SUMMARY  In conscious dogs static pressure-flow relationships (I-P curves) were obtained both for the normal autoregulating kidney.

THE SIGNIFICANCE of blood vessel distensibility in regard to the pressure-flow relationship was realized early. The view that there is no vascular tone in the kidney is contradictory. The view that there is no vascular tone in the kidney is contradictory. The view that there is no vascular tone in the kidney is contradictory.

The purpose of our investigation was to study the static I-P curve when vascular smooth muscle tone had been abolished pharmacologically. It was expected that under these experimental conditions the static I-P curve would follow a power function with an exponent comparable to that of a dynamic I-P curve obtained at a low mean arterial pressure, when smooth muscle tone also is low. The literature concerning smooth muscle tone in the kidney is contradictory. The view that there is no vascular tone in the previous study, the dynamic I-P curves for the autoregulating kidney vasculature were described as following a power function. These curves were obtained within a few seconds about 50 mm Hg, above which the I-P curves were straight lines.

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kidney below a pressure level of 80–90 mm Hg1 has been widely accepted. In contrast, early investigations on reactive hyperemia8 and more recent studies concerned with the action of vasodilating drugs on the phenomenon of autoregulation6 indicate that there is marked vascular tone in this pressure range. Therefore we decided to investigate the lowest mean arterial pressure level at which vascular tone could be detected under physiological conditions in the unanesthetized dog.

Methods

The data presented in this study were collected from successful measurements made between the 12th day and the 6th week after an implantation operation performed on three mongrel dogs: Dog S, body wt = 38.8 kg, kidney wt = 76 g; dog N, body wt = 29.5 kg, kidney wt = 88.4 g; dog H, body wt = 22.5 kg, kidney wt = 44.2 g. Before the operation, the previously dewormed and vaccinated dogs were trained to lie quietly on a soft pad in the laboratory. The dogs were offered free access to a standard diet containing 0.5 g of Na per 100 g of the diet (Altromin 4010, Tierlabor Service, Lagelippe, Germany) and water.

After premedication with atropine, droperidol (Thalamonal, Janssen), and propionylpromazine (Combelen, Hoechst), anesthesia was introduced by intravenous injection of sodium pentobarbital, 20 mg/kg, and maintained with halothane and N2 O. Under sterile conditions the left neck, where they were brought out and sewn to the skin. After the operation the dogs were treated with antibiotics for 8 days and were allowed to recover for 12 days.

Prior to implantation the flow probes had been calibrated in a perfusion system on dialysis tubes with physiological saline. With the implanted flow probe in place the calibration was checked under pentobarbital anesthesia before the dogs were killed. A calibrated extravascular flow probe (IVM Systems, type H-1AC) was inserted into the left renal vein and the output signals of the two flowmeters were compared in an x-y plot. The calibration curves were straight lines passing through the origin. The difference in sensitivity between the calibration in vivo and on dialysis tubes was less than 12%.

For concentration-response curves, drug concentrations were calculated as the ratio of the quantity of injected drug per unit of time (mg/min) to the corresponding actual blood flow (ml/min). The concentration-response curves were plotted to determine the suramaximal doses to be used for the I-P curve experiments (usually 1 mg of acetylcholine per minute). Drugs were dissolved in sterile, isotonic sodium chloride solution. The concentrations amounted to 200 µg/ml for acetylcholine, 40 mg/ml for papaverine hydrochloride, and 120 mg/ml for papaverine sulfate. Infusions were performed with a syringe-pump (Unita I, Braun, Melsungen, Germany).

During the experiments no sedatives or anesthetics were given. The dogs lay quietly on their right side and were connected to the recording instruments by an extension cable. All experiments in which the dogs moved or became alerted were discarded. Pressure and flow signals were amplified and mean values derived (time constant = 2 seconds) by means of operational amplifiers. The data were stored on an analog tape recorder (VR 3200, Bell and Howell). For visual control and original recordings an oscillographic recorder (DR 8, Electronics for Medicine) was used. A data acquisition system (Siemens, Germany) delivered digital printouts of the measured variables every second. Power functions of the I-P curves were calculated in a linear regression after double logarithmic transformation of the original data. For individual I-P curves the blood flow values were averaged over pressure intervals of 5 mm Hg. Mean values and standard errors were calculated; for statistical analysis Student's t-test was used.

