PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 174, 328–335 (1983)

Impaired Blood Flow Autoregulation in Nonfiltering Kidneys: Effects of Theophylline Administration (41744)

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Abstract. To investigate blood flow autoregulation in filtering and nonfiltering kidneys, renal blood flow was determined during graded reductions in renal perfusion pressure in seven anesthetized dogs containing both a filtering and nonfiltering kidney. In each dog, one kidney was made nonfiltering by the method of EH Blaine, JO Davis, and RT Witty (*Circ Res* 27:1081–1089, 1970). Renal perfusion pressure was decreased from 129 to 115, 99, and 83 mm Hg by stepwise constriction of the suprarenal aorta. In filtering kidneys, the maximum decrease in renal perfusion pressure reduced renal blood flow only 20.1% of control whereas renal blood flow of nonfiltering kidneys decreased by 41.0% of control. During aortic constriction, renal vascular resistance of nonfiltering kidneys remained unchanged or slightly increased. These hemodynamic changes were associated with significantly greater autoregulation indices in nonfiltering kidneys. In eight dogs with nonfiltering kidneys, competitive inhibition of adenosine with theophylline (9 mg/kg iv) restored autoregulation of renal blood flow as shown by significant decreases in renal vascular resistance. These data indicate that in the nonfiltering kidney model, autoregulation of renal blood flow is impaired. It is suggested that this impaired autoregulatory response may result from renal ischemia and the vasoconstrictor influence of elevated intrarenal adenosine concentration.

The vasculature of the normal filtering kidney maintains renal blood flow, glomerular filtration rate and, consequently, filtration fraction constant over a wide range of renal arterial pressures (1–3). In addition, renal blood flow remains constant with increases in renal venous pressure up to 50 mm Hg and glomerular filtration rate is unchanged at venous pressures up to 30 mm Hg (4).

Two possible mechanisms are currently considered to be the basis for the autoregulation of renal blood flow and glomerular filtration rate: an intrarenal myogenic mechanism and tubuloglomerular feedback (3). The myogenic mechanism proposes that autoregulatory adjustments of renal vascular resistance result from a response of the vessel wall smooth muscle to transmural pressure. Tubuloglomerular feedback regulation of glomerular hemodynamics during changes in renal perfusion pressure may result from a signal sensed by the macula densa of the distal nephron which produces feedback control of hemodynamics in the glomerulus of the same nephron. This proposal is attractive since the macula densa and afferent arteriole are anatomically contiguous.

The synthesis and release of different intrarenal humoral factors may influence renal blood flow autoregulation by changing renal vascular resistance at control renal perfusion pressure or by modulating tubuloglomerular feedback from the macula densa to the afferent arteriole. Osswald (5) has suggested that intrarenal adenosine facilitates blood flow and filtration rate autoregulation of normal filtering kidneys in response to alterations in distal tubular sodium chloride delivery. Adenosine, however, also has been implicated as an important intrarenal hormone mediating renal vasoconstriction following renal artery occlusion (6–8).

The purpose of this study was to further characterize the impaired renal blood flow autoregulatory ability of the ischemic nonfiltering kidney and test the hypothesis that the renal vasoconstrictor action of adenosine is responsible for the observed defect. Since the macula densa receptor is functionally inoperative in the ischemic nonfiltering kidney

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0037-9727/83 $1.50

model, this study focuses on the myogenic mechanism.

Methods. Experiments were conducted on 18 mongrel dogs weighing 15–25 kg. In each animal, the left kidney was rendered nonfiltering by the method of Blaine *et al.* (9). Briefly, dogs were anesthetized with sodium pentobarbital (30 mg/kg iv) and the left kidney was exposed by a flank incision using sterile technique. The ureter was ligated and a 2-hr period of renal ischemia was induced by clamping the renal artery. Following the ischemic period, the clamp was removed, the incision closed, and the animal allowed to recover.

