Patterns in autoregulation of renal blood flow in the dog

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Patterns in autoregulation of renal blood flow in the dog. Am. J. Physiol. 220(6): 1621-1626. 1971.—Experiments were designed to provide data to support or refute mathematical models of the autoregulation of renal blood flow. Renal arterial inflow increased only 0.0107 ± 0.0068 (SE) ml/sec per mm Hg increase in arterial pressure over the range of 70–130 mm Hg. Normalized to the flow at 100 mm Hg, the slope was only 0.035 ± 0.044 (SE) % per mm Hg over the range of 80–120 mm Hg. Neither slope is significantly different from zero. Elevating renal venous pressure 10 mm Hg displaced the autoregulatory curve an amount equal to the change in renal venous pressure. Increasing renal venous pressure 10–20 mm Hg degraded the autoregulation, and increasing ureteral pressure to 50 mm Hg nearly abolished it. The results of this study are summarized here because of a paucity of comprehensive data in the literature obtained using similar techniques and carefully controlled conditions and of sufficient number and accuracy to be used for statistical evaluation.

Flow-pressure relationship; myogenic autoregulation; renal venous pressure; simulation; ureteral pressure

In the understanding of a complex physiological phenomenon, such as the autoregulation of renal blood flow (16, 23), it is helpful to develop and evaluate various models. These models, whether verbal or mathematical, are needed to summarize masses of diverse data and to provide a basis for suggesting experiments which will discriminate between various alternative hypotheses. The experiments were performed to provide data to characterize the renal arterial bed and to support or refute a mathematical model of renal blood autoregulation. The model developed by one of us (22) is based on the assumption that a myogenic mechanism acts to maintain a constant hoop stress in the walls of the preglomerular arterioles. In order to evaluate this model, it was necessary to have sufficient data of the renal arterial flow-pressure relationship to compare the model to biological reality.

Methods

Male mongrel dogs weighing 24.7 ± 3.7 (SD) kg were anesthetized with sodium pentobarbital to provide a stable level of anesthesia throughout the procedure. A catheter was placed in a femoral artery and connected to a Statham P23Db pressure transducer for recording systemic arterial blood pressure. A double-lumen catheter, with a balloon at its tip, was passed into the suprarenal segment of the inferior vena cava.

The left kidney was approached through an extraperitoneal flank incision. If at least 1.0 cm of single renal artery was not available, the right kidney was used. Kidney weights averaged 71.0 ± 13.3 (SD) g. A double-lumen catheter was placed in the ureter at about the ureteropelvic junction; one lumen was connected to a Statham P23AA pressure transducer for recording ureteral pressure while the second lumen allowed free flow of urine or elevation of ureteral pressure by occlusion or connection to a hydrostatic pressure bottle.

The animal was then suspended by the dorsal skin from an overhead frame. In this position, the weight of the kidney slightly stretches the renal vessels, providing sufficient length for placement of transducers near the origin of the renal artery without the need for mechanical traction (12). The renal vessels were dissected free from the surrounding tissue and the adventitia stripped.

Renal blood flow was measured using an electromagnetic flowmeter (Carolina Medical Electronics, Inc., model 321 A). A noncannulating flow transducer (EMP series 400) was placed on the renal artery at its origin; transducers of 8- or 10-mm circumference were used to provide a fit producing a 5–20% reduction in vessel diameter. An occlusion cuff, fabricated from 0.005-inch Silastic sheet rubber in the shape of a sphygmomanometer cuff 3 mm wide, was placed about the renal artery distal to the flow transducer; it was restrained in place with a C-shaped piece of Plexiglas the same width as the cuff.

Renal arterial pressure was measured by inserting a 23-gauge thin-walled needle, shaped like a question mark (Fig. 1) with taper point and two lateral holes near the tip, into the renal artery, distal to the occlusion cuff, and with the tip pointing upstream. This needle was connected to a Statham P23Db pressure transducer by thick-walled vinyl tubing (0.5 mm id X 0.75 mm wall). The system was continually flushed with sterile saline using a reservoir pressurized with air at 300 mm Hg. Flow was limited to 0.5 ml/min by interposition of 7 cm of 30-gauge (150-μ id) needle stock; the resistance of this perfusion system was such that the frequency response of the needle system was not impaired (12). Using a bellows-type pressure generator, monitored with a...
FIG. 1. Schematic diagram of measurement and servo control systems. Servo valve, fabricated in our shops, was driven by a modified loudspeaker magnet and coil. Power amplifier was a Hewlett-Packard 6823A power supply/amplifier. Operational amplifiers were part of an Electronics Associates, Inc. model TR20 computer. Limiters to prevent overload on A02, O3, and O4 were of type shown for +10-v limit of A02. Integral plus proportional control was used. Reference pressures were set on alternate potentiometers permitting rapid (< 1 sec) change in arterial pressures. Switch SW1 was a relay comparator used to minimize transit time.

