 µg of hydrocortisone per day via the saline infusion.

Control measurements were made for two days, the animals subjected to ABD (10 rats) or sham (5 rats) operation and the study ended five days later.

Experiment 9. The Role of ADH in ABD Hypertension

Six Brattleboro and six Long-Evans rats were instrumented with arterial and venous catheters, then housed in metabolism cages for the duration of the study, as described. Cardiovascular (MAP and HR) and metabolic measurements were performed daily throughout the study. All rats received a 24 hr continuous infusion of saline. In addition, the

Brattleboro rats received 240 mU/day (i.v.) of vasopressin via the continuous infusion. After two control days all rats were subjected to ABD. The study ended 5 days later.

Experiment 10. Effects of ABD on Fluid Replete Rats

This experiment consisted of two nearly identical studies. In both studies, rats were catheterized and placed in metabolic cages, after which daily cardiovascular (MAP and HR) and metabolic measurements were performed daily throughout the study. In addition, all rats received continuous saline infusions, as described. After two days of control measurements, rats were subjected to ABD or sham operation. The studies ended 5 days later.

In one study (10-I) six ABD and seven sham-operated rats were studied, while the other study (10-II) used seven ABD and five sham-operated rats. The studies differed in that study 10-II included measurements of plasma volume and extracellular fluid volume on the first control day and on the first and fifth days after ABD or sham operation.

Studies on Chronic ABD Rats

Experiment 11. Ventricular Hypertrophy in ABD Rats

Rats were subjected to ABD (8 rats) or sham operation (6 rats) at 21 days of age. After two months, arterial catheters were implanted in the rats and resting values for MAP and HR were determined, as described. The rats were then sacrificed and the degree of ventricular hypertrophy was determined as described.

Experiment 12. Cardiovascular Control and Fluid Volume Characteristics in Chronic ABD Rats

This experiment consisted of three studies. In the first study (12-I), animals were subjected to ABD (8 rats) or sham operation (8 rats). One month later, arterial and venous catheters were implanted, as described.

After 2-3 days of recovery, a one hour recording session of MAP was begun. Systolic, diastolic and MAP were noted at exactly 5-minute intervals throughout the hour (12 measurements). During this hour, the behavior of the rats ranged from quiet sitting to grooming behavior. Eating and drinking were not allowed. Average pressures were calculated from the 12 interval measurements, and the standard deviation of these pressures for each rat was calculated by the usual formula.

In a second study (12-II) of 30 rats (15 sham-operated, 15 ABD), MAP, HR, PV, ECFV and the response to total autonomic blockade were assessed 1 month after ABD or sham operation. The protocol at the end of the month is as follows.

One or two days after placement of indwelling arterial and venous catheters as previously described, MAP and HR were recorded by the methods described under General Methods. After these measurements, plasma and extracellular fluid volumes were determined, as described. The following day MAP and HR were again determined and averaged with the previous day's recording. The animals were then subjected to total autonomic blockade, as described previously.

A third study (12-III) examined baroreflex control of HR in 11 sham-operated and 8 ABD rats. Arterial and venous catheters were implanted one month after sham or ABD operation.

Baroreflex curves were determined by increasing arterial pressure in steps by infusion of phenylephrine (10-200 $\mu\text{g/kg/min}$), then lowered by infusion of nitroglycerin (50-200 $\mu\text{g/kg/min}$) alone or in combination with phentolamine (0.2-0.5 mg/kg). Changes in HR during steady-state MAP alterations were determined by the usual method already described, or measured continuously using a cardiometer (Grass 7P4C) triggered by the pulse pressure. Baroreflex curves were constructed by plotting MAP versus heart period ($\text{HP} = 60,000/\text{HR}$ (beats/min)).

Experiment 13. Determination of MAP in Chronic ABD Rats Using 24-Hour Continuous Recording

Rats were subjected to ABD (10 animals) or sham operation (10 animals). One to three months later, arterial and venous catheters were implanted into rats, the rats were placed in metabolism cages, and allowed 2-7 days to recover before the start of 24-hour continuous MAP recording. Continuous MAP recording, as described earlier, was performed for 3 consecutive days. This resulted in obtaining 288 individual MAP determinations in each rat. Heart rate was obtained 3-5 times per 24 hr by the usual method described earlier.

Following the three days of continuous recording, the rat was disconnected from the recording apparatus and housed in a large plastic cage. Starting 24 hours later, MAP was recorded once a day

for three days using the technique previously described for brief recording sessions.

Experiment 14. Vascular Reactivity and the Neural Component of Resistance in the Kidney of the ABD Rat

Indirect blood pressure measurement was performed on sixteen rats 3 times a week for 2 weeks as a control period. The rats were then subjected to ABD (8 rats) or sham operation (8 rats), and blood pressure measured 3 times a week for the next four weeks.

After this period, arterial catheters were implanted into the rats and MAP and HR were measured directly 2 days later, as described. On the same day as these determinations, the left kidney of each rat was autoperfused as described previously.

Experiment 15. Vascular Reactivity and Components of Resistance in the Autoperfused Hindquarters of Chronic ABD Rats

This experiment consisted of three similar studies. In the first study (15-I) rats were subjected to ABD (13 animals) or sham operation (12 animals). Weight changes and the presence of bilateral ptosis post-operatively was recorded in all animals. Nine days later, the hindquarters were autoperfused as described previously. One ABD and one sham-operated rat were studied per day, and the order of study for a given day was determined randomly.

The other studies differed only in that animals were studied 30 days (15-II) after ABD (11 rats) or sham operation (11 rats), or 90 days (15-III) after ABD (12 rats) or sham operation (12 rats). In addition, the degree of ventricular hypertrophy was assessed in 6 ABD

and 6 sham-operated rats in study 15-III at the end of the autoperfusion procedure.

Experiment 16. Cardiovascular Control and Pathological Changes in Rats One Year After ABD

Indirect blood pressure determinations were performed in 25 rats for two control days. The rats (67 ± 2 g body weight) were then subjected to ABD (14 animals) or sham operation (11 animals). Indirect blood pressure measurements were taken at 3 and 14 days after operation and then once every four weeks after operation up until 9 months post-operatively. Indirect blood pressure was measured again, approximately 47 weeks after the initial operation. During that time one ABD rat died suddenly of unknown causes, and one which developed a tumor in its leg was not studied. This left 12 ABD rats for the terminal study.

Commencing about one year after ABD on sham operation the terminal study was begun. One ABD and one sham-operated rat were run simultaneously through all procedures where possible.

On the first day of the study, arterial and venous catheters were implanted via the left femoral artery and vein, respectively. The rats were housed individually in metabolism cages. Urine output and water intake were measured daily while the animals were in these cages. No differences between groups were seen with respect to these parameters.

After a two day recovery period, two consecutive days of 24 hr/day continuous MAP recording, as described, were begun. In addition, HR was recorded by the usual method near noon on each day of the continuous recording.

A few hours after the continuous recording session ended, baroreflex control of HR was determined using a modification of the method of Gordon et al. (1981). Animals were given graded bolus doses of phenylephrine (0.25-4.0 $\mu\text{g/kg}$, i.v.) to raise arterial pressure. A small dose of phentolamine was administered (0.13 ± 0.02 mg/kg, i.v. for shams, 0.19 ± 0.05 mg/kg, i.v. for ABD rats) before graded bolus doses of nitroglycerin (10-160 $\mu\text{g/kg}$, i.v.) were used to lower pressure. All drugs were injected in a volume of less than 100 μl . The blood pressure and heart period at the peak blood pressure response to each injection (including flushing of the drugs out of the catheter) was recorded and plotted. Baroreflex gain was determined for each rat as the slope of the linear portion of the heart period versus blood pressure relationship.

The response to total autonomic blockade, performed as described earlier, was assessed the next day. Two days later, the isolated hindquarters of each rat was autoperfused using a modification of the method previously described. The modification consisted of removing the arterial catheter used for MAP recording and ligating the left iliac artery near the bifurcation of the abdominal aorta. This resulted in perfusion of only one hindlimb. In addition, the untouched carotid artery was briefly occluded after establishing the extracorporeal flow circuit, and the change in MAP resulting from this procedure was recorded. Successful perfusion was indicated by absence of stiffness in the perfused hindlimb.

At the end of the perfusion, the animals were sacrificed by exsanguination. The degree of ventricular (total, right and left)

hypertrophy was assessed as previously described. The right kidney was also removed, weighed, sectioned sagittally and preserved in 10% formalin solution. The left kidney was examined grossly.

In some animals, the brain was quickly removed and preserved in 10% formalin solution. In some animals, the intactness of the blood brain barrier was assessed according to the method of Heistad (personal communication).

This method consisted of infusing 20 mg/kg of Evans Blue dye, allowing one-half hour circulation time, and examining the external surface of the brain.

The kidneys were taken to the MSU Department of Pathology for sectioning and staining for examination by light microscopy. The slides were coded so that the person examining the slides did not know the treatment a particular rat had received.

The brains will be sectioned and examined at the University of Iowa (Heistad, personal communication).

Loss of animals in this study occurred because of technical difficulties, or, in the case of 3 ABD rats, sudden death. Two of these three ABD rats died of massive cerebral hemorrhage. The other rat was not carefully autopsied, but a great deal of froth around the snout was noted in this rat.

Associated Studies

Experiment 17. Autoperfusion of the Hindquarters of the Spontaneously Hypertensive Rat

This study was designed to show that the hindquarters perfusion technique described earlier (General Methods and Experiment 15) could detect changes in the various parameters measured.

In this study 10 SHR and 9 WKY rats underwent the hindquarter perfusion technique described earlier.

Experiment 18. Effectiveness of Total Autonomic Blockade (TAB)

This experiment evaluated the ability of the TAB procedure described earlier to block the cardiovascular actions of exogenous drugs.

The MAP and HR responses to graded bolus doses of norepinephrine (0.1-1.0 $\mu\text{g/kg}$, i.v.), acetylcholine (10-100 $\mu\text{g/kg}$, i.v.) and isoproterenol (0.1-10 $\mu\text{g/kg}$, i.v.) given in that order were assessed before and after TAB in three rats previously instrumented with catheters.

Experiment 19. TAB in Acute Hypertension of Non-Neurogenic Origin

This experiment was designed to assess the effect of TAB on a predominantly non-neurogenically mediated form of hypertension.

In this experiment, 10 rats were instrumented with arterial and venous catheters, as described. The effect of TAB on acute angiotensin-induced hypertension (10-30 ng/min, i.v., adjusted to raise MAP to levels typically observed 1 day after ABD) was determined.

Experiment 20. Hemodynamic Effects of Anemia

This experiment was performed to demonstrate that Doppler flowmetry could detect day-to-day changes in flow. Anemia was used as a stimulus to increase cardiac output (Guyton, 1981).

Eight rats were instrumented with Doppler flowprobes, allowed to recover and catheterized as described in Experiment 6. Cardiac

output, MAP, HR, total peripheral resistance and stroke volume were measured once daily on two control days and four days after the production of anemia. Anemia was produced by removing 2 ml of blood per 100 grams body weight, separating plasma from cells by centrifugation and then infusing the plasma into the animal. The degree of anemia was assessed by measuring hematocrit on the first control day and on each day after the blood removal.

Experiment 21. Cardiovascular and Body Fluid Volume Changes
Following Food and Water Restriction

This experiment was designed to assess the effects of food and water restriction at levels seen following ABD on cardiovascular and body fluid parameters.

Six rats were housed individually in plastic cages throughout the study. Arterial and venous catheters were implanted. The animals were allowed two days to recover before control measurements of body weight (BW), food (FI) and water (WI) intakes, HR, MAP, ECFV and PV were made. The animals were then restricted to amounts of food and water consumed by ABD rats in the first five post-operative days (see Experiment 3). FI and WI were measured on these five days to ensure that the animals ingested their rations (some occasionally did not). BW was measured daily for the duration of the study. MAP and HR were measured one, two and five days after the control day. PV and ECFV were measured again five days after the control day.

Experiment 22. Measurement of Hindquarter Vascular Resistance

This experiment was designed to assess if the procedures used for the hindquarter autoperfusion studies created artifactual values of resting vascular resistance.

Eight rats were studied: four at 9 days after ABD (2 animals) or sham operation (2 animals) and four at 30 days after ABD (2 animals) or sham operation (2 animals).

Arterial catheters were placed in the brachial artery for MAP recording and an electromagnetic flow probe (Carolina Medical Electronics, King, NC) was placed around the abdominal aorta just distal to the left renal artery. The animals were allowed to stabilize (while anesthetized), and control hindquarter vascular resistance (MAP/abdominal aortic flow) was determined. The peak and steady-state responses to ligation of the left common carotid artery was assessed in four (2 ABD, 2 sham) rats. Since no differences between the subgroups was seen, the data was pooled for analysis.

RESULTS

Experiment 1. Hemodynamic Response to ABD in Anesthetized Rats

The results of this experiment are summarized in Table 1. Hypertension occurred within one minute after ABD, and pressure returned to control levels within 30 minutes. The hypertension occurred as a result of increased vasoconstriction, since TPRI increased significantly, while CI was unaffected by ABD (Table 1). The pressor response to BLC0 was enhanced following ABD (Table 1), indicating that the procedure significantly disrupted aortic baroreceptor afferents. The degree of enhancement of the BLC0 response was not correlated with the change in blood pressure after ABD ($r = 0.235$, $df = 15$, $p > 0.05$).

Experiment 2. Continuous MAP Recording in Acute ABD Hypertension

Figure 4 shows that hypertension occurs within 30 minutes after the deafferentation. A secondary peak occurred at night. This effect appears to be the result of a diurnal rhythm, since blood pressure is higher at nighttime compared to daytime in the rats prior to ABD (Figure 4).

The average blood pressures before and after ABD were 104 and 129 mmHg (significantly different at $p < 0.05$, ANOVA, standard error for the difference = 4 mmHg), respectively. The standard deviation of MAP was greater after ABD (14.0 vs. 7.7 mmHg) than before, but the difference

TABLE 1
Hemodynamic Changes Following ABD in Anesthetized Rats

	Before ABD	After ABD
MAP (mmHg)	107	123 ⁺
TPRI (mmHg/mls/min/100 g)	3.93	4.30 ⁺
CI (mls/min/100 g)	29.8	31.3
BLCO* (mmHg)	6	28 ⁺

Values are means from 11 rats. Standard errors are: BP - 3, TPRI - 0.084, CI - 3.3, BLCO - 3. ⁺Value is significantly different from value before ABD ($p < 0.05$, one way blocked analysis of variance). *Change in MAP 30 seconds after bilateral carotid occlusion. Other abbreviations as explained in text.

Figure 4. Twenty-four hour continuous blood pressure recording 24 hours before and after ABD. Vertical dashed bar indicates time of ABD. Black bars on X-axis indicate periods of darkness.

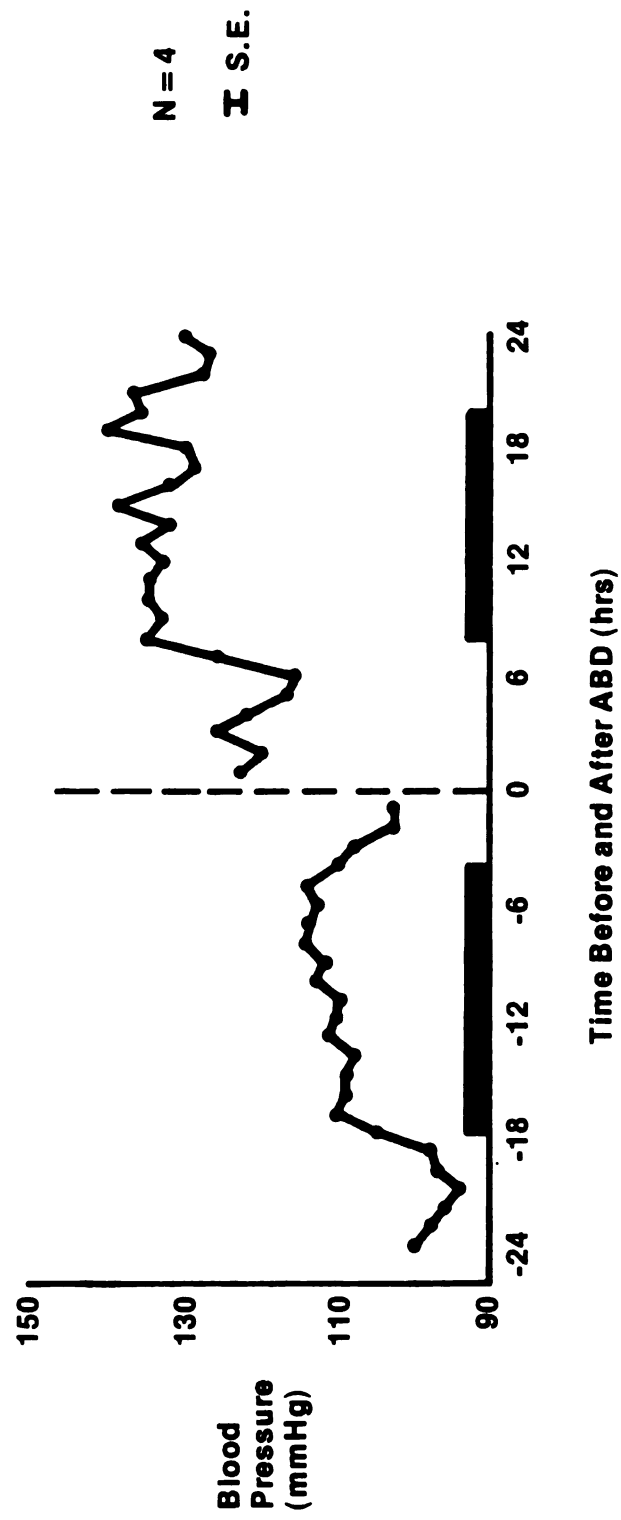


Figure 4

was not statistically different ($p > 0.05$, ANOVA, S.E. for difference = 2.7 mmHg).

Experiment 3. Cardiovascular and Body Fluid Responses to ABD

Study 3-I. The results of HR and MAP measurements are illustrated in Figure 5. There was a sharp increase in both parameters on the day after ABD, with MAP rising from 132 to 162 mmHg and HR rising from 451 to 535 beat/min. HR and MAP in ABD animals then declined over the test period to levels slightly above predeafferentation levels and those of sham-operated animals. Sham operation did not affect MAP or HR significantly.

Figure 6 represents the changes in body fluid volumes after ABD. ECFV fell from 66.5 to 55 ml after ABD, whereas PV declined from 16 to 11 ml. Figure 7 expresses fluid volumes as a fraction of body weight. This figure shows that ECFV did not change after ABD, while PV declined significantly. Figure 8 shows the relationship between PV (mls/100 g) and MAP before and after ABD or sham operation. There was no significant correlation between these variables before or after either operation.

Table 2 shows how changes in water balance and body weight relate to the decreases in fluid volumes. Water balance, the difference between water intake and urine output, dropped from 22 ml the day before ABD to -5 ml on the day after. Water balance remained significantly depressed 2 and 3 days after ABD, but was normal on the last 2 days of the study. Water balance was significantly correlated with the appropriate daily changes in body weight for ABD and sham animals on all days of the study. Table 2 shows the correlation for the water

Figure 5. Blood pressure and heart rate before and after ABD or sham operation. Points represent mean values. Bar is within group standard error. Arrow signifies that ABD or sham was performed after determination. ‡Value significantly different from same group day 0 value ($p < 0.05$, Tukey test). *Value significantly different from same day sham-operated group ($P < 0.05$, Tukey test).

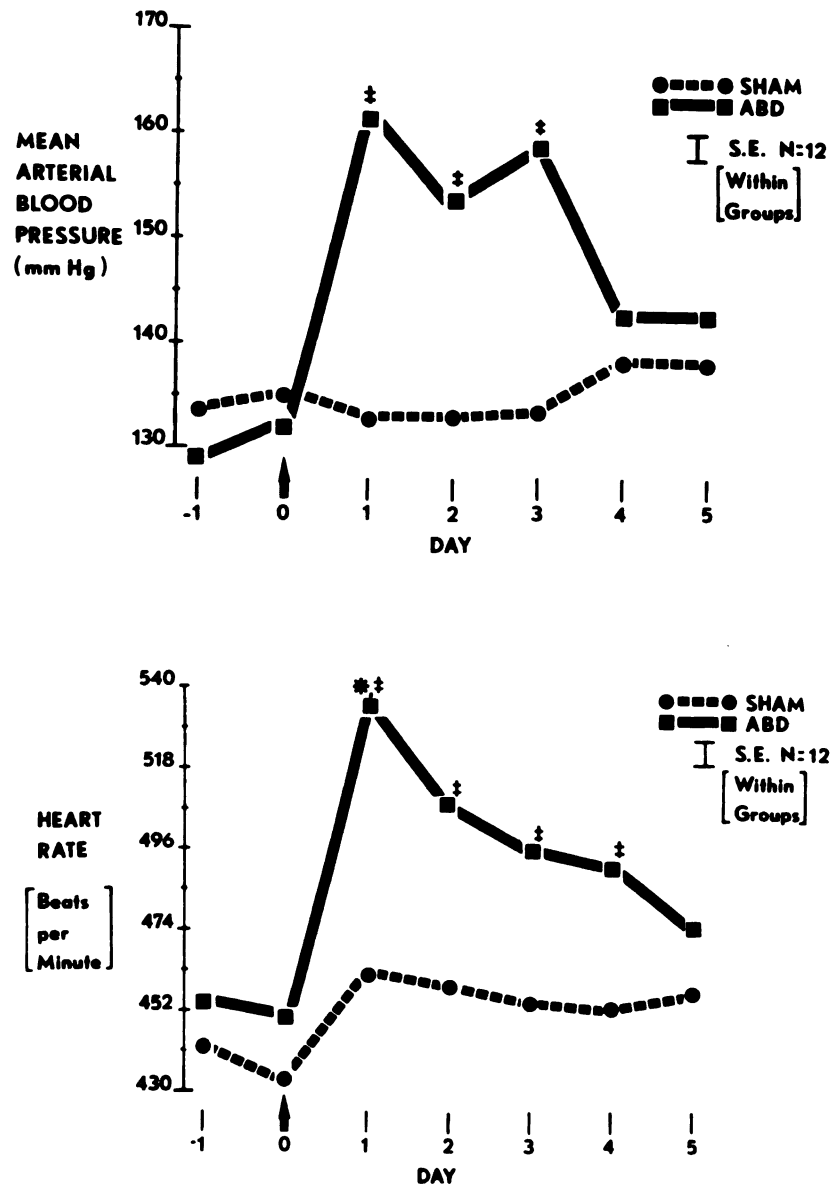


Figure 5

Figure 6. Changes in body fluid volumes before and after ABD or sham operation. Points, bar, and * as in Figure 5. Day 0 is determination just before ABD or sham operation, day 5 is 5 days after ABD or sham operation.

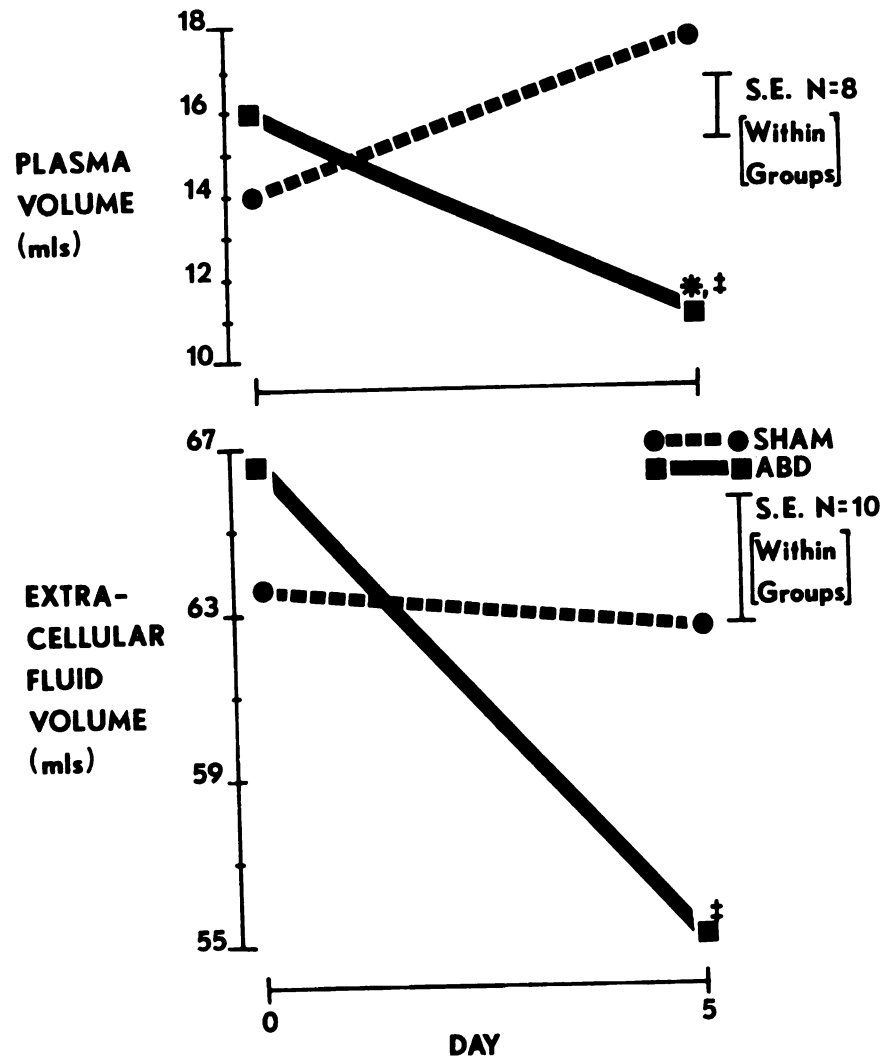


Figure 6

Figure 7. Changes in body fluid volumes (expressed as a fraction of body weight) before and after ABD or sham operation. Symbols as in Figure 6.

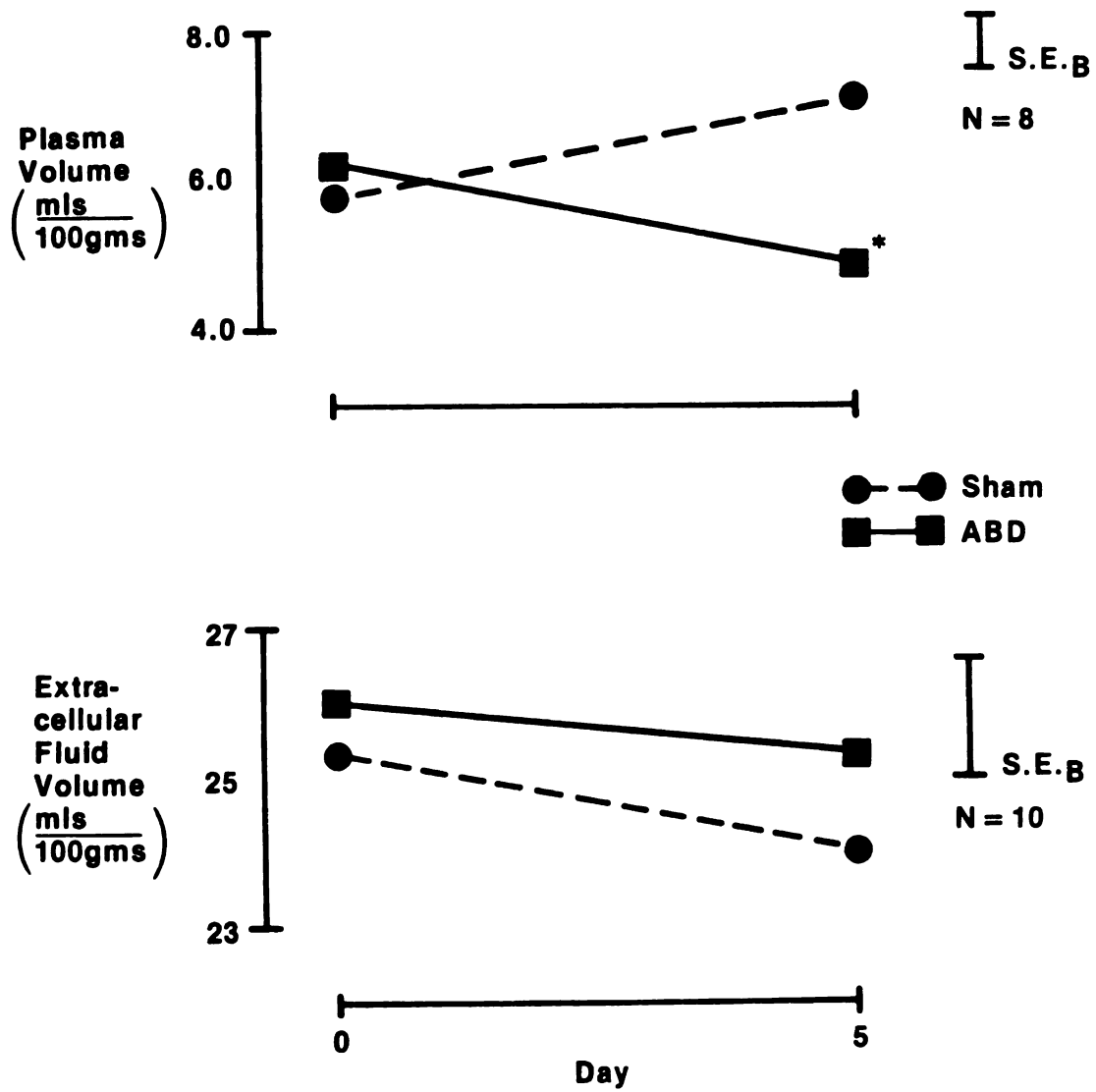


Figure 7

Figure 8. Relationship between plasma volume and blood pressure before and after ABD or sham operation. Points represent individual values. Day 0 is control, day 5 is 5 days after ABD or sham operation.

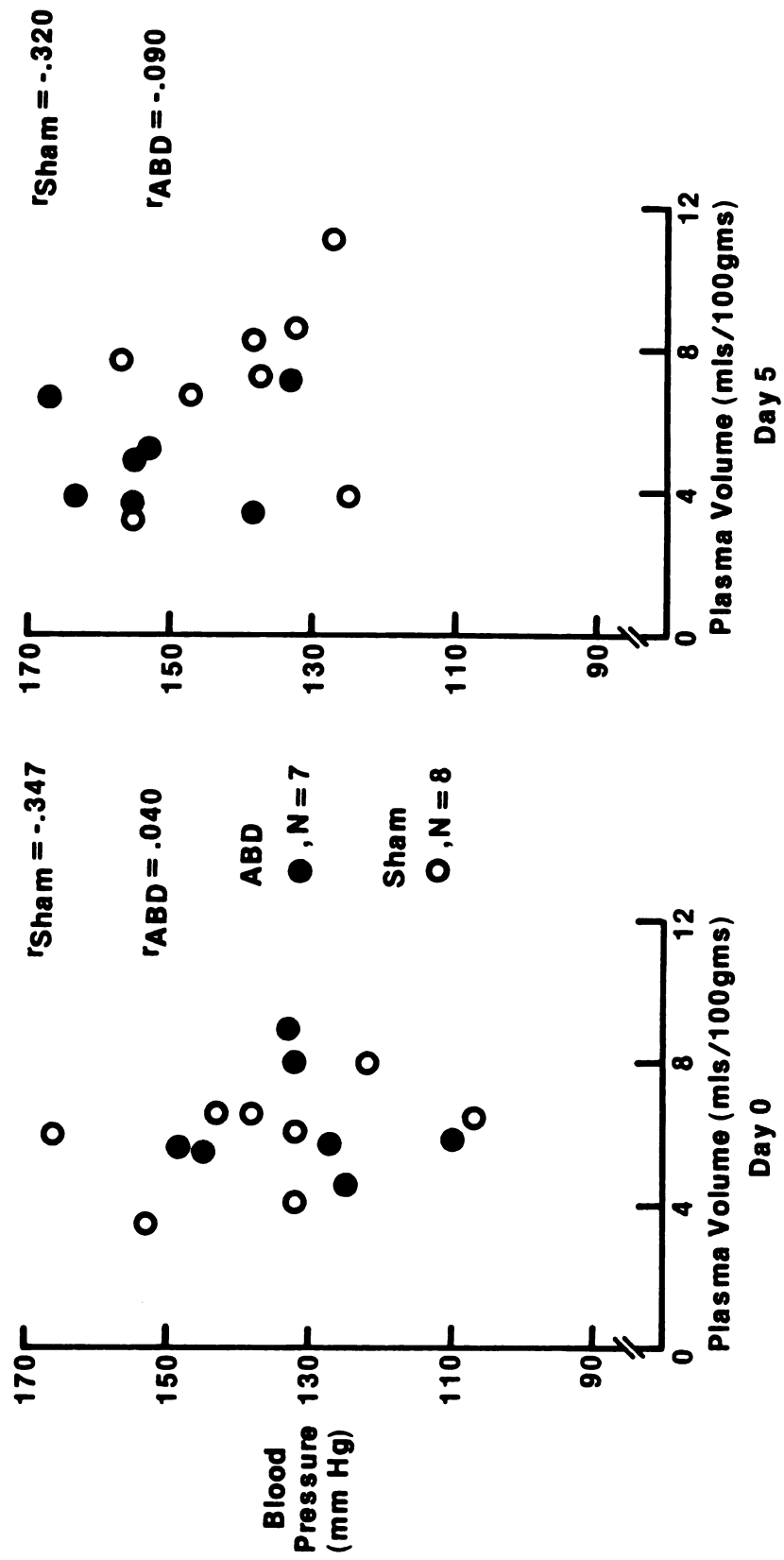


Figure 8

TABLE 2

Relationships Between Body Weight, Water Balance and Fluid Volumes

	Day ¹						
	-2	-1	0	1	2	3	4
Body Weight (gms)	254	248	248	245	250	252	258
	253	251	254	224*	222*	217*	222*
Water Balance (gms)	24	14	17	16	23	20	19
	26	16	22	-5*,†	13*,†	13+	18

Correlations²

Parameters	r	df	P
Change in Extracellular Fluid Volume ³ vs. Change in Body Weight ⁴	.714	9	<.05
Change in Plasma Volume ⁵ vs. Change in Body Weight ⁴	.704	5	>.05
Day 1 Water Balance vs. Change in Body Weight ⁴	.746	12	<.05

*Significantly different from same day sham-operated group ($p < .05$, Tukey's test). † Significantly different from within group day 0 value ($p < .05$, Tukey's test).

¹Days before and after ABD or sham operation, Day 0 determinations being made before the operations.

²For ABD animals only.

³ECFV Day 5 minus ECFV Day 0.

⁴Body weight on Day 1 minus body weight on Day 0.

⁵Plasma volume on Day 5 minus plasma volume on Day 0.

balance and body weight changes after ABD, which implies that the body weight loss was due to the decreased net influx of fluids over that time. Table 2 also illustrates that the decrease in body weight during the period of the study after ABD was related to the loss of ECFV. There was also a relatively strong but nonsignificant correlation between body weight loss and decreased plasma volume.

Figure 9 shows the components of water balance: water intake and urine output. Urine output increased slightly in both groups before the day of ABD or sham operation (Day 0). The day after ABD, urine output declined slightly from 12 to 10 ml, then was significantly depressed the next 3 days, and returned to normal on day 5. Sham operation did not affect urine output.

Water intake before sham operation or ABD was fairly constant, with a slight decline the day after catheterization. Water intake was unaffected by sham operation, while reduced after ABD, with a trend to return to control values by the last day of the study (Day 5).

Renal electrolyte excretion was also altered after ABD. Figure 10 illustrates daily sodium ($U_{Na}+V$) and potassium (U_K+V) excretions. Sodium excretion followed a pattern similar to that of urine output; pre-ABD excretion was equivalent to that of shams, remained unchanged the day after ABD, then declined significantly for 3 days, and returned to near control values on Day 5. Potassium excretion followed a slightly different pattern; it fell significantly the first day after ABD and never reached control levels. Sham operation had no effect on potassium excretion.

Figure 9. Water intake and urine output before and after ABD or sham operation. Symbols as in Figure 5.

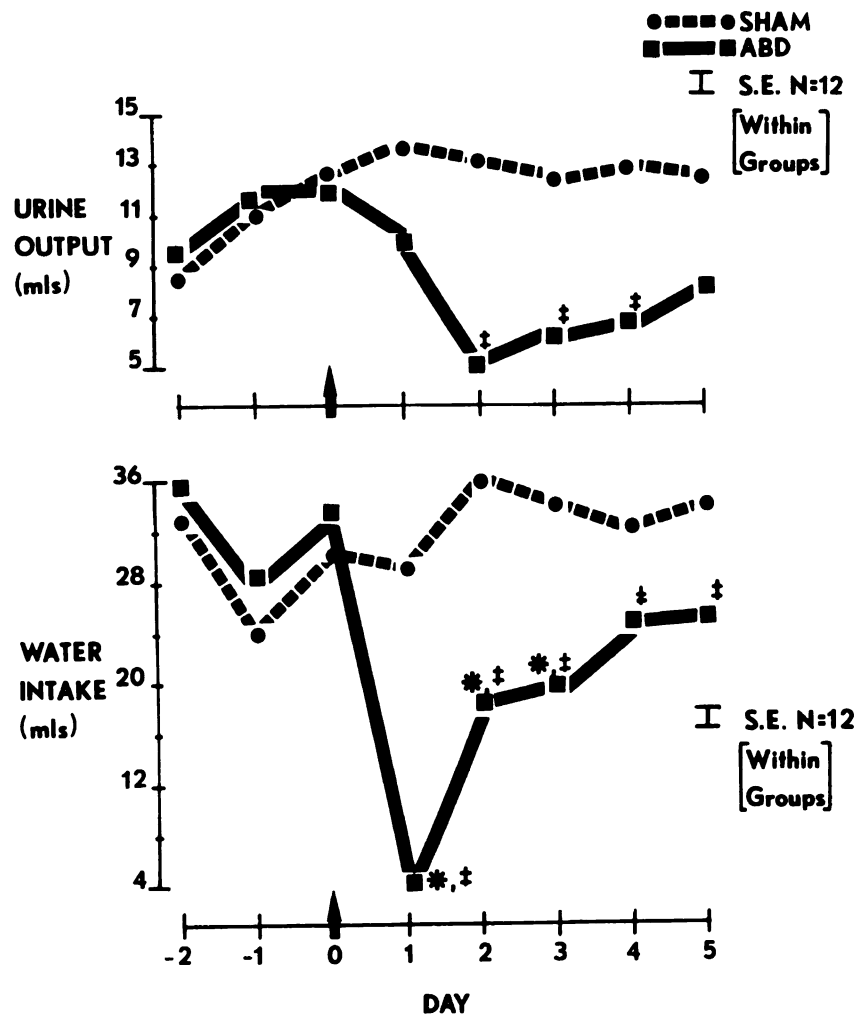


Figure 9

Figure 10. Renal electrolyte excretion before and after ABD or sham operation. Symbols as in Figure 5.

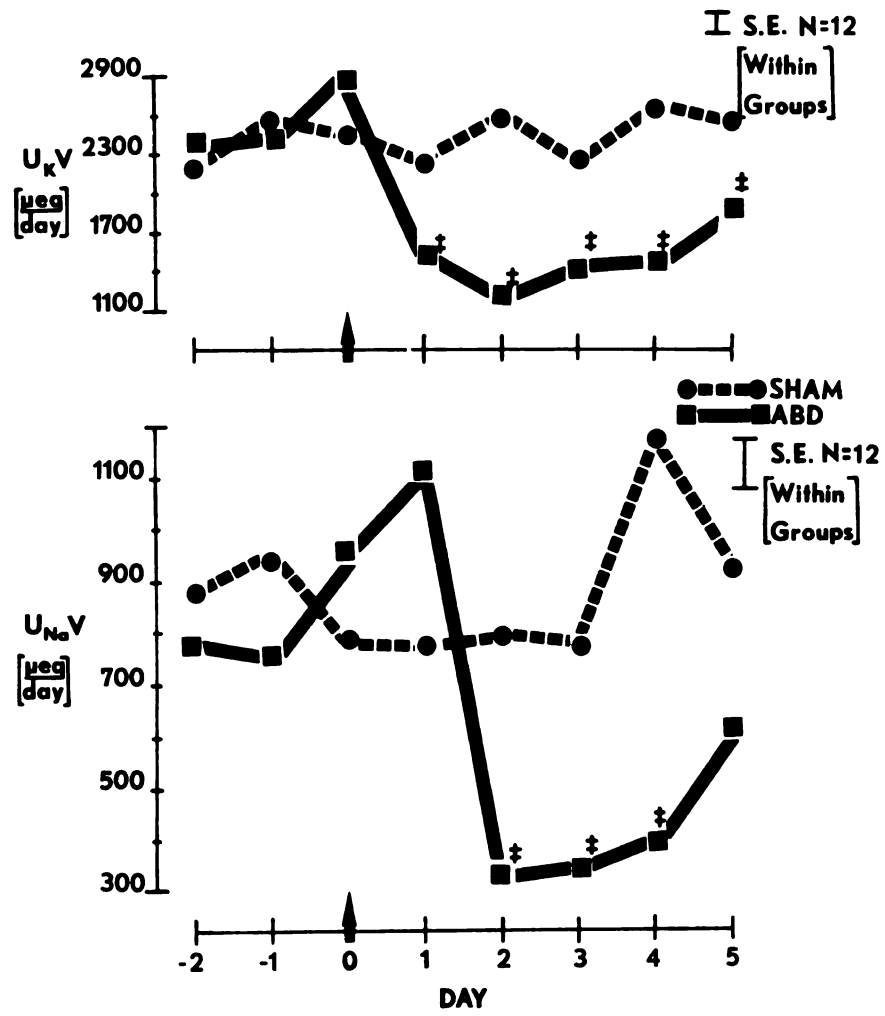


Figure 10

Study 3-II. This study was designed to examine the possibility that electrolyte balance of animals after ABD was not equal to sham-operated animals. This study also repeated many of the determinations of study 3-I without the removal of a fairly large amount of blood necessary for PV and ECFV measurements.

Table 3 summarizes some of the data from this study. Changes in HR, urinary output, water intake, $U_{Na}+V$ and U_K+V which were measured but not shown in Table 3, were similar to the results of Study 3-I. Sodium balance (intake-urinary output) declined after ABD, from 452 to -594 μ Eq. However, an equivalent decline from 642 to -188 μ Eq was also observed in sham-operated animals. Sodium balance returned to control values 2 days after sham operation and ABD. Potassium balance did not change significantly after ABD or sham operation.

Study 3-II also examined plasma sodium and potassium concentrations in four sham and six ABD rats. Plasma sodium increased slightly after ABD from 139 to 144 mEq/l, then declined to 141 mEq/l on the fifth day of the study; these changes were not statistically significant. Sham operation had no effect on plasma sodium concentrations. Plasma potassium concentrations did not change significantly after either sham operation or ABD.

Study 3-II also demonstrated that ABD results in a transient period of reduced food intake as well as hypodipsia. The combination of these two events explains the changes in body weight observed in both experiments.

TABLE 3

Results of Study 3-II

	Groups	N ¹	Day	-3	-2	-1	0 ²	1	2	3	4	5
Food Intake (gms)	Sham ABD	8 8		18 19	20 18	9 12	15 15	9 4*	13 8*	12 8*	14 13	14 13
Blood Pressure (mmHg)	Sham ABD	4 7				124 119	119 114	119 148*	116 143*	117 138*	117 148*	119 137*
Plasma Sodium (μ Eq/L)	Sham ABD	4 6				141 139		139 144				142 141
Plasma Potassium (μ Eq/L)	Sham ABD	4 6				3.5 3.7		4.2 3.7				4.4 3.3
Sodium Balance (μ Eq/day)	Sham ABD	8 8		548 702	560 448	-81* 177	649 452	-188* -594*	231 335	224 104	338 568	8 464
Potassium Balance (μ Eq/day)	Sham ABD	8 8		1255 1284	1030 901	-58 560	695 679	-206 -435	338 279	420 -104	973 722	414 838

*Significantly different from within group day 0 value ($p < 0.5$, Tukey' test).

Within groups standard errors were the following: Potassium balance 355

Food intake 1.5

Plasma sodium 54

Sodium balance 147

Blood Pressure 4

Plasma potassium 0.5

¹Number of animals in each group.

²ABD or sham operation was performed following this day's measurements.

Experiment 21. Cardiovascular and Body Fluid Changes Following Food and Water Restriction

This experiment was designed to assess the effects of reduced food and water intake, at levels seen after acute ABD hypertension, on cardiovascular and body fluid parameters.

Following the control period, the animals ate 4.2, 8.5, 8.2, 13 and 13.4 grams of food on days 1-5, respectively. They drank 4, 18, 19, 24 and 25 ml of water on days 1-5, respectively, after the control period. This regimen reduced their body weight (Figure 11) by the same amount that occurs following ABD. Heart rate was unchanged, except for a decrease on the second day of restriction (Figure 11). The deprivation did not affect blood pressure (Figure 11). Fluid volumes (ECFV and PV) expressed as absolute values or as a fraction of body weight did not change significantly five days after food and water deprivation (Figure 11).

This experiment indicates that the hypodipsia and hypophagia accompanying ABD does not account for the cardiovascular or body fluid volume changes seen after ABD.

Experiment 10. Effects of ABD on Fluid Replete Rats

This experiment examined the cardiovascular and fluid volume response following acute ABD-induced hypertension in fluid replete rats.

In study 10-I it was found that ABD hypertension in fluid replete rats was similar to that seen in rats with ad lib. access to water (compare Figure 12 from study 10-I to Table 3). In contrast, urine volume and urinary sodium excretion ($U_{Na} + V$) were significantly in-

Figure 11. Effects of food and water restriction on cardiovascular parameters and body fluid volumes. Days -1 and 0 are control days. Food and water were rationed on Days 1 through 5. N is number of animals studied. Bars represent within group standard error. Solid vertical line separates control (on the left) values from values determined during restriction (on the right). Points represent mean values. †Value significantly different from Day 0 control value.

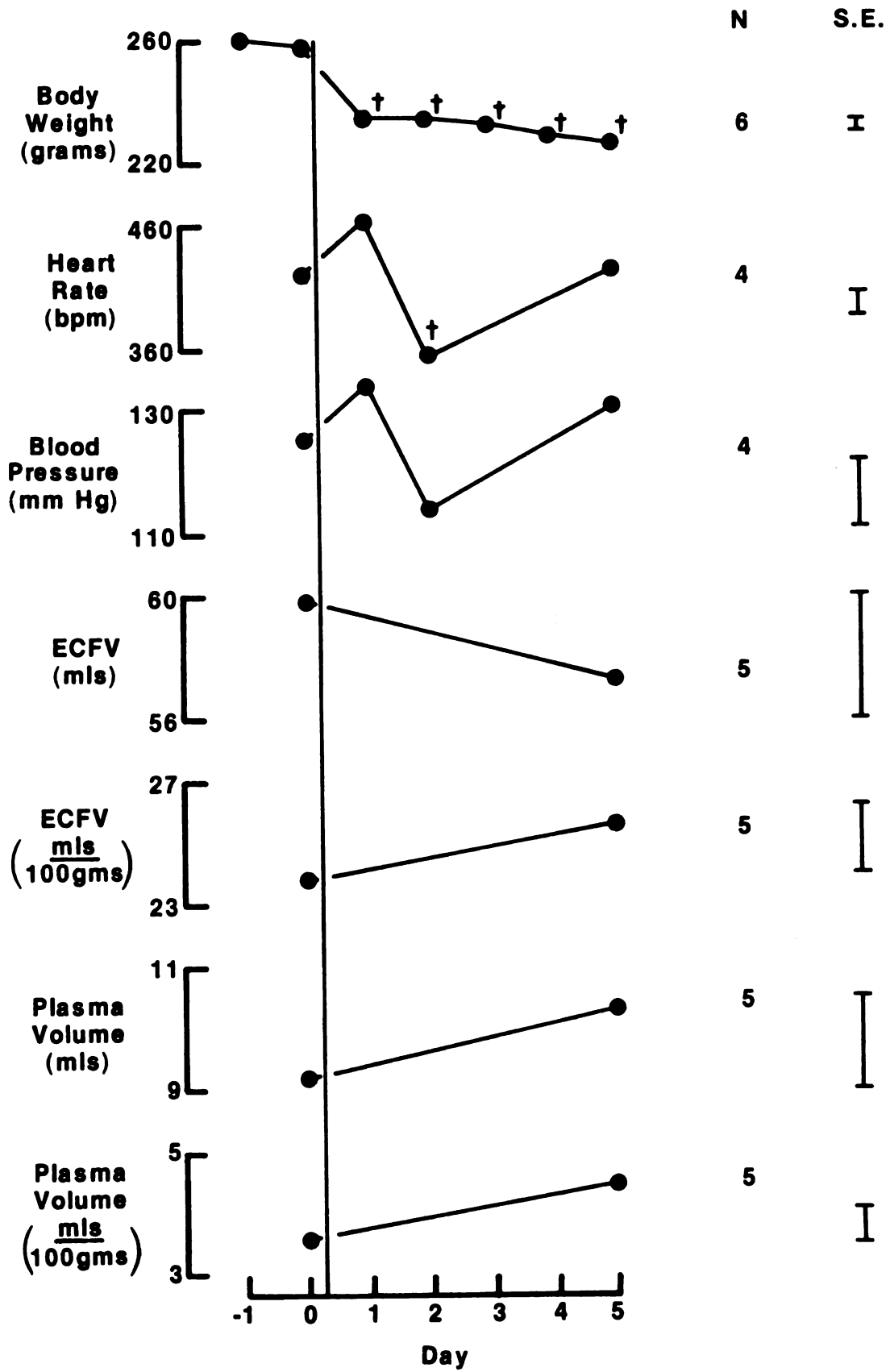


Figure 11

Figure 12. Cardiovascular and fluid changes in rats on controlled fluid intake subjected to ABD or sham operation. $C_{1,2}$ = first (C_1) and second (C_2) control days. P_{1-5} = first (P_1) through fifth (P_5) days after ABD or sham operation. Solid vertical line indicates day of ABD or sham operation. FI = fluid intake; UO = urine output. *Significantly different from C_2 value ($p < 0.05$, Tukey test). Other abbreviations explained in text. Bars represent within groups standard error.

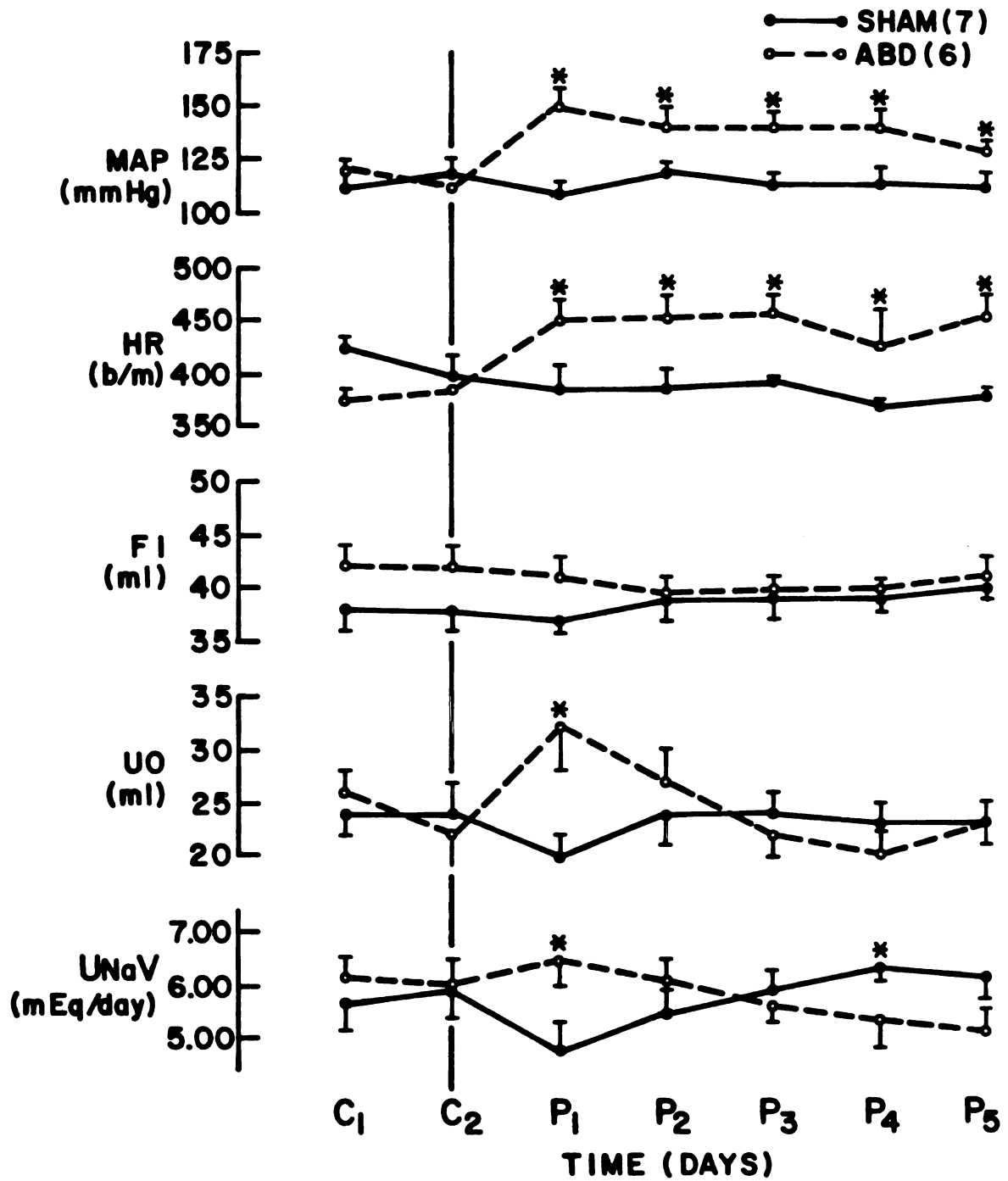


Figure 12

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creased on the first day after ABD (Figure 12), and normal thereafter.

Study 10-II (Figure 13) produced results similar to those of study 10-I. In addition, plasma and extracellular fluid volumes did not change five days after ABD in fluid replete rats (Figure 13).

These studies indicate that controlled fluid intake following ABD does not alter the cardiovascular response to ABD. It is also concluded that the ABD procedure results in decreased body fluid volumes only if the animals are allowed to decrease their fluid intake.

Experiment 4. Effects of Total Autonomic Blockade in Acute ABD Hypertension

This experiment used pharmacological autonomic blockade to assess the role of the sympathetic nervous system in acute ABD hypertension.

Blood pressure was significantly elevated one day after ABD, but not sham operation (Table 4). Atropine and propranolol injections lowered MAP slightly in ABD rats, but not to normotensive levels. Complete blockade following phentolamine normalized blood pressure in ABD rats.

Atropine increased HR to a greater degree in sham-operated than in ABD rats (ABD: 17 ± 8 beats/min (10) vs. Sham: 67 ± 8 beats/min (5), $p < 0.05$, t-test). Propranolol decreased HR to a greater degree in ABD than in sham-operated rats (ABD: -85 ± 5 beats/min (10) vs. Sham: -62 ± 8 beats/min (5), $p < 0.05$, t-test). Phentolamine treatment affected HR equally in ABD and sham-operated rats (Table 4).

Figure 14 demonstrates that the magnitude of the fall in MAP following autonomic blockade in ABD but not sham-operated rats was significantly correlated with the resting blood pressure.

Figure 13. Cardiovascular and fluid volume changes in rats on controlled fluid intake subjected to ABD or sham operation. PV = plasma volume; ECFV = extracellular fluid volume; ISF = interstitial fluid volume. Other symbols as in Figure 12.

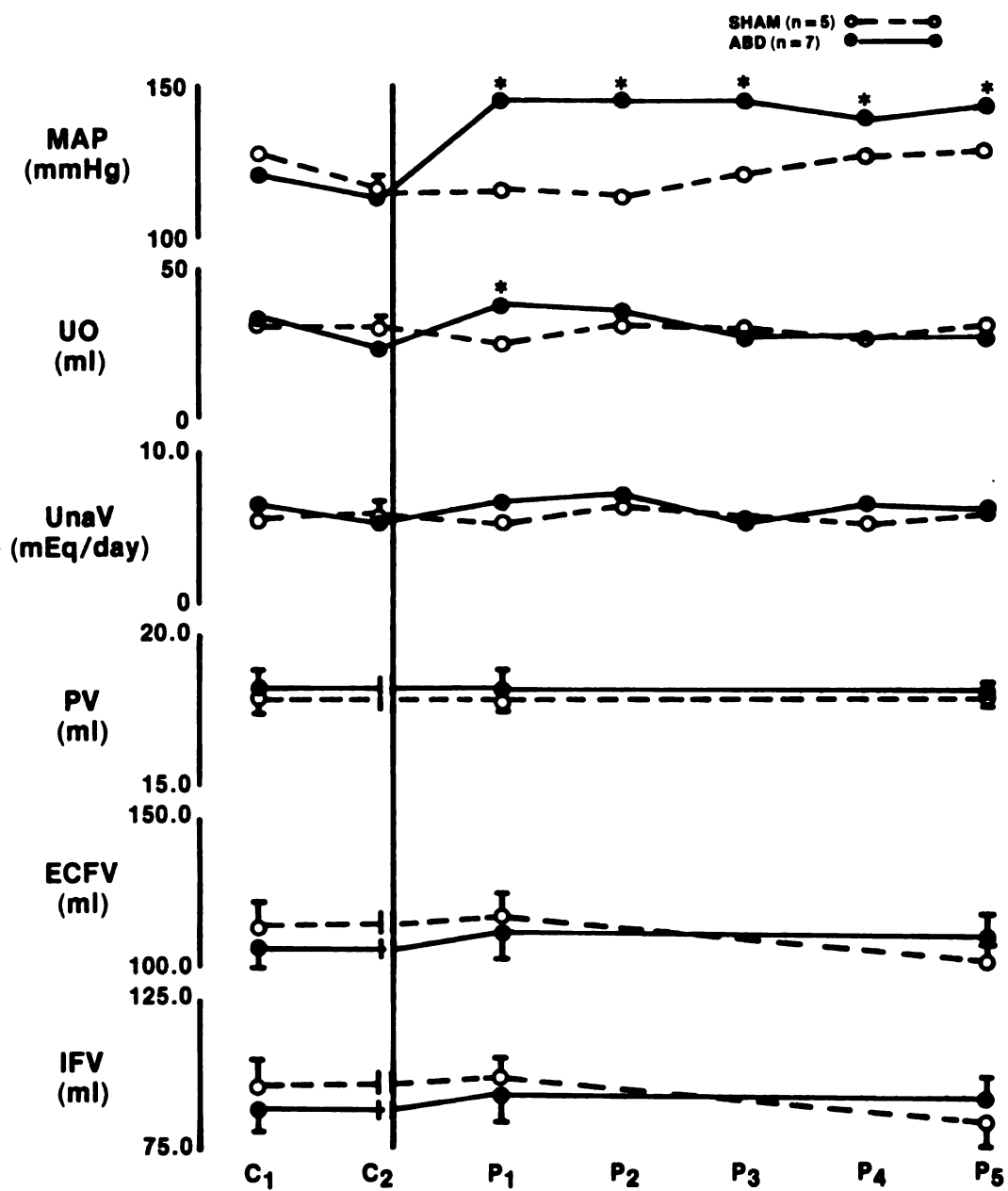


Figure 13

TABLE 4
Total Autonomic Blockade in Acute ABD

		DAY 1			
		DAY 0		DAY 1	
		Control ₀	Control ₁	Atropine	Phentolamine
Sham (N=5)					
MAP	126± 3 [‡]	126± 2	125± 2	121± 4	114± 4
HR	420±16	408±13	475±11*	413± 6	396± 5
ABD (N=10)					
MAP	125± 4	157± 4 [†]	150± 3	142± 3*	106± 4
HR	419± 9	488±17	505±15*	420±16*	402±15*

*Significantly different from control₁ value (p<0.05, paired t-test).

[†]Significantly different from day 0 value (p<0.05, paired t-test).

[‡]All values are mean ± S.E.M.

Figure 14. Correlation between resting arterial pressure and the fall in arterial pressure after total autonomic blockade ($\Delta BP_{\text{autoblock}}$) in rats 1 day after ABD or sham operation. The correlation was significant ($p < 0.05$) in ABD but not sham-operated animals. The regression (slope) of $\Delta BP_{\text{autoblock}}$ on resting arterial pressure was significant ($p < 0.05$, ANOVA) in ABD rats, but not significantly different from zero in sham-operated rats. Points represent individual values. Solid line represents regression line for sham-operated rats. Dashed line represents regression line for ABD rats. Sham-operated rats. ABD rats.

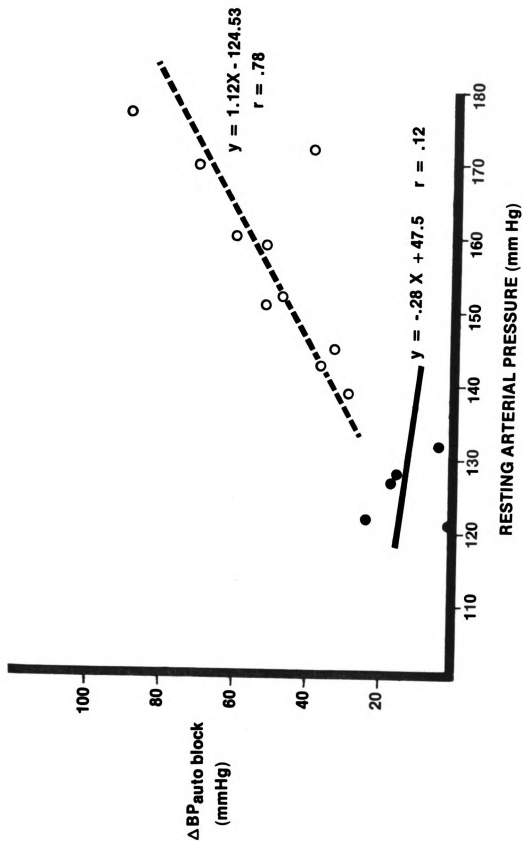


Figure 14

Experiment 19. TAB in Acute Hypertension of Non-Neurogenic Origin

This experiment was designed to assess the effect of TAB on HR and MAP in acute hypertension produced by angiotensin, a predominantly non-neurogenically mediated form of hypertension.

Total autonomic blockade did not change blood pressure in rats with acute angiotensin-induced hypertension to a greater extent than in rats with a sham ABD operation (compare Tables 4 and 5). The magnitude of the fall in MAP following autonomic blockade in this acute hypertension was not significantly correlated ($r = -0.346$, $df = 8$, $p > 0.05$) with the resting MAP.

This experiment indicates that the effect of TAB on ABD rats (Experiment 4) was not a non-specific consequence of initial conditions in ABD rats.

Experiment 5. Prevention of ABD Hypertension by Inactivation of the Sympathetic Nervous System

This experiment examined the roles of the orthosympathetic nervous system and adrenomedullary catecholamines in the genesis of acute ABD-induced hypertension.

Figure 15 summarizes the results of this experiment. Blood pressure increased an average of 21 mmHg after ABD in control rats. Prior adrenalectomy, adrenal demedullectomy or guanethidine treatment did not prevent acute ABD-induced hypertension. Only prior adrenal demedullectomy combined with guanethidine pretreatment prevented ABD-induced hypertension. This experiment shows that the orthosympathetic nervous system and adrenomedullary catecholamines play a crucial role in the development of acute hypertension following ABD.

TABLE 5

Total Autonomic Blockade in Acute
Angiotensin-induced Hypertension

	C ¹	AII ²	ATR ³	PRO ⁴	PHE ⁵	REC ⁶
MAP	127 [†]	158	158	157	153	113
HR	421 [†]	361	428 [†]	397 [†]	346	351

Values are means values from 10 rats. Standard errors: MAP = 3, HR = 7. [†]Value significantly different from AII value ($p < 0.05$, Tukey's test). ¹Control, ²angiotensin II infusion, ³atropine treatment, ⁴propranolol treatment, ⁵phentolamine treatment, ⁶value obtained after cessation of AII infusion. Details of methods are described in text.

Figure 15. Effect of various pretreatments on ABD-induced hypertension. Blocks represent mean values. Bars are errors for paired comparisons. Δ increase in blood pressure after ABD. NONE = sham adrenalectomy. Abbreviations explained in text. *Significant difference between values before and after ABD ($p < 0.05$, paired t-test).

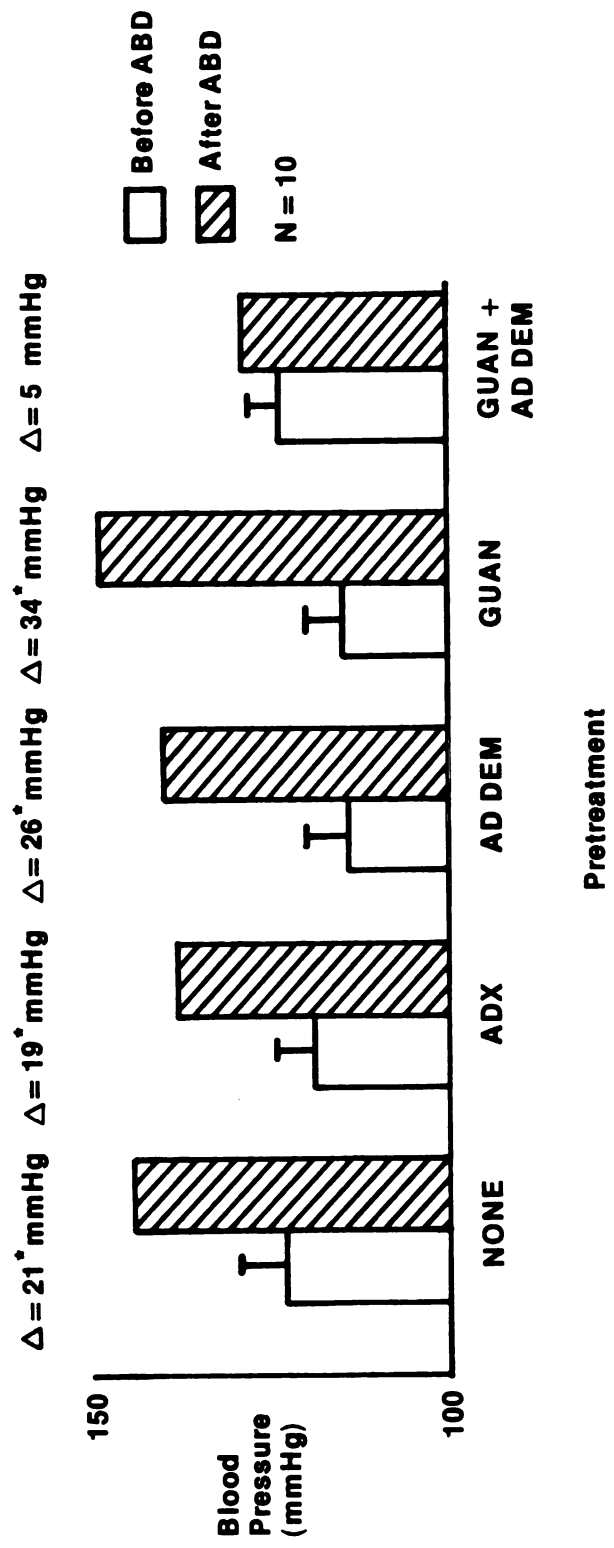


Figure 15

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Experiment 6. Hemodynamic Basis of Acute ABD Hypertension

This experiment was designed to examine whole body hemodynamic changes in conscious rats in acute ABD-induced hypertension.

Figure 16 illustrates that blood pressure was significantly increased for 4-5 days following ABD. Cardiac output (Figure 17) did not change significantly at any time after ABD, although output tended to be reduced over the first 48 hours after deafferentation. Total peripheral resistance (Figure 18) was significantly elevated 24 hours after ABD, but declined slightly by the end of the study. Heart rate (not shown) was significantly elevated at all times after ABD, while stroke volume (not shown) was not significantly changed after ABD. Blood pressure, cardiac output, total peripheral resistance (Figures 16-18), heart rate and stroke volume (not shown) were unaffected by sham operation.

Total autonomic blockade reduced blood pressure in 5 control rats ($13 \pm 4\%$, $p < 0.05$, lsd test). The reduction in blood pressure could be attributed to a reduction of total peripheral resistance ($6 \pm 7\%$, $p > 0.05$) or cardiac output ($5 \pm 7\%$, $p > 0.05$). One and five days after ABD (3 rats) the reduction in blood pressure ($41 \pm 3\%$, $p < 0.05$, lsd test) following complete blockade could be attributed to a decrease in total peripheral resistance ($38 \pm 7\%$, $p < 0.05$, lsd test), and cardiac output did not change significantly ($-1 \pm 8\%$, $p > 0.05$).

Propranolol (in the presence of atropine) decreased blood pressure significantly ($-8 \pm 2\%$, $p < 0.05$, lsd) one day after ABD (3 rats) but not in control rats (5 animals). The hemodynamic basis of this

Figure 16. Blood pressure before and after ABD or sham operation. Points represent mean values. Bars are standard errors for each group. Vertical dashed line indicates when sham or ABD was performed. Post-op indicates value measured after recovery from anesthesia (see text). +Value significantly different from same group day 0 value ($p < 0.05$, least significant difference test).

Figure 17. Cardiac output before and after ABD or sham operation. Symbols as in Figure 16.

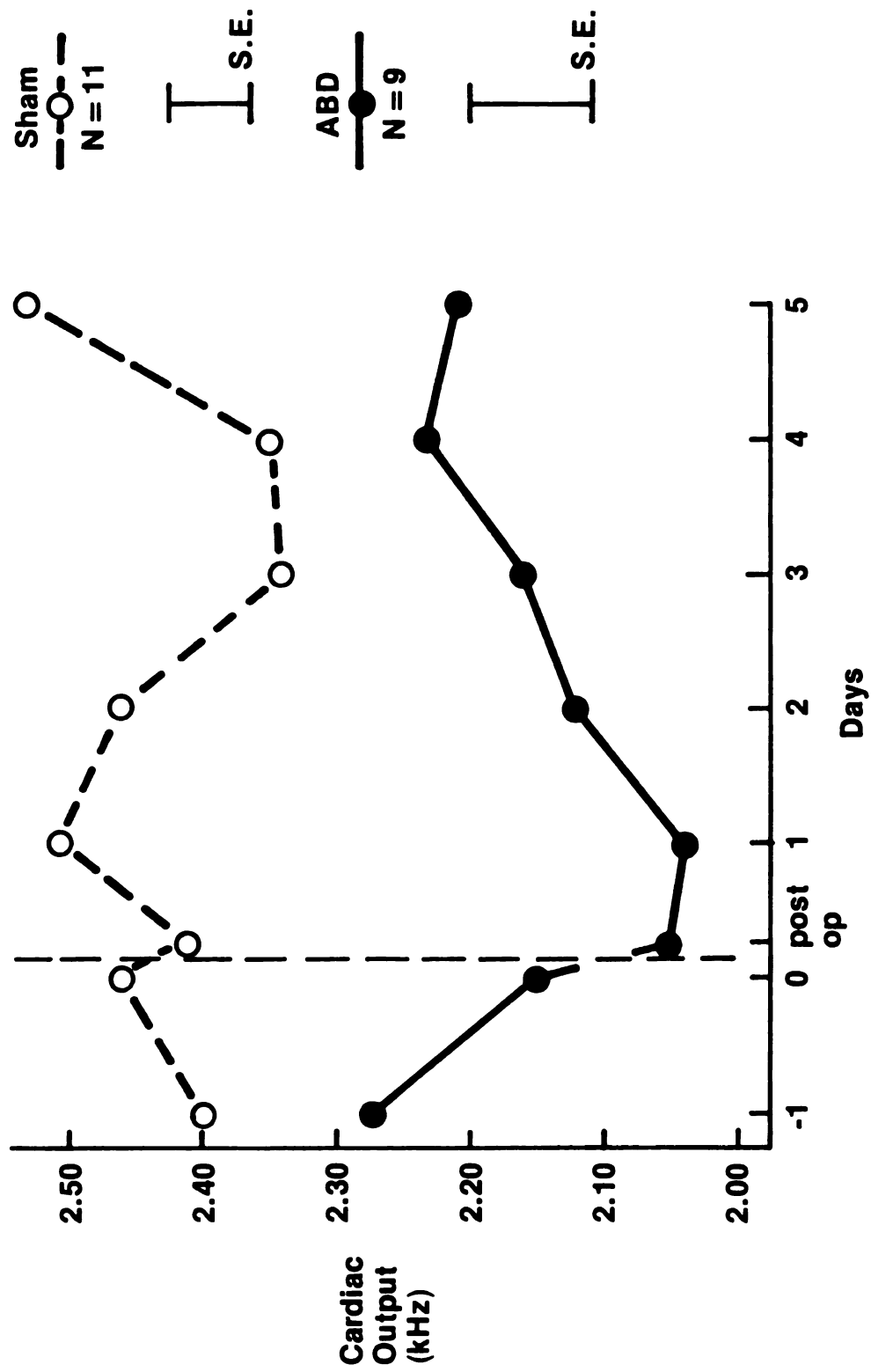


Figure 17

Figure 18. Total peripheral resistance before and after ABD or sham operation. Symbols as in Figure 16.

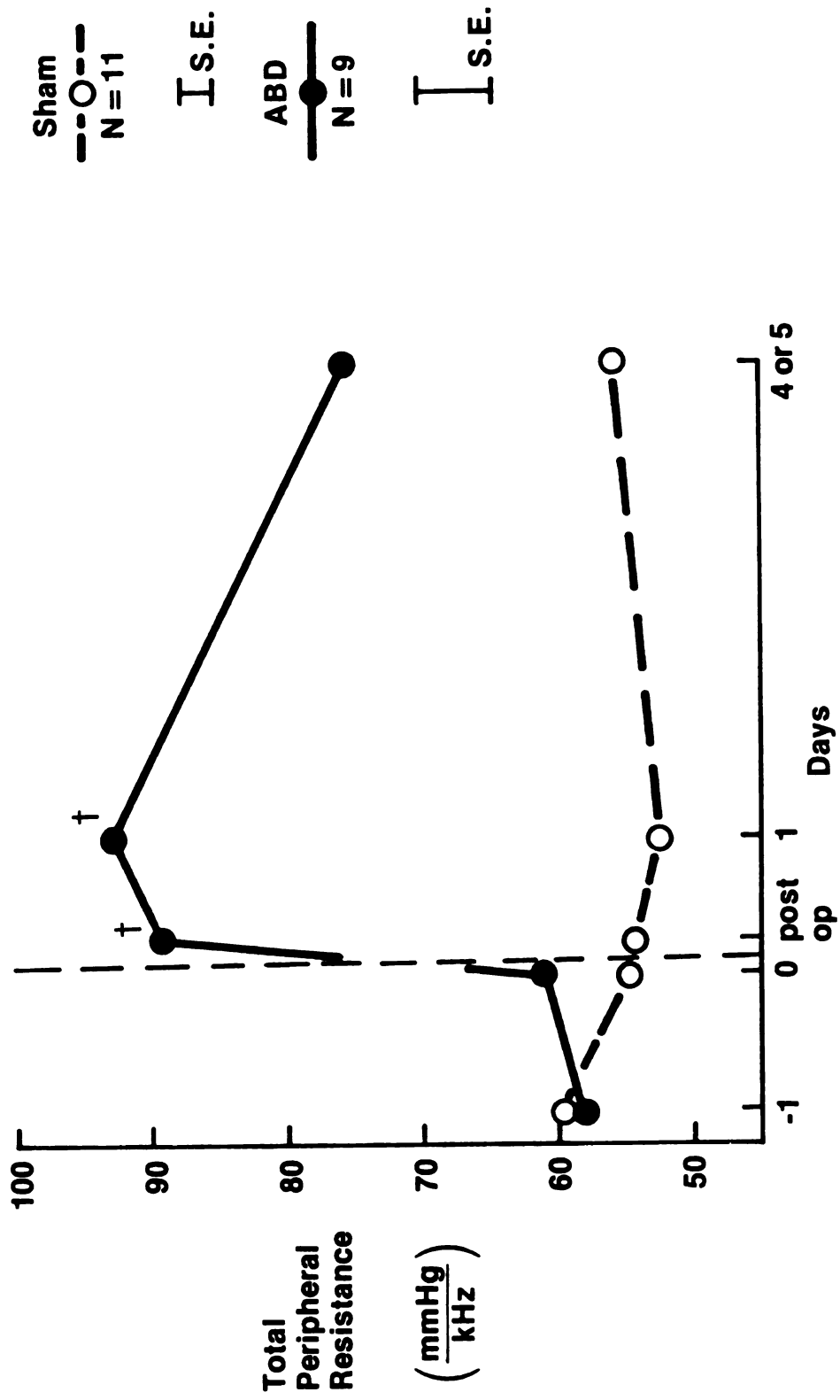


Figure 18

hypotensive effect was a decrease in total peripheral resistance ($4\pm 7\%$) or cardiac output ($3\pm 7\%$).

This experiment demonstrates that acute hypertension following ABD is exclusively mediated by an increase in resistance.

Experiment 20. Hemodynamic Effects of Anemia

This experiment was designed to show that Doppler flowmetry could be used to detect day-to-day changes in cardiac output in the conscious rat.

Cardiac output was significantly elevated on all days, excepting the first, following the production of anemia by blood withdrawal (Figure 19). Blood pressure tended to decrease on the first day after the production of anemia, but did not change significantly at any time. Total peripheral resistance decreased and stroke volume increased significantly on all days after blood removal (Figure 19). The bottom panel of Figure 19 illustrates that the blood removal successfully reduced hematocrit. Heart rate (not shown) varied significantly between the two control days, but post-anemia values were not different from the value on the second control day.

This experiment shows that Doppler flowmetry can detect day-to-day changes in cardiac output.

Experiment 7. The Role of the Renal Nerves in Acute ABD Hypertension

This experiment was designed to examine the role of the renal nerves in acute hypertension following ABD.

The results of study 7-I (Figure 20) and study 7-II (Figure 21) show that prior renal denervation did not affect the development of

Figure 19. Hemodynamics of anemia. Points represent mean values. Bars are standard errors for each group. Solid vertical line indicates when blood removal occurred. †Value significantly different from day -1 control value ($p < 0.05$, least significant difference test).

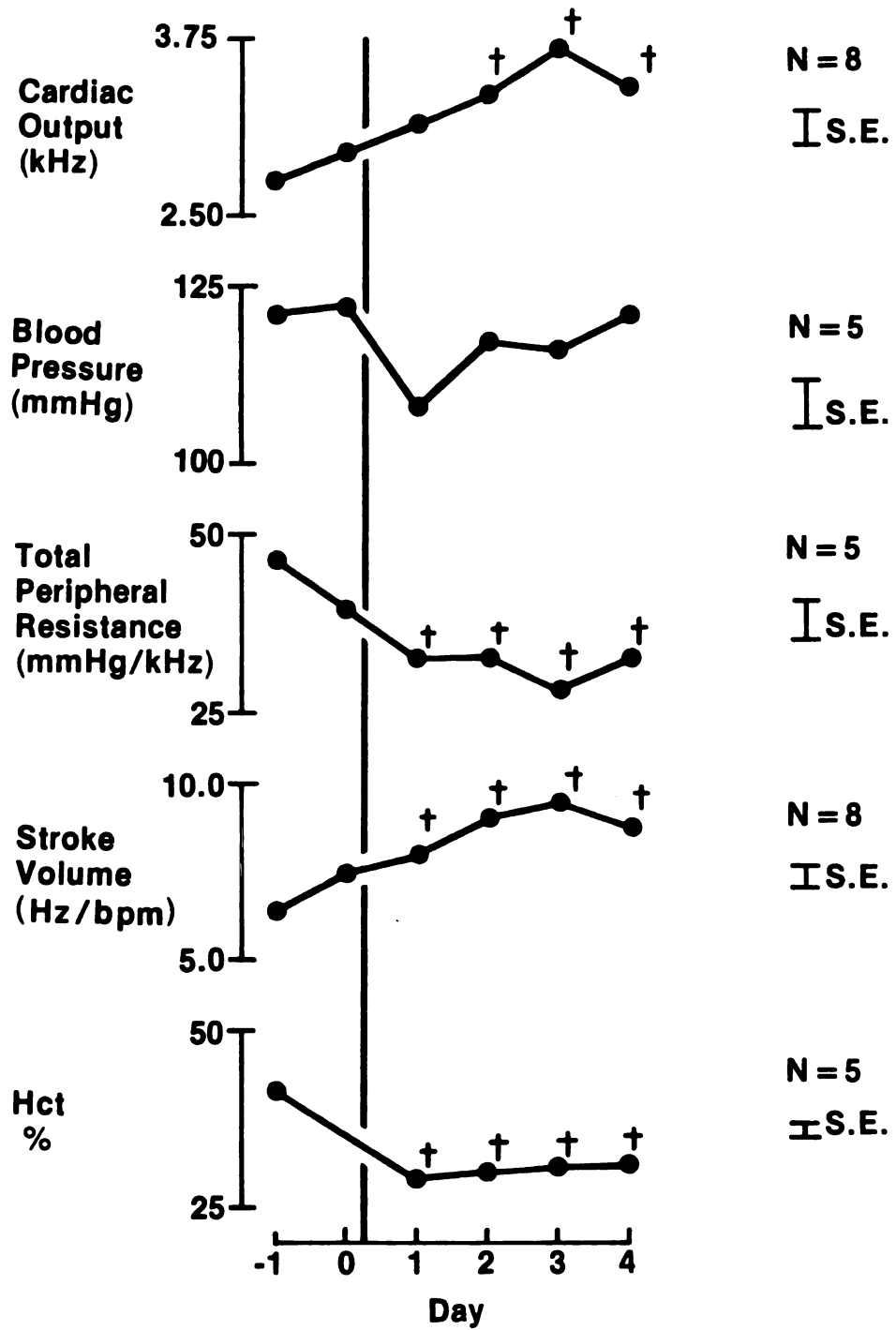


Figure 19

Figure 20. Cardiovascular, fluid and electrolyte handling changes in rats before and after ABD in renal denervated and sham-operated rats. Solid vertical line indicates day of ABD. WI = water intake. Other abbreviations explained in text. Bars represent standard errors for each group.

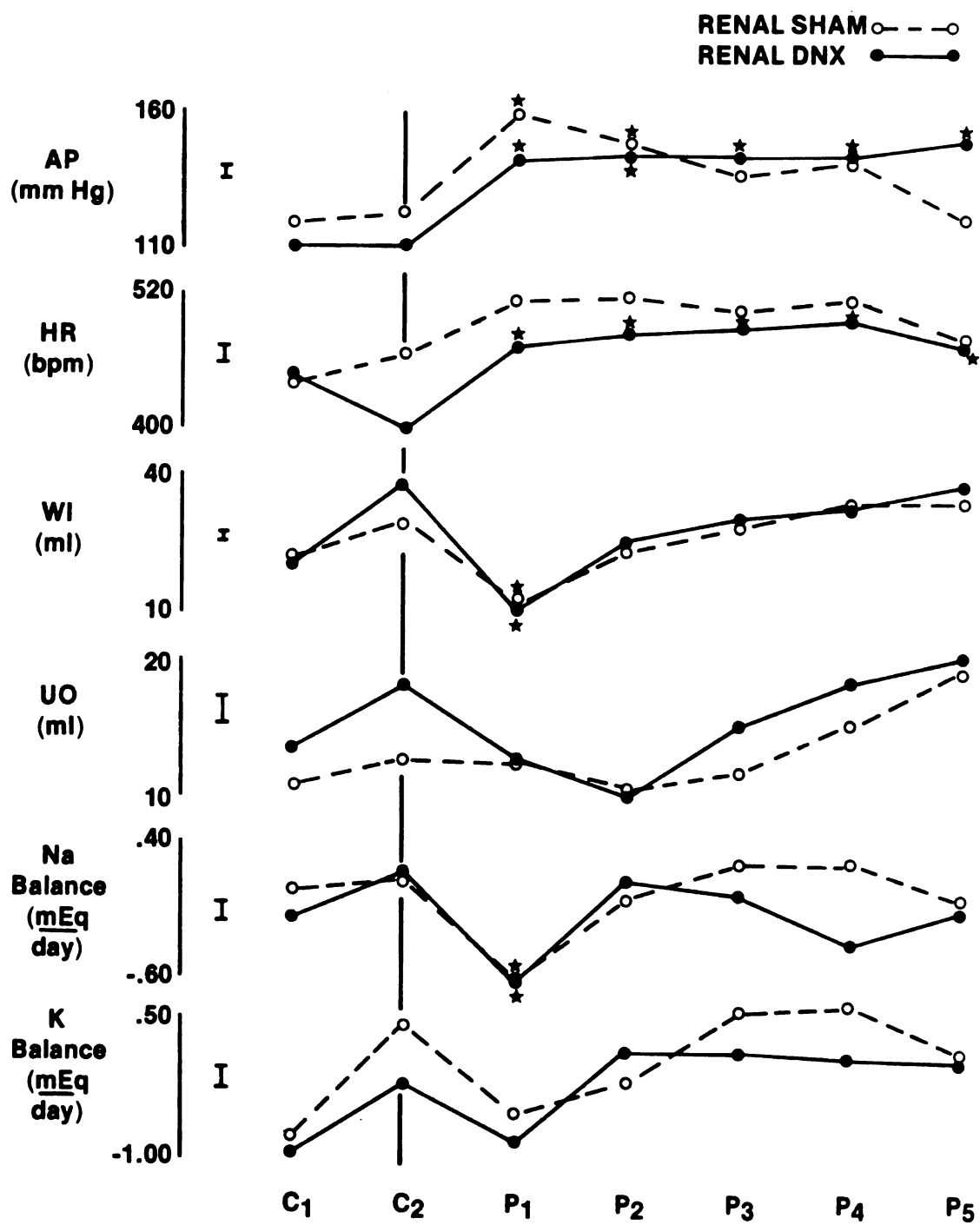


Figure 20

Figure 21. Effects of ABD on fluid replete renal denervated and sham-operated rats. Stars and crosses indicate significant difference between that value and within group C_2 value ($p < 0.05$, Tukey's test). Other symbols as in Figure 12.

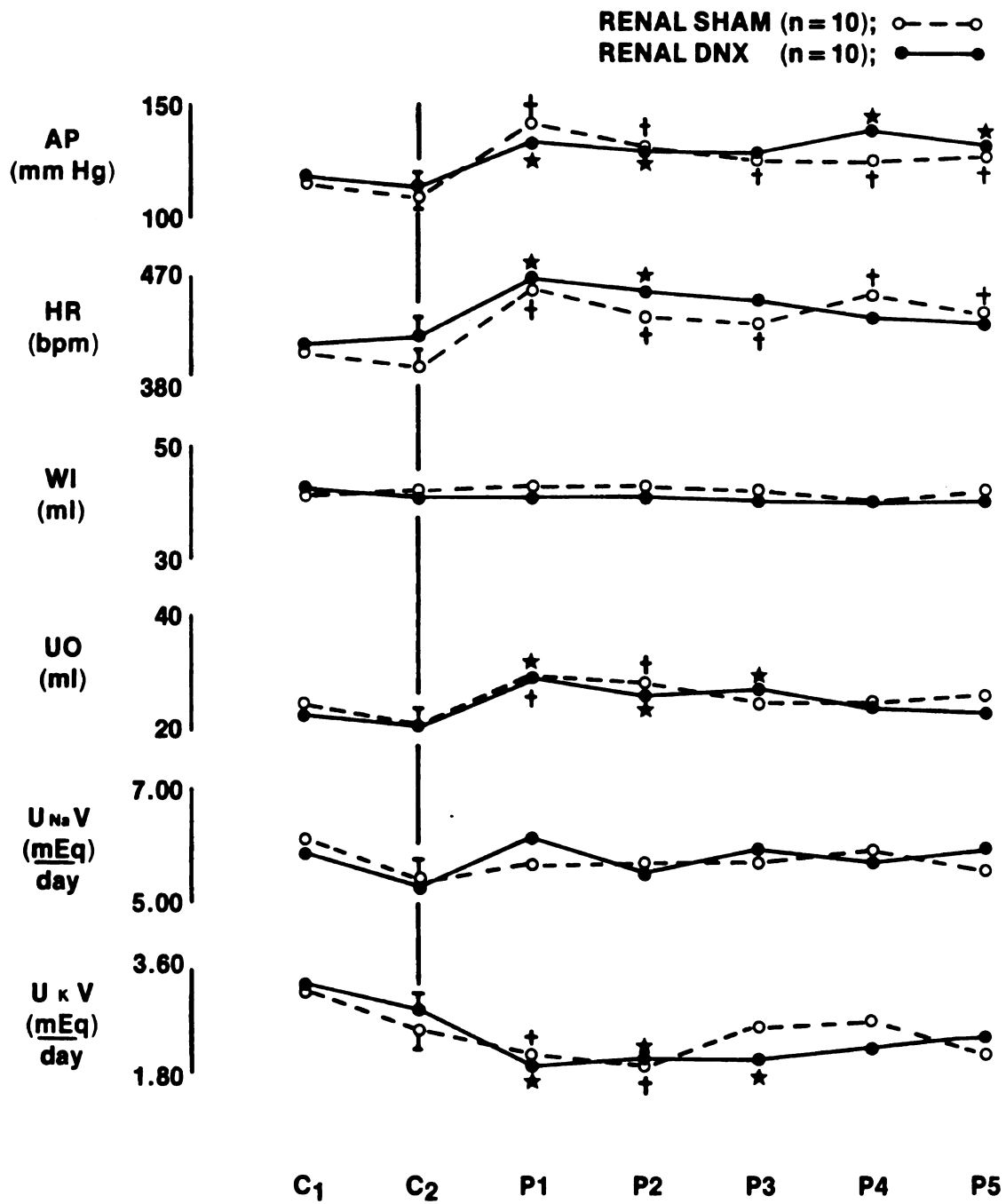


Figure 21

ABD-induced hypertension in both fluid replete (study 7-II) or fluid depleted (study 7-I) rats. In addition, renal denervation did not affect the renal excretion of fluid and electrolytes (Figures 20 and 21),

Experiment 8. Role of the Adrenal Glands in Acute ABD Hypertension

This experiment examined the role of the adrenal glands in the development of acute ABD-induced hypertension in fluid replete rats.

The inability to change levels of adrenocortical hormones did not affect the genesis of ABD-induced hypertension (Figure 22). While MAP did not increase as much as usual following ABD in the adrenalectomized rats, MAP actually decreased in adrenalectomized rats after sham ABD operation (Figure 22).

ABD rats with constant levels of adrenocortical hormones did not show major differences in renal fluid and electrolyte handling when compared to sham-operated rats also with constant levels of adrenocortical hormones.

This experiment shows that the inability to regulate adrenocortical hormones does not affect the hypertensive response to ABD.

Experiment 9. The Role of ADH in ABD Hypertension

This experiment examined the role of ADH in the acute cardiovascular and renal fluid handling responses after ABD.

Brattleboro rats developed hypertension of somewhat smaller magnitude and duration than did Long-Evans control rats (Figure 23). In addition, Long-Evans but not Brattleboro rats showed a brief period of increased urine output and urinary sodium excretion after ABD (Figure 23).

Figure 22. Effects of ABD and sham operation on fluid replete, adrenalectomized rats. Symbols as in Figure 21.

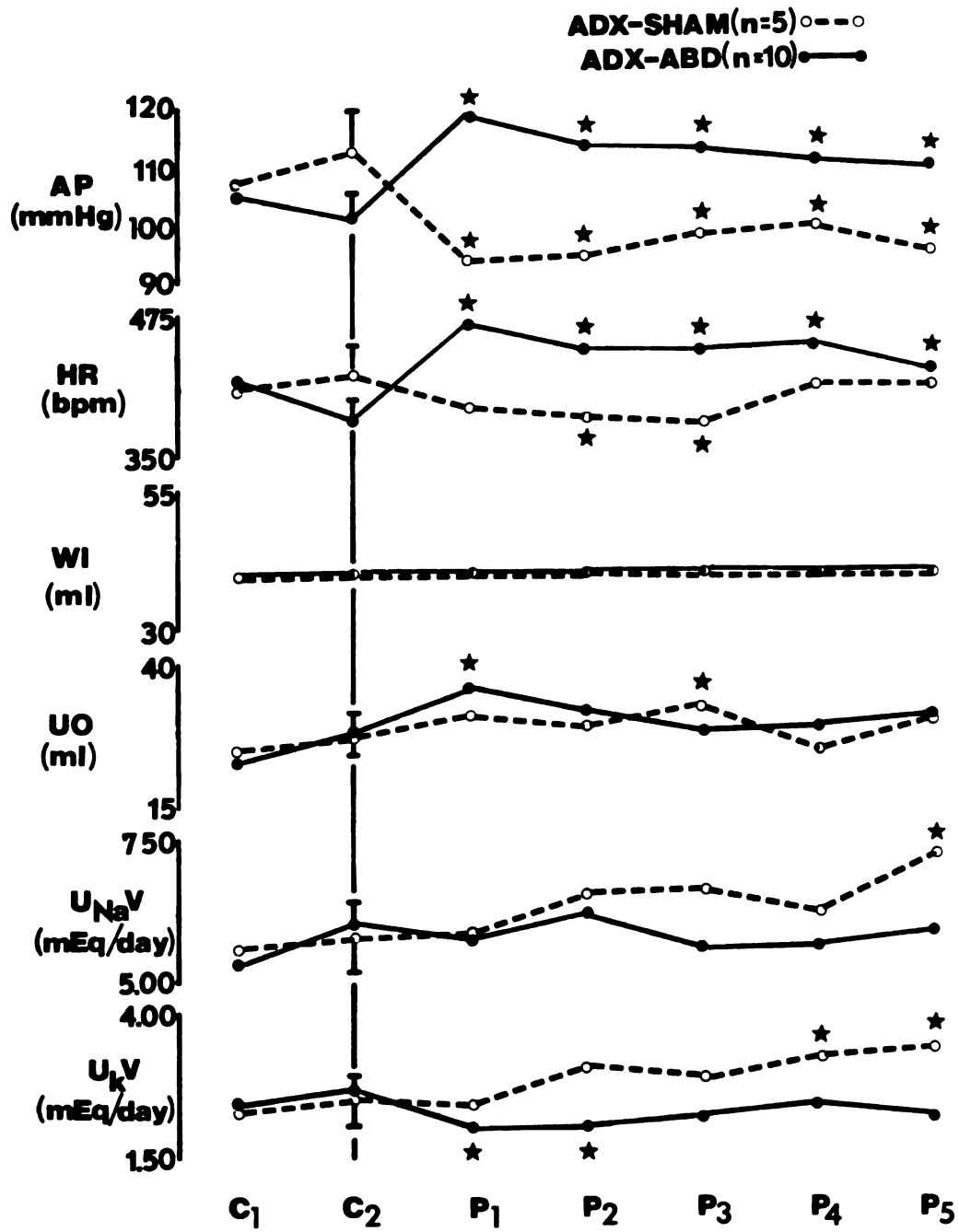


Figure 22

Figure 23. Effects of ABD on fluid replete rats with and without the ability to regulate endogenous ADH levels. Symbols as in Figure 21.

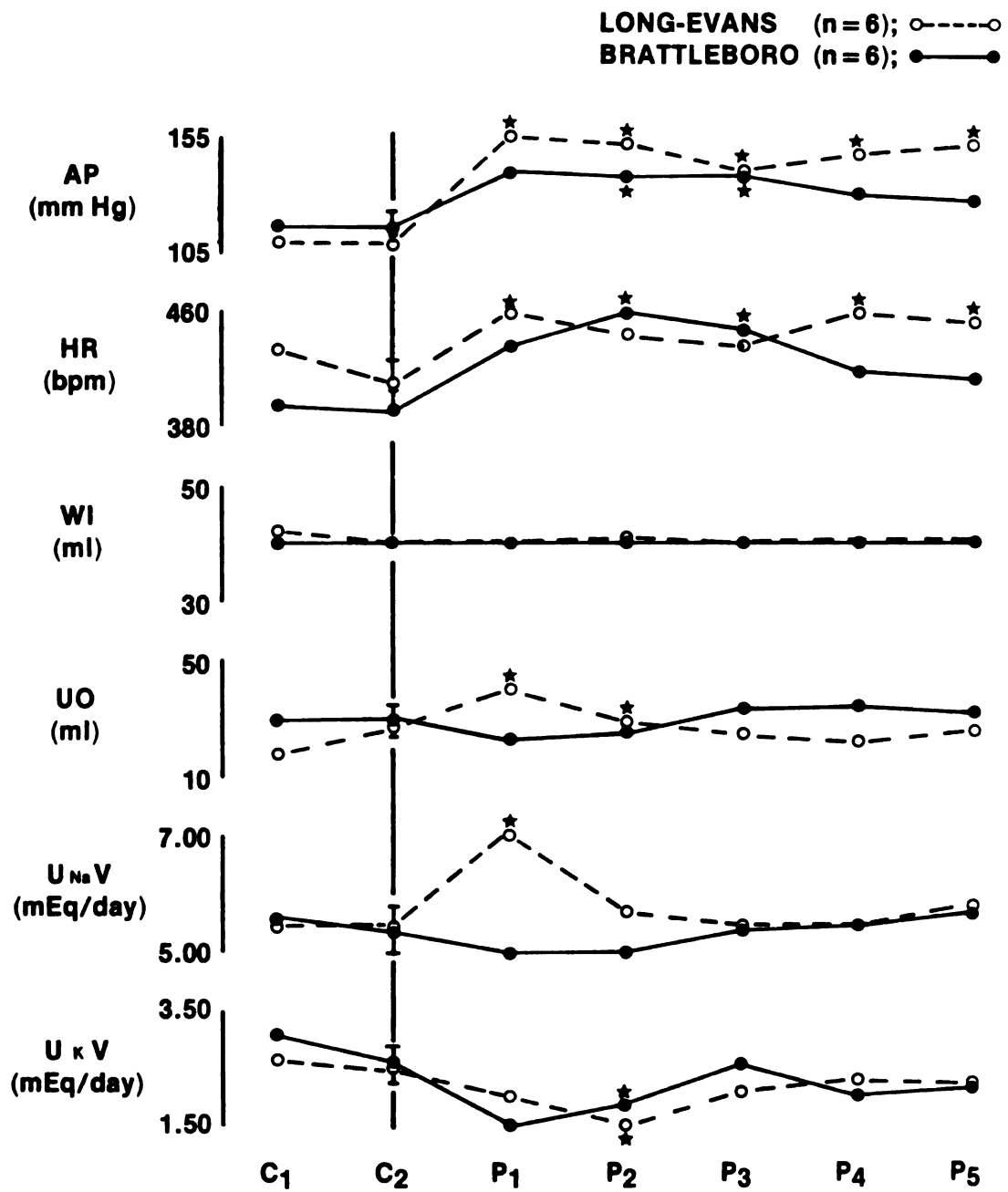


Figure 23

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These data suggest that ADH may play a role in the cardiovascular and renal fluid handling responses to ABD.

Chronic ABD Hypertension

Experiment 11. Ventricular Hypertrophy in ABD Rats

This experiment was designed to determine if ventricular hypertrophy was associated with chronic ABD-induced hypertension.

Two months following operation, MAP was higher in ABD than sham-operated rats (ABD: 138 ± 4 (8), Sham: 118 ± 2 (6) mmHg, $p < 0.05$, t-test). The ABD rats showed a mild, but significant ventricular hypertrophy (Table 6).

Experiment 12. Cardiovascular Control and Fluid Volume Characteristics of Chronic ABD Rats

This experiment was designed to examine 1) cardiovascular and body fluid characteristics, and 2) the role of the autonomic nervous system in the maintenance of chronic hypertension following ABD.

Study 12-I. Table 7 illustrates arterial pressure and variability in a group of rats 1 month following ABD or sham operation. Systolic, diastolic and MAP were significantly greater in ABD rats than in control animals. The variability of these pressure readings over a one hour period (standard deviation), however, was not significantly different between the two groups.

Study 12-II. Mean arterial pressure and heart rates of another group of 15 sham-operated and 15 ABD rats are shown in Figure 24. Average mean arterial pressure in the ABD rats (134 ± 4 mmHg) was significantly higher than that of sham-operated rats (120 ± 2 mmHg).

TABLE 6

Ventricular Hypertrophy Two Months After ABD

	N	Ventricle Weight (mg)
		Body Weight (grams)
ABD	8	2.87±0.058 ^{*1}
Sham	6	2.50±0.061

*Significantly different from sham ($p < 0.05$, test).

¹All data are mean $\pm$ S.E.M.

TABLE 7.

Blood Pressure Level and Blood Pressure Variability in
Rats 1 Month Following Aortic Baroreceptor Deafferentation

Animals (n=8)	Systolic	Mean	Diastolic
AP (mmHg)			
Sham-operated	163±3	129±3	112±3
ABD	178±5*	145±3*	129±3*
SD of AP			
Sham-operated	8±1	7±1	6±1
ABD	9±1	9±1	8±1

SD = standard deviation; AP = arterial pressure.

*Difference significant at $p < 0.05$ (t-test).

Figure 24. Mean arterial pressures and heart rates in conscious rats 1 month following ABD or sham operation. Points represent individual values. Points with bars indicate the group mean $\pm$ S.E.M. *Significant difference ($p < 0.05$, t-test) between groups.

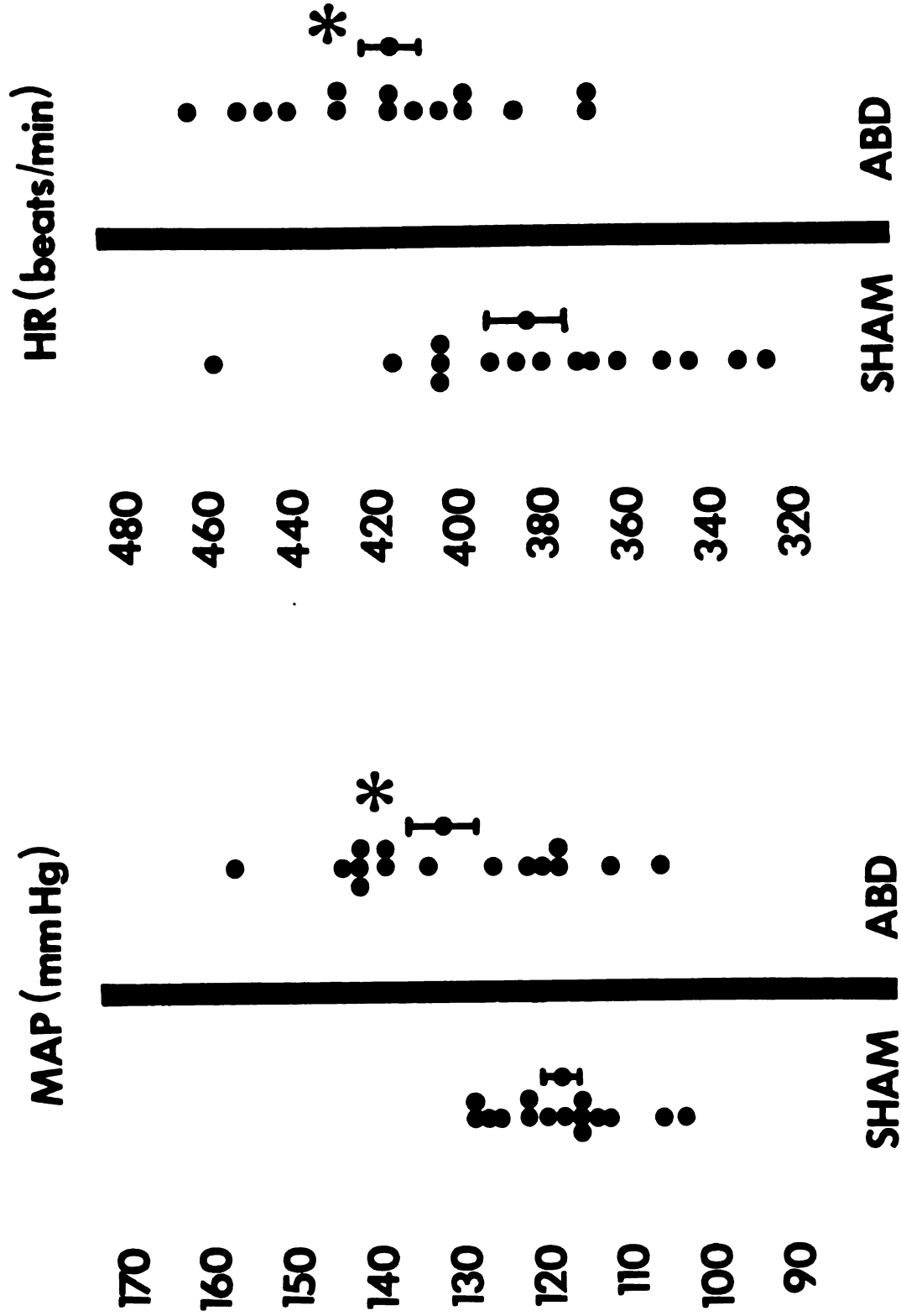


Figure 24

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Although all animals with ABD did not have arterial pressures outside the range of normal rats, note that eight of 15 rats with ABD had pressures greater than the highest values seen in control rats. Average heart rate in ABD rats (419 ± 7 beats/min) was also significantly higher than in the sham-operated rats (384 ± 9 beats/min). Again note, however, that some rats with ABD had heart rates within the normal range. There was no significant correlation between heart rate and arterial pressure in either group of rats. Figure 25 shows the effect of total autonomic blockade on arterial pressure in this group of rats. Total cardiac autonomic blockade (atropine + propranolol) did not significantly lower arterial pressure in either group of rats. Following the administration of all three autonomic blockers, MAP was the same in ABD (105 ± 3 mmHg) and sham-operated rats (107 ± 3 mmHg). The decrease in arterial pressure during total autonomic blockade was significantly greater in ABD rats (29 ± 3 mmHg, 22%) than in sham-operated controls (13 ± 2 mmHg, 11%). The decrease in blood pressure caused by total blockade was significantly correlated with resting MAP in the ABD ($r = 0.56$, $df = 13$, $p < 0.05$), but not sham-operated rats ($r = 0.04$, $df = 13$, NS).

Figure 26 shows that atropine treatment increased HR to the same level in ABD (470 ± 12 beats/min) and sham-operated rats ($471 \pm$ beats/min). Further treatment with propranolol and phentolamine decreased HR identically in the two groups of animals.

Plasma and extracellular fluid volumes of sham-operated and ABD rats 1 month following operation are shown in Figure 27. Plasma volume in ABD rats (3.02 ± 0.28 ml/100 g) was significantly less than

Figure 25. Changes in mean arterial pressure during consecutive intravenous administration of atropine (ATR), propranolol (PROP), and phentolamine (PHENT) in conscious rats 1 month following ABD or sham operation. C = control measurements. Points represent mean $\pm$ S.E.M. *Value significantly different from corresponding value for sham-operated rats ($p < 0.05$, Tukey's test).

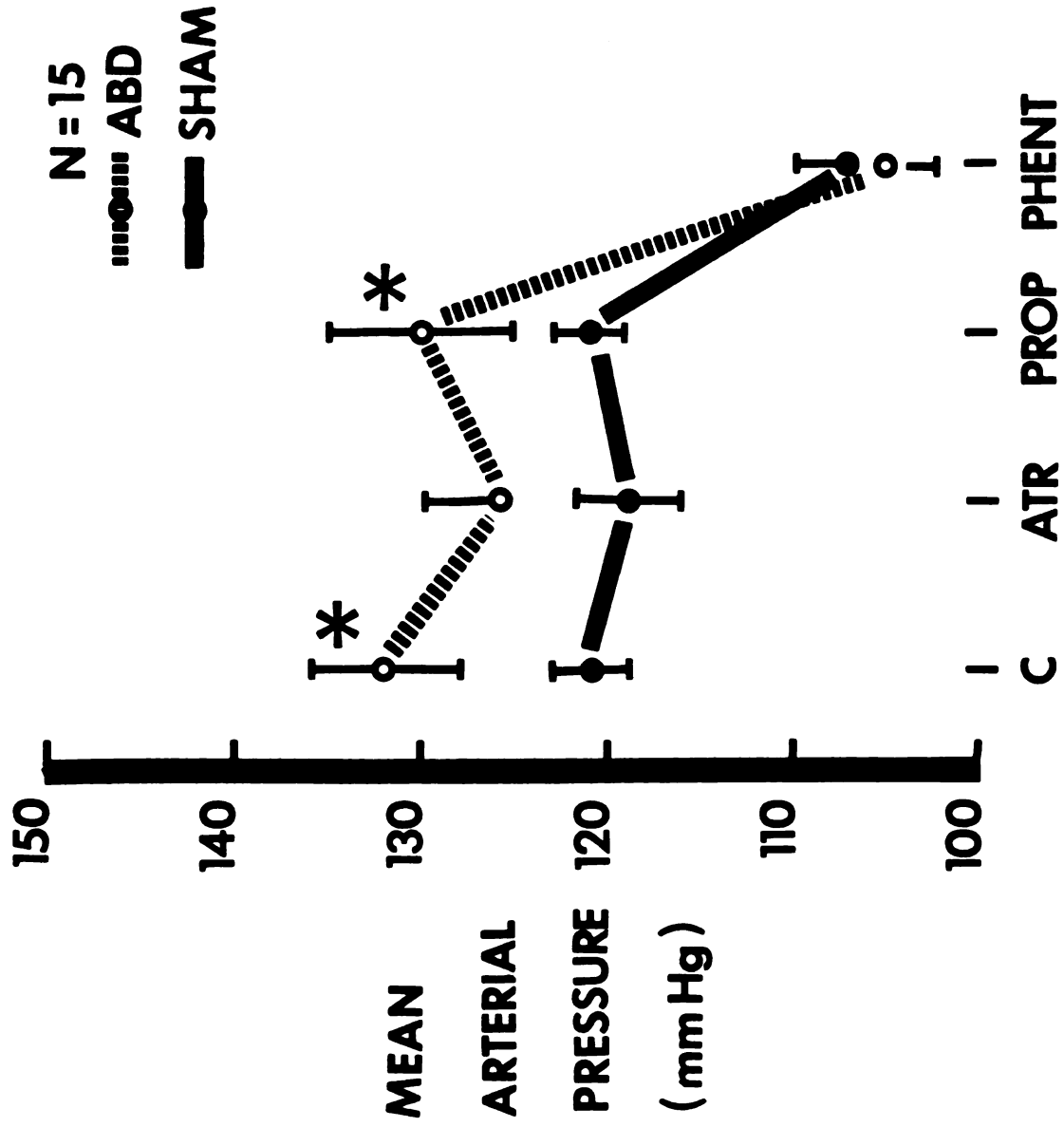


Figure 25

Figure 26. Changes in heart rate during total autonomic blockade. Symbols as in Figure 25.

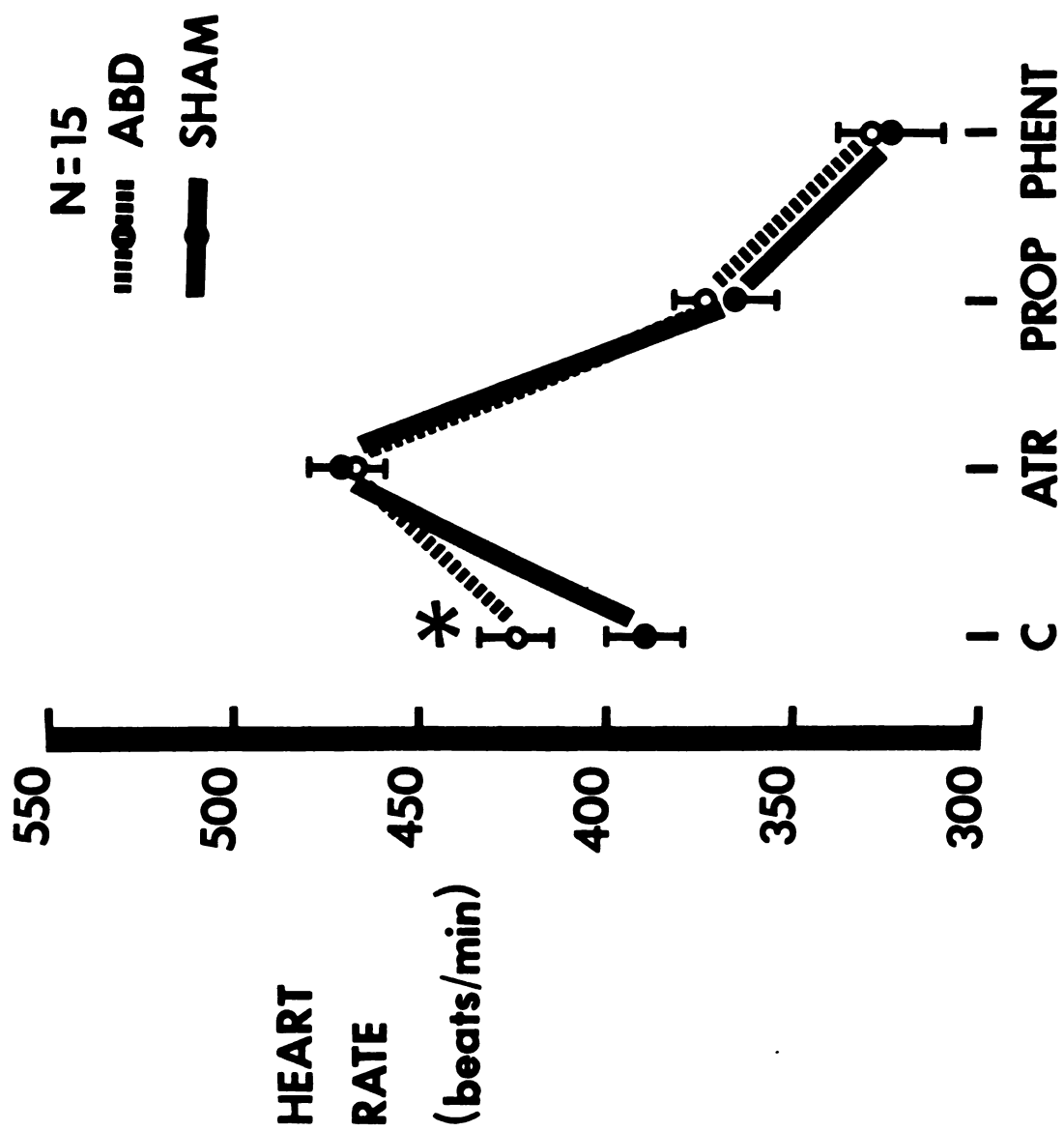


Figure 26

Figure 27. Plasma and extracellular fluid volume in conscious rats 1 month following ABD or sham operation. Symbols as in Figure 24.

Figure 27

that of sham-operated rats (3.91 ± 0.30 ml/100 g), but extracellular fluid volume was similar in the two groups (Sham: 27.0 ± 2.4 ml/100 g; ABD: 25.9 ± 2.0 ml/100 g). Figure 28 illustrates the correlation between resting MAP and plasma volume in these rats. MAP exhibited a significant ($p < 0.01$) positive correlation ($r = 0.74$) with plasma volume in ABD rats, but only a slight positive correlation ($r = 0.33$) in control rats. The slope of the regression of MAP on PV was significantly ($p < 0.05$) greater in ABD rats than in sham-operated rats. The individual regression of MAP on PV was significant in ABD rats ($p < 0.01$) but was not different from zero in sham-operated rats.

Study 12-III. Figure 29 demonstrates the marked attenuation of overall baroreflex regulation of heart rate in rats with ABD. The gain of the reflex was significantly lower in ABD rats (0.40 ± 0.06 msec/mmHg) than in sham-operated rats (1.50 ± 0.10 msec/mmHg), and the overall baroreflex (HP [saturation pressure] - HP [threshold pressure]) was also significantly reduced in ABD rats (35 ± 3 msec) compared to that of controls (86 ± 4 msec). Threshold pressure, saturation pressure, and pressure at maximum sensitivity (BP_{50}) were similar in the two groups of rats. Resting MAP (136 ± 5 vs. 125 ± 2 mmHg) and HR (426 ± 12 vs. 382 ± 7 beats/min) were both significantly higher in the ABD rats than in the sham-operated rats. There was not a significant correlation, however, between the baroreflex gain and the resting MAP in ABD ($r = 0.21$, $df = 6$) rats.

Figure 28. Correlation between plasma volume (PV) and mean arterial pressure (MAP) in conscious rats 1 month following ABD or sham operation. The correlation was significant ($p < 0.01$) in ABD rats but not in the sham-operated animals. The regression (slope) of MAP on PV was highly significant ($p < 0.01$) in ABD rats, but was not significantly different ($p > 0.05$) from zero in sham-operated rats. In addition, analysis of covariance indicated a significant difference ($p < 0.05$) between the slopes of the regression lines from ABD and sham-operated rats.

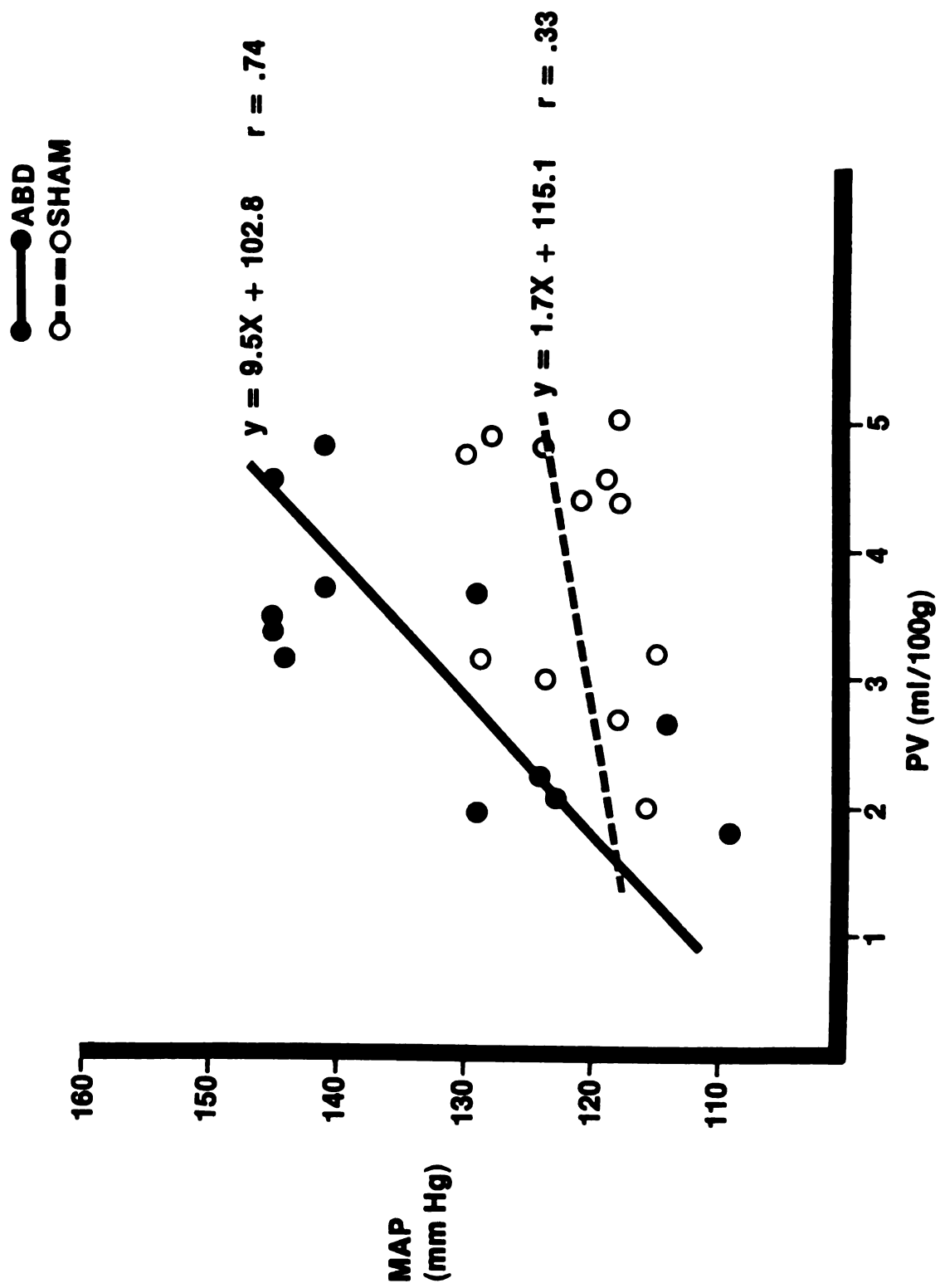


Figure 28

Figure 29. Baroreflex effects on heart rate in conscious rats 1 month following ABD (open circles, n=8) or sham operation (black circles, n=11). Triangles indicate average resting values for mean arterial pressure and heart period. Bars indicate S.E.M.

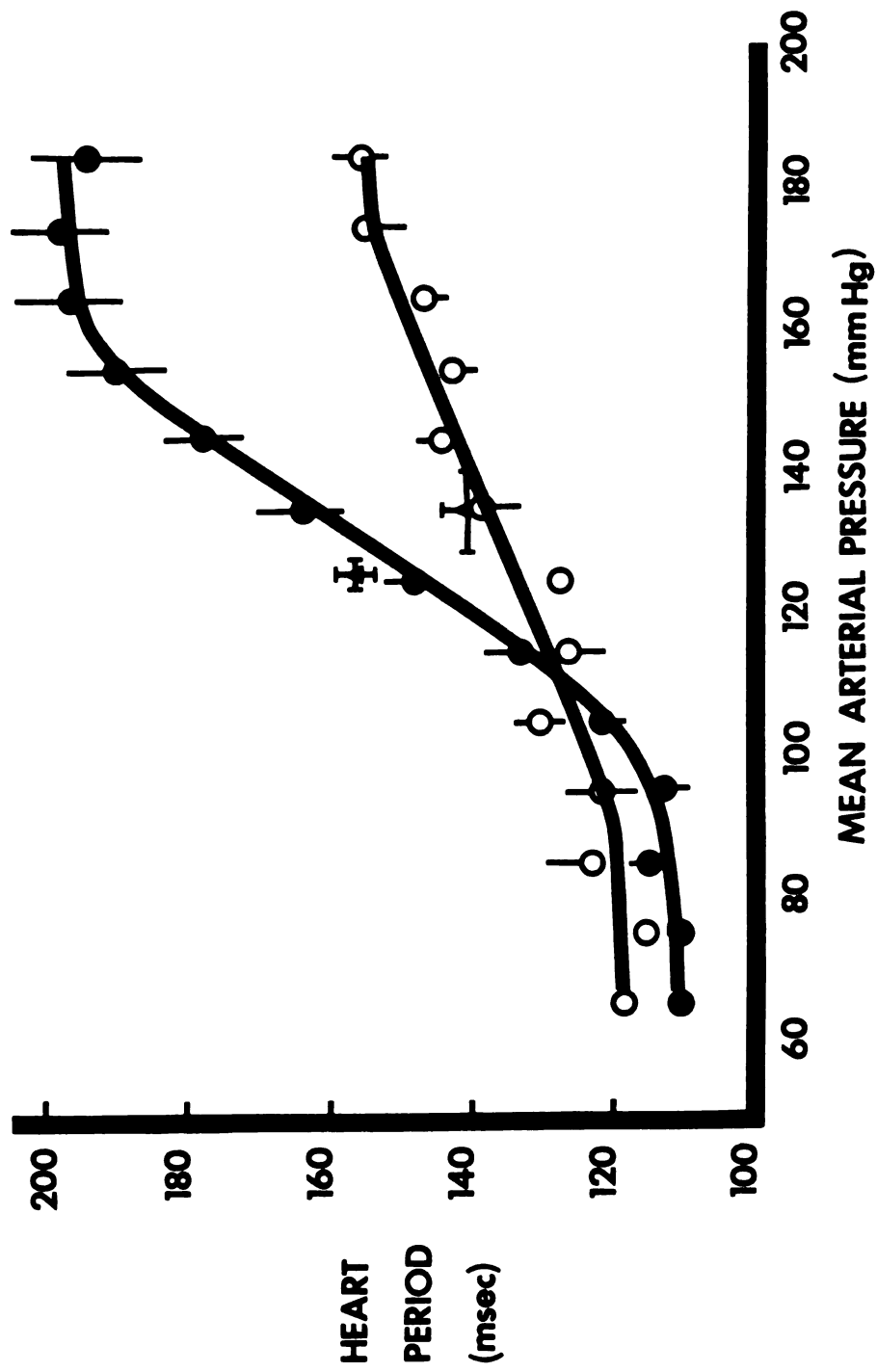


Figure 29

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Experiment 13. Determination of MAP in Chronic ABD Rats Using 24-Hour Continuous Recording

This experiment was designed to determine if once-daily MAP measurements are a reliable estimate of time-averaged MAP measurements in chronic ABD rats.

Figure 30 illustrates hourly MAP values averaged over 3 consecutive 24 hr periods of continuous blood pressure recording in conscious, freely moving rats. Arterial pressure was significantly higher in ABD rats than in sham-operated rats throughout the 24 hours of the day. A small but nonetheless significant diurnal variation in MAP also was evident in both sham-operated and ABD rats. Average MAP during the 72 hr continuous recording period was 120 ± 3 mmHg in ABD rats and 104 ± 2 mmHg in sham-operated rats, a statistically significant difference. Periodically measured heart rates also were significantly different during this time in sham-operated (386 ± 9 beats/min) and ABD (420 ± 6 beats/min) rats.