Results

At rest mean arterial blood pressure was 95.5 ± 6.6 mm Hg (dog S), 96.6 ± 6.5 mm Hg (dog N), and 98.0 ± 6.5 mm Hg.
Hg (dog N) (70 measurements for each dog). Kidney blood flow, in relation to the kidney weight, ranged from 3.1 to 5.8 ml/min per g. The effect of intra-arterial acetylcholine and papaverine on kidney blood flow at the normal mean arterial blood pressure of the conscious dog (see above) is shown in Figure 2 by the concentration-response curves. A maximal increase in blood flow of 110-132% was found during the infusion of acetylcholine, and increases of 75-90% were found during infusion of papaverine sulfate (dog H). In one of the experiments with papaverine (dog N) a maximal dilation could not be achieved, because of the low solubility (40 mg/ml) of papaverine hydrochloride. Therefore papaverine sulfate was used for all other experiments. Maximal dilation was obtained with concentrations of acetylcholine of $3 \times 10^{-5}$ to $2 \times 10^{-4}$ mg/ml and of papaverine, $1 \times 10^{-5}$ to $3 \times 10^{-4}$ mg/ml. In all these experiments mean aortic blood flow, in relation to the kidney weight, ranged from 3.1 to 5.8 ml/min per g. The effect of intra-arterial acetylcholine and papaverine on kidney blood flow at the normal mean arterial blood pressure remained unchanged during the infusion.

Figure 2 shows an original record of the effect of an infusion of acetylcholine followed by an aortic occlusion after kidney blood flow had reached its maximum. The dose of acetylcholine was supramaximal in relation to the concentration-response curves. Note that aortic pressure was not changed by the infusion. The aorta was compressed by gently inflating the pneumatic cuff; thus aortic pressure was decreased in 30 seconds and elevated again in 13 seconds. Since papaverine showed a relatively small effect at high concentrations (Fig. 2) only acetylcholine was used to study the static I-P curves under the conditions of minimal vascular tone.

Two characteristic single I-P curves under the influence of acetylcholine are shown in Figure 4 as a double logarithmic plot. It is clearly shown that both curves up to a pressure of about 50 mm Hg may be described by the power function, $I = a \cdot P^n$, where $I$ = blood flow, $P$ = aortic pressure, $a$ is a coefficient, and $n$ is an exponent. Although obtained for two kidneys with a remarkable difference in absolute blood flow (329 ml/min in dog N and 116 ml/min in dog H), both curves exhibit a distinct break at a comparable pressure. Above this break the exponent $n$ approaches 1, indicating a proportionality of the pressure-flow relationship.

To compare the I-P curves obtained in different dogs in different experiments the individual I-P curves were normalized to control blood flow ($I_c$) and control blood pressure ($P_c$): $I/I_c = a \cdot (P/P_c)^n$. The data for nine single I-P curves during the infusion of supramaximal doses of acetylcholine are listed in Table 1. Specified are the pressure at which the break occurred ($P_{break}$) either with increasing or decreasing pressure. The exponent $n$, the coefficient $a$, and the correlation coefficient $r$ of the normalized power functions describing the I-P curves below the break (low pressure range) are given both for increasing and decreasing pressure. For pressures higher than $P_{break}$ (high pressure range) a linear regression gave a good correlation as indicated by the high correlation coefficients both for the curves obtained with increasing or decreasing pressure. Indicated are also the coefficients $b = \Delta I'/\Delta P'$, where $\Delta I' = \Delta I/I$, and $\Delta P' = \Delta P/P_c$. Mean values and standard errors are calculated out of nine single experiments. The exponent $n$ was found to have an average value of 1.74 when blood pressure was increasing and 1.62 when blood pressure was decreasing. Neither this difference nor the difference in the coefficient $a$ was statistically significant when ascending and descending curves were compared. With decreasing pressure the break in the I-P curve occurred at 48.7 mm Hg; with increasing pressure it occurred at 56.0 mm Hg. This difference was statistically significant ($P < 0.02$). Above the break the coefficient $b$ of the linear regression with increasing pressure (3.38 ± 0.24) was significantly greater than that of the regression with decreasing pressure (2.29 ± 0.21) ($P < 0.001$).

Figure 5 shows for one dog (N) mean values and standard errors of 12 control I-P curves compared to those of nine I-P...
Acetylcholine 750 μg/min

FIGURE 3  Original record of the effect of an aortic compression during acetylcholine infusion on pulsatile (J) and mean (J) renal blood flow, pulsatile (P) and mean (P) aortic pressure.

