Bioassay in Vivo for Circulating Vasoactive Agents after Renal Artery Constriction in Dogs

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SUMMARY. We used the gracilis muscle vascular bed to bioassay blood from the two renal veins, vena cava, and aorta continuously for the presence of vasoactive agents before and for 45 minutes after partial occlusion of the left renal artery in dogs. Compared to comparable blood samples from control dogs, left renal venous, vena caval, and aortic blood, but not right renal venous blood, from dogs with arterial constriction developed vasoconstrictor activity. This was associated with increased renin concentration in plasma from the left renal vein and the vena cava and an increase in systemic arterial pressure. In dogs pretreated with indomethacin, blood from the right renal artery also showed vasoconstrictor activity. Pretreatment with antirenin serum abolished all of the differences between control and experimental dogs. These findings suggest that during acute unilateral renal artery constriction the constricted kidney releases renin and the contralateral kidney releases prostaglandins in sufficient quantity to produce systemic vascular effects.

Removal of the contralateral kidney intensifies the hypertension; thus the presence of an intact contralateral kidney may attenuate the hypertension, perhaps by releasing antihypertensive substances. In this regard, it has been demonstrated recently that vasoconstrictor prostaglandins are released by both kidneys following acute unilateral renal artery constriction in dogs; prostaglandins in renal venous blood from the contralateral kidney were shown to be greater than those from the renal artery in the same dogs.

DATA FROM a number of laboratories indicate that the early development of hypertension following unilateral renal artery constriction is associated with increased renal release of renin and systemic generation of angiotensin II. 1, 2, 3, 4 L. A study of this interaction involves the relationship between the contralateral kidney and the renin concentrating effect of the vena cava. 1, 2, 3, 4

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Supported by U.S. Public Health Service Grant HL-15146 from the National Heart and Lung Institute and by a research grant from the Michigan Heart Association.

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blood were identified by chemical characterization as well as by superperfusion of nonvascular smooth muscle. Another group of investigators directly bioassayed renal venous blood in the hindpaw vascular bed of the dog following reduction of renal artery pressure and observed that hindpaw vascular resistance was reduced and vascular responses to sympathetic nerve stimulation were depressed. These effects could be removed by initial passage of the renal venous blood through the lung, suggesting that the active agent was prostaglandin. These investigators did not bioassay venous blood from the opposite untouched kidney.

In the present study we used the vascular bed of the isolated gracilis muscle to bioassay venous blood from both kidneys, the vena cava, and the aorta following partial constriction of one renal artery. We also studied the effects on the responses of pretreatment with antirenin and with indomethacin. Our results suggest that, following acute unilateral renal artery constriction, the ipsilateral kidney releases renin and the contralateral kidney releases prostaglandins in sufficient quantity to produce systemic vascular effects. Our results support the hypothesis that prostaglandins may be involved in the antihypertensive function of the contralateral untouched kidney in early two-kidney Goldblatt hypertension.

Methods

Sixty-eight healthy, male, mongrel dogs, weighing 18–28 kg, were anesthetized with sodium pentobarbital (35 mg/kg, iv) and were mechanically ventilated (Harvard apparatus) to maintain an arterial pH of 7.39–7.41. All initial surgical preparations were similar. The right gracilis muscle was isolated surgically except for the main gracilis artery and vein. Both ends of the muscle were tied to exclude collateral flow. The muscle was denervated by cutting the gracilis nerve. The temperature of the gracilis muscle preparation was maintained at 37°C by a heat lamp and the preparation was kept moist with saline at 37°C. An externally adjustable clamp was placed on the left renal artery through a midline abdominal incision. Both renal veins and the vena cava were cannulated (PE 240, Clay-Adams) through branches of the femoral vein. The tip of the inferior vena cava catheter was located 3–4 inches upstream from the openings of the renal veins. A fourth catheter of the same size was passed through the femoral artery into the abdominal aorta. The four catheters were connected to a manifold (Fig. 1) that permitted separate bioassay of blood from each source. Blood from the remaining catheters drained into a reservoir. From the reservoir the blood was returned via a pump into the dog’s external jugular vein. Aortic blood pressure was recorded continuously through a T-tube connected to the femoral artery catheter.

