Renal Vascular Adjustments to Partial Renal Venous Obstruction in Dog Kidney

Ulrik Abildgaard, Ole Amtorp, Kim Agerskov, Erik Sjøntoft, Niels J. Christensen, and Ole Henriksen

Blood flow studies were conducted in neurolept anesthetized dogs to characterize the involvement of renal nerves in ipsilateral renal vasoconstriction seen during acute elevation of renal venous pressure above 30 mm Hg. Renal blood flow was measured electromagnetically. The vasoconstrictor response was almost abolished by acute surgical denervation of the kidney, since renal vascular conductance remained unchanged during renal venous pressure elevation from 30–60 mm Hg. However, following additional α-adrenoceptor blockade or chronic renal denervation, renal vascular conductance increased progressively during renal venous pressure elevation to 60 mm Hg. The effect of acute decapsulation of kidney was studied in another group of dogs. Decapsulation induced a vasoconstriction. The decrease in renal vascular conductance observed during renal venous pressure elevation was unaffected by acute surgical denervation of decapsulated kidney, but was almost abolished following additional α-adrenoceptor blockade or chronic denervation. In decapsulated chronically denervated kidney, the increase in renal vascular conductance during renal venous pressure elevation to 60 mm Hg was still present but considerably attenuated as compared with the chronically denervated kidney with intact capsule. The renin-angiotensin system did not participate in acute vascular adjustments to renal venous stasis in intact kidney or in decapsulated acutely surgically denervated kidney. The data favor the view that neurogenic and myogenic mechanisms significantly influence the vasoconstrictor response to renal venous pressure elevation in dog kidney. The neurogenic contribution to the vasoconstrictor response comprises intrarenal and extrarenal vasoconstrictor mechanisms evoked reflexively by renal venous pressure elevation, and the myogenic contribution to the vasoconstrictor response comprises opposing vasodilator mechanisms due to increase in renal interstitial tissue pressure during renal venous pressure elevation. (Circulation Research 1987; 61:194–202)

Results of previous studies indicate that renal venous pressure (RVP) elevation decreases renal blood flow (RBF) and renal vascular conductance (RVC) in dog and rat kidney. In a recent work from our laboratory, stepwise RVP elevation of more than 40 mm Hg was found to elicit an ipsilateral renal vasoconstriction. Haddy and Haddy et al suggested that the vasoconstrictor response to RVP elevation in dog kidney was due mainly to a nonlocal neurogenic reflex and that participation of a local neurogenic reflex was negligible. Their conclusion was based on the finding that the response was abolished by acute surgical denervation of the kidney. Our recent study indicated that stimulation of neural activity capable of producing vasoconstriction arises from the renal capsule and involves the spinal cord. The evidence for such a neurogenic reflex was that the application of lidocaine on the renal surface or the acute surgical denervation of the kidney largely abolished the vasoconstrictor response to RVP elevation.

The present study attempts to characterize more completely the involvement of renal nerves in ipsilateral renal vasoconstriction seen during acute RVP elevation. The effect of elevation of RVP confirmed our previous observations in innervated and acutely surgically denervated kidneys. Additional experiments were conducted to elucidate the effect of chronic renal denervation or pharmacologic blockade of α-adrenoceptors on the renal vascular response to elevated RVP. Finally, experiments were performed in decapsulated kidneys to determine whether the vasoconstrictor response could be eliminated by decapsulation and to elucidate the effect of the sympathetic nervous system on the vascular response to RVP elevation in decapsulated kidney.

Materials and Methods

Studies were performed on 62 mongrel dogs of either sex weighing 16–30 kg. The dogs were deprived of food overnight but had free access to water.

Experimental Preparation

Anesthesia was induced by diazepam (Stesolid R, Dumex, Denmark) 0.75 mg/kg and fentanyl (Haldid R, Janssen, Belgium) 0.70 mg/kg i.v., and after orotracheal intubation, anesthesia was maintained with 75% NO₂–25% O₂ using a constant volume respirator. Fentanyl and pancuronium bromide (Pavulon R, Organon, Holland) were infused throughout the experiment at a rate of 0.4 μg/kg/min and 1.6 μg/kg/min.
respectively. An intravenous infusion of Ringer's solution (0.2 ml/kg/min) was started immediately and continued at the same rate throughout the experiment. Body temperature was maintained at 38° C by external heating and was controlled by a thermocouple placed in the rectum.