Acute experiments were conducted 4 days following the initial surgery. Animals were again anesthetized with sodium pentobarbital (30 mg/kg iv). A cuffed endotracheal tube was inserted and the animals were artificially ventilated. Catheters were inserted into the right femoral and right brachial arteries for the measurement of arterial pressures. The right femoral vein and left jugular vein also were cannulated for the infusion of 0.9% saline and an inulin solution, respectively. Inulin in 0.9% saline was infused at 1.0 ml/min in a dose which maintained the plasma inulin concentration at approximately 30 mg/dl. Normal saline was infused intravenously at 2.0 ml/min to replace urinary (right filtering kidney), blood, and fluid losses. A curved 18-gauge needle connected to polyethylene tubing was placed into the left renal vein for the collection of renal venous blood samples and a flowmeter probe was placed on the left renal artery.

In seven dogs with left nonfiltering kidneys, autoregulation of blood flow in the right filtering kidney was simultaneously compared to autoregulation of the contralateral ischemic nonfiltering kidneys. The right kidney was approached by a midline incision and a flowmeter probe was placed on the right renal artery. Renal perfusion pressure was regulated by a mechanical occluder positioned on the descending aorta above both renal arteries. Renal perfusion pressure was monitored via a catheter advanced from the femoral artery to the level of the renal arteries. Arterial pressures were measured using pressure transducers (Statham P23Db) and both arterial pressure and renal blood flow were recorded on a direct writing oscillograph (Beckman, Dynograph). Experiments were conducted at least 1 hr following the completion of surgery.

In seven experiments, autoregulation of renal blood flow was compared between right filtering kidneys and left nonfiltering kidneys. After blood flow to both kidneys was constant, renal blood flow, renal perfusion pressure, and mean arterial pressure were determined for 10 min. An arterial and left renal venous blood sample were collected at the midpoint of this period. Renal perfusion pressure then was reduced by suprarenal aortic constriction from 129 ± 4 mm Hg to 115 ± 2, 99 ± 1, and 83 ± 2 mm Hg. After each aortic constriction, renal blood flow was recorded for 10 min. Arterial and left renal venous blood were obtained at each perfusion pressure for the determination of glomerular filtration rate in the nonfiltering kidney.

In eight additional dogs, autoregulation of blood flow in left nonfiltering kidneys was determined before and after intravenous theophylline administration. In these experiments, renal blood flow was determined for 5 min at control renal perfusion pressure (141 ± 5 mm Hg) and after aortic constriction to 115 ± 1, 101 ± 1, 84 ± 1, 69 ± 1, and 53 ± 1 mm Hg. The aortic constriction then was released and at least 20 min were allowed for renal blood flow to stabilize. Theophylline (9 mg/kg iv) then was injected and after 10 min, renal blood flow was recorded as renal perfusion pressure was reduced from 130 ± 4 mm Hg to 115 ± 1, 85 ± 1, 71 ± 1, and 54 ± 1 mm Hg. During both series of aortic constrictions, arterial and renal venous blood were collected at control renal perfusion pressure and after renal perfusion pressure reduction to approximately 85 and 55 mm Hg. Three additional experiments were conducted according to the same protocol with the exception that saline vehicle was administered rather than theophylline.

Plasma inulin concentrations were determined colorimetrically (10). The product of renal plasma flow and inulin extraction from ischemic nonfiltering kidneys was used to estimate glomerular filtration rate. Renal vascular resistance (*RVR*) was calculated as the quotient of renal perfusion pressure and renal blood flow with (mm Hg/ml/min) taken as

resistance units. The autoregulation index was calculated by the method of Semple and deWardener (11). This is calculated by the formula:

Autoregulation Index

$$= \frac{RBF_2 - RBF_1}{RBF_1} \div \frac{RPP_2 - RPP_1}{RPP_1}$$

where RBF = renal blood flow and RPP = renal perfusion pressure. All data are expressed as the mean ± standard error of the mean. Renal blood flow and renal perfusion pressure at each level of aortic constriction were compared with control renal blood flow and control renal perfusion pressure using analysis of variance. Differences between filtering and nonfiltering kidneys as well as before and after theophylline administration were tested using a paired t analysis. The 0.05 level of probability was utilized as the criterion of significance.