After surgery, a period of 30 minutes was allowed for hemostasis. Then heparin (5 mg/kg, iv) was administered. The gracilis artery was cannulated, and the denervated, collateral-free gracilis muscle was pump-perfused (Sigmamotor) at constant flow sequentially with blood from the left renal vein (LRV), right renal vein (RRV), and the vena cava (VC) catheters. Gracilis perfusion pressure, monitored downstream from the pump with a Statham P23Gb pressure transducer, was set to approximate aortic pressure in each dog by adjusting pump flow. Thereafter, pump flow was not changed during the experiment (pump flow was measured with a calibrated cylinder and stopwatch at the end of each experiment). Blood from the gracilis muscle drained through the intact gracilis vein. The duration of gracilis perfusion with blood from each vessel was that which established a steady state perfusion pressure or 10 minutes, whichever occurred first. During an initial control period these sequential perfusions were repeated in the same order until two consecutive perfusion pressures during perfusion with blood from the same vessel were within ±10 mm Hg of each other. Net perfusion pressures (perfusion pressure minus pressure drop across gracilis artery cannula) for each vessel blood during the control period were averaged.

At the end of each experiment sodium nitroprusside, 0.005 mg, was injected into the rubber tubing upstream from the pump to test whether the vascular bed of the muscle still was capable of vasodilation. The gracilis muscle then was excised and weighed to the nearest 0.5 g. Perfusion flow rate in ml/min per 100 g of gracilis muscle was calculated.

EXPERIMENTS

Three types of experiments were performed. In the first (group A), the left renal artery was partially constricted while blood from the LRV was being bioassayed. Then blood from the RRV, the VC, and the aorta was sequentially bioassayed, as had been done during the control period. In the second (group B), before the left renal artery was constricted, the dogs were pretreated with antirenin serum. Then the bioassay procedures were carried out as for group A. The purpose of group B experiments was to determine whether the renin-angiotensin system played a role in the bioassay responses we had observed with group A. In the third type of experiment (group C), the dogs received an infusion of indomethacin before renal artery constriction.
Then the bioassay procedures were carried out as in group A. The purpose of group C experiments was to determine whether prostaglandins played a role in the bioassay responses we had observed with group A. Detailed protocols of these experiments were as follows:

**Group A.** In 12 dogs (experimental group), after a control perfusion period (see above), the left renal artery was rapidly constricted by adjusting the clamp until the artery was completely occluded. The clamp then was opened quickly to produce a 2-mm gap. In 12 other dogs (control group), after a similar control perfusion period, the clamp was handled but the renal artery was not constricted (sham constriction). During a 45-minute period following constriction (or sham constriction), the gracilis muscle was perfused with blood from the LRV, the RRV, the VC, and in some dogs from the aorta. Steady state perfusion pressure was recorded at least twice during perfusion with blood from each vessel (see above).

Net perfusion pressures in each dog were plotted against time. From these plots we derived percent changes in gracilis perfusion pressures at standardized time intervals following constriction (or sham constriction) of the left renal artery (Fig. 2). Within each group of dogs, percent changes in gracilis perfusion pressure produced by blood from the various vessels were compared with one another by paired Student's t-test. Percent changes in perfusion pressure in experimental dogs were compared with corresponding values in control dogs by nonpaired Student's t-test.

Blood from the LRV produced gracilis perfusion pressures that were higher than those produced by RRV blood. These differences were maximal about 25 minutes after renal artery constriction. Therefore, samples of LRV, RRV, VC, and aortic blood were collected anaerobically at that time and hematocrit, pH, PO₂, PCO₂, and serum electrolytes 25 minutes after renal artery manipulation.

**Group B.** Seven experimental and seven control dogs received a bolus intravenous injection of 0.5 ml (75 U) of homologous antirenin serum following a control perfusion period lasting 60-80 minutes. Then the gracilis muscle was sequentially perfused before and after constriction (or sham constriction) of the left renal artery, following the group A protocol. Percent changes in net perfusion pressures following constriction (or sham constriction) were calculated as for group A dogs. Toward the end of the experiment the dogs were challenged with 2 U of lyophilized dog renin in saline injected intravenously.

For all these dogs, blood samples were collected for estimation of hematocrit, pH, PO₂, PCO₂, and serum electrolytes 25 minutes after renal artery manipulation.

**Group C.** Eight experimental and eight control dogs received an intravenous infusion of indomethacin (5 mg/kg), following a control perfusion period lasting 60-80 minutes. Indomethacin, dissolved in buffered saline (0.9 mg/ml), was infused over a period of 15-20 minutes. Then the gracilis muscle was sequentially perfused before and after constriction (or sham constriction) of the left renal artery according to group A protocol. Percent changes in net perfusion pressures following constriction (or sham constriction) were calculated as for group A animals.