From a right femoral cutdown, polyethylene catheters (5F) were advanced into the renal veins and into the abdominal aorta at the level of renal arteries. A Swan-Ganz thermodilution catheter (Gould, Inc., Cleveland, Ohio) was inserted through the right external jugular vein, and the tip was placed in the pulmonary artery. Catheters were connected to Statham pressure transducers (P23Db, Gould). All pressures were measured with reference to midaxillary line, set for each experiment. Cardiac output (CO) was measured recurrently during the experiment. Experimental dogs were excluded from the study due to stromal bleeding. Of 35 dogs, 2 were excluded from the study due to stromal bleeding.

Decapsulation of kidney (41 kidneys in 33 dogs) was performed by removing the capsule from at least 80% of the surface area including the poles. By means of ophthalmologic pincettes and scissors, the capsule was slit open in 0.5-cm 2 pieces and carefully removed. This procedure was done with minimal disruption of the renal nerves. Electromagnetic flow probes (Statham SN-68918, Gould) calibrated in vitro with whole blood were placed around renal arteries to measure RBF. Adjustable occluders were placed around the renal veins near the junction with the vena cava.

Through a median laparotomy, kidneys were mobilized from their retroperitoneal position. A segment of the renal arteries adjacent to the aorta was dissected free from surrounding tissue and renal veins with minimal disruption of the renal nerves. Electromagnetic flow probes (Statham SN-68918, Gould) calibrated in vitro with whole blood were placed around renal arteries to measure RBF. Adjustable occluders were placed around the renal veins near the junction with the vena cava.

Decapsulation of kidney (41 kidneys in 33 dogs) was performed by removing the capsule from at least 80% of the surface area including the poles. By means of ophthalmologic pincettes and scissors, the capsule was slit open in 0.5-cm 2 pieces and carefully removed. This procedure was done with minimal disruption of the stroma; no stromal bleeding was allowed. Of 35 dogs, 2 were excluded from the study due to stromal bleeding.

Surgical denervation of the kidney (52 kidneys in 38 dogs) was performed by cutting all visible nerves in the renal pedicle when they passed from the aorticorenal ganglion.

Throughout the experiments, mean aortic pressure (MAP), mean pulmonary artery pressure (MPAP), RVP, RBF, ECG, and body temperature were continuously recorded. CO was measured recurrently during each experiment. Experimental dogs were excluded from the study if MAP, MPAP, heart rate (HR), or CO changed more than 10% during the experiment. The tidal volume and the rate of the respirator were adjusted to maintain arterial blood pH 7.35–7.45, Pco2 30–40 mm Hg, and Po2 130–160 mm Hg.

**Experimental Procedure**

At reference RVP (3.2–6.0 mm Hg), baseline hemodynamic and respiratory variables were recorded. The investigation consisted of unilateral stepwise RVP elevation in 10 mm Hg increments to 60 mm Hg by manual constriction of the renal vein. At each pressure level, RVP was kept constant for 5 minutes. This procedure was chosen because in preliminary experiments steady RBF was achieved after 3–4 minutes at each new pressure level. RBF was measured at the end of the 5-minute period at each new pressure level and at 5 minutes after release of venous stasis.

**Experimental Protocol**

The dogs were allowed to stabilize for 60–90 minutes to recover from any surgical intervention. Table 1 summarizes the numerous experimental protocols.

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<tr>
<th>Group</th>
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<th>Id</th>
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</table>

1. kidney with intact capsule; II, decapsulated kidney; III, AIIA-treated kidney; a, control; b, acute surgical denervation; c, a-receptor blockade of the surgically denervated kidney; d, chronically denervated kidney.

