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The role of low versus high pressure baroreceptors in the regulation of fluid balance

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The role of low versus high pressure baroreceptors in the regulation of fluid balance.

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Dedicated to

my parents

Wen Kai, and **Ruey Feng Lee**

for their love, support, and education to their children.

my sister, **Mu Feng Lee**

for her unselfish help and love.

my wife, **Mei Yu Lee**

for her love, understanding, and encouregement.

my son, **Shang Che Lee**

for making everything worthwhile.

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Abstract

The relative roles of cardiopulmonary, sinoaortic, and renal baroreceptors in the regulation of plasma renin activity (PRA), vasopressin, and cortisol, were evaluated in dogs with chronically implanted cuffs around the ascending aorta, pulmonary artery, or the abdominal aorta just proximal to both renal arteries. Inflation of the cuffs was adjusted to cause a reduction of distal arterial pressure and hence, renal perfusion pressure (RPP) of 0, 5, 10, 20, or 30% of control for 1 hour.

Reducing RPP by inflation of the suprarenal cuff (N=4) led to a significant ($p<0.05$) increase in PRA throughout the dose range examined. However, constriction of the ascending aorta (N=7) to cause identical reductions in RPP failed to increase PRA. The apparent paradox in these results may be explained by differential effects of the two maneuvers on left atrial pressure. Left atrial pressure increased dose dependently during inflation of the ascending aortic cuff but did not change during inflation of the suprarenal cuff. In spite of the profound systemic hypotension caused by constriction of the ascending aorta, vasopressin and cortisol also failed to increased.

To determine if elevated right atrial pressure (RAP) inhibits the release of renin, vasopressin, and cortisol following systemic hypotension, another group of dogs (N=4) were prepared with cuffs around the pulmonary artery. Inflation of the pulmonary cuff to cause similar systemic hypotension led to significant ($p<0.05$) increases in PRA, vasopressin, cortisol, and RAP.

To further elucidate the efferent pathway which mediates the

potent inhibition of renin release, we performed a series of ascending aortic and suprarenal cuff inflations in dogs with bilateral renal denervation (N=5). Comparing the renin response to inflation of the ascending aortic or suprarenal cuff suggest that there is an increase in the threshold required to elicit a renin response to graded reduction of RPP caused by inflation of the ascending aortic cuff. Since the kidney were denervated, the shift in threshold must be caused by an humoral substance (s).

Therefore, we conclude that powerful inhibitory signals, arising from the left heart, can inhibit the release of renin, vasopressin, and cortisol in response to systemic hypotension.

Contents

Chapter 1

Introduction

A constant blood volume is important for normal function of the circulatory system. However, the regulation of blood volume is intimately related to that of the extracellular volume (Manning and Guyton, 1983). The extracellular fluid is composed of water and electrolytes, mainly sodium chloride. In the case of water balance, precise control is achieved by a control of fluid intake via thirst mechanisms and the control of output by vasopressin. Mammals exhibit a remarkable capacity to conserve sodium. When sodium supply is not limiting, then the renin-angiotensin-aldosterone system provides the major influence over the control of sodium balance. Finally, glucocorticoids might be important in water homeostasis, since physiologic doses of hydrocortisone may produce hypotonic urine in patients with hypopituitarism and an inability to dilute their urine (Agus and Goldberg, 1971). As sodium and water balance are intimately concerned with the regulation of extracellular, and hence, blood volume, it is not surprising to find reflexes emananting from the circulation which control the secretion of vasopressin, cortisol, and renin.

There are receptors in the circulatory system which detect the changes of pressure or volume of the system and reflexly, or directly, regulate the secretion of vasopressin, cortisol, and renin. These receptors are classified, according to their anatomic position and function, as sinoaortic, cardiopulmonary, and renal baroreceptors. In most species, the major high pressure baroreceptor activity is found in the carotid sinus and in the aortic arch (Downing, 1980; Angell-James

and Daly, 1970). Baroreceptors are also found in the four chambers of the heart and the pulmonary circulation (Bishop et al., 1983). There are hypothetical receptors in the kidney which may alter plasma renin activity in response to changes in renal perfusion pressure (Davis and Freeman, 1976). Although these receptors are named renal baroreceptors, they are different from the classical arterial baroreceptors since they exert their function intrarenally without involving a central reflex arc. Although previous investigators have shown that cardiopulmonary, sinoaortic, and renal baroreceptors are able to regulate the secretion of vasopressin, cortisol, and renin, the relative roles of these baroreceptors in the regulation of hormones are much less certain, especially in conscious animals. Thus the aims of this thesis are:

(1) to determine the relative roles of cardioplumonary and sinoaortic baroreceptors in the control of vasopressin and cortisol in conscious dogs.

(2) to determine the relative roles of cardiopulmonary, sinoaortic, and renal baroreceptors in the control of plasma renin activity in conscious dogs.

(3) to further examine the efferent pathway of the baroreflexes in the regulation of plasma renin activity.

This was accomplished by preparing different groups of dogs with cuffs implanted around the ascending aorta, the abdominal aorta just proximal to both renal arteries, or the pulmonary artery. Thus, graded inflation of any of the three cuffs could be used to bring out a similar reduction in pressure distal to the cuff accompanied by differential changes in pressure in the low and high pressure areas of the thoracic

circulation. To assess whether renal nerves mediate the inhibition of renin secretion from the low pressure baroreceptors, the ascending aortic or suprarenal balloon was inflated in another group of dogs with bilateral renal denervation to achieve graded reduction in renal perfusion pressure.

Historical Review

The historical review will cover the sinoaortic, cardiopulmonary baroreceptors and how they regulate the secretion of vasopressin, cortisol, and renin

Sinoaortic Baroreceptors

The first idea that the cardiovascular system may be regulated by neural reflexes originating in the heart and great vessels came with the discovery of the depressor (aortic) nerve by Cyon and Ludwig (1866). They found that stimulation of the central end of the nerve caused marked bradycardia and hypotension. They believed that the nerve arose from endings of the heart itself and monitored intracardiac pressure. If the heart beat too strongly, these endings would diminish cardiac work by reflexly slowing the heart and reducing arterial pressure. Although their observations helped to develop the concept of reflex neural control of the heart, they incorrectly concluded that the aortic nerve arose in the heart. Four decades later, Koester and Tschermark (1902) proved, by degeneration experiments, that the aortic nerve arose from the aortic arch and the origin of the great vessels.

The discovery of carotid baroreceptors, however, was 20 years later than that of the aortic baroreceptors. For many years it had been known that cardiac slowing could be produced by external pressure on the upper

neck and a rise of blood pressure and heart rate followed carotid occlusion. The former was named "vagus pressure test" by Tschermark (1868) and the mechanism was attributed to a direct stimulation of the vagal trunk. The mechanism of hypertension induced by carotid occlusion was attributed to ischemia of the brain stem. Although it had been shown that occlusion of the carotid arteries did not markedly decrease the cerebral medullary blood flow by Bayliss in 1893, the carotid baroreflex was not identified by Hering until 1923. Hering clearly demonstrated this to be reflex in nature, with sensory fibers in the carotid sinus and bifurcation. He showed that the afferent pathway (the sinus or Hering nerve) resides in a branch of the glossopharyngeal nerve, and that stimulation of the sinus or its nerve produced reflex cardiac slowing and hypotension that was independent of the accompanying bradycardia (Hering, 1927).

In spite of species difference, the major high pressure baroreceptors are located in the carotid sinus, and the arch of the aorta at the origin of the great vessels. However, baroreceptors can be found in the occipital arteries, bifurcation of the brachiocephalic artery, and both common carotid arteries at the origin of the superior thyroid arteries (Heymans and Neil, 1958; Kirchheim, 1976). Actually, as Koch pointed out in 1931, these receptor sites were those which survived of the embryonic visceral arch vessels (Heymans and Neil, 1958) Despite these species difference in topography, the areas supplied most densely with receptor endings in man and in mammals are composed mainly of elastic tissue. For example, the sinus has a thinner media, contains less smooth muscle, and shows a higher collagen and elastin content

(86%) than adjacent segments of the common (74%) and internal (65%) carotid arteries.

Two types of sensory nerve endings have been found in the carotid sinus or aortic arch of mammals, diffuse type 1 receptors and compact type 2 receptors. Although unmyelinated C fibers were also found, the majority of the sinoaortic baroreceptors were connected to myelinated nerve fibers. This could be the result of a sampling bias during single fiber study of the sinus or the aortic nerve, because, when recordings are made initially from multifiber filaments, the silent C fibers may be missed and the more active A fibers selected (Baker et al, 1979).

The fibroelastic tissue of the vascular wall transmits the intensity of the stimulus by causing mechanical deformation of the receptor generator region (Paintal, 1972). The natural stimuli for the baroreceptors were the mechanical deformation of the receptor areas within the arterial wall rather than the intraarterial pressure changes per se. Hauss (1949) had shown that the reflex fall of blood pressure produced by an increase of carotid sinus pressure was abolished if stretching of the sinus was prevented by a plaster cast applied to the outside. Moreover, bilateral placement of rigid casts around the carotid sinus had been reported to produce sustained hypertension in rabbits, presumably also by preventing pulsatile deformation of the sinus wall thereby abolishing tonic carotid barorecepor inhibition of sympathetic activity (Burstyn, 1972). Thus, the sinoaortic baroreceptors were stretch receptors and responded to mechanical deformation of the vascular wall.

A pulsatile pressure in the sinoaortic region was a more effective

stimulus for baroreceptors than a nonpulsatile pressure, when mean intracarotid pressure and the frequency of pulsation were kept constant (Ead et al., 1952). Increasing the pulse amplitude from 0 to 75 mmHg without changing the mean perfusion pressure also resulted in increased baroreceptor activity (Gero and Gerova, 1967). Even when the pulse frequency of a sinusoidally varying carotid sinus pressure was increased while the pulse pressure and the mean pressure were kept constant, a fall of systemic resistence was observed. Thus, besides the mean pressure, the dynamic part of the blood pressure (pulse pressure, frequency, even dP/dT) was important in deciding the overall baroreceptor activity (Kirchheim, 1976).

The efferent limb of the sinoaortic reflex is mediated through both the sympathetic and parasympathetic systems to regulate heart rate, contractility, cardiac output, and peripheral resistence (Kirchheim, 1976). Unloading the sinoaortic baroreceptors usually leads to a pressor response of the cardiovascular system, conversely, overloading the sinoaortic baroreceptors usually results in a depressor reflex. The sinoaortic baroreflex can also regulate hormones that control fluid and electrolytes balance, this will be reviewed in detail later.

Since the sinoaortic baroreceptors are stretch receptors responsive to mechanical deformation of the arterial wall, the baroreceptor function could be significantly affected by alteration in compliance or distensability of the sinus wall, which might result from catecholamine stimulation, acidosis, etc.. Whether the sensitivity of the sinoaortic baroreflex can be regulated by the sympathetic system might be of physiologic importance and has aroused considerabel interest recently.

Sympathetic innervation of the sinus was demonstrated both by traditional microscopy and by electronmicroscopy (Kirchheim, 1976). Application of epinephrine or stimulation of sympathetic efferents to the sinus increased the sensitivity of single baroreceptor units to static and pulsatile pressure (Peverler et al., 1980). Thus, the sensitivity of the high pressure baroreceptors can be regulated by sympathetic nervous system.

On the contrary, angiotensin II has been reported to attenuate the baroreflex control of heart rate in dogs (Lumbers et al., 1979; Guo et al., 1984). When the action potential of the sinus nerve was recorded during equivalent increases of sinus pressure caused by infusion of angiotensin II, and by phenylephrine, or by inflation of an aortic balloon, there was no difference in the discharge of single carotid sinus nerve fibers in response to any level of blood pressure elevation caused by any maneuver. When action potential was recorded from vagal efferent fibers, activity increased when blood pressure was increased by infusion of phenylephrine, or inflation of an aortic balloon. However, when blood pressure was elevated by angiotensin II, vagal efferent fiber activity was either decreased, unchanged, or increased much less than it did in response to phenylephrine (Lumbers et al., 1979). Guo et al. showed that IV infusion of angiotensin II in dogs caused attenuation of baroreceptor control of heart rate, however, when angiotensin II infusion was confined to the isolated carotid sinus, the attenuation disappeared. Thus angiotensin II appeared to have no effect on baroreceptor sensitivity , it did attenuate the arterial baroreflex arc through an effect on the central nervous system.

In contrast to angiotensin II, current data suggest that vasopressin is capable of augmenting the overall strength of the sinoaortic baroreceptors and these alterations can occur at plasma concentrations that are well within the physiological range.

The possible modulation of sensitivity of the sinoaortic baroreflex arc by the sympathetic nervous system or peptides such as angiotensin II or vasopressin must be kept in mind during interpretation of the activity of high pressure baroreceptors, especially when the activity of the reflex arc is assessed by pressure perfusing the receptor areas. When the sensitivity of two baroreflex arcs is different (for example: one system perfused with catecholamine, the other angiotensin II), the reflex effect of the two reflex arcs could be different in spite of the same perfusion pressure.

Both carotid and aortic baroreceptors adapt to both static and dynamic pressure after a few minutes in dogs (Sleight et al., 1977; Coleridge et al., 1980). Also the baroreceptor reset phenomenon had been demonstrated in chronic hypertensive animals. Impulse traffic in the sinus nerve was less in the hypertensive dogs at all levels of carotid sinus pressure, and maximal discharge frequency of the hypertensive animals never reached the level of normal animals (Kezdi, 1962). Thus if high pressure baroreceptors adapt, it is difficult to imagine how such a system would be responsible for long term blood pressure control. In a carefully controlled study using a chronic sinoaortic denervated dog preparation, Cowley et al. (1973) found that the average 24 hours mean arterial pressure was only 11.1 mmHg higher than that of the control dogs. However, the daily range of blood pressure deviation in normal

dogs was only 50 mmHg, whereas, in the denervated dogs, the range was 125 mmHg. Thus the primary function of the baroreflex perhaps is not to set the chronic level of arterial pressure but, instead, to minimize variations in systemic arterial pressure (Cowley et al., 1973).

The carotid baroreceptors were believed to have a more powerful buffering action than did the aortic baroreceptors. Indeed the latter had been thought to contribute to control of peripheral resistence and heart rate only when mean arterial presure was higher than normal (Pelletier et al., 1972). These differences were attributed to differences in baroreceptor characteristics because the relationship between total nerve activity and pressure for carotid sinus nerve appeared to be much steeper and to cover lower pressure range than that of the aortic nerve. However, single nerve recording failed to demonstrate any obvious differences between the two as suggested by total nerve recording (Arndt and Samodelov, 1980). Coleridge et al. (1980) found that there were unmedullated C fibers and medullated A fibers in dog aortic nerve. Indeed the C fibers and small medullated A fibers had thresholds well above normal blood pressure, however, the conventional aortic baroreceptors with large medullated A fibers appeared to be active at normal arterial pressure. Thus, Coleridge et al. concluded that the "small-fibre baroreceptors" of dog aortic nerve might have their greatest importance in protecting against an increase in arterial pressure, the conventional aortic baroreceptors, were highly sensitive to deviations on either side of normal mean arterial pressure, and protected against decreases as well as increases in pressure. Recently, Ito and Scher (1979) showed that dogs developed hypertension

after complete aortic denervation. So, the aortic baroreceptors might be as important as carotid baroreceptors in regulating blood pressure. Unfortunately, there are no data regarding the relative importance of carotid versus aortic baroreceptors in the regulation of hormones.

Cardiopulmonary Baroreceptors

Cardiopulmonary receptors are present in each of the four cardiac chambers, in the coronary vessels, and in the pulmonary circulation. The pressure in the right heart, the pulmonary circulation, the left atrium, and the left ventricle in diastole is relatively low compared with that of the systemic circulation. Although the receptors in the left ventricle fired during systole in dogs or cats (Sleight and Widdicombe, 1965; Thoren, 1977), their activity appeared to be related more linearly to changes in left ventricular end diastolic pressure than to left ventricular systolic pressure. Thus, even left ventricular receptors seemed to monitor diastolic pressure rather than systolic pressure. Since the cardioplumonary baroreceptors monitored mainly the low pressure areas of the circulation, they were referred to as low pressure baroreceptors.

The receptors are connected by myelinated and unmyelinated afferent fibers to the central nervous system, and the fibers run centrally in two sets of nerves; the vagi and the cardiac sympathetic nerves. However, only receptor endings in the atrial wall discharging into myelinated fibers in the vagi have been confirmed by both physiologic and anatomic approach (Coleridge et al., 1957). Most of the unmyelinated vagal and both myelinated and unmyelinated sympathetic fibers are identified neurophysiologically, by isolating nerve filaments, recording

nerve impulse, and calculating conduction velocity. Actually, the sympathetic afferent fibers, running to the upper thoracic segments of the spinal cord, have been neglected until recently (Malliani, 1982). Thus, the heart as a cardiovascular reflexogenic organ is unique since it has dual input (medullary and spinal) to the CNS. Whereas, the sinoaortic reflexogenic zones have medullary inputs only (Brown, 1980).

Anatomy of receptor endings Two types of nerve endings have been described histologically: (1) complex unencapsulated endings arising from thicker myelinated fibers, (2) end net, an anastomosing network of thin fibers. The complex unencapsulated endings were found mainly in the endoatrium of the atria. They were located mainly at the junctions of the superior and inferior vena cavae and the right atrium , and the pulmonary veins and the left atrium (Nonidez, 1937; Coleridge et al., 1957). That the unencapsulated endings were sensory nerve endings discharging in the vagi was confirmed using degeneration studies. Nettleship (1936) showed in the cats that the complex unencapsulated endings disappeared following bilateral infra-nodose but not supra-nodose vagotomy, thus concluding that they were sensory in nature. Degeneration of the endings was observed by Holmes (1957) following unilateral vagotomy in the dogs. Interestingly, degeneration of the endings were not limited to the ipsilateral side, suggesting cross innervation of the atria by the vagus nerve. Coleridge et al. (1957) recorded impulses from the cervical vagus in dogs and defined the position of the receptors by various snaring techniques and probing, first with the fingers and then with a fine glass probe. They then examined histologically the tissue beneath the surface of the small area

($1mm^2$) of endocardium. In every event, complex unencapsulated endings were always observed in the stimulated areas. Thus, it is clear that the complex unencapsulated endings are the receptors of the vagal endings.

By using the degeneration technique, the total number of complex unencapsulated endings in the whole atrial endocardium were estimated between 150 to 300 (Holmes, 1957; Miller and Kasahara, 1964). The distribution ratio between the right and the left atria varied between 1:2 to 1:4 in dogs (Holmes, 1957). Since most of the reflex activity from the atria was attributed to stimulation of this type of ending (see below), this might imply a relatively important role of left versus right atrium in reflex activities. The atrial appendages are quite free of nerve endings, especially the complex unencapsulated type. However, reflex tachcardia was demonstrated by inflating a small balloon in the appendages, the authors were convinced that there must be receptors in the atrial appendages. After careful search, they were able to find 10 nervous endings of the complex unencapsulated type in each appendage. Thus, if receptors exist in the appendage at all, the number must be small. Actully in 73 atrial endings of the myelinated afferents identified by Coleridge et al. (1964), only 1 was found in the appendage. Thus, we feel safe to catheterize the atria via the appendage.

End nets are found in the endocardium of the atria and the ventricle (Miller and Kasahara, 1964). Although the unencapsulated endings were proved to be the sensory endings of the vagus nerve, the nature of the end net is still controversial. Degeneration studies including bilateral vagotomy, unilateral and bilateral vagotomy,

bilateral stellate gaglionectomy, and even bilateral dorsal root ganglionectomy has led to conflicting results (Floyd, 1979). This puzzle needs to be solved by using newly available techniques to selectively detect the presence of neurotransmitters. Currently, the end nets could be the endings of unmyelinated vagal fibers, sympathetic afferents or even sympathetic efferents.

Electrophysiology of Receptors The recording of impulses in the vagus nerve had been accomplished by Amann and Schaefer, Walsh and Witteridge et al. (Paintal, 1953). Nevertheless, there were controversies regarding the origin of the impulses in the vagus nerve, the relationship between the pattern of activity in these nerve and the atrial events of the cardiac cycle. Paintal recorded action potentials from the vagus nerve in the cat. After obtaining a single nerve recording, he then rapidly opened the chest. By successively increasing pressure within the atrial chambers, he was able to locate the origin of the receptor endings.

According to Paintal, the discharge patterns of atrial receptors (all from myelinated vagal fibers) can be classified as type A and B according to their temporal occurence in the cardiac cycle. Type A receptors discharged mainly during atrial systole, in time with the 'a' wave of the atrial pressure pulse. Whereas, type B receptors discharged during atrial filling, in time with the 'v' wave of the atrial pressure pulse. The type A discharge was characterized by a short burst of constant duration and peak frequency around 200Hz in closed chest animals. However, the type B discharge was of low frequency of around 30 to 40 Hz.

Paintal proposed that type A and B receptors might be two different types of receptors and subserve different reflex function (Paintal, 1971). Type A receptors were found mainly in cats but were unusual in dogs. The ratio of type A vs type B receptors was 1:1 in the cats but 1:10 in the dogs (Bishop et al., 1983). The natural stimuli for type A receptors was an increase in tension in the atrial wall due to atrial systole itself and due to a rise in the intraatrial pressure during the 'a' wave. Since the activity of type A receptors was related to changes in heart rate and not to the amplitude of the 'a' wave, mean atrial pressure, Arndt et al. (1971) believed that the function of these endings was to signal changes in heart rate. However, there are no data to support such a hypothesis.

Since the type B receptors did not respond to 'a' wave, when the pressure was highest in the atrium, instead, these receptors responded linearly to changes in atrial filling. Thus, Paintal concluded that type B receptors are stretch receptors and respond to pulsatile changes in atrial volume (1957). So far no method is available to measure the pulsatile changes in atrial volume. However, the relationship between atrial volume and pressure in the isolated atrium was linear over a certain range of volume (Little, 1960). Actually, activity of the type B receptors is related to mean atrial pressure, peak pressure of the 'v' wave, and the amplitude of the 'v' wave. Among the three, the amplitude correlated best with activity of type B receptors.

Although Paintal suggested that type A and B receptors were different, this concept was recently challenged by Linden and Kappagoda (1982) for the subsequent reasons:

(1) Histologically, the type A and B receptors were not different.

(2) They had similar conduction velocity.

(3) The identification of an intermediate type receptor, which discharged in response to both atrial contraction and atrial filling.

(4) A, B, and the intermediate type receptors could be converted to one another by maneuvers such as volume infusion or hemorrhage.

(5) When an isolated, innervated strip of atrial muscle was stretched and the discharge from atrial endings in the strip was recorded, type A and B receptors appeared to originate from a homogeneous group of mechanoreceptors.

Linden and Kapagodda concluded that the difference in type A and B discharge in vivo are probably related to the receptor sites in the atria and are not due to different basic properties. However, Gupta (1977) found that the distribution of type A and B endings in the atria was the same, and suggested that the difference in discharge patterns of type A abd B endings in vivo was the results of difference of arrangement in the atrial wall with respect to the contractile elements. In conclusion, there is not enough data to suggest whether A, B, and intermediate type receptors are of a homogeneous group or not, and it is premature to attribute a specific reflex to any one of them (such as the

relationship between type B receptors and Gauer and Henry reflex, which will be discussed later).

Receptors from unmyelinated vagal fibers had also been identified in the atria of dogs (Coleridge et al., 1973) and cats (Thoren, 1976). They showed either no activity or only sparse discharge at rest, whereas type A, or B receptors always showed cardiac rhythm at rest. As atrial pressure was increased by transfusion or by occlusion of the aortic, mitral, or tricuspid orifices, an increase in firing occurred, and this firing always related to the atrial 'v' wave. Thus, these atrial C fibers seemed to responded to atrial filling rather than atrial contraction. Although they were silent at rest, they might be important during voulme expansion. In contrast to the classical type A and B receptors, the C-fiber endings were located throughout the atria and in the interatrial septum and even appendages.

In contrast to sinoaortic baroreceptors, the sensitivity of type A and B receptors were not affected by sympathetic or efferent vagal stimulation in closed chest animals (Bishop et al., 1983). However, the effect of angiotensin II on type A or B receptors is unknown. Similar to sinoaortic baroreceptors, a reset phenomenon had been demonstrated for atrial vagal fibers in spontaneous hypertensive rats.

The ventricles received few myelinated afferent fibers from the vagus nerve, but were innervated by many unmyelinated fibers, the left ventricle being more profusely innervated than the right (Coleridge and Coleridge, 1980). This might imply a relatively more important role for the left ventricle than the right ventricle in eliciting reflexes. Coleridge et al. (1964) were the first to describe both the myelinated

and unmyelinated vagal afferent fibers innervating ventricles of the dogs. Myelinated afferents have pulse synchronous discharge under basal condition, whereas most of the unmyelinated ventricular vagal fibers were silent or showed irregular discharges (Gupta and Thames, 1983). All unmyelinated vagal fibers were in or near the epicardium, in contrast, myelinated vagal afferents were equally distributed between the endocardium and the epicardium (Coleridge et al., 1964; Gupta and Thames, 1983). Myelinated vagal afferents had discrete receptive fields (1-2mm^2), whereas those of unmyelinated ones were much larger (1cm^2). Myelinated vagal fibers also had lower threshold, higher sensitivity, and higher maximal firing frequencies than unmyelinated vagal afferents.

The search for natural stimuli for the ventricular vagal fibers was more complicated than atrial vagal fibers. Both ventricular myelinated and unmyelinated vagal fibers discharged during systole. However, during graded aortic occlusion, the receptors normally did not respond to an isolated increase in ventricular systolic pressure (Thoren, 1979; Baker et al, 1979; Gupta and Thames, 1983). Discharge of both groups was linearly related to left ventricular diastolic pressure but not to left ventricular systolic pressure. Thus, it would seem that the receptors function as distension receptors. However, as we have discussed earlier, these receptors are activated mainly during systole. The importance of ventricular systole for receptor activation was illustrated by several facts (Bishop et al., 1983).

(1) During ventricular fibrillation, the receptor discharge did not increase in spite of high left ventricular end diastolic pressure, but it increased immediately after normal ventricular

contraction began.

(2) At a constant ventricular diastolic pressure, the activity of ventricular receptors changed in the direction of changes of contractility, thus, isoprotorenol increased the contrctility and the activity of ventricular receptors.

(3) A combination of increases in ventricular diastolic and systolic pressure, such as aortic constriction, raised the firing more than increases in ventricular diastolic pressure only, such as transfusion.

In conclusion, the discharge of ventricular receptors is related linearly to ventricular filling, however, the slope of the line could be affected by the ventricular contractility.

According to Coleridge et al. (1980), the ventricular vagal C fibers they investigated were not of a homogeneous group. They varied markly from receptors that were sensitive to mechanical stimulation, such as aortic occlusion, to receptors that were sensitive to chemicals. In between these two extremes were receptors that could be stimulated by both mechanical and chemical stimuli. A variety of chemicals had been used to stimulate receptor endings. Veratrum alkaloids had a depolarizing action on excitable membrane generally, and the reflex they evoke probably result from stimulation of all kinds of vagal afferents. However, capsaicin and phenylbiguanide stimulate only certain endings. When injected in doses that produced profound cardiovascular depression, these chemicals did not stimulate mechanoreceptors in the atria, ventricles or aorta. Besides foreign chemicals, the chemosensitive endings can be stimulated by natural chemicals, such as prostaglandins

or bradykinin, that are formed and released in tissue in response to hypoxia, (eg. myocardial ischemia). Thus, these chemosensitive receptors might have very important roles in mediating cardiovascular reflexes in a pathological situation such as myocardial infarction.

Sympathetic afferent fibers have been neglected until very recently, although they might elicit important reflexes and transmit pain during myocardial ischemia (Malliani, 1982). Endings of both myelinated and unmyelinated sympathetic afferent fibers were identified in both the atria and the ventricles. Since the majority of them are more sensive to light touch than a large increase in transmural pressure, perhaps they are very close to the surface of the structure they innervate (Coleridge and Coleridge, 1980). Both atrial and ventricular sympathetic afferent fibers are sensitive to increases in atrial of ventricular filling and contraction (Bishop et al., 1983).

Sympathetic afferent fibers differ from vagal afferent fibers in several aspects:

(1) Myelinated vagal afferents with atrial endings usually yield bursts of impulse per cardiac cycle, however, both myelinated and unmyelinated afferent sympathetic fibers with atrial endings yield at most one action potential per cycle.

(2) In contrast to one small receptor ending of vagal afferent fibers, the receptor endings of sympathetic afferent fibers were relatively large and about half the fibers had many receptor endings, i.e., they were multiterminal (Banzett et al., 1975).

(3) Unlike vagal mechanoreceptors, sympathetic mechanoreceptors are also stimulated by chemicals, i.e., they were bimodal.

(4) The receptors of vagal afferent fibers adapted very slowly, it had been shown that some atrial receptors did not adapt at all when an atrial appendage was dilated for 15 minutes with a balloon (Gilmore and Zucker, 1974). However, endings of sympathetic afferent endings adapted within 5 to 7 seconds, sometimes reverting to control level (Coleridge and Coleridge, 1980), thus these sympathetic endindgs may monitor only sudden changes of blood pressure only.

Reflexes eliciated by Cardiopulmonary Receptors Many reflexes have been elicited by mechanical or chemical stimulation of the cardiopulmonary receptors. Stimulation of sympathetic afferent fibers usually causes a pressor effect and stimulation of vagal afferent fibers usually causes a depressor effect. However, it is very difficult to selectively stimulate only one type of ending. This may explain why there are many controversies in the literature relating to cardiopulmonary reflexes. Also, most of the experiments were done by using anesthetized, acutely surgerized animals. It is well known that anesthesia could affect the autonomic nervous system profoundly (Vatner and Braunwald, 1975; Zimpfer et al., 1982). Thus, the results of these experiments must be interpretated cautiously. Only the reflexes that are relevant to this thesis will be reviewed.

Bainbridge reflex In 1915, Bainbridge reported an increase in heart rate when blood or saline was infused into anesthetized dogs (Bainbridge, 1915). He postulated that receptors in the atria reflexly increase heart rate. Since then, many experiments were designed to study the relatioship between atrial receptors and heart rate, and heart rate

was reported to be increased, unchanged, or decreased (Coleridge and Linden, 1955). Actually, when the control heart rate was slow, an infusion, or inflation of a balloon at the pulmonary vein-left atrial junction increased heart rate, conversely, when the initial heart rate was fast, this maneuver tended to decrease heart rate. Interestingly, volume load in awake dogs always produced a significant tachycardia (Horwitz and Bishop, 1972; Vatner et al., 1975). The tachycardia was slightly reduced after beta-receptor blockade, but totally disappeared after cholinergic blockade. Thus, it is clear that the Bainbridge tachycardia is mediated mainly by reducing vagal tone. Since anesthetics, such as phenobarbital can reduce vagal tone and cause tachycardia, it is understandable why previuos investigators failed to induce the Bainbridge reflex in anesthetized animals with high heart rate, perhaps their vagal tone was too low to be reduced by saline infusion.