Statham P23Db transducer with its diaphragm flush with the pressure chamber, the frequency response of the system was found to have a damped natural frequency greater than 60 Hz and a uniform (±5%) frequency response from 0 to 20 Hz. Usually microscopic air bubbles could be removed well enough for the resonant frequency to be over 80 Hz; the system was not used if the resonant frequency was below 60 Hz. At the beginning of each run, it was checked by occluding the side holes, suddenly releasing them, and noting the subsequent oscillations. The zero-pressure reference was set at the level of the renal arterial needle. It was set the same for all transducers by periodically opening sidearms located at the same hydrostatic level to the atmosphere and adjusting for zero.

A similar system with a 20-gauge thin-walled, question-mark needle was used to monitor renal venous pressure. Renal venous pressure was elevated by inflating the balloon placed in the suprarenal segment of the inferior vena cava.

Inflation of the cuff of the renal arterial occluder was controlled with the servo valve system illustrated in Fig. 1. Using an Electronics Associates, Inc., TR-20 analog computer, the pressure could be switched rapidly and the desired pattern developed. A similar system was used to control renal venous pressure.

The electromagnetic flowmeter was calibrated at the end of each experiment. The renal artery distal to the probe was cannulated without disturbing the relationship between the blood transducer and the vessel. Following heparinization of the animal, flows were obtained at various rates between 0.5 and 10.0 ml/sec. Collections were made in a graduated cylinder at intervals of 10–60 sec, and the recorded analog signal was related to the timed collection of flow. Six to 15 different flows were obtained per calibration; the shed blood often had to be returned to the animal to maintain the systemic arterial pressure. Due to differences in wall thickness and internal lumen diameter of the arteries, differences in hematocrit and possible changes in flowmeter gain during the weeks of experimentation, the sensitivity of the transducer varied somewhat, but the coefficient of variation was only about 10% between calibration runs.

Data were recorded on a six-channel Beckman Dynograph type S and a six-channel Beckman Dynograph type R. The renal arterial pressure and flow data were also recorded on analog magnetic tape, using a three-channel Precision Instruments model 6204 recorder at 3.75 inches/sec, for subsequent dynamic data reduction and model development. Over 20 hr of high-fidelity data are on analog magnetic tape. These are being used to develop equations to characterize the dynamic nature of the renal arterial bed.

To provide a perfusion pressure greater than 120 mm Hg, the vagi were cut or one of the carotid arteries was occluded in six of the 13 experiments. The mean systemic arterial pressures of the pentobarbital anesthetized dogs were 110–140 mm Hg without blockage of part of the baroreceptor system; with partial blockage of the baroreceptor system, the pressures were 150–200 mm Hg. In two experiments both carotids were occluded only during the intervals when the perfusion pressure was to be above 140 mm Hg. In four experiments in which the carotid arteries were occluded, the systemic arterial pressure increased 28 ± 12%. The perfusion pressure to the kidney was held constant by the servo system, and the renal blood flow decreased an insignificant 2.9 ± 5.8 SD%. This suggests blockage of the sympathetic nerve supply to the kidney by the process of removing the adventitia around the artery in preparation for placement of the flow probe. Other evidence exists that these maneuvers do not significantly influence renal autoregulatory ability (1, 8, 10).

After arterial pressure changes, the pressure-flow relationship was evaluated when flow had stabilized (< 2% change per half-minute). This required 0.5–2 min. After ureteral occlusion, the studies were delayed for 32 ± 18 (sn) min for stabilization. Pressure-flow data were not used unless ureteral pressure, renal blood flow, and renal venous pressure had been stable for at least 5 min. During the intervals (> 2 min) before or after the step changes in renal venous pressure, the heart rate did not change (< 2 beats/min). Likewise there was no discernible change in systemic arterial blood pressure (< 2 mm Hg).

RESULTS

Autoregulation was present in all experiments under control conditions. The gross pattern of the flow (means ± SD) at various arterial pressures is shown in Fig. 2. Because of the high variability seen and the possibility that autoregulation is degraded at high blood flows, the data were divided into three groups. The mean flow pattern for the five kidneys
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with highest flows and that for the kidneys of the five lowest flows were computed and are also shown in Fig. 2. Over the range of 70 through 130 mm Hg arterial pressure, flow increased 0.0107 ± 0.0068 (SE) ml/sec per mm Hg increase in pressure using 82 pairs of pressure and flow data from the 13 experiments. This slope was not significantly different from zero. The mean flow through the single kidneys perfused at an arterial pressure of 100 mm Hg was 3.96 ± 1.30 (SD) ml/sec. This averaged 3.59 ± 1.31 (SD) ml/min/g of kidney and is comparable to the 3.40 ml/min/g reported by others (16).

Because of the wide differences in renal blood flows in these dogs (the coefficient of variation was 36.5%), data were normalized by calculating the ratios of the flows at the various arterial pressures to that of the average flow for that particular kidney at 100 mm Hg pressure (Fig. 3). For the average flow at 100 mm Hg, the number of observations available per experiment was 6.0 ± 3.8 (SD). The normalizing reference of 100 mm Hg was used because this is approximately the normal mean arterial blood pressure in dogs. Autoregulation of flow between 80 and 120 mm Hg, the normal arterial pressure range, was excellent, for flow increased only 0.035% per mm Hg increase in pressure (b = 0.00035/mm Hg; s_b = 0.00044; n = 62). Again, the slope was not significantly different from zero over this range (P = 0.45).

The effect of increased renal venous pressure on arterial inflow is reported in Fig. 4A. The flow at corresponding renal arterial pressures is clearly depressed by increased renal venous pressure. If the perfusion pressure—the arterial-to-venous pressure gradient—is used, then the influence of moderate changes in venous pressure is reduced (Fig. 4B). Nonetheless, increased venous pressure degrades autoregulation, for the slope of the perfusion pressure-flow relationship over the range of 80 through 120 mm Hg at a renal venous pressure of 10 mm Hg was 0.35 ± 0.16 (SE) %/mm Hg. This was significantly different from zero at the 5% level in contrast to the insignificant 0.035 ± 0.044%/mm Hg slope at normal venous pressures of 1.9 ± 1.9 (SD) mm Hg. At a 20-mm Hg venous pressure, the slope of 0.46 ± 0.24%/mm Hg was different from zero at the 10% probability level over the arterial-venous gradients of 80 to 120 mm Hg.

Ureteral pressure elevation to 50 mm Hg or more impaired autoregulation (Fig. 5). A pressure bottle was elevated to provide 50 mm Hg pressure. With arterial pressures above about 25 mm Hg, the flow increased almost proportionately to the increased arterial pressure rather than showing autoregulation. The ureteral pressure was not transmitted entirely to all the perivascular spaces, for flow was observed at arterial pressures of only 40 mm Hg while...
the ureteral pressure was 50 mm Hg. At high arterial pressures, the autoregulatory constriction of the renal vasculature was opposed to such an extent that blood flow at elevated ureteral pressures was greater than that seen at the normal low ureteral pressures. These data are consistent with the findings of Nash and Selkurt (9) and must be predicted by an inclusive model.

Arterial inflow was stopped for 30 sec at various times during an experiment by inflation of the control cuff. The pattern of flow following release of this occlusion appears to be closely related to renal autoregulation. The peak flow occurred 5.5 ± 3.1 sec after restoration of flow and was 43 ± 22 (SD)% greater than that before occlusion. Flow equilibrated to within 3.6 ± 5.0% of the preocclusion value by 135 ± 58 sec after release of occlusion. In about half of the determinations the peak flow was followed by a decrease in flow which subsequently increased again, suggesting a damped oscillatory response.

The transient responses to sudden changes from 100 mm Hg perfusion pressure are described by Fig. 6. Each mean value is the average of the available data from one to nine experiments. As with the overshoot on restoration of flow following complete arterial occlusion, it is apparent that autoregulation requires a finite time to develop. The values of maximal flow, on suddenly increasing the perfusion pressure, and the values of minimal flow, on decreasing the pressure, are nearly linearly related to the perfusion pressure. Little or no autoregulation is present and the pattern is comparable in pattern, but not necessarily in mechanism, to the effect of ureteral pressure elevation. The time-to-peak flow was about 4 sec and to equilibrium 66 sec. The peak flows here and following release arterial occlusion were probably underestimated since the time constant of the averaging circuit was 2.5 sec.

The arterial pressure at the end of the 30-sec period of no flow was 13.2 ± 1.4 (SD) mm Hg (Fig. 2). The zero flow pressure for the four of the five high-flow kidneys studied showed a pressure of 11.1 ± 2.0 mm Hg, while the five low-flow kidneys had 14.9 ± 3.4 mm Hg. The difference was significant ($P < 0.025$) by group comparison. The exceed-
ingly high resistance at about 15 mm Hg can be explained by a perivascular tissue pressure which is higher than zero-flow arterial pressure or by an elastic closure of the resistance vessels resulting from passive or myogenic activity.

**DISCUSSION**

With normal renal venous and pelvic pressures, the renal arterial flow-pressure relationship is such in dogs that in the range of 80-120 mm Hg arterial perfusion pressure the arterial flow increased by but 2% from a 50% increase in perfusion pressure (Fig. 3). Furthermore, this 2% change is not significantly different from zero. This high degree of arterial compliance and there were no noticeable changes in heart rate or arterial blood pressure, it seems unlikely that the autoregulatory changes following elevation of venous pressures were mediated by sympathetic effects or other changes outside the kidney.

*Elevated venous pressure.* The fact that elevation of renal venous pressure results in a decrease in renal blood flow at a given arterial perfusion pressure has been reported by others (6, 13, 18, 20). Hinshaw et al. (6) reported that increases in renal venous pressure did not abolish autoregulation by the isolated, perfused kidney. From our experiments, consideration of the relationship between renal blood flow and arterial perfusion pressure suggests that elevation of renal venous pressure progressively impairs autoregulation. However, when flow is related to the perfusion pressure gradient, it is apparent that the autoregulatory ability was degraded but not abolished at renal venous pressure up to 20 mm Hg. The mechanism of this effect cannot be defined without valid measures of interstitial pressure just outside the resistance vessels. Since the kidney was probably denervated, and there were no noticeable changes in heart rate or arterial pressure, the circulatory autoregulation on the dog's kidney perfused in situ. Clin. Sci. 11: 267-272, 1952.


REFERENCES