Figures show the number of kidneys exposed to each intervention.
weeks after surgical denervation of the left kidney. On the day of experiments, the left kidneys were investigated. At the end of experiment, biopsies from left and right kidneys were taken. The biopsies were frozen at a temperature of −80°C and later analyzed for tissue concentration of norepinephrine and epinephrine by a single isotope-derivative technique according to Christensen et al.6

II. DECAPSULATED KIDNEY. The ability of decapsulated kidney to respond to vasodilatory and vasoconstrictive stimuli was tested in preliminary experiments. In 2 dogs, 2 mg papaverine were injected into the renal artery of kidney with intact capsule and in 2 other dogs into decapsulated kidney. Further, in 2 dogs, 2 μg norepinephrine were injected into the renal artery of kidneys with intact capsule and in 2 other dogs into decapsulated kidney. Changes in RBF were registered.

a) Control. Nine dogs were used. The right kidneys were decapsulated. Measurements were performed 60 minutes after decapsulation and during subsequent RVP elevation.

b) Acute surgical denervation. Eight dogs were used. The right kidneys, which were acutely surgically denervated and decapsulated, were investigated.

c) Acute surgical denervation with local α-adrenoceptor blockade. Ten dogs were used. The left kidneys were acutely surgically denervated and decapsulated. Phentolamine was infused into the left renal artery as described above. Measurements were performed before and after decapsulation, after phentolamine infusion, and during subsequent RVP elevation.

d) Chronic denervation. The 8 dogs used in IIIb) were studied 2–4 weeks after surgical denervation of the left kidneys. On the day of experiments, right contralateral kidneys were acutely surgically denervated, and these kidneys were used in IIIb) 60–90 minutes after decapsulation of both kidneys. Measurements were performed 90 minutes apart on both kidneys. The order in which left and right (IIb) kidneys were investigated was determined by randomization. At the end of experiments, biopsies were taken from both kidneys for determination of norepinephrine and epinephrine as described above.

In 16 additional experiments performed on kidney with intact capsule, changes in kidney weight during unilateral RVP elevation to 60 mm Hg were determined as the difference in weight between ipsilateral kidney and contralateral kidney subjected to reference RVP. In 8 other experiments, changes in weight of decapsulated kidney during unilateral RVP elevation to 60 mm Hg were determined as the difference in weight between ipsilateral kidney and contralateral control kidneys.

III. ANGIOTENSIN II (ALLI) BLOCKADE.

a) Kidney with intact capsule. Six dogs were used. (1-sarcosine 8-alanine) angiotensin II (Sarenin R, Röhm Pharma, FRG) at a rate of 0.50 μg/kg/min in 0.15 ml/min isotonic saline was infused through an angled 21-gauge needle into the right renal artery. After 90 minutes and during continued infusion of AIIA, the right kidney was investigated. Measurements were performed before and during AIIA infusion and during subsequent RVP elevation at 10 mm Hg increments to 60 mm Hg. When RBF and RVC were normalized after release of renal venous stasis, the adequacy of AIIA blockade was tested by injection of 50 ng AII (Hypertensin R, Ciba Geigy) into the right renal artery; no significant changes in RBF were disclosed. In contrast, close intra-arterial injection of AII into the contralateral left kidney caused reduction in RBF of 62% (53–79%).

b) Decapsulated kidney. Six dogs were used. The kidneys were decapsulated and acutely surgically denervated. AIIA was infused into the right renal artery as described above. RVP was elevated stepwise to 60 mm Hg and RBF recorded. Injection of 50 ng AII into the right renal artery caused no reduction in RBF, confirming the adequacy of right kidney AIIA blockade, whereas injection of AII into the left kidney caused reduction in RBF of 71% (57–82%).

Calculations

Renal vascular conductance (RVC) was calculated as the recorded RBF divided by the difference between mean arterial pressure and RVP.

Renal hemodynamic responses to RVP elevation were measured by taking the average value at reference RVP before and 5 minutes after RVP elevation and comparing it with the values obtained during RVP elevation. There were no significant differences between prestasis and posttasis values.