The receptors responsible for the Bainbridge reflex were carefully studied by Linden and Kappagoda. In their preparation, a small silastic balloon (5mm in length) was inserted in each of the pulmonary veins and tied so that the tip lay at the junction of the vein and left atrium. The root of the lung was then tied immediately distal to the balloons. Thus, inflation of the balloon by 0.5 to 1.5 ml warm saline would stimulate mainly the Paintal type receptors without affecting left atrial pressure and cardiac output (Ledsome and Linden, 1964). (However, it is not known whether a direct stretch of the receptors by the balloon is a physiological stimulus). Distension of small balloons in the pulmonary vein-left atrial junction clearly increased heart rate by an

average of 24 beats/min. Although most of the receptor endings found around the junction of great vein and the atria were Paintal type receptors, endings of C fibers could still be found in the same area. Thus, inflation of a balloon in that junction might also stimulate atrial C fibers, and the Bainbridge reflex might not be solely attributed to Paintal type receptors. Kappagoda et al. (1979) had examined this problem by using a differential cooling technique. They cooled the vagus in $2^{0}C$ increments and observed that the increase in heart rate and the discharge in Paintal type fibers were blocked at 8 to $12^{0}C$. In contrast, the atrial C fibers were blocked at either higher or lower temperature. They concluded that atrial myelinated fibers were essential for these reflex responses.

However, atrial myelinated fibers might not be the only afferent fibers that could elicite the Bainbridge reflex. Gupta (1975) found that infusion of blood elicited tachycardia in dogs with intact autonomic innervation and in dogs with beta-receptor blockade. In contrast, infusion caused bradycardia in dogs with their spinal cord setioned at C6 to C8. He concluded that tachycardia elicited by infusion might be partially due to a reflex with its afferent pathway in the spinal cord, i.e., the sympathetic afferent nerves.

The reflex effect of atrial C fibers was much less clear. By inflation of a somewhat bigger balloon (1.5 cm long) in the pulmonary vein-left atrial junction, Edis et al. (1970) was able to induce hypotension and variable changes in heart rate (depending on the control heart rate) in dogs. According to Bishop et al. (1983), inflation of the larger balloon by Edis probably induced combined activation of atrial

myelinated and unmyelinated C fibers. Reflexes from the unmyelinated fibers seemed to dominate and resulted in a depressor reflex and a general vasomotor inhibition. However, the volume injected by Edis et al. was not different from that injected by Kappagoda and Linden (0.5-1.5ml V.S. 0.5-2ml). Inflation of the "small" ballon by Kapagodda and Linden actually stimulated both myelinated and unmyelinated C fibers. Thus, Bishop's interpretation might be wrong and more experiments have to be done to elicite the reflex effects induced by atrial C fibers alone.

Gauer-Henry Reflex It was Peters who first suggested the importance of a hypothetical volume regulatory mechanism, using nervous elements in the vascular wall to sense "the fullness of the blood stream", which, "may provoke the diuretic response on the part of the kidney". Because of the larger compliance of the pulmonary and venous circulation as opposed to the arterial system, Gauer and Henry (1954) argued that the volume regulatory mechanism (the stretch receptors) might be located in this part of the circulation. Since endings similar to those in the carotid sinus had been found in the thoracic circulation (Nonidez, 1937), they postulated that stretch receptors in the thoracic ciculation may sense the blood volume and control urine excretion. The evidence to support this hypothesis was derived from their positive and negative pressure breathing experiments. Positive pressure breathing, which decreased intrathoracic blood volume, also decreased urine excretion in dogs (Drury et al., 1953). Conversely, negative pressure breathing, which increased intrathoracic blood volume, also increased urine excretion in dogs and humans (Gauer and Henry, 1954). Coincident

with Gauer's experiments and development of theories of how blood volume might be controled, was discovery of the atrial B fibers activity, which, according to Paintal, correlates with atrial filling (Paintal, 1953). In 1956, Henry and Pearce increased urine excetion by inflation of balloons implanted in the atria of dogs. There were simultaneous increases in the discharge of type B receptors accompanying the diuresis caused by the above maneuvers. Conversely, they also showed that small hemorrhage decreased both the discharges of the receptors and urine excretion. The diuretic response was abolished by vagal cooling, thus suggesting the afferent pathway was the vagus nerve. From then on, the link between atrial B fibers and control of fluid volume has been the subject of intense investigation.

One drawback of inflation of a big balloon in the atrium was that the distension of the balloon decreased, or increased arterial blood pressure, and thus the specific effects of atrial receptor activation are difficult to access. Linden's group in the University of Leeds had examined instead the renal responses to distension of small balloons at the junctions of the pulmonary veins and left atrium, since this maneuver stimulated atrial receptors surrounding the balloon without changing left atrial or systemic aterial pressure. They found small balloon inflation caused water diuresis and slight increases in solute excretion (Kappagoda, 1979). By differential cooling of the vagus nerve, he claimed that the atrial myelinated afferent fibers were responsible for the reflex diuresis.

Although the afferent pathway of the Gauer-Henry reflex was agreed to be the vagus nerve, the efferent pathway for this reflex increase in

urine flow caused by inflation of left atrial balloons remains a source of controversy. The renal nerves were not critically involved, since renal denervation did not (Ledsome, 1961) or only slightly (Kappagoda et al., 1979a) diminished the reflex increases in free water and solute excretion caused by inflation of atrial balloons. Furthermore, an increase in urine flow could also be observed in isolated perfused kidneys perfused with blood from a dog whose atrial receptors were stimulated (Carswell, et al., 1970). Thus humoral factors were likely to participate in this response. Gauer and Henry suggested that the diuresis was the result of a simultaneous decrease in plasma vasopressin (Gauer et al., 1970). This idea was challenged by Linden's group. They were unable to detect a reduction of vasopressin by use of their bioassay technique (Kappagoda et al., 1974), however, the sensitivity of their bioassay is very questionable. Furthermore, they demonstrated that inflation of small balloons could still induce diuresis in dogs with the posterior pituitary gland destroyed (Kappagoda, 1975), although the histological evidence of a complete posterior hypophysectomy was also very questionable. They also showed that, in spite of constant infusion of vasopressin, inflation of atrial balloons still resulted in diuresis (Ledsome et al., 1961).

However, by using a more sensitive radioimmunoassay, De Torrente et al. (1975) inflated an atrial balloon in dogs and found a reduction of plasma vasopressin concentration from 27.6 to 12.3 pg/ml and a simultaneous diuresis. Recently by using a radioimmunoassay to measure vasopressin, Linden confirmed De Torrente's results and agreed that decreases in plasma vasopressin were caused by discrete stimulation of

atrial receptors. However, they still disagreed that there's a link among atrial receptors, vasopressin and urine flow as suggested by Gauer and Henry for the subsequent reasons:

(1) Diuresis occurred in response to atrial balloon inflation despite a simultaneous infusion of exogeneous vasopressin or predestruction of the pituitary gland.

(2) Although vasopressin decreased from 27.6 to 12.3 pg/ml during inflation of atrial balloons by De Torrente et al., a 12.3 pg/ml plasma concentration of vasopressin perhaps was still too high to explain all the diuresis.

(3) They were able to detect a diuretic factor by a bioassay using Malpighian tubules of Rhodnius Prolixus (Kappagoda, 1979).

They could be right that a reduction in plasma concentration of vasopressin could not explain all of the diresis caused by inflation of the atrial balloons. Recently, Kaufmen and Stelfox (1984) had designed an elegant study in support of their ideas. When a balloon was inflated at the junction of the right superior vena cava and right atrium in conscious Wistar rats, diuresis and natriuresis were noted whether the kidneys were intact or denervated. When the same experiments were repeated in rats with diabetes insipidus, there were still significant increases in free water and solute excretion when the balloon was inflated. They concluded, the reflex diuresis and natriuresis that accompanied stimulation of the right atrial receptors must be mediated, at least in part, by some unidentified humoral factors. A candidate for this very interesting factor might be the recently purified atrial natriuretic peptide (Atriopeptin) described by Curri et al. (1984). This

peptide was found in the atria, was a potent vasodilator and caused diuresis and natriuresis when injected into the rats. Although regulation of the secretion of atriopeptin is unknown, it would be logical to speculate that the a direct stretch of the atrial wall by volume expansion or inflation of a balloon could stimulate release of atriopeptin.

Besides tachycardia and diuresis, inflation of atrial balloons also decreased the renal sympathetic nerve activity without changing the lumbar and splenic sympathetic nerve activity (Karim et al, 1972).

Bezold-Jarish Reflex In 1867, Von Bezold and Hert observed that moderate doses of veratrine caused a decrease in blood pressure and bradycardia, which could be prevented by sectioning the vagus nerve (Krayer, 1961). Although various receptors in the lungs, ventricles, and atria were activated by veratridine, by selectively sectioning vagal nerves innervating the above organs, Jarisch was able to limit the reflexogenic zone to the heart. It was Dawes (1947) who combined the use of the smallest effective dose of veratrine with localized administration to the target organs. He found that the left ventricle is the main receptor station responsible for this reflex. To further determine the preferential distribution of the receptors sensitive to veratrine in the ventricles of the dogs, Walker et al. (1978) compared the reflex effects elicited by injection of nicotine or veratridine into the left anterior descending or circumflex coronary arteries in dogs. Injection of drugs into left circumflex coronary arteries, which supplied mainly the inferoposterior left ventricle, always induced larger decreases in heart rate, arterial pressure, and peripheral

resistence. This agreed very well with their clinical observation that 77% of patients with acute infarction of the inferoposterior wall of the left ventricle developed bradycardia and hypotension within 30 minutes of the onset of infarction, whereas, only 32% of patients with anterior infarction exhibit these clinical findings.

Since unmyelinated C fibers were the most common fibers supplying the left ventricle and the Bezold-Jarisch reflex could be mimicked by afferent stimulation of the cardiac nerves, but only by intensities that activate C fibers. Thus, the ventricular C fibers were considered the main station of the reflex. Since both chemosensitive and mechanosensitive C-fiber endings were activated by veratrum alkaloids, both of them might contribute to the reflex elicited by injection of veratrum alkaloids. Recently the Bezold-Jarisch reflex was studied in conscious dogs by Barron and Bishop (1982). They found that intracoronary injection of veratridine reduced mean arterial pressure, heart rate, and maximal rate of rise of left ventricular pressure. Bilateral cervical vagal cold block eliminated the depressor and bradycardia response of veratridine. The negative inotropic response to veratridine was reversed to a positive inotropic response after vagal cold block. Thus, after vagal cold block, veratridine elicited a reflex positive inotropic response, which may have resulted from activation of cardiac sympathetic afferent fibers.

Distension of the left ventricle also initiated a reflex vasodilatation and bradycardia (Daly and Verney, 1927). In cats, Oberg and Thoren (1972) stimulated ventricular receptors by aortic occlusion and found a considerable reduction in heart rate, almost entirely due to

vagal activation, and a reflex dilatation of renal and muscular resistence vessels and of the muscular capacitance vessles. However, aortic occlusion might increase left atrial pressure and the reflex caused by aortic occlusion might not be completely attributed to pure stimulation of left ventricular receptors. This question was answered by Mark et al. in an elegent study. They implanted balloons in the left ventricle to obstruct either the outflow or the inflow tract. Outflow tract obstruction increased both left ventricular and atrial pressure and produced significant peripheral vascular dilatation. In contrast, inflow obstruction, which resulted in increases in left atrial pressure comparable to those with outflow obstruction, failed to produce vasodilatation. Thus, these authors concluded that vasodilatation in response to aortic occlusion was caused by stimulation of left ventricular receptors.

Reflex caused by Sympathetic Afferents: Afferent sympathetic nerves with cardiovascular endings can mediate cardiovascular reflexes, which usually are predominantly excitatory. However, most of the reflex effects can only be demonstrated in animals in which vagal and sinoaortic afferents were abolished. Malliani et al. (1979) recently identified a reflex caused by sympathetic afferent fibers in dogs with intact vagal and sinoaortic afferent nerves. They stretched a short segment of thoracic aorta by using a rigid core cannula covered by an inflatable rubber cylinder in conscious dogs. The distension did not cause behavioral evidence of pain, however, caused a rise in mean arterial pressure of 31 mmHg and an increase of heart rate of 20 beats/min (Malliani et al., 1979). This experiment supported the role of

sympathetic afferent fibers in the elicitation of a cardiovascular reflex, however, the physiologic significance of sympathetic afferent fibers remained to be determined.

Interaction of Sinoaortic and Cardiopulmonary baroreceptors in Cardiovascular regulation. A number of studies had indicated an interaction between cardiopulmonary and sinoaortic baroreflexes (Bishop et al, 1983). For example, previous sinoaortic denervation increased the arterial pressure rise in response to vagal cold block. Similarly, the arterial pressure rise to carotid occlusion was greater in the abcence of vagal afferents in aortic denervated animals. Recently, Mancia et al. (1976) studied the interplay among carotid sinus, and cardiopulmonary reflexes in dogs. They found that during vagal cold block, increases in arterial pressure and in renal, mesenteric, and muscle vascular resistence varied inversely with the carotid sinus pressure. Vasoconstriction was absent when the carotid sinus pressure was high and maximal when carotid sinus presure was low. This was also true when the inhibition from the cardiopulmonary baroreceptors was augmented by volume expansion. Thus, there is a dominant role of carotid sinus baroreceptors in terms of regulation of blood pressure and vascular resistence.

Mancia's finding was confirmed by Guo et al. in rabbits (1982). They found that bilateral carotid or aortic denervation caused significant abrupt increases in arterial pressure, vascular resistence, and heart rate. However, bilateral vagotomy in the presence of intact carotid and aortic baroreceptors caused only very small increases in arterial pressure and resistence. Thus, they also concluded a dominant

role of sinoaortic versus cardiopulmonary baroreceptors in the reflex control of heart rate and vascular resistence.

Vasopressin

Vasopressin is synthetized by the magnocellular neurons in the supraoptic and paraventricular nuclei and is transported to the posterior pituitary for release. The secretion of vasopressin is regulated mainly by osmotic and hemodynamic stimuli. However, angiotensin II, emesis, glucopenia can also stimulate vasopressin release (Robertson, 1980). Although the vasoactive activity of vasopressin was recognized many years before its antidiuretic activity was documented, the antidiuretic role of vasopressin was the predominant area of interest (Cowley, et al., 1982). After the discovery that in sinoaortic denervated animals, the pressor activity of vasopressin was as potent as that of angiotensin II, people began to realize the importance of vasopressin in the regulation of blood pressure. By using a specific antagonist of the vasoconstrictor activity of vasopressin, Sondeen (1983) found that vasopressin played an important role in blood pressure regulation during mild hemorrhage in conscious dogs. Blockade of angiotensin II had no effect on the dog's ability to maintain its blood pressure in response to a 20 ml/kg hemorrhage, however, blockade of vasopressin caused the blood pressure to fall lower than that during the control hemorrhage. Thus, vasopressin is very important in the regulation of blood volume by its antidiuretic effect and in the regulation of blood pressure by its vasoconstrictor effect.

Osmotic Regulation of Vasopressin Release Most of the principles relating to osmotic control of vasopressin release were presented in the

classic Croonian lecture entitled "The antidiuretic hormone and the factors which determine its release" by Professor E. B. Verney in 1947. He demonstrated that the rapid injection of hypertonic saline over a 10-s period into a carotid artery was associated with a rapid fall in urine flow in conscious, trained dogs undergoing a water diuresis (Verney, 1947). Since this antidiuresis could be produced by similar intracarotid injection of non sodium containing solutions, such as hypertonic sucrose, he proposed the existence of an "osmoreceptor" rather than a "sodium receptor". Moreover, since the antidiuresis produced by these intracarotid injection could be mimicked by injection of posterior pituitary extract, he suggested that the osmoreceptor induced the release of vasopressin from the posterior pituitary gland. Finally, by sequentially ligating the branches of the carotid artery, the osmoreceptors were located in the anterior hypothalamus.

The concept of an "osmoreceptor" rather than a "sodium receptor" was challenged by Anderson et al (1980). They suggested, at least in goats, there were juxtacerebroventricular sodium receptors regulating the release of vasopressin. They found that intracerebroventricular (I.C.V.) infusion of hypertonic mannitol (dissolved in sodium free artificial CSF) induced a marked drop in plasma vasopressin and water diuresis in non hydrated goats, whereas, the corresponding infusion of equiosmolar hypertonic NaCl had the reverse effect on plasma vasopressin.

The controversy between osmoreceptors and sodium receptors was further investigated in conscious dogs by Ramsay et al. (1980). Intravenous infusion of hypertonic NaCl, or sucrose stimulated drinking

and plasma vasopressin after 14.1 and 16 minutes, respectively. Conversely, intravenous infusion of glucose and urea failed to elicite drinking or vasopressin release. However, infusion of all solutes, whether they caused drinking and vasopressin release or not, caused an increased in CSF sodium concentration. Thus, at least in dogs, it is the osmoreceptors but not sodium receptors that control drinking or vasopressin release. The latency of drinking and vasopressin release in response to I.V. and I.C.V. infusion of sucrose was further compared by the same authors. They found that, despite a higher CSF osmolality during I.C.V. than during I.V. infusion of sucrose, the latency was much longer during I.C.V. infusion of sucrose. Thus Ramsay et al. suggested that the receptors must be located in an area lacking blood brain barrier. In a later work, they found that after lesioning OVLT (Organ Vasculosum of the Lamina Terminalis) in dogs, the functional relationship between plasma osmolality and vasopressin was eliminated. They thus suggested that OVLT contained osmoreceptors in the dogs (Thrasher et al., 1982).

The relationship between osmolality and plasma vasopressin concentration was carefully studied by Robertson (1980). He suggested that the effects of the osmoreceptors on plasma vasopressin were like those of a discontinious or "set point" receptor. If plasma osmolality fell below a certain minimum or threshold level, plasma vasopressin was uniformally supressed to concentrations sufficiently low to permit the developement of a maximal water diuresis. Above this threshold, plasma vasopressin rose in direct proportion with plasma osmolality. The slope or sensitivity was such that a 5% change in plasma osmolality elevated

vasopressin concentrations to maximally concentrate urine. However, in human, a fall in systemic arterial pressure of 10% usually produced no or little rise in plasma vasopressin. Thus, Robertson suggested that osmotic stimuli was more important than hemodynamic stimuli in the regulation of plasma vasopressin on a day to day basis. However, this did not rule out the role of henodynamic stimuli in the regulation of vasopressin for the subsequent reasons.

(1) Although the "sensitivity" of hemodynamic stimuli might be less than that of osmotic stimuli, the "gain" of the former was greater than that of the latter. For example, vasopressin concentration averaged 6.5 microunits/ml in humans after 16 hours of dehydration, whereas, the values as high as 900 microunits/ml were observed a few minutes after mean arterial pressure was dropped to 50 mmHg in anesthetized dogs (Share, 1974).

(2) The sensitivity and threshold of osmotically mediated vasopressin release was changed by hemodynamic stimuli. For example, hypotension and/or hypovolemia lowered the set of the system and hypertension and hypervolemia had exactly the opposite effect (Robertson, 1980).

(3) 24 hours water deprivation was a physiologic stimulus for animals as well as humans. This maneuver not only increased plasma osmolality but also decreased extracellular volume. Wade et al. (1983) found that following 24 hours of dehydration in dogs, vasopressin increased from 1.4 to 5.3 pg/ml. After isotonic fluid replacement without changing plasma osmolality,

plasma vasopressin was reduced by 33% of control. However, with correction of osmolality, by intracarotid infusion of water until jugular venous osmolality was lowered to control euhydrated state, plasma vasopressin was decreased by 70%. Thus, following dehydration in dogs, the rise of vasopressin was due to changes in both hemodynamic and osmotic stimuli.

Hemodynamic regulation of Plasma Vasopressin There are several techniques used by previous investigators to specifically activate high pressure or low pressure baroreceptors. However, none of them are really specific, they will be discussed as follows:

(1) Nonhypotensive Hemorrhage A loss of less than 10 to 20 % of blood volume usually caused a slight reduction of pulse pressure without changing mean arterial pressure, however, this degree of hemorrhage usually resulted in significant reduction in atrial pressure . Thus Gauer and Henry argued that nonhypotensive hemorrhage activated specifically the low pressure baroreceptors and permitted a differentiation between the effects of the stretch receptors of high versus low pressure systems. This suggestion was supported later by Gupta et al. (1966). Blood volume was stepwise reduced by hemorrhage and discharge in the aortic or atrial nerves was recorded in dogs. They found that even with a 20% blood volume loss the integrated aortic firing was still 94% of control. Conversely, the integrated atrial firing was reduced by 80% of control. They thus concluded that, in response to moderate hemorrhage, the drive from the classical high pressure receptors remained relatively constant per unit

time in contrast to an immediate decrease in impulses per unit time from the low pressure receptors. Since then on, any hormonal changes in response to nonhypotensive hemorrhage was attributed to activation of the low pressure baroreceptors. However, examining their results more carefully, the discharge in aortic nerve did decreased by 40% of control during the hemorrhage if the discharge was measured as impulses/beat instead of impulses/unit time. There were still controversies, whether the CNS analyzed the discharge from high pressure receptors according to impulses/beat or impulse/unit time. Furthermore, although a 10% hemorrhage failed to cause a significant reduction in mean arterial pressure, the same hemorrhage did decrease the mean arterial pressure by 36 mmHg after sinoaortic denervation (Hosomi and Sagawa, 1979). Thus it is inappropriate to use nonhypotensive hemorrhage as a tool to "specifically" stimulate the low pressure baroreceptors.

(2) Bilateral Carotid Occlusion Because of collateral circulation from the Circle of Willis, carotid occlusion sometimes failed to produce carotid hypotension, thus, it was mandatory to measure carotid sinus pressure during carotid occlusion. Unless the aortic nerve was denervated, the hypertension accompanying carotid occlusion would stimulate the aortic baroreceptors and cause reflex effect opposite to that of carotid occlusion, thus, the reflex effect of carotid occlusion might be obscured by that from aortic baroreceptors.

(3) Vagotomy or Vagal Cooling Vagal cooling or vagotomy was

used to interrupt the signals from cardiopulmonary receptors. However, it must be kept in mind that afferents from aortic baroreceptors also run in the vagus, thus, denervation of the aortic arch was mandatory before vagal cooling or vagotomy. Even so, it is still difficult to attribute the effect of vagotomy solely to interruption of signals from cardiopulmoanry receptors. Only a small fraction of vagal fibers carry impulses related to cardiopulmonary receptors, and other vagal fibers that innervate numerous abdominal and thoracic structure might well influence renal function or the release of hormones (Goetz et al., 1975). Thus, vagotomy or vagal cooling is not a specific tool to study cardiopulmonary baroreceptors.

Share was the first to present evidence that baroreceptors could regulate vasopressin release. By using a bioassay to measure plasma vasopressin concentration, Share and Levy showed that bilateral carotid occlusion caused release of vasopressin in dogs, but only after bilateral vagotomy (Share and Levy, 1962). However, when the mean arterial pressure was kept constant by use of an external reservior during carotid occlusion, plasma vasopressin increased in dogs with intact vagus nerve (Share, 1965). This response was blocked by the simultaneous inflation of a balloon in the left atrium. Balloon inflation was ineffective in the vagotomized dogs. Share concluded that activation of stretch receptors of the left atrium resulted in inhibition of vasopressin release. This was confirmed by Johnson et al. (1969), and Brennan et al. (1971) by using the same bioassay for vasopressin. Johnson et al. found that plasma vasopressin concentrations

decreased linearly with increasing left atrial pressure up to 7 cm of water. Brennan found that increases in left atrial pressure decreased plasma vasopressin, however, an equivalent increase in right atrial pressure failed to do so. Thus, they suggested a differential effect of the atria in the regulation of vasopressin release.

By using a more sensitive radioimmunoassay to measure vasopressin concentration, De Torrente et al. (1975) and Zucker et al. (1979) consistently observed a reduction of plasma vasopressin in response to inflation of atrial balloons. However, inflation of left atrial balloons increased left atrial as well as pressure in the pulmonary circulation, thus the reflex inhibition of vasopressin might not be caused solely by receptors in the left atrium. Recently Schultz et al. (1982) inflated a balloon in the left atrium in conscious dogs and there was a reduction in plasma vasopressin and renin. Since inflation of balloons in the atrium was associated with an increase in pulmonary vein and artery pressure, they further inflated a balloon in the pulmonary artery or pulmonary veins to cause an equivalent increase of pulmonary pressure without changing left atrial pressure. This maneuver, however, failed to reduce plasma vasopressin and renin activity. Thus, they concluded that it was the receptors in the left atrium, instead of the pulmonary circulation, that were responsible for this reflex regulation of hormonal secretion. However, inflation of the atrial balloon also increased systemic arterial pressure by 10 mmHg in their experiments, thus, an inhibition from the high pressure receptors should also be considered in their interpretation.

The anatomical relationship between atrial receptors and

vasopressin releasing neurons was presented by Menninger. He found that stretching the left atrium directly inhibited over 70% of the supraoptic neurons, conversely, all neurons responding to left atrial stretch were excited by hypertonic saline (Menninger, 1979). In a second series of studies, he found that stretching the right atrium also resulted in a significant inhibition of supraoptic neurons and decrease of plasma vasopressin.

The importance of ventricular C fibers in the regulation of vasopressin was studied by Thames et al. (1980). Intracoronary crytenamine failed to change the resting vasopressin concentration. However, the rise of plasma vasopressin in response to hemorrhage was abolished by injection of crytenamine into the left circumflex artery in dogs with sinoaortic denervation. Thus, stimulation of ventriccular C fibers could inhibit vasopressin release.

The interaction of high versus low pressure baroreceptors in the regulation of vasopressin was studied by Thames and Schmid (1979, 1981). However, their results were complicated by the extremely high resting vasopressin concentrations, as high as 100 times that of conscious animals. In spite of the high resting vasopressin concentrations, they concluded that cardiopulmoanry receptors with vagal afferents prevented increases in vasopressin release following sinoaortic denervation. Vagal cold block increased plasma vasopressin only when carotid sinus pressure was maintained at 50 mmHg, but not when the carotid sinus pressure was normal or high. Thus, it seemed that both high and low pressure receptors may inhibit vasopressin release.

In view of the extremely high resting vasopressin values in

anesthetized dogs, the effects of vagal afferents was further evaluated in conscious dogs with aortic nerve sectioned (Bishop et al., 1984). In the presence of intact carotid baroreflex, vagal cold block increased plasma vasopressin from 2.9 to 6.7 microU/ml. However, after complete sinoaortic denervation, vagal cold block increased plasma vasopressin from 4.4 to 33.4 microU/ml. Thus, vagal afferents exert a significant tonic inhibitory influence on vasopressin release in conscious dogs with aortic nerve sectioned. However, by comparing the effect of vagal cold block in dogs with aortic denervation only or in dogs with complete sinoaortic denervation, the carotid sinus also played a significant role in inhibiting vasopressin release. In summary, all the experiments mentioned so far had not given a quantitative assessment of the relative importance of cardiopulmonary and sinoaortic baroreceptor in the control of vasopressin release in a physiologic sense.

CRF-ACTH-Glucocorticoid system

After the purification and sequencing of a 41 amino acid ovine hypothalamic corticotropin releasing factor (CRF), the CRF-ACTH-glucocorticoid axis was completely identified (Vale et al, 1981). Several naturally occuring substances including vasopressin, oxytocin, catecholamine, and angiotensin II have been found to stimulate ACTH and glucocorticoid secretion (Brodish and Lymangrover, 1977; Ramsay et al., 1978). In the past vasopressin had been considered as a candidate for CRF. Although vasopressin was more potent than CRF in elevating endogenous plasma ACTH concentrations in freely moving rats, , in animals whose endogenous CRF release was blocked, vasopressin elicited a lower ACTH release than CRF. Also, Brattleboro rats, which genetically

lack vasopressin, were capable of responding to stress with a nearly normal secretion of corticosteroid. Although vasopressin is not CRF by definition (mediating ACTH response to stress), vasopressin could stimulate ACTH release in experimental maneuvers which resulted in elevation of vasopressin. This is also true for angiotensin II and catecholamines. Actually, some hemodynamic stimuli might bypass CRF and stimulate ACTH release by increasing vasopressin release. Thus, although vasopressin might not be the classical CRF which mediates the ACTH response to stress, in the case of hemodynamic stimuli, vasopressin may function as a main stimulus for ACTH release (Evidence for this idea will be presented in the results section).

The first work relating the release of corticosteroid and atrial receptors were presented by Anderson et al. (1959). By passing sutures through the atria, they were able to stretch the right or left atrium in a circumferential manner without changing the general orientation of the heart. Hydrocortisone secretion was significantly decreased (50%) after stretching either the right or left atria. However, there were no information on systemic arterial or atrial pressure during stretching of the atria. After their pioneer work, Gann did a series of work to investigate the relationship between baroreceptors and corticosteroid secretion (Gann et al., 1981). He found that both hemorrhage and hypotension produced by ganglionic blocker consistently stimulated the secretion of corticosterone in dogs (Gann and Egdahl, 1965). Norepinephrine abolished the hypotension and corticosteroid response to ganglionic blocker, but failed to abolish the corticosteroid response to hemorrhage, even when the hypotension due to hemorrhage was corrected by

norepinephrine. This made them conclude that both volume and pressure receptors were involved in the regulation of corticosteroid secretion.

To further identify the mechanism mediating adrenal activation in response to hypotension, he performed bilateral carotid occlusion in dogs with either bilateral vagotomy or femoral nerve section (Gann, 1966). Carotid occlusion increased 17-OHCS secretion after bilateral vagotomy only and the response was abolished after combined denervation of the carotid sinus and the junction of thyroid and carotid arteries.

Since carotid occlusion failed to increase 17-OHCS secretion in dogs withour prior vagotomy, vagal afferents must maintain tonic inhibition over secretion of 17-OHCS. However, the vagus nerve contained afferents from both the aortic and cardiopulmonary baroreceptors. To further differentiate the contribution of aortic versus cardiopulmonary baroreceptors, Cryer and Gann (1973) performed ascending aortic constriction in anesthetized dogs. The desigh was elegant, since ascending aortic constriciton clearly differentiated the reflex effects between high and low pressure receptors. However, it is difficult to understand how they interpreted the results. They found that aortic constriction led to a reduction of both systemic arterial pressure (less than 20 mmHg) and 17-OHCS secretion. Unfortunately, they measured only the pressure in the right atrium and the changes in right atrial pressure was merely mentioned in the discussion section as: "the right atrial pressure increased slightly (on the order of 1 cm of water)", and there was no statistical analyses carried out on the 1 cm water increase of right atrial pressure. Totally neglecting that ascending aortic constriction might have stimulated left heart receptors more than right

heart receptors, they attributed the inhibition of 17-OHCS secretion to receptors in the right atrium.

To further prove the importance of right atrial receptors in the regulation of 17-OHCS secretion, they inflated a balloon in the right atrium of dogs during a 5 ml/kg hemorrhage and found that inflation of the balloon diminished the elevation of 17-OHCS in response to hemorrhage (Cryer and Gann, 1973). Finally, they applyed sinusoidal volume changes (1± ml) at 1 Hz to the right or left atrium of 25 anesthetized cats and measuring ACTH and cortisol at the same time. They found that right atrial receptors dominated in the response of ACTH to hemodynamic stimuli, sinoaortic receptors appeared to be less effective, and left atrial receptors appeared to be least effective (Baertschi et al., 1976). Unfortunately, the stimuli to receptors in each compartment of circulation was so unclearcut that their conclusion was doubtful. For example, sinusoidal volume changes caused a 40 to 60 mmHg fall in systemic arterial pressure when applied to the left atrium but not to the right atrium.

Renin Angiotensin System

The cascade of the renin angiotensin system starts from angiotensinogen, an alpha globulin systhetized by the liver. Angiotensinogen is cleaved by renin and a decapeptide, angiotensin I is liberated. Angiotensin I by itself is relatively inactive, but it is converted to angiotensin II, by a series of converting enzymes that existed mainly in the lung. Angiotensin II, the active component of the system, has several important physiological actions. The first of these to be identified was its pressor action and for many years, it was felt

that the sole function of the renin angiotensin system was regulation of blood pressure. A new dimension was added in 1960 with the discovery that angiotensin II stimulated the secretion of aldosterone and was therefore in a position to exert important effects on salt and water balance. Recently, it was found that this peptide can increase the secretion of catecholamines from the adrenal and facilitate adrenergic transmission. It also acts directly on the brain to increase blood pressure via sympathetic and parasympathetic pathways, to produce thirst and to stimulate the secretion of vasopressin and ACTH (Ramsay et al., 1978; Reid et al., 1978). Through these actions, the renin angiotensin system plays an important role in the regulation of blood pressure and of the volume and composition of the extracellular fluid (Reid et al., 1978).

Most of the renin containing cells or juxtaglomerular cells (JG cells) are located in the renal afferent arteriolar wall, but to a less extent the JG cells have been observed in the efferent arteriolar wall and even in the mesangium (Barajas, 1979). Renin is released from the JG cells into the renal bloodstream and lymph. Plasma renin activity (PRA) is measured most frequently in the peripheral venous or arterial blood and this value usually reflects the rate of renin release (Davis and Freeman, 1976). However, under conditions such as reduced hepatic flow, changes in PRA also reflect altered inactivation of renin by the liver.

Regulation of renin release There are at least 5 mechanisms that can control renin release:

(1) A renal baroreceptor that apparently responds to changes in wall tension in the afferent arterioles.

(2) A macula densa receptor that appears to detect changes in the rate of delivery of sodium or chloride to the distal tubule.

(3) The renal sympathetic nerves and both alpha and beta adrenergic receptors.

(4) Several humoral agents such as catecholamines, angiotensin II and vasopressin.

(5) Electrolytes, such as sodium, potassium, and calcium.

Renal Baroreceptors Tobian et al. were the first to suggest the existence of a baroreceptor in the kidney that can regulate renin release in response to changes in renal perfusion pressure (Tobian et al., 1959). They observed decreased granulation in the JG cells with a rise in renal perfusion pressure and suggested that the JG cells acted as stretch receptors and changed their rate of renin secretion as the arteriolar wall changes its degree of stretch. Skinner et al. (1964) also showed that a reduction of renal perfusion pressure as small as 5 to 12 mmHg, caused by suprarenal aortic constriction, stimulated renin release without changing renal blood flow. However, a reduction in renal perfusion pressure might decrease the NaCl delivered to the distal tubule and stimulated renin release via the macula densa mechanism; thus suprarenal aortic constriction was not a specific maneuver to specifically demonstrate the existence of a renal baroreceptor. Blaine and Davis (1971) developed a nonfiltering kidney model to make the macula densa mechanism nonfunctional. The renal arteries were clamped for two hours to cause hypoxia and the ureters were ligated and sectioned, then the dogs were dialyzed for four days before the experiments. In this model, a striking increase in PRA occured in

response to a 20 ml/Kg hemorrhage or suprarenal aortic constriction in conscious dogs. To further isolate the renal baroreceptor mechanism from the sympathetic system, renal denervation and adrenoectomy were added to the nonfiltering kidney model, and they found that the PRA response to both hemorrhage and aortic constriction was still present. The anatomic location of renal baroreceptors was still unknown, however, Witty et al. (1971) suggested that the baroreceptors could be located in the renal arterioles since infusion of papaverine into the renal arteries relaxed the vascular smooth muscle and blocked both the autoregulation (an afferent arteriolar function) and the PRA response to hemorrhage and aortic constriction.

According to Tobian, the natural stimulus for baroreceptors was stretch. Thus, a high perfusion pressure stretched the vessel wall and inhibited renin release. However, either systemic or renal arterial hypotension which induced renin release was usually associated with renal vasodilatation (Keeton and Campbell, 1980). According to the stretch receptor theory, vasodilatation should stretch the vascular wall and inhibit renin release, unless it was assumed that intravascular pressure rather than the radius of the afferent was the predominant factor that influenced "stretch". Along these lines. Vander (1967) proposed that the actual stimuli for renal baroreceptors might be :

(1) A decrease in the transmural pressure gradient.

(2) A decrease in the intraluminal pressure at the level of JG cells.

(3) A decrease in the tension within the vascular wall.

Tension is the product of transmural pressure times radius. Thus,

renal baroreceptors could be activated during renal afferent arteriolar dilatation by a decrease in wall tension if the decrease in transmural pressure overrides the influence of an increase in arteriolar radius (Davis and Freeman, 1976). However, it seems to me that it is the active tension rather than total tension that really determines the activity of the renal baroreceptors. In papaverine treated animals, a reduction in renal perfusion pressure failed to increase renin renin release. After papaverine treatment, the arterioles were fully dilated, thus, a further reduction of perfusion pressure should result in a further decrease in total tension (but not active tension). Thus, a reduction in total tension should stimulate renin release. However, renin failed to increase in response to reduced renal perfusion pressure in animals pretreated with papaverine. Thus, perhaps a reduction in active tension is more important than total tension (as calculated by the Laplace law) in activating the renal baroreceptors.

Macula Densa mechanism Vander and Miller (1964) proposed that renin release is controlled by the flow or sodium load at the level of the macula densa, and renal venous renin activity is inversely related to the rate of sodium excretion. In an attempt to determine whether changes in intrarenal sodium concentration altered renin release by a vascular or a tubular mechanism, Shade and colleaques (1972) infused hypertonic saline into the renal artery of caval constricted dogs with a filtering or nonfiltering kidney; in the former, renin release was markedly reduced, but the infusion had no effect in the latter. They concluded, therefore, that a tubular rather than a vascular sensor regulated renin release in response to changes in intrarenal sodium. On

the other hand, Fray (1976) varied the sodium concentration of fluid perfusing isolated rat kidneys from 85 to 204 mM without altering the rate of renin release, despite large changes in sodium excretion. Hence the role of the macula densa in the regulation of renin release is still unclear.

Sympathetic Nervous System The JG cells, arterioles and tubules were innervated by sympathetic efferent fibers, however, it was not clear whether these structures were also innervated by the cholinergic nervous system (Barajas, 1979). Vander was the first to show that stimulation of renal nerves increased renin release, however, renal nerve stimulation also decreased renal blood flow (RBF) and glomerular filtration rate (GFR). To limit the renin response to a direct sympathetic stimulation of JG cells, Johnson et al. (1971) showed that stimulation of the renal nerves in nonfiltering kidneys treated with papaverine resulted in an increased secretion of renin. Furthermore when the renal nerve was stimulated at 0.5 Hz, renin release increased without affecting renal perfusion pressure, RBF, GFR, or urinary sodium excretion. Thus, DiBona (1982) suggested that the sympathetic nervous system can directly stimulate JG cells and increase renin release. The renin response to low frequency renal nerve stimulation could be blocked by beta-1 adrenoreceptor blockade with atenolol, but it was unaffected by renal beta-2 adrenoreceptor blockade with butoxamine (Osborn et al., 1981). Thus, DiBona concluded that renin release solely due to renal nerve stimulation, i.e., without changing the input stimuli to either baroreceptor or macula densa mechanisms, was mediated by beta-1 receptors located on the JG cells (DiBona, 1982).

The effect of alpha adrenoreceptor stimulation on renin release , however, was very controversial. Part of the reason was due to the difficulty in differentiating the effects of stimulating the vascular alpha and nonvascular alpha receptors. The vascular alpha adrenoreceptors led to vasoconstriction which would stimulate renin release via the macula densa or the renal baroreceptor mechanism. Thus, the in vitro studies, which isolated the nonvascular alpha receptors, all showed an inhibition of renin release. Conversely, Blair (1980) showed that infusion of an alpha agonist, which did not affect RBF or GFR, increased renin release. This controversy can be solved by use of the nonfiltering kidney model plus infusion of papaverine to isolate the vascular from the nonvascular alpha receptors in vivo.

There were important interactions between signals from renal baroreceptors, macula densa, or sympathetic nervous system in the regulation of renin release and these signals were integrated on JG cells to alter renin relese. The importance of a tonic renal nerve activity in the modulation of the secretion of renin release mediated by renal baroreceptors or macula densa mechanism had been emphasized (perhaps overemphasized) by Stella et al. (1976) and Thames and DiBona (1979). The effect of suprarenal aortic constriction or hemorrhage on renin release was compared between an intact and a denervated kidney in the anesthetized cat or dog. They showed that the denervated kidney had a blunted renin release in response to suprarenal aortic constriction or hemorrhage. However, in conscious dogs, Grandjean et al. (1978) showed that venous plasma renin activity increased identically in the denervated and intact kidneys in response to a 8 ml/kg hemorrhage. Also,

Gibbons found that increasing concentrations of epinephrine within physiological range shifted the PRA response to changes in renal perfusion pressure to the right without changing the slope. The differences between conscious and anesthetized animals might be caused by the use of anesthetics or surgical trauma. Lifschitz (1978) suggested that anesthesia caused an increase in renal sympathetic tone and this increased sympathetic tone allowed denervation to have an effect. For example, the renal nerves had always been claimed to have an important role in the regulation of sodium secretion in anesthetized animal experiment. However, in conscious dogs, the denervated kidney could reabsorb or excrete sodium as well as the control kidney under stresses of volume expansion and depletion. Thus, the importance of a tonic sympathetic tone in the modulation of baroreceptor or macula densa regulation of renin release has to be reevaluated in conscious animals.

Angiotensin and Vasopressin In 1967, Bunag et al. showed that large doses of vasopressin could inhibit the release of renin in anesthetized dogs (Bunag et al., 1967). However, the physiologic significance was not clear. Thus, Tagawa et al. (1971) showed that small increases in plasma vasopressin could supress the PRA elevation in response to sodium excretion in conscious dogs. Recently, Malayan et al. (1980) found that an increase in plasma vasopressin of 2.1 pg/ml, caused by infusion of arginine vasopressin, supressed PRA by 15%; increases of 4.2 pg/ml, supressed PRA by 34 %. Thus a very small increase in plasma vasopressin was potent enough to inhibit basal PRA. This interaction is very important when both vasopressin and renin are stimulated simulataneously, it is possible that the increased plasma vasopressin

may supress PRA, and the elevation of PRA is diminished or even totally obscured. Since vasopressin could inhibit PRA in kidney slices and isolated perfused kidney, at least the mechanism could be attributed partially to a direct renal effect.

In 1965, Vander and Geelhold described the inhibition of renin secretion in dogs by very low doses of angiotensin II, and suggested the operation of a negative feedback system. This had been confirmed both in vivo and in vitro.

Although the concept of Ca^{++} as a mediator in stimulus secretion coupling was developed and extended to many endocrine systems, the secretion of renin was an exception (Gibbons et al, 1984). Both vasopressin and angiotensin II inhibited renin by increasing a Ca^{++} influx into the JG cells, since their inhibition was blocked by verapamil, a Ca^{++} influx antagonist (Park et al, 1981). Interestingly, ouabain can inhibit renin release both in vivo and in vitro. As a Na^{+}-K^{+} ATPase inhibitor, ouabain inhibited the sodium pump, increased intracellular Na and finally increased Ca^{++} influx through a Na^{+}-Ca^{+} exchange pump. This increased calcium influx might be the mechanism for ouabain's ability to inhibit renin release. Thus, a putative natriuretic hormone, endoxin, might be able to inhibit renin release since endoxin was a Na^{+}-K^{+} ATPase inhibitor.

Sodium and Potassium Gibbons et al. showed that sodium depletion increased the slope of PRA response to changes in rena perfusion pressure in dogs. However, this effect could not be totally attributed to macula densa, since sodium depletion affected the volume status of the animals too. However, a very big change of plasma sodium was

necessary to alter renin release. Conversely, small changes in serum potassium concentrations (0.3 to 1.4 meq/l) had been reported to affect renin release.

Regulation of Renin by Baroreceptors The influence of high pressure baroreceptors on renin release was very controversial. In 1964, Skinner et al. found that bilateral carotid sinus occlusion failed to change renin release in 3 vagotomized dogs. This was confirmed by Brennan et al. (1974) and Rocchini et al. (1977). However, other investigators found that carotid occlusion did increase PRA (Hodge, 1966; McPhee and Lakey, 1971; Yun et al, 1976). During carotid occlusion, systemic arterial pressure increased and so was the renal perfusion pressure, which might inhibit renin release and mask the effect of carotid hypotension. Realizing that the role of renal perfusion pressure might have caused the controversies, bilateral carotid occlusion was performed with and without regulation of renal perfusion pressure in both anesthetized (Jerechi et al., 1978) and conscious (Rocchini et al., 1979) dogs. Bilateral carotid occlusion resulted in significant increases in PRA or renin release when renal perfusion pressure was maintained at control level, but not when renal perfusion pressure was allowed to rise.

Cardiopulmonary afferents had been shown to affect renin secretion. Brennan et al. (1971) inflated balloons in either atria of anesthetized dogs. The balloon inflation increased atrial pressure without affecting cardiac output or systemic arterial pressure. They found that PRA increased significantly in response to increases in right atrial pressure but not to increases in left atrial pressure. Their result, was

contradicted by that of Zehr et al. (1976). By inflation of a left atrial balloon, the left atrial pressure increased by 5 cm of water, and renin release decreased by 56% of control. Mancia et al. (1975) also demonstrated that cardiopulmonary receptors with afferents in the vagus exerted a tonic inhibition on renin release in dogs. In aortic nerve sectioned dogs, vagal cooling increased systemic arterial pressure and renin release when carotid sinus pressure was maintained at 40 mmHg. A nonhypotensive hemorrhage, which had been suggested to "selectively" unload the cardiopulmoanry receptors, also increased PRA in both anesthetized (Thames, 1977) and conscious (Mursch and Bishop, 1980) dogs.

The importance of ventricular C fibers in the regulation of renin release was examined by Thames (1977). He found that injection of crytenamine into the left circumflex artery abolished the increased renin release caused by nonhypotensive hemorrhage. Myocardial ischemia caused by ligation of the left circumflex coronary artery also inhibited renin release in response to nonhypotensive hemorrhage, presumably by activation of the ventricular chemosensitive and mechanosensitive receptors (Livnat and Zehr, 1982). Thus it is clear that cardiopulmonary receptors can regulate renin release. The afferent pathway runs in the vagus nerve, since the reflex inhibition of renin release was abolished by vagotomy. The efferent pathway might be in the renal nerve since renal denervation also abolished the reflex inhibition of renin release caused by inflation of atrial balloons (Zehr, 1976, Livnat and Zehr, 1982). However, all these experiments were done in anesthetized animals with, perhaps, a high renal nerve activity.

The interaction of cardiopulmonary and carotid baroreceptors were studied by Thames et al. (1977) in anesthetized dogs. They found that vagal cold block increased arterial pressure but not renin secretion in dogs with the aortic nerve cut and carotid sinus intact. Renin release increased only after the carotid sinus was isolated and perfused with control blood pressure. They thus suggested that carotid baroreceptors could markedly or totally inhibit the release of renin which resulted from complete interruption of afferent vagal traffic from cardiopulmonary receptors.

Chapter Two

Materials and Methods

Animals All the experiments were performed on Mongrel dogs of either sex, weighing between 13 and 22 Kg. The conditioning schedule involved a month of observation before experimentation under veterinary care. The dogs were treated for any infections, parasites, or dietary insufficiencies during 30 days to insure a good state of health.

The dogs were housed individually in a room lighted from 0700 to 1800 and maintained at 22^{0}C and 70% humidity. The dogs were given 200 to 300gm of dry chow (Purina) well mixed with one can of food (Kal Kan) daily at 1400 and had water available ad libitum. Since the body weight for each dog did not decrease, we were sure that they had enough food intake. All experiments were carried out in the morning at 8:00 A.M. and a minimum of two days were allowed between experiments on each dog. Before surgery, the dogs were trained to stand or sit quietly in a loose cloth sling (Alice King Chatham Medical Arts, Los Angeles, CA) which provided support but minimal restraint.

Cuffs Since the research strategy was to use cuffs implanted around the ascending aorta, pulmonary artery and abdominal aorta in order to achieve graded pressure reduction in the low and high pressure areas of the thoracic circulation, the first logical step was to design a cuff which was strong enough to hold pressures of 200mmHg for hours. The cuff was initially prepared from a silastic outer casing (0.63 inch I.D., 0.88 inch O.D., Dow Corning, Midland, Michigan) enclosing a silastic inflatable balloon (0.062 inch I.D., 0.125 inch O.D.) The width of the outer casing was 15mm and the balloon is further connected with a

tygon tubing (0.05 inch I.D., 0.09 inch O.D., Norton, Arkon, OH). When tested in anesthetized dogs subsequent to implantation, the cuff was succesfully used to constrict the ascending aorta and reduce the systemic arterial pressure by 30% of control for 1 hour. However, when tested again two weeks after surgery, the cuff failed to reduce the systemic arterial pressure by even 5 mmHg. During autopsy, we found postsurgical fibrosis between the cuff and the ascending aorta, and this fibrosis explained why the cuff failed to constrict the ascending aorta. Thus, a Foley catheter (12 French, Bard^{R}, Murray Hill, N.J.) was used to replace the silastic tubing as the balloon.

This new cuff was tested again and both the ascending aorta and the pulmonary artery were constricted successfully even two months after the implantation. To prevent erosion of the ascending aorta by the cuff, the inner surface of the cuff was covered with a strip of 100% noninterwoven dacron material. The cuff, with the dacron covering, was soaked in Betadine solution at least 24 hours before use for sterilization.

To fit the size of the ascending aorta (the diameter ranging from 14 to 19 mm in the dogs used), a silastic connecting piece (same material as the outer casing) was used to increase the diameter of the cuff. Otherwise a cuff smaller than the diameter of the aorta could have produced coarctation of the aorta.

Another cuff was designed to constrict the abdominal aorta just proximal to both renal arteries, (the suprarenal cuff). This cuff was prepared from a silastic outer casing (0.38 inch I.d., 0.62 inch O.D.) enclosing a silastic inflatable balloon (0.062 inch I.D., 0.125 inch O.D.). The width of the outer casing was 8mm. The cuff was tested and

successfully constricted the abdominal aorta in both acute and chronic preparations for hours. No dacron was used to cover the inner surface of the suprarenal cuff.

Surgical Procedure

Group 1: Dogs with the **Ascending Aortic Cuff**

Four dogs were prepared with cuffs around the ascending aorta (Ascending aortic cuff). The surgical procedure was carried out using full aseptic precautions. After being pretreated with Acepromazine Maleate (0.25mg/lb, s.c., Aveco Co., Fort Dodge, IA), the dogs were anesthetized with pentobarbitol (25mg/Kg, Fort Dodge laboratories, Inc., Fort Dodge, IA), intubated, and placed on a respiration pump (Harvard Apparatus, Millis, MA). The chest was opened through the left fourth intercostal space and the lungs were retracted with saline soaked gauzes. A small pericardial vault was then made, and the connective tissue between the ascending aorta and the pulmonary artery was cleared with caution to minimize damage to the nerves of the heart. The pad of fat on top of the aorta was removed. The cuff was implanted around the ascending aorta proximal to the brachiocephalic trunk. Both atria were catheterized with tygon tubing (0.05 inch I.D., 0.09 inch O.D.) via the atrial appendage and secured by purse string sutures. Powders of polymyxin B-Bacitracin-Neomycin (Neosporin^{R}, Wellcome, Triangle Park, NC) were spreaded locally before closure of the pericardium. The chest was then closed in layers, with a chest drain and underwater seal to insure full expansion of the lungs. Arterial blood pressure was monitored by placing a tygon tubing in the femoral artery and the tip of the catheter was advanced to the abdominal aorta at the level of the

renal arteries. These catheters were made of tygon microbore tubings (0.05 inch I.D., 0.09 inch O.D.) on which two narrow rings, made of slices from the end of an 8-French polyvinyl feeding tube (Pharmaseal, Inc., Toa Alta, Puerto Rico), were glued with cyclohexanone (Fisher Scientific Co., Fair Lawn, NJ). The catheters were inserted into the vessels up to the level of the second ring and a ligature was tied around the catheter and the vessel wall between the two rings, securing the catheter into the vessel. The catheters were routed subcutaneously and exteriorized, along with the cuff tube, between the shoulder blades. All catheters were wrapped with gauze and protected by placing them in the pocket of a jacket (Alice King Chatham Medical Arts, Los Angeles, CA). The dogs were given Penicillin (20,000U/Kg) combined with streptomycin (25mg/Kg) i.m. right after surgery and trimethoprim-sulfamethoxazole (Septra^{R}, Wellcome) 1 tablet p.o., b.i.d. for another 5 days. One tablet of Meperidine HCl (Demoral^{R}, 100mg/tablet, Winthrop Laboratories, New York, NW) was given orally, b.i.d., for 1 to 2 days for postsurgical analgesia. The dogs were allowed a minimum of two weeks to recover from the surgical procedures. Patency of the catheters was maintained by flushing with saline and filling with sodium heparin (1000U/ml, Organon Inc., W. Orange, NJ) to which antibiotics had been added (Chloramphenicol sodium succinate, Chloromycetin^{R}, 100mg/ml heparin, Parke-Davis, Morris Plains, NJ) on alternate days.

Group 2: Dogs with the **Suprarenal** and **Ascending Aortic Cuff**

Four dogs were prepared with cuffs around both the ascending aorta proximal to the brachiocephalic trunk and the abdominal aorta proximal to both renal arteries. (Suprarenal Cuff)

A cuff was placed around the ascending aorta and a catheter inserted in the left atriumm (as described for group 1 dogs). The right atrium was not catheterized in this group of dogs. Since the right renal artery is 1.5 to 2 cm higher than the left renal artery, we decided to implant the cuff around the aorta from the right side. Thus, we can be sure that the cuff will be placed above both renal arteries. A right flank incision, one inch below the right costal margin, was made to expose the right renal artery and the abdominal aorta. The right phrenicoabdominal artery was then ligated at its origin from the aorta and cut. The abdominal aorta between the superior mesenteric and the right renal artery was freed from the surrounding connective tissue and the cuff was placed around this free segment of the aorta.

Blood pressure proximal and distal to the suprarenal cuff was monitored by placing two tygon catheters (0.05 inch I.D., 0.09 inch O.D.) via both femoral arteries and the tips of the catheters were located in the abdomianl aorta, one proximal and the other distal to the suprarenal cuff. All catheters were routed subcutaneously, exteriorized between the shoulder blades, and protected as previously described. The whole surgical procedure was completed in one day. The dogs were allowed at least two weeks to recover from surgery and received the same postsurgical treatment as the dogs in group 1.

Group 3: Dogs with the **Pulmonary Artery Cuff**

Another group of four dogs were used in this series of experiments. This group was prepared with a cuff around the pulmonary trunk (Pulmonary artery cuff), catheters in both atria, and another catheter introduced into the abdominal aorta via the left femoral artery. The tip

of the femoral catheter was advanced to the level of the renal arteries. The surgical technique and the postsurgical treatment were as described for the group 1 dogs.

Group 4: Dogs with **Bilarteral Renal Denervation** , plus the **Ascending Aortic** and the **Suprarenal Cuff**

Six dogs were used in this series of experiments. The dogs were prepared with an ascending aortic cuff, a left atrial catheter, and allowed seven days to recover from the chest surgery. The dogs were then anesthetized again and two tygon catheters (as above) were placed via both femoral arteries and the tips of the catheters were located in the abdominal aorta, one above and one below the renal arteries. After this, both kidneys were denervated.

A left flank incision about 1 cm below the costal margin was used to expose the left kidney. The kidney was freed from the surrounding fat, peritoneal reflection and wrapped with saline soaked gauze. The connective tissue around the hilar area was cleared to free the renal artery, vein and the ureter. All visible nerves in the hilum were cut, and the renal artery and vein were stripped of their adventitia by use of a fine tip forceps. Finally, the renal artery, vein and the ureter were all painted with a solution of 10% phenol in absolute alchohol. During the application of phenol sulotion, the kidney and the adjacent tissue were carefully protected from this chemical. After painting with phenol, the incision was closed layer by layer. Another right flank incision was made to expose the right kidney. The right kidney was carefully denervated as described for the left side. Then the suprarenal cuff was placed around the abdominal aorta between the superior

mesenteric and the right renal artery, as described for group 3 dogs. The cuff tube was routed subcutaneously, and exteriorized, along with the two femoral catheters, between the shoulder blades. The catheters were protected as described above. The dogs were then allowed another 7 days to recover from surgery. At the end of the experiments, the kidneys were removed for measurement of norepinephrine to insure completeness of renal denervation (see **Methods of Measurement**)

Experimental Protocols

The experiments were carried out in a quiet room with the dogs in a sling (as above) which provided support but minimal restraint. The dogs were brought to the laboratory at 8:00 A.M. and allowed at least 30 minutes to became accustomed to the surroudings. After the catheters were connected to the pressure transducers and polygraph, systemic arterial and atrial pressure were monitored for another 30 minutes as the control period. Rectal temperature was then measured since febrile dogs might have fluid and electrolytes imbalance and different hormoral response to the experimental manuever. If the temperature was normal ($<39^{0}C$), two control arterial samples seperated by 5 minutes were then taken at the end of the control period. After the second control sample, the cuff was inflated until the mean arterial pressure below the cuff was reduced by 5%, 10%, 20%, or 30% of control mean arterial pressure for a total of 60 minutes or not inflated as a time control. Thus each dog implanted with either an ascending aortic (group 1) or a pulmonary cuff (group 3) received five treatments. The dogs with both ascending aortic and suprarenal cuffs, and with renal nerves intact (group 2), received 4 levels of constriction with each cuff, a time control for a

total of nine experiments. The renal denervated dogs (group 4) received 10%, 20%, and 30% level of pressure reduction caused by inflation of each cuff plus a time control for a total of 7 experiments. The different levels of pressure reduction were carried out on each dog in a random order and were seperated by a minimum of two days.

The cuff was inflated with warm saline. For the ascending aortic or pulmonary cuff, injection of 1 ml of saline did not cause any major hemodynamic change. However, another 0.2 ml of saline would cause a sudden drop of systemic arterial pressure from 100mmHg to 40mmHg. Thus, there seemed to be a threshold for the volume in the ascending aortic or pulmonary cuff to reduce the systemic arterial pressure. Since a 0.2 ml addition would drop the blood pressure from 100mmHg to shock level, a 1ml syrynge was used for fine adjustment of the volume of saline injected into or withdrawn from the cuff. For the suprarenal cuff, the threshold volume was about 0.3ml. Another 0.1 ml would sometimes cause a 50mmHg drop of the renal perfusion pressure.

In general, the required reduction in pressure distal to the cuff was achieved within one or two minutes. In order to maintain a constant reduction in pressure distal to the cuff for sixty minutes, the volume of the cuff had to be adjusted manually, especially during the first 15 minutes. Arterial blood samples were then taken at 5, 10, 15, 30, 45, and 60 minutes after the inflation of the cuff and 30 minutes after the deflation of the cuff. The volume of blood taken in each sample was between 8 and 12 ml and the same volume 0.9% NaCl was given to replace the blood removed. The blood was immediately divided into chilled tubes containing heparin (for measurement of AVP, cortisol, eletrolytes,

osmolality, hematocrit, and protein concentation) or 0.3M EDTA (0.3 ml EDTA/3 ml blood, for measurement of PRA). Following centrifugation, aliquots of plasma were frozen at -20^{O}C until assayed. Red blood cells from the heparin tubes were resuspended in saline and reinfused after the experiments.

In order to insure that vagal afferents were not damaged as a result of implantation of the ascending aortic or pulmonmary artery cuff, the following test was conducted at the end of the experimental protocols. The dogs were anesthetized and chest opened through the left 4th intercostal space, a pericardial vault was made. A home-made injection set, including a 26-gauge needle connected with a silastic tube (0.020 inch I.D., 0.037 inch O.D.), was used to infuse a bolus of veratridine (0.3ug/Kg, Sigma, San Louis, MO) into the left circumflex coronary artery. This intracoronary veratridine caused a fall in systemic arterial prssure (from 92$\pm$7 to 70$\pm$4) and heart rate (from 145$\pm$8 to 102$\pm$10). Thus the Bezold-Jarish reflexes was demonstrated in all dogs tested (N=7), showing integrity of this reflex pathway.

Methods of Measurement

In all experiments, arterial and atrial pressures were measured with Gould Statham P23Db transducers (Gould Statham, Hato Rey, Puerto Rico) and recorded on a Grass Model 7 polygraph. The ouput from the polygraph was further fed to a Buxco cardiovascular analyzer (Model CVA-1, Buxco Electronics, Inc., Sharon, CN) coupled to a Buxco data Logger (Model DL12). The hemodynamic variables were averaged over one minute periods for subsequent analysis and were printed out on a printer (Silent 700, Texas Instruments Inc., Houston, TX).

