REFLEX SUPPRESSION OF RENIN SECRETION DURING DISTENTION OF CARDIOPULMONARY RECEPTORS IN DOGS

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SUMMARY We studied the effect of brief periods of left atrial-pulmonary vein distention on the rate of renin secretion in sodium-restricted dogs anesthetized with chloralose and breathing spontaneously. Series 1 consisted of 32 trials in seven dogs with intact renal nerves and intact vagi. Renin secretion, calculated as the product of renal venous minus arterial renin activity (radioimmunoassay) times renal plasma flow (electromagnetic flowmeter), was depressed to 56% of control during atrial distention despite no change in arterial pressure, central venous pressure, or renal blood flow. Series 2 consisted of 58 trials in 12 dogs which had undergone unilateral renal denervation several days prior to the studies. Simultaneous, bilateral determinations indicated that renin secretion from the innervated kidney was depressed to 58% of control during atrial distention; secretion from the denervated kidney was unchanged. Series 3 consisted of 30 trials in six dogs with bilateral cervical vagotomy. Atrial distention evoked no changes in renin secretion. We conclude that left atrial distention reflexly reduces the rates of renin secretion via vagal afferent and renal sympathetic efferent pathways.

Numerous studies indicate that the sympathetic nervous system may play a role in controlling renin secretion.1 Direct electrical stimulation of the renal nerves,2-4 the medulla oblongata,5 the mesencephalon,4 and the pons7 results in increased renin activity and renin secretion. These experimental procedures have a common denominator in that they mimic an enhanced level of central and renal nervous activity. In a previous study4 we reported that intermittent electrical stimulation of suprabulbar vasodopressor areas in the central nervous system of conscious dogs resulted in a decrease in plasma renin activity. Since this response was dependent upon intact renal nerves, we suggested that some fraction of basal renin secretion was modulated by tonic activity of renal sympathetic nerves which arose from structures higher in the central nervous system, and that a reduction in adrenergic outflow had been responsible for the observed decrease in renin activity. Several recent studies have shown that cardiopulmonary receptors tonically suppress the vasomotor center of the dog and that blood flow10 and the firing rates of adrenergic nerves11 to peripheral vascular beds, including the kidney, are under these inhibitory influences. Furthermore, Mancia and co-workers12 recently have demonstrated that cardiopulmonary receptors tonically suppress renin secretion via pathways which are independent of alterations in renal blood flow but which are dependent upon intact renal sympathetic nerves. The present studies were designed to test the hypothesis that activation of vagally innervated cardiopulmonary receptors will acutely depress renin secretion via reflex mechanisms.

Methods

Studies were conducted on 25 mature dogs (8.6-24.8 kg) of both sexes that had been maintained, for 5 days prior to the experimental procedures, on a diet (H/D prescription diet, Hill Packing Co., Topeka) which provided less than 5 mEq of sodium per day. The purpose of this period of prior sodium restriction was to induce moderate elevations in resting renin levels so that the hypothesized reflex reduction in renin secretion could be expressed. Water was provided ad libitum at all times. The dogs were anesthetized with sodium methohexitol (Brevital, 12 mg/kg, iv), followed by 10 ml/kg of a 1% solution of α-chloralose (100 mg/kg, iv) in 0.9% saline. Supplemental chloralose was given at the rate of approximately 10 mg/kg per hour or, on occasion, as required to maintain a steady plane of anesthesia. A catheter (PE 240), introduced into a femoral artery, was advanced to approximately the level of the renal artery and was used to monitor arterial pressure and for blood sampling. A catheter in the external jugular vein was advanced to the junction of the great veins and used to monitor central venous pressure. The dogs were intubated with a cuffed endotracheal tube and ventilated with a Harvard respirator throughout the procedures which required surgical thoracotomy. An end-expiratory pressure of 3-4 cm H₂O was maintained to minimize atelectasis.