Statistics

Student's t test for paired and unpaired data, Dunnett’s test for multicomparsion of the different experiments with control experiments,7 and an analysis of variance in a two-way factorial (2 × 4) design including the Bonferroni method for multiple comparison24 were used for statistical analyses. The factorial design was chosen to determine if the difference in change of RVC during RVP elevation between kidney with intact capsule and decapsulated kidney (the decapsulation effect) was the same in the four experimental conditions: control, acute surgical denervation, acute surgical denervation with α-adrenoceptor blockade, chronic denervation (the denervation effect). The level of significance was 0.05. Values are expressed as mean ± SEM.

Results

MAP, RBF, and RVC at reference RVP were not statistically different in any of the experimental groups in series I, II, and III of control experiments (Ia). Tables 2 and 3 present absolute values of MAP, RBF, and RVC during RVP elevation from reference pressure level to 30 mm Hg and 60 mm Hg in kidney with intact capsule (series I) and decapsulated kidney (series II), respectively.

I. KIDNEY WITH INTACT CAPSULE

a) In control kidney (Table 2, Figure 1), RVC increased significantly by 14.0 ± 4.8% when RVP was elevated to 30 mm Hg but was significantly reduced by
### Table 2. Hemodynamics in Kidneys With Intact Capsule

<table>
<thead>
<tr>
<th>Condition</th>
<th>CX</th>
<th>AC.DX.</th>
<th>AC.DX.</th>
<th>CHR.DX.</th>
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<td>REF</td>
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<tr>
<td>MAP (mm Hg)</td>
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<td>112±7</td>
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<td>RBF (ml min⁻¹)</td>
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<td>RVC (ml min⁻¹ mm Hg⁻¹)</td>
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<td>30 mm Hg</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>108±4</td>
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<tr>
<td>RBF (ml min⁻¹)</td>
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<td>240±21</td>
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<td>RVC (ml min⁻¹ mm Hg⁻¹)</td>
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<td>3.10±0.33*</td>
<td>3.02±0.26*</td>
<td>2.55±0.24*</td>
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<td>60 mm Hg</td>
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</tr>
<tr>
<td>MAP (mm Hg)</td>
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<td>RBF (ml min⁻¹)</td>
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<td>RVC (ml min⁻¹ mm Hg⁻¹)</td>
<td>1.78±0.20*</td>
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Mean aortic pressure (MAP), total renal blood flow (RBF), and renal vascular conductance (RVC) in control kidneys with preserved innervation (CX), acutely surgically denervated kidneys (AC.DX.), acutely surgically denervated kidneys with α-receptor blockade (AC.DX.α), and chronically denervated kidneys (CHR.DX.) at reference conditions (REF) and during subsequent renal venous pressure (RVP) elevation to 30 mm Hg and 60 mm Hg.

REF is the average value at reference renal venous pressure before and five minutes after renal venous pressure elevation.

*p<0.05, REF vs. 30 mm Hg and REF vs. 60 mm Hg. Values are expressed as mean ± SEM.

24.0 ± 4.6% of reference value when RVP was raised to 60 mm Hg.

b) Acute surgical denervation (Table 2, Figure 1) did not change RBF or RVC when compared with ipsilateral values obtained before denervation (230 ± 18 ml/min and 2.29 ± 0.20 ml/min/mm Hg, not significantly different from those in control kidney). RVC increased significantly by 26.0 ± 7.0 when RVP was stepwise elevated to 30 mm Hg. When RVP was further elevated to 60 mm Hg, there was a statistically insignificant decrease in RVC. When compared with the reference value, RVC significantly increased 18.4 ± 6.1% at 60 mm Hg RVP.

c) α-Receptor blockade of acutely surgically denervated kidney (Table 2, Figure 1) caused no significant changes in arterial or venous mean pressures or in reference values of RBF and RVC when compared with ipsilateral values before α-adrenoceptor blockade (223 ± 17 ml/min and 2.21 ± 0.19 ml/min/mm Hg, not significantly different from those in control kidney). Following local α-receptor blockade, RVC increased significantly by 24.1 ± 6.2% when RVP was elevated from reference RVP to 30 mm Hg. When RVP was further elevated to 60 mm Hg, RVC increased progressively; at 60 mm Hg RVP, RVC increased by 62.0 ± 10.5% of reference value.

d) In chronically denervated kidney (Table 2, Figure 1), RVC increased significantly by 21.7 ± 6.2% when RVP was elevated to 30 mm Hg. RVC increased progressively when RVP was further raised to 60 mm Hg. At 60 mm Hg RVP, RVC increased by 62.0 ± 10.5% of reference value.

