Kidney International. Vol. 31 (1987), pp. 65–71

The contribution of vascular obstruction to the functional defect that follows renal ischemia

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The contribution of vascular obstruction to the functional defect that follows renal ischemia. Experiments were performed on rats subjected to renal ischemia and various treatment procedures to determine the origin and functional consequences of vascular obstruction. To this end, its occurrence and severity was assessed qualitatively and quantitatively in the outer medulla, where it is particularly prominent. The incidence of medullary hyperemia was not influenced by inhibiting thrombocyte aggregation with 5 or 70 mg/kg of acetyl salicylic acid or preventing fibrin deposition with 100 IE/kg of heparin before ischemia, and these substances produced no improvement renal function. The incidence and degree of hyperemia, however, could be substantially reduced or completely eliminated by acutely raising blood pressure after ischemia or by decreasing the number of circulating erythrocytes before ischemia. These procedures were effective in raising filtration rate and tubular reabsorption from 20% to 60% of normal, in restoring renal blood flow and vascular resistance to completely normal, and in diminishing epithelial damage both three and 18 hours after ischemia. The following conclusions are drawn: first, vascular obstruction, which is not lessened by inhibiting thrombus formation but is easily reversed or prevented by raising perfusion pressure or decreasing hematocrit, is probably caused by erythrocyte aggregation during ischemia. Second, vascular obstruction, which appears to raise renal vascular resistance and lower blood flow and filtration rate, cannot be limited to the medulla but must also be present in the cortex. Finally, reversing or preventing vascular obstruction can fully restore renal perfusion, partially restore glomerular and tubular function, greatly reduce tubular necrosis and thus prevent renal failure.

Following a period of temporary renal ischemia the capillaries of the outer medullary inner stripe are engorged and congested with blood, so that the medulla of the experimentally–damaged kidney displays a hyperemia [1] very reminiscent of that seen in the shock–kidney in man [2]. This vascular obstruction can be found throughout the entire kidney during the period of arterial occlusion, but upon reperfusion largely disappears from the cortex and inner medulla, remaining prominent only in the outer medulla. Here, in the inner stripe, it is evident as a hyperemia of variable intensity, visible both macroscopically and microscopically, whose severity can be assessed using qualitative or quantitative procedures [1].

The dense packing of the erythrocytes and the scarcity of blood plasma around them suggested that erythrocyte aggregation accompanying the loss of blood plasma from the vasculature may be the cause of vascular obstruction in the outer medulla. The spontaneous reversal of congestion in the cortex and inner medulla upon reperfusion and the paucity of fibrin deposits or thrombocyte aggregates in the congested medulla [1] were consistent with this interpretation, but were not sufficient to exclude the participation of clotting mechanisms. The natural variability in the degree of medullary hyperemia and a similar variability in the functional impairment to the kidney further suggested that vascular obstruction might be an important determinant of renal function. The observation that increasing degrees of medullary hyperemia were associated with a successive loss in renal function [1] was compatible with this concept, but could not determine whether vascular congestion was the cause or the result of the functional impairment.

The present experiments were performed to obtain further information about the occurrence and the nature of the vascular obstruction that follows renal ischemia and about its contribution to the deficit in renal function. First, to assess whether clotting mechanisms contribute to vascular congestion, acetyl salicylic acid and heparin were examined for their ability to prevent medullary congestion. Second, to determine whether erythrocyte aggregation could be the cause of vascular obstruction simple rheological procedures, designed to mobilize aggregated cells (raising perfusion pressure) or hinder aggregation (lowering the number of circulating erythrocytes), were tested for their effectiveness in alleviating medullary congestion. Finally, to evaluate whether vascular obstruction determines renal function and if so, to what extent, procedures which reduced medullary congestion after ischemia were examined for their influence on renal function.

Methods

Animal preparation

The experiments were performed on male, Sprague–Dawley rats (Mus, Biberach, FRG), weighing 200 to 290 g, given free access to tap water and a standard pellet diet (Altromin 1324, Lage, FRG). The animals were prepared for clearance studies exactly as described previously [1, 3].

Renal ischemia was produced by occluding the renal artery with an atraumatic clip for 45 minutes under Inactin anesthesia (Byk, Gulden, Constance, FRG) in short–term experiments or under Nembutal anesthesia (Abbott, Kela, Hoogstraten, Belgium) in long–term experiments. At the end of the experiment,

Received for publication November 29, 1984
and in revised form March 25 and June 30, 1986

one half of the left kidney was immersion fixed in formalin for histological evaluation and morphometric assessment of the percentage of the inner stripe occupied by capillaries, as described earlier [1]. The other half was blotted, examined carefully and graded according to the appearance of the outer medulla, exactly as described previously [1].

Glomerular filtration rate was determined two to three hours or 18 hours following ischemia by measuring the clearance of ^{3}H-methoxy-inulin (New England Nuclear, Dreieich, FRG). Urine flow rate, determined by weighing, was multiplied by the urine to plasma inulin concentration ratio, as determined by liquid scintillation counting (Beckman Instruments, Irvine, California, USA). Tubular reabsorption was calculated as filtration rate minus urine flow rate. Urine osmolality was measured by vapor pressure depression (Wescor, Logan, Utah, USA). Free water removal was calculated as the difference between urine flow rate and osmolar clearance, taking plasma osmolality to be 300 mOsm/kg.