Results. In seven filtering kidneys, aortic constriction from 129 ± 4 mm Hg to 115 ± 2, 99 ± 1, and 83 ± 2 mm Hg reduced renal blood flow from 234 ± 26 ml/min by 4.6 ± 4, 11.1 ± 2, and 20.1 ± 6.9%, respectively. In contrast, these reductions of renal perfusion pressure decreased renal blood flow of seven contralateral ischemic nonfiltering kidneys from 69 ± 18 ml/min by 14.1 ± 4.2, 27.8 ± 5, and 41.0 ± 8.2% of control, respectively. Renal blood flow decreased significantly more in ischemic nonfiltering kidneys compared to filtering kidneys after each reduction of renal perfusion pressure. Glomerular filtration rate of ischemic nonfiltering kidneys averaged less than 3 ml/min in all animals studied. In addition, lissamine green dye was injected into the left renal artery of five dogs. The absence of the appearance of dye on the renal surface verified the lack of glomerular filtration and tubular fluid flow in these ischemic nonfiltering kidneys.

The change in renal vascular resistance from control after graded reductions of renal perfusion pressure in both filtering and ischemic nonfiltering kidneys are shown in Fig. 1. The renal vascular resistance of filtering kidneys decreased by 0.084 ± 0.046 resistance units ($P < 0.05$) as renal perfusion pressure decreased from 129 ± 4 to 83 ± 2 mm Hg. In contrast, renal vascular resistance of ischemic nonfiltering kidneys increased by 0.573 ± 0.487 resistance units ($P < 0.05$) during this same reduction of renal perfusion pressure. A comparison of the changes in renal vascular resistances between filtering and ischemic nonfiltering kidneys demonstrated significant differences ($P < 0.05$) at renal perfusion pressures of 99 and 83 mm Hg (Fig. 1).

Autoregulation indices were calculated for filtering and ischemic nonfiltering kidneys comparing renal blood flow and renal perfusion pressure to control values at each of the three levels of aortic constriction (Table I). An autoregulation index of 0 indicates complete autoregulation and an index of 1.0 or greater indicates no autoregulation (11). After each aortic constriction, the autoregulation indices of ischemic nonfiltering kidneys were significantly greater than those of the contralateral filtering kidneys (Table I).

The inability of the ischemic nonfiltering kidney to autoregulate blood flow is illustrated with the original record from a representative experiment in Fig. 2. In this experiment, renal perfusion pressure (femoral artery) was reduced from 153 to 127 mm Hg. This aortic constriction produced a transient rise in brachial artery pressure. In the filtering kidney, blood flow remained constant after aortic constriction while renal blood flow of the con-

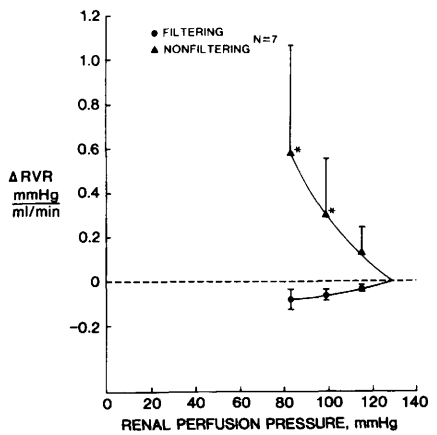

FIG. 1. Effect of decreasing renal perfusion pressure on changes in renal vascular resistance (ΔRVR) from control in filtering and nonfiltering kidneys. The changes in renal vascular resistance between filtering and nonfiltering kidneys are significantly different at renal perfusion pressures of 99 and 83 mm Hg. (*$P < 0.05$)

TABLE I. AUTOREGULATION INDICES OF FILTERING AND NONFILTERING KIDNEYS DURING GRADED REDUCTIONS OF RENAL PERFUSION PRESSURE

RPP	Filtering kidney	Nonfiltering kidney
129 → 115	0.452 ± 0.229	1.349 ± 0.407*
129 → 99	0.466 ± 0.182	1.172 ± 0.254*
129 → 83	0.542 ± 0.187	1.138 ± 0.212*

Note. Values presented as means ± standard error, $N = 7$. RPP = change in renal perfusion pressure (mm Hg).