II. Decapsulated Kidney

Close intra-arterial injection of 2 mg papaverine into kidney with intact capsule and into decapsulated kidney caused increases in RBF of 127–161% and 154–183%, respectively; injection of 2 μg norepinephrine into renal arteries of kidney with intact capsule and into decapsulated kidney caused decreases in RBF of 38–45% and 33–47%, respectively.

a) In the decapsulated control kidney (Table 3, Figure 1), RVC remained unchanged when RVP was elevated to 30 mm Hg but was significantly reduced by...
42.1 ± 8.2% of reference value when RVP was further raised to 60 mm Hg.

b) Acute surgical denervation of the decapsulated kidney (Table 3, Figure 1). Values of RBF and RVC obtained after acute surgical denervation did not differ significantly from those preceding acute surgical denervation of decapsulated right kidney (217 ± 24 ml/min, 2.05 ± 0.23 ml/min/mm Hg). RVP elevation caused changes in RBF and RVC that were qualitatively and quantitatively similar to the changes observed in decapsulated control kidney.

c) Acute surgical denervation with local α-adrenoceptor blockade of decapsulated kidney (Table 3, Figure 1). In this group of experiments, the effect of denervation on RBF and RVC was elucidated by comparing ipsilateral predecapsulation with postdecapsulation values. Decapsulation of the acutely surgically denervated kidney reduced RBF significantly from 241 ± 16 ml/min to 200 ± 16 ml/min and RVC significantly from 2.35 ± 0.18 ml/min/mm Hg to 1.93 ± 0.18 ml/min/mm Hg. Close intra-arterial infusion of phenolamine into the acutely surgically denervated decapsulated kidneys caused no changes in arterial and venous mean pressures, but phenolamine increased RBF and RVC significantly to 227 ± 22 ml/min and 2.26 ± 0.23 ml/min/mm Hg, respectively. Following local α-receptor blockade, RVC increased significantly by 19.1 ± 5.6% when RVP was raised to 30 mm Hg. At 60 mm Hg RVP, RVC significantly increased by 23.1 ± 10.7% of reference value.

d) In the chronically denervated and decapsulated kidney (Table 3, Figure 1), RVC increased significantly by 20.8 ± 6.5% when RVP was raised from reference pressure level to 30 mm Hg, and by 23.5 ± 4.3% when RVP was further raised to 60 mm Hg. At 60 mm Hg RVP, RVC significantly increased by 16.1 ± 5.3% as compared with the reference value.

Figure 2 presents individual changes in RVC when RVP was elevated from reference pressure level to 30 mm Hg and from reference pressure level to 60 mm Hg in the experimental series I and II. The analysis of variance for RVC change during RVP elevation to 30 mm Hg indicates a significant effect of decapsulation (sums of squares, SS, 1.199; degrees of freedom, DF, 1; F, 6.3 at p<0.05), with an estimated mean difference in RVC changes between kidney with intact capsule and decapsulated kidney of 0.30 ± 0.09 ml/min/mm Hg (mean ± 1 SD). No significant interaction between the decapsulation effect and the denervation effect was found (SS, 0.771; DF, 3; F, 1.4 at p>0.05), and no significant differences in changes of RVC were found among the 4 experimental conditions (SS, 1.212; DF, 3; F, 2.1 at p>0.05); i.e., no significant denervation effect was found.