Plasma sodium and potassium concentrations were measured by flame photometry (Model 343, Instrumentation Laboratories, Lexington, MA). Sodium concentration was reproducible to ±0.7mEq/L and potassium concentration was reproducible to ±0.03mEq/L. Plasma osmolality was measured on a Fiske Osmometer (Model OR, Fiske Associater, Uxbridge, MA) in the first series and on an Advanced Osmometer (Model 3W, Advanced Instruments, Needham Heights, MA) in the second series. The Fiske was reproducible to ±1% and the Advanced was reproducible to ±2mosm/Kg water.

Plasma vasopressin was measured by radioimmunoassay following extraction with bentonite (Skowsky, Rosenbloom, and Fisher, 1974; Keil and Severs, 1977). For the assay, synthetic arginine vasopressin (357 U/mg) was used to prepare standards. The recovery of vasopressin during extraction was determined to be 70%. The levels of vasopressin reported are not corrected for recovery. The minimum detectable level of the assay was 0.3 pg/ml. The intraassay and interassay coeefficients of variability were 8.7 and 8.9%, respectively. Plasma renin activity was measured using a radioimmunoassay for angiotensin I generated during a 3-hour incubation in vitro at pH 5.5 (Stockight, Collins, and Biglieri, 1971; Reid et al., 1972). The minimum detectable level of the assay was 0.015 ngAI/ml-3hr. The intraassay and interassay coefficients of variability were 7.9 and 20.6%, respectively.

Renal catecholamine contents were measured as an index of completeness of renal denervation. The dogs were anesthetized and both kidneys were removed by bilateral flank incision. Two to three pieces (total weight 200 to 300 mg) of cortex were taken at random from both

kidneys. The tissue was placed in a test tube containing 0.2N HC104 (1gm tissue/4ml HC104), homogenized, and stored in -70^{0}C freezer until assayed. A radioienzymatic assay was used to measure catecholamine in the homogenate (Peuler and Johnson, 1977).

Data Analysis

A two way analysis of variance, repeated on time and dose (level of pressure reduction) was performed for PRA, cortisol, and vasopressin (Winer, 1971). If there was a significant effect (p value <0.05) with respect to either time or dose, the Newman-Keuls test (Zar, 1974) was performed on the means to determine differences among appropriate means. If there was a significant interaction effect, the interaction mean square error was used and comparisons were made between the individual means in each row or column. If there was no significant interaction, the means were averaged over each row or column, depending on which factor was significant, and the Newman-Keuls test was performed using those means and the mean square error associated with that factor.

Additional analyses were performed by comparing the average change in PRA, cortisol, and vasopressin and the hemodynamic variables in response to various degree of cuff inflation. These "average" values were calculated for each dog as the difference between the integrated response during the experimental period and the preceding control period. The variances of the average change of PRA and hemodynamic variables were not homogeneous (Bartlett's test), therefore a non-parametric procedure (Kruskal-Wallis test) was used to test for differences among the means. If the Kruskal-Wallis test detected a significant difference ($p<0.05$), a non-parametric multiple range test

was used to compare the means. (Zar, 1974).

The responses to ascending aortic cuff inflation were not different between the dogs in group 1 (ascending aortic cuff only) and group 2 (both ascending aortic and suprarenal cuffs), therefore these data were pooled for statistical analysis.

Chapter 3

Results

The hemodynamic and hormonal data will be presented first, followed by electrolytes and osmolality.

Ascending aortic cuff inflation in 7 normal dogs.

Inflation of the ascending aortic cuff was intended to produce reductions in mean systemic arterial pressure (MAP) distal to the cuff of 5%, 10%, 20%, and 30% of control. The pressure reduction achieved was 5.4±0.2%, 10.4±0.7%, 20.3±0.5%, and 29±0.4%, respectively (Fig. 1, top panel). Thus, the renal perfusion pressure measured from the aortic catheter with its tip placed at the renal arteries, ranged from 83±2 mmHg during the 5% reduction in MAP down to 65±3 mmHg during the 30% reduction in MAP (Table 1). In spite of the systemic hypotension, plasma vasopressin concentrations and renin activity did not change throughout the range of blood pressures examined (Fig. 2, 3, vasopressin; Fig. 4, 5, PRA). Plasma cortisol concentrations did not change in response to 5, 10, and 20% reduction in MAP, however, they increased significantly when MAP was reduced by 30% of control (Fig. 6, 7).

Heart rate (Fig. 8) and left atrial pressure (Fig. 9) increased dose dependently in response to inflation of the ascending aortic cuff. In contrast, right atrial pressure did not change during the 5% reduction in MAP, but, decreased significantly during 10%, 20%, and 30% reduction in MAP (Fig. 10). The pulse pressure also decreased significantly in response to all levels of systemic hypotension following inflation of the ascending aortic cuff (Fig. 11).

Pulmonary artery cuff inflation in 4 normal dogs.

Inflation of the pulmonary cuff was intended to produce reductions in MAP of 5,10, 20, or 30% of control. The pressure reduction achieved was 6.4±0.5%, 10.8±0.9%, 20±0.9% and 28.2±0.4%, respectively (Fig. 1, middle panel). Thus, the renal perfusion pressure measured from the aortic catheter with its tip placed at the level of the renal arteries, ranged from 84±1 mmHg during the 5% reduction in MAP down to 66±1 mmHg during the 30% reduction in MAP (Table 1). In spite of comparable systemic hypotension, the hormonal responses were very different between constriction of the ascending aorta and the pulmonary artery. Plasma vasopressin (Fig. 2, 12) and cortisol (Fig. 6, 13) increased dose dependently in response to graded inflation of the pulmonary cuff. Plasma vasopressin increased 12 fold during the 5% reduction in MAP and 75 fold during 30% reduction in MAP following inflation of the pulmonary cuff (Fig. 2), however, the response of vasopressin to comparable graded systemic hypotension caused by inflation of the ascending aortic cuff was essentially flat (Fig. 3). Plasma renin activity increased significantly in response to 20% and 30% reductions in renal perfusion pressure caused by constriction of the pulmonary artery, but did not change in response to 5% and 10% reductions in renal perfusion pressure (Fig. 4, 14).

Heart rate increased dose dependently in response to graded inflation of the pulmonary cuff (Fig. 8). However, in contrast to inflation of the ascending aortic cuff, right atrial pressure (Fig. 10) increased dose dependently. At the same time left atrial pressure (Fig. 9) declined dose dependently in response to graded inflation of the pulmonary cuff. Pulse pressure also decreased significantly in response

to each level of systemic hypotension following constriction of the pulmonary artery. The percent reduction in pulse pressure was not different between the corresponding levels of constriction of the ascending aorta and pulmonary artery (Fig. 11).

Suprarenal cuff inflation in 4 normal dogs.

Inflation of the suprarenal cuff was intended to produce reductions in MAP distal to the cuff of 5, 10, 20, and 30% of control. The pressure reduction achieved was 5.2±0.5%, 10.1±0.8%, 20.1±1.5%, and 29.5±0.8%, respectively (Fig. 1, bottom panel). Renal perfusion pressure measured from the aortic catheter with its tip placed at the level of the renal arteries, ranged from 83±3 mmHg during the 5% reduction in MAP down to 65±1 mmHg during the 30% reduction in MAP (Table 1). Plasma renin activity increased significantly in response to each level of pressure reduction caused by inflation of the suprarenal cuff (Fig. 4, 15). These results are in marked contrast to those obtained with inflation of the ascending aortic cuff, even though both treatments led to identical reductions in renal perfusion pressure (Table 1).

During inflation of the suprarenal cuff, MAP above the cuff increased dose dependently (Fig. 16). However, heart rate and left atrial pressure did not change during graded inflation of the suprarenal cuff (Fig. 8, 9). Pulse pressure decreased significantly in response to each level of reduction in renal perfusion pressure. The percent reductions of pulse pressure following inflation of the suprarenal cuff were not different from that caused by inflation of the ascending aortic or pulmonary cuff (Fig. 11).

Comparison of ascending aortic and suprarenal cuff inflation in normal

dogs.

We were able to complete the entire series of ascending aortic and suprarenal cuff inflations in three of the four dogs implanted with both cuffs. Thus, in these three dogs, direct comparisons of changes in PRA, in response to identical reductions in renal perfusion pressure and pulse pressure could be made. The time couse of changes in PRA in response to reductions in renal perfusion pressure are shown in Fig. 17. Inspection of the curve shows that reducing renal perfusion pressure by constriction of the ascending aorta does not lead to an increase in PRA throughout the 60 min period of cuff inflation. In contrast. PRA increased sharply in response to constriction of the aorta just above the renal arteries and remained elevated throughout the 60 min of cuff inflation. Comparison of the average changes in PRA indicates that constriction of the ascending aorta actually produced a significant reduction in PRA throughout the range of renal perfusion pressure examined (Fig. 18). In contrast, an equal reduction in renal perfusion pressure caused by constricting the aorta just above the renal arteries led to large increases in PRA throughout the entire dose range.

Suprarenal cuff inflation in 5 renal denervated dogs.

Inflation of the suprarenal cuff was intended to produce reductions in MAP distal to the cuff of 10, 20, and 30% of control. The pressure reduction achieved was 10.4±0.4%, 18.8±0.4%, and 28±0.7%, respectively (Fig. 19). Renal perfusion pressure, measured from the aortic catheter with its tip placed at the level of the renal arteries, ranged from 83±3 mmHg during the 10% reduction in MAP down to 69±2 mmHg during the 28% reduction in MAP (Table 2). The resting control PRA of renal denervated

dogs was significantly lower than that of normal dogs (0.9±0.3 vs 2.5±0.2 ng AI/ml/hr, respectively, $p<0.01$). However, plasma renin activity increased significantly in response to each level of pressure reduction caused by inflation of the suprarenal cuff in renal denervated dogs (Fig. 20, 21). These results were similar to those obtained with inflation of the suprarenal cuff in intact dogs.

During inflation of the suprarenal cuff, mean arterial pressure above the cuff increased dose dependently (Fig. 22). However, heart rate and the left atrial pressure did not change during graded inflation of the suprarenal cuff (Fig. 23, 24, respectively). Pulse pressure decreased significantly in response to each level of reduction in renal perfusion pressure (Fig. 25).

Ascending aortic cuff inflation in renal denervated dogs.

Inflation of the ascending aortic cuff was intended to produce reductions in MAP distal to the cuff of 10, 20, and 30% of control. The pressure reduction achieved was 9.6±0.4%, 18.5±0.4%, and 27.6±0.7%, respectively (Fig. 26). Renal perfusion pressure measured from the aortic catheter with its tip placed at the level of the renal arteries, ranged from 83±3 mmHg during the 10% reduction in MAP down to 70±3 mmHg during the 30% reduction in MAP (Table 2). Plasma renin activity did not change in response to a 10% reduction of renal perfusion pressure caused by inflation of the ascending aortic cuff in renal denervated dogs (Fig. 21, 27). This is in sharp contrast to a 3.5±1.0 ng AI/ml/hr increase in PRA caused by identical reduction of renal perfusion pressure during inflation of the suprarenal cuff in the same group of renal denervated dogs (Fig. 21). However, plasma renin activity did increase

significantly in response to 20% and 30% reduction of renal perfusion pressure following inflation of both the ascending aortic and the suprarenal cuffs (Fig. 21, 27).

Heart rate (Fig. 23) and left atrial pressure (Fig. 24) increased dose dependently in response to inflation of the ascending aortic cuff in denervated dogs. However, pulse pressure decreased significantly in response to each level of reduction in renal perfusion pressure (Fig. 25). The reductions of pulse pressure were not different between constriction of the ascending aorta and the abdominal aorta just above renal arteries in renal denervated dogs.

The completeness of denervation was evaluated by measuring the renal norepinephrine content. The renal norepinephrine content in intact kidney was 165±20 ng/g tissue, however, after renal denervation, the norepinephrine content was undetectable. Since the lowest sensitivity of the norepinephrine assay in our laboratory is 12 ng/g, the renal norepinephrine content was depleted by more than 92%.

Comparison of ascending aortic and suprarenal cuff inflation in renal denervated dogs.

Since inflation of both cuffs caused identical reductions in renal perfusion pressure and pulse pressure in the same group of renal denervated dogs, we were able to compare the PRA response to both ascending aortic and suprarenal cuff inflation in the same group of animals. Comparison of the average changes in PRA following inflation of the ascending aortic and suprarenal cuffs by two way ANOVA with repeated measurement indicated a significant effect of dose (the level of pressure reduction, $F_{2,8}=7.92$, $p<0.05$), and a significant effect of

treatment (Ascending aortic vs suprarenal cuff inflation, $F_{1,4}=8.44$, $p<0.05$). However, there was no dose by treatment interaction ($F_{2,8}=0.12$, $p>0.25$). The lack of significant interaction between dose and treatment means that the slope of the PRA response to inflation of ascending arotic and suprarenal cuffs were similar (Fig. 21). Therefore, the difference between the responses in the two treatments was an increase in the threshold required to elicit a response during inflation of the ascending aortic cuff. Indeed, a 10% reduction of renal perfusion following inflation of the ascending aortic cuff failed to increase PRA, whereas the same reduction of renal perfusion pressure following inflation of the suprarenal cuff significantly increased PRA.

Electrolytes and osmolality.

The effects of reducing systemic MAP in the five series of experiments on plasma sodium and potassium are shown in Table 3, 4, and 5. Plasma sodium was not significantly affected by any of the experimental maneuvers (Table 3 and 5). In contrast, plasma potassium concentration declined significantly (Table 4, 5), compared to the preconstriction control values, in each of the protocols. However, as plasma potassium fell an equivalent amount in the time control experiments, the effect cannot be attributed to a response induced by the experimental treatment. Plasma osmolality did not change in response to inflation of the ascending aortic or pulmonary cuff (Table 6, 7, respectively).

Table 1. Mean arterial pressure distal to the indicated cuff

% Reduction in blood Pressure	Ascending aortic cuff		Suprarenal cuff		Pulmonary cuff	
	Control	Tx	Control	Tx	Control	Tx
Time control	90 3	91 1	92 4	91 3	92 3	91 4
5%	88 2	83 2	88 2	83 3	88 3	84 1
10%	90 2	81 2	89 1	80 3	91 2	82 2
20%	92 3	73 3	91 2	73 1	91 2	73 1
30%	92 4	65 3	92 2	65 1	92 2	66 1

Values shown are means ± one SE in mmHg

Control = Blood pressure averaged over the 30 min period preceding inflation of the cuff.

Tx = Blood pressure averaged over the 60 min period of cuff inflation.

Table 2. Mean arterial pressure distal to the indicated cuff in renal denervated dogs.

% Reduction in blood pressure		Ascending aortic cuff			Suprarenal cuff		
	time control	10%	20%	30%	10%	20%	30%
Control	92 3	94 3	94 4	99 4	93 3	96 5	97 3
Treatment	95 2	83 3	75 3	70 3	83 3	77 4	69 2

Values shown are ± one SE in mmHg.

Control = blood pressure averaged over the 30 min period preceding inflation of the cuff.

Treatment = Blood pressure averaged over the 60 min period of cuff inflation.

Table 3. Effects of reductions in renal perfusion pressure on plasma sodium.

% Reduction in blood pressure	Plasma Sodium (mEq/l)					
	Ascending aortic cuff		Suprarenal cuff		Pulmonary cuff	
	Before	After	Before	After	Before	After
Time control	147 1	146 1	146 1	145 1	146 1	146 1
5%	146 1	147 1	147 1	147 1	147 1	146 1
10%	146 1	147 1	145 2	144 2	146 1	146 1
20%	146 1	147 1	145 1	145 1	146 1	146 1
30%	147 1	147 1	147 1	147 1	146 1	146 1

Values are mean ± one SE of plasma sodium concentration before inflation of the cuff (Before) and after 60 min of cuff inflation (After). Reductions in blood pressure are distal to the indicated cuff.

Table 4. Effect of reduction in renal perfusion pressure on plasma potassium.

% reduction in blood pressure	Plasma potassium (mEq/L)					
	Ascending aortic cuff		Suprarenal cuff		Pulmonary cuff	
	Before	After	Before	After	Before	After
Time Control	4.5 0.1	4.3* 0.1	4.6 0.1	4.4* 0.2	4.7 0.1	4.4* 0.1
5%	4.6 0.1	4.2* 0.1	4.7 0.1	4.4* 0.1	4.7 0.1	4.3* 0.1
10%	4.4 0.1	4.1* 0.1	4.7 0.1	4.4* 0.1	4.7 0.1	4.3* 0.1
20%	4.5 0.1	4.1* 0.1	4.7 0.1	4.5* 0.1	4.6 0.1	4.3* 0.2
30%	4.5 0.1	4.2* 0.1	4.8 0.1	4.5 * 0.1	4.7 0.1	4.4* 0.1

Values are means ± one SE of plasma potassium concentration before inflation of the cuff (Before) and after 60 min of cuff inflation (After).

Reductions in blood pressure are distal to the indicated cuff.

* Significantly different from preconstriction control values.

Table 5. Effect of reduction in renal perfusion pressure on plasma sodium and potassium in renal denervated dogs, N=5

% reduction in MAP	plasma Na^{++}		plasma K^{+}	
	Before	After	Before	After
Time control	146 1	146 1	4.5 0.1	4.3** 0.1
10% A.O.	145 1	146 1	4.5 0.1	4.2** 0.1
20% A.O.	145 1	145 1	4.6 o.1	4.3** 0.1
10% Supra.	146 1	146 1	4.6 0.1	4.4* 0.1
20% Supra.	145 1	145 1	4.6 0.1	4.3* 0.1
30% Supra	146 1	145 1	4.6 0.1	4.4* 0.1

Values are means ± 1SE of plasma sodium and potassium concentration (mEq/L) before inflation of the cuff (Before) and after 60 min of cuff inflation (After)

A.O. : ascending aortic cuff inflation; Supra. : Suprarenal cuff inflation.

Reductions in mean arterial pressure (MAP) are distal to the indicated cuff.

*, ** Significantly different from "Before" value, $p < 0.05$, $p<0.01$, respectively.

Table 6. Effects of reduction in mean arterial pressure on plasma osmolality in dogs with ascending aortic cuffs.

% Reduction in blood pressure	Time (min)					
	0	15	30	45	60	90
Control	297 1	297 1	298 1	297 1	296 1	297 1
5%	297 1	297 1	297 2	298 2	298 2	298 2
10%	297 1	296 1	297 1	297 1	298 1	298 1
20%	297 2	297 2	297 2	297 2	298 2	298 2
30%	296 2	295 2	295 2	297 2	297 2	297 2

Values are means ± one SE of plasma osmolality in response of inflation of the ascending aortic cuff.

Reductions in blood pressure are distal to the Ascending aortic cuff.

Table 7. Effect of reduction in systemic arterial pressure on osmolality in dogs with pulmonary cuffs.

% reduction in MAP	Time (min) 0	15	30	45	60	90
Control	298	298	298	298	298	298
	1	1	1	1	1	1
5%	300	300	299	299	299	300
	2	2	1	1	2	1
10%	299	298	298	298	298	298
	1	1	1	1	1	1
20%	298	297	298	298	297	298
	1	1	1	1	1	1
30%	300	301	300	301	302	302
	1	1	1	1	1	1

Values are means ± 1SE of plasma osmolality in response to inflation of the pulmonary cuff.

Reductions in blood pressure are distal to the pulmonary cuff.

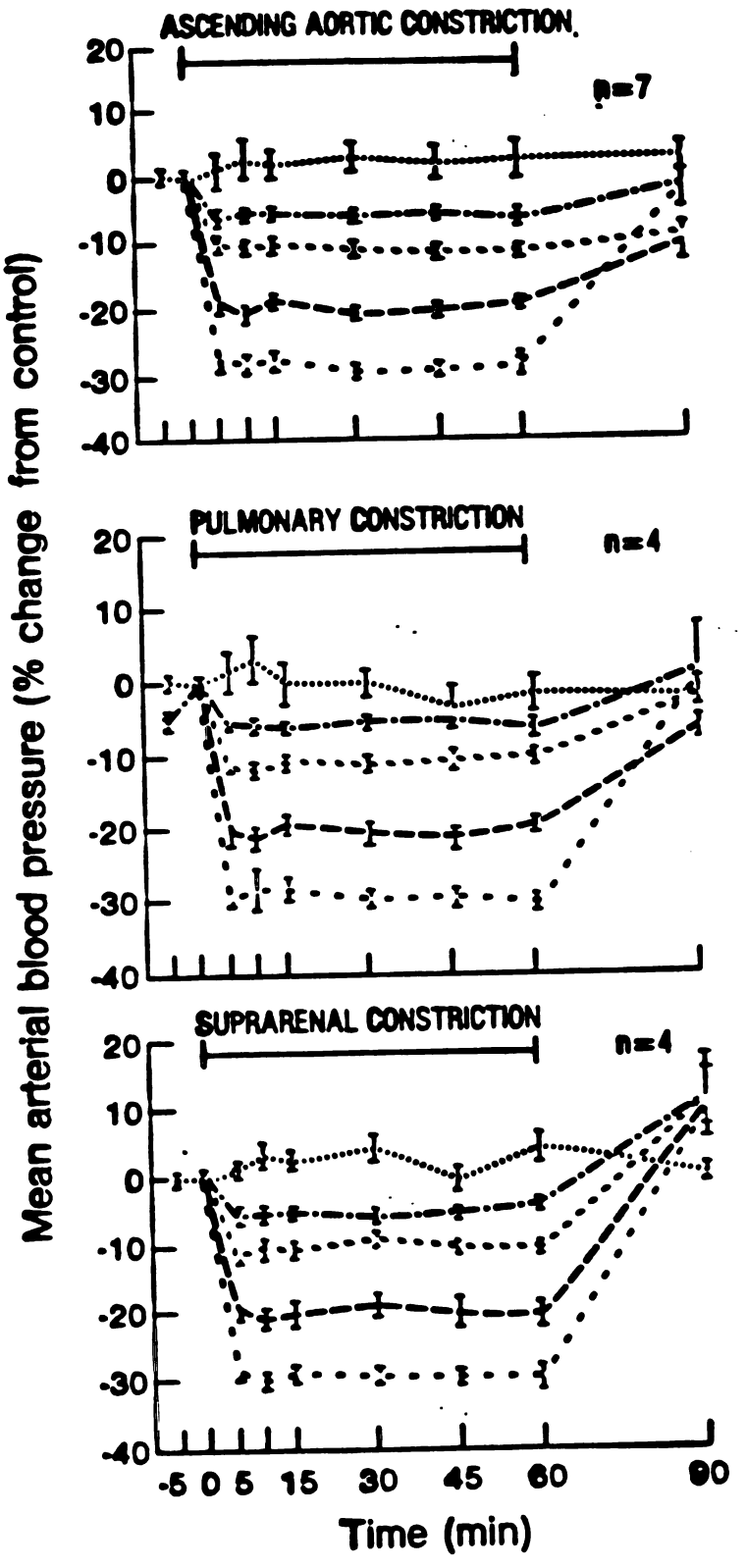
ASCENDING AORTIC CONSTRICTION
n=7
PULMONARY CONSTRICTION
n=4
SUPRARENAL CONSTRICTION
n=4
Mean arterial blood pressure (% change from control)
20
10
0
-10
-20
-30
-40
-5 0 5 15 30 45 60 90
Time (min)

Fig. 1. Time control; 5%; 10%; 20%; and 30% reduction in mean systemic arterial pressure, or distal aortic pressure in response to graded inflation of the ascending aortic, pulmonary, and suprarenal cuff. The cuff was inflated between time 0 and 60. Reduction of mean arterial pressure was achieved immediately and maintained constant during this period. See Table (1) for preconstriction control pressures.

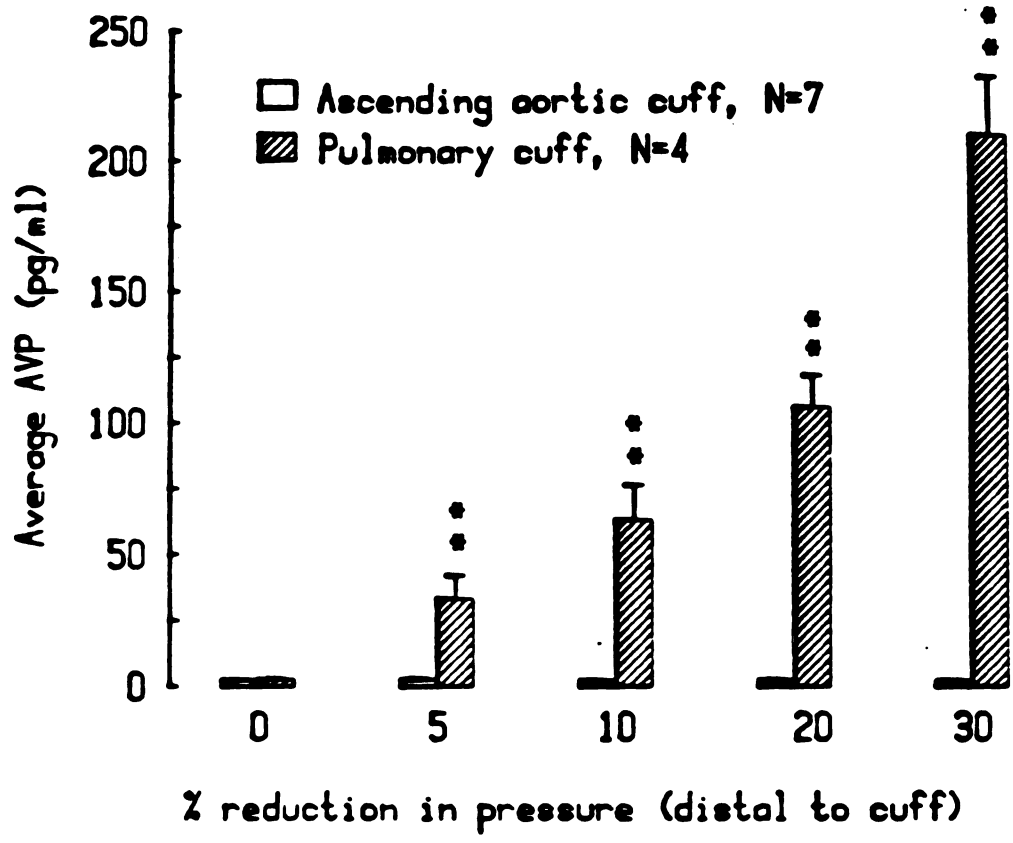

Fig. 2. Plasma vasopressin (AVP) concentrations increased dose dependently in response to graded systemic hypotension caused by inflation of the pulmonary cuff ($F_{4,12}=44$, $p<0.01$), but did not change in response to identical systemic hypotension following inflation of the ascending aortic cuff ($F_{4,24}=1.2$, $p>0.25$). * $p<0.05$, ** $p<0.01$, compared to time control (0% reduction).

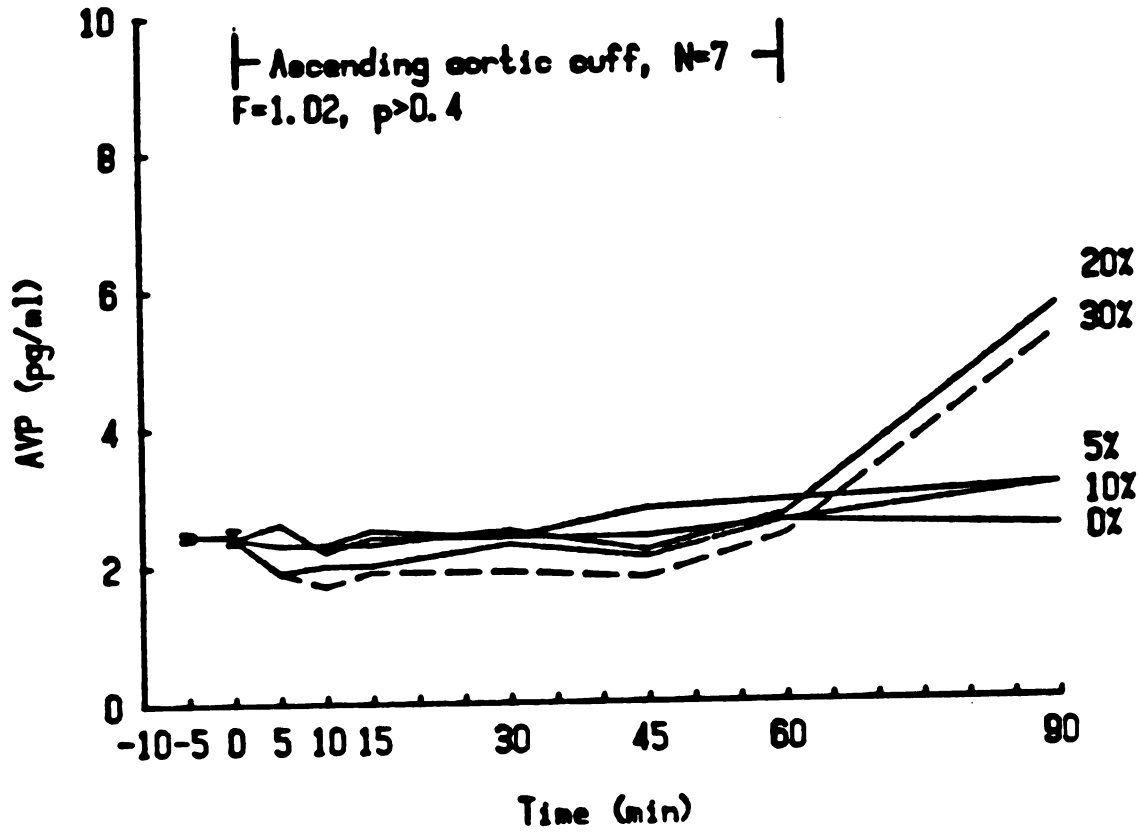

Fig. 3. During the 60 min of ascending aortic cuff inflation, plasma vasopressin (AVP) concentrations did not change in response to any of the 4 levels of systemic hypotension ($F_{4,24}=1.02$). There were apparent increases in AVP at time 90 during 20 and 30% reduction in systemic arterial pressure. When the AVP at 90 min was compared with the preconstriction control AVP and the average AVP during the 60 min period of cuff inflation, two way ANOVA with repeated measurements indicated a significant difference among the three ($F_{2,10}=5.21$, $p<0.05$).