FIGURE 4 Double logarithmic plot of static I-P curves under acetylcholine in dog N (upper curve) and dog H (lower curve). The arrows indicate whether the curves were obtained with increasing (O) or decreasing (•) pressure. The dashed lines represent the extrapolation of the regression curves to higher pressures. Dog N: I = 0.96 \cdot P^{0.44}; r = 0.998, error probability < 0.001. Dog H: I = 0.21 \cdot P^{0.41}; r = 0.992, error probability < 0.001. For explanation of P^{0.44} and P^{0.41}, see text.

ARTERIAL BLOOD PRESSURE (mmHg)

KIDNEY BLOOD FLOW (ml/min)

Discussion

Infusions of acetylcholine or papaverine into the renal artery are known to cause an increase in renal blood flow. The blood flow increase of 110–132% at 95 mm Hg described in this paper corresponds to the highest values reported in the literature using direct and indirect methods. However, the latter measurements were performed in anesthetized dogs at much higher levels of mean blood pressure. To estimate the vasodilator effect of a drug on
TABLE 1  Data for Nine Single Pressure-Flow (I-P) Curves in Experiments with Acetylcholine

<table>
<thead>
<tr>
<th>Dog and experiment*</th>
<th>Low pressure range</th>
<th>High pressure range</th>
<th>( P_{\text{max}} ) (mm Hg)</th>
<th>( P_{\text{max}} ) (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rising</td>
<td>Falling</td>
<td>Rising</td>
<td>Falling</td>
</tr>
<tr>
<td></td>
<td>( n )</td>
<td>( a )</td>
<td>( r )</td>
<td>( n )</td>
</tr>
<tr>
<td>N, IV (10)</td>
<td>1.55</td>
<td>3.34</td>
<td>0.999</td>
<td>1.41</td>
</tr>
<tr>
<td>N, VIII (6)</td>
<td>1.61</td>
<td>3.65</td>
<td>0.999</td>
<td>1.56</td>
</tr>
<tr>
<td>N, VIII (11)</td>
<td>1.76</td>
<td>3.56</td>
<td>0.999</td>
<td>1.81</td>
</tr>
<tr>
<td>N, VIII (13)</td>
<td>1.84</td>
<td>7.21</td>
<td>0.999</td>
<td>1.59</td>
</tr>
<tr>
<td>N, VIII (14)</td>
<td>1.62</td>
<td>4.09</td>
<td>0.999</td>
<td>1.53</td>
</tr>
<tr>
<td>N, X (11)</td>
<td>2.03</td>
<td>7.90</td>
<td>0.998</td>
<td>1.82</td>
</tr>
<tr>
<td>N, X (12)</td>
<td>1.53</td>
<td>5.32</td>
<td>0.999</td>
<td>†</td>
</tr>
<tr>
<td>H, VII (8)</td>
<td>1.74</td>
<td>3.83</td>
<td>0.997</td>
<td>1.62</td>
</tr>
<tr>
<td>H, VII (9)</td>
<td>1.97</td>
<td>4.06</td>
<td>0.994</td>
<td>1.65</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>1.74 ± 0.06</td>
<td>4.77 ± 0.36</td>
<td>1.62 ± 0.05</td>
<td>4.08</td>
</tr>
<tr>
<td>N†</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

\( n = \text{exponent}, a = \text{coefficient}, r = \text{correlation coefficient of the normalized power function} \left[ I/I_C = a \left( P/P_C \right)^n \right] \) with decreasing (falling) or increasing (rising) pressure for the pressure range below (low pressure range) the pressure \( P_{\text{max}} \) at which the I-P curves exhibit a break. For the pressure range above the break (high pressure range) the coefficient \( b \) and the correlation coefficient \( r \) of a linear regression are listed both for the rising and the falling phase. Mean values and standard errors also are indicated.

* The roman numbers denote the experimental day, the arabic numbers in parentheses denote the number of the individual experiment.
† In this experiment no data for this part of the I-P curve were obtained.
† N = number of averaged data.

autoregulating vessels, the control blood pressure and the pressure changes occurring during the infusion must be considered. In our study control blood pressure was the normal arterial mean blood pressure of an unanesthetized dog; this did not change during the infusion.