The analysis of variance for the changes in RVC during RVP elevation from reference pressure level to 60 mm Hg, indicates a significant decapsulation effect (SS, 4.500; DF, 1; F, 12.0 at p<0.01), with an estimated mean difference in RVC changes between kidney with intact capsule and decapsulated kidney of 0.62 ± 0.15 ml/min/mm Hg (mean ± 1 SD). A significant interaction between decapsulation effect and denervation effect was found (SS, 26.3; DF, 3; F, 2.34 at p<0.01) is not the same in kidney with intact capsule and in decapsulated kidney. By the Bonferroni method of multiple comparison, changes in RVC during RVP elevation to 60 mm Hg were separately elucidated in kidney with intact capsule and decapsulated kidney. Results of t tests are shown in Figure 2.

During unilateral RVP elevation to 60 mm Hg, the weight increase of 8 decapsulated kidneys was 74.7 ± 5.1%, significantly higher than the increase of 28.3 ± 4.1% in 16 kidneys with intact capsule.

Tissue concentrations of norepinephrine and epinephrine in the 8 kidneys with preserved innervation were 394 ± 47 ng/g and 21 ± 4 ng/g and in the 8 acutely

Table 3. Hemodynamics in Decapsulated Kidneys

<table>
<thead>
<tr>
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<th>DC.X</th>
<th>DC.AC.DX.</th>
<th>DC.AC.DX.α</th>
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<tr>
<td>MAP (mm Hg)</td>
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<td>RBF (ml min⁻¹)</td>
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</table>

Variables at reference conditions (REF) and during subsequent renal venous pressure elevation in decapsulated kidneys with preserved innervation (DC.X), acutely surgically denervated (DC.AC.DX.), acutely surgically denervated with α-receptor blockade (DX.AC.DX.α) and chronically denervated (DC.CHR.DX.).

Symbols and abbreviations as in Table 2. Values are expressed as mean ± SEM.
a) Kidney with intact capsule. RVC increased significantly from 2.43 to 3.04 ml/min/mm Hg (25.1 ± 6.1%) when RVP was elevated to 30 mm Hg, but RVC was significantly reduced to 1.77 ml/min/mm Hg (27.1 ± 5.3% of reference value) when RVP was elevated to 60 mm Hg. These changes were not significantly different from those obtained in control kidney.

b) Decapsulated kidney. RVC remained unchanged when RVP was elevated to 30 mm Hg (from 2.33 ± 0.24 to 2.30 ± 0.38 ml/min/mm Hg), but RVC was significantly reduced to 1.63 ± 0.25 ml/min/mm Hg (30.1 ± 7.9% of reference value) when RVP was elevated to 60 mm Hg. These changes were not significantly different from those obtained in decapsulated acutely surgically denervated kidney without AII blockade.

**Discussion**

*Role of a Local Sympathetic Reflex Mechanism for Vasoconstriction Induced by Renal Venous Stasis*

Responses that occurred in decapsulated kidney to vasodilatory and vasoconstrictive stimuli as produced by injection of papaverine, AII, and norepinephrine into the renal artery were similar to those obtained in kidney with intact capsule, validating the use of the decapsulated kidney model.

Our observations in decapsulated kidney demonstrate that RVP elevation to 60 mm Hg elicits an ipsilateral renal vasoconstriction. This vasoconstrictor response was completely abolished by close intra-arterial infusion of phentolamine into the renal artery and by chronic denervation of the kidney. This shows that the vasoconstriction is due to sympathetic reflex mechanisms. A crucial point for understanding the nature of this reflex is our finding that the vasoconstrictor response is preserved following acute surgical denervation of the decapsulated kidney. Tissue concentration of norepinephrine was considerably lower in chronically denervated kidney than in both acutely surgically denervated kidney and kidney with preserved innervation. This suggests that effective denervation of distal sympathetic nerve fibers was achieved following chronic denervation, whereas acute surgical denervation leaves distal nerve fibers functionally intact. Therefore, the finding that chronic denervation completely abolished the vasoconstrictor response, still present following acute surgical denervation of decapsulated kidney, supports the idea that vasoconstrictor response to RVP elevation in decapsulated kidney is due mainly to a local sympathetic reflex mechanism (Figure 3).