The thorax was opened at the 4th left intercostal space, the ribs were retracted, and the pericardium was slit. The left atrial appendage was opened, a Foley urinary retention catheter (Fr. 12-14) was advanced into the left atrium and anchored in place by a ligature around the appendage. Inflation of the retention balloon served to partially obstruct the mitral orifice while the collection catheter was used to monitor left atrial pressure. A catheter (Fr. 5), used to monitor intrathoracic pressure, was anchored to the atrial catheter so that the tip was positioned just external to the atrium. After the chest had been closed and the pneumothorax reduced, the dog was allowed to resume spontaneous ventilation and maintain it throughout the experiment. The dogs were suspended in an upright position and a renal artery and vein were exposed retroperitoneally through a flank incision. Special care was taken to avoid trauma to the renal nerve supply. A noncannulating electromagnetic flow probe was fitted around the renal artery and a curved 20-gauge needle, attached to a length of thin-wall Silastic...
Renal blood flow was measured with a Zepeda model SW-3 square wave electromagnetic flowmeter. Zero flow was determined by momentary arterial occlusion at least 30 minutes before the initial experimental period and again after completion of the final observation. To avoid the renin secretion which results from renal artery occlusion, occlusive flow zeros were not determined during the experimental procedures; however, electronic zeros were checked periodically. In our experience the Zepeda SW-3 flowmeter exhibits excellent signal-to-noise and frequency response characteristics and is subject to minimal baseline drift. Flow probes were calibrated in vivo on a femoral artery with flow controlled by a Harvard infusion-withdrawal syringe pump. Arterial, atrial, central venous, and intrathoracic pressures were measured with Statham P23Db strain gauge transducers and recorded continuously with renal blood flow, on a Beckman type R M six-channel ink-writing Dynograph. A period of at least 1 hour was allowed for equilibration after completion of surgery and before experimental procedures were initiated.

**EXPERIMENTAL PROTOCOL**

Atrial-pulmonary mechanoreceptors generally are regarded as being sensitive to stretch or volume; therefore, the instantaneous atrial to intrathoracic pressure gradient was taken as the best index of atrial-pulmonary vein distention. Thus, the term atrial distention as used in this report refers to the instantaneous atrial to intrathoracic pressure gradient.

Since the goal of these experiments was to examine the neural reflex effect of atrial-pulmonary vein distention on rates of renin secretion, a protocol was developed which allowed multiple, short-term observations in each dog. In all instances replicate 5-minute periods of atrial-pulmonary vein distention by approximately 5–6 cm H₂O were chosen as the uniform stimulus parameter. A 5-minute sequence was observed because, if a reflex pathway were present, this duration should allow an expression of the response and yet permit multiple trials in each dog.

A single observation consisted of a 5-minute control period followed immediately by a 5-minute period of atrial distension. All pressure transducers were briefly rechecked for zero stability midway through each control and experimental period. Cardiovascular data were analyzed over the instantaneous, bilateral renin secretion rates were determined. Because the results of this series indicated that the rate of renin secretion had been suppressed at the end of 5 minutes of atrial distension, two additional groups of experiments were undertaken to characterize the efferent and afferent pathways responsible for the response.

**Series 2: Atrial Distention in Dogs with Unilateral Renal Denervation and Intact Vagi.** This series was designed to examine the influence of the renal sympathetic nerves in causing the decrease in renin secretion after atrial distention that had been observed in series 1. Twelve dogs were subjected to unilateral renal denervation 3–4 days before the day of the experiment by cutting all visible nerves and stripping the fascia from the renal artery and vein before painting them with a solution of 10% phenol in absolute ethanol. A total of 58 control and experimental periods were studied in these 12 dogs; a protocol identical to that previously described was employed, except that simultaneous, bilateral renin secretion rates were determined. This allowed a direct comparison of the response of the innervated kidney with the simultaneous response of the denervated kidney and provided information on the efferent pathway involved.