Balint et al.29 and Nahmod and Lanari27 reported a complete abolition of autoregulation of kidney blood flow under acetylcholine-induced vasodilation. Baer et al.8 found autoregulation abolished but provided no passive I-P curves, whereas Ono et al.31 found that blood flow autoregulation was only diminished. In our study it is clearly shown that autoregulation of renal blood flow is abolished by acetylcholine and that the pressure-flow relationship is passive (Fig. 5).

In none of these previous studies were concentration-response curves presented which alone would provide unequivocal evidence for a maximal drug effect. To our knowledge the curves shown in this study are the only ones in the literature to exhibit the typical S-shape for the effect of both acetylcholine and papaverine. Vander28 found a maximal increase in renal plasma flow during the infusion of acetylcholine, 25–50 \( \mu \text{g/min} \); at higher infusion rates, however, renal plasma flow decreased again. Similar observation were made by McGiff et al.,22 Åstrom et al.,23 and Maines et al.24 The latter tried to explain this paradoxical effect of acetylcholine by postulating an acetylcholine-induced release of norepinephrine at intrarenal nerve endings because the effect was potentiated by an increased catecholamine content. The negligibly low part played by sympathetic activity or by catecholamines in the generation of resting vascular tone in the kidney of unanesthetized dog may account for the difference between the anesthetized and the conscious dog in response to high doses of acetylcholine.

To study a wider pressure range of the I-P curves, mean arterial pressure was reflexly elevated by clamping both common carotid arteries. As was previously shown,22 this

FIGURE 5 Static I-P curves (dog N) under normal conditions (lower pair, 12 experiments) and under maximal acetylcholine-induced vasodilation (upper pair, nine experiments) with decreasing (O) and increasing (●) pressure as indicated by the arrows. Mean values with standard errors are plotted. For the acetylcholine curves the regression curves are depicted for the pressure range above the break as straight lines and for the pressure range below the break as a power function. The dashed line represents the power function extrapolated to higher pressures.
procedure has no sympathetic vasoconstrictor effects on the kidney in unanesthetized dogs; more recently this also has been observed when kidney perfusion pressure was kept constant during bilateral carotid occlusion. As there is negligible sympathetic vasoconstrictor tone in the kidney vasculature at rest, a reflexly reduced sympathetic activity due to a pressure rise proximal to the aortic cuff cannot be effective. If, on the other hand, the pressure fall distal to the aortic cuff would induce an increase of sympathetic activity or circulating catecholamines, these constrictor effects would decrease renal blood flow in the pressure range below the normal resting blood pressure. This decrease would appear as a shift of the break in the control I-P curve to a higher pressure. However, in studies in which these possible constrictor effects are eliminated, as in studies in isolated perfused dog kidneys or in the intact dog with an isolated control of renal arterial pressure, the break is identical with that found in our study.

The exponent of the static I-P curve obtained for the maximally dilated kidney vasculature corresponds to the exponent of dynamic I-P curves when starting from a mean arterial pressure of 35 mm Hg, a pressure which probably induces only little myogenic vascular tone. This comes close to the pressure level above which acetylcholine became effective in our study.

The significant difference between the static pressure-flow relationship at rest and under maximal dilatation shows that an appreciable vascular tone exists even at the low pressure of 20 mm Hg. This is in contrast to findings of Thurau and Kramer, who observed no increase of renal blood flow during the infusion of papaverine at arterial pressures below 90 mm Hg in the anesthetized dog. Two reasons may provide an explanation for this difference. It is shown in our study (1) that the concentrations of papaverine necessary for a maximal effect are higher than those used by Thurau and Kramer, and (2) that papaverine was less effective in reducing vascular tone than acetylcholine. The hysteresis in the control pressure-flow relationship observed when pressure was decreasing or increasing possibly is an effect of a "reactive hyperemia." However, a similar hysteresis loop is found during maximal vasodilation. Since vascular smooth muscle tone was minimized and changes were abolished pharmacologically, it seems reasonable to assume that physical factors are responsible when the vessels are maximally dilated. Under these conditions there are two distinct breaks. The linear pressure-flow relationship above the breaks indicates that the kidney vessels behave in a manner similar to that of rigid tubes in this pressure range. The flow resistances are higher and the differential (dP/dt) remains unchanged with further pressure increases; they differ with rising and falling pressure.