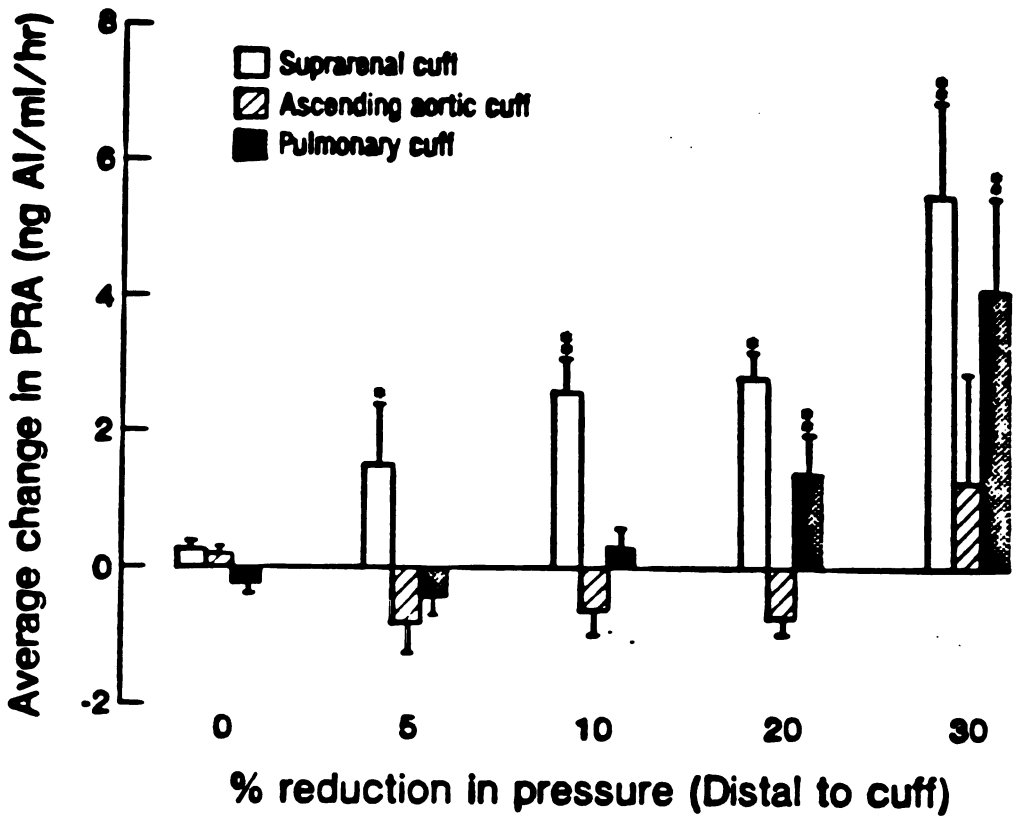

Figure 4. Graded reduction in renal perfusion pressure caused by inflation of the suprarenal cuff led to significant increases in PRA. However, identical reductions in renal perfusion pressure during inflation of the ascending aortic cuff did not cause an increase in PRA. Reduction in renal perfusion pressure of 20% and 30%, but not 5% and 10% during inflation of the pulmonary cuff led to significant increases in PRA. Control PRA was 2.1±0.1, 2.6±0.2, and 1.8±0.6 ng AI/ml/hr for dogs with suprarenal (N=4), ascending aortic (N=7), and pulmonary (N=4) cuff, respectively. * $p<0.05$, ** $p<0.01$ compared to time control (0% reduction).

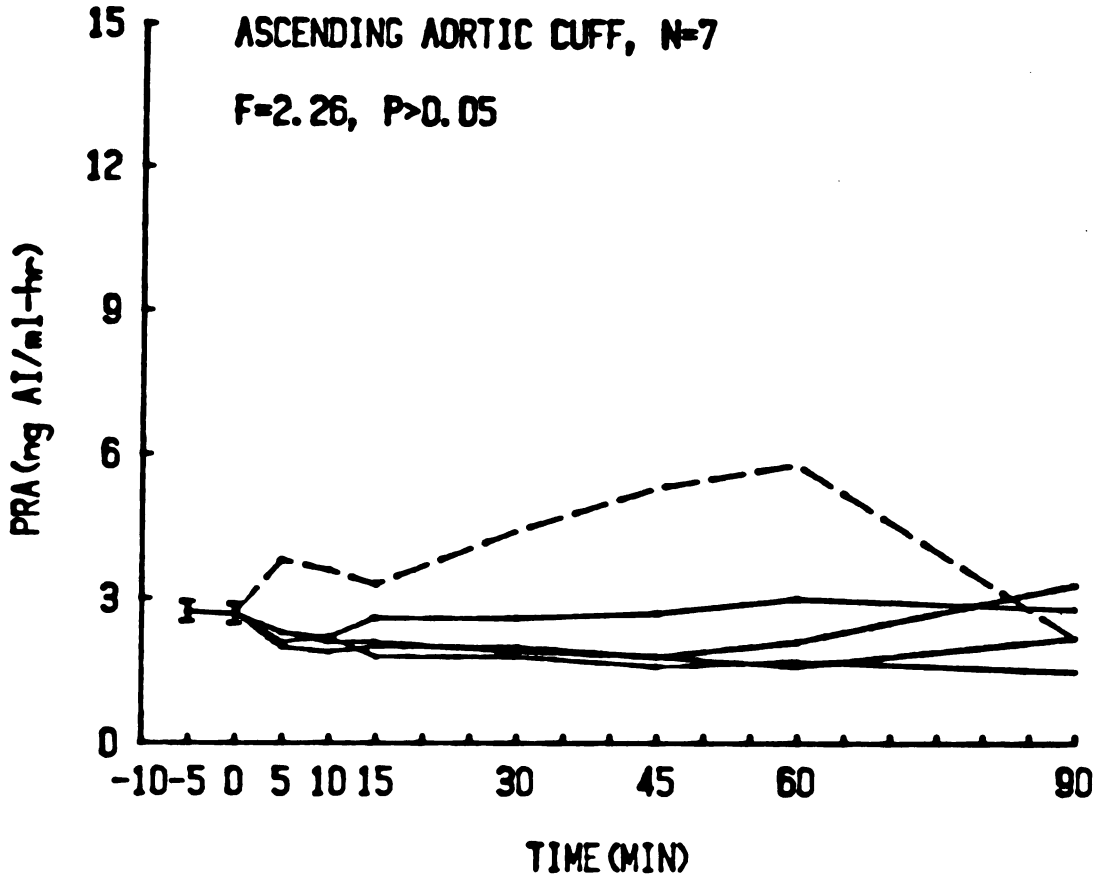

Figure 5. During the 60 min period of ascending aortic cuff inflation, plasma renin activity (PRA) did not change in response to any of the four levels of systemic hypotension.

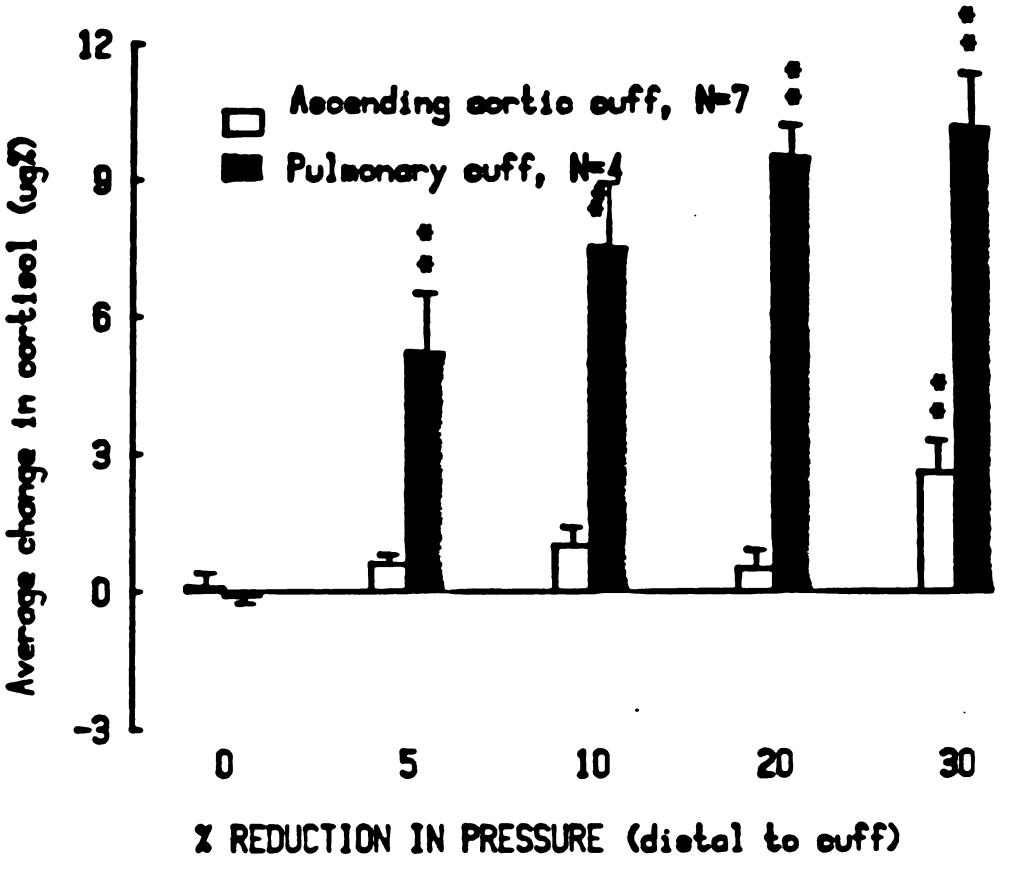

Figure 6. Plasma cortisol concentrations increased dose dependently in response to graded inflation of the pulmonary cuff. Plasma cortisol did not change in response to 5%, 10%, and 20% reduction of systemic arterial pressure during inflation of the ascending aortic cuff, however, they did increase signficantly when the systemic arterial pressure was reduced by 30% of control. The increases of plasma cortisol during the 30% reduction of systemic pressure following constriction of the ascending aorta were smaller than those of the same level of systemic hypotension following constriction of the pulmonary artery ($p<0.01$). ** $p<0.01$ compared with time control.

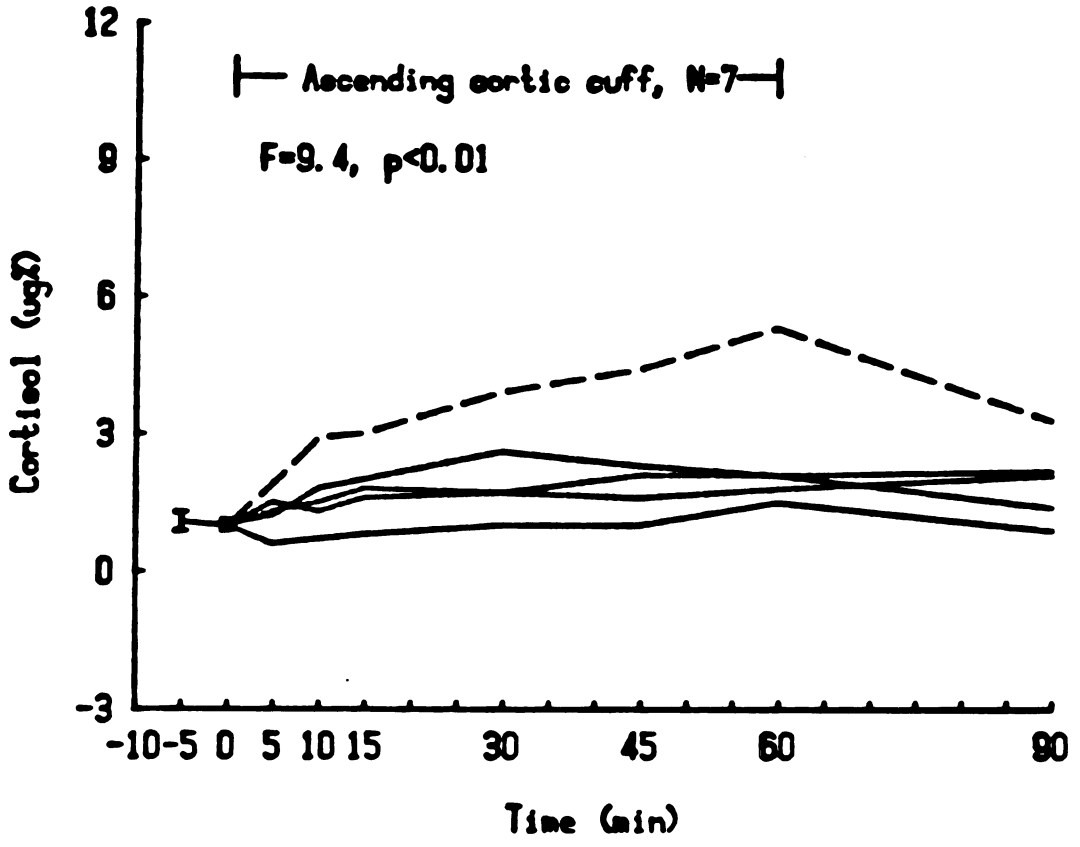

Figure 7. Plasma cortisol concentrations did not change in response to 5%, 10%, 20%, and 30% reduction of systemic arterial pressure following inflation of the ascending aortic cuff. However, plasma cortisol increased when systemic arterial pressure was reduced by 30% of control and the increase was maintained for 60 minutes.

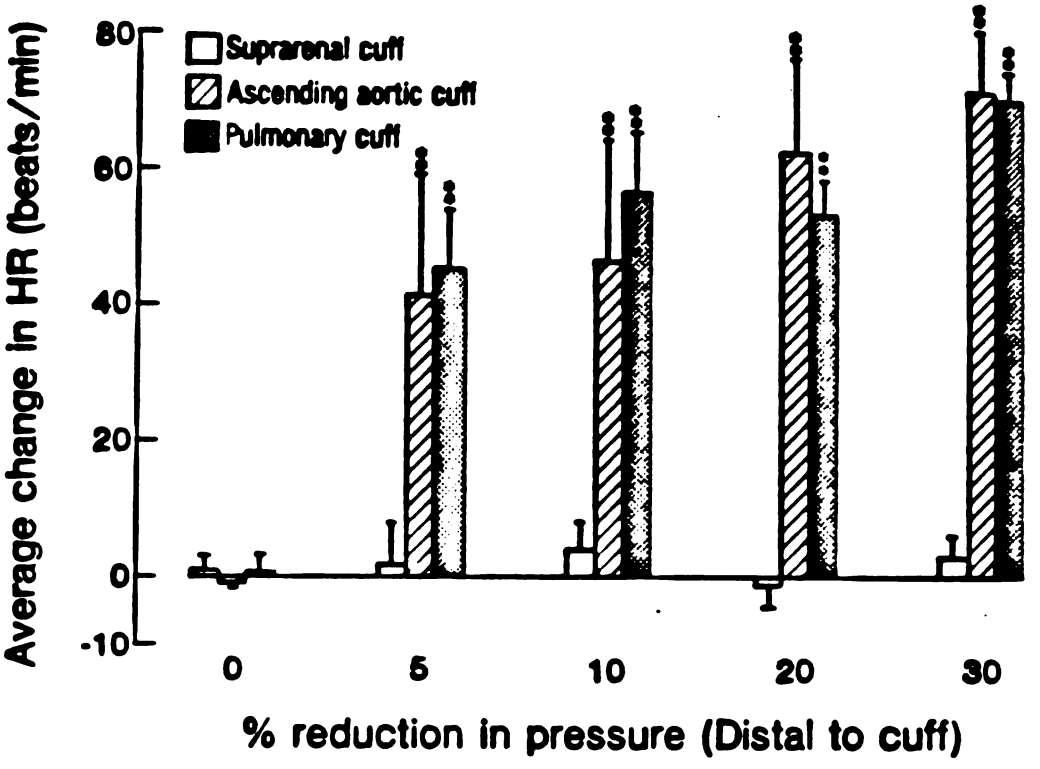

Figure 8. Heart rate (HR) increased in response to graded inflation of the ascending aortic (n=7) and pulmonary (n=4) cuff but did not change during graded inflation of the suprarenal cuff (n=4). Control HR were 54±4, 58±4, and 67±5 beats/minute for suprarenal, ascending aortic, and pulmonary cuff experiments, respectively. **$p<0.01$, compared to time control (0% reduction).

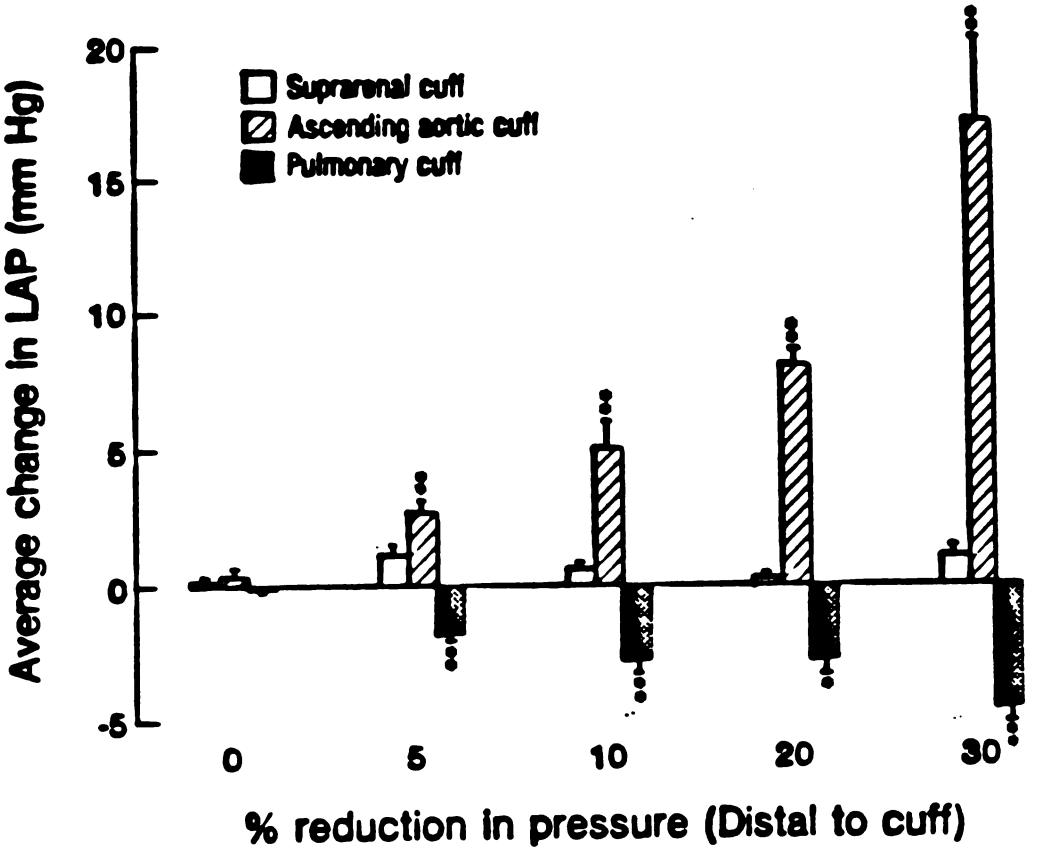

Figure 9. Left atrial pressure (LAP) did not change during graded inflation of the suprarenal cuff (n=4), but increased in response to graded inflation of the ascending aortic cuff (n=7) and decreased in response to graded inflation of the pulmonary cuff (n=4). Mean LAP during the control period was 4.1±1 mmHg, 4.4±1 mmHg, 4.0±0.3 mmHg for suprarenal, ascending aortic, and pulmonary cuff experiments, respectively. *$p<0.05$, **$p<0.01$ compared to time control (0% reduction).

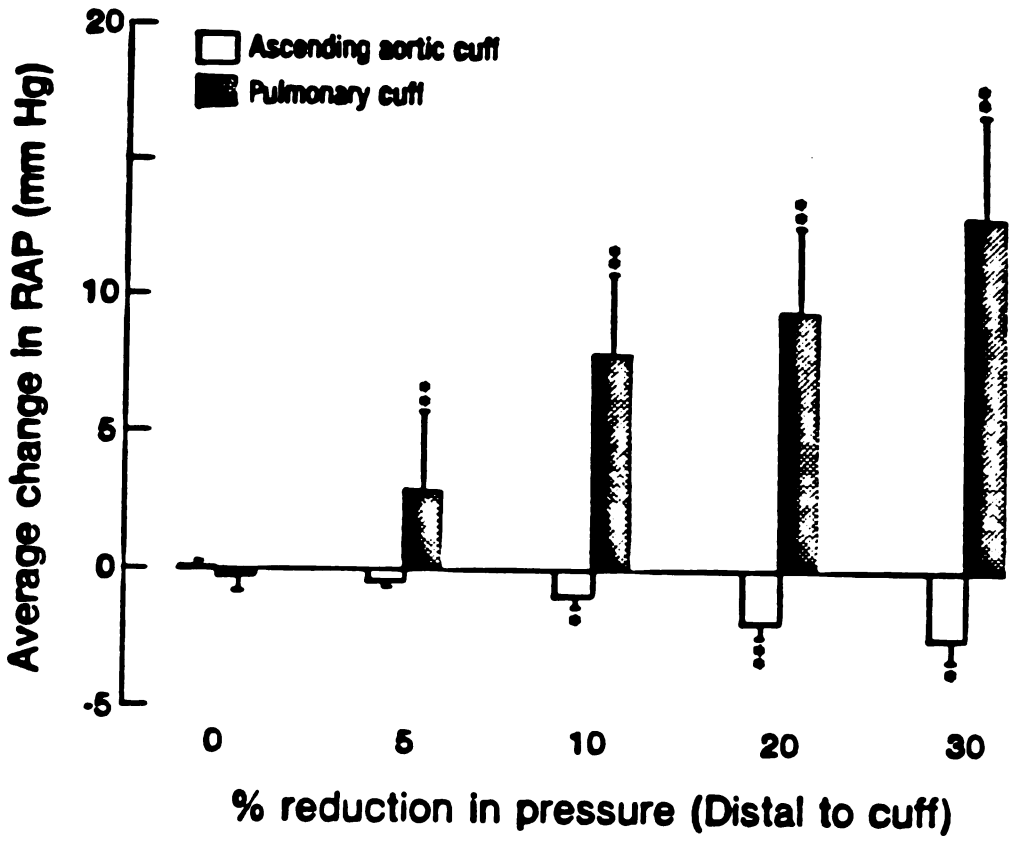

Figure 10. Right atrial pressure (RAP) decreased during graded inflation of the ascending aortic cuff (n=4) but increased dose dependently during graded inflation of the pulmonary cuff (n=4). The control RAP prior to inflation was 0.1±0.1 mmHg and 0.2±0.3 mmHg for ascending aortic and pulmonary cuff experiments respectively. *$p<0.05$; **$p<0.01$ compared to response during time control (0% reduction).

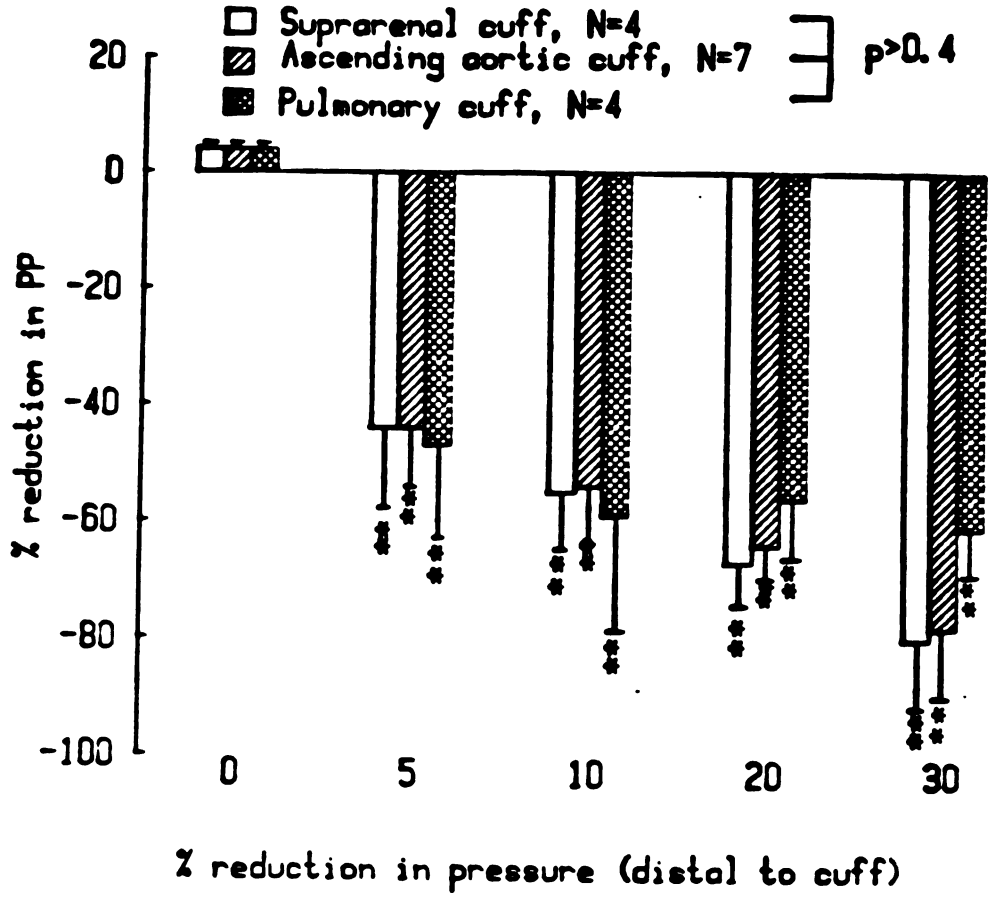

Figure 11. Pulse pressure decreased significantly in response to each level of reduction of renal perfusion pressure following inflation of the suprarenal, ascending aortic, or pulmonary cuff. The reduction of pulse pressure in response to each level of cuff inflation was not different among the three cuff experiments. Mean pulse pressure during the control period was 55±5, 54±5, and 50±7 mmHg for suprarenal, ascending aortic, and pulmonary cuff experiments, respectively. ** $P<0.01$ compared to time control (0% reduction)

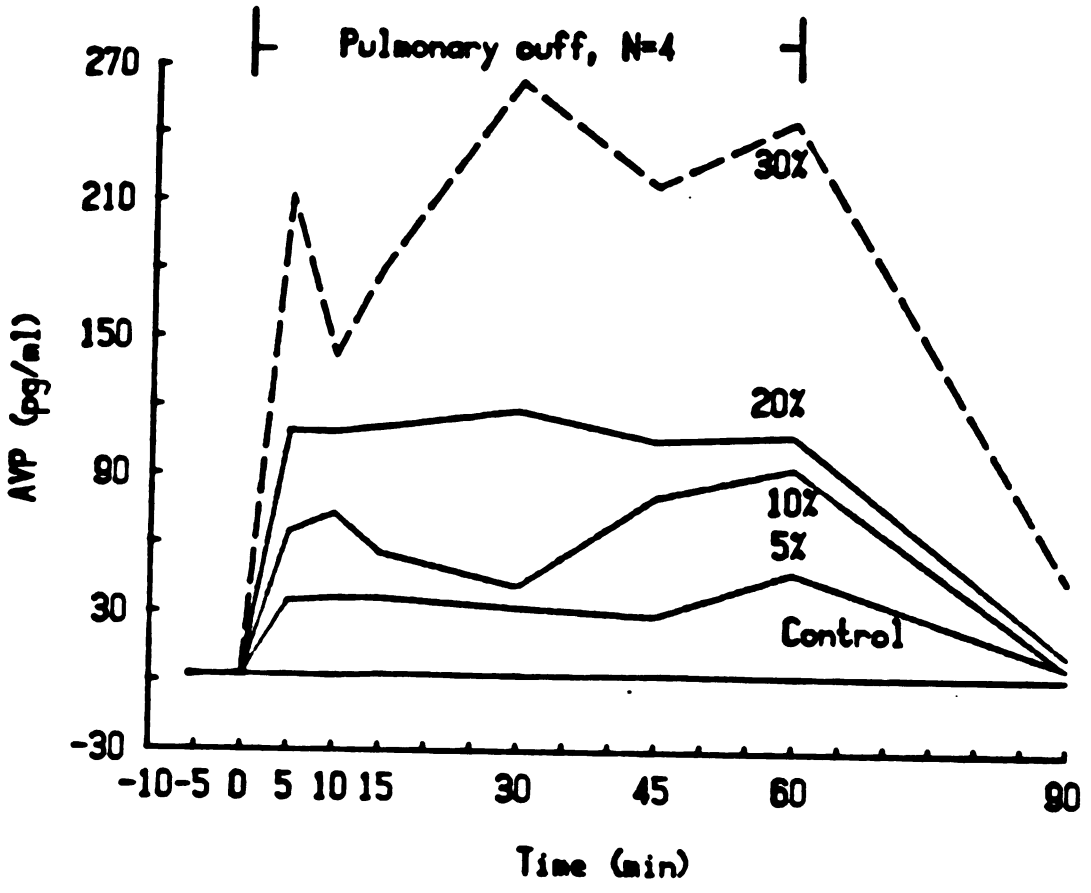

Figure 12. Plasma vasopressin (AVP) concentrations increased dose dependently in response to 4 levels of systemic hypotension caused by inflation of the pulmonary cuff ($F_{4,24}=24.4$, $p<0.01$). The increases ranged from 10 fold during a 5% reduction in systemic arterial pressure up to 100 fold during a 30% reduction in pressure. The increases were maintained for 60 minutes.

