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Effect of Renal Nerve Stimulation on Renal Blood Flow Autoregulation and Antinatriuresis During Reductions in Renal Perfusion Pressure (41238)

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Abstract. Renal nerve stimulation increases renal vascular resistance and decreases glomerular filtration rate and urinary sodium excretion. The purpose of this study was to determine whether neurally mediated changes in renal vascular resistance, glomerular filtration rate, and urinary sodium excretion at control renal perfusion pressure modified the autoregulation of renal blood flow and glomerular filtration rate and the antinatriuresis observed during reductions in renal perfusion pressure in pentobarbital-anesthetized dogs. Renal blood flow, glomerular filtration rate, and urinary sodium excretion were determined during stepwise reductions in renal perfusion pressure from 137 to 55 mm Hg (suprarenal aortic constriction) before and during electrical stimulation of the renal nerves at 0.5, 1.0, 2.0, and 4.0 Hz. In the absence of renal nerve stimulation, renal blood flow and glomerular filtration rate remained constant until renal perfusion pressure was reduced to 70 and 85 mm Hg, respectively. Urinary sodium excretion decreased linearly as renal perfusion pressure decreased. Renal nerve stimulation at 0.5, 1.0, 2.0, and 4.0 Hz increased renal vascular resistance and decreased glomerular filtration rate and urinary sodium excretion. These frequencies of renal nerve stimulation, however, did not alter the decreases in renal vascular resistance and glomerular filtration rate or the antinatriuretic response to stepwise reductions in renal perfusion pressure to 55 mm Hg. These data demonstrate that increased renal vascular resistance at either the afferent or efferent arteriole does not change the responses of these vessels to reductions in renal perfusion pressure. Renal nerve stimulation at frequencies which decrease urinary sodium excretion at control renal perfusion pressure also does not enhance the antinatriuretic response to reductions in renal perfusion pressure.

The renal vasculature has an intrinsic mechanism which maintains glomerular filtration rate and renal blood flow constant as renal perfusion pressure is reduced to approximately 100 and 70 mm Hg, respectively (1). Robertson *et al.* (2) have reported that the afferent arteriole is the primary locus for the decrease in renal vascular resistance during reduction of renal perfusion pressure. The interlobular artery also has been suggested as a possible preafferent arteriolar site which is responsive to decreases in transmural pressure within the renal vasculature (3).

Holdaas *et al.* (4) have used the latter observation that the interlobular arteries are vasoactive to propose that renal nerve stimulation may increase vascular resistance in the interlobular arteries resulting in decreased transmural pressure at the afferent arteriole and therefore vasodilation of this preglomerular vessel. In these circumstances (i.e., decreased afferent arteriolar resistance at control renal perfusion pressure), the maximal autoregulatory capacity of the kidney may be reduced. The major goal of this study was to determine whether renal nerve stimulation at frequencies which increased renal vascular resistance altered the autoregulation of renal blood flow and glomerular filtration rate during reductions of renal perfusion pressure. Renal nerve stimulation also has been shown to decrease urinary sodium excretion (5) by increasing proximal tubular sodium reabsorption (6). In addition, reduction of renal perfusion pressure decreases glomerular filtration rate and peritubular capillary hydrostatic pressure thereby promoting sodium reabsorption (7). The second goal of this study was to investigate whether renal nerve stimulation

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which decreases urinary sodium excretion at control renal perfusion pressure (5, 6) enhances the antinatriuetic response to decreasing renal perfusion pressure.

Methods. Experiments were conducted in 14 mongrel dogs weighing 15–25 kg. All animals were anesthetized with sodium pentobarbital (30 mg/kg iv). A cuffed endotracheal tube was inserted and the animals were artificially ventilated. A catheter was inserted via a femoral artery into the abdominal aorta and the tip positioned near the renal artery for the determination of renal perfusion pressure. Catheters also were inserted into femoral and jugular veins for the infusion of inulin and isotonic saline and for the administration of supplemental doses of anesthetic. In 9 of the 14 dogs studied, an inulin solution was infused at 1 ml/min to maintain plasma inulin concentration at approximately 30 mg/dl. Following induction of anesthesia, animals were infused with isotonic saline at 2.0 ml/min to maintain urine flow rate constant and replace blood and fluid losses.