For all animals of group C, blood samples were collected for estimation of hematocrit before and 25 minutes after manipulation of the renal artery.

**MEASUREMENTS OF PLASMA RENIN CONCENTRATION**

For both group A and group C dogs, blood samples (5 ml) from five experimental and five control dogs were collected in ethylenediaminetetraacetic acid (EDTA) tubes for estimation of plasma renin concentration 25 minutes after renal artery constriction (or sham constriction). Plasma renin concentration was measured by adding 25 μl of plasma to renin-free dog renin substrate extracted from plasma of nephrectomized dogs by the method of Skegg et al. The angiotensin I generated was measured by the radioimmunoassay technique of Haber et al.

**Results**

**GROUP A**

After left renal artery constriction in the experimental dogs of group A there was a significant increase ($P < 0.05$) in the mean arterial pressure, as indicated by paired Student's t-test. No increase occurred in control dogs (Table I).

Following sham constriction of the left renal artery in control dogs there was a slow, steady increase in gracilis perfusion pressure with the passage of time (Fig. 2). The initial value of gracilis perfusion pressure when perfused with aortic blood (mean ± SEM) was 139.6 ± 4.1 mm
TABLE 1  Effect of Unilateral Renal Artery Constriction (Experimental Dogs) and Sham Constriction (Control Dogs) on Mean Arterial Pressure (MAP) in group A Dogs

<table>
<thead>
<tr>
<th>Dogs</th>
<th>MAP (mm Hg), control period*</th>
<th>MAP (mm Hg) during experimental period [minutes following (sham) constriction]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 min</td>
<td>10 min</td>
</tr>
<tr>
<td>Control (n = 12)</td>
<td>139.2</td>
<td>138.8</td>
</tr>
<tr>
<td></td>
<td>Δ MAP†</td>
<td>−0.4±0.4</td>
</tr>
<tr>
<td>Experimental (n = 12)</td>
<td>130.5</td>
<td>133.1</td>
</tr>
<tr>
<td></td>
<td>Δ MAP†</td>
<td>2.6±1.8</td>
</tr>
</tbody>
</table>

All values are means ± SEM.

* MAP before renal artery constriction or sham constriction.
† Change in MAP after sham constriction or constriction of renal artery.

Effect of Unilateral Renal Artery Constriction (Experimental Dogs) and Sham Constriction (Control Dogs) on Mean Arterial Pressure (MAP) in group A Dogs

Hg. This perfusion pressure increased by 9.1 ± 2.5 mm Hg over the course of 45 minutes. The experimental increase in perfusion pressure was similar whether the muscle was perfused with aortic LRV, RRV, or VC blood. In the experimental dogs, as compared to control dogs, perfusion with either LRV, VC, or aortic blood after constriction of the left renal artery evoked significant increases (P < 0.001) in gracilis perfusion pressure. In the case of aortic blood these increases averaged 32.9 ± 5.0 mm Hg over the course of 45 minutes. In contrast, no significant increase (P > 0.1) in gracilis perfusion pressure was evoked by RRV blood. Despite these differences in perfusion pressures, the slopes of LRV, VC, and RRV, curves during the 25-45 minutes after constriction did not significantly differ (P > 0.05) and appeared similar to those of the control group (Fig. 2). In the eight experimental dogs in which the gracilis muscle was also perfused with aortic blood (not shown in Fig. 2), the aortic blood evoked increases in perfusion pressure similar to those evoked by LRV and VC blood and also significantly greater (P < 0.02) than perfusion pressures evoked by RRV blood. Despite these differences in perfusion pressures the hematocrit, pH, PO2, PCO2, and serum electrolyte concentrations measured in RRV blood in experimental dogs 25 minutes after constriction did not significantly differ from values in LRV blood. [In RRV blood hematocrit (vol %) = 43.9 ± 0.9; pH = 7.40 ± 0.01; Pco2 = 26.9 ± 3.7 mm Hg; PO2 = 56.7 ± 6.0 mm Hg; serum electrolytes (mEq/liter) were Na+ = 143.1 ± 1.5; K+ = 3.9 ± 0.2; Ca2+ = 4.9 ± 0.1; Mg2+ = 1.97 ± 0.04. In LRV blood hematocrit (vol %) = 43.7 ± 1.0; pH = 7.40 ± 0.01; Pco2 = 27.0 ± 2.5 mm Hg; PO2 = 60.0 ± 5.1 mm Hg; serum electrolytes (mEq/liter) were Na+ = 143.1 ± 1.5; K+ = 3.9 ± 0.2; Ca2+ = 5.0 ± 0.1; Mg2+ = 1.93 ± 0.03.] In addition, the pH, PO2, Pco2, hematocrit, and serum electrolytes of LRV, RRV, VC, and aortic blood from experimental dogs did not significantly differ from respective values in control dogs.

GROUP B

In these dogs bolus intravenous injection of 0.5 ml of homologous antirenin had no effect (P > 0.5) on the mean arterial pressure (MAP). (In control animals MAP before and after antirenin injection was 133.6 ± 8.1 and 135.1 ± 6.7 (M ± SEM) mm Hg, respectively; in experimental dogs MAP before and after antirenin injection was 143.9 ± 4.7 and 142.7 ± 4.3 mm Hg, respectively.) In contrast to results for group A, constriction of the left renal artery after injection of antirenin serum failed to produce a rise in blood pressure (Table 2). Gracilis perfusion pressure increased with time in control dogs of group B just as it had in controls of group A. In contrast to group A, however, constriction of the left renal artery in experimental dogs did not increase gracilis perfusion pressure over that of the controls when perfused with LRV, VC, or aortic blood (Fig. 3). As in group A, the blood pH, PO2, Pco2, hematocrit, and serum electrolytes of LRV, RRV, VC, and aortic blood from experimental dogs did not differ from respective values for the controls.

At the end of each experiment, intravenous injection of lyophilized dog renin failed to produce an increase in blood pressure or an increase in gracilis perfusion pressure, indicating effective blockade of renin activity by antirenin antibodies throughout the experiment.

GROUP C

Infusion of indomethacin into both control and experimental dogs significantly increased MAP (P < 0.02) within

TABLE 2  Effect of Unilateral Renal Artery Constriction (Experimental Dogs) and Sham Constriction (Controls) on Mean Arterial Pressure (MAP) in Group B Dogs

<table>
<thead>
<tr>
<th>Dogs</th>
<th>MAP (mm Hg), control period*</th>
<th>MAP (mm Hg) during experimental period [minutes following (sham) constriction]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 min</td>
<td>10 min</td>
</tr>
<tr>
<td>Control (n = 7)</td>
<td>135.1</td>
<td>134.7</td>
</tr>
<tr>
<td></td>
<td>Δ MAP†</td>
<td>−0.4±1.2</td>
</tr>
<tr>
<td>Experimental (n = 7)</td>
<td>142.7</td>
<td>143.4</td>
</tr>
<tr>
<td></td>
<td>Δ MAP†</td>
<td>0.7±0.7</td>
</tr>
</tbody>
</table>

All values are means ± SEM.

* MAP before renal artery constriction or sham constriction.
† Change in MAP after sham constriction or constriction of renal artery.
FIGURE 3 Gracilis perfusion pressures (means ± SEM) plotted against time (group B). Effect on gracilis perfusion pressure as the muscle is perfused with left renal vein (LRV), right renal vein (RRV), vena caval (VC), and aortic (FA) blood after constriction of the left renal artery (LRA) following immunization against renin. The ordinate and abscissa are as in Figure 2.

20 minutes after the beginning of the infusion (Table 3). The gracilis resistance also was elevated (P < 0.01) in these dogs in comparison to the dogs that did not receive indomethacin. Constriction of the left renal artery after indomethacin infusion produced a significant increase (P < 0.01) in MAP within 5 minutes, and the pressure remained elevated throughout the experiment (Table 4). Again there was no increase in arterial pressure in controls after sham constriction. In the experimental dogs, as compared to the controls, after constriction of the left renal artery, gracilis perfusion with LRV, VC, aortic and also RRV blood evoked similar significant increases (P < 0.01) in perfusion pressures (Fig. 4). Hematocrit of arterial blood estimated before and 25 minutes after manipulation of the left renal artery did not differ between the two groups (hematocrit of controls before sham constriction = 42.4 ± 0.4 (M ± SEM), after sham constriction = 41.5 ± 0.5; hematocrit of experimental dogs before constriction = 42.4 ± 0.4, after constriction = 41.5 ± 0.5).

At the end of every bioassay experiment injection of 0.005 mg of sodium nitroprusside solution into the perfusion system lowered the gracilis perfusion pressure by 30-50 mm Hg in all dogs studied, indicating that the gracilis muscle was capable of responding to vasodilator agents.

TABLE 3 Effect of Intravenous Infusion of Indomethacin on Mean Arterial Pressure (MAP)

<table>
<thead>
<tr>
<th>Dogs</th>
<th>MAP (mm Hg), control period</th>
<th>10 min</th>
<th>20 min</th>
<th>30 min</th>
<th>40 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 8)</td>
<td>135.6</td>
<td>137.5</td>
<td>140.6</td>
<td>141.2</td>
<td>144.0</td>
</tr>
<tr>
<td>∆ MAP</td>
<td>1.9 ± 1.4</td>
<td>5.0 ± 1.6*</td>
<td>5.6 ± 1.5†</td>
<td>8.4 ± 2.0†</td>
<td></td>
</tr>
<tr>
<td>Experimental (n = 8)</td>
<td>138.8</td>
<td>141.2</td>
<td>143.8</td>
<td>147.2</td>
<td>147.5</td>
</tr>
<tr>
<td>∆ MAP</td>
<td>4.2 ± 1.2</td>
<td>5.0 ± 1.2†</td>
<td>8.4 ± 1.2†</td>
<td>8.7 ± 1.2†</td>
<td></td>
</tr>
</tbody>
</table>

All values are means ± SEM. MAP, control period = MAP before infusion of indomethacin; ∆ MAP = MAP following infusion of indomethacin; probability values indicate comparisons of mean aortic pressure before and after indomethacin infusion in each group.

* P < 0.02.
† P < 0.01.
‡ P < 0.001.

TABLE 4 Effect of Unilateral Renal Artery Constriction (Experimental Dogs) and Sham Constriction (Controls) on Mean Arterial Pressure (MAP) in Group C Dogs

<table>
<thead>
<tr>
<th>Dogs</th>
<th>MAP (mm Hg) during experimental period [minutes following (sham) constriction]</th>
<th>5 min</th>
<th>10 min</th>
<th>15 min</th>
<th>25 min</th>
<th>35 min</th>
<th>45 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 8)</td>
<td>144.5</td>
<td>144.1</td>
<td>144.9</td>
<td>145.2</td>
<td>143.4</td>
<td>143.8</td>
<td>143.0</td>
</tr>
<tr>
<td>∆ MAP†</td>
<td>-0.4±0.9</td>
<td>0.4±0.7</td>
<td>0.7±0.9</td>
<td>-1.1±1.0</td>
<td>-0.7±1.9</td>
<td>-1.5±1.8</td>
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</tr>
<tr>
<td>Experimental (n = 8)</td>
<td>147.5</td>
<td>153.4</td>
<td>154.6</td>
<td>155.2</td>
<td>158.8</td>
<td>159.4</td>
<td>159.6</td>
</tr>
<tr>
<td>∆ MAP‡</td>
<td>5.9±1.6†</td>
<td>7.1±1.71</td>
<td>7.7±1.61</td>
<td>11.3±1.98</td>
<td>11.9±1.98</td>
<td>12.1±1.88</td>
<td></td>
</tr>
</tbody>
</table>

All values are means ± SEM.

* MAP before renal artery constriction (or sham constriction) but after indomethacin infusion.
† MAP after sham constriction or constriction of renal artery.
‡ Significantly different from blood pressure during control period (P < 0.01).
§ Significantly different from blood pressure during control period (P < 0.001).

Discussion

These bioassay studies show that, after acute unilateral renal artery constriction, perfusion of the gracilis muscle with venous blood from the constricted kidney or with systemic blood increases gracilis vascular resistance. These results are similar to those of Haddy et al.,* who observed in the dog that blood from a constricted kidney increased limb vascular resistance. Because the hematocrit, and therefore
probable the viscosity of bloods did not change in the present experiments, the evoked increase in gracilis resistance may be attributed to vasoconstriction. This vasoconstriction was not due to changes in serum concentrations of Na+, K+, Ca2+, and Mg2+, nor to changes in blood gas tensions or pH. Pretreatment with antirenin antibodies prevented this increase in vasoconstrictor activity of renal venous and systemic blood, indicating, in association with the increases in venous blood plasma renin concentrations, that the vasoconstriction was causally associated with an increased activity of the renin-angiotensin system.