Average MAP over 3 days of once-a-day measurements in the same group of 20 rats was 124 ± 3 mmHg for ABD rats and 107 ± 3 mmHg for sham-operated rats. Average heart rates of the two groups at these measurement times were 441 ± 8 beats/min in ABD rats and 402 ± 8 beats/min in sham-operated rats. Both MAP and HR were significantly higher in ABD and sham-operated rats, but there were no significant differences in MAP or HR when continuous recording averages were compared to daily recording averages in either group of rats. Furthermore, there existed a significant correlation between MAP measured continuously

Figure 30. Hourly averages of mean arterial pressure from 3 consecutive 24 hr periods of continuous pressure recording in 10 sham-operated (SHAM) and 10 ABD rats. Bars represent the standard error for within group comparisons. Mean arterial pressure was significantly higher ($p < 0.05$, ANOVA) in ABD rats than in SHAM rats throughout the 24 hr cycle. The lowest hourly average arterial pressure was at 3:00 p.m. in both groups of rats. Average arterial pressure was significantly greater ($p < 0.05$, Tukey's test) than this minimum value between 11:00 p.m. and 8:00 a.m. in SHAM rats, and between 12:00 a.m. and 10:00 a.m. in ABD rats.

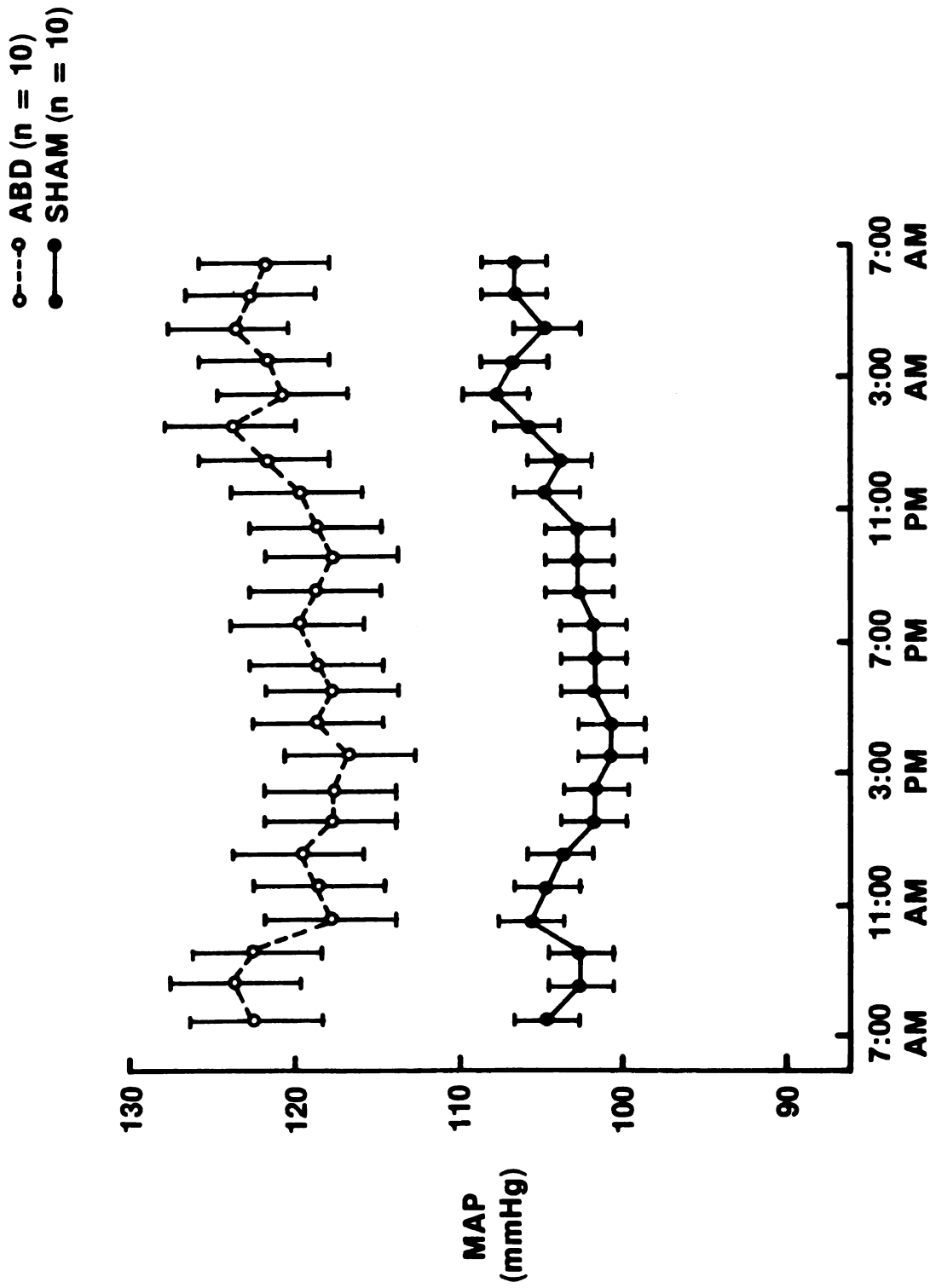


Figure 30

and daily ($r = 0.64$, $p < 0.01$), and between HR measured during the continuous recording period and the daily recording period ($r = 0.53$, $p < 0.05$).

Daily MAP averages for ABD and sham-operated rats throughout the 6 consecutive recording days are shown in Table 8. Note the very close agreement of daily MAP values within groups, with only a small apparent upward shift in MAP when once-daily MAP measurements were begun.

The greater lability of MAP in the ABD rats can be seen in the frequency distributions of MAP shown in Figures 31 and 32. Note the markedly wider distribution of individual MAP values in the ABD rats (Figure 31 vs. 32): average standard deviation of MAP calculated from these distributions was significantly higher in ABD rats ($SD = 14.4 \pm 1.3$ mmHg, Figure 33) than in sham-operated rats (8.3 ± 0.4 mmHg, Figure 33). An additional pertinent finding concerning MAP distribution in ABD rats is illustrated by the two representative frequency distributions shown in Figure 33. In contrast to the typically symmetrical distribution of MAP in the sham-operated rat, the distribution in the ABD rats shows an obvious negative skew. That is, when MAP changes markedly in the ABD rat, the direction of that change is virtually always downward. Prominent negative skewing of this type was observed in 8 out of 10 ABD rats examined here. Furthermore, it was observed that an immediate fall in MAP of ABD rats in this study occurred when they were exposed suddenly to loud noises or other environmental disturbances: situations in which the response of sham-operated rats consisted of a more slowly developing increase in MAP.

TABLE 8
Average Mean Arterial Pressure in Sham-operated (SO) and Aortic
Barodenervated (ABD) Rats During 6 Consecutive Days

	DAYS					
	Continuous Recording			Daily Measurement		
	1	2	3	4	5	6
SO (n=10)	103±2	105±2	104±2	107±4	108±5	107±5
ABD (n=10)	119±4	120±3	121±4	125±3	124±4	120±3

Averages for the continuous recording period (day 1-3) represent 288 individual measurements per rat per day. Averages for the daily measurement period represent 1 individual measurement per rat per day. Values represent mean ± SE.

Figure 31. Frequency distributions of MAP over a 24 hr period of continuous pressure recordings (288 individual data points per rat) in 10 sham-operated rats.

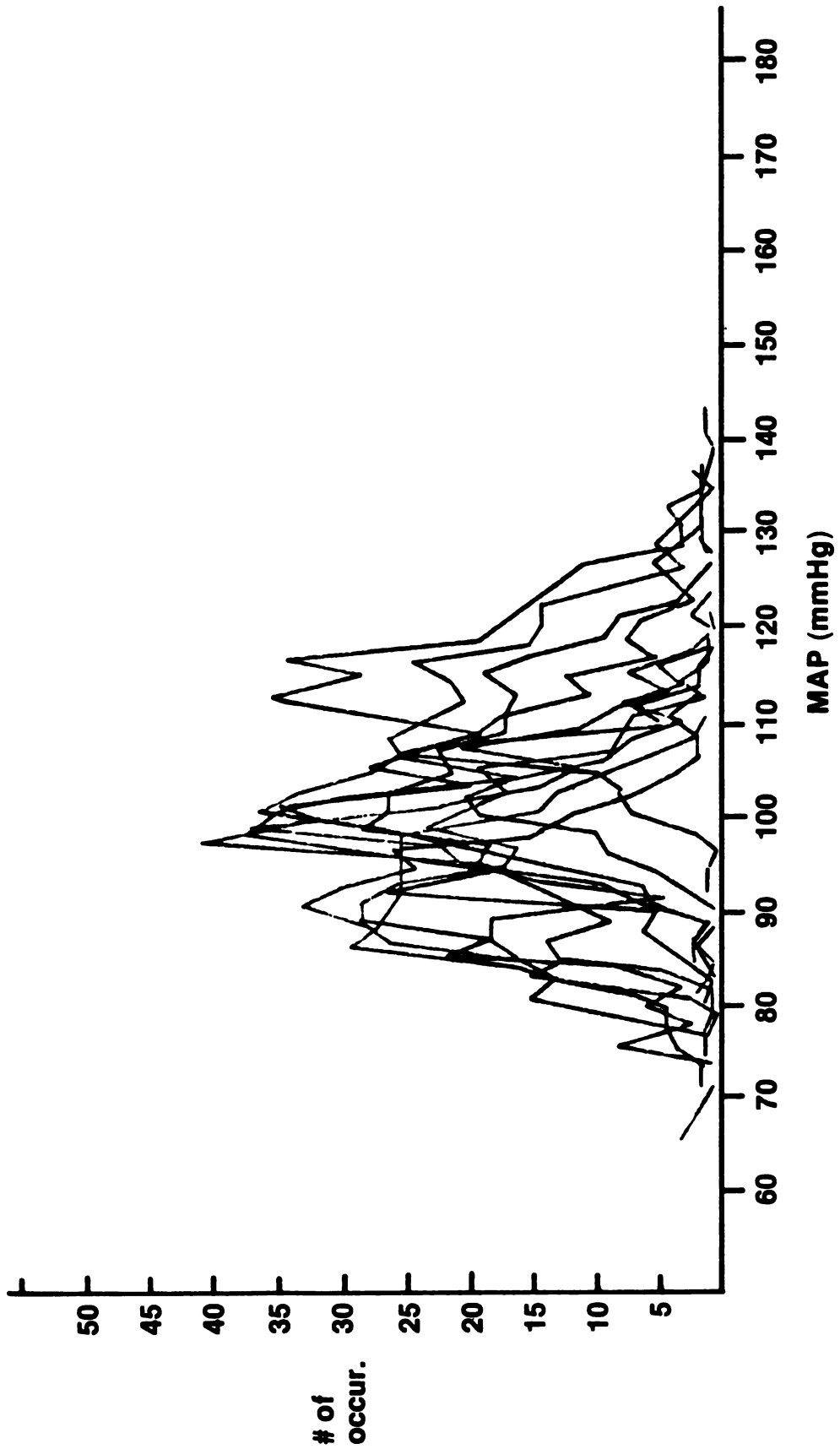
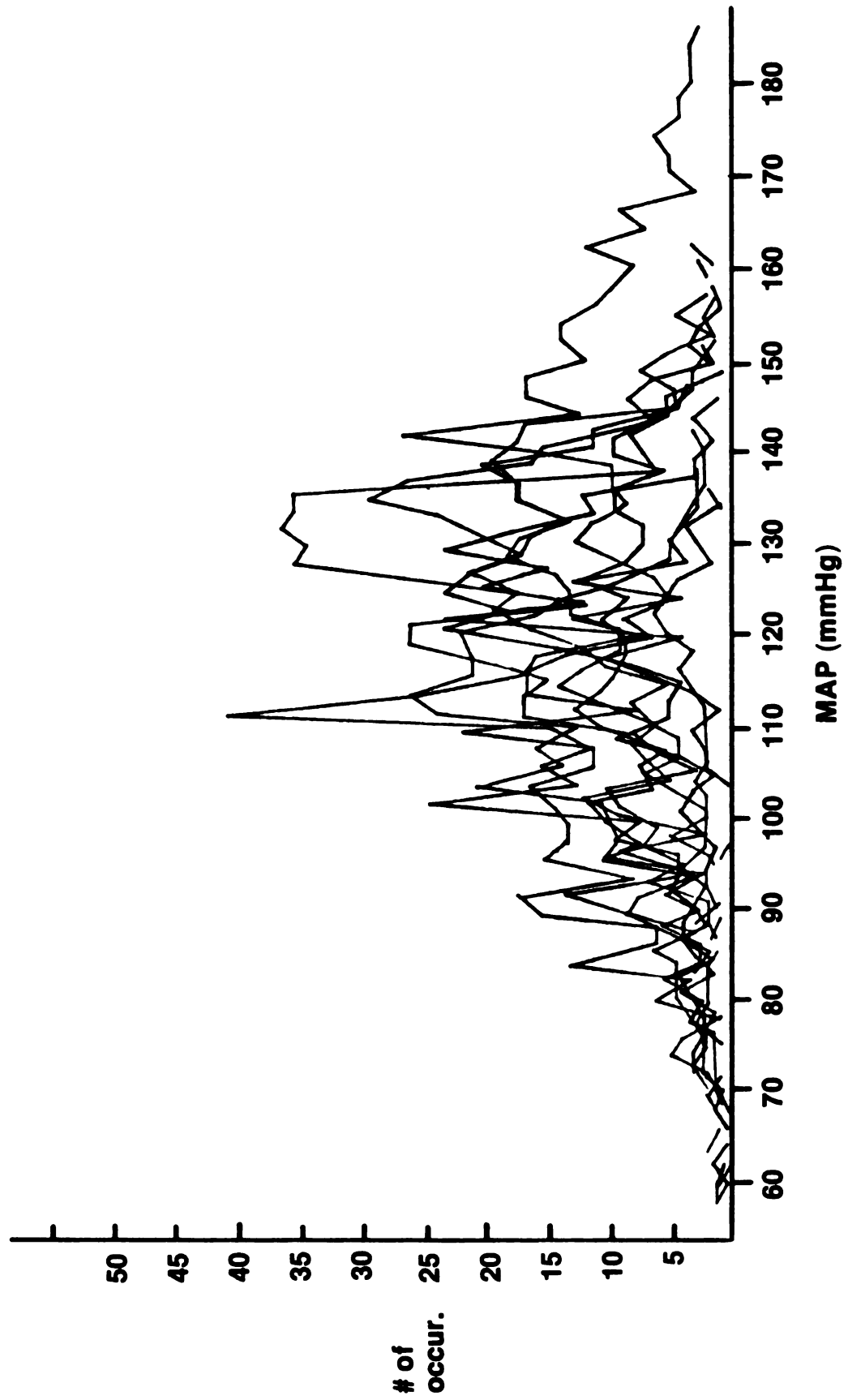


Figure 31

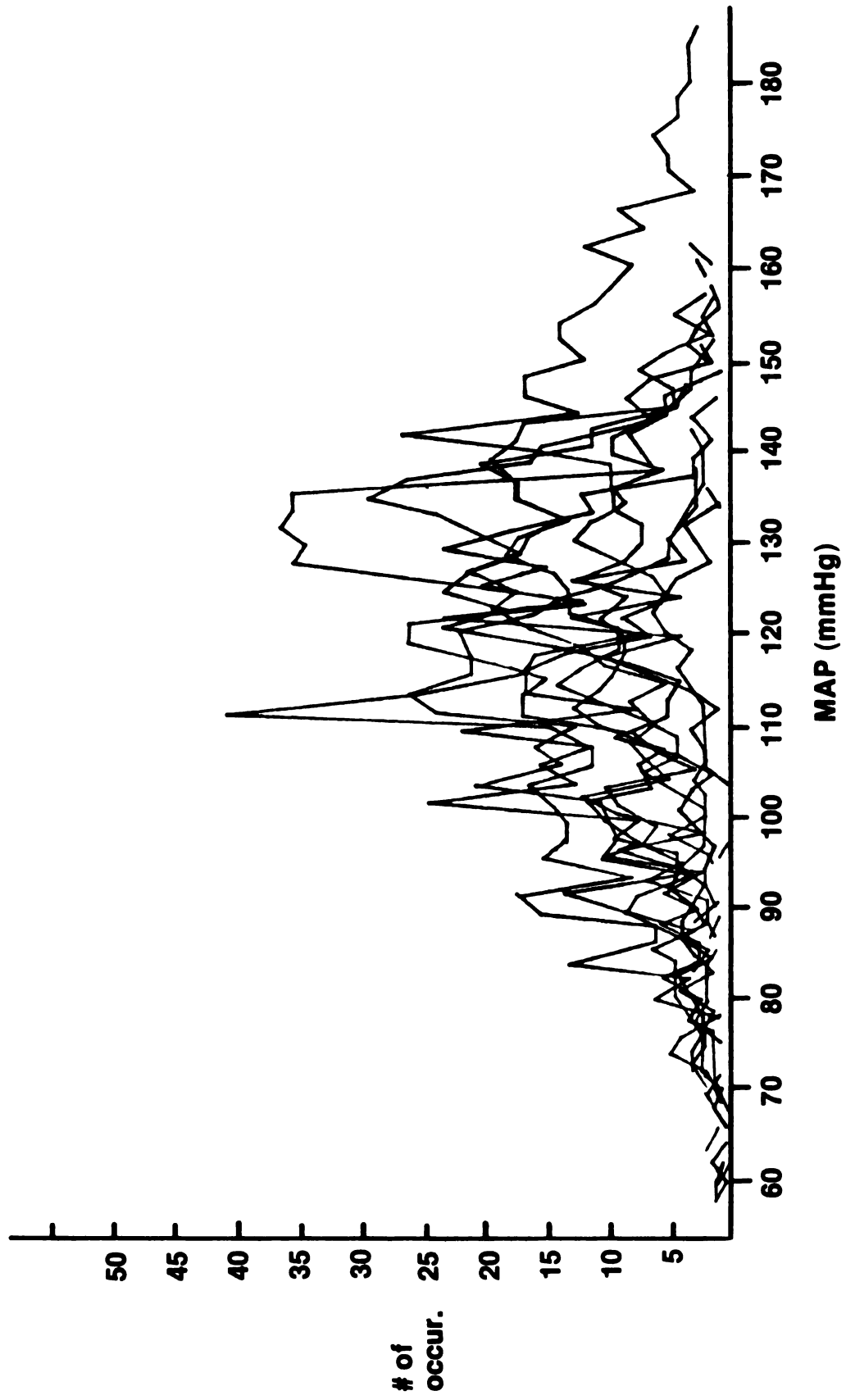
Figure 32. Frequency distributions of MAP over a 24 hr period of continuous pressure recordings (288 individual data points per rat) in 10 ABD rats.



MAP (mmHg)

Figure 32

Figure 32. Frequency distributions of MAP over a 24 hr period of continuous pressure recordings (288 individual data points per rat) in 10 ABD rats.



MAP (mmHg)

Figure 32

Figure 33. Representative frequency distributions of MAP in a sham-operated (SHAM) and ABD rat.

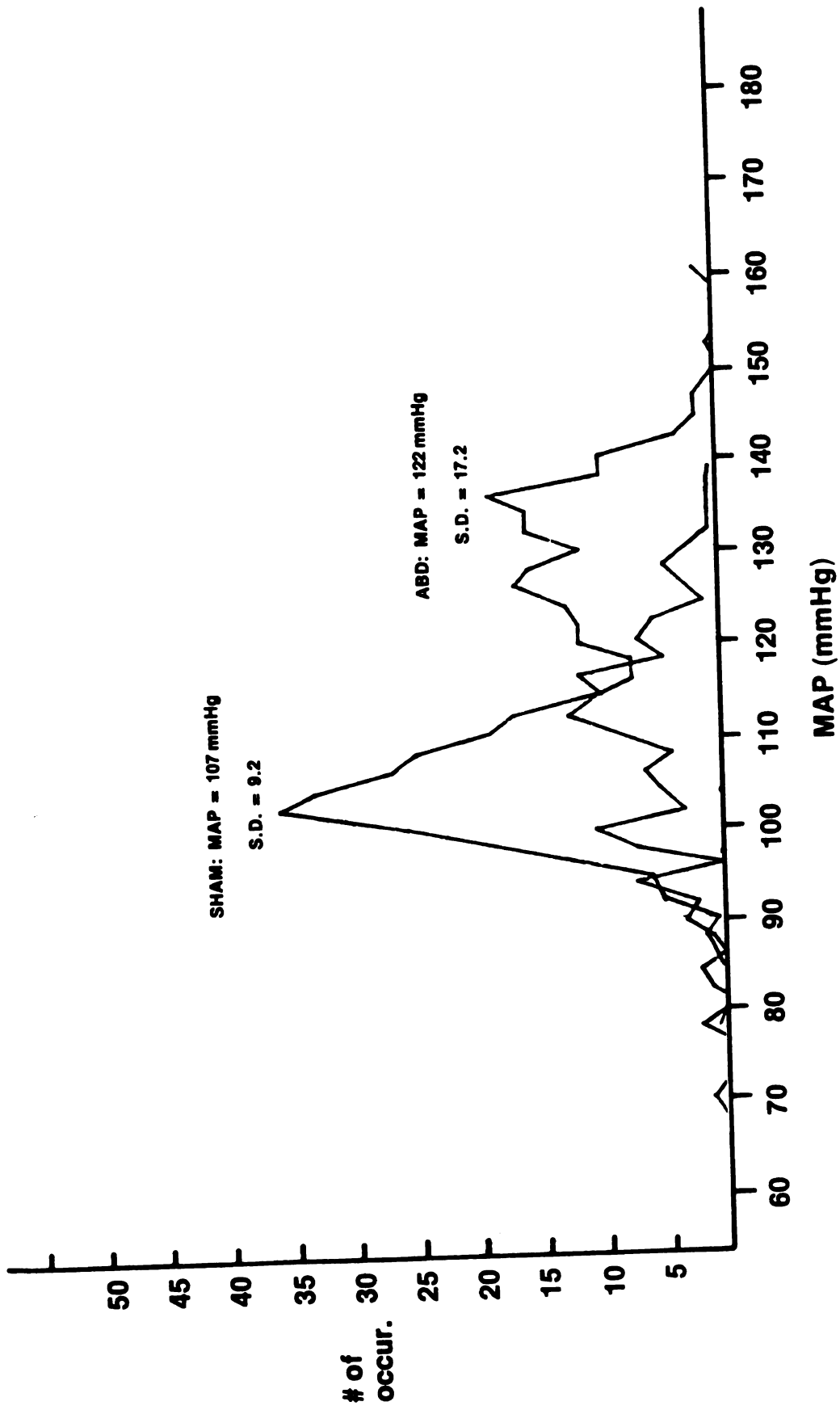


Figure 33

This experiment indicates that once-daily recording is a reliable way to obtain average MAP in ABD rats, despite their increased variability over a 24 hr period.

Experiment 14. Vascular Reactivity and the Neural Component of Vascular Resistance in the Kidney of the ABD Rat

This experiment was designed to examine vascular reactivity and the neurogenic component of vascular resistance in the autoperfused kidneys of chronic anesthetized ABD rats.

The effects of ABD on blood pressure are illustrated in Figure 34. Indirectly measured systolic blood pressure rose immediately following ABD (from 123 to 152 mmHg during the first week) and remained significantly higher than that of sham-operated rats throughout the 4 week period of study. Four to five weeks after ABD, direct intra-arterial pressure measurements in conscious unrestrained rats indicated that both mean arterial pressure and heart rate in rats with ABD were significantly higher than in sham-operated rats (Figure 34). However, the difference in MAP (16 mmHg) between the two groups was considerably less than the difference in indirectly measured systolic blood pressure (33 mmHg).

Baseline hemodynamic data from anesthetized rats prepared for renal autoperfusion are illustrated in Table 9. Note that MAP was lowered by anesthesia and surgical preparation in both groups of rats, but that pressure remained significantly higher in ABD rats relative to the sham-operated controls. Renal denervation did not alter steady-state arterial pressure over the time course of these experiments. Prior to renal denervation, renal vascular resistance was

Figure 34. Arterial pressure in rats prior to and following ABD or sham operation (SHAM). Circles represent average weekly measurements of systolic pressure using a tail-cuff method in conscious rats. Squares represent average mean arterial pressures determined in conscious rats with indwelling catheters on day of acute renal vascular studies. Bars represent SE for any paired comparison between groups. Asterisks indicate a significant ($p < 0.05$, lsd test) difference between ABD and sham-operated rats at any time period.

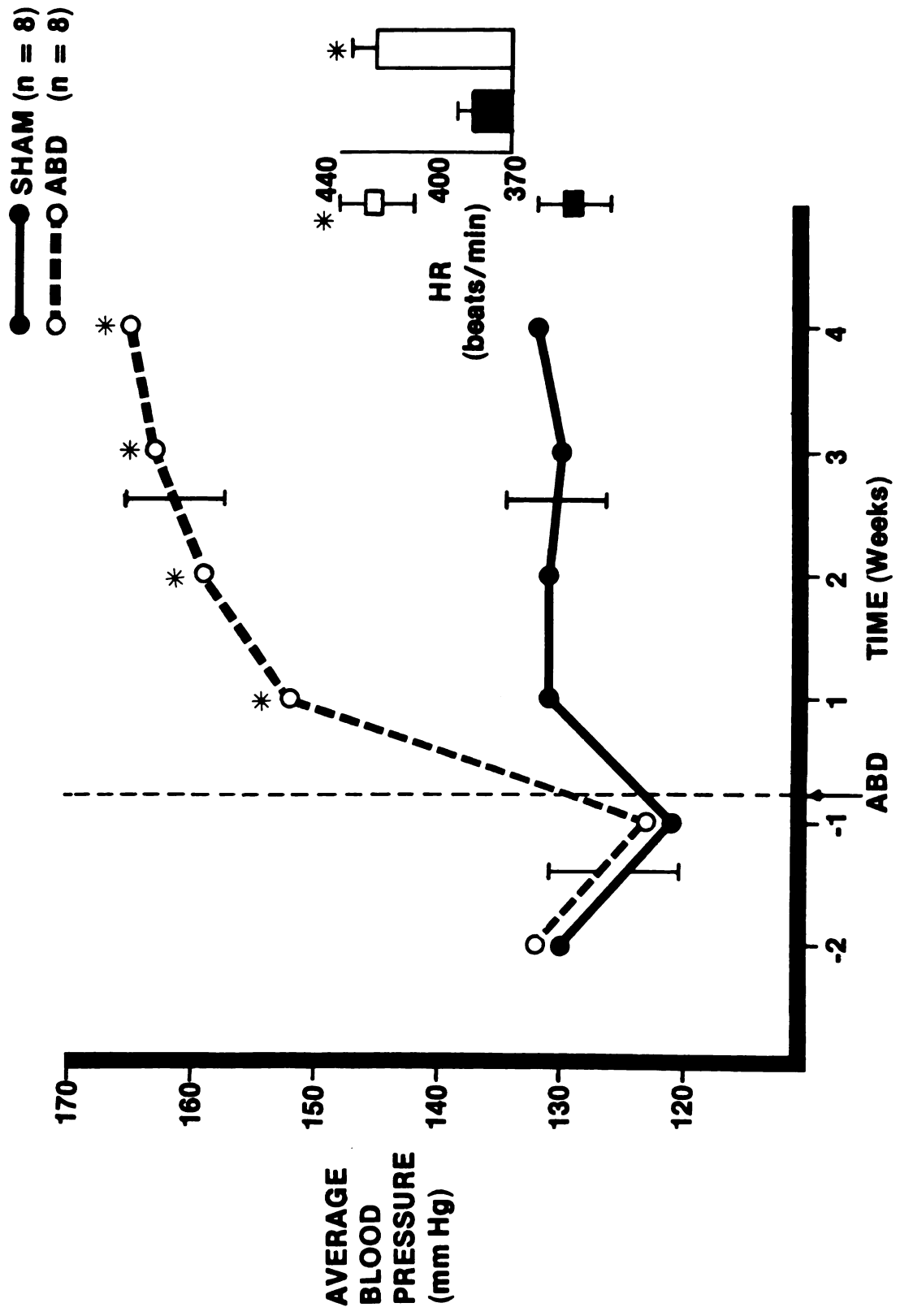


Figure 34

TABLE 9
Hemodynamic Measurements in Anesthetized Rats
During Renal Autoperfusion

	Sham-Operated (n=8)	ABD (n=8)	P
Mean arterial pressure, mmHg	105±4	119±5*	
Renal blood flow, mm·g ⁻¹ ·min ⁻¹			
Preden	5.4±0.4	5.1±0.4	NS
Postden	5.6±0.4	5.6±0.4	NS
Renal vascular resistance, mmHg/ml·g ⁻¹ ·min ⁻¹			
Preden	19.4±1.0	23.2±1.5*	
Postden	18.7±1.2	21.2±1.8 [†]	NS
Kidney wt, g	1.38±0.04	1.47±0.05	NS

Values are means ± SE; n = number of rats. ABD, aortic baroreceptor deafferentation. Den, renal denervation. Renal denervation did not alter steady-state arterial pressures in either group of rats. NS, nonsignificant at the P<0.05 level. *Significantly different from sham-operated rats at P<0.05 (t-test). [†]Significant difference between values before and after acute renal denervation (paired t-test).

significantly higher in the hypertensive ABD rats than in the normotensive controls following denervation, renal vascular resistance remained slightly higher in the ABD rats, but this difference was not statistically significant. The remaining difference in renal vascular resistance was largely the result of autoregulatory adjustments in the ABD kidneys, which were being perfused at an average pressure of 119 mmHg compared to an arterial pressure of only 105 mmHg in sham-operated rats. However, when pressure-flow curves were determined at the end of the experiment (not shown), vascular resistance was still slightly higher in ABD rats than in sham-operated rats over a pressure range from 40 to 120 mmHg (i.e., 19.8 and $18.7 \text{ mmHg} \cdot (\text{ml}/\text{min})^{-1}$ in ABD and sham-operated rats, respectively, at 105 mmHg arterial pressure), but this difference was not statistically significant.

Renal vascular responses to acute renal nerve section and electrical activation are shown in Figure 35. Renal vascular resistance decreased significantly ($p < 0.05$, paired t-test) following renal nerve section in ABD rats. Nerve section decreased average renal vascular resistance in sham-operated rats, but this decrease was not significant. The change in renal vascular resistance produced by nerve section also was significantly greater in ABD rats than in sham-operated rats ($p < 0.05$, t-test). Renal vascular responses to renal nerve stimulation were slightly lower in the ABD rats, but a significant difference between the two groups was evident only at the highest stimulation frequency (6 Hz). Figure 36 shows that changes in renal vascular resistance to intra-arterial administration of norepinephrine and angiotensin II were identical in ABD and sham-operated

Figure 35. Changes in renal vascular resistance following acute renal denervation and renal nerve stimulation in rats with ABD or sham operation. RVR = renal vascular resistance. Bars represent SE for any paired comparison between ABD and sham-operated rats. *Value significantly ($p < 0.05$, 1sd test) different between ABD and sham-operated rats at a given frequency.

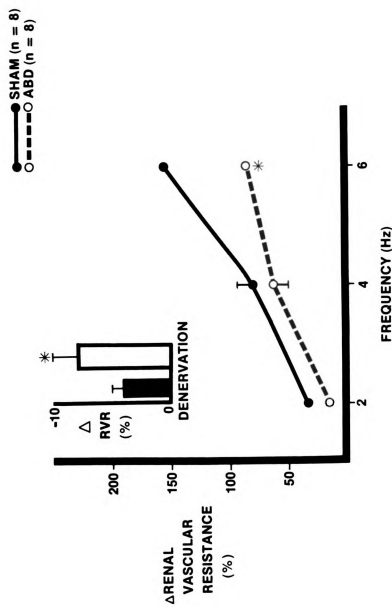


Figure 35

Figure 36. Changes in renal vascular resistance following intra-arterial injection of nor-epinephrine (NE) and angiotensin II (AII) in rats with ABD or sham operation. Bars represent SE for any paired comparison between ABD and sham-operated rats at a given drug dose.