**Series 3: Atrial Distention in Dogs with Intact Renal Nerves and Bilateral Cervical Vagotomy.** These studies were designed to identify the efferent pathway for the responses seen in the previous two series. Because cardiopulmonary receptors are vagally innervated, a group of six dogs were studied which had undergone bilateral cervical vagotomy early during the surgical preparation. A total of 30 control and experimental periods were studied in this series under an experimental protocol identical to that of the previous studies. Spontaneously ventilating, vagotomized dogs exhibit altered ventilatory patterns resulting from loss of the Hering-Breuer reflex; therefore arterial blood gases and pH were measured periodically throughout the experimental procedures to assess the acid-base state of the animal. Blood for arterial Po₂, PCO₂, and pH was collected in plastic syringes and immediately analyzed with an Instrument Laboratories model IL 213 digital blood gas analyzer. Blood gases and pH remained constant and within normal limits throughout these procedures. Mean values (±SD) for the
dogs in this series were: \( \text{P}_{\text{co}_2} \), 35.0 ± 1.3 mm Hg; \( \text{P}_{\text{o}_2} \), 88.0 ± 5.8 mm Hg; and pH, 7.329 ± 0.02.

**RENNIN ASSAY**

Two-milliliter samples of arterial and renal blood were drawn simultaneously over a period of 15-20 seconds into 3-ml plastic syringes which contained 0.1 ml of 10% sodium ethylenediaminetetraacetate (EDTA), immediately transferred to iced glass tubes and chilled to 0°C. Hematocrits were determined by microhematocrit methods. After separation, 0.5 ml of plasma was added to an equal volume of 0.05 M phosphate buffer (pH 7.4) which contained 0.125% neomycin sulfate as a bacteriostatic agent. Ten microliters of 0.806 M dimercaprol and 20 \( \mu l \) of 0.340 M 8-hydroxy-quinoline sulfate were added to each sample as inhibitors of angiotensinase and converting enzyme. All samples were incubated at 39°C for a period of 2 hours to permit generation (ng/ml per hour); renin secretion was calculated activities multiplied by the renal plasma flow \( [\text{RBF} - \Delta \text{renin activity}] \). Renal plasma flow was determined by correcting the renal blood flow for hematocrit.

**DATA REDUCTION AND ANALYSIS**

Cardiovascular parameters were continuously recorded but, because these data were to be matched with renin samples taken during the final 30 seconds of the respective periods, they were analyzed only over the final 1 minute of the control and experimental periods. Dynography recordings were sampled at 10-second intervals over the final minute of the period and averaged to a single value for each variable. Data describing cardiovascular function and renin secretion during a single period of atrial distention were compared with the control data obtained immediately prior to that experimental period. Replicate trials were conducted in each dog and the data from the replications were averaged to a single point which was taken as that dog’s response. In this way the degrees of freedom during statistical analysis are based on the number of dogs rather than replications. Each dog acted as his own experimental control during the application of a paired, two-tailed Student’s t-test which compared the experimental data with those of the control period for each series of studies. Minimum criteria for rejection of the null hypothesis was the 95% confidence level.

**RESULTS**

**SERIES 1: ATRIAL DISTENTION IN DOGS WITH INTACT RENAL NERVES AND INTACT VAGI**

The purpose of the studies on this group of dogs was to provide basic information regarding cardiopulmonary influences on short-term renin secretion rates. The rate of renin secretion, determined after 5 minutes of atrial distention, was reduced as compared to control values in 25 of the 32 trials despite very modest alterations in arterial pressure and renal blood flow. Minor changes that had occurred in these parameters were in a direction that would be expected to increase rather than decrease renin secretion. During this series, atrial distention was increased by an average of 5.4 cm H\(_2\)O during the experimental period. Limiting the balloon inflation to this degree resulted in little, if any, transient cardiovascular responses. Figure 1 is a reproduction of an original recording from one dog in this series during a balloon inflation that increased atrial pressure by 4.9 cm H\(_2\)O. The lack of major transients was assured, because our protocol dictated that balloon inflation be stopped at the earliest indication of changes in arterial or central venous pressure. These dogs, however, uniformly exhibited increased heart rates \( (P < 0.05) \) during atrial distention. Table 1 shows the means \( \pm SE \) of the cardiovascular variables during the control and experimental periods and Table 2 shows the averaged replicate renin data for the individual dogs in this series. A paired two-tailed analysis shows that renin secretion rates were reduced \( (P < 0.01) \) by an average of 116 ± 19.6 \( \text{SE} \) ng/min after 5 minutes of left atrial distention. This represents a reduction in the overall rate of renin secretion to 56% of the control. Since the control and experimental renal blood flows and arterial renin activities were essentially constant, the reduction in renin secretion was largely a result of a reduction of renal venous renin activity. This indicates a reduced rate of release from the juxtaglomerular cells. Table 2 indicates that one dog (dog 6) exhibited an apparent “negative” renin secretion during the experimental period as a result of a negative renal venous to arterial gradient. To avoid a potential distortion in the calculation of the renin secretion response which would result if a “negative” secretion rate were subtracted from the control data, this value was assumed to be zero for calculations of the renin and statistical evaluation.

**SERIES 2: ATRIAL DISTENTION IN DOGS WITH UNILATERAL RENAL DENERVATION AND INTACT VAGI**

Fifty-eight trials in this group of 12 unilaterally denervated dogs were made to assess the efferent pathways for the renin response seen in the previous series. Table 3 indicates that cardiovascular parameters responded in a manner very similar to that observed previously. Experimental atrial distention was increased by an average of 5.9 cm H\(_2\)O from control. This caused a mild tachycardia accompanied by little, if any, alteration in arterial pressure and renal blood flow.

Table 4 shows the individual determinations of renin activity, and Table 5 the data for renin secretion for individual dogs in this series. During the control period, simultaneously determined rates of renin secretion from the
innervated and denervated kidneys were similar, 439 ng/min and 413 ng/min, respectively. Renin secretion from the innervated kidney was depressed ($P < 0.002$) during the experimental period by an average of 183 $\pm$ 44 (SE) ng/min. This represents a reduction to 58% of the control secretion rate. Stated in terms of percent of control, the response of the innervated kidney in the dogs of this series was almost identical to that of series I (58% vs. 56% of control). On the other hand, mean renin secretion from the denervated kidney tended to increase, although not with a 95% level of confidence ($P > 0.2$), during atrial distention. As in the previous series, two dogs exhibited apparent "negative"

TABLE 1  Mean Cardiovascular Data Taken during the 5th Minute of the Control Period and the 5th Minute after Left Atrial Balloon Inflation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Experimental</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>138.9 $\pm$ 14.2</td>
<td>154.6 $\pm$ 10.1</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>120.8 $\pm$ 6.4</td>
<td>117.4 $\pm$ 6.2</td>
<td></td>
</tr>
<tr>
<td>Central venous pressure (cm H$_2$O)</td>
<td>$-5.1 \pm 3.7$</td>
<td>$-5.3 \pm 3.8$</td>
<td></td>
</tr>
<tr>
<td>LAP-ITP (cm H$_2$O)</td>
<td>5.9 $\pm$ 1.1</td>
<td>11.3 $\pm$ 5.1</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Renal blood flow (ml/min)</td>
<td>105.5 $\pm$ 8.8</td>
<td>101.8 $\pm$ 9.2</td>
<td></td>
</tr>
</tbody>
</table>

LAP = left atrial pressure; ITP = intrathoracic pressure.

Thirty-two control and experimental periods were studied in seven dogs (11.5 kg) with intact renal nerves and intact vagi. Each dog's replicate data were averaged to a single point. Values shown are the mean $\pm$ SE of the averaged replicate data. To determine $P$, a paired two-tailed Student's $t$-test with 6 degrees of freedom was used.

TABLE 2  Arterial and Renal Venous Renin Activity and Renin Secretion Rates Taken during the 5th Minute of the Control Period and the 5th Minute after Left Atrial Balloon Inflation

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Arterial activity (ng/ml per hr)</th>
<th>Arterial secretion (ng/min)</th>
<th>Renal venous activity (ng/ml per hr)</th>
<th>Renal venous secretion (ng/min)</th>
<th>Control</th>
<th>Experimental</th>
<th>$\Delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.8</td>
<td>13.5</td>
<td>13.5</td>
<td>710</td>
<td>442</td>
<td>$-268$</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>1.9</td>
<td>2.4</td>
<td>48</td>
<td>26</td>
<td>$-22$</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>34.9</td>
<td>36.2</td>
<td>47.2</td>
<td>346</td>
<td>305</td>
<td>$-131$</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.7</td>
<td>2.3</td>
<td>3.5</td>
<td>260</td>
<td>182</td>
<td>$-78$</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4.3</td>
<td>4.5</td>
<td>4.9</td>
<td>102</td>
<td>38</td>
<td>$-64$</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>7.5</td>
<td>6.8</td>
<td>6.1</td>
<td>138</td>
<td>$-42$</td>
<td>$-138$</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>8.3</td>
<td>8.8</td>
<td>9.2</td>
<td>137</td>
<td>25</td>
<td>$-112$</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>10.2 $\pm$ 4.3</td>
<td>10.6 $\pm$ 6.1</td>
<td>14.1</td>
<td>261</td>
<td>145</td>
<td>$-116$</td>
<td></td>
</tr>
</tbody>
</table>

Thirty-two control and experimental periods were studied in seven dogs with intact renal nerves and intact vagi. The individual dog's replicate data were averaged to a single point and are shown in this table. A paired two-tailed Student's $t$-test, based on 6 degrees of freedom, compares renin secretion during the control and experimental periods.

* $t = 3.923$; $P < 0.01$. 

FIGURE 1  Reproduction of an actual recording taken during atrial inflation of 4.9 cm H$_2$O in a 14.5-kg dog of series I. Throughout the course of these studies inflation of 3-6 cm H$_2$O induced little, if any, transient adjustments in any of the parameters measured.
replications in these dogs. With the exception of the fifth replication, for which data from only 10 dogs were available, each data point represents the average for the 12 dogs in the series. Figure 2 shows that, in each of the five replications, renin secretion from the innervated kidney was reduced during atrial distention, while the response on the denervated side indicated no clear-cut trend. Figure 2 also indicates that in each replication on the innervated side the control secretion rate rebounded to a level higher than that found during the preceding experimental period, and that after the first trial there was a consistent downward trend in the control and experimental secretion rates.

| TABLE 3 | Mean Cardiovascular Data Taken during the 5th Minute of the Control Period and the 5th Minute after Left Atrial Balloon Inflation in Unilaterally Denervated Dogs |
| Control | Experimental | P |
| Heart rate (beats/min) | 140.0 ± 5.5 | 162.2 ± 7.5 | <0.05 |
| Mean aortic pressure (mm Hg) | 107.4 ± 7.4 | 105.8 ± 7.4 |
| Central venous pressure (cm H₂O) | −2.8 ± 1.4 | −2.9 ± 1.4 |
| LAP-ITP (cm H₂O) | 4.6 ± 0.5 | 10.5 ± 0.9 | <0.001 |
| Renal blood flow (ml/min) | 152.2 ± 14.6 | 149.8 ± 14.9 |
| Denervated | 140.1 ± 13.7 | 137.0 ± 20.4 |

LAP = left atrial pressure; ITP = intrathoracic pressure.

Fifty-eight control and experimental periods were studied in 12 dogs (15.5 kg) with prior unilateral renal denervation and intact vagi. Each dog's replicate data were averaged to a single point. Values shown are the mean ± SE of the averaged replicate data. To determine P, a paired two-tailed Student's t-test, based on 11 degrees of freedom, compares the rate of renin secretion during the control (C) and experimental (E) periods in both the intact and denervated kidneys.

Fifty-eight control and experimental periods were studied in 12 dogs that had undergone prior unilateral renal denervation. The individual dog's replicate data were averaged to a single point and are shown on this table. A paired two-tailed Student's t-test, based on 11 degrees of freedom, compares the rate of renin secretion during the control (C) and experimental (E) periods in both the intact and denervated kidneys.

\[ t = 4.158; P < 0.001. \]

\[ \bullet \text{ Not significant.} \]

SERIES 3: ATRIAL DISTENTION IN DOGS WITH INTACT RENAL NERVES AND BILATERAL CERVICAL VATOGOMY

Dogs in this series were used to assessafferent pathways responsible for the renin response during atrial distention. Thirty trials were conducted in the six dogs of this group. Table 6 indicates that cardiovascular parameters were again unchanged by atrial distention. Control heart rates were elevated from those of the previous series and remained constant during the experimental period, a response that would be anticipated in vagotomized dogs. Individual renin activity and secretion rates for each dog are shown in Table 7. In these bilaterally vagotomized dogs, renin secretion rates were not reduced by atrial distention as had been the case in the two previous series. In fact, Table 7 indicates a trend toward increased renin secretion, although these changes were not statistically significant (P > 0.2).