Blood flow to the whole kidney and to the different nephron types was measured two to three hours or 18 hours following ischemia using approximately 10^6 microspheres, with a mean diameter of 9.3 ± 1.3 μm (3M Deutschland, Neuss, FRG), as described in detail elsewhere [1, 3]. The microspheres, suspended in 0.1 ml of saline, were injected into the ascending aorta from a catheter in the right carotid artery. At the same time a blood sample was obtained from the femoral artery to determine the ratio between blood flow rate and number of microspheres. The number of micropheres trapped in different populations of glomeruli was counted microscopically and the number trapped in the entire kidney was calculated, allowing both glomerular and whole kidney blood flow to be derived.

Treatment procedures

To prevent thrombocyte aggregation during ischemia, acetyl salicylic acid (Sigma, Munich, FRG), dissolved in water at 38°C to give a concentration of 0.3 g/liter or 4.6 g/liter, was given by gastric lavage one hour before anesthesia. It was applied as 15 ml/kg body weight to give a final dosage of 5 mg/kg body weight (low dose aspirin) or 70 mg/kg body weight (high dose aspirin) exactly three hours before inducing renal ischemia. Animals given the same gastric load of water served as controls. These doses are at and much above the minimum dose that inhibits platelet aggregation within a few hours in man, and both caused an increase in bleeding during surgery. To inhibit fibrin deposition during ischemia, 100 IE/kg body weight of heparin (Thrombophob, Nordmark, FRG) were administered intravenously 5 minutes before ischemia and neutralized by an equivalent amount of protamine (Roche, Basel, Switzerland) five minutes after the renal artery had been clamped. This procedure increased clotting time from an average of 3-1/2 minutes before heparin to more than 10 minutes after heparin, and returned it to an average of 4-1/2 minutes after protamine. Animals given the same intravenous load of isotonic saline served as controls.

To raise perfusion pressure acutely the same types of procedure were used as commonly employed in autoregulation studies. First, neck surgery and catheterization of the carotid artery were used to raise arterial blood pressure, which rose and fell repeatedly by about 25 mm Hg and stabilized at this higher level when surgery was complete. Second, an aortic clamp, applied after neck surgery, was released, retightened and subsequently removed, to raise and lower pressure by 25 mm Hg before allowing it to stabilize at the higher level, and thus imitate at a later stage the pressure profile caused by neck surgery. In control experiments (untreated ischemia) neck surgery was performed *before* ischemia, so that blood pressure was raised, but stable, at 128 ± 2 mm Hg at the end of ischemia and 125 ± 3 mm Hg 30 minutes later. In the first experimental group (delayed neck surgery) neck surgery was performed *after* ischemia, so that blood pressure rose from 104 ± 6 mm Hg at the end of ischemia before neck surgery to 129 ± 7 mm Hg 30 minutes later. In the second experimental group (aortic declamping), designed to dissociate the effects of acutely raising blood pressure from other possible effects of neck surgery, neck surgery was performed *before* ischemia, as in the control experiments. An aortic clamp was applied *during* ischemia, enabling renal perfusion pressure to be raised *after* ischemia from 109 ± 5 mm Hg at the end of ischemia before clamp removal to 135 ± 4 mm Hg 30 minutes later. In all three groups blood pressure was the same two hours after ischemia when the clearance measurements were begun, at 125 ± 5, 124 ± 4, and 125 ± 4 mm Hg, respectively.

To reduce the number of circulating erythrocytes, whole blood withdrawn from the left femoral artery was exchanged with warmed rat plasma and infused into the left femoral vein. The rat plasma was obtained from Inactin anesthetized rats by giving 100 IE/kg of heparin (Thrombophob, Nordmark, FRG) (heparin plasma) or by collecting the blood into citrate–dextrose solution (Fenwal, Deerfield, Illinois, USA) (citrate plasma) to prevent clotting. A blood volume corresponding to 1.5% of body weight, was exchanged in six to eight minutes at a pump rate 30 ml/hr, using a reciprocal pump constructed to infuse and withdraw fluid synchronously (Braun, Melsungen, FRG). This isovolemic transfusion procedure caused no change in respiration rate, heart rate, or arterial blood pressure. Upon completing the transfusion, oxygen was provided as a precaution against hypoxia, and 15 minutes later renal ischemia was induced. After ischemia had ended the erythrocytes were replaced by briefly centrifuging the warm blood and reinjecting the packed erythrocytes, while an equivalent volume of diluted blood was withdrawn. The packed erythrocytes from this blood were similarly reinjected, while the same volume of blood was withdrawn. This procedure lowered arterial hematocrit from 47 ± 3% initially to 32 ± 3% after transfusion, and raised it again after erythrocyte replacement to 42 ± 4% in short–term experiments and to 43 ± 4% after 18 hours in long–term experiments.

Statistical analysis of the data

Differences in the macroscopic appearance of the outer medulla and in the microscopic appearance of the tubular cells, as assessed by grading, were tested for statistical significance using the Kolmogorov–Smirnov test. Quantitative determinations of medullary hyperemia and of renal functional parameters were pooled for each treatment group and expressed as mean ± SEM throughout. Differences between the groups were tested for statistical significance using the Student's *t*-test for single comparisons and Dunnett's test for multiple comparisons. Each test was only considered to indicate statistically significant differences when the null–hypothesis could be rejected with a two–tailed probability of 0.05 or less.

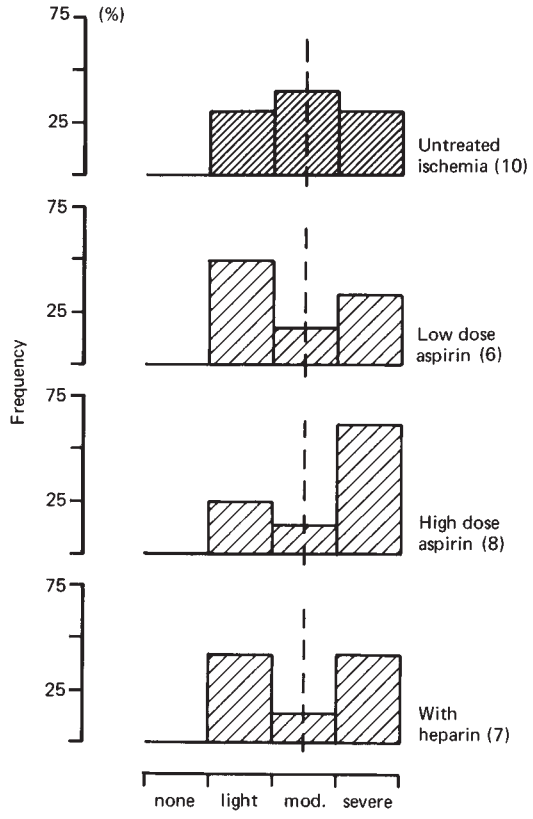

Fig. 1. *The frequency in % with which each degree of medullary hyperemia occurs in untreated animals or animals exposed to various antithrombotic procedures.* The dotted line indicates the median of the untreated group.

Table 1. Values of renal function in untreated animals and those exposed to various antithrombotic procedures

	µl/min/100 g			
	GFR	V̇	Reabs	Reabs %
Untreated ischemia	73 ± 11 (10)	5.1 ± 1.0 (10)	68 ± 11 (10)	91.7 ± 1.8 (10)
Low dose aspirin	81 ± 25 (6)	5.2 ± 2.8 (6)	76 ± 24 (6)	92.1 ± 3.3 (6)
High dose aspirin	69 ± 26 (8)	3.1 ± 1.1 (8)	58 ± 25 (8)	92.1 ± 1.8 (8)
Heparin	104 ± 33 (7)	4.0 ± 0.8 (7)	100 ± 34 (7)	92.3 ± 3.0 (7)

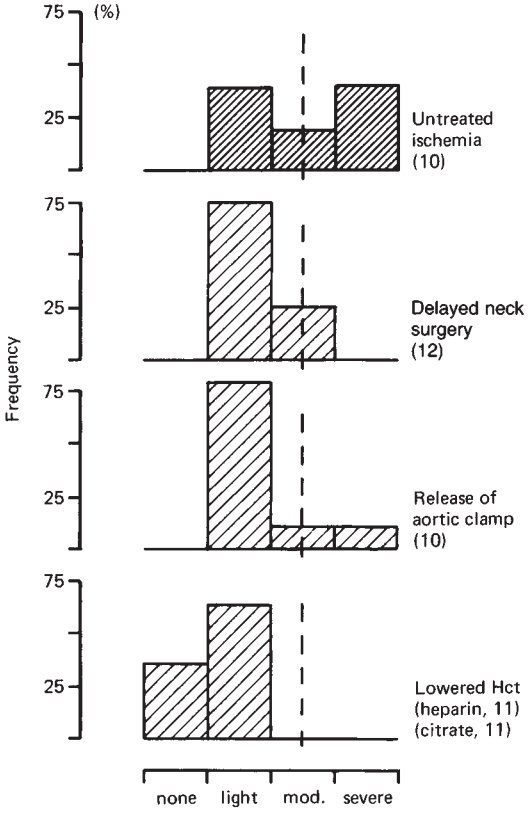

Fig. 2. *The frequency in % with which each degree of medullary hyperemia arises in untreated kidneys or kidneys exposed to various rheological procedures.* In the last group transfusing heparin–plasma or citrate–plasma produced identical results. The dotted line indicates the median of the untreated group.

Results

Two to three hours after ischemia

The frequency of each degree of medullary hyperemia obtained after ischemia with low or high dose aspirin and after ischemia with prior administration of heparin is given in Figure 1. The corresponding values of renal function are listed in Table 1. Compared to the untreated controls, neither dosage of aspirin nor heparin administration produced any significant alteration in the frequency of each degree of hyