Effect of pH Change upon Renal Vascular Resistance and Urine Flow

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With the collaboration of Jerry Scott, M.S.

In the dog kidney, acute increase and decrease in hydrogen ion concentration results in decrease and increase in renal vascular resistance respectively. These changes occur predominantly on the alkaline side of pH 7.3 and result from some direct effect upon vascular smooth muscle. The resistance changes are less apparent in nerve intact than nerve sectioned kidneys due to opposing effects mediated through extrinsic nerves.

The preceding paper and other publications indicate that the level of hydrogen ion concentration is one factor affecting blood vessel caliber in certain vascular beds. A review of the literature, however, has revealed no studies relating pH to renal resistance which utilized direct measurements for resistance calculations and no studies which explored renal resistance and urine flow rate changes on the alkaline side of pH 7.4. Dowds, Brickner, and Seikurt explored the acid side of pH 7.4 and found that renal resistance, calculated from indirect measurements, did not change significantly. The preceding paper suggested that larger changes might be observed on the alkaline side of pH 7.4.

The present study was undertaken to observe the effects of acute variation of hydrogen ion concentration upon dog renal vascular resistance and urine flow rate over both the acid and alkaline sides of pH 7.4. In order to elucidate mechanisms producing resistance changes, studies were conducted in kidneys with intact renal nerves, sectioned extrinsic nerves, and blocked or potentiated local nerves both with controlled and uncontrolled renal blood flow rate.

**METHODS**

Caliber changes in the renal vessels of laparotomized dogs during acute respiratory acidosis and alkalosis were inferred from changes in calculated renal vascular resistance. Arterial pressure, venous pressure, and urine flow rate were measured with blood perfusion rate maintained constant with a pump and also with blood flow rate uncontrolled.

Thirty-two mongrel dogs weighing 30 to 40 pounds were anesthetized with sodium pentobarbital. With the animal on its left side, the right kidney was exposed through a flank incision. A tracheal cannula was inserted. In order to assure adequate hydration, 5 per cent glucose in water was continuously infused intravenously at the approximate rate of 5 ml./min.

In the first series of experiments, renal blood flow rate was maintained constant while noting the effect of pH change upon renal artery and vein pressures and urine flow rate in kidneys that were innervated, denervated, and denervated and infused with phentolamine methanesulfonate. The renal artery and vein were exposed near the aorta and the vena cava. Blunt dissection was employed throughout in order to preserve as many nerve fibers as possible. The ureter was cannulated and the animal heparinized. The femoral artery was connected to the renal artery with a 400 cm. length of polyethylene tubing, 3 mm. O. D., which coursed through an independent Sigmamotor pump. The renal artery end of the polyethylene tubing was attached to a 1 inch length of high pressure rubber tubing and this was fitted to a right angle brass cannula. The cannula was inserted into the renal artery close to the aorta. The pump was immediately set in motion thereby supplying the kidney with arterial blood. Needles were inserted into the rubber tubing and renal vein for determination of renal artery and vein pressures. Pressures were measured utilizing a 0 to 75 cm. Hg resistance wire pressure transducer. The blood pump was adjusted so as to produce a mean renal artery pressure of approximately 80 to 100 mm. Hg. At this pressure, the flow ranged from 75 to 140 ml./min. in individual animals but was maintained constant throughout an experiment in any given animal.

The experimental sequence for acute variation of pH consisted of 4 consecutive 5 min. periods; an initial control period of spontaneous air breathing, ventilation with 20 per cent CO₂ in oxygen via a respirator, hyperventilation with air, and a final control period of spontaneous air breathing.
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**Fig. 1.** Average effect of acute pH change on renal vascular resistance, renal artery and vein pressures, and urine flow rate in 10 nerve intact and in 10 separate kidneys which were denervated, and denervated and phentolaminized. Renal blood flow rates were maintained constant at the average values indicated. Numbers with arrows are average pH values during initial control period, ventilation with 20 per cent CO₂, hyper-ventilation and final control period.

Pressures were measured at the first, third, and fifth minute of each period. Between the third and fifth minute, urine flow rate was measured and blood was withdrawn from the renal artery. Blood pH was immediately determined by a Beckman pH meter while maintaining the sample at 37 C. Ten animals with intact renal nerves were subjected to the above procedure.

In an additional 10 animals, the kidney was immediately denervated following exposure by meticulously removing all nerve fibers and other tissue from the artery, vein, ureter and hilar area. The blood pump was interposed between the femoral and renal arteries. The experiment was performed as outlined. In the same 10 kidneys, a 0.005 per cent solution of phentolamine methanesulfonate in isotonic saline was infused* into the rubber tubing just proximal to the renal artery cannula at the rate of 1 ml./min. The infusion was continuous while repeating the experimental sequence. In 3 of the 10 experiments 1 mg. of eserine salicylate was added to the remaining phentolamine solution (approximately 100 ml.). The infusion was continued at the

* Constant Infusion Machine, Model ES-4B, Engineering Specialties, Madeira, Ohio.
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Table 1.—Changes in Renal Resistance, Arterial Pressure, and Urine Flow Rate Following Change of pH from 7.0 to 7.6

<table>
<thead>
<tr>
<th>Nerves</th>
<th>Constant blood flow rate</th>
<th>Uncontrolled blood flow rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Renal resistance (mm. Hg/ml./min.)</td>
<td>Renal artery pressure (mm. Hg)</td>
</tr>
<tr>
<td>Intact</td>
<td>+0.43 ± 0.54†</td>
<td>+37 ± 45†</td>
</tr>
<tr>
<td>Denervated</td>
<td>+0.82 ± 0.71*</td>
<td>+79 ± 65*</td>
</tr>
<tr>
<td>Denervated Phentolaminized</td>
<td>+0.75 ± 0.51*</td>
<td>+74 ± 48*</td>
</tr>
</tbody>
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*p = <0.01.
† p = 0.05-0.01.

rate of 1 ml./min. while again repeating the experimental sequence. Total renal vascular resistance was calculated by dividing the pressure gradient from renal artery to vein by the blood flow rate and expressed as mm. Hg/ml./min.

In a second series of 12 experiments, pH was varied while observing urine flow rate from kidneys whose blood flow was not controlled. Catheters were inserted into the femoral artery and vein and advanced to the abdominal aorta and inferior vena cava for pressure measurements. The kidney was exposed, the ureter cannulated and the experimental sequence outlined above was carried out with the preparation innervated, denervated and denervated and phentolaminized.

RESULTS

Constant Blood Flow Rate. Figure 1 presents average absolute values for renal vascular resistance, blood pressure and urine flow rate in 3 preparations during various changes in pH. Table 1 summarizes the results in terms of magnitude and variability of change upon pH shift 7.0 to 7.6.

A significant increase in arterial pressure and calculated resistance was associated with pH change 7.0 to 7.6 in each of the 3 preparations. The changes were of lesser magnitude and regularity in nerve intact kidneys than in nerve sectioned or nerve sectioned phentolaminized kidneys. Changes were observed predominantly on the alkaline side of pH 7.3. Accompanying the elevation of arterial pressure and resistance was a significant increase in urine flow rate in each of the 3 preparations.

The addition of eserine to 3 kidneys in order to potentiate local parasympathetic activity resulted in changes in resistance, pressure, and urine volume which were not significantly different from those observed in denervated and denervated phentolaminized kidneys.

Uncontrolled Blood Flow Rate. Under the conditions of the study, a relationship between pH and urine flow rate was not apparent in kidneys not perfused with the blood pump. Average control values for pH, urine flow rate and aortic pressure in nerve intact kidneys were 7.38, 1.10 ml./min., and 119 mm. Hg respectively. Following 5 min. of ventilation with 20 per cent CO2, the values were 7.11, 0.75, and 101. Five minutes of hyperventilation with room air resulted in a pH increase to 7.6, but no further change in urine flow rate (table 1). Aortic pressure increased to 117 mm. Hg. After 5 min. of spontaneous ventilation with room air, the values for pH, urine flow rate and aortic pressure were 7.39, 0.95, and 125 respectively. The changes were not significantly different following denervation and denervation plus phentolamine (table 1).