The left kidney was exposed using a flank incision. An electromagnetic flowmeter probe was positioned on the left renal artery and the left ureter was cannulated. A mechanical occluder (Blalock clamp) was placed on the aorta proximal to the left renal artery. All visible renal nerves were isolated and severed. The distal renal nerve bundle then was placed on bipolar platinum electrodes so that the only sympathetic nerve activity passing to the kidney was evoked by electrical stimulation. A marked reduction in renal blood flow during strong renal nerve stimulation (10 V, 1 msec, 10 Hz) before and after each experiment verified that the renal nerves remained functional for the duration of the experiment.

At least 1 hr was allowed for stabilization following the completion of surgery. Control mean arterial pressure and renal blood flow initially were determined for 5 min. Renal perfusion pressure then was reduced to 115, 100, 85, 70, and 55 mm Hg by suprarenal aortic constriction. After each reduction of renal perfusion pressure, renal blood flow was allowed to stabilize for 2 min at which time mean arterial pressure and renal blood flow were recorded for another 5-min period. In 9 of the 14 dogs studied, urine also was collected during this 5-min period for the determination of urinary sodium excretion and glomerular filtration rate. An arterial blood sample (5 ml) was obtained during control and at renal perfusion pressures of 85 and 55 mm Hg. The aortic clamp then was released and 20 min was allowed for renal perfusion pressure and renal blood flow to stabilize at control values. Renal nerve stimulation (10 V, 1.0 msec) was begun at frequencies of 0.5, 1.0, 2.0, or 4.0 Hz and after 5 min the series of aortic constrictions was repeated. After each series of aortic constrictions, the aortic clamp was released and renal nerve stimulation was stopped for 20 min so that renal perfusion pressure and renal blood flow could return to control values. A different frequency of renal nerve stimulation then was initiated and the aortic constriction series was repeated. Reductions of renal perfusion pressure in the absence (control) and presence of renal nerve stimulation at various frequencies were randomized among all dogs studied.

Renal perfusion pressure was measured using a pressure transducer (Statham P23Db) and a direct writing oscillograph (Beckman Dynograph). Renal blood flow was measured with a square wave electromagnetic flowmeter and recorded on the oscillograph. Plasma and urinary sodium concentrations were determined by flame photometry. Plasma and urinary inulin concentrations were determined colorimetrically (8). Glomerular filtration rate was calculated as the clearance of inulin from the plasma. Data are presented as the mean ± standard error of the mean. Values were compared by a one-way analysis of variance and mean differences were tested by the Student–Neuman–Keuls procedure. The 0.05 level of probability was utilized as the criterion of significance.

Results. At control renal perfusion pressure (137–151 mm Hg), renal nerve stimulation decreased renal blood flow, increased renal vascular resistance, and decreased glomerular filtration rate and urinary sodium excretion in a frequency dependent manner (Table I). Since renal nerve stimulation alone altered these parameters of renal

TABLE I. EFFECT OF RENAL NERVE STIMULATION (RNS) AT 0.5, 1.0, 2.0, AND 4.0 HZ ON RENAL BLOOD FLOW (RBF), RENAL VASCULAR RESISTANCE (RVR), GLOMERULAR FILTRATION RATE (GFR), AND URINARY SODIUM EXCRETION ($U_{Na}V$) AT CONTROL RENAL PERFUSION PRESSURE

	RNS (Hz)				
	0	0.5	1.0	2.0	4.0
RBF (ml/min) $n = 14$	190 ± 15	169 ± 12*	156 ± 13*	140 ± 16*	146 ± 16*
RVR (mmHg/ml/min) $n = 14$	0.76 ± 0.05	0.89 ± 0.06	0.97 ± 0.09*	1.19 ± 0.13*	1.19 ± 0.15*
GFR (ml/min) $n = 9$	38 ± 3	38 ± 3	34 ± 3	27 ± 5*	22 ± 5*
$U_{Na}V$ (μeq/min) $n = 9$	107 ± 32	92 ± 36	85 ± 25*	61 ± 25*	24 ± 7*

* Significantly different from 0 Hz at $P < 0.05$.

function at control renal perfusion pressures, the responses to reductions in renal perfusion pressure before and during each frequency of renal nerve stimulation are presented as the percentage change from those values obtained at control renal perfusion pressure.