In striking contrast to the significant increase in gracilis vasoconstriction evoked by venous blood from the constricted kidney and also by systemic blood, no vasoconstriction occurred when the gracilis was perfused by blood from the opposite untouched kidney. This difference in bioassay response cannot be explained by differences in plasma renin concentrations, blood viscosity, serum electrolyte concentrations, pH, or blood gas content. Thus the absence of vasoconstrictor activity in venous blood from the opposite untouched kidney indicates that this kidney either inactivated circulating angiotensin II (or other constrictor substances) or secreted vasodilator substance(s), or both. After blockade of prostaglandin synthesis by indomethacin, vasoconstrictor activity of venous blood from the constricted kidney increased. But vasoconstrictor activity also increased to an equal extent in blood from the vena cava and from the aorta in these dogs. Thus, this finding cannot be used to support the conclusion that there had been any more vasodilator activity in left renal venous blood than in systemic blood after left renal artery constriction.

Following renal artery constriction the stimulus for the renal release of prostaglandins is reported to be the elevated level of circulating angiotensin II or the elevated blood pressure. Our data for dogs pretreated with antirenin serum would support either conclusion. If the rise in systemic arterial pressure stimulated the release of prostaglandins, this may help to account for the observed differences in the release of these substances by the two kidneys, because the increase in systemic pressure would have a greater effect on the untouched kidney than on the constricted kidney.

Additionally we have shown that immediately after acute unilateral renal artery constriction in dogs there is a significant increase in systemic arterial pressure related to the activity of the renin-angiotensin system, as has been reported by many other investigators. Because this increase in systemic blood pressure was not observed after intravenous injection of antirenin antibodies, it is unlikely that any vasoconstrictor other than the renin-angiotensin.
system plays a role in the early stages of Goldblatt hypertension.

In the dogs that received indomethacin, in contrast to those that did not, the systemic arterial pressure was elevated within 5 minutes after renal artery constriction and remained elevated throughout the experiment. Thus the earlier and more sustained hypertension in indomethacin-treated dogs was probably due at least in part to the inhibition of prostaglandin release. Apparently the opposite untoucched kidney attenuates Goldblatt hypertension, at least its early stages, not only by its excretory function but also by the release of vasodepressor prostaglandins.

Acknowledgments

We are deeply grateful to Dr. Francis J. Haddy for help and encouragement during the course of this study and preparation of this manuscript. During Dr. Overbeck's absence, Dr. J B Scott provided valuable guidance. We are greatly indebted to Dr. D. Bailey for determinations of plasma renin concentrations. We thank Dr. Sibbly Hooiberg for supplying us with antirenin serum and Dr. Erwin Haas, Beaumont Memorial Research Laboratories, for the renin. We also acknowledge the valuable technical assistance of Donald L. Anderson, Booker T. Swondall, and Josephine Johnston, and the excellent secretarial help of Lynn Detrich.

References


Single-Passage Extraction and Permeability Estimation of Sodium in Normal Dog Lungs

TADA YIPINTSOI, M.D., PH.D.

SUMMARY

Bolus injections of 125I-albumin, and indocyanine green dye were made into the right atria of anesthetized, ventilated dogs. Blood was sampled from the femoral artery, and plasma flows (Fp) were determined for sodium at various renin concentrations. We thank Dr. Sibbly Hooiberg for supplying us with antirenin serum and Dr. Erwin Haas, Beaumont Memorial Research Laboratories, for the renin. We also acknowledge the valuable technical assistance of Donald L. Anderson, Booker T. Swondall, and Josephine Johnston, and the excellent secretarial help of Lynn Detrich.

PULMONARY capillary permeability is thought to be altered in several disease states, independent of whether the lung is the primary or secondary organ of involvement. However, quantification of pulmonary capillary permeability in intact animals and man is difficult because (1) there is an intrinsically high blood flow, (2) regional distribution of flow in the lung may change when total blood flow increases or decreases, and (3) limitations exist in the techniques currently used for measurement of capillary permeability.

Supported by American Heart Association Grant 74 938 and U.S. Public Health Service Grant HI, 17417, 16476.

Received July 11, 1975; accepted for publication June 3, 1976.
Bioassay in vivo for circulating vasoactive agents after renal artery constriction in dogs.
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Circ Res. 1976;39:517-523
doi: 10.1161/01.RES.39.4.517

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