According to Wezler and Sinn, the break in the I-P curve may be related to the sudden change in distensibility of a blood vessel when it is maximally widened, so that the collagenous fibers are stretched. When the linear part of the I-P curve is extrapolated to lower pressures, however, the curves do not pass through the origin as was to be expected according to this hypothesis. The pressure (Pmax) at which the rate of change in resistance is suddenly altered coincides with the pressure level at which glomerular filtration probably starts. Thus with increasing arterial pressure the filling of the renal tubules will induce an elevated tissue pressure. This in turn may counteract the intravascular pressure and explain the linear pressure-flow relationship at higher pressures during maximal vasodilation.

Further experimental work is needed to decide what mechanisms are responsible for the break in the I-P curves and the observed hysteresis loops. However, the present study shows that the kidney vasculature behaves passively up to a pressure level of 50 mm Hg, when vascular tone is abolished; under physiological conditions the kidney vessels exhibit a remarkable basal tone even at very low levels of blood pressure.

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We are greatly indebted to Annette Brautlecht and Inge Keller for their skilful technical assistance.

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The Effects of Altered Sodium Balance and Adrenergic Blockade on Renin Release Induced in Rats by Angiotensin Antagonism

T. KENT KEETON, PH. D., WILLIAM A. PETTINGER, M.D., AND WILLIAM B. CAMPBELL, PH.D.

SUMMARY Circulating angiotensin II is said to inhibit renin release by a direct, intrarenal action. This effect of angiotensin was studied indirectly using the selective angiotensin II antagonist saralasin (L-Sar-8-Ala-angiotensin II) in conscious normal, sodium-depleted, and sodium-loaded rats. Saralasin caused a dose-related increase in plasma renin concentration (PRC) in normal and sodium-depleted rats, but had no effect on PRC in sodium-loaded animals. However, saralasin was 300 times more active in sodium-depleted rats than in normal rats. Saralasin caused hypotension and tachycardia in sodium-depleted rats, but not in normals. Propranolol inhibited saralasin-induced renin release by 99% in normal rats and by 75% in sodium-depleted rats but did not alter the hypertensive effect of saralasin in the latter. Saralasin potentiated phenolamine-induced renin release, hypotension, and tachycardia in normal rats, and this potentiated renin release was blocked by propranolol. We conclude that a portion of saralasin-elicited renin release in sodium-depleted rats is mediated by hypotensive activation of the carotid baroreceptor reflex which increases sympathetic nervous activity in the kidney. However, in sodium-depleted rats saralasin induced a 42-fold increase in PRC, whereas an equivalent hypotensive dose of the vasodilator hydralazine caused only a 3.5-fold increase in PRC. Thus, we find that saralasin appears to have a selective effect on renin release over and above its hypotensive effect, which suggests an angiotensin-mediated, feedback mechanism inhibitory to renin release. Thus, we have come to the conclusion that for part of saralasin-induced renin release appears to be caused by dis inhibition of angiotensin suppression of renin secretion. This “short-loop” feedback mechanism is closely associated with intrarenal β-adrenergic receptors, since propranolol impaired saralasin-induced renin release under all circumstances in our experiments.

A DECADE AGO, Vander and Geelhoed proposed a pressure-independent mechanism by which circulating levels of angiotensin II inhibited renin secretion through a direct intrarenal action. In the ensuing years, support for their hypothesis has been provided by other investigators, and these later studies have supported an intrarenal site of action which appears to be independent of sodium metabolism. The use of specific angiotensin antagonists in the study of this mechanism has been limited to one study with the isolated perfused kidney, and to several studies in vivo on animals exposed to anesthesia, an intervention which alters renin release per se.

The selective angiotensin receptor blocking agent saralasin (1-Sar-8-Ala-angiotensin II) has been shown to potentiate the hypotensive action and renin release elicited by a peripheral vasodilating agent. In addition, saralasin itself elevates serum renin activity 5-fold in the absence of any change in blood pressure or heart rate in rats and in man. Recent studies on vasodilator-treated, hypertensive patients have demonstrated propranolol blockade of saralasin-induced renin release. These recent observations and the limitations, i.e., anesthesia and surgical intervention, of the previous studies, prompted an examination of the in vivo renin-releasing properties of saralasin in conscious rats because, in the absence of anesthesia, this species is well suited for studies of the renin-angiotensin-aldosterone axis. The characterization of saralasin-induced...
Basal vascular tone in the kidney. Evaluation from the static pressure-flow relationship under normal autoregulation and at maximal dilation in the dog.

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