* $P < 0.05$, nonfiltering kidney versus filtering kidney.

tralateral ischemic nonfiltering kidney decreased from 77 to 66 ml/min. It should be noted that in this animal these changes in the ischemic nonfiltering kidney occurred at renal perfusion pressures well above the limit of renal blood flow autoregulation (circa 80 mm Hg) for filtering kidneys.

The changes in renal vascular resistance of eight ischemic nonfiltering kidneys following aortic constriction before and after theophylline administration (9.0 mg/kg iv) are shown in Fig. 3. In the first series of aortic constrictions (control), renal blood flow averaged 127 ± 18 ml/min and renal vascular resistance was 1.37 ± 0.28 mm Hg/ml/min. Following each step reduction in renal perfusion pressure from 141 ± 5 to 55 ± 1 mm Hg, renal blood flow decreased to 66 ± 13 ml/min and renal vascular resistance remained unchanged (Fig. 3). Thus, autoregulation of renal blood flow in the ischemic nonfiltering kidney again was markedly impaired. Following release of the aortic clamp, renal perfusion pressure increased to 142 ± 5 mm Hg; however, renal blood flow returned to only 102 ± 19 ml/min (compared to control renal blood flow of 127 ± 18 ml/min). Thus, renal vascular resistance increased following the initial aortic constriction to 1.88 ± 0.41 mm Hg/ml/min. After theophylline administration renal blood flow remained unchanged (104 ± 16 ml/min) despite a significant decrease in renal perfusion pressure to 130 ± 4 mm Hg (from 142 ± 5 mm Hg). Thus, theophylline decreased renal vascular resistance at control renal perfusion pressure to 1.59 ± 0.32 mm Hg/ml/min (from 1.88 ± 0.41 mm Hg/ml/min). Aortic constriction after theophylline resulted in significant decreases in renal vascular resistance from 1.59 ± 0.32 to 1.33 ± 0.24, 1.20 ± 0.22, 1.02 ± 0.18, 0.90 ± 0.19, and 0.82 ± 0.18 mm Hg/ml/min at renal perfusion pressures 115, 100, 85, 70, and 55 mm Hg, respectively. These decreases in renal vascular resistance

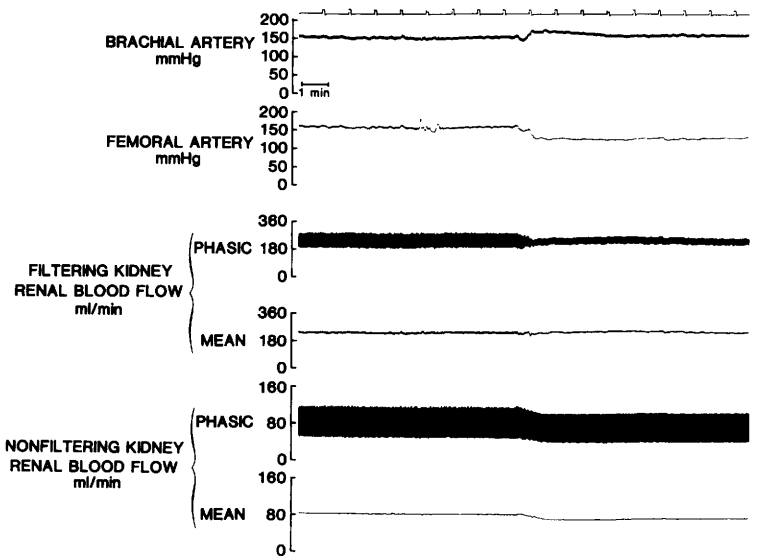

FIG. 2. Original record of renal blood flow in filtering and nonfiltering kidneys, mean renal perfusion pressure (femoral artery) before and after suprarenal aortic constriction.