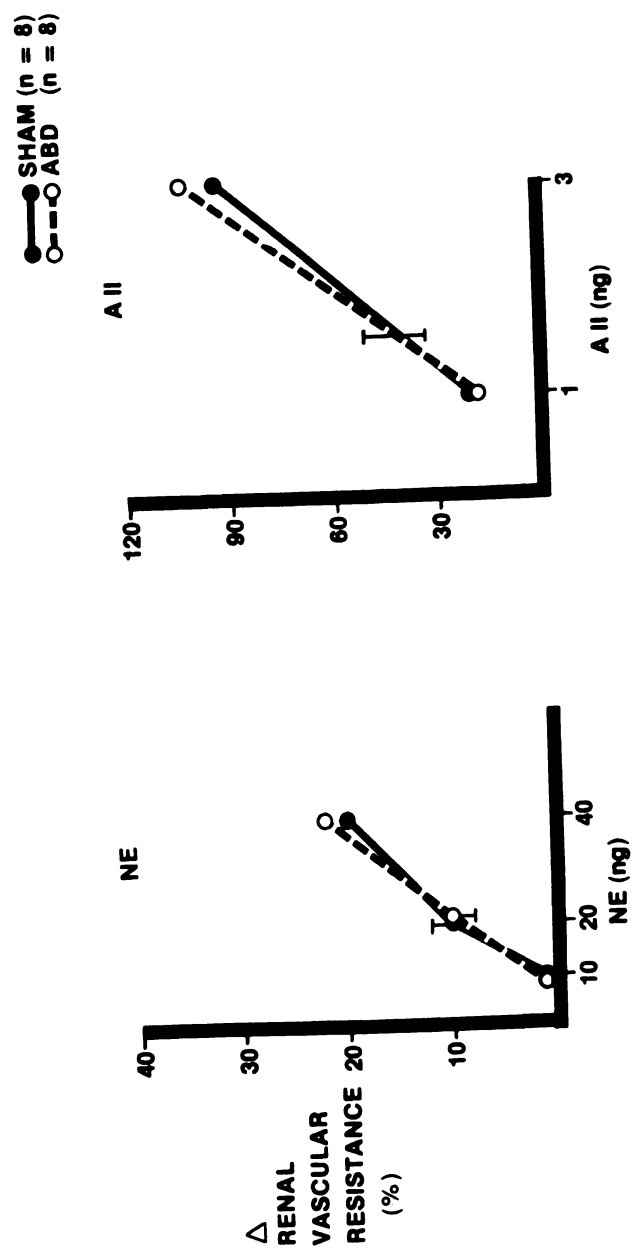


Figure 36

rats. In addition, no differences in vasodilation responses to acetylcholine were observed between ABD and sham-operated rats (not shown).

This experiment suggests that ABD causes a sustained increase in renal nerve activity.

Experiment 15. Vascular Reactivity and Components of Resistance in the Autoperfused Hindquarters of Chronic ABD Rats

This study was designed to examine vascular reactivity in, and the components of resistance of the isolated autoperfused hindquarters of chronic ABD rats.

ABD rats showed the typical acute weight loss (not shown) and bilateral ptosis seen following ABD.

Under anesthesia, the blood pressures of ABD rats were higher than those of sham-operated rats at 9 and 30, but not 90 days post-operatively (Table 10). Table 10 shows that further surgery normalized the blood pressure differences in the 9 and 30 day groups but revealed a slightly increased blood pressure in ABD rats in the 90 day group. Perfusion pressure was the same in all groups at all times (Table 10).

Vascular reactivity to sympathetic nerve stimulation was normal in all ABD rats (Figure 37). It should be noted that the slightly depressed reactivity to nerve stimulation at 16 Hz seen at 9 and 30 days after ABD was not as pronounced in the 90 day group.

Vascular reactivity to graded doses of norepinephrine was normal in all ABD rats (Figure 38). The results for reactivity to norepinephrine and nerve stimulation are the same whether expressed as an

TABLE 10

Blood Pressure During Hindquarter Perfusion at Various
Stages of the Procedure in Experiment 15

		9 Days ¹	30 Days	90 Days
MAP anesth ³	Sham	136±4 ²	150±5	147±4
	ABD	151±4*	169±6*	148±5
MAP pre-crush ⁴	Sham	106±4	115±3	105±3
	ABD	106±4	123±4	119±2*
Perfusion Pressure ⁵	Sham	97±5	107±2	100±4
	ABD	97±3	113±4	103±3

*Significantly different from sham control ($p < 0.05$, t-test).

¹Number of days after sham or ABD operation.

²All data are mean $\pm$ S.E.M.

³MAP just after carotid catheterization.

⁴MAP just prior to crushing sympathetic chains.

⁵Determination of perfusion pressure explained in Materials and Methods.

Figure 37. Changes in hindquarter vascular resistance following sympathetic chain stimulation 9, 30 and 90 days following ABD or sham operation. Points represent mean values. Bars represent standard errors for between groups comparison.

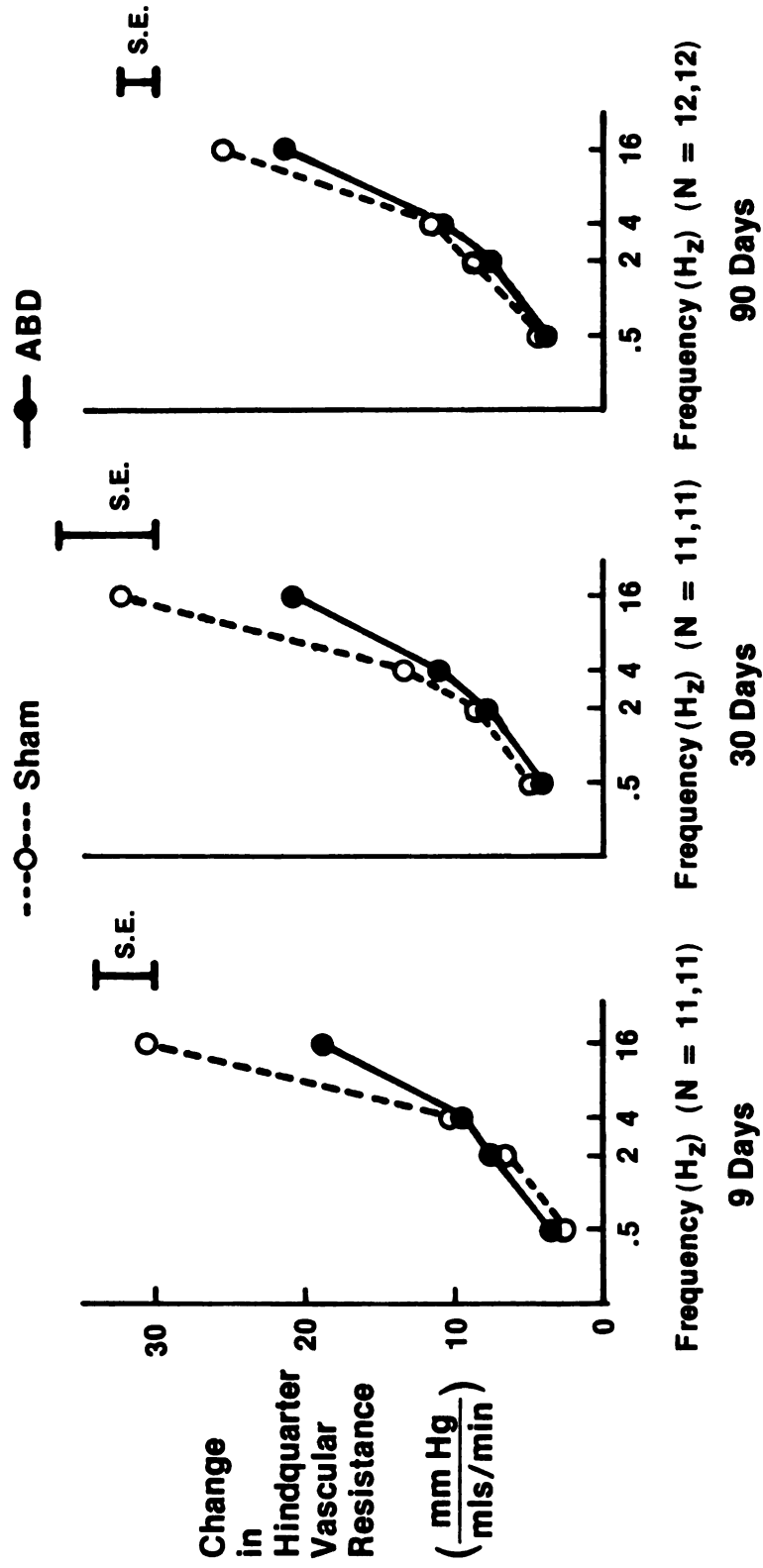


Figure 37

Figure 38. Changes in hindquarter vascular resistance following graded doses of norepinephrine. Zero dose is saline injection. Symbols as in Figure 37.

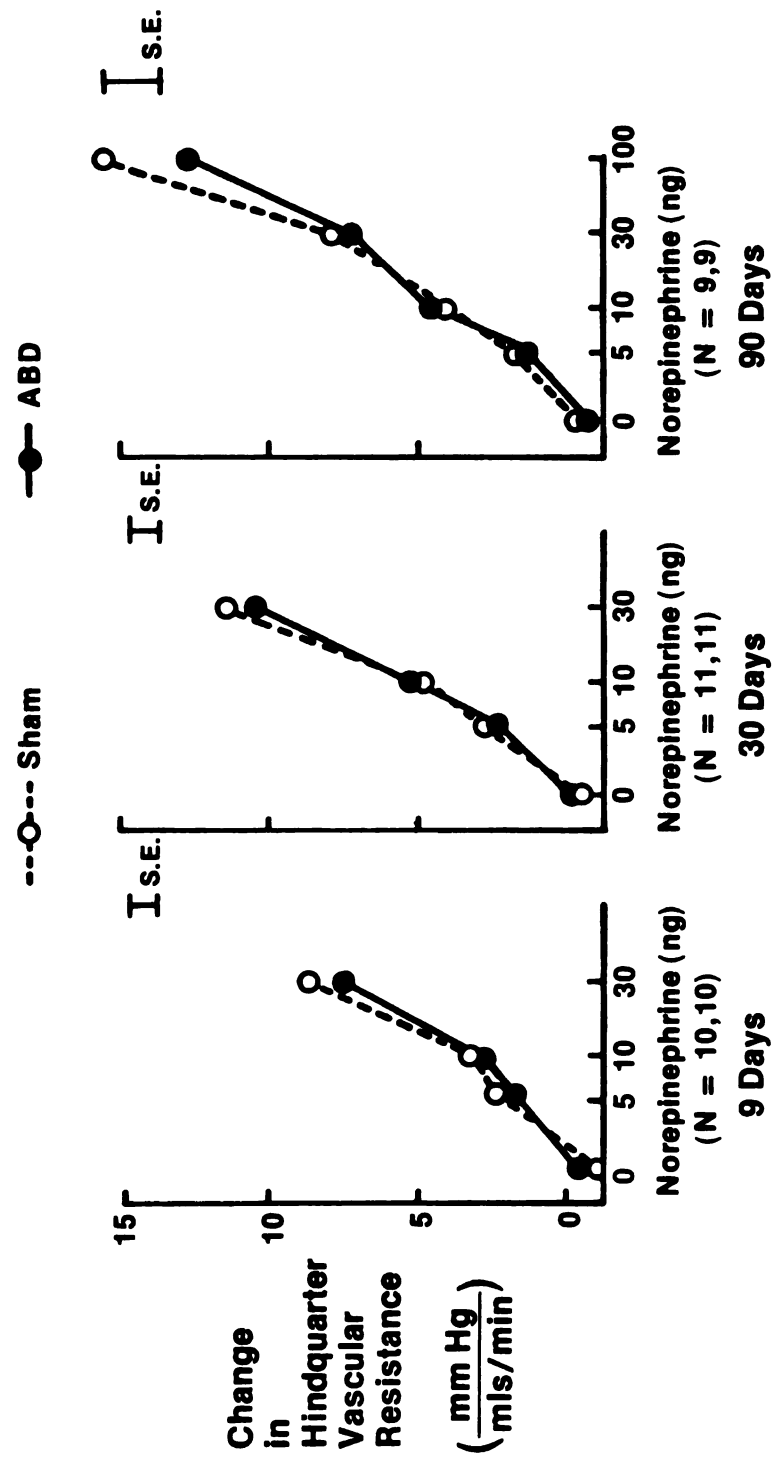


Figure 38

absolute (as in Figures 36 and 37) or percent change (not shown) in resting resistance.

Vascular reactivity to graded doses of acetylcholine was normal in all ABD rats (Figure 39).

Basal vascular resistance was not significantly changed over the course of the vascular reactivity tests (not shown) as determined by comparing the vascular resistance 5 minutes after nerve crush, to the resistance just before the first dose of papaverine.

The components of vascular resistance are illustrated in Figure 40. Resting vascular resistance was elevated only in the 90 day ABD group. This increased resistance could not be attributed to any individual component. The neurogenic component, expressed as a percent of resting resistance, was elevated only in the 9-day ABD's. This group also had a reduced humoral-myogenic component of resistance (Figure 40). There were no other differences in any of the other components.

All rats tested showed reactive hyperemia following occlusion (1-2 min) of the extracorporeal circuit (not shown), and the legs were not stiff at the end of the perfusion. These observations indicate that there was adequate perfusion of the hindquarters.

Figure 41 shows that there was a mild but significant ventricular hypertrophy in ABD rats 90 days post-operatively.

Experiment 17. Autoperfusion of the Hindquarters of the Spontaneously Hypertensive Rat

This study was designed to show that the hinsquarter perfusion technique used in the previous experiment could detect changes in the various parameters measured.

Figure 39. Changes in hindquarter vascular resistance following graded doses of acetylcholine (ACh). Symbols as in Figure 38.

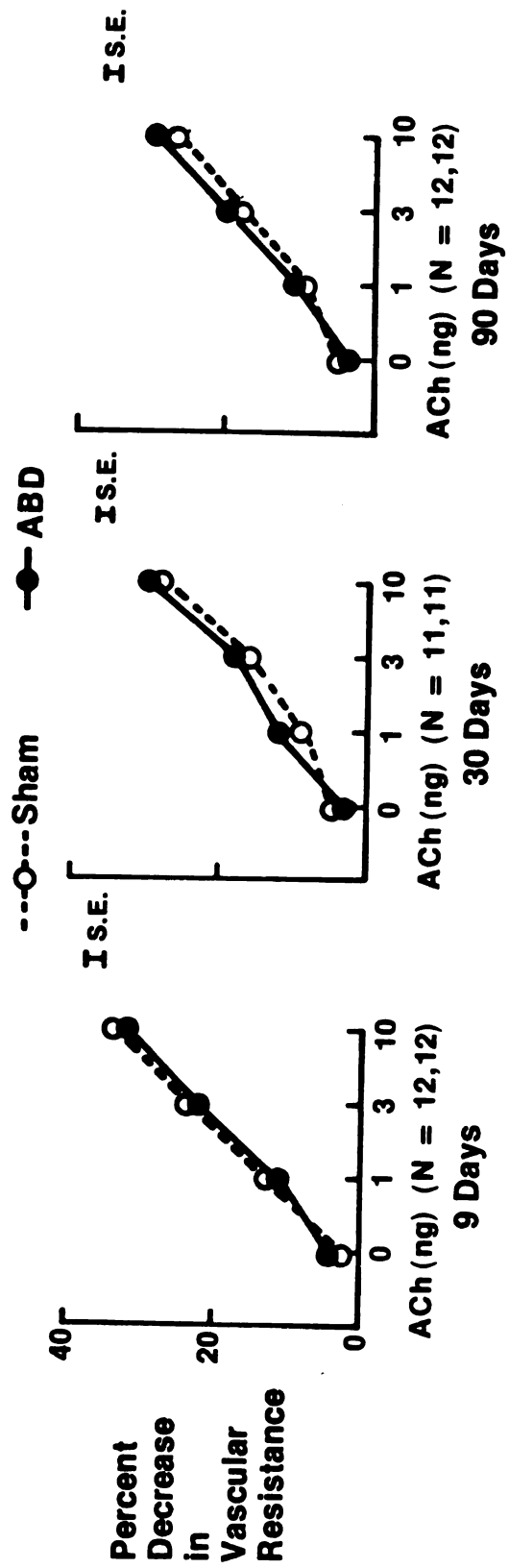


Figure 39

Figure 40. Components of hindquarter vascular resistance 9, 30 and 90 days after ABD or sham operation. Blocks represent mean values. Bars above blocks represent S.E. for resting vascular resistance. Bars within blocks represent 2 times S.E. for each component. Other symbols explained in Figure 3.

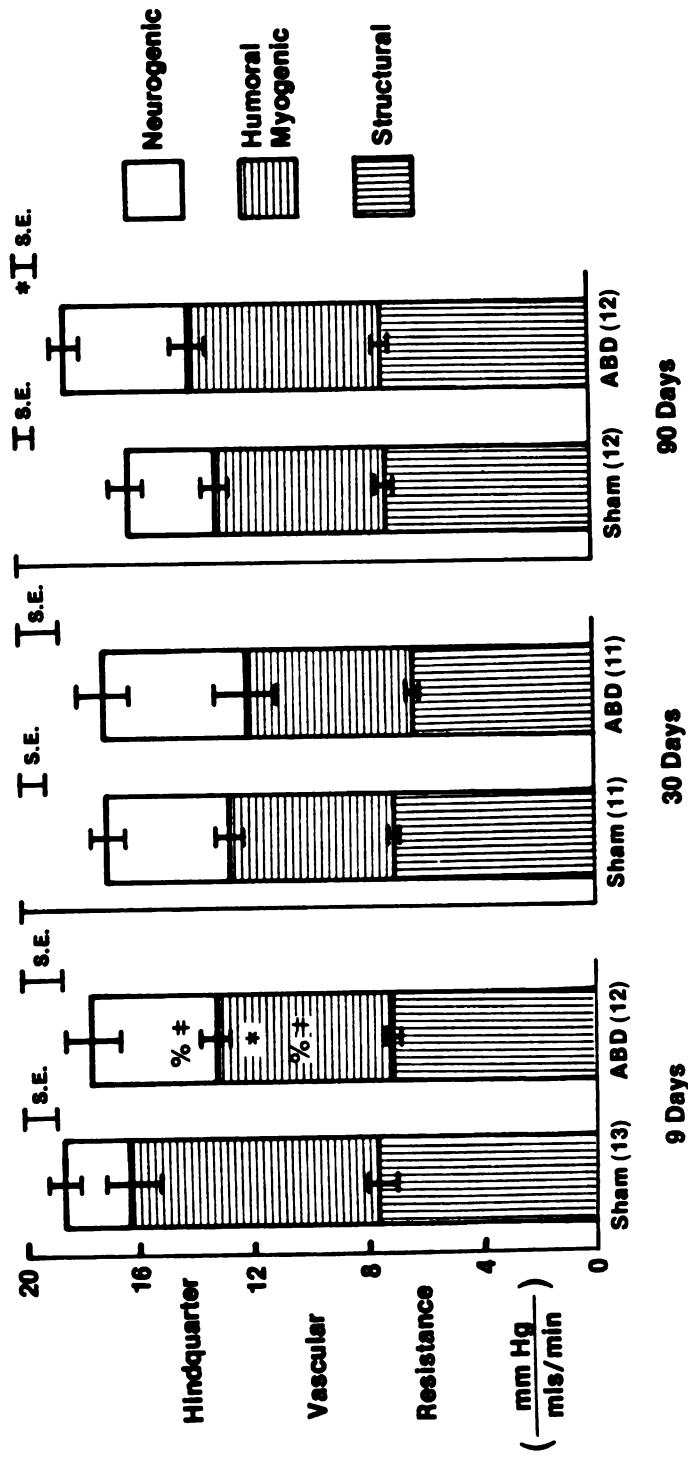


Figure 40

Figure 41. Ventricular hypertrophy in ABD rats 90 days post-operatively. Blocks represent mean values. Bars represent S.E.M. *Value significantly different than sham-operated rats ($p < 0.05$, t-test).

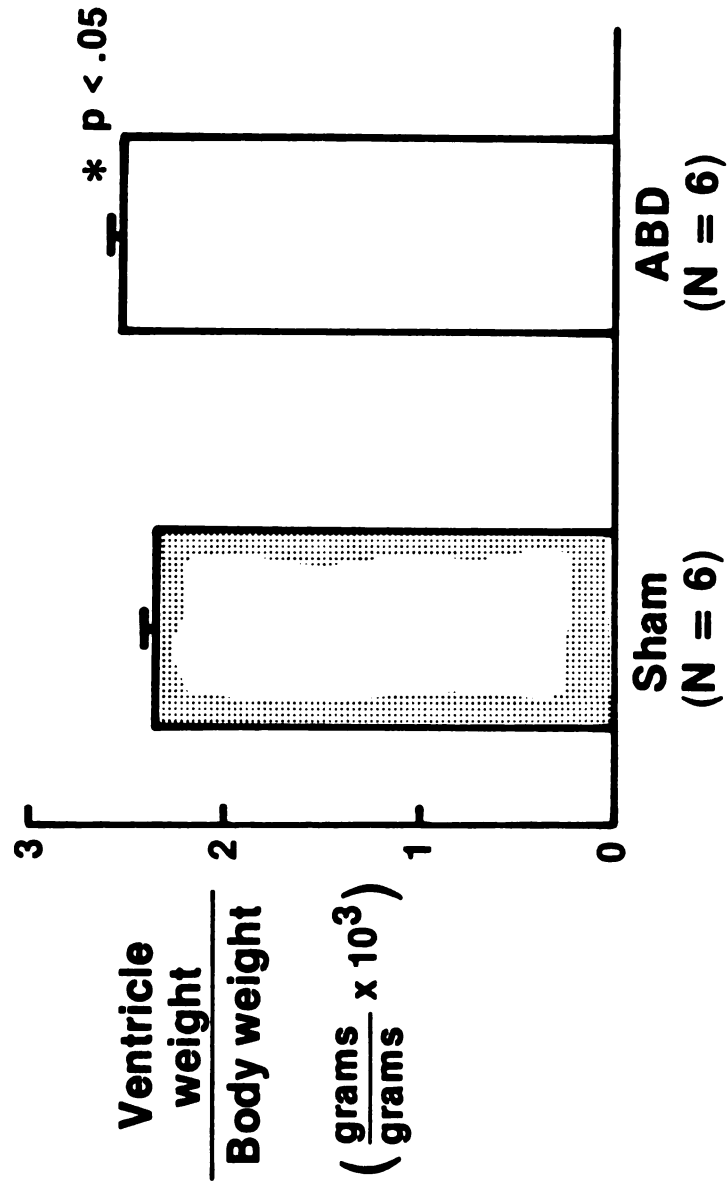


Figure 41

Increased vascular reactivity to acetylcholine (expressed as a percent and absolute change) and nerve stimulation (expressed as absolute change), and higher perfusion pressures were observed in the SHR (not shown). SHR had increased resting vascular resistance, and elevated humoral-myogenic and structural components of resistance (Figure 42). These results indicate that the hindquarters perfusion technique used in other experiments was able to detect differences in vascular reactivity and components of vascular resistance.

Experiment 22. Measurement of Hindquarter Vascular Resistance

This experiment was designed to assess if the procedures used for the hindquarter autoperfusion studies created artificial values of resting vascular resistance.

The results of this experiment (Table 11) show that the hemodynamic variables obtained by this method and that of the extracorporeal flow techniques give similar values (compare values in Table 11 with Figure 40 and Table 10 (pre-crush MAP)). In addition, ligation of the left common carotid artery caused only a transient dilation in the hindquarters (not shown).

This experiment indicates that the extracorporeal flow technique did not artificially affect hindquarter resistance in the anesthetized, laparotomized rat.

Experiment 16. Cardiovascular Control and Pathological Changes in Rats One Year After ABD

This experiment had three goals: 1) to determine if ABD causes a persistent hypertension lasting for a significant fraction of a rat's lifetime, 2) to determine the factors responsible for maintaining the

Figure 42. Components of hindquarter vascular resistance in adult SHR and WKY rats. Symbols as in Figure 40 except as noted.

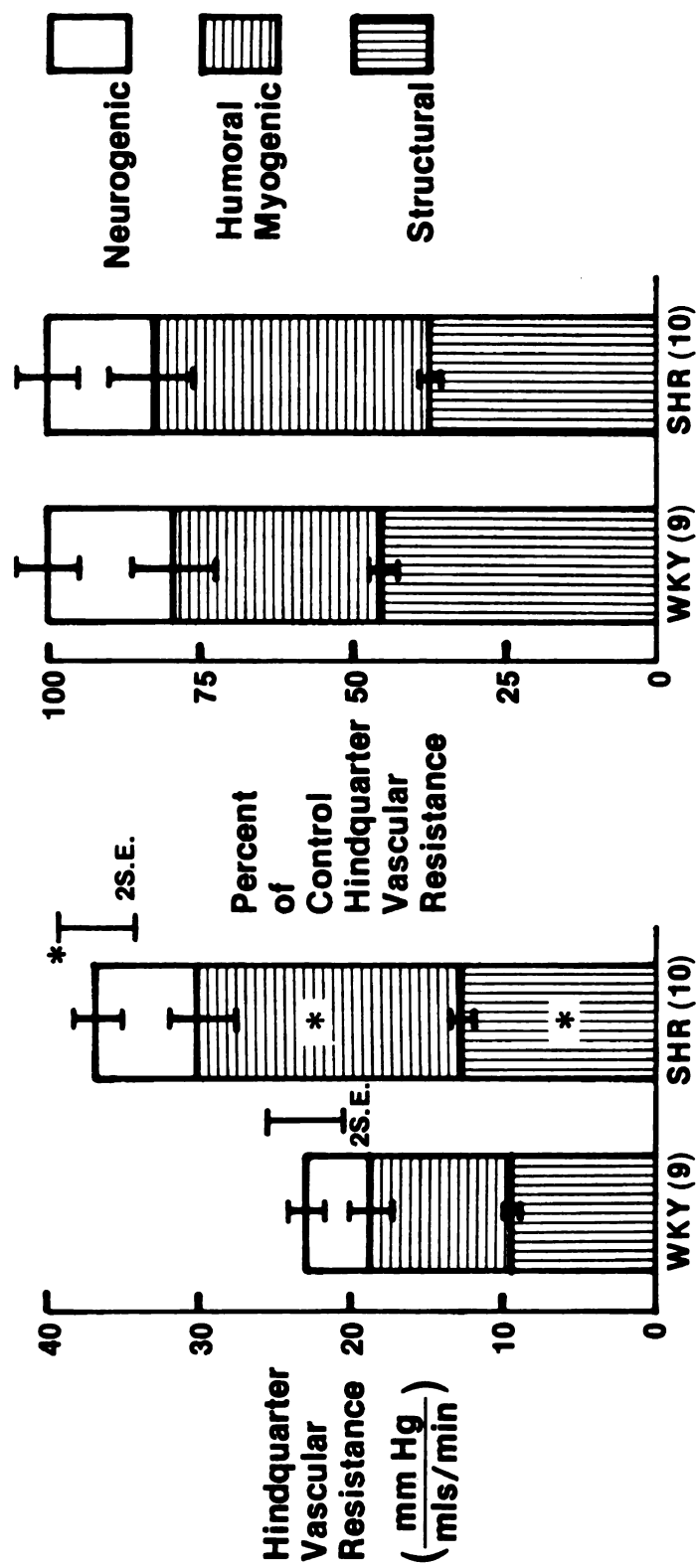


Figure 42

TABLE 11

MAP (Brachial Artery), Flow in the Abdominal
Aorta and Hindquarter Resistance in
Anesthetized Rats

MAP (mmHg)	120±7 ¹
Flow (mls/min)	7.2±0.76
Resistance (mmHg/mls/min)	18.2±2.5

¹All data are mean ± S.E.M. in 8 rats.

elevated pressure (if elevated), and 3) determine if chronic ABD hypertension was associated with known hypertension-related diseases.

Blood pressure, measured indirectly, was elevated at all times after ABD (Figure 43). Sham-operated rats showed an increase in blood pressure associated with aging. ABD rats also showed this aging-related increase in blood pressure superimposed on the elevated blood pressure produced by ABD.

Figure 44 shows the arterial blood pressure in ABD and sham-operated rats as determined by direct, 24 hour, continuous MAP recording for two days. The average MAP of ABD rats (137 ± 3.7 mmHg) was slightly but not significantly greater than that of sham-operated (126 ± 3.0 mmHg) controls. However, it should be noted that 5 of the ABD rats had pressures above the range observed in sham-operated rats. In addition, one ABD rat, which died of a stroke, is not included in this data. This rat had the highest blood pressure of all rats during the last indirect blood pressure determination. There was a significant correlation ($r=0.516$, $df = 19$, $p<0.05$) between the blood pressure determined during the last tail-cuff measurements and the 24 hour average MAP. These observations suggest that the ABD rat which died before direct MAP could be determined would have had a high MAP.

Quantitative analysis of the frequency distributions of MAP (measured continuously over 24 hours) revealed that ABD rats showed a strong tendency of negative skewing. Measurement of kurtosis of the distributions did not reveal any differences between ABD and sham-operated rats. In addition, casual observations of rats revealed that

Figure 43. Blood pressures (tail-cuff method) in chronic ABD and sham-operated rats. Points represent mean values. Pre = first control measurement. Time in weeks after ABD or sham operation. Bar is standard error between groups. [~]47 Value measured between 46 and 49 weeks after ABD or sham operation. +Value significantly different than sham-operated rats at corresponding time ($p < 0.05$, lsd test).

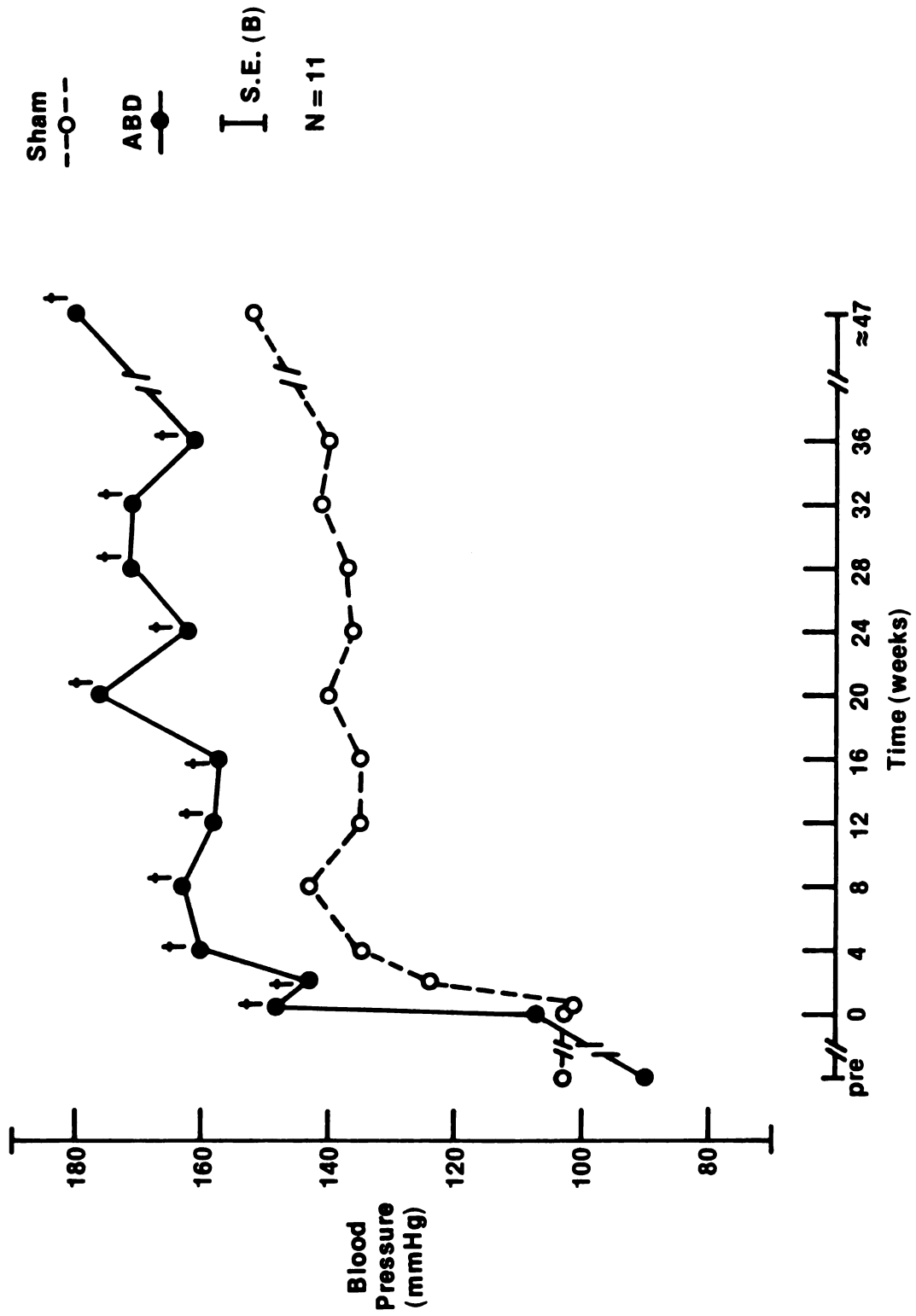


Figure 43

Figure 44. Blood pressures (24 hour recording) in rats approximately 1 year after ABD or sham operation. Symbols as in Figure 24.