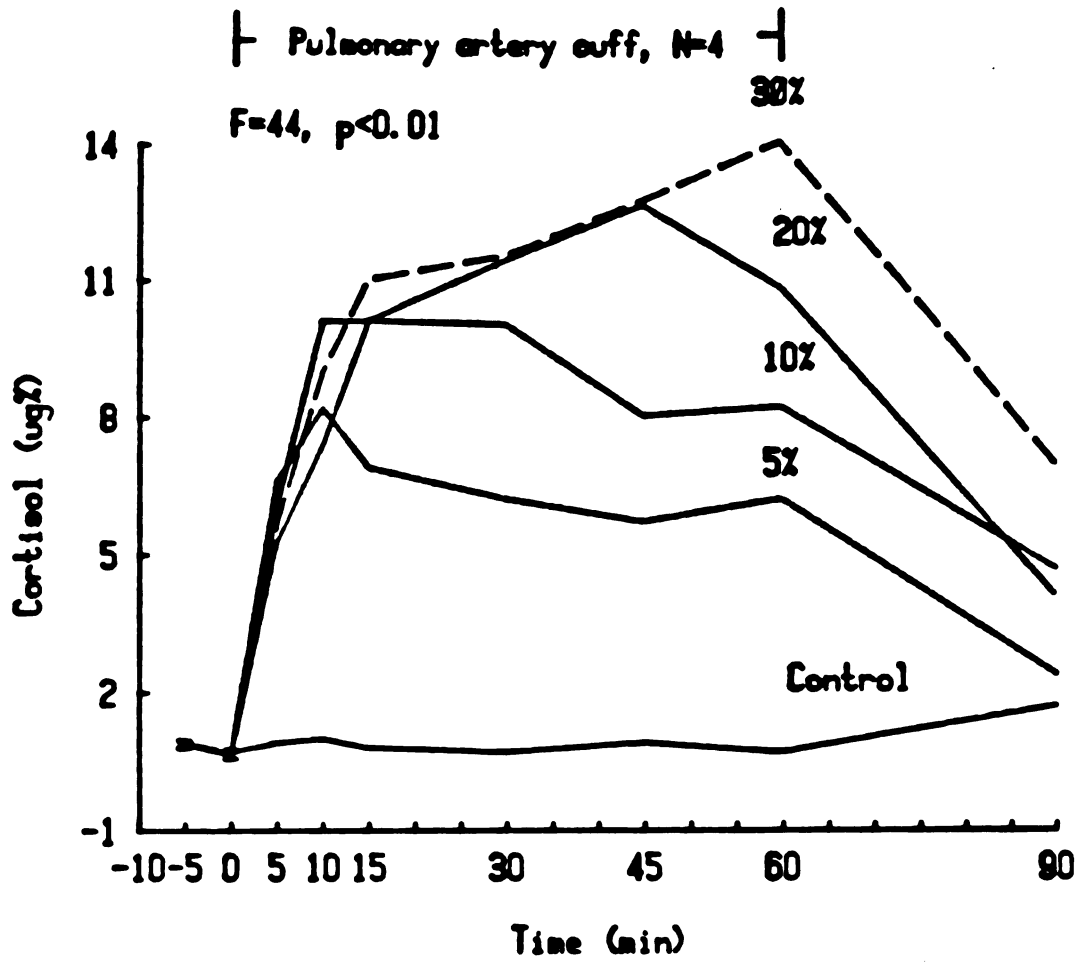

Figure 13. Plasma cortisol concentrations increased dose dependently in response to graded systemic hypotension caused by inflation of the pulmonary cuff. The increase was maintained for 60 minutes.

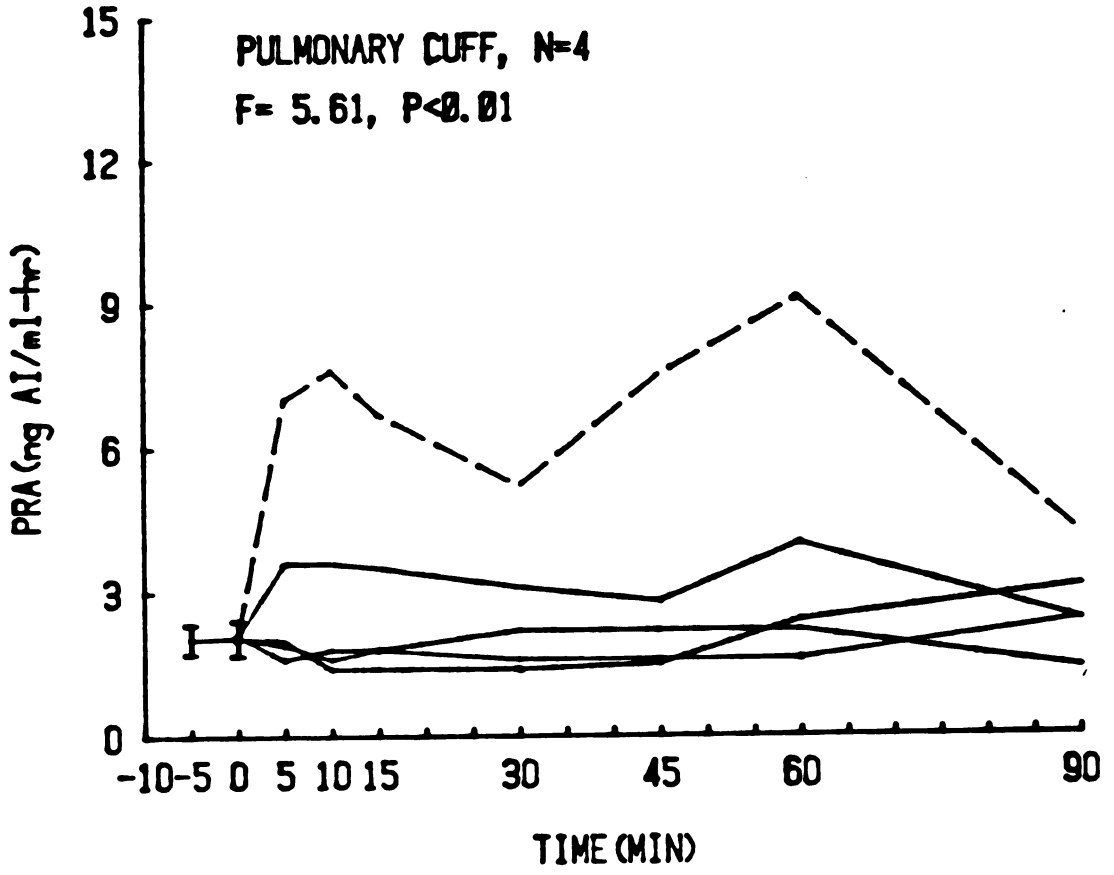

Figure 14. Plasma renin activity (PRA) increased significantly in response to 20% and 30%, but not to 5%, and 10% reduction in renal perfusion pressure following inflation of the pulmonary cuff. The increase was maintained during the period of inflation.

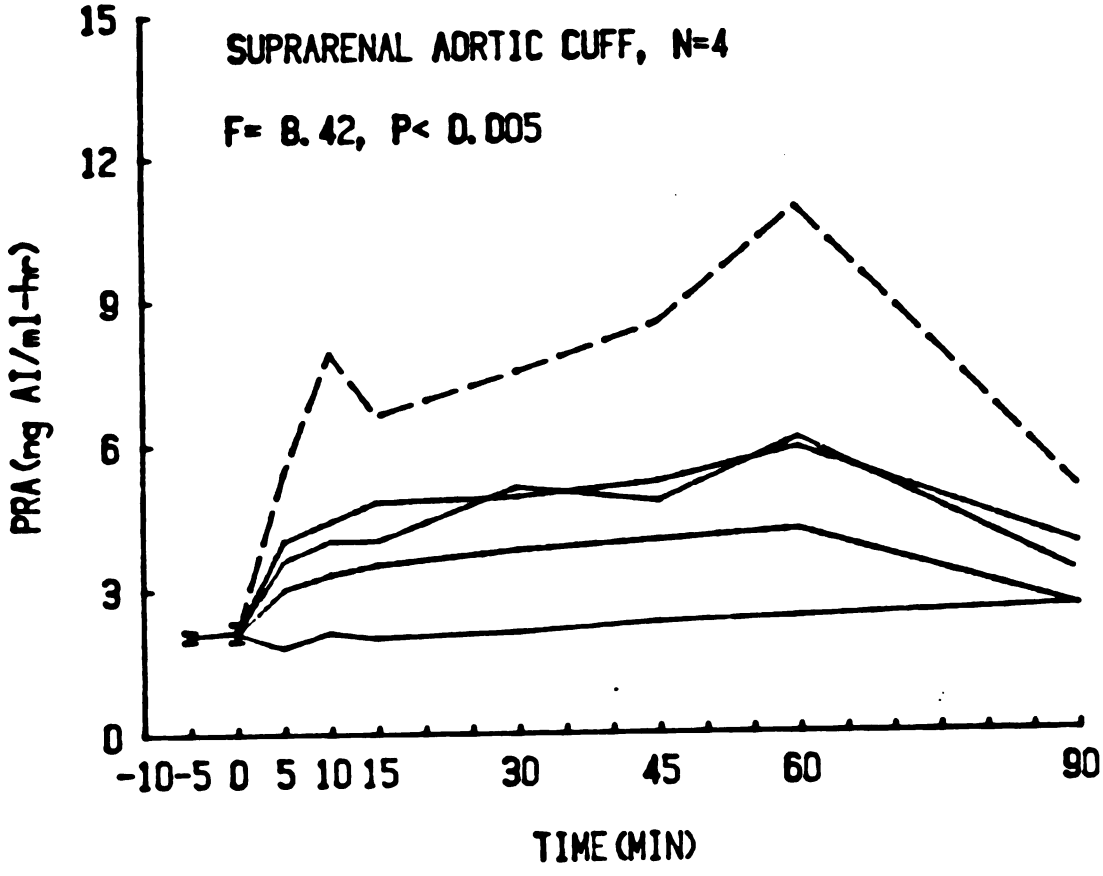

Figure 15. Plasma renin activity (PRA) increased in response to all levels of reduction in renal perfusion pressure following inflation of the suprarenal aortic cuff. The increase of PRA was maintained for 60 minutes. The PRA responses were similar between the 10%, and 20% level of reduction in renal perfusion pressure.

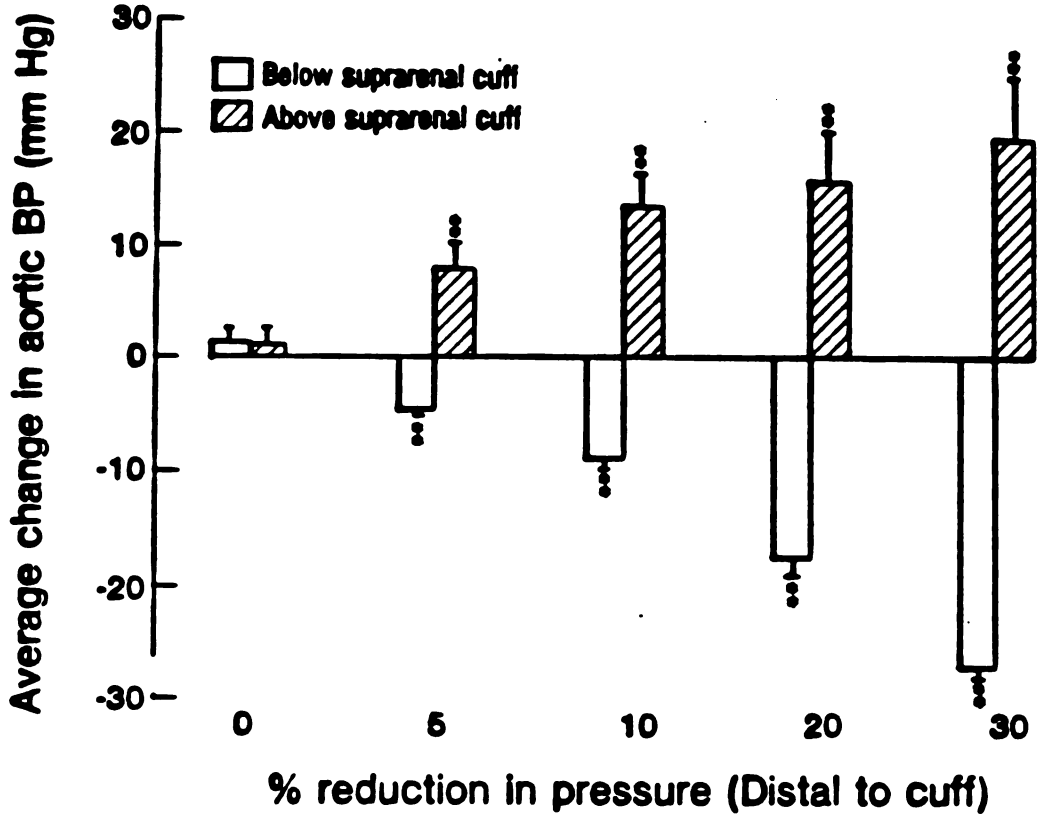

Figure 16. Inflation of the suprarenal cuff caused graded decreases in renal perfusion pressure but graded increases in mean blood pressure above the cuff. **$p<0.01$ compared with time control (0% reduction).

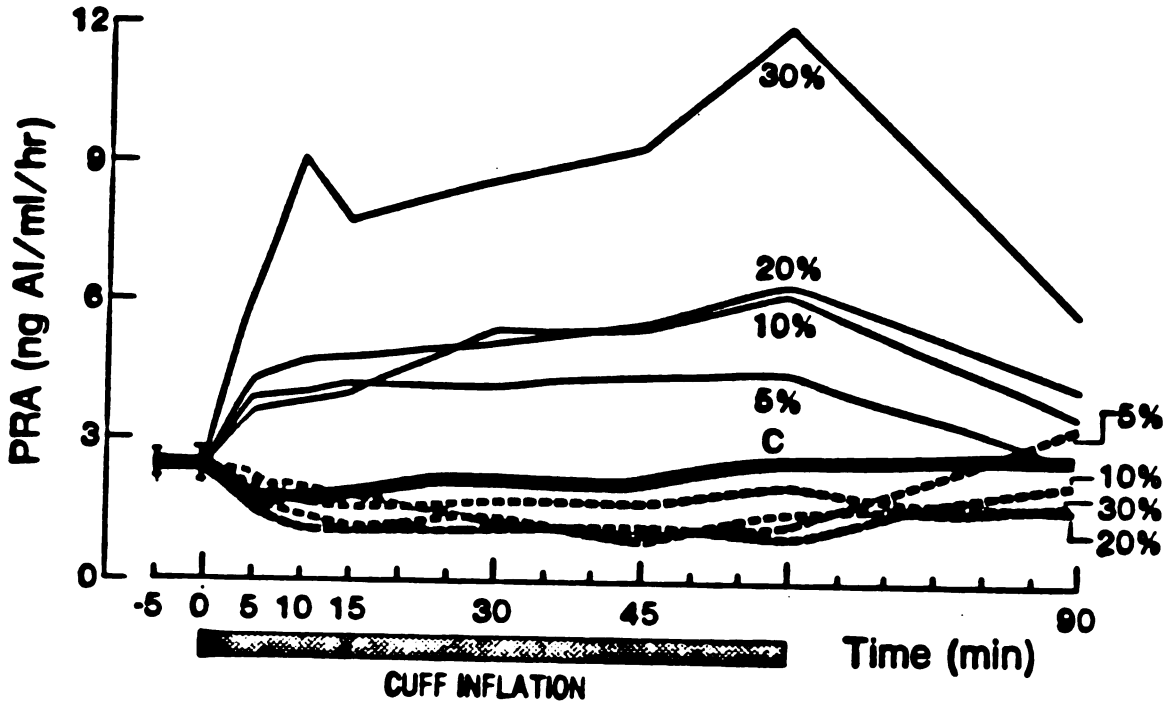

Figure 17. We were able to complete both ascending aortic and suprarenal cuff experiments in 3 out of 4 dogs implanted with both cuffs. In these dogs, plasma renin activity increased 5 minutes after reduction in renal perfusion pressure during inflation of the suprarenal cuff (solid lines). However, PRA decreased when similar reductions in renal perfusion pressure were achieved by inflation of the ascending aortic cuff (broken line). The time control (c) is shown as the heavy solid line.

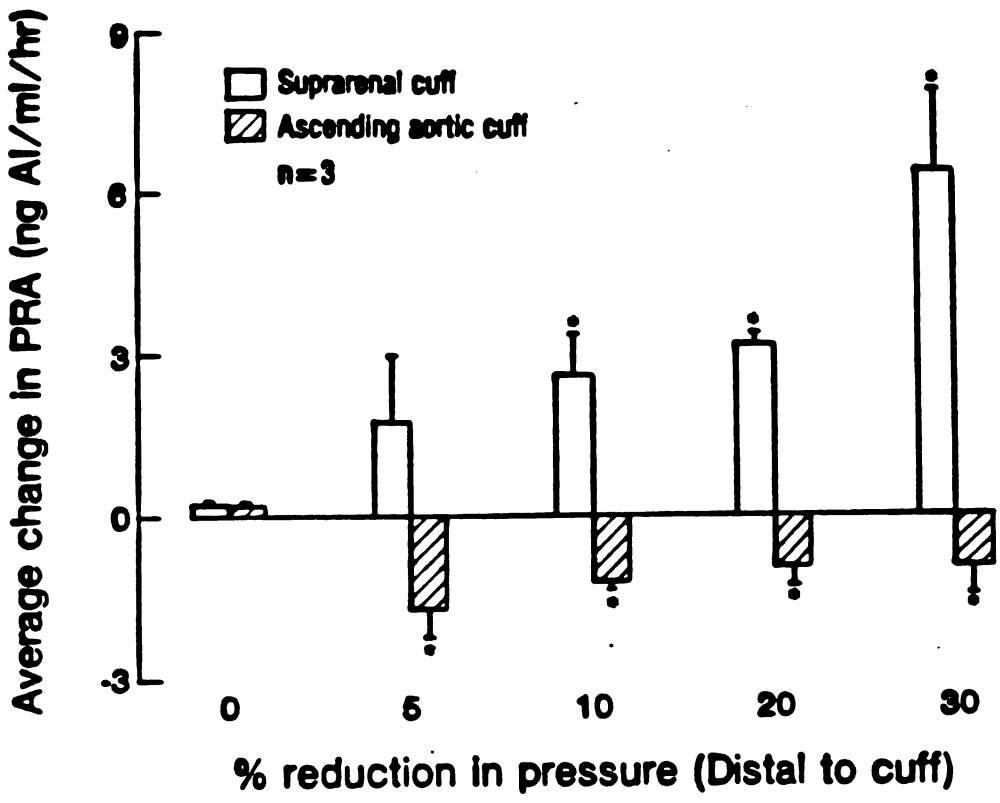

Figure 18. In dogs implanted with both ascending aortic and suprarenal cuffs, either cuff was inflated to achieve the same reduction in renal perfusion pressure. Thus, in the same dogs, with the same reduction in renal perfusion pressure, PRA increased dose dependently in response to inflation of the suprarenal cuff but decreased during inflation of the ascending aortic cuff. *$p<0.05$ cmpared with time control (0% reduction).

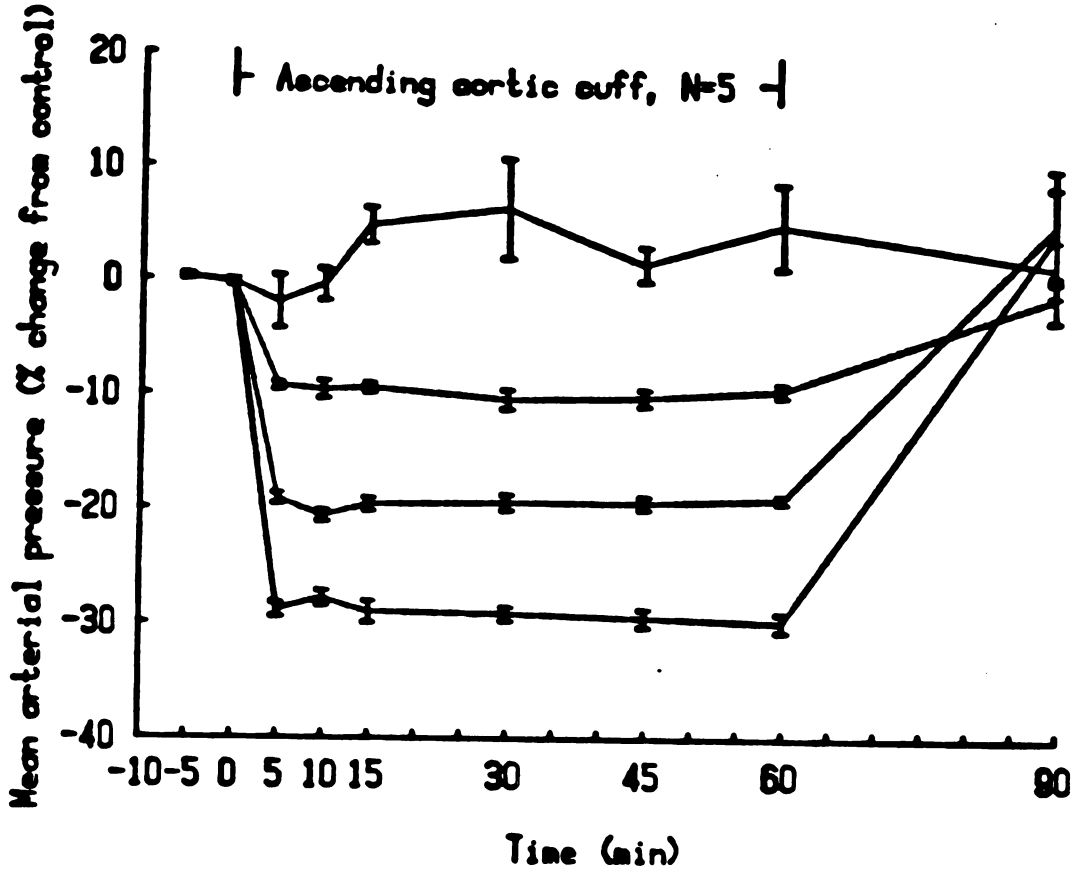

Figure 19. Time control; 5%; 10%; 20%; and 30% reduction in mean arterial pressure in response to graded inflation of the ascending aortic cuff in dogs with bilateral renal denervation. The cuff was inflated between time 0 and time 60. Reduction of mean arterial pressure was achieved immediately and maintained constant during this period. See Table (2) for preconstriction control pressures.

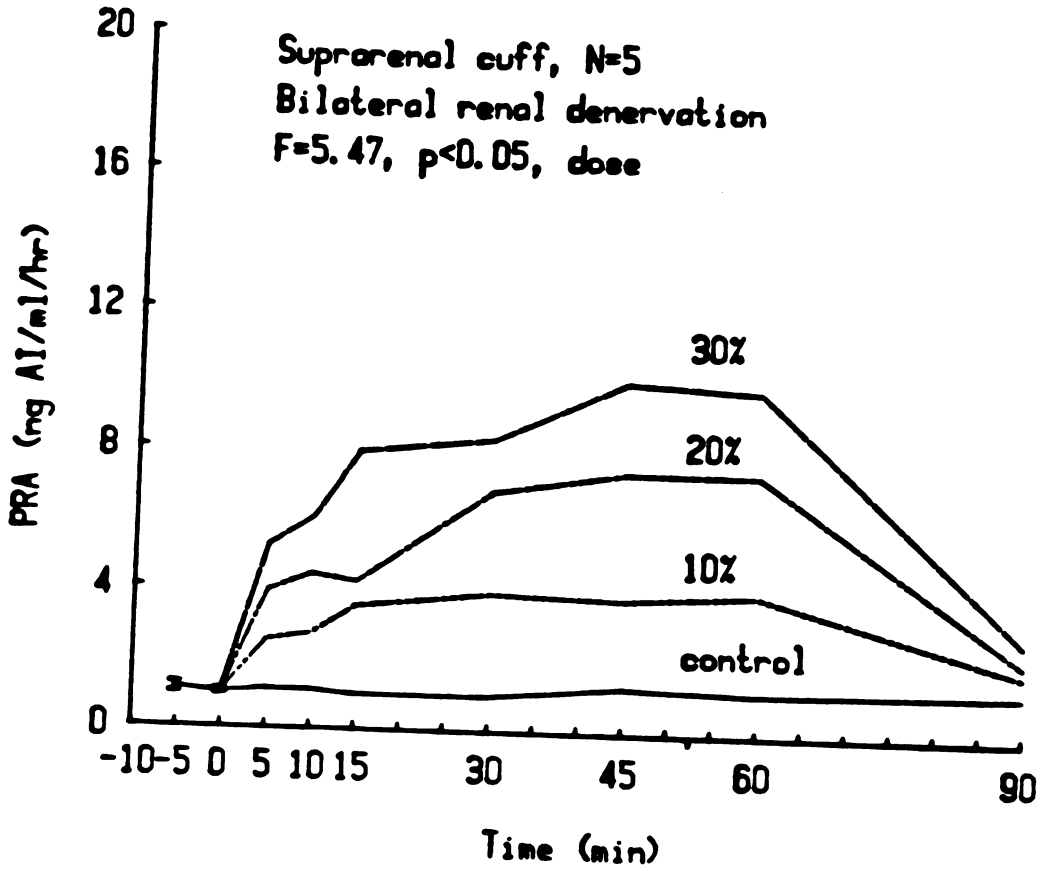

Figure 20. Renal denervation decreased the resting control PRA, however, PRA increased dose dependently in response to graded inflation of the suprarenal cuff in dogs with bilateral rena denervation. The increases in PRA were maintained during the whole period of cuff inflation.

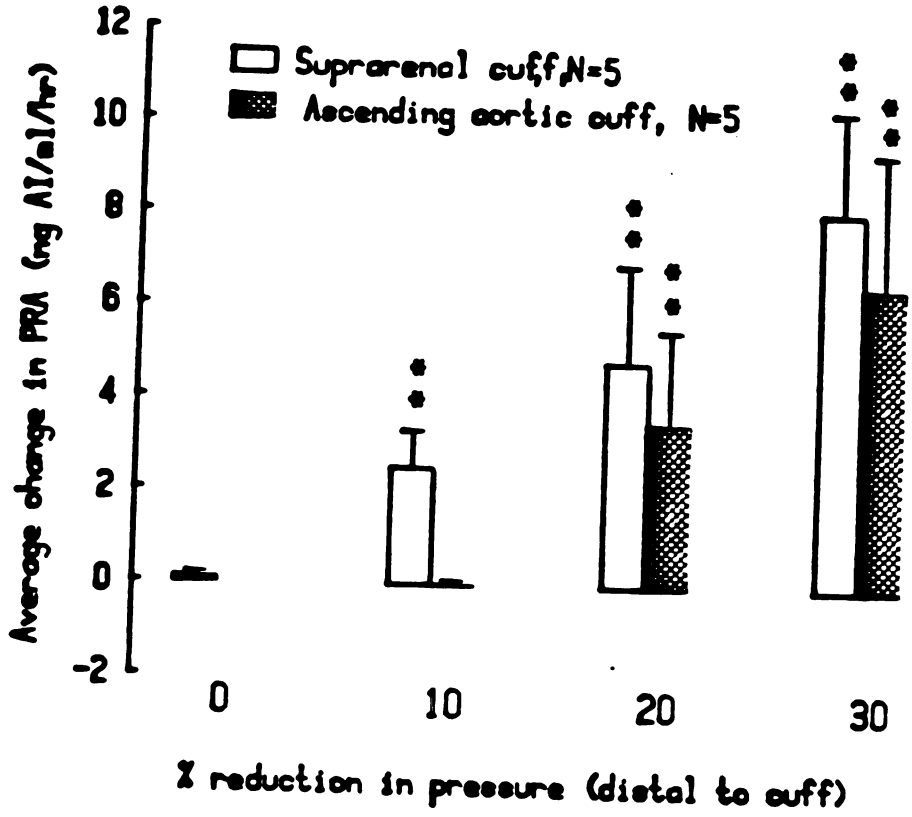

Figure 21. The plasma renin activity (PRA) increased dose dependently in response to all levels of reduction of renal perfusion pressure during inflation of the suprarenal cuff ($p<0.01$) in dogs with bilateral renal denervation, however, it failed to increase in response to 10% reduction of renal perfusion pressure caused by inflation of the ascending aortic cuff. Plasma renin activity did increase in response to 20% and 30% of reduction in renal perfusion presusure during inflation of the ascending aortic cuff. ** $p<0.01$ copmpared to time control (0% reduction).

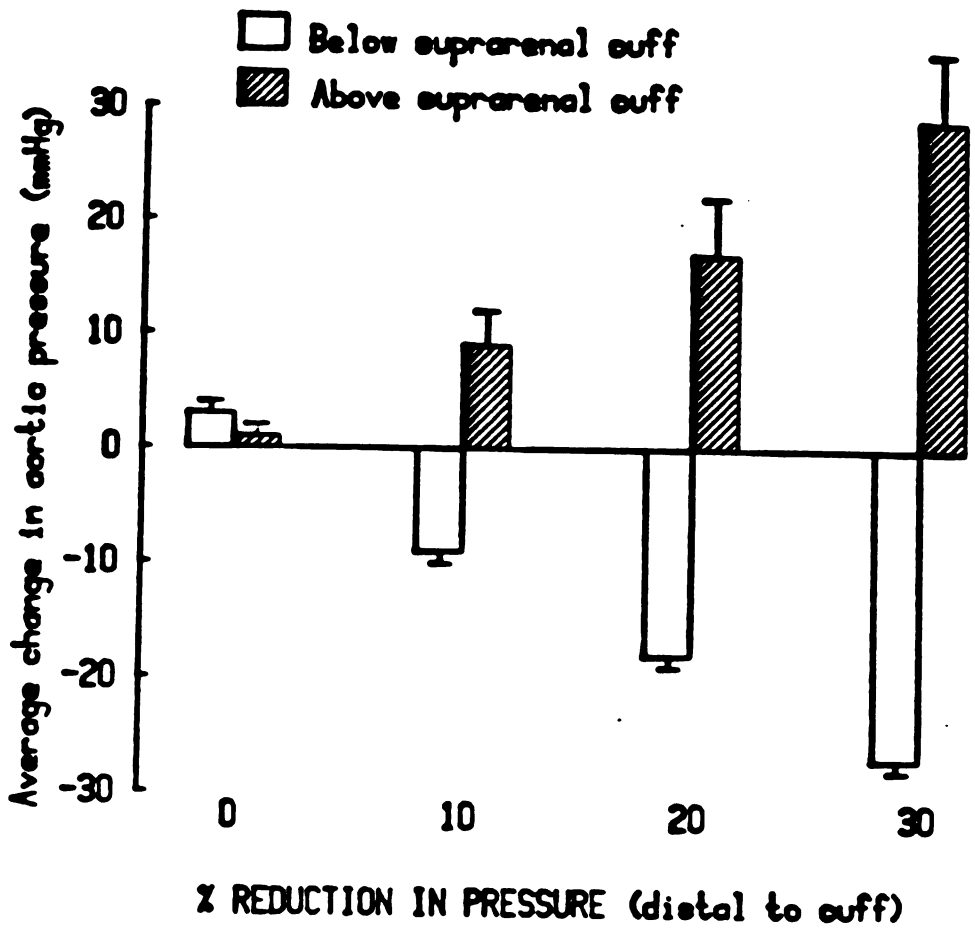

Figure 22. Inflation of the suprarenal cuff caused graded increases in mean arterial pressure as the renal perfusion pressure declined gradually in dogs with bilateral renal denervation. The response was similar to that of dogs with intact kidneys.