The effect of local α-adrenoceptor blockade was taken to constitute an acute denervation of the entire sympathetic nerve tree in the kidney. Injection of 2 μg norepinephrine close intra-arterially into kidney treated with phentolamine (5 μg/kg/min) for 45 minutes did not change RBF, indicating the adequacy of α-adrenoceptor blockade. It should be stressed that the effect of phentolamine cannot be explained by a direct inhibition of myogenic activity of vascular smooth
muscle cells because the local maximum concentration of the drug would be less than $10^{-6}$ M, a dose that does not affect myogenic activity. Taken together, these results indicate that vasoconstriction induced in decapsulated kidney during RVP elevation is due to a local $\alpha$-adrenergic reflex mechanism. Distension and stimulation of mechanoreceptors in the venous bed may have elicited this vasoconstrictor response in small arteries and arterioles by means of a local sympathetic axon reflex mechanism, as demonstrated in muscle and subcutaneous tissue in the dog hind leg. Alternatively, the distension of renal tissue in decapsulated kidney, as evidenced by the pronounced increase in kidney weight during RVP elevation with stimulation of mechanoreceptors located in the renal parenchyma, may have contributed to the vasoconstriction. This interpretation was supported by the finding that decapsulation induced a vasoconstriction that could be abolished by intra-arterial infusion of phentolamine.

**Role of a Sympathetic Reflex Mechanism Comprising the Spinal Cord for Renal Venous Stasis Induced Vasoconstriction**

RVP elevation to 60 mm Hg in kidney with intact capsule and preserved innervation elicited an ipsilateral renal vasoconstriction. Similar findings have been reported by Haddy,1 Haddy et al,2 Hayase,13 and Hirano14 for the dog and by Dilley et al1 for the rat. In the present study, the vasoconstrictor response in kidney with intact capsule was partly abolished by acute surgical denervation, suggesting that this response to RVP elevation involves spinal or supraspinal neural vasoconstrictor mechanisms as suggested by Haddy1 and Haddy et al.2 A recent study from our laboratory suggests that this extrarenal neural reflex is elicited from the renal capsule (Figure 3), since topical application of lidocaine on the renal surface blocked the ipsilateral renal vasoconstriction.3

The question arises why the results from the acutely surgically denervated decapsulated kidneys differed from those obtained in the acutely surgically denervated kidneys with intact capsule. The data showed that RVP elevation to 60 mm Hg caused an attenuated weight increase in kidneys with intact capsule as compared with decapsulated kidneys. This could explain why the renal capsule inhibits a local sympathetic reflex mechanism since stimulation of intrarenal mechanoreceptors by distension of renal tissue was largely avoided.

**Contributory Role of a Myogenic Mechanism**

Observations of the kidney with intact capsule show that RVP elevation to 30 mm Hg causes an ipsilateral vasodilation, which is in agreement with previous findings.15,16 This vasodilation was essentially unaffected by both acute and chronic renal denervation and $\alpha$-adrenoceptor blockade, suggesting that a local "non-neurogenic" mechanism may contribute to the vasodilation. Partial obstruction of a renal vein produces an increase in renal interstitial pressure as measured in the subcapsular space in both dogs17 and rats.18,19 Decreasing transmural pressure in small arteries and arterioles by selectively elevating interstitial pressure should cause vasodilation by an intrinsic myogenic mechanism.20-25 Thus, the observed increase in RVC during RVP elevation to 30 mm Hg was probably the result of a myogenic vasodilation due to an increase in interstitial pressure. RVC increased progressively when RVP was further raised to 60 mm Hg in kidneys with intact capsule and chronic renal denervation or pharmacologic blockade of $\alpha$-adrenoceptors but not following acute surgical denervation. This demonstrates that an appropriate vasodilation occurred during RVP elevation when local neural vasoconstrictor reflex mechanisms were completely blocked. However, in acutely surgically denervated kidneys with intact capsule, RVC remained essentially unchanged in the RVP interval from 30–60 mm Hg; this observation suggests that in these kidneys some increased activity in intrarenal $\alpha$-adrenergic vasoconstrictor fibers actually occurred, but it was counteracted by a "non-neurogenic" vasodilation due to myogenic mechanisms.