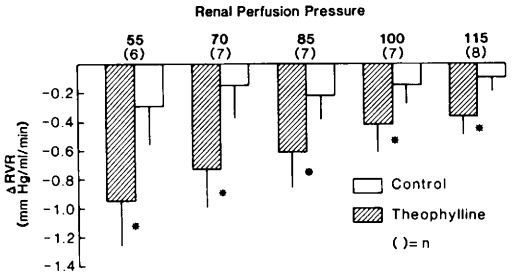

FIG. 3. Effect of decreasing renal perfusion pressures on changes in renal vascular resistance (ΔRVR) of nonfiltering kidneys before (control) and after the administration of theophylline (9 mg/kg iv). The changes in RVR following theophylline are signficantly different from control at each renal perfusion pressure tested. (*$P < 0.05$)

were significantly different from those observed during control at each renal perfusion pressure studied (Fig. 3). Table II presents the autoregulation indices for these studies. After theophylline administration, the autoregulation index at each step reduction of renal perfusion pressure was significantly reduced.

In three additional dogs with ischemic nonfiltering kidneys, consecutive aortic constriction series were conducted before and after administration of saline vehicle. There were no changes in renal vascular resistance following each reduction of renal perfusion pressure either before or after vehicle infusion (Table III). Thus, the improved renal blood flow autoregulation after theophylline administration did not result from two consecutive step reductions in renal perfusion pressure.

Discussion. Previous investigators have indicated that ischemic (12, 13) and nonischemic (14–16) nonfiltering kidneys may have an impaired ability to autoregulate renal blood flow. Gotshall *et al.* (13) reported in one series of experiments that reduction of renal perfusion pressure by 21% decreased renal blood flow by 17%. Conversely, in three other dogs, these authors also reported that reduction of renal perfusion pressure by 16–25% resulted in minimal decreases in renal blood flow. Adams *et al.* (12) have reported that in a model of ischemic acute renal failure where renal blood flow is normal 24 hr following the ischemic insult, renal blood flow autoregulation is markedly reduced. Furthermore, Navar *et al.* (17) have demonstrated that interruption of distal delivery of tubular fluid impairs the ability of single nephrons to autoregulate glomerular capillary pressure. These studies suggest that normal distal tubule fluid delivery is required for autoregulation of renal blood flow.

The present experiments investigated the ability of both filtering and ischemic nonfiltering kidneys to maintain constant blood flow during graded reductions of renal perfusion pressure. In each animal studied, the left kidney was rendered nonfiltering by combining 2 hr of renal ischemia with 4 days of complete ureteral ligation. This technique eliminates tubuloglomerular feedback by preventing tubular fluid flow past the macula densa region of the distal nephron. Therefore, in the absence of tubuloglomerular feedback, any renal blood flow autoregulatory responses may be ascribed, in part, to the operation of the functionally intact myogenic mechanism.

When the renal blood flow autoregulatory responses of filtering and ischemic nonfiltering kidneys were studied in the same animal over

TABLE II. AUTOREGULATION INDICES OF NONFILTERING KIDNEYS DURING CONTROL AND AFTER THEOPHYLLINE ADMINISTRATION (9 mg/kg iv)

Control		Theophylline	
RPP	Index	RPP	Index
141 → 115	0.751 ± 0.169	130 → 115	0.184 ± 0.059*
141 → 101	0.661 ± 0.140	130 → 101	0.153 ± 0.036*
141 → 84	0.674 ± 0.125	130 → 85	0.123 ± 0.042*
141 → 69	0.716 ± 0.141	130 → 71	0.11 ± 0.036*
141 → 53	0.686 ± 0.150	130 → 54	0.380 ± 0.096*

Note. Values are presented as mean ± standard error, N = 6–8. RPP change in renal perfusion pressure (mm Hg).
* $P < 0.05$, theophylline versus control.