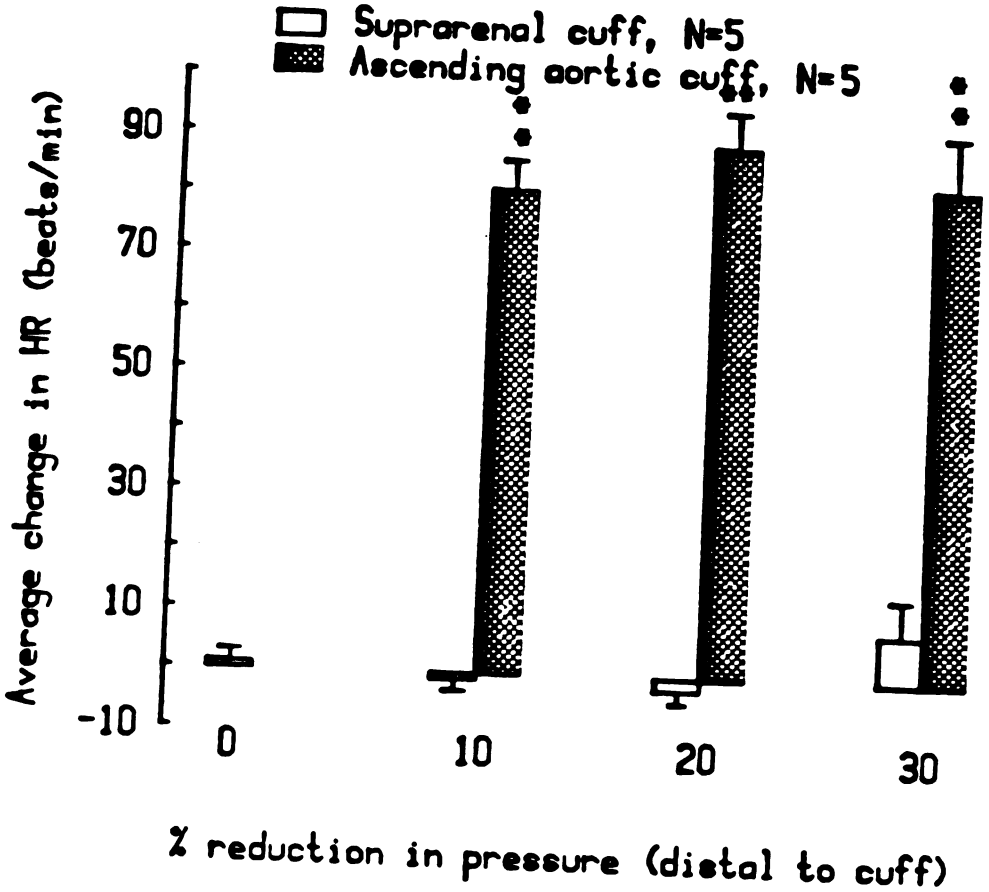

Figure 23. Heart rate (HR) increased in response to graded inflation of the ascending aortic cuff ($F_{3,12}$=42, $p<0.01$), but did not change in response to inflation of the suprarenal cuff ($F_{3,12}$=1.7, $p>0.1$) in the same group of renal denervated dogs. Control heart rates were 62±3 beats/min, and 64±2 beats/min for ascending aortic and suprarenal cuff experiments, respectively. ** $p<0.01$ compared to time control (0% reduction).

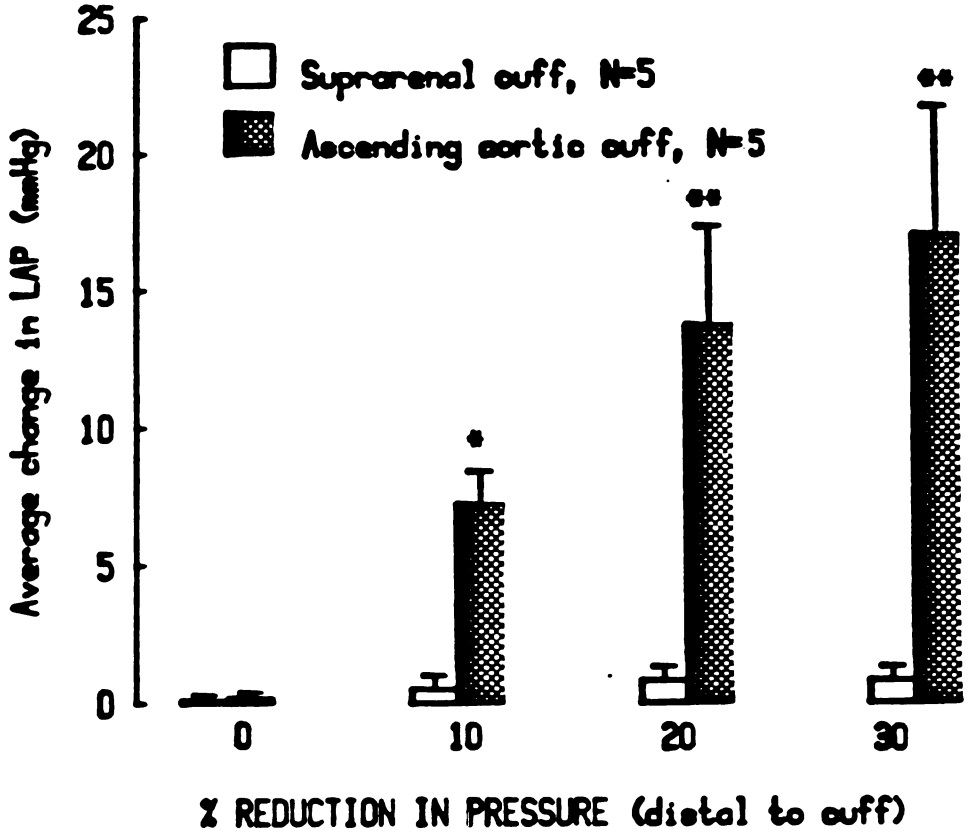

Figure 24. Left atrial pressure (LAP) did not change in response to graded inflation of the suprarenal cuff ($F_{3,12}=0.9$, $p>0.25$), but increased in response to graded inflation of the ascending aortic cuff ($F_{3,12}=17$, $p<0.01$) in the same group of renal denervated dogs. Mean LAP during the control period was 6.7 ± 0.1 and 6.6 ± 0.3 mmHg for suprarenal and ascending aortic cuff experiments, respectively. * $p<0.05$, ** $p<0.01$, compared with time control (0% reduction).

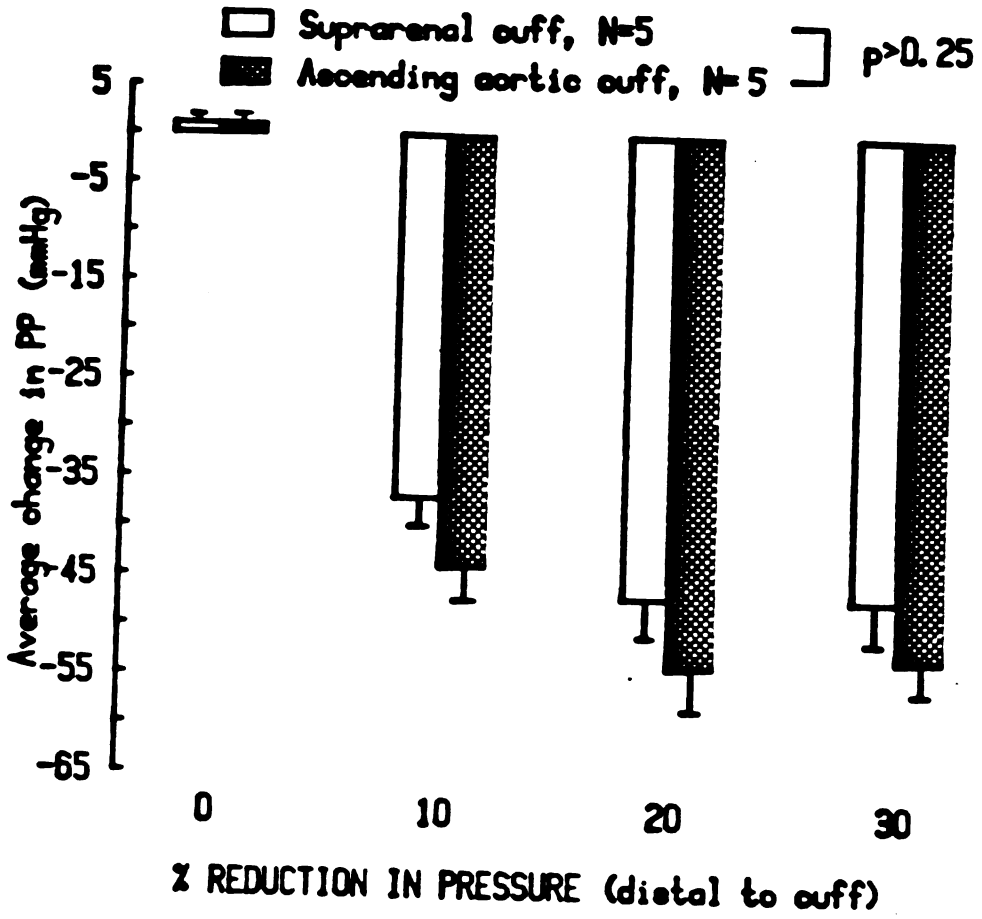

Figure 25. Pulse pressure decreased significantly in response to each level of reduction in renal perfusion pressure during inflation of both ascending aortic ($F_{3,12}$=78, $p<0.01$) and suprarenal cuff ($F_{3,12}$=144, $p<0.01$) in the same group of renal denervated dogs. The reduction in pulse pressure was not different between the two cuff experiments ($F_{1,4}$=1.2, $p>0.25$). The control pulse pressure prior to inflation was 67±2 mmHg and 64±2 mmHg for suprarenal and ascending aortic cuff experiments, respectively. ** $p<0.01$ compared to time control (0% reduction).

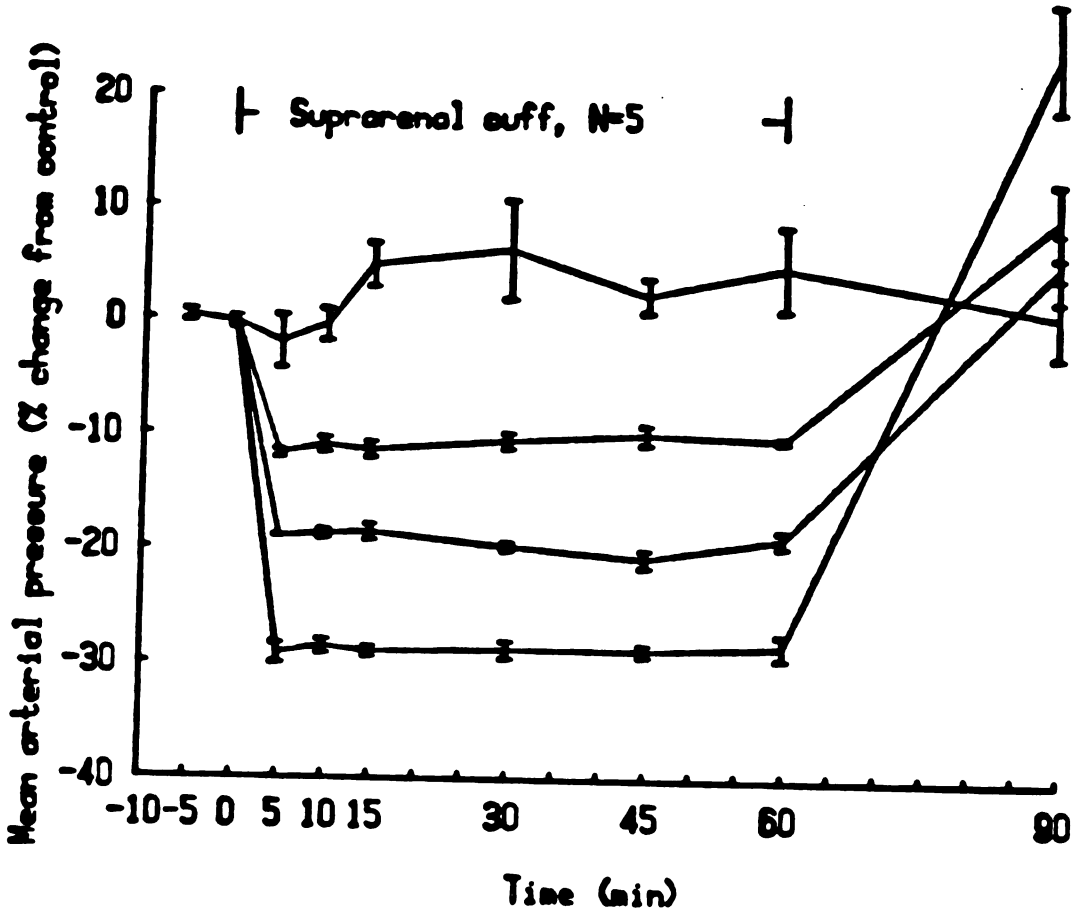

Figure 26. Time control; 10%; 20%, and 30% reduction in mean arterial pressure in response to graded inflation of the ascending aortic cuff in dogs with bilateral renal denervation. The cuff was inflated between time 0 and 60. Reduction of mean arterial pressure was achieved immediately and maintained constant during this period. See Table 2 for preconstriction control pressures.

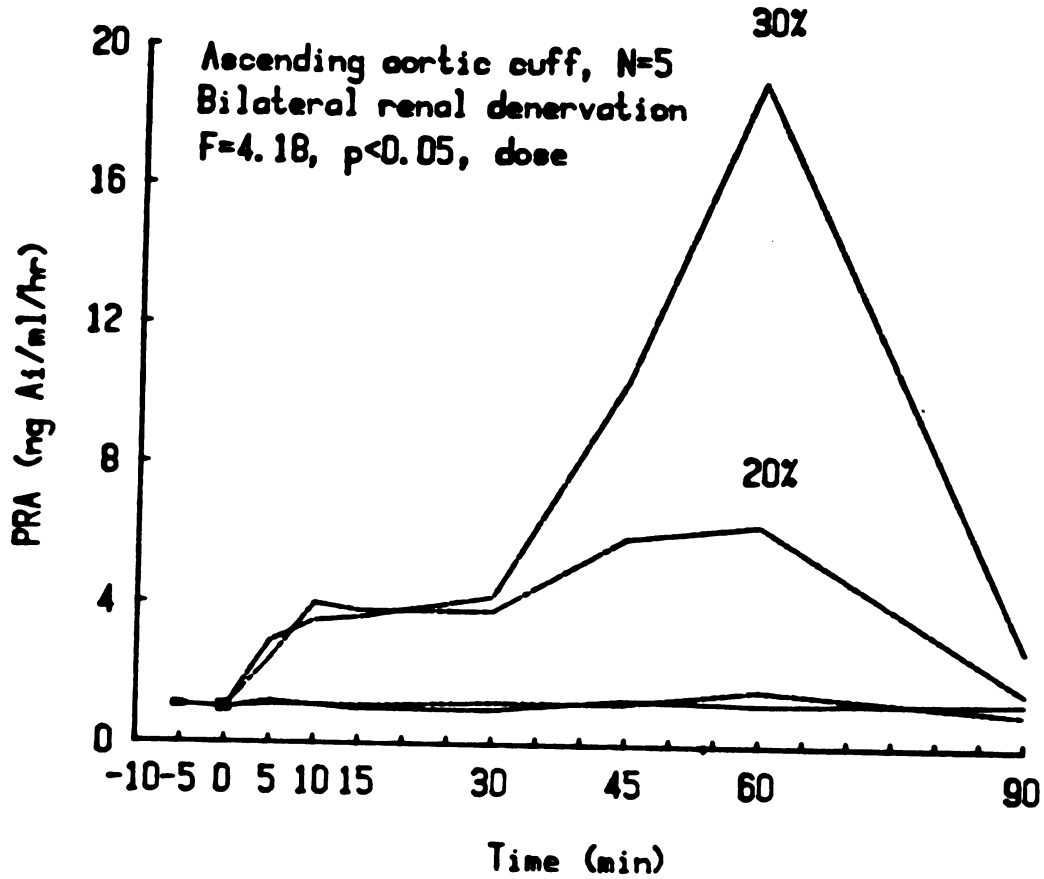

Figure 27. Plasma renin activity (PRA) did not change at all in response to a 10% reduction of renal perfusion pressure during inflation of the ascending aortic cuff in dogs with bilateral renal denervation. However, it did increase in response to 20% and 30% reductions in renal pefusion pressure during inflation of this cuff. The peak increase of PRA at time 60 during 30% reduction in renal perfusion pressure was due to one dog which showed signs of anxiety and had a PRA of 66 ng AI/ml/hr.

Chapter 4

Discussion

The aim of this series of experiments is to evaluate the relative role of cardiopulmonary, sinoaortic, and renal baroreceptors in the regulation of vasopressin and cortisol secretion, and PRA. Since most of the previous investigators had suggested a dominant role for sinoaortic baroreceptors in the regulation of blood pressure and vascular resistence (Mancia et al., 1976; Guo et al., 1982), our working hypothesis was that sinoarotic high pressure baroreceptor input had an important part to play in the regulation of vasopressin, cortisol, and PRA. However, our results indicate a dominant role of cardiopulmonary baroreceptors in the regulation of these hormones. The hemodynamic changes in response to cuff inflation will be discussed first, followed by the changes in hormones.

Hemodynamic changes in response to inflation of the cuffs.

Ascending aortic cuff inflation Inflation of the ascending aortic cuff led to similar hemodynamic changes in normal dogs and dogs with bilateral renal denervation, thus the results from the two groups will be discussed together. The purpose of ascending cuff inflation is to decrease systemic arterial pressure, at the same time, increase the pressure in the heart and the pulmonary circulation. Thus, during inflation of the ascending aortic cuff, high pressure baroreceptor input decreases and inhibitory signals from the low pressure baroreceptors increase.

By frequent adjustment of the volume in the cuff, we were able to maintain constant reductions in MAP distal to the cuff of 5, 10, 20, 30%

of control during the 60 minutes of cuff inflation (Fig. 1, top panel). Thus, all the baroreceptors in the arterial side of circulation should receive a constant signal during inflation of the cuff. Inflation of the ascending aortic cuff decreased not only the mean arterial pressure but also the pulse pressure significantly (Fig. 11).

Inflation of the ascending aortic cuff should increase pressure in the left atrium and the left ventricle. We did not measure the pressure in the left ventricle, but left atrial pressure provides a reasonable estimate of left ventricular end diastolic pressure. During graded inflation of the ascending aortic cuff, the increases in the left atrial pressure ranged from 2.7±4 mmHg in response to a 5% reduction in MAP up to 17±3 mmHg in response to a 30% reduction in MAP. The ranges of increases in left atrial pressure can be mimicked by moderate volume expansion. For example, rapid saline infusion (1.1±0.1 liters) increased left atrial pressure by 14±1 mmHg in conscious dogs (Vatner et al., 1975). Although left atrial pressure increases dose dependently in response to inflation of the ascending aortic cuff, this does not mean that the discharges from low pressure baroreceptors also increased dose dependently. Gilmore and Zucker (1979) showed that the discharges of type B receptors of dogs increased dose dependently in response to moderate increases (<10 mmHg) in left atrial pressure. However, at higher levels of atrial pressure (>10 mmHg), the increases in receptor discharge attenuated with further increases in pressure.

The reduction of right atrial pressure in response to inflation of the ascending aortic cuff was not anticipated, since we expected pressure would back up proximal to the cuff and include the right

atrium. Fater et al. (1982) inflated a balloon in the left atrium to increase left atrial pressure without changing systemic arterial pressure, and found a significant reduction of central venous pressure (from 1.3 to 0 mmHg) in conscious intact dogs but not in cardiac denervated dogs. Thus, the reduction of right atrial pressure in response to inflation of the ascending aortic cuff could be explained by:

(1) High compliance of the pulmonary circulation.

or (2) A reduced cardiac output caused by constriction of the ascending aorta.

or (3) A reflex vasodilatation, especially of the compliance vessles caused by stimulation of the low pressure baroreceptors, as suggested by Fater et al. (1982). Both (2) and (3) can lead to a reduction in venous return.

Although ascending aortic occlusion caused bradycardia in anesthetized animals (Daly and Verney, 1927; Oberg and Thoren, 1972), inflation of the ascending aortic cuff in our conscious dogs consistently induced tachycardia. (Fig. 8). The disparity could be explained by the effect of anesthetics on the autonomic system (Vatner and Braunwald, 1975) and the different resting heart rates in the conscious and anesthetized states (Coleridge and Linden, 1955).

Pulmonary cuff inflation By frequent adjustment of the volume in the pulmonary cuff, we were able to maintain constant reduction in MAP by 5, 10, 20, and 30% of control during the 60 minutes of pulmonary cuff inflation (Fig. 1, middle panel). Inflation of the cuff reduced both the mean systemic arterial pressure and the pulse pressure (Fig. 11).

Since the reductions of both the mean systemic arterial pressure and the pulse pressure during inflation of the pulmonary cuff were similar to those caused by inflation of the ascending aortic cuff, the sinoaortic baroreceptors received comparable stimuli in terms of reductions in static and dynamic pressure during inflation of either cuff. However, the stimuli to low pressure baroreceptors were very different between inflation of the ascending aortic and the pulmonary cuffs. Pulmonary artery constriction increased the pressure in the right atrium and ventricle but decreased the pressure in the left heart and the pulmonary circulation (Fig. 9, 10). Conversely, ascending aortic constriction decreased the pressure in the right atrium but increased the pressure in the left heart and the pulmonary circulation. Thus, by comparing the results of constriction of the ascending aorta and the pulmonary artery, we should be able to deduce the relative roles of receptors in the left heart and pulmonary circulation versus those in the right heart.

Suprarenal cuff inflation Inflation of the suprarenal cuffs led to similar hemodynamic changes in normal dogs and dogs with bilateral renal denervation, thus the cardiovascular results from the two groups will be considered together. The purpose of inflation of the suprarenal cuff was to reduce the renal perfusion pressure without overloading the low pressure baroreceptors, especially those in the left heart. By frequent adjustment of the cuff, we were able to maintain reductions in MAP distal to the cuff to within $\pm$1.5% during 60 minutes of inflation of the suprarenal cuff (Fig. 1, bottom panel). Constriction of the abdominal aorta just above the renal arteries decreased both the mean renal

perfusion and pulse pressures which were comparable to those produced by inflation of the ascending aortic cuff.

Left atrial pressure did not change thoroughout the range of graded suprarenal cuff inflation (Fig. 9). Although we did not measure pressure in the left ventricle, the left ventricular end diastolic pressure was unlikely to change since left atrial pressure, which is a reasonable estimate of the left ventricular end diastolic pressure, did not change. However, during graded abdominal aortic constriction, left ventricular end systolic pressure might have increased since the aortic systolic pressure proximal to the constriction increased. Thoren (1979) found that during graded aortic constriction, left ventricular receptors did not respond to increases in left ventricular end systolic pressure unaccompanied with simultaneous increases in left ventricular end diastolic pressure, the receptor discharge increased only after left ventricular end diastolic pressure started to rise. Thus, discharges from low pressure baroreceptors probably did not change during graded inflation of the suprarenal cuff.

The pressure above the suprarenal cuff increased dose dependently in response to inflation of the cuff (Fig. 16). This is similar to the chronic hypertension associated with coarctation of aorta in humans (Meachan et al., 1977). In conscious dogs, Whitlow and Katholi (1982) inflated a cuff implanted around the thoracic aorta to maintain a 17 mmHg reduction of pressure distal to the cuff for 24 hours, and found a 27 mmHg increase of pressure above the constriction. The mechanism of this coarctation hypertension has not been fully elucidated. However, activation of the renin-angiotensin system may contribute to the

development and maintainence of coarctation hypertension (Whitlow and Katholi, 1982).

Heart rate did not decrease in spite of a simultaneous increase in pressure above the cuff during constriction of the abdominal aorta (Fig. 8). This could be explained by a low control heart rate (54±4 beats/min) in our trained, conscious dogs. Also, inflation of the suprarenal cuff did activate the renin angiotensin system, and angiotensin II has been reported to attenuate the baroreflex control of heart rate in dogs (Lumbers et al., 1979) and rabbits (Guo et al., 1984). In dogs with coarctation of the thoracic aorta for 5 months, Igler et al. (1981) reported that the carotid sinus baroreceptors were reset to operate at higher pressures. This might also explain why heart rate did not decrease during inflation of the suprarenal cuff. However, we do not know if this can also be applied to our dogs during acute constriction of the abdominal aorta.

Hormonal changes in response to inflation of the cuffs.

Vasopressin In spite of a profound systemic hypotension during inflation of the ascending aortic cuff, plasma vasopressin concentrations did not change (Fig. 2, 3). However, it had been shown that bilarteral carotid occlusion increased plasma vasopressin concentrations in dogs with previous vagotomy (Share and Levy, 1962). When the mean arterial pressure was kept constant by use of an external reservior during carotid occlusion, plasma vasopressin concentrations increased in dogs with intact vagus nerve (Share, 1965). Furthermore, in conscious cardiac-denervated dogs (presumably removed of afferents from baroreceptors in the heart), systemic hypotension induced by hemorrhage

still increased plasma vasopressin concentrations significantly (Wang et al., 1983). Thus it is clear that unloading the high pressure baroreceptors can stimulate vasopressin release. However, a uniform reduction of pressure throughout the arterial system failed to increase plasma vasopressin concentrations during inflation of the ascending aortic cuff. This could be caused by a simultaneous increase in the metabolic clearence of vasopressin or a simultaneous inhibition of vasopressin release. Since the metabolic clearance rate of vasopressin does not increase during moderate systemic hypotension (Lauson, 1974), thus, there must be a simultaneous inhibition of vasopressin release caused by inflation of the ascending aortic cuff.

The primary factor which regulates vasopressin release is osmolality, however, osmolality was unchanged during these experiments (Table 6), thus inhibition of vasopressin release was not caused by changes in osmolality.

We propose that the failure of vasopressin to increase in response to systemic hypotension caused by inflation of the ascending aortic cuff is due to simultaneous inhibition of vasopressin release arising from cardiopulmonary baroreceptors and that the inhibiton is sufficiently potent to override the stimulation of vasopressin release arising from the arterial baroreceptors. During inflation of the ascending aortic cuff, pressure in the left heart and pulmonary circulation increased while pressure in the right atrium decreased (Fig. 9, 10). Thus, the inhibition must originate in the left heart and pulmonary circulation.

Besides causing comparable reductions in systemic arterial and pulse pressure to constriction of the ascending aorta, pulmonary artery

constriction decreased pressure in the left heart and pulmonary circulation but increased pressure in the right heart. Therefore, in another groups of dogs, the pulmonary cuff was inflated to test whether an elevated right heart pressure would also inhibit the increase in vasopressin concentrations in response to systemic hypotension. A 5% reduction in mean systemic arterial pressure following inflation of the pulmonary cuff led to a 12 fold increase in plasma vasopressin concentration, and plasma vasopressin increased dose dependently in response to further reduction in systemic arterial pressure (fig. 2, 12). Thus, profound systemic hypotension failed to increase plasma vasopressin concentration when it was accompanied by a simultaneous increase in left heart and pulmonary circulation pressure. Conversely, a 5 mmHg reduction in systemic arterial pressure when accompanied with only a very small reduction of left atrial pressure (1.7 mmHg), increased plasma vasopressin concentration 12 fold. Therefore, comparison of the vasopressin response to inflation of the ascending aortic and the pulmonary cuffs suggests that baroreceptors in the left heart and pulmonary circulation have a dominant role in the regulation of vasopressin release.

Receptors located in the left atrium (De Torrente et al, 1975; Zucker et al., 1977) and left ventricles (Thames et al., 1980) are implicated in the regulation of vasopressin release. However, the importance of receptors in the pulmonary circulation in the regulation of vasopressin is questioned by Schultz et al. (1982). Constriction of the ascending aorta should stimulate receptors in both the left atrium and the left ventricle. Thus it is not clear whether receptors in the

left atrium or receptors in the left ventricle, or both of them are responsible for the powerful inhibition of vasopressin release during inflation of the ascending aortic cuff. In future experiments, by use of techniques such as reversible mitral stenosis, we should be able to differentiate the effect of left atrium versus left ventricle in the regulation of vasopressin release.

Although Menninger (1981) has shown that right atrial stretch decreased supraoptic neurosecretory activity and plasma vasopressin in cats, our results indicate that increases in right atrial pressure are much less potent than increases in left heart pressure in supressing vasopressin responses to systemic hypotension. The role of right atrial baroreceptors in the regulation of vasopressin release can be further assessed by comparing the vasopressin responses to comparable graded systemic hypotension caused by constriction of the inferior vena caval or the pulmonary artery. We actually did such an experiment in one dog (Fig. 28). The dog was subjected to a 25% reduction in systemic arterial pressure by inflation of the ascending aortic, pulmonary, or inferior vena caval cuffs respectively. Plasma vssopressin concentration did not change during constriction of the ascending aortic cuff, but increased dramatically during constriction of the pulmonary artery or the inferior vena cava. If the right atrial receptors are important in the regulation of vasopressin release, it was anticipated that inferior vena cava constriction will give a bigger vasopressin response compared with pulmonary artery constriction. However, the increase in vasopressin concentrations was very similar during inflation of either cuff. Thus, the role of right atrial baroreceptors was further questioned by these

data. By inflation of balloons in either atria and measuring plasma vasopressin by bioassay, Brennan et al. (1971) found that inflation of the left atrial balloon, but not the right atrial balloon, induced a significant fall in plasma vasopressin concentrations. Their results also supported a dominant role of left versus right atrial baroreceptors in the regulation of vasopressin release.

The importance of low pressure baroreceptors in the regulation of vasopressin release was also suggested by Wang et al. (1984). They compared the vasopressin response to graded hemorrhage in sham-operated and cardiac denervated dogs. After 10 ml/kg body weight of blood had been removed, vasopressin increased in sham-operated but not in cardiac denervated dogs. After 20% and 30% ml/Kg body weight of blood had been removed, vasopressin increased in all dogs, but the response was markedly attenuated in cardiac denervated dogs. Thus, their results also suggest a dominant role of low pressure baroreceptors in the regulation of vasopressin in dogs.

However, the importance of low pressure baroreceptors in the regulation of vasopressin was questioned in humans by Goldsmith et al. (1982). By applying graded negative pressure suction to the lower extremities in humans, they found that levels of lower body suction that decreased central venous pressure only, without affecting mean arterial pressure failed to change vasopressin concentrations. Vasopressin increased only when overt hypotension was produced by a high level of negative suction. Conversely, Epstein et al. (1975), using the technique of head out immersion, have shown that an increase in central blood volume does depress vasopressin. Thus, the role of low pressure

baroreceptors in human is still controversial.