DISCUSSION

These experiments demonstrate that decrease in hydrogen ion concentration results in active increase in renal vascular resistance, probably through some mechanism directly affecting vascular smooth muscle. This effect occurs predominantly on the alkaline side of pH 7.3 and is less apparent in nerve intact kidneys due to opposing effects produced by extrinsic nerves.

There can be little doubt that the resistance changes observed result from active changes in vascular geometry. Passive caliber changes due to varying transmural pressures cannot account for the observed changes in calculated...
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resistance since intraluminal pressure and resistance changes were directionally the same. Dynamic changes in blood viscosity cannot be considered as an initiating factor in the resistance changes reported since resistance increased with blood flow rate and hence velocity held constant. There remains only the conclusion that active changes in vascular muscle length and hence vessel radius initiated the observed resistance changes.

The resistance changes reported in the intact kidney appear to result from two opposing mechanisms, one directly affecting vascular smooth muscle and another less forceful one indirectly effecting muscle through extrinsic nerves. The conclusion regarding a direct muscular effect is based upon the fact that resistance changes persisted in the absence of central nervous connections, circulating and locally released epinephrine and norepinephrine, and following local parasympathetic potentiation. The conclusion regarding opposing central nervous effects is supported by the similarity of the resistance changes in all preparations with sectioned extrinsic nerves and the lesser magnitude of change in nerve intact kidneys.

Previous workers have suggested that the response of smooth muscle to pH change results from the antagonistic effect of an indirect sympathoadrenal discharge and some direct local effect. The present studies support this contention in part. The studies failed to demonstrate an adrenal effect in the dog kidney and demonstrated it only questionably in the foreleg.

The observation that large resistance changes do not occur on the acid side of pH 7.4 is in agreement with that reported by Dowds et al. The findings that the change occurs predominantly on the alkaline side is similar to that reported for the foreleg in the preceding paper.

These studies reveal differences in the response of total foreleg and total renal vascular resistance to pH change. Comparisons are permissible since the techniques employed and the range of pH change were similar. In denervated preparations, pH change effects large changes in renal vascular resistance and comparatively smaller changes in total foreleg resistance. Whereas a pH increase of as little as 0.3 pH unit might double renal vascular resistance, the same pH change might effect only a 20 per cent increase in total foreleg resistance. The influence of extrinsic nerves appears to be less effective in controlling antagonistic local changes in the kidney than in the foreleg. In the latter preparation, total resistance did not change significantly with nerves intact whereas resistance increased considerably in most nerve intact kidneys.

SUMMARY

The effect of pH change upon renal vascular resistance and urine flow rate has been studied in 32 laparotomized dogs. Blood pH was varied from 7.4 to 7.0 to 7.6 by ventilation with 20 per cent CO2 and hyperventilation over 5 min. periods. Observations were made with the nerves intact, following denervation and after denervation plus infusion of a sympatholytic and adrenolytic agent.

The results indicate that acute decrease of hydrogen ion concentration results in increased renal vascular resistance through some mechanism directly affecting vascular smooth muscle. This effect is less apparent in intact kidneys due to opposing effects produced by extrinsic nerves. The resistance change occurs predominantly on the alkaline side of pH 7.3 and is of considerably greater magnitude than in the foreleg. The study failed to demonstrate a relationship between blood pH and urine flow rate in the circulatory intact kidney.

Change in pH must be considered as one factor affecting renal resistance and hence blood flow rate, especially in denervated preparations.
quite per infusiones de un agente sympatholytic e adrenolytic.

Le resultatos indica que le reduction acute del concentration de ions de hydrogeno effectua un acrescite resistencia reno-vascular per le un o le altere mechanismo que affecte directemente le lisie musculos vascular. Iste effecto es minus apparente in renes intacte in consequentia del effectos contrari que es producite per nervos extrinsec. Le alteration del resistencia occurre predominantemente al latere alcalin de pH 7,3, e illo es de un magnitude considerablemente plus grande que in legamba anterior. Le studio monstrava nulle relation inter le pH sanguine e le fluxo de urina in renes a circulation intacte.

Alterationes de pH debe esser considerate como un factor que affecte le resistencia renal e assi le fluxo de sanguine, specialmente sub le conditiones de enervation experimental.

REFERENCE

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