In the absence of renal nerve stimulation (0 Hz), renal vascular resistance decreased significantly as renal perfusion pressure decreased from 137 to 55 mm Hg (Fig. 1). At each renal perfusion pressure tested, the magnitudes of the decreases in renal vascular resistance were not different before (0 Hz) or during renal nerve stimulation at 0.5, 1.0, 2.0, or 4.0 Hz (Fig. 1).

In nine dogs, changes in glomerular filtration rate and urinary sodium excretion were determined in response to acute reductions in renal perfusion pressure before and during renal nerve stimulation. In the absence of renal nerve stimulation (0 Hz), glomerular filtration rate did not significantly decrease until renal perfusion pressure was reduced to 85 mm Hg (Fig. 2). In addition, during renal nerve stimulation at 0.5, 1.0, 2.0, and 4.0 Hz, the decreases in glomerular filtration rate in response to reductions of renal perfusion pressure were not different from those responses observed in the absence of renal nerve stimulation (Fig. 2).

The antinatriuretic responses of these nine dogs to decreasing renal perfusion pressure before and during renal nerve stimulation are shown in Fig. 3. Reduction of renal perfusion pressure alone (i.e., 0 Hz) decreased urinary sodium excretion at each perfusion pressure tested. Although renal nerve stimulation decreased urinary

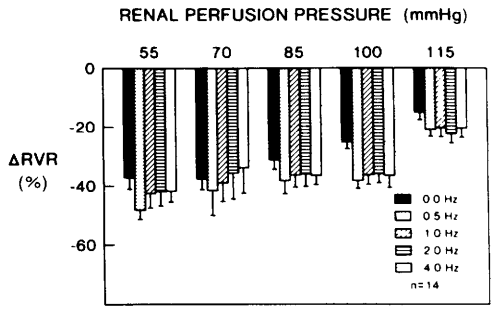

FIG. 1. Percentage decreases in renal vascular resistance (RVR) from control after reduction of renal perfusion pressure to 115, 100, 85, 70, and 55 mm Hg before (0 Hz) and during renal nerve stimulation at 0.5, 1.0, 2.0, and 4.0 Hz.

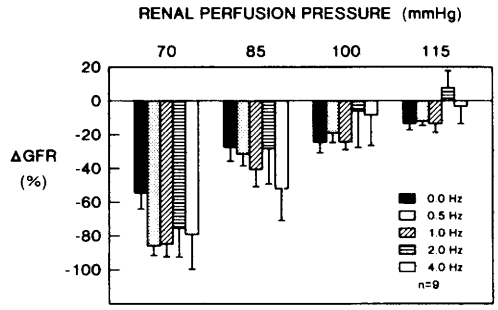

FIG. 2. Percentage decreases in glomerular filtration rate (GFR) from control after reduction of renal perfusion pressure to 115, 100, 85, and 70 mm Hg before (0 Hz) and during renal nerve stimulation at 0.5, 1.0, 2.0, and 4.0 Hz.

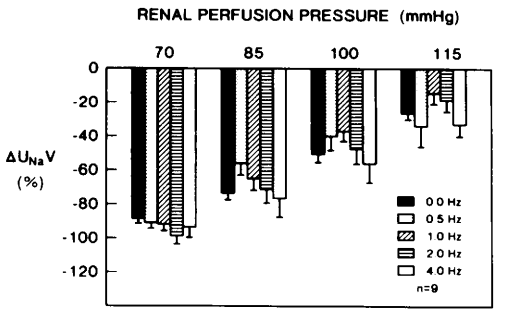

FIG. 3. Percentage decreases in urinary sodium excretion ($U_{Na}V$) from control after reduction of renal perfusion pressure to 115, 100, 85, and 70 mm Hg before (0 Hz) and during renal nerve stimulation at 0.5, 1.0, 2.0, and 4.0 Hz.

sodium excretion at control renal perfusion pressure (Table I), the presence of renal nerve activity at 0.5, 1.0, 2.0, and 4.0 Hz did not enhance the antinatriuretic responses to reductions of renal perfusion pressure over the entire range tested (Fig. 4).