Although vasopressin did not change during inflation of the ascending aortic cuff, vasopressin did increase 30 minutes after deflation of the cuff (Fig. 3). One explaination for this paradoxical rise of vasopressin is that the low pressure baroreceptors were reset to operate at higher pressures during inflation of the ascending aortic cuff (Bishop, 1983). After deflation of the cuff, the pressure in the left heart decreased toward preconstriction levels and "relatively" unloaded the low pressure baroreceptors which had been reset. Thus vasopressin secretion increased in response to this "relative" unloading of low pressure baroreceptors.

In summary, our data suggest that potent inhibition of low pressure baroreceptors originated mainly from the left heart can totally supress the vasopressin response to systemic hypotension (as low as 65±3 mmHg) in conscious dogs.

Cortisol The response of plasma cortisol and vasopressin to inflation of the ascending aortic cuff is very similar. In spite of graded reduction of systemic arterial pressure down to 20% of control during inflation of the ascending aortic cuff, plasma cortisol concentration did not change (Fig. 6). This is in sharp contrast to a significant increase in plasma cortisol concentration in response to only 5% reduction in mean arterial pressure caused by inflation of the pulmonary cuff. Although plasma cortisol did increase significantly in response to a 30% level of reduction in mean arterial pressure following inflation of the ascending aortic cuff, the increase of plasma cortisol was only one third of that caused by the same level of reduction in mean arterial

pressure during inflation of the pulmonary artery (Fig. 6).

These data suggest that the inhibition of cortisol release from low pressure baroreceptors was potent enough to override the increases of cortisol release resulting from decreases in high pressure baroreceptor input in response to graded reductions in mean arterial pressure down to 20% of control. A reduction of mean systemic arterial pressure to 30% of control should further decrease the high pressure baroreceptor input (Kirchheim, 1976) and lead to further increases of cortisol release. However, although left atrial pressure increased from 8±0.6 mmHg in response to a 20% reduction in MAP to 17±3 mmHg in response to a 30% reduction in MAP caused by inflation of the pulmonary cuff, the discharges from the low pressure baroreceptors during a 30% reduction could be lower than those during a 20% reduction in MAP. This paradox can be explained by Gilmore and Zucker's findings (1979). They found that the discharges of type B receptors of dogs increased dose dependently in response to moderate increases (<10 mmHg) in left atrial pressure. However, as atrial pressure further increased (>10 mmHg), the receptor discharge attenuated with further increases in pressure. Thus, the inhibition of cortisol release from low pressure baroreceptors in response to a 8±0.6 mmHg increase (20% reduction) in left atrial pressure could be higher than the inhibition of cortisol release in response to a 17±3 mmHg increase (30% reduction) in left atrial pressure. This can explain why the inhibition of cortisol release from low pressure baroreceptors failed to suppress the stimulation of cortisol release as the systemic arterial pressure was further reduced.

In spite of a simultaneous increase in right atrial pressure,

constriction of the pulmonary artery caused significant increases in plasma cortisol concentrations. Thus our results indicate a dominant role of receptors in the left versus right side of heart in the regulation of cortisol. In great contrast, Cryer and Gann (1973) suggested a dominant role of receptors in the right versus left atrium in the regulation of cortisol by the results from similar aortic constriction experiments in anesthetized dogs. Their results were not different from ours in conscious dogs. However, they did not measure left atrial pressure, and their measurement of right atrial pressure was questionable (see historical review). Thus, their interpretation might be misleading.

Another piece of evidence in support of a relatively unimportant role of right atrial pressure receptors in the regulation of cortisol secretion was obtained in our pilot dog (Fig. 29). A 25% reduction in mean arterial pressure was carried out by inflation of the ascending aortic, pulmonary, or inferior vena caval cuff. Cortisol concentrations did not change in response to inflation of the ascending aortic cuff, but, increased in response to inflation of the pulmonary or the inferior vena caval cuffs. The increase in plasma cortisol concentrations was very similar in response to inflation of either cuff. The data from this dog did not support a significant role of right atrial receptors in the regulation of cortisol.

The increase in plasma cortisol following inflation of the pulmonary cuff could be caused by an increase in secretion or by a decrease in metabolic clearance. Cortisol is metabolized mainly in the liver. At physiologic concentration, only 10 to 20% of plasma cortisol

Although the increase in plasma cortisol during inflation of the pulmonary cuff is probably caused by an increase in secretion, it is not clear whether the increase in cortisol secretion can be totally accounted for by an increase in CRF release. Since the response of vasopressin and cortisol to inflation of the pulmonary cuff was very similar, and vasopressin has been reported to be able to stimulate ACTH and cortisol release (see historical review), we speculate that at least part of the increase of cortisol release in response to constriction of the pulmonary artery could be due to a simultaneous increase in vasopressin secretion. Evidence in support of this speculation came from one dog pretreated with a vasopressin blocker specific for blocking the pressor effect of vasopressin. A bolus dose (10 ug/kg body weight) of O-methyl, tyr^2, arg^8-vasopressin (Penisula labs., San Carlos, CA) was given 5 minutes before inflation of the pulmonary cuff. The cortisol response to a 10% reduction in systemic arterial pressure following inflation of the pulmonary cuff was almost totally abolished (Fig. 30). Thus, the data from this pilot dog suggest that vasopressin plays an important role in the stimulation of the release of cortisol in response to systemic hypotension caused by inflation of the pulmonary cuff. Even though CRF is the classical releasing factor for ACTH or cortisol in response to stress, vasopressin might be involved in the cortrol of ACTH release in response to hemodynamic stimului.

In summary, our data suggest that potent inhibition of cortisol release from low pressure baroreceptors, originated mainly from the left side of the heart, can override the stimulation of cortisol release in response to moderate systemic hypotension. The large increase of plasma

cortisol following graded inflation of the pulmonary cuff may be caused by a simultaneous increase of vasopressin. The role of vasopressin as a main releasing factor of ACTH and cortisol in response to hemodynamic stimuli should be reinvestigated.

Renin In spite of a profound systemic hypotension (as low as 65±3 mmHg) caused by inflation of the ascending aortic cuff, plasma renin activity failed to increase (Fig. 4, 5). During systemic hypotension, unloading receptors in the carotid sinus should increase PRA provided that renal perfusion pressure does not rise (Rocchini and Barger, 1979; Gross et al., 1981). Also, a reduction in renal perfusion pressure would be expected to increase PRA directly via the renal baroreceptor mechanism (Davis and Freeman, 1976). Thus, during systemic hypotension, there were stimulatory signals for renin release arising from both the sinoaortic and renal baroreceptors. However, a 30% reduction in both carotid sinus and renal perfusion pressure caused by constriction of the ascending aorta failed to increase PRA (Fig. 4, 5).

In order to insure that the stimulus to the renal baroreceptor was sufficient to increase PRA in response to ascending aortic constriction, similar reductions in renal perfusion pressure were achieved by inflation of the suprarenal cuff. Graded constriction of the aorta just above the renal arteries produced dose dependent increases in PRA (Fig. 4, 15) in spite of a simultaneous increase in carotid sinus pressure (Fig. 16). These results are in agreement with the finding of Skinner et al. (1964) in anesthetized dogs and Gross et al. (1981) in conscious dogs. These investigators showed that PRA doubled when renal perfusion pressure fell as little as 5-12 mmHg. Thus, we have confirmed that a

reduction in renal perfusion pressure caused by inflation of a suprarenal aortic cuff is a very potent stimulus to secretion of renin.

We propose that the failure of PRA to increase in response to systemic hypotension caused by constriction of the ascending aorta is due to simultaneous inhibition of renin release arising from cardiopulmonary receptors, which override the stimulation of renin release from both the carotid sinus and renal baroreceptors. Evidence for this proposal is based on differential effects of the two protocols on left atrial pressure (Fig. 9). Constriction of the ascending aorta led to dose-dependent increases in left atrial pressure. In contrast, constriction of the aorta just above the renal arteries did not affect left atrial pressure. These results suggest to us that the elevated pressure in the left heart could be the cause of the powerful inhibition of renin release during inflation of the ascending aortic cuff.

In another series of experiments, the pulmonary artery was constricted to test whether an elevated right atrial pressure would inhibit the increase in PRA in response to systemic hypotension. Constriction of the pulmonary artery to cause a 30% reduction in systemic blood pressure led to a significant rise in PRA (Fig. 4, 14) and a large increase in right atrial pressure (Fig. 10). Thus, increased right atrial pressure is less potent than increased left heart pressure in supressing the increase in PRA caused by sytemic hypotension. These results are in agreement with Zehr et al. (1976) and Fater et al. (1982) but disagree with Brennan et al. (1971). However, comparison of the PRA response caused by constriction of the pulmonary artery to these induced by suprarenal aortic constriction over the

entire does-response range, suggests that the two treatments are not equivalent (Fig. 4). Thus, constriction of the pulmonary artery caused significant increases in PRA in response to 20% and 30% reductions in systemic arterial blood pressure, but not to 5% and 10% reductions. These results indicate that the threshold of renin release in response to reduced renal perfusion pressure was shifted to between 10 and 20 mm Hg during constriction of the pulmonary artery. Therefore, it is possible that inhibitory signals arising from elevated pressure in the right atrium may alter secretion of renin in response to systemic hypotension. Alternatively, graded constriction of the pulmonary artery increased plasma vasopressin, ranging from 12 fold in response to a 5% reduction in mean arterial pressure to 75 fold in response to a 30% reduction in mean arterial pressure (Fig. 2, 12). As it is known that even a small increase in plasma vasopressin (as small as doubling the resting plasma vasopressin level) inhibit renin release in various experimental situations (Tagawa et al., 1971; Malayan et al., 1980), it could be argued that the PRA response to reduced renal perfusion pressure caused by constriction of the pulmonary artery is attenuated by vasopressin.

Our results indicate that increased pressure in the left heart and/or pulmonary circulation can inhibit release of renin in response to stimulatory signals activated by systemic hypotension. Receptors in the left heart and pulmonary circulation have been identified, and these receptors are stimulated by increased volume or pressure and can inhibit the secretion of renin (Thoren, 1979). Although the importance of receptors in the pulmonary circulation in the regulation of plasma renin

activity has been questioned (Schultz et al, 1982), receptors located in both the left atrium (Zehr, 1976) and left ventricle (Thames, 1977) are known to be involved in the regulation of renin release. In the current experiments, constriction of the ascending aorta should stimulate receptors in both the left atrium and ventricle. Thus, it is not clear whether receptors in the left atrium or receptors in the left ventricle, or both are responsible for this powerful inhibition of renin release.

Although afferents in the vagus nerve probably mediate inhibition of renin release (Mancia et al., 1975; Zehr, 1976), the efferent pathway of this inhibition is not clear. One possibility is through inhibition of sympathetic tone to the kidney. Thus, Stella et al. (1976) and Thames and DiBona (1979) showed that the denervated kidney had a blunted renin release in response to suprarenal aortic constriction in cats and dogs. However, it is difficult to reconcile complete suppression of renin release throughout the range of renal perfusion pressures examined, with a mechanism based solely on reducing sympathetic tone to the renin secreting cells. Also, the role of renal nerves in the modulation of renal baroreceptor activity in conscious animals is questional (see historical review). Therefore, a second possibility should be considered. Elevated pressure in the left heart could lead to either reflex inhibition of renin secretion mediated by a hitherto unknown neural input to the renin secreting cells or secretion of a humoral substance that inhibits renin release. Although, vasopressin could be a candidate in this regard, our results indicate that plasma vasopressin did not change in response to systemic hypotention caused by inflation of the ascending aortic cuff. (Fig. 2, 3).

To further elucidate the efferent pathway of this powerful inhibition of renin, we performed a series of ascending aortic and suprarenal cuff inflation in dogs with bilateral renal denervation. From these results we should be able to differentiate the contribution of renal nerve and humoral substances in the potent inhibition of renin release from the left heart.

Chronic renal denervation is usually complicated by reinnervation (Kline and Mercer, 1980) and the time course of reinnervation ranges from 2 weeks to 3 months (Nomura et al., 1972; Kline and Mercer, 1980). However, even after clear reinnervation had occured 6 months later in dogs, Nomura et al. (1972) found that the renin response to suprarenal aortic constriction was highly depressed compared with control dogs. Thus, they suggested that the reinnervation was non functional. All our experiments were performed within one month following bilateral renal denervation, and renal norepinephrine was essentially undetectable. Furthermore the resting PRA in these dogs was significantly lower than that of the control dogs. Thus, the interpretation of our data should not be complicated by reinnervation.

In spite of the bilateral renal denervation, plasma renin activity increased dose dependently following graded inflation of the suprarenal cuff (Fig. 20, 21). The average changes in PRA in response to 10%, 20%, and 30% levels of reduction of renal perfusion pressure following inflation of the suprarenal cuff were not different in dogs with innervated kidneys and dogs with bilateral renal denervation (Fig. 4, 21). In marked contrast, a 10% reduction in renal perfusion pressure caused by constriction of the ascending aorta failed to change PRA in

dogs with bilateral renal denervation. Since the kidneys were denervated, the difference of PRA response to a 10% reduction in renal perfusion pressure caused by either the suprarenal or the ascending aortic cuff cannot be explained by renal nerves. Thus, the involvement of humoral substances must be considered to explain the difference of PRA response to the ascending aortic and the suprarenal cuff inflation in dogs with bilateral renal denervation.

Although PRA did not change in response to 10% reduction in renal perfusion pressure caused by constriction of the ascending aorta in dogs with bilateral renal denervation, plasma renin activity did increase significantly when renal perfusion pressure was further decreased to 20% and 30% of control (Fig. 21, 27). Compared with the failure of renin to increase in response to 20% and 30% reductions in renal perfusion pressure during inflation of the same cuff in dogs with intact kidneys, these results suggest that renal nerves are also involved in the inhibition of renin release in intact dogs during constriction of the ascending aorta. However, another alternative must be considered to explain the increases in PRA in response to 20%, and 30% reduction in renal perfusion pressure caused by inflation of the ascending aortic cuff (see below).

It has been reported that bilateral carotid occlusion caused a significant increase in systemic arterial norepinephrine and epinephrine concentrations (Reison et al., 1983). Thus, it is very likely to find increases in plasma catecholamine concentrations in response to systemic hypotension. Furthermore, the chronically denervated kidneys might develop a hypersensitivity to norepinephrine. For example, Korner et al.

(1967) reported that moderate hemorrhage increased vascular resistance in intact and denervated kidneys in rabbits, but the increase in vascular resistance was much greater on the innervated side. However, severe hemorrhage, which presumably caused marked increases in circulating catecholamines, produced a greater degree of vasoconstriction in the denervated kidney when compared to the response in the contralateral innervated kidney (Korner et al., 1967). In anesthetized rats. Kline and Mercer (1980) showed a hypersensitive vascular reactivity to exogenous norepinephrine in the denervated kidney. The hypersensitive state was present during the first 2 weeks after denervation, and was still present between 24 and 32 days after denervation. It can be speculated that the denervated kidney will also show a hypersensitive renin response to circulating catecholamine. Thus, it can be argued that the increase of PRA in response to 20% and 30% reduction in MAP following inflation of the ascending aortic cuff was caused by the effect of elevated plasma catecholamines on the hypersensitive, denervated kidneys. Thus, the roles of renal nerves in the contribution of the potent inhibition of renin release is not clear. This problem can be solved by repeating the same graded inflation of the ascending aortic and the suprarenal cuffs in dogs treated with continuous intravenous infusion of a beta-blocker.

Although the role of the renal nerves in the contribution of inhibition of renin release in response to ascending aortic constriction is not clear, the involvement of a humoral substance is very likely. Comparing the renin response to inflation of the ascending aortic or the suprarenal cuff by two way ANOVA with repeated measurements suggest

that, there is an increase in the threshold required to elicit a renin response to graded reduction of renal perfusion pressure caused by inflation of the ascending aortic cuff. Since the kidneys are denervated, the shift in the threshold must be caused by a humoral substance.

Vasopressin should be considered as a candidate for its ability to inhibit renin release. However, our results indicate that vasopressin did not increase in response to graded inflation of the ascending aortic cuff in normal dogs. Although we did not measure vasopressin in dogs with bilateral renal denervation, it is unlikely that the vasopressin response to inflation of the ascending aortic cuff in renal denervated dogs will be different from the vasopressin response in renal innervated dogs. Thus, another humoral substance (or substances) should be considered. I would like to propose the recently purified atriopeptin (Currie et al. 1984) as a candidate. The hormone is located mainly in the atria and there are experimental results which suggest the release of a "natriuretic factor" when the atria were distended (Reinhardt, 1980). Thus, it is logical to speculate that direct stretch of the atrial wall by volume expansion or ascending aortic constriction should stimulate the release of atriopeptin. The peptide is a potent vasodilator and caused diuresis and natriuresis when injected into the rats (Currie et al., 1984). As discussed in the historical section, papaverine, a vasodilator can block the renin release to suprarenal aortic constriction (Witty et al, 1971). Thus, it would not be surprising to find that atriopeptin can block the renin response to suprarenal aortic constriction. Actually, systemic hypotension induced

by infusion of atriopeptin failed to increase PRA (Edward Blaine, personal communication). Thus, it is possible that the potent inhibition of renin release during inflation of the ascending aortic cuff is mediated, at least partially, by atriopeptin.

In summary, our findings document, for the first time in conscious animals, the existence of powerful inhibitory signals originating in the left heart which are potent enough to overcome the combined stimulation of renin release by both the renal baroreceptors and the carotid sinus. The efferent pathway of this inhibition of renin release is mediated, at least partially, by an humoral substance (or substances). The role of renal nerve in the mediation of this potent inhibition of renin release is not clear.

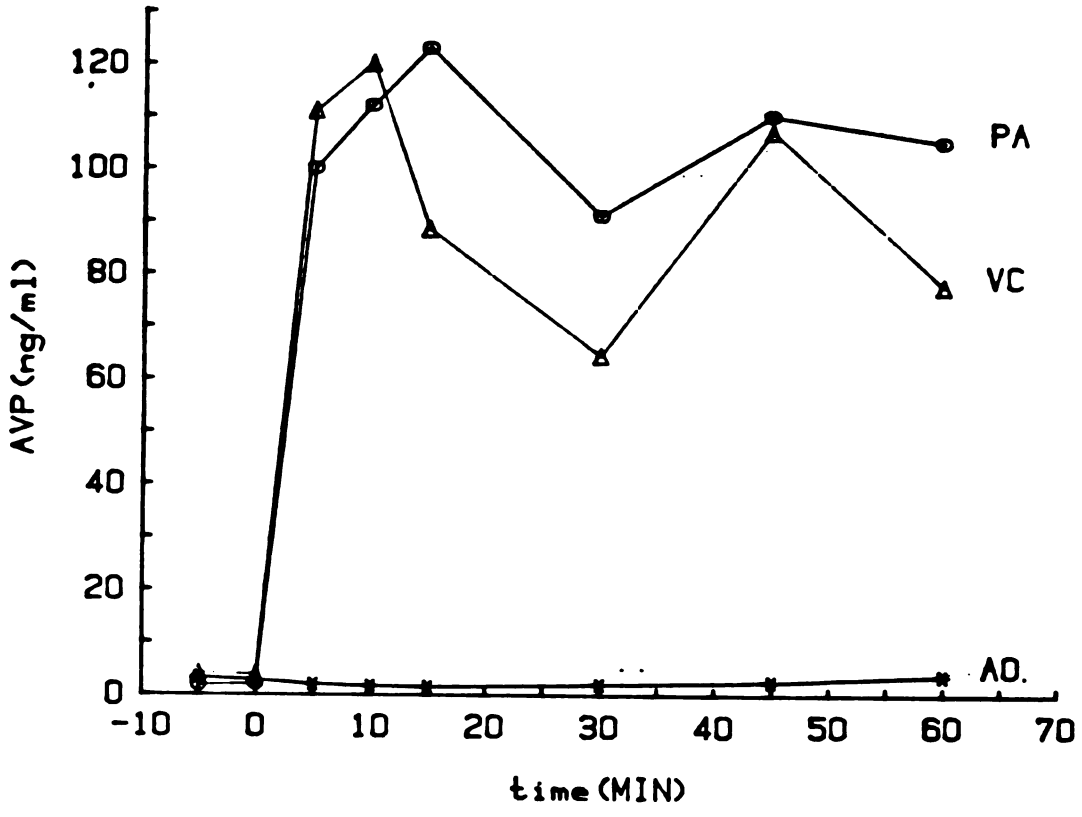

Figure 28. The vasopressin response of one dog (81-58R) to a 25% reduction in mean systemic arterial pressure caused by inflation of the ascending aortic (AO), pulmonary artery (PA) or inferior vena caval cuff (VC). The cuff was inflated between time 0 and time 60.

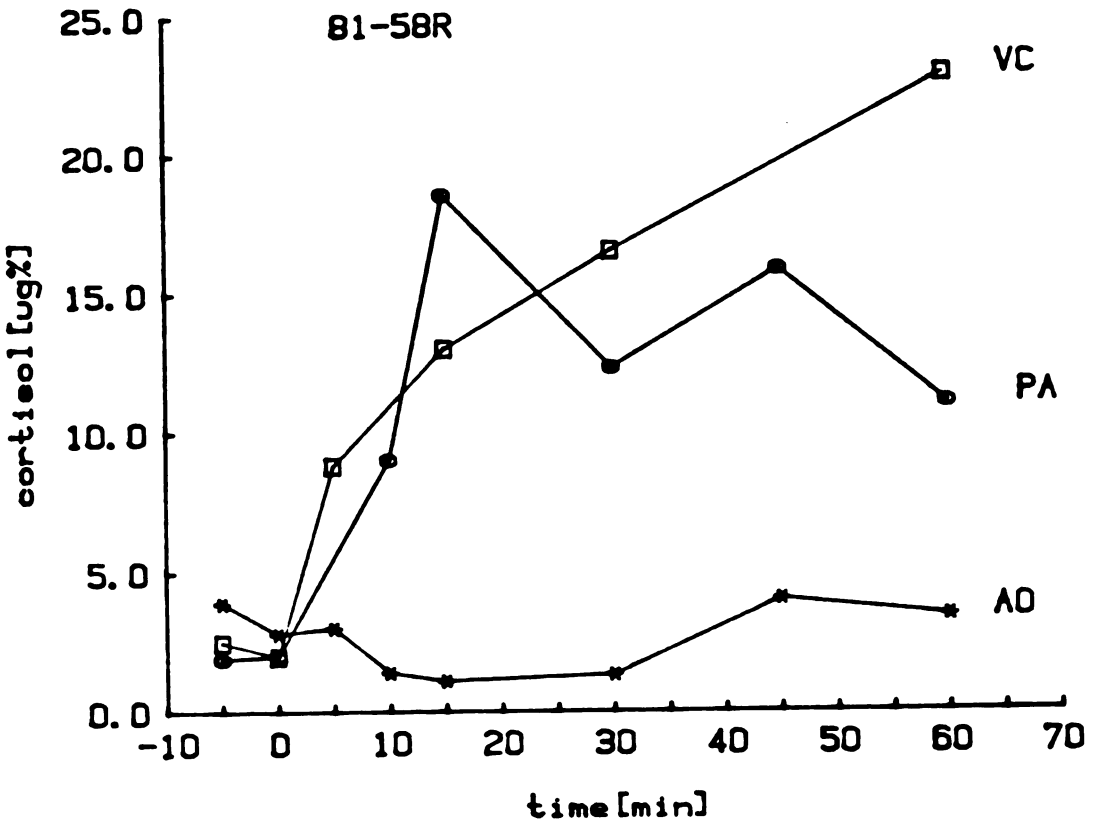

Figure 29. The cortisol response of the same pilot dog (as fig. 28) to a 25% reduction in mean arterial pressure caused by inflation of the ascending aortic (AO), the pulmonary (PA) or the inferior vena caval (VC) cuff. The cuff was inflated between time 0 and time 60.

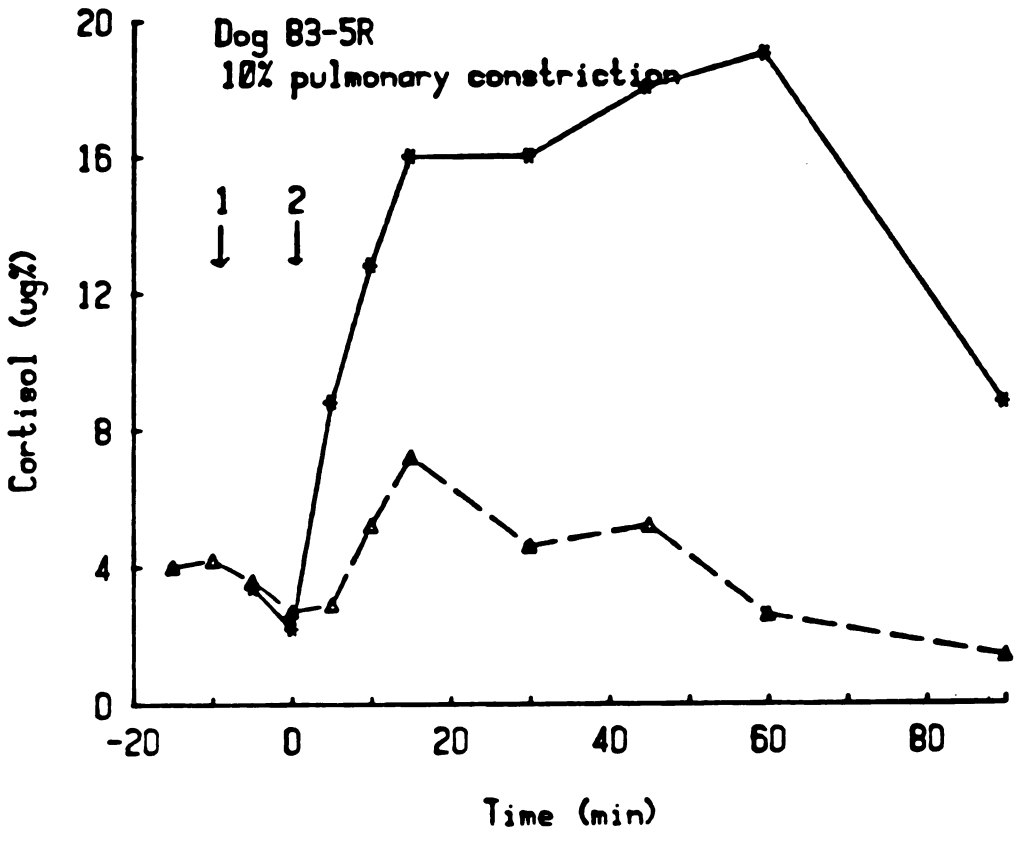

Figure 30. The cortisol response of dog 83-5R to 10% reduction of systemic arterial pressure caused by inflation of the pulmonary cuff. The dog was either pretreated (broken line) or not pretreated (solid line) with vasopressin blocker. The vasopressin blocker was given at arrow 1; the pulmonary artery was constricted at arrow 2. The constriction lasted for 60 minutes.

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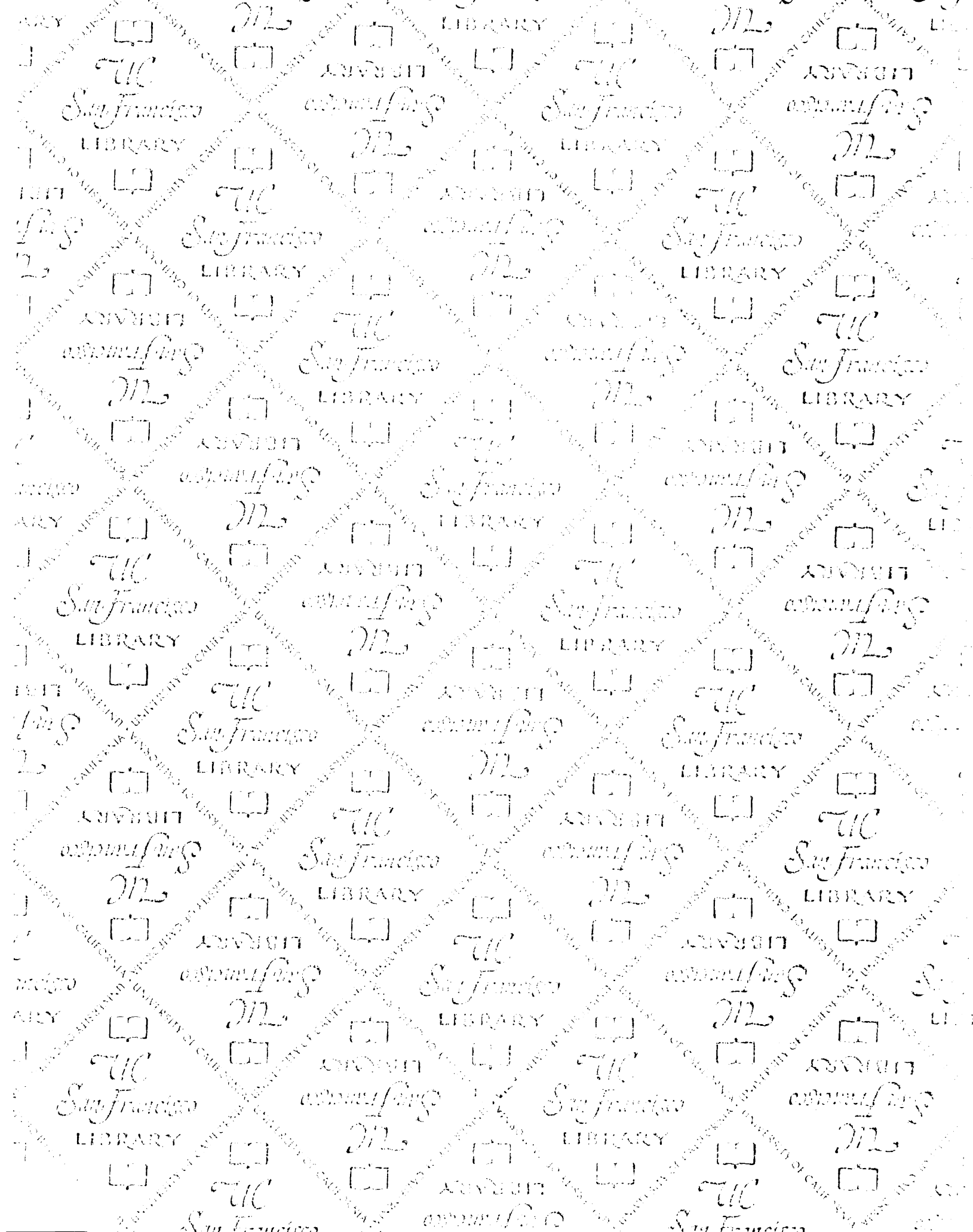
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