Discussion

These studies were undertaken to test the hypothesis that activation of vagally innervated, cardiopulmonary receptors will reflexly influence the rate of renin secretion. A study of singular neural reflex effects requires that other factors known to control renin release remain reasonably constant. Of particular importance in the present study was a constancy of renal blood flow and perfusion pressure. Furthermore, it would be anticipated that, if such a reflex could be shown, the response would be relatively rapid and reproducible and that the afferent and efferent limbs of the arc would be demonstrable. We believe these considerations have been met in the present study. The data of series 1 (Table 1 and 2) indicate that, in dogs with intact renal nerves
Atrial and Renal Venous Renin Activity and Renin Secretion Rates Taken during the 5th Minute of the Control Period and the 5th Minute after Left Atrial Balloon Inflation in Bilaterally Vagotomized Dogs

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Arterial venous</th>
<th>Arterial venous</th>
<th>Control</th>
<th>Experimental</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.2 ± 1.8</td>
<td>8.0 ± 2.6</td>
<td>7.5</td>
<td>10.4</td>
<td>364 ± 18.0</td>
</tr>
<tr>
<td>2</td>
<td>6.3 ± 1.8</td>
<td>9.0 ± 1.5</td>
<td>8.3</td>
<td>11.1</td>
<td>101 ± 7.4</td>
</tr>
<tr>
<td>3</td>
<td>5.4 ± 0.5</td>
<td>8.5 ± 2.5</td>
<td>6.4</td>
<td>10.9</td>
<td>167 ± 13.1</td>
</tr>
<tr>
<td>4</td>
<td>9.8 ± 2.5</td>
<td>10.3 ± 2.5</td>
<td>9.3</td>
<td>12.0</td>
<td>77 ± 8.2</td>
</tr>
<tr>
<td>5</td>
<td>20.7 ± 2.5</td>
<td>24.3 ± 2.5</td>
<td>18.8</td>
<td>17.4</td>
<td>80 ± 8.4</td>
</tr>
<tr>
<td>6</td>
<td>3.6 ± 0.5</td>
<td>5.1 ± 0.5</td>
<td>3.7</td>
<td>4.5</td>
<td>90 ± 5.2</td>
</tr>
</tbody>
</table>

Mean = 8.7 ± 2.56

Thirty control and experimental periods were studied in six vagotomized dogs. Individual dog's replicate data were averaged to a single point and are shown in this table. A paired two-tailed Student's t-test, based on 5 degrees of freedom, compares renin secretion during the control and experimental periods.

*Δ = 1.83; not significant.

Little information is available concerning renin release during reflexly induced decreases in renal nerve activity. We previously reported that intermittent stimulation of suprabulbar vasodepressor structures in conscious dogs leads to a depression of renin activity despite periodic reductions in blood pressure that would be expected to increase renin secretion. Since this response was dependent on intact renal nerves, it was suggested that a reduced level of basal renal nerve firing, acting directly on the juxtaglomerular cells, was responsible.

At rest, renal sympathetic activity plays a minor role in the maintenance of renal vascular tone; however, existing low frequency renal nerve activity may exert a tonic influence on juxtaglomerular cells to establish a basal level of renin secretion. If low frequency tonic neural traffic, acting on renin secretory cells, were responsible for some fraction of basal renin secretion, then a reduction of that traffic might be expected to result in a decrease in the rate at which renin is secreted. The concept of functional, direct sympathetic innervation of the juxtaglomerular cells, capable of independently stimulating renin release, is strongly supported by the work of Johnson et al., who showed that electrical stimulation of the renal nerves in papaverinized, nonfiltering kidneys resulted in increased renin secretion. There is clear anatomical evidence that adrenergic nerve endings are found in the region of the juxtaglomerular and macula densa cells.

These presumably are capable of directly stimulating renin release without eliciting secondary changes in renal hemodynamics.

In our study, atrial distention produced rapid reductions in the rate of renin secretion despite little, if any, change in renal blood flow or arterial pressure (Table 1, Fig. 1). The results in series 2 demonstrate that the acute depression of renin secretion under these conditions was dependent upon intact renal nerves (Table 5) and that the response was consistently observed throughout the five replications (Fig. 2). Finally, series 3 results show that vagal afferent influences are required for the response to occur (Table 7). Therefore, the criteria previously outlined for identification of a cardiopulmonary receptor-renin secretion reflex arc appear to have been met.

Although it is clear that activation of the renal sympathetic nerves results in increased renin secretion, which may occur independently of alterations in either renal and vagi, atrial distention produced an acute reduction in the rate of renin secretion despite little, if any, change in renal blood flow or arterial pressure (Table 1, Fig. 1). The results in series 2 demonstrate that the acute depression of renin secretion under these conditions was dependent upon intact renal nerves (Table 5) and that the response was consistently observed throughout the five replications (Fig. 2). Finally, series 3 results show that vagal afferent influences are required for the response to occur (Table 7). Therefore, the criteria previously outlined for identification of a cardiopulmonary receptor-renin secretion reflex arc appear to have been met.

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nerve firing rates which probably acted directly on cells secreting renin. It is doubtful that changes in arterial blood pressure or renal blood flow of the magnitude evidenced during our studies could have influenced the renin response we observed. In fact, if such an influence had been present the changes in these parameters were in a direction that would increase, rather than decrease, renin secretion. It also is improbable that reductions in arterial pressure of this magnitude could have reflexly altered renin secretion, especially in view of the fact that large, controlled decrements in carotid sinus pressure have yielded variable results with regard to renin secretion.

In a series of studies Mancia and co-workers demonstrated that, in dogs, vagally innervated cardiopulmonary receptors exert a tonic restraint on central vasomotor mechanisms and on adrenergic outflow to peripheral beds, including the kidney. In a recent experiment that is a converse to that of our present study, they also showed that within 2 minutes after removal of tonic cardiopulmonary receptor nerve traffic by cold block of the vagus, renin secretion is markedly increased despite only minor changes in arterial pressure or renal blood flow. Since the renal sympathetic nerves were required for an expression of the response, the conclusion was reached that cardiopulmonary receptors place tonic restraint on renin secretion mechanisms via neural pathways. Their data and those of our present study are in agreement with the conclusion that cardiopulmonary receptors are capable of reflex suppression of renin secretion, in the first instance by removal of tonic cardiopulmonary restraining influences and thus allowing unrestrained sympathetic outflow to be expressed as reflexly induced increases in renin secretion, while in the second instance, increasing the level of tonic restraint and thereby producing reflex inhibition of renin secretion.

Contrary to the results in our study, Brennan et al. concluded that 30 minutes of left atrial distention had no influence on renin activity in open-chested, morphine-seized, anesthetized dogs. However, they report reductions in peripheral renin activity following a similar period of right atrial distention. The reason for the discrepancy between their observation and ours is not clear, but probably is related to the fact that peripheral renin activity is a less sensitive index of reflex renin responses than are short-term measurements of secretion rates. Alternatively, we have no information that would suggest that the reduction in renin secretion we observed is maintained at a new steady state. Indeed, vagal influences on renin secretion undoubtedly are complex and probably involve at least two components, a rapidly responding reflex component illustrated by our study and the study of Mancia et al. and a long-term neurohumoral component.

Schrier et al. have shown that renin is decreased 30 minutes after vagotomy in volume-expanded dogs undergoing a water diuresis and have suggested that, under these conditions, removal of cardiopulmonary inhibition of vasopressin secretion by vagotomy results in increased circulating vasopressin levels which, in turn, may suppress renin secretion by direct action on the juxtaglomerular cells. Even though surgical stresses probably resulted in initially elevated vasopressin levels, these neurohumoral mechanisms may have further contributed to the reduced level of renin secretion observed during our studies on vagotomized dogs (Table 7), since vagotomy was performed before the 1-hour equilibration period. However, our studies using repetitive short-term responses of renin secretion rates precluded an expression of these neurohumoral influences during the course of our actual experimental protocol. The rapid reduction in renin secretion during the moderate but uniform degree of atrial distention which was employed during these studies suggests a high level of sensitivity of the low-pressure cardiopulmonary sensors, at least in these sodium-restricted dogs. Claybaugh and Share have shown that renin activity is enhanced by controlled blood losses as small as 2 ml/kg and have suggested that low pressure cardiopulmonary receptors are very sensitive in effecting renin release. Although our studies were not designed to evaluate the transfer function between atrial pressure and renin secretion, the data suggest that a sensitive, cardiopulmonary mechanism for inhibition of renin secretion is possible. Although our data clearly indicate that renal sympathetic efferent pathways were required for the response to be elicited, it is not certain what precise mechanisms were involved. The most direct explanation would be that atrial distention resulted in a reduced level of tonic renal sympathetic outflow to renin secretory cells and thereby removed a fraction of basal renin secretion. Although this is a simple and attractive explanation, other considerations must be entertained because the innervated and denervated kidneys of series 2 dogs exhibited essentially equal mean renin secretion rates under control conditions. If low frequency tonic renal firing rates were a partial contributor to basal renin secretion, we would expect that the denervated kidney would show reduced renin output as compared to the innervated kidney, especially since several studies indicate that renin activity in circulating blood is reduced after bilateral renal denervation. One possible explanation for the failure of the denervated kidney to show a depressed level of renin secretion during the control period is that, as indicated in Table 5, the first two dogs in this series show grossly higher secretion rates from the denervated kidney than from the contralateral innervated kidney. The reason for this is not clear but these data are in contrast to those for the rest of the dogs, since nine of the ten remaining dogs in this group show reduced rates of secretion from the denervated kidney. Although an outlying observation test was not performed, exclusion of these two dogs would result in mean control levels of 519 ng/min and 330 ng/min from the innervated and denervated kidneys, respectively. Since the data from these two dogs contributed very little to the mean response of the innervated kidney (Table 5), we further suspect that they represent aberrant subjects.

An alternate explanation for the equality of renin secretion from the two kidneys during control periods might be that, during the several days which had elapsed after renal denervation, the renin secretory cells of the denervated kidney may have become sensitized to circulating catecholamines, particularly epinephrine, which one would predict would be elevated by the stresses of anesthesia and surgical procedures. Although we know of no data which might support this idea with regard to renin secretion, denervation...
hypersensitivity is well recognized for vascular smooth muscle. This may have relevance, because the juxtaglomerular cells represent a specialized type of vascular smooth muscle. In addition, postdenervation adjustments of sodium excretion and distribution of renal blood flow in the denervated kidney may have acted to reset nonadrenergic components of the renin control mechanisms and thus cause renin output from the innervated and denervated kidneys to be similar during the control periods. A final, and most straightforward, explanation for the equality of renin secretion between the innervated and denervated kidneys during control periods is the possibility that tonic sympathetic renal nerve traffic has no influence on renin secretory mechanisms and thus there is no difference between the kidneys after unilateral renal denervation. However, to accept this alternative in light of the data from the present study requires that an active, sympathetically mediated inhibitory process be recruited as an explanation for the reflex reduction in renin secretion during atrial distention. This hypothesis, at present, is without foundation. Especially difficult to resolve is the fact that the hypothesized mechanism would be induced during experimental maneuvers which have been shown to reduce firing of renal nerves.

All factors considered, we believe that the reflex reduction in renin secretion observed during these studies can best be explained as a reduction in ongoing renal nerve activity, probably acting at the level of the juxtaglomerular cells. This hypothesis appears most consistent with the presently recognized cardiopulmonary-renal nerve axis and need not evoke secondary intrarenal mechanisms.

It should be emphasized that the methods used for our studies do not precisely localize the cardiopulmonary receptor sites involved, because atrial distention using balloon techniques probably elicited increased pressures throughout the pulmonary bed. Coleridge et al. have shown histologically and electrophysiologically that both right and left atrial-venous receptors initiate vagal afferent activity. However, since central venous pressure remained constant at all times, it is doubtful that the right atrium was involved.

In summary, the data indicate that left atrial distention is capable of eliciting rapidly responding reductions in the rate of renin secretion. This response is mediated by renal sympathetic efferent and by vagal afferent pathways.

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