Discussion. The renal vasculature maintains blood flow and glomerular filtration rate constant when renal perfusion pressure is reduced to approximately 70 and 100 mm Hg, respectively (1). Robertson *et al.* have shown that during reduction of renal perfusion pressure, the autoregulatory response of decreasing renal vascular resistance occurs primarily at the afferent arteriole (2). Kallskog *et al.* (3), however, have reported that norepinephrine infusion increases vascular resistance of the interlobular arteries. Therefore, preafferent arteriolar vasoconstriction would reduce perfusion pressure within the afferent arteriole which thereby could elicit preglomerular vasodilation (i.e., autoregulatory response). Thus, during interlobular artery vasoconstriction, partial afferent arteriolar vasodilation might reduce the maximal autoregulatory capacity of the renal vasculature.

The present study investigated this possibility by evaluating the autoregulation of renal blood flow before and during renal nerve stimulation at graded frequencies in pentobarbital anesthetized dogs. Stepwise reductions of renal perfusion pressure from 137 to 70 mm Hg (in the absence of renal nerve stimulation) progressively decreased renal vascular resistance (Fig. 1). Glomerular filtration rate remained constant until renal perfusion pressure was reduced to 85 mm Hg (Fig. 2). At control renal perfusion pressure, renal nerve stimulation at 0.5–4.0 Hz decreased renal blood flow and glomerular filtration rate in a frequency-dependent manner (Table I). When renal perfusion pressure was reduced in the presence of renal nerve stimulation (i.e., increased renal vascular resistance at control renal perfusion pressure), renal vascular resistance and glomerular filtration rate decreased equally to that observed in the absence of renal nerve stimulation (Figs. 1 and 2).

Using strong stimulation of renal efferent nerves which decreased renal blood flow at control renal perfusion pressure by 30–60% (i.e., increased renal vascular resistance), other investigators have examined the influence of renal nerve activity on renal blood flow autoregulation (4, 9–11). These studies have produced conflicting results. Kiil *et al.* (10) and Carlson and Schramm (11) reported that strong renal nerve stimulation did not alter renal blood flow autoregulation. Folkow and Langston (9), however, showed that increases in sympathetic nerve activity evoked by elevating intracranial pressure abolished renal blood flow autoregulation in vagotomized cats. Recently, Holdaas and colleagues working in the laboratory of Kiil (4) reported that direct electrical renal nerve stimulation impaired the autoregulation of renal blood flow. None of these investigators evaluated the effect of renal nerve stimulation on the autoregulation of glomerular filtration rate. The present data indicate that renal nerve stimulation over a range of frequencies which increased renal vascular resistance at control renal perfusion pressure by 17–56% does not impair the autoregulation of renal blood flow or glomerular filtration rate during reductions of renal perfusion pressure. Thus, during renal nerve stimulation, increased renal vascular resistance at the interlobular arteries, afferent or efferent arterioles does not alter the responses of these vessels to reductions in renal perfusion pressure.

Reduction of renal perfusion pressure also reduces urinary sodium excretion (Fig.

3) via decreases in glomerular filtration rate and by decreasing peritubular capillary hydrostatic pressure (7). It is now well established that low-frequency stimulation of the renal nerves also decreases urinary sodium excretion independent of any changes in renal hemodynamics or glomerular filtration rate (5). This antinatriuresis during renal nerve stimulation occurs at least in part by increasing proximal tubular sodium reabsorption (6). Therefore it was of interest to determine whether renal nerve stimulation enhanced the antinatriuresis observed during acute reductions of renal perfusion pressure.

At control renal perfusion pressure, stimulation of the renal nerves decreased urinary sodium excretion in a frequency-dependent manner (Table I). Similarly, in the absence of renal nerve stimulation (0 Hz), reduction of renal perfusion pressure to 70 mm Hg progressively decreased urinary sodium excretion (Fig. 3). The antinatriuretic responses observed during reduction of renal perfusion pressure before and in combination with renal nerve stimulation (0.5–4.0 Hz) were not different from each other (Fig. 3). Thus, although renal nerve stimulation decreases urinary sodium excretion at control renal perfusion pressure, stimulation of the renal nerves up to 4.0 Hz does not enhance the antinatriuretic response to decreasing renal perfusion pressure.

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