TABLE III. CHANGES IN RENAL VASCULAR RESISTANCE (mm Hg/ml/min) OF THREE NONFILTERING KIDNEYS IN RESPONSE TO REDUCTION OF RENAL PERFUSION PRESSURE BEFORE AND AFTER ADMINISTRATION OF SALINE VEHICLE

		Renal perfusion pressure (mm Hg)				
	Dog	115	100	85	70	55
Control	1	−0.04	−0.06	−0.10	−0.17	−0.21
	2	—	0.06	0.21	0.41	0.59
	3	−0.18	0.05	0.22	0.22	0.12
Vehicle	1	−0.02	−0.06	−0.07	−0.11	−0.16
	2	—	0.00	0.14	0.01	0.03
	3	−0.12	−0.03	−0.08	−0.09	−0.46

the same range of renal perfusion pressures, several important points emerged. The renal blood flow of the ischemic nonfiltering kidney at spontaneous renal perfusion pressure was markedly lower (i.e., higher basal renal vascular resistance) than that of the contralateral filtering kidney. It is possible that this was related to the increased renal content of adenosine, produced by renal ischemia (6–8), which was exerting a potent renal vasoconstrictor action. When theophylline was administered at spontaneous renal perfusion pressure, renal blood flow was unchanged (102 ± 19 versus 104 ± 16 ml/min) and renal perfusion pressure decreased (142 ± 5 to 130 ± 4 mm Hg). Thus, after theophylline administration, renal vascular resistance decreased (1.88 ± 0.41 to 1.59 ± 0.32 mm Hg/ml/min) supporting the view that increased renal tissue adenosine concentration was contributing to the increase in basal renal vascular resistances seen in the ischemic nonfiltering kidney. It is known that ureteral occlusion results in increased renal synthesis of vasoconstrictor prostanoids which can contribute to the renal vasoconstriction (18). During stepwise reduction of renal perfusion pressure, renal vascular resistance of the filtering kidneys significantly decreased and that of the ischemic nonfiltering kidneys significantly increased. These significantly divergent responses in renal vascular resistance were also reflected in the significantly different autoregulation indices.

The mechanism(s) which attenuate autoregulation of blood flow in the ischemic nonfiltering kidney may be associated with structural alterations of the renal vasculature, decreased transmural pressure, decreased release of a vasodilator substance, increased release of a vasoconstriction substance, or impairment of tubuloglomerular feedback. Blaine *et al.* (9) have histologically examined sections of nonfiltering dog kidneys. These authors reported that glomerular perfusion of ischemic nonfiltering kidneys was maintained and the primary area of necrosis involved the renal tubules. Structural damage to the vasculature was minimal. Thus, alterations of renal vascular structure are likely not directly responsible for the impaired autoregulation of renal blood flow. The observation that theophylline restored blood flow autoregulation also supports the notion that permanent structural damage to the renal vasculature cannot be entirely responsible for the impaired autoregulation if ischemic nonfiltering kidneys.

Ureteral occlusion increases intrarenal pressure which decreases transmural pressure and results in near maximal vasodilation so that reduction in renal arterial pressure does not lead to further renal vasodilation; renal blood flow decreases reflecting impaired autoregulatory capacity in this nonischemic nonfiltering kidney model (15, 16). However, concurrent lowering of renal arterial pressure by aortic constriction counteracts the rise in intrarenal pressure and decrease in transmural pressure associated with ureteral occlusion. Further, if a decreased transmural pressure related to ureteral occlusion was a major contributing factor to the impairment of renal blood flow autoregulation, then an ischemic nonfiltering kidney model without ureteral occlusion might be expected to possess dif-

ferent autoregulatory capability. However, the ischemic nonfiltering kidney model used by Adams *et al.* (12) involved only renal artery occlusion (no ureteral occlusion) and demonstrated similar impairment of renal blood flow autoregulation.

The normal kidney's output of the vasodilator prostaglandin E_2 (18) and vasoconstrictor renin (19) is enhanced in conditions of both renal ischemia and ureteral occlusion but ureteral occlusion also leads to the renal release of vasoconstrictor thromboxane A_2 (18). Thus, an imbalance between the renal release of vasoconstrictor and vasodilator substances could, with a predominance of the vasoconstrictor substances, contribute to the marked reduction in renal blood flow and impairment of normal autoregulatory renal vasodilatation observed.