The increase in RVC during RVP elevation to 30 mm Hg was absent in decapsulated kidney with preserved innervation and after acute surgical denervation; furthermore, in the chronically denervated kidneys, as well as following local $\alpha$-adrenoceptor blockade, we found that RVP elevation to 60 mm Hg caused a much attenuated increase in RVC in decapsulated kidney. It is, therefore, tempting to speculate that the increment in interstitial pressure and, thereby, the decrement in transmural pressure in small arteries and arterioles during partial renal venous obstruction is less pronounced in decapsulated kidney than in kidney with intact capsule, which may explain that part of the decapsulation effect is mediated by intrinsic myogenic mechanisms.
Role of the Renin-Angiotensin System in Acute Vascular Adjustments to Renal Venous Stasis

Kastner et al. and Kopp et al. have shown that RVP elevation increases renin output as measured in venous effluent blood from dog kidney. Some investigators have suggested that All acts primarily on the afferent arteriole and mediates tubuloglomerular feedback control on glomerular filtration rate, but other investigators have suggested that the potent constrictor-action of All is confined primarily to the efferent arterioles with almost no direct action on preglomerular vessels. Although controversies exist as to the influence of intrarenal All activity, part of the acute vascular adjustments to RVP elevation might be due to intrarenally produced All. To elucidate the role played by All in extrarenal as well as intrarenal sympathetic components of the vasoconstrictor response to RVP elevation above 30 mm Hg or the vasodilator response to RVP elevation to 30 mm Hg, blockade of intrarenal All during graded renal venous stasis was performed. The study was designed so that the action of intrarenally produced All could be investigated by local administration of All, suitable to vascular action of All, since the drug has no agonist effect on renal vasculature as demonstrated in isolated dog kidney depleted of renin. The dose of All was chosen to produce maximal All receptor blockade as confirmed by its ability to block selectively the renal vasoconstrictor effect of close intra-arterial injection of All. Injection of All into the renal artery of the contralateral kidney, produced a significant vasoconstriction indicating that an insignificant or no spillover of All had occurred from the ipsilateral kidney. During RVP elevation in the AllA-treated intact kidney (Ill) and the AllA-treated decapsulated kidney (IIlb), the pattern of responses were qualitatively similar to the respective responses obtained in intact kidney without AllA (Ia) and decapsulated kidney without AllA (IIb). Thus, these data provide no evidence for a contributory role played by intrarenal All formation to a myogenically mediated increase or a neurogenically mediated decrease in RVC induced by RVP elevation.

Hinshaw et al. and Kastner et al. failed to demonstrate a vasoconstrictor response to stepwise RVP elevation up to 50-70 mm Hg in the intact dog kidney with preserved innervation. The discrepancy may be explained by differences in experimental conditions, including the anesthesia used. A recent study suggests that pentobarbital anesthesia almost abolishes the myogenic mechanism is less sensitive to barbiturate than the neurogenic vasoconstrictor response. Hebert et al. did not find any significant changes in RBF when dog kidney was decapsulated; however, these dogs were pentobarbital anesthetized. In summary, data from the present study and those from our earlier study seem to indicate that acute elevation of RVP above 30 mm Hg excites intrarenal and extrarenal neural reflexes that cause ipsilateral renal vasoconstriction, the latter initiated by distension and stimulation of mechanoreceptors located in the renal capsule, the former from mechanoreceptors located in renal parenchyma. The most striking feature during acute RVP elevation to 30 mm Hg was the pronounced increase in RVC. In the absence of neural vascular control, increase in RVP to 60 mm Hg produced an even more intense increase in RVC. This vasodilation is thought to be due to myogenic vasodilation as schematically presented in Figure 3.

Thus, renal circulatory adjustments to gradual RVP elevation is apparently determined by a balance between neural α-adrenergic vasoconstrictor and myogenic vasodilator forces.

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References


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