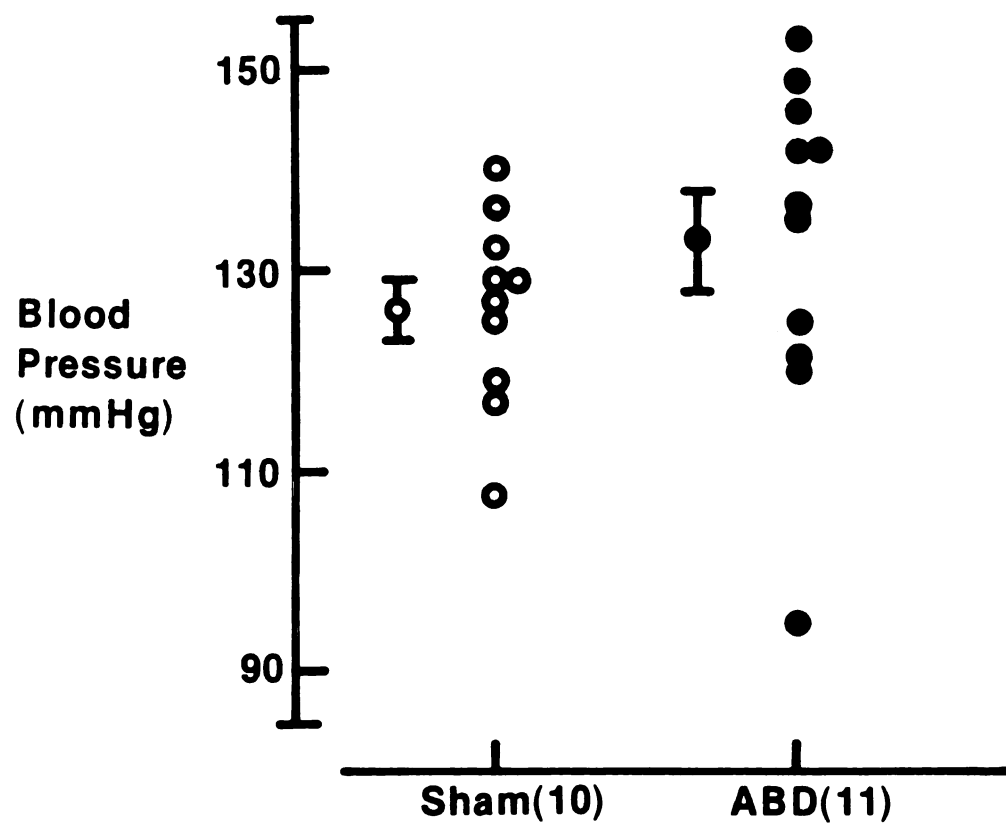


Figure 44

ABD but not sham-operated rats responded to environmental stimuli (noise, changing food and water) with decreases in blood pressure.

Heart rate varied over the course of the study. In general, there was no difference between the heart rates of ABD and sham-operated rats ($p > 0.05$, ANOVA). Arrhythmias were observed in some rats. The incidence of irregular heartbeats appeared to be the same in both groups of rats.

Figures 45 and 46 show various parameters related to the status of the baroreflexes. Figure 45 shows that baroreflex gain was slightly but not significantly reduced in ABD rats. The standard deviation of blood pressure (determined by 24 hr continuous recording) was elevated in ABD rats on both days of recording (Figure 45). This increase was statistically significant only on the first day of recording. The standard deviation of blood pressure for the first day of recording showed a weak, inverse correlation with the baroreflex gain ($r = -0.382$, $df = 12$, $p > 0.05$). This observation is consistent with the hypothesis that lack of baroreflex control of heart rate reflects (to a small degree) the lack of baroreflex control of vascular resistance. The response to carotid occlusion (during hindquarter autoperfusion) was slightly greater in ABD rats (Figure 45). Figure 46 shows that ABD rats had increased pressor sensitivity to phenylephrine. These observations are consistent with the hypothesis that aortic baroreflex function was slightly impaired one year after ABD.

It has been suggested that the blood pressure level following barodenervation is related to the degree (or "completeness") of

Figure 45. Standard deviation of MAP over 24 hours, baroreflex gain and response to bilateral carotid occlusion (BLCO) in rats approximately 1 year after ABD or sham operation. Day 1 is first day of continuous MAP recording, Day 2 is second day of continuous MAP recording. Blocks represent average values. Bars represent S.E.M. Numbers in parentheses represent number of animals tested in each group. *Value significantly different than sham-operated control ($p < 0.05$, t-test).

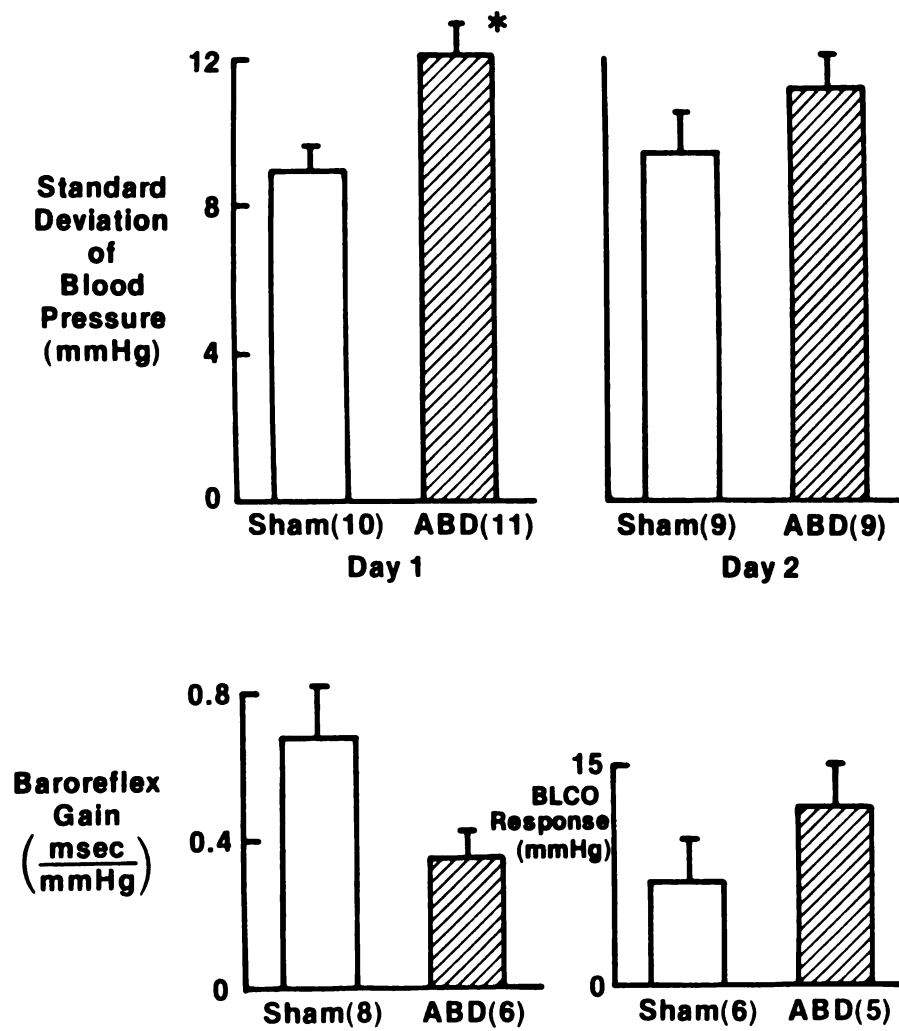


Figure 45

Figure 46. Change in blood pressure elicited by graded doses of phenylephrine in rats approximately 1 year after ABD or sham operation. Points represent mean values. Bar represents standard error between groups. Numbers in parentheses represent number of animals tested in each group. *Value significantly different than sham-operated control at same dose ($p < 0.05$, 1sd test).

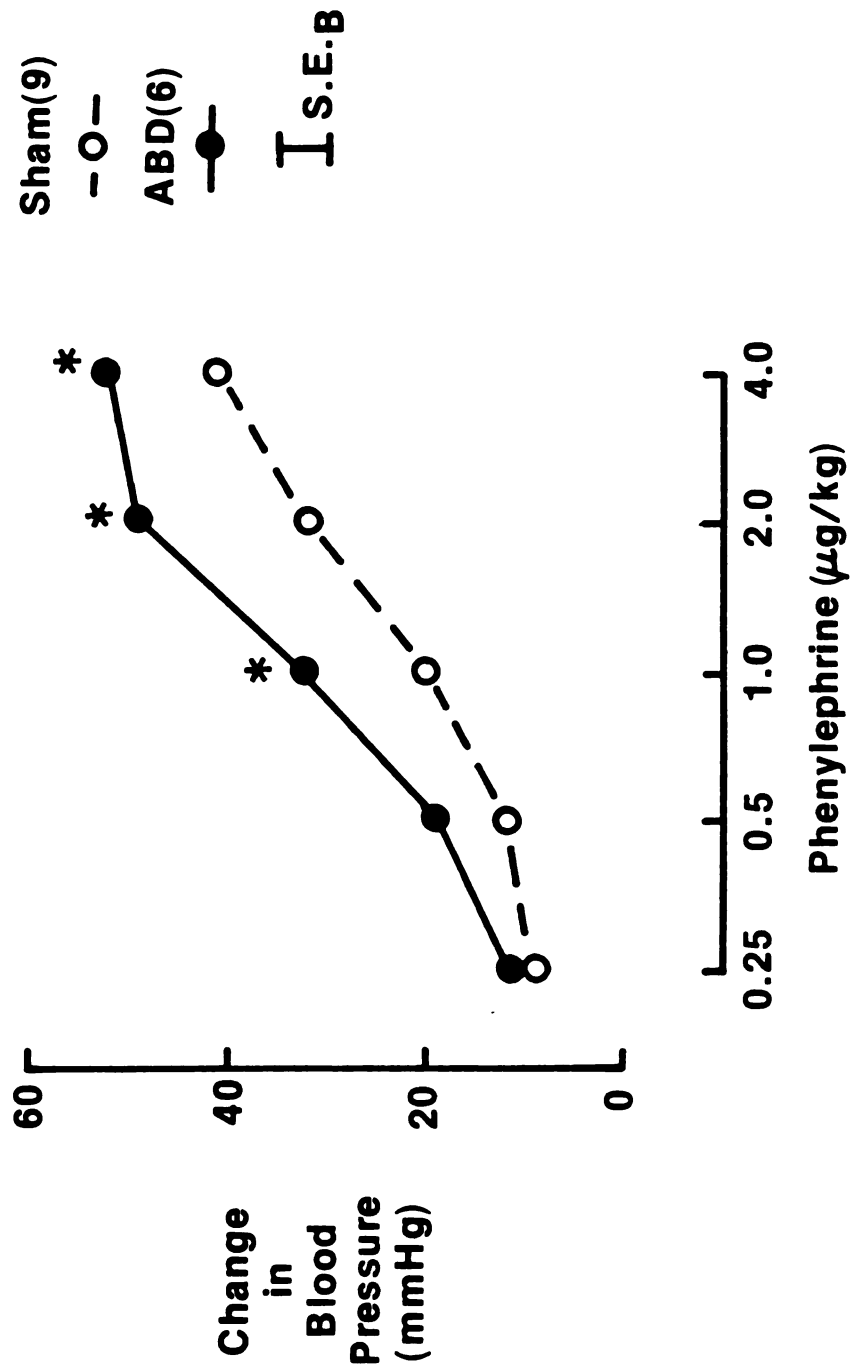


Figure 46

barodenervation (see Introduction). In ABD rats, baroreflex gain showed a weak positive correlation ($r = 0.474$, $df = 4$, $p > 0.05$) with the averaged MAP. This result is not consistent with the hypothesis that the blood pressure level after barodenervation is related to the degree of barodenervation.

Total autonomic blockade obliterated ($p < 0.05$ for F interaction from split-plot ANOVA) the slight blood pressure difference between ABD and sham-operated rats (Figure 47). The correlation between the decrease in MAP after TAB versus the resting MAP was slightly more positive in ABD than sham-operated rats (Figure 48). This difference was not statistically significant ($p > 0.05$, analysis of covariance).

Each drug administered during total autonomic blockade affected heart rate equally in both groups (not shown).

These data suggest that ABD rats, one year post-operatively, have an increased neurogenic drive to the blood vessels, but normal neural control of the heart.

Vascular reactivity of the hindquarters to nerve stimulation is shown in Figure 49. Reactivity (expressed as an absolute change) was significantly elevated in ABD rats at a stimulation frequency of 16 Hz. This difference was also seen when the data are expressed as percent change in resistance. However, the difference was not statistically significant.

Vascular reactivity to norepinephrine was increased in ABD rats (Figure 50). There was a significant correlation between the percent change in vascular resistance in response to 300 ng of norepinephrine

Figure 47. Blood pressure changes after supramaximal doses of atropine (Atr), propranolol (Pro) and phentolamine (Phen) in rats approximately 1 year after ABD or sham operation. Sal = injection of saline vehicle; C = resting blood pressure. Points represent mean values. Bar represents standard error between groups. *Value significantly different than corresponding value for sham-operated controls ($p < 0.05$, lsd test). †Value significantly different than value for resting blood pressure in same group ($p < 0.05$, lsd test).

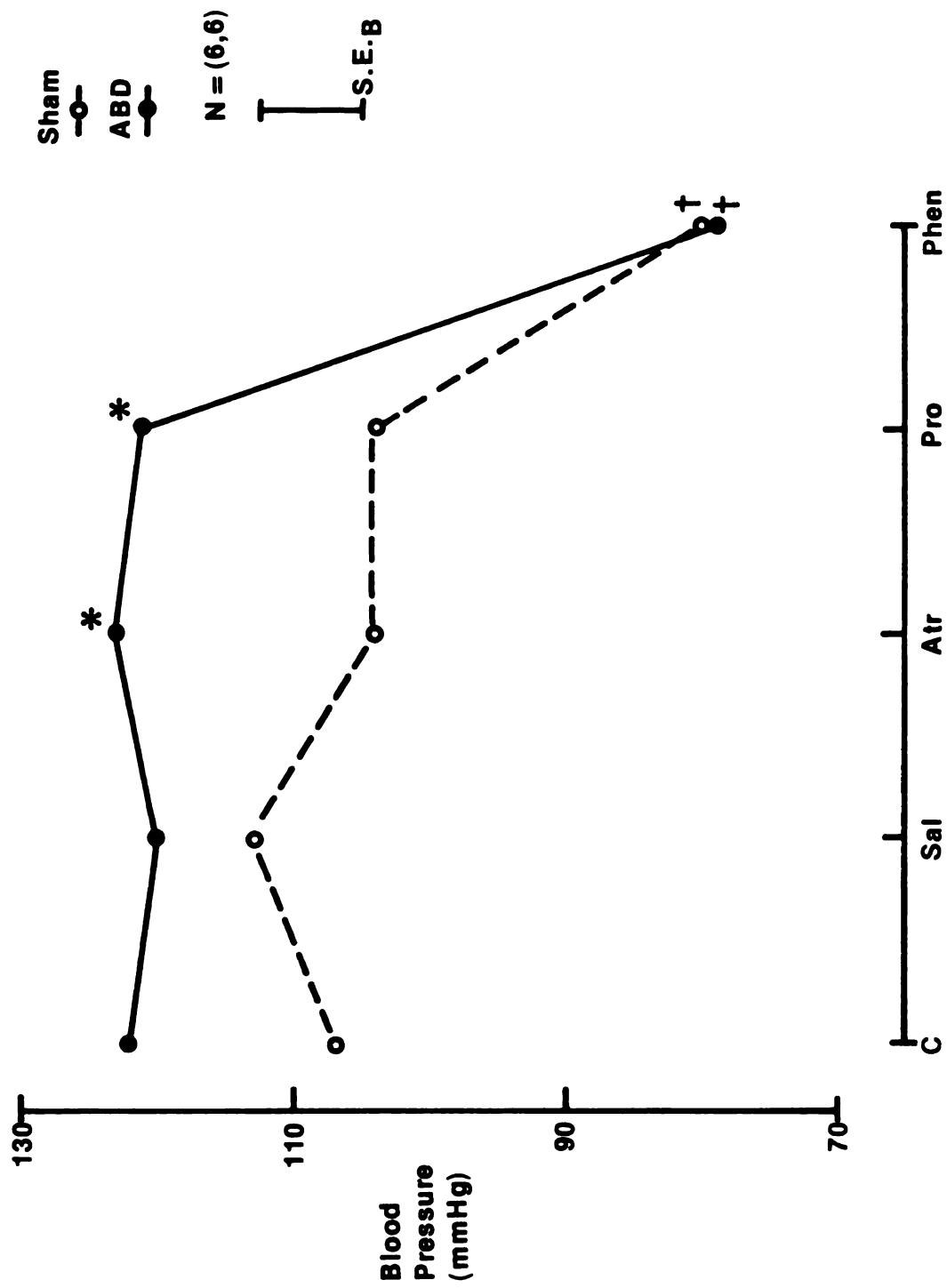


Figure 47

Figure 48. Relationship between decrease in blood pressure following total autonomic blockade and resting blood pressure before total autonomic blockade in rats approximately 1 year after ABD or sham operation. Points represent individual values. Numbers in parentheses represent number of rats tested in each group. Solid line is regression line for ABD rats. Dashed line is regression line for sham-operated rats. r = correlation coefficient, slope = slope for regression line.

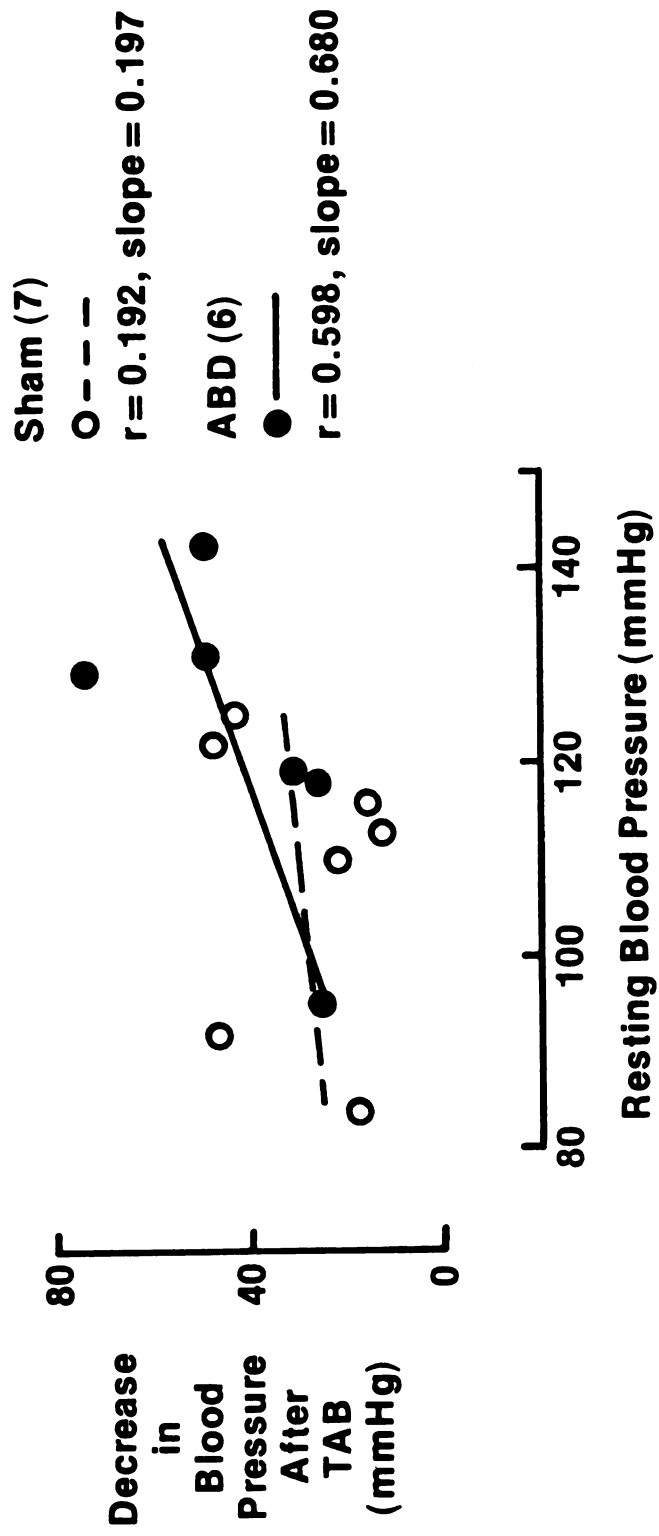


Figure 48

Figure 49. Changes in hindlimb vascular resistance following sympathetic nerve stimulation in rats approximately 1 year after ABD or sham operation. Points represent mean values. Numbers in parentheses represent number of animals tested in each group. Bars represent standard error between groups. *Value significantly different from sham-operated group at a given frequency ($p < 0.05$, lsd test). $\% \Delta$ = Percent change in.

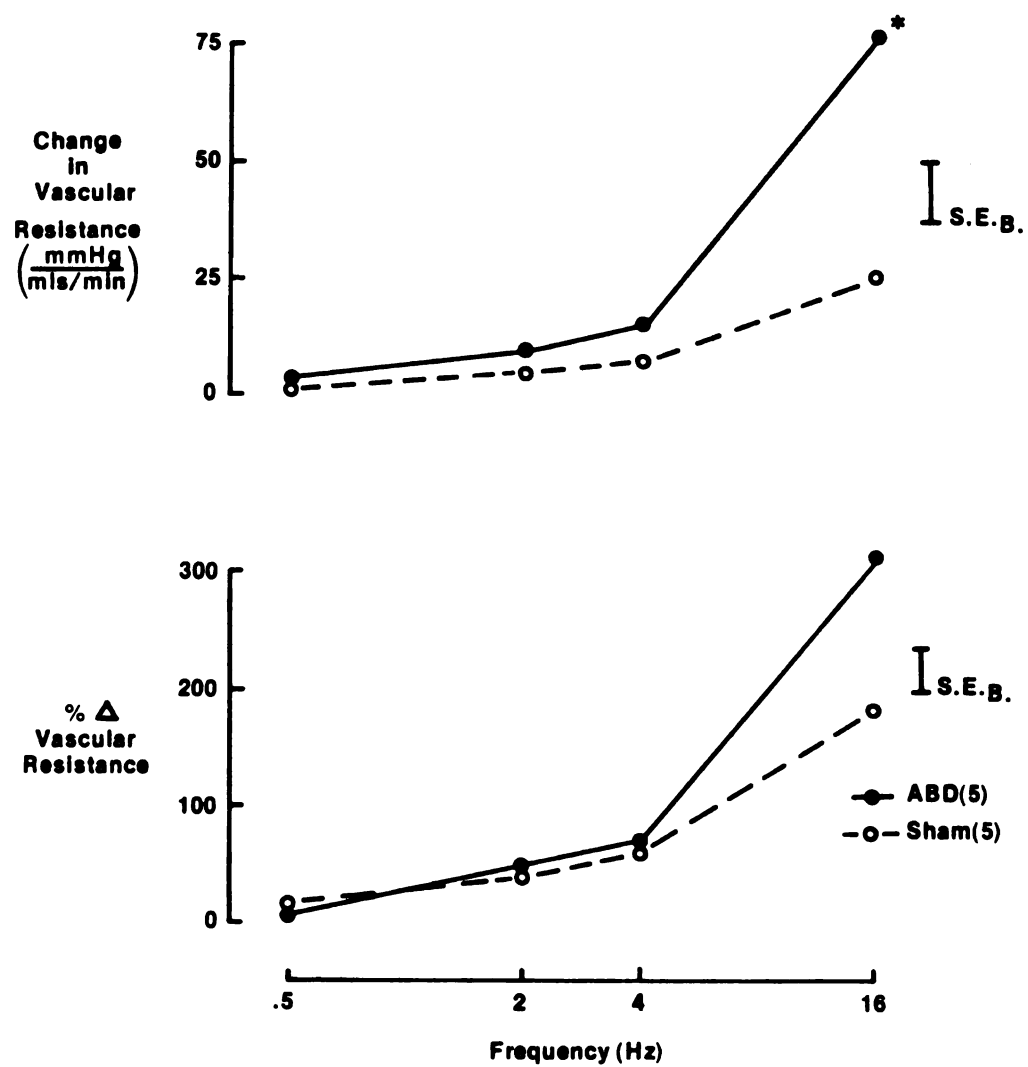


Figure 49

Figure 50. Changes in hindlimb vascular resistance following graded doses of norepinephrine in rats approximately 1 year after ABD or sham operation. C = responses to injection of saline vehicle. Symbols as in Figure 49.

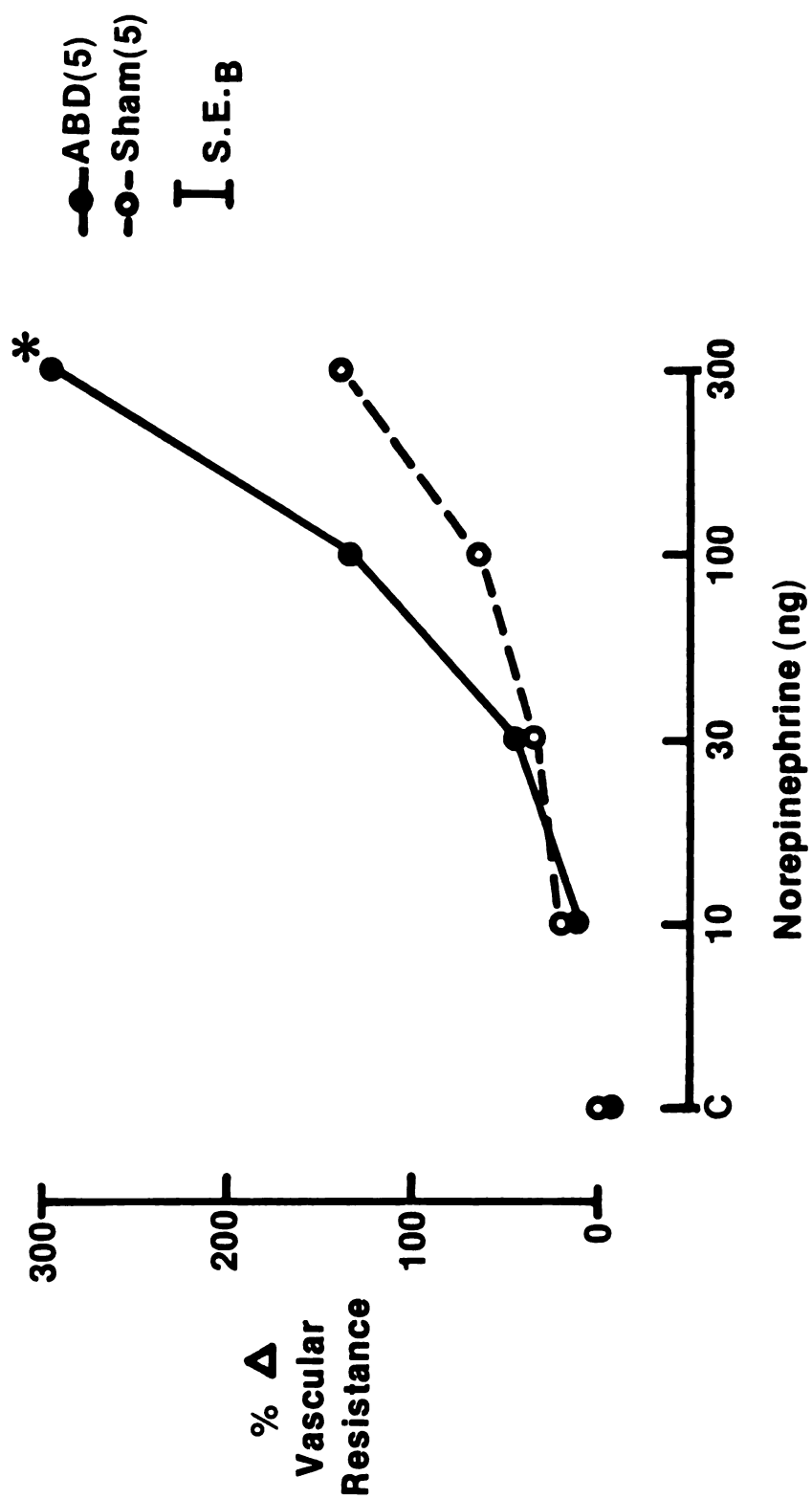


Figure 50

and the resistance at maximal vasodilation ($r = 0.922$, $df = 7$, $p < 0.05$), when data from all rats was examined.

Vascular reactivity to acetylcholine (expressed as percent change) was normal in ABD rats (Figure 51).

Figure 52 shows that resting vascular resistance was elevated in ABD rats. The only individual component of resistance which was significantly elevated in ABD rats was the structural component.

There was no evidence of ventricular hypertrophy in ABD rats one year after operation (not shown). Examination of the brain following infusion of Evans Blue dye revealed only one rat with a significant disruption of the blood brain barrier (a sham). Three sham-operated and four ABD rats underwent this latter procedure.

The kidneys of 11 ABD and 10 sham-operated rats have been prepared for histological examination.

Examination of the brains of 8 ABD and 8 sham-operated will be performed at the University of Iowa (Heistad, personal communication).

Experiment 18. Effectiveness of Total Autonomic Blockade (TAB)

This experiment was performed to evaluate the ability of the TAB procedure to block the cardiovascular actions of exogenous drugs.

The pressor response to norepinephrine, the depressor response to acetylcholine and isoproterenol-induced tachycardia were significantly attenuated following TAB in three rats (not shown).

This result indicates that the procedure can block the cardiovascular responses to exogenous drugs, implying that receptors at autonomic neuroeffector junctions are also blocked.

Figure 51. Changes in hindlimb vascular resistance following graded doses of acetylcholine in rats approximately 1 year after ABD or sham operation. Symbols as in Figure 50.

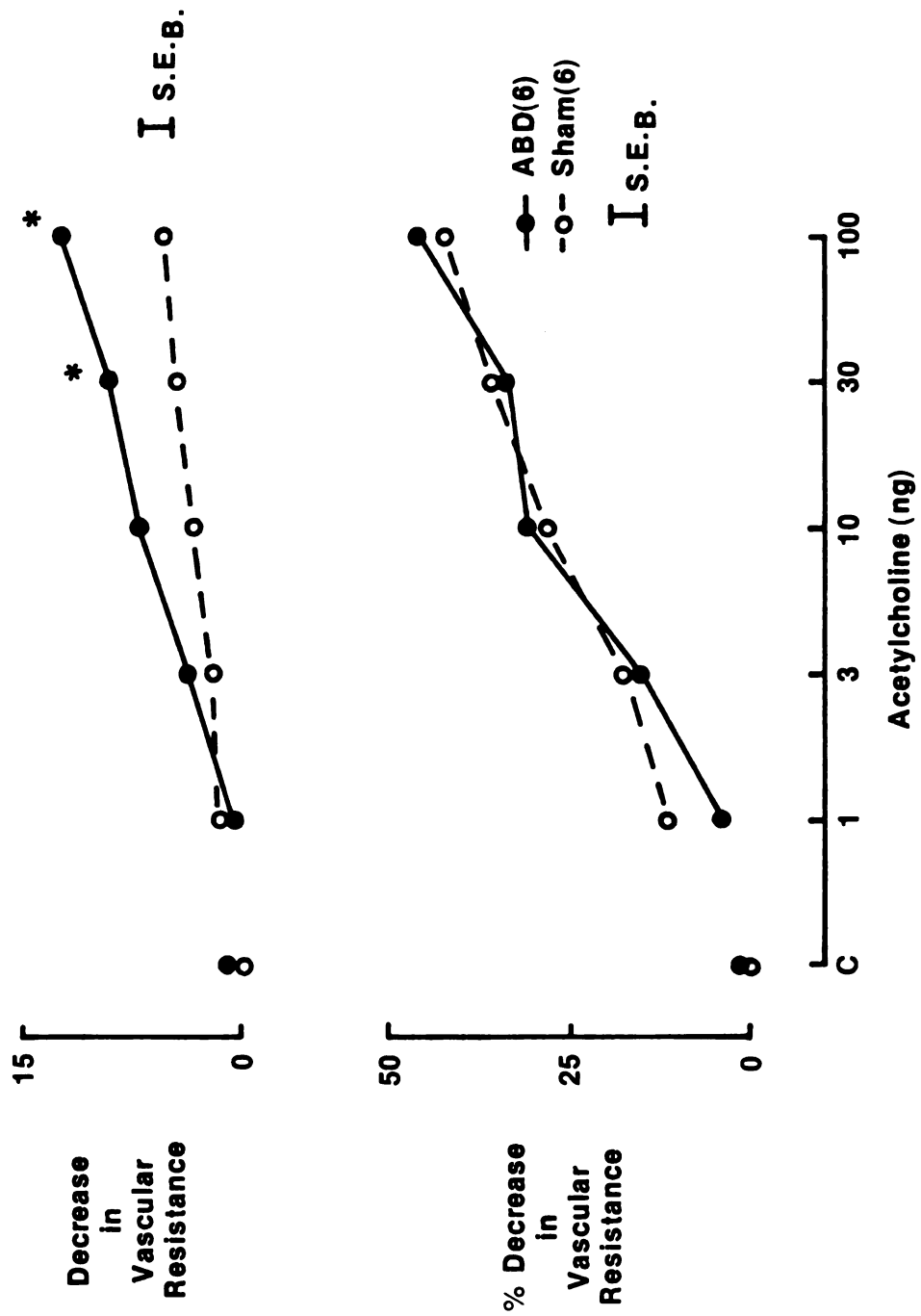


Figure 51

Figure 52. Components of hindlimb vascular resistance in rats approximately 1 year after ABD or sham operation. Numbers in parentheses represent number of animals tested in each group. Symbols explained in Figure 3. *As in Figure 3 ($p < 0.05$, Rank-sums test).

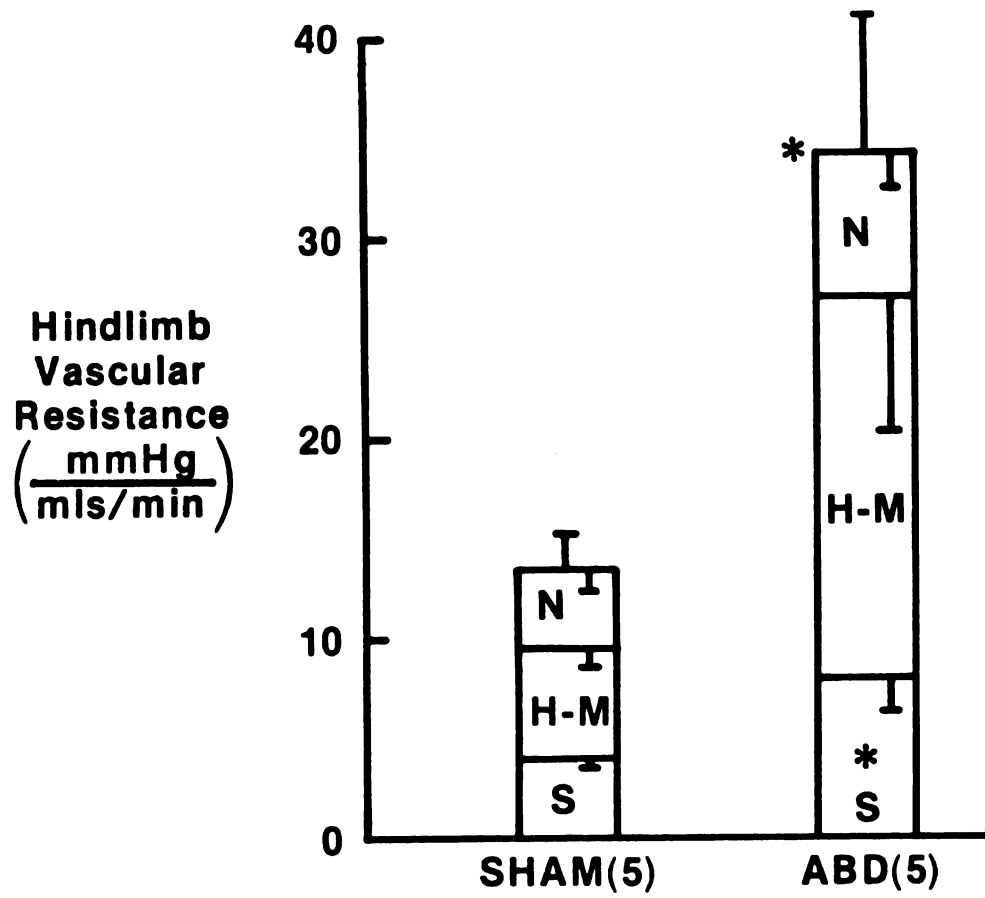


Figure 52

DISCUSSION

The purpose of the experiments performed in this thesis was to identify the factor or factors responsible for the genesis and maintenance of the elevated arterial pressure produced by aortic baroreceptor deafferentation in the rat. The role of the factors examined will be reviewed, and a hypothesis of the critical events involved in the genesis and maintenance of ABD hypertension will be outlined.

Characteristics of Blood Pressure Following ABD

As reviewed in the Introduction, it is agreed that blood pressure 1) rises immediately after baroreceptor deafferentation, 2) returns to at least near normal values within a few hours after nerve section and 3) is highly variable. Following this initial transient increase in blood pressure, some authors report that 1) animals are normotensive for about one week after SAD before chronic hypertension is observed (Schmitt and Laubie, 1979; also see Introduction), 2) hypertension does not occur at all (see Introduction), or 3) peak hypertension occurs soon after recovery from anesthesia, decreases slightly and remains elevated permanently (see Introduction).

It was found that ABD rats followed the latter pattern. Blood pressure rose significantly immediately after ABD (Experiment 1) but returned to normal within 30 minutes after ABD in the anesthetized

rat. Blood pressure was elevated over the first 24 hours after ABD (Figure 4) as compared to the 24 hour period before deafferentation. Peak blood pressure on the day after ABD occurred at night, but a similar diurnal rhythm was also observed on the day before ABD.

A number of other experiments (Experiments 3-10) confirmed these findings and indicate that blood pressure declines slightly over the first five days after ABD. The increased pressure following ABD was sustained for at least one to three months (Experiments 11-14). One year after ABD (Experiment 16) blood pressure was still slightly elevated, but the difference was not statistically significant.

Other investigators (Kreher and Nitschkoff, 1976; Masson et al., 1966; Krieger, 1964, 1970; Patel et al., 1981; Touw et al., 1979) have shown that ABD produces hypertension in rats. However, Kreher and Nitschkoff (1976), Krieger (1964) and Masson et al. (1966) used tail cuff plethysmography to measure blood pressure. The accuracy of this method in determining the blood pressure of baroreceptor deafferented rats has been questioned (Norman et al., 1981). Touw et al. (unpublished results) and Ciriello et al. (1980), using direct recording of arterial pressure, have shown that ABD in rats produces chronic hypertension. The work in this thesis confirms and extends this previous work by 1) examining the initial blood pressure changes more closely, 2) measuring blood pressure one year after ABD using minimally stressful techniques, and 3) being the first to show that baroreceptor nerve section leads to chronic hypertension using 24 hours/day continuous blood pressure measurement.

The 24 hour blood pressure was more variable in ABD rats (Experiments 2 and 13). This is consistent with previous work (see Introduction). However, blood pressure was very stable (compared to controls) in ABD rats during brief recording sessions (Study 12-I).

The Role of the Sympathetic Nervous System in ABD Hypertension

Since sympathetic nervous system activity varies inversely with baroreceptor nerve activity, one would expect that baroreceptor deafferentation-induced hypertension would result from increased sympathetic nervous system activity.

The role of the sympathetic nervous system in hypertension following baroreceptor deafferentation has been examined by surgical, pharmacological and biochemical techniques (see Introduction). However, attempts at blocking baroreceptor deafferentation-induced hypertension have used, almost exclusively, surgical techniques.

As discussed earlier (see Introduction), a number of investigators have found that sympathectomy blocked the production of acute hypertension produced by SAD. Unfortunately, surgical sympathectomy removes afferent as well as efferent nerves. These afferents may be important in cardiovascular control and the development of hypertension (Brody, 1981; Malliani et al., 1979).

Acute hypertension following ABD was blocked by a combination of prior adrenal demedullectomy and guanethidine treatment (Experiment 5). This experiment confirms the observation that inactivation of the sympathetic nervous system prevents hypertension produced by baroreceptor deafferentation.

The results of Experiment 5 also indicate that both the ortho-sympathetic nervous system and the release of adrenomedullary catecholamines play a critical role in the development of ABD hypertension, as neither guanethidine nor adrenal demedullectomy alone blocked acute ABD hypertension. The fact that neither treatment alone blunted ABD hypertension suggests that the sensitivity of one system increases in the absence of the other. The same observations and conclusions were reached by Doba and Reis (1974) who found that adrenal demedullectomy had to be combined with 6-hydroxydopamine treatment in order to block NTS hypertension.

The observation that prior bilateral adrenalectomy did not prevent hypertension following ABD confirms previous findings (Hermann et al., 1959; Jourdan and Collet, 1951) in SAD dogs.

A number of investigators (see Introduction) have found that pharmacological interference with sympathetic efferent function reverses hypertension produced by baroreceptor deafferentation. The results presented in this thesis using total autonomic blockade (Experiments 4, 12 and 16) confirm these earlier studies. Additionally, it was found that the hypertension could be reversed one day and one year after ABD, time points not examined in earlier studies.

Recent biochemical studies (Patel et al., 1981; Alexander, 1980) have suggested that initially elevated sympathetic nervous system activity wanes with time after baroreceptor nerve section. Alexander (1980) has suggested that these biochemical studies indicate that chronic (6 weeks post-operatively) hypertension produced by SAD is not maintained by increased sympathetic nervous system activity.

Total autonomic blockade one day (Table 4), one month (Figure 25) and one year (Figure 47) after ABD normalized blood pressure. These results suggest that increased sympathetic nervous system activity is responsible for the elevated blood pressure in ABD hypertension. In addition, the fall in blood pressure after autonomic blockade was strongly related to the resting blood pressure in ABD but not sham-operated rats. These relationships after total autonomic blockade did not occur in hypertension of predominantly non-neural origin (Experiment 19).

Experiment 14 demonstrated that there was increased renal sympathetic nerve activity one month after ABD. This increased nerve activity was responsible for the increased renal vascular resistance seen in chronic, anesthetized ABD rats.

A number of observations are consistent with the hypothesis that sympathetic nerve activity waned with time after ABD. It was found that the relative contribution of the sympathetic nervous system to resting hindquarter vascular resistance in the anesthetized rat was increased 9 days but not 30, 90 or 360 days after ABD (Figures 40 and 52). Increased sympathetic drive to the heart (determined by the change in heart rate after propranolol) was elevated one day but not 30 or 360 days after ABD (Experiments 4, 12 and 16). Finally, the strength of the correlation between the drop in blood pressure after total autonomic blockade and resting MAP became weaker over time (Experiments 4, 12 and 16), suggesting that sympathetic nervous system activity became a less important determinant in the progression of ABD hypertension.

In summary, the data presented in this thesis supports the hypothesis that sympathetic nervous system hyperactivity wanes (perhaps non-uniformly) with time after ABD. However, the data in this thesis are consistent with the hypothesis that increased sympathetic nervous system activity is an important determinant of elevated arterial pressure in chronic ABD rats, even up to one year after surgery.

Relationship Between the Degree of Baroreceptor Deafferentation and the Degree of Hypertension

As reviewed previously (see Introduction), it has been suggested that the degree of baroreceptor deafferentation determines the degree of hypertension produced by baroreceptor deafferentation. This hypothesis has been used to argue that only complete baroreceptor deafferentation can result in chronic hypertension (Scher, 1981). However, as reviewed in the Introduction, the hypothesis that the degree of barodeafferentation determines the degree of hypertension produced by barodeafferentation has not been adequately tested.

The results in this thesis do not support the hypothesis that the degree of baroreceptor deafferentation determines the degree of blood pressure elevation following baroreceptor deafferentation. It was found that the gain of the baroreflex was not inversely related to resting blood pressure in ABD rats (Experiments 12 and 16). Such an inverse relationship would be expected if the hypothesis stated above was true. In addition, the increase in response to bilateral carotid occlusion after ABD (a rough index of the degree of aortic baroreceptor deafferentation) was not significantly correlated with the rise in blood pressure after ABD (Experiment 1).

The failure to observe these relationships suggests that the degree of inhibition of a central nervous system sympathoexcitatory center is not the sole determinant of the elevated MAP seen following ABD.

Whole Body Hemodynamics of Acute Hypertension Produced by ABD

A number of investigators have found that cardiac output or total peripheral resistance increases in acute SAD hypertension in rabbits, dogs and cats (see Introduction).

Krieger et al. (1979) has found that TPR increases and cardiac output decreases significantly 6 hours after SAD in rats. Acute ABD-induced hypertension was characterized by increased total peripheral resistance in the anesthetized (Table 1) and conscious (Figure 17) rat.

It was found that cardiac output decreased slightly in the acute, awake ABD rat (Figure 17). By the third day after ABD, cardiac output was completely normal. A similar study could not have been done in rats made hypertensive by lesion of the NTS or anterior hypothalamus, since these animals die a few hours after placement of the lesions (Doba and Reis, 1974; Nathan and Reis, 1975). Daily measurements of cardiac output during the first few days after SAD have not been performed previously in rats, but cardiac output 6 months after deafferentation is normal (Krieger, 1967; Krieger et al., 1979). If the hemodynamic response of sino-aortic deafferented rats is similar to that of ABD rats, the results of Experiment 6 indicate that cardiac output returns to normal within one week after the onset of neurogenic hypertension in the rat.

Doppler flowmetry was used to measure cardiac output in Experiments 6 and 20. This is a relatively new technique, and a major limitation is recognized. The measured Doppler shift is only proportional to blood velocity, the proportionality factor being the angle formed by the path of the soundwave and the central axis of the blood vessel (Haywood et al., 1981). Therefore, a change in flow occurring as a result of a change in vessel cross sectional area would not be detected by this method. Despite this theoretical limitation, Haywood et al. (1981) have found that Doppler shift is significantly correlated with volume flow measured by electromagnetic flowmetry. Fletcher et al. (1976) have used Doppler flowmetry to measure daily changes in cardiac output. They found that Doppler flowmetry could detect the expected acute changes in cardiac output induced by selected drugs. Experiment 20 showed that Doppler flowmetry could detect the expected increase in cardiac output during anemia (Guyton, 1981). Also, recent studies (Pagani et al., 1979; Compagno et al., 1977) performed on conscious animals suggest that aortic diameter does not change significantly after acute hypertension in adult animals. It is concluded that Doppler flowmetry is a reliable technique for measuring day-to-day changes in cardiac output.

It has been hypothesized that chronic hypertension occurs as a result of an autoregulatory induced increase in total peripheral resistance or a reduced renal perfusion pressure (Guyton et al., 1981). Since ABD produces chronic hypertension (Experiments 11-14 and 16), the possibility that ABD hypertension might go through an early phase of increased cardiac output was examined.

No increase in cardiac output was found at any time following ABD (Table 1 and Figure 17). This suggests that whole body autoregulation is not a pathogenetic factor in this form of hypertension. However, cardiac output was not measured continuously over the first 24 hours after ABD. An autoregulatory-induced rise in peripheral resistance could have occurred in the three hours between nerve section and recovery. In support of this hypothesis, Liedtke et al. (1973) have shown that whole body autoregulation can occur within a few minutes in the SAD dog. However, it should be noted that ABD rats still have the carotid sinus nerves intact, differentiating ABD and SAD animals. Also, Levy et al. (1954) have shown that SAD dogs may not demonstrate whole body autoregulation. Alexander and DeQuattro (1974a) reported that the increased total peripheral resistance seen in chronic SAD rabbits may be preceded by a phase of increased cardiac output. This high output phase lasted approximately 40 hours. Liard et al. (1975) found that hypertension produced by stellate ganglion stimulation in conscious dogs went through an initial transient phase of increased cardiac output followed by a stable increase in total peripheral resistance. The increase in cardiac output lasted more than 2 but less than 24 hours after onset of stimulation. These last two observations indicate that measuring cardiac output a few minutes and three hours after ABD as was done in Experiments 1 and 6 would detect an increased flow if it had occurred.

Pathophysiology of ABD Hypertension

As reviewed previously, there have been few well designed studies examining the pathophysiology of SAD hypertension. These studies suggest that rabbits but not rats are susceptible to cardiovascular lesions following SAD.

Pathophysiological studies on chronic ABD rats have not been completed. However, it should be noted that 4 of 14 ABD rats and 0 out of 11 sham-operated rats in Experiment 16 died suddenly. The cause of death of two of these rats was not determined. The other two rats died following cerebral hemorrhage, a condition highly associated with human hypertension (Kannel, 1977).

Recent work may suggest how ABD rats may be more prone to a stroke than sham-operated rats. Bevan and Tsuru (1981) have found that sympathectomy in young animals results in retarded growth of blood vessels. Hart et al. (1980) have found that sympathetic denervation of cerebral blood vessels also retards the growth of these vessels. In addition, there is increased incidence of cerebral hemorrhage in the sympathetically denervated hemisphere of the brains of stroke-prone SHR (Sadoshima et al., 1981). It is suggested that sympathetic denervation of cerebral blood vessels may occur in ABD rats as a result of cutting the cervical sympathetic chains. This might result in an increased incidence of stroke in these rats.

Cardiac hypertrophy was found in rats 60 (Table 6) and 90 (Figure 41) days after ABD, but not one year after ABD (Experiment 16). The failure to find cardiac hypertrophy one year after ABD was an unexpected finding, since it has been thought that elevated arterial

pressure invariably leads to cardiac hypertrophy (Ostman-Smith, 1981). However, Ostman-Smith (1981) has suggested that there is no good evidence indicating that increased cardiac work leads to cardiac hypertrophy. Ostman-Smith (1981) has suggested that increased sympathetic drive to the heart leads to cardiac hypertrophy. The results in this thesis are compatible with this latter hypothesis.

It was found that there was increased sympathetic neural drive to the heart (as determined by the change in heart rate after propranolol) one day (Table 4) but not 30 (Experiment 12) or 360 days (Experiment 16) after ABD. Thus, after the stimulation for cardiac hypertrophy (increased cardiac sympathetic nerve activity) was gone, the hypertrophy regressed. This conclusion is supported by the observations of Velly et al. (1973) who observed that cardiac hypertrophy regressed in SAD rats. Also, DeQuattro et al. (1969) found that the heart weight to body weight ratio 2 and 21 days after SAD was significantly related to cardiac norepinephrine stores but not MAP. These observations are consistent with the hypothesis of Ostman-Smith (1981).

As reviewed previously (see Introduction), it has been suggested that hypertension invariably leads to an increase in the wall to lumen ratio of the arterioles. This increase can be detected by observing an increased resistance at maximal vasodilation and a non-specific increase in vascular reactivity.

Jones and Hallbäck (1978) did not find an increased vascular resistance at maximal vasodilation in the isolated perfused hind-quarters of rats 4 months after SAD. In Experiment 15 it was found

that resistance at maximal dilation was not increased in rats 9, 30 and 90 days after ABD. These results confirm the observations of Jones and Hallbäck (1978).

Langer et al. (1975) reported that vascular reactivity was increased in the isolated perfused mesenteric vascular bed of rats 6 months after SAD. They found that this increased reactivity was of postsynaptic origin, but did not examine vascular resistance at maximal dilation. In Experiment 16, increased vascular reactivity in ABD rats one year post-operatively was associated with an increase in vascular resistance at maximal dilation. This result confirms the observations of Langer et al. (1975) and indicate that the increased reactivity seen by those investigators may have been the result of "structural" changes in the vasculature. The results reported in this thesis and those of others suggest that these structural changes occur approximately 6 months after barodeafferentation in rats.

The observation that total autonomic blockade normalized MAP in ABD rats one year post-operatively suggests that these rats did not have an important structural component to their blood pressure (Reid et al., 1973). This discrepancy can be resolved by examining the relationship between blood pressure after total autonomic blockade and vascular resistance at maximal vasodilation. It was found that MAP after autonomic blockade in rats with a vascular resistance at maximal vasodilation greater than 5.0 mmHg/ml/min (3 ABD rats) was 9 mmHg higher (difference not statistically significant) than MAP after blockade in rats with a vascular resistance at maximal vasodilation

less than 5.0 mmHg/ml/min (4 sham-operated and 1 ABD rat). This observation indicates that the elevated blood pressure of certain ABD rats one year post-operatively was partially maintained by an increased "structural" component.

Role of the Kidneys in ABD Hypertension

Renal Nerves. As discussed previously (see Introduction) there have been occasional reports that hypertension does not occur after baroreceptor deafferentation in animals without their renal nerves. None of the investigators reporting this finding could adequately explain their results. There have also been reports that renal denervation does not prevent hypertension produced by baroreceptor deafferentation (see Introduction). The results in this thesis (Experiment 7) confirm these latter studies. Hypertension occurred after ABD in rats without a functional renal innervation.

Renal Hydraulic System. Guyton et al. (1981) have proposed that the renal hydraulic system controls long-term blood pressure levels. They have proposed that the set point of this system must be changed in order for the blood pressure to remain elevated indefinitely. It was found that ABD produced hypertension with no initial pressure diuresis (Figure 9) as might have been predicted by Guyton et al. (1981). Therefore, experiments were performed to determine what factors might reduce this expected pressure diuresis. Elimination of such factors should result in the re-establishment of normal arterial pressures in ABD rats following a pressure diuresis.

Experiments 8, 9 and 10 and study 7-II showed that normal fluid intake alone or in combination with renal denervation or with controlled levels of adrenocortical hormones or ADH, did not result in a pressure diuresis of sufficient magnitude to normalize arterial pressure after ABD. While a diuresis did occur on the first day after ABD in almost all of these studies, it was not sustained despite the continued blood pressure elevation. These experiments indicate that some other factor or a different combination of factors already tested is responsible for the blunting of the expected pressure diuresis. An alternative explanation for these results is that the renal hydraulic system controlling blood pressure is actually self-limiting, and does not have infinite gain as proposed by Guyton et al. (1974).

The Role of ADH in ABD Hypertension

Very recent observations indicate that ADH is critical for the development of hypertension produced by baroreceptor deafferentation. Alexander and Morris (personal communication) have found that ADH levels increase significantly following SAD in rats when compared to appropriate controls. Berecek et al. (personal communication) have found that hypertension does not occur after SAD in anesthetized Brattleboro rats. These rats had a reduced but measurable pressor response to stimulation of the central nervous system, implying that a lack of ADH reduced blood vessel reactivity to adrenergic stimuli. In Experiment 9 it was found that hypertension occurred following ABD in Brattleboro rats receiving replacement doses of ADH and maintained on a normal fluid intake.

These results suggest that ADH plays an important permissive role in the expression of hypertension following baroreceptor deafferentation. It is hypothesized that ADH must be present in order for sympathetic vasoconstriction to occur following baroreceptor nerve section. This synergistic action of adrenergic stimuli and ADH has been observed in isolated blood vessels (Bartelstone and Nasmyth, 1965; for review, see Altura and Altura, 1977).

Plasma Volume in ABD Hypertension

Plasma volume in chronic ABD rats was significantly lower than that of sham-operated control rats (Figure 27). This result is predicted by the systems model of Guyton et al. (1974) to occur in physiologic response to any increase in arterial pressure. It was also observed that plasma volume was reduced 5 days after ABD in rats with ad lib. access to food and water (Figure 7). If it is assumed that volume contraction in this model is a result of hemodynamic alterations occurring with increased arterial pressure, the persistence of plasma volume contraction in ABD rats (up to one month) and the failure of volume contraction to persist in rats with SAD (Alexander, 1979) offers evidence that ABD hypertension in rats is a more stable variety than that seen following SAD.

According to the systems model (Guyton et al., 1974), a contraction of plasma volume should lead eventually to a restoration of normal arterial pressure; this failed to occur in rats with ABD. Nevertheless, it is of considerable interest to note the positive correlation between plasma volume and mean arterial pressure in rats

with chronic ABD (Figure 28) hypertension. It is apparent that this relationship develops between 5 and 30 days after ABD, as MAP and plasma volume were not significantly correlated at 5 days after ABD (Figure 8). This long time course is predicted by the model of Guyton et al. (1974).

It appears that those rats undergoing ABD that are least able to contract plasma volume during a neurogenically induced rise in arterial pressure maintain the highest level of arterial pressure in the chronic situation.

The ABD Rat as a Model of Human Essential Hypertension

There is no animal model of hypertension which perfectly resembles human essential hypertension (McGiff and Quilley, 1981; Julius and Esler, 1976). Despite this limitation, it is necessary to use these animal models in order to obtain detailed information on the pathogenesis and maintenance of human hypertension, since research on human patients is necessarily limited. It would be desirable to study the pathogenesis and maintenance of hypertension in animal models which at least closely resemble human essential hypertension. Therefore, it is relevant to ask the question: does the ABD rat resemble human essential hypertension?

Before answering this question, one must consider the hypothesis that human essential hypertension may be a multifactorial disease (Khosla et al., 1979). If this is true, then one should rephrase the question posed above to: do ABD rats resemble a subgroup of human essential hypertension?

It appears that ABD rats resemble human 'borderline' hypertension. These patients often progress to higher blood pressure levels (Carey and Ayers, 1976) and are at increased risk of developing cardiovascular disease (Julius and Schork, 1971; Kannel et al., 1980). These patients often have signs of increased activity of the sympathetic nervous system (reviewed by Julius and Esler, 1975), such as elevated levels of plasma catecholamines (reviewed by DeChamplain et al., 1981). Enhanced sympathetic nervous system activity in ABD rats is indicated by the observations that total autonomic blockade normalizes blood pressure and heart rate in ABD rats, plasma volume is decreased, and there is enhanced sympathetic activity to the hind-quarters and kidneys of ABD rats at certain times post-operatively.

Increased cardiac output is found in some (reviewed by Julius and Schork, 1971) but not all (Eich et al., 1962; Safar et al., 1973; Messerli et al., 1978; Hofman et al., 1981) borderline hypertensive patients. Since increased total peripheral resistance and normal cardiac output is associated with ABD hypertension, it appears that ABD rats resemble borderline hypertensives with low or normal cardiac output.

It has been reported that there is increased blood pressure variability (Kannel et al., 1977), increased vascular reactivity (Julius and Esler, 1975; Weidmann et al., 1980; Safar et al., 1975; Suck et al., 1971), an increased "structural" component of vascular resistance (Takeshita and Mark, 1978; Niederle et al., 1976; Sannerstedt, 1976), and decreased baroreflex function (Takeshita et al., 1975; Gribbin et al., 1971; Eckberg, 1977) in borderline hypertensive

patients. In addition, Mancía et al. (1978) have found decreased non-carotid (presumably aortic) baroreflex function in essential hypertension. All of these characteristics listed above have been observed in the ABD rats (Experiments 12, 13 and 16).

Whether all of the characteristics of the ABD rat occur simultaneously in any subgroup of hypertensive patients is unknown. In addition, plasma volume is usually inversely related to blood pressure in hypertensive patients (Tarazi et al., 1970; Tarazi and Dustan, 1973). There was a positive correlation between these two variables in chronic ABD rats (Figure 28), and no correlation in acute (5 days post-operatively) ABD rats (Figure 8). Despite these exceptions, it seems that the ABD rat is a good model of those cases of essential hypertension associated with sympathetic hyperfunction.

Summary - Pathogenesis and Maintenance of ABD Hypertension

The purpose of the experiments in this thesis was to determine the factor or factors responsible for the pathogenesis and maintenance of hypertension produced by aortic baroreceptor deafferentation in the rat. This summary will identify these factors and present more detailed hypotheses about how these factors change during ABD hypertension.

The data presented in this thesis indicate that hyperactivity of the sympathetic nervous system is a critical determinant of the hypertension produced by ABD. However, this elevated activity wanes with time. Also, sympathetic activity is not diffusely elevated in chronic ABD hypertension. There appears to be a specific pattern of elevated

sympathetic outflow in chronic ABD rats. In other words, in chronic ABD hypertension, there may be increased sympathetic activity in only some nerves, and normal activity in others.

Following the acute phase of ABD hypertension, factors controlling plasma volume or plasma volume itself become a more important determinant of ABD hypertension. This hypothesis is suggested by the significant positive correlation between mean arterial pressure and plasma volume in chronic ABD rats. While there is no clear explanation for this relationship, it is tempting to speculate that ADH is an important determinant of this correlation. If ADH is elevated to varying levels after ABD, those animals with higher levels would be likely to retain more fluid than other ABD rats. In addition, the synergistic action of ADH and adrenergic stimuli on blood vessels would be expected to cause enhanced vasoconstriction in ABD rats with elevated levels of ADH. Therefore, the vascular and renal effects of ADH could explain the positive correlation between plasma volume and mean arterial pressure in chronic ABD rats. It was found that rats with constant levels of ADH did not sustain ABD hypertension (Experiment 9). Unfortunately, this result is only preliminary evidence suggesting that elevated ADH may be an important factor in determining long-term hypertension in ABD rats. Further experiments examining the role of ADH in ABD hypertension seem to be indicated.

Chronic ABD hypertension of about one year duration was associated with an increased 'structural' component of vascular resistance (Experiment 16). This observation is expected in chronic hypertension

(Jones and Hallbäck, 1978). Thus, ABD hypertension eventually becomes 'fixed'.

In summary it appears that ABD hypertension is initially characterized by increased sympathetic vasoconstriction (Experiment 6); progresses to a stage where volume factors become an important determinant of the elevated arterial pressure; and after a sufficiently long time, becomes 'fixed' by structural vascular changes. However, this sequence of events clearly does not occur in every rat subjected to ABD.

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