Other investigators using different ischemic and nonischemic nonfiltering kidney models also have reported impairment of autoregulation of renal blood flow. Sadowski and Wocial (14) examined autoregulation of blood flow in kidneys made nonfiltering by the *in situ* filling of tubules with a low-viscosity oil. In this nonischemic model, tubular oil filling abolished glomerular filtration rate and significantly increased the autoregulation index. Adams *et al.* (12) also reported that 18–24 hr after 90-min period of renal ischemia glomerular filtration rate was reduced 77% from control. In these dogs with reduced glomerular filtration rate, the renal blood flow autoregulatory capacity was severely attenuated. Using a combination of mannitol diuresis with superimposed ureteral occlusion, a nonischemic model of the nonfiltering kidney is produced (16) which exhibits impaired renal blood flow autoregulation (15, 16). Thus, in both ischemic and nonischemic models of the nonfiltering kidney, a marked decrease or absence of glomerular filtration, presumably associated with decreased delivery of fluid to the distal tubule and absence of tubuloglomerular feedback, is associated with impaired capacity to autoregulate renal blood flow.

An attractive and potentially unifying hypothesis focuses on adenosine. Adenosine, the metabolite of ATP hydrolysis, can act as a vasoconstrictor in the kidney (7, 8) and during renal ischemia, intrarenal tissue adenosine concentrations are markedly elevated (6). Adenosine has been proposed as a humoral mediator of the tubuloglomerular feedback mechanism (5). The nonfiltering kidney is produced by a 2-hr ischemic insult and is characterized by a low renal blood flow and high renal vascular resistance at control renal perfusion pressure. Thus, we hypothesized that in the ischemic nonfiltering kidney elevated tissue adenosine concentrations may exert a potent vasoconstrictor influence on the renal vasculature, thereby limiting renal blood flow autoregulation.

To test this possibility, autoregulation of blood flow in ischemic nonfiltering kidneys was examined both before and after competitive adenosine blockade with theophylline. Theophylline markedly improved the autoregulation of renal blood flow as evidenced by significant decreases in renal vascular resistance of ischemic nonfiltering kidneys during reduction of renal perfusion pressure (Fig. 3) and improvement in autoregulation indices (Table II). It should be noted that this low dose of theophylline (9 mg/kg iv) is less than that dose required to produce inhibition of rabbit renal phosphodiesterase (20). Thus, the restoration of renal blood flow autoregulation likely resulted from competitive inhibition of adenosine rather than decreased degradation of cyclic nucleotides. Adenosine improved the renal blood flow autoregulatory capability of the ischemic nonfiltering kidney without changing its nonfiltering status so that tubuloglomerular feedback presumably remained absent. Thus, it seems unlikely that impairment of tubuloglomerular feedback plays a major role in the abnormal renal blood flow autoregulation of the ischemic nonfiltering kidney. However, since other nonfiltering kidney models (14–16), also lacking tubuloglomerular feedback and normal autoregulation, do not require renal ischemia for their production, it is possible that the contribution of absence of tubuloglomerular feedback is of less importance than adenosine in the impaired autoregulatory ability of the ischemic nonfiltering kidney. As a corollary, the impaired autoregulation of nonischemic nonfiltering kidneys may be more dependent on the absence of tubuloglomerular feedback.

These results suggest that impaired blood

flow autoregulation in the ischemic nonfiltering kidney may result from increased tissue adenosine formation (6).

This work was supported by USPHS Grants AM 15843, NL 14388, and HL 23989 and by grants from the Veterans Administration and American Heart Association, Iowa Affiliate. Dr. Osborn was supported by a Postdoctoral Research Fellowship from the Iowa Kidney Foundation and USPHS Institutional Research Fellowship HL 07121.

1. Selkurt EE. The relation of renal blood flow to the effective arterial pressure in the intact kidney of the dog. Amer J Physiol **147**:537–549, 1946.
2. Shipley RE, Study RS. Changes in renal blood flow, extraction of inulin, GFR, tissue pressure and urine flow with acute alterations of renal artery blood pressure. Amer J Physiol **167**:676–688, 1951.
3. Navar LG, Marsh DJ, Blantz RC, Hall J, Ploth DW, Nasjletti A. Intrinsic control of renal hemodynamics. Fed Proc **41**:3022–3030, 1982.
4. Kishimoto T, Maekawa M, Miyazaki M, Yamamoto K, Ueda J. Effects of renal venous pressure elevation on renal hemodynamics, urine formation and renin hemodynamics, urine formation and renin release. Japan Circ J **36**:439–447, 1972.
5. Osswald H, Nabakowski G, Hermes H. Adenosine as a possible mediator of metabolic control of glomerular filtration rate. Int J Biochem **215**:263–267, 1980.
6. Osswald H, Scharitz HJ, Kemper R. Tissue content of adenosine, inosine and hypoxanthine in the rat kidney after ischemia and postischemic recirculation. Pfluegers Arch **371**:45–49, 1977.
7. Spielman WS, Osswald H. Characterization of postocclusive response of renal blood flow in the cat. Amer J Physiol **235**:F286–F290, 1978.
8. Spielman WS, Thompson CI. A proposed role for adenosine in the regulation of renal hemodynamics and renin release. Amer J Physiol **242**:F423–F435, 1982.
9. Blaine EH, Davis JO, Witty RT. Renin release after hemorrhage and after suprarenal aortic constriction in dogs without sodium delivery to the macula densa. Circ Res **27**:1081–1089, 1970.
10. Fuhr J, Kaczmarczyk J, Druttgen CD. Eine einfache colorimetrische Methode zur inulinbest immung fur Nierenclearance-Utersuchungen be: Stoffwechselgesunden und Diabetikern. Klin Wochenschr **33**:729–730, 1955.
11. Semple SJ, deWardener HE. Effect of increased renal venous pressure on circulatory autoregulation of isolated dog kidneys. Circ Res **7**:643–648, 1959.
12. Adams PL, Adams FF, Bell PD, Navar LG. Impaired renal blood flow autoregulation in ischemic acute renal failure. Kidney Int **18**:68–76, 1980.
13. Gotshall RW, Davis JO, Blaine EH, Mussachia XJ, Braverman B, Freeman R, Johnson JA. Increased renin release during renal arteriolar dilatation in dogs. Amer J Physiol **227**(2):251–255, 1974.
14. Sadowski J, Wocial B. Renin release and autoregulation of blood flow in a new model of nonfiltering non-transporting kidney. J Physiol (London) **266**:219–233, 1977.
15. Raeder M, Ornvik P, Kiil F. Renal autoregulation: Evidence for the transmural pressure hypothesis. Amer J Physiol **228**:1840–1846, 1975.
16. Holdaas H, DiBona GF, Kiil F. Effect of low-level renal nerve stimulation on renin release from nonfiltering kidneys. Amer J Physiol **241**:F156–F161, 1981.
17. Navar LG, Chomedj B, Bell PD. Absence of estimated glomerular pressure autoregulation during interrupted distal delivery. Amer J Physiol **229**:1596–1603, 1975.
18. Currie M, Kawasaki A, Jonas P, Davis B, Needleman P. The mechanism and site of the enhanced arachidomate metabolism in ureter obstruction. In: Dunn MJ, Patrono C, Cinotti GA, eds. Prostaglandins and the Kidney. New York, Plenum, pp 299–308, 1983.
19. Reid IA, Morris BJ, Ganong WF. The renin–angiotensin system. Annu Rev Physiol **40**:377–410, 1978.
20. Fredholm BB, Hedquist P, Vernet L. Effect of methylxanthine and related compounds on rabbit renal cyclic nucleotide phosphodiesterase, 5′ nucleotidase and adenosine deaminase. Biochem Pharmacol **27**:2845–2840, 1978.

Received April 29, 1983. P.S.E.B.M. 1983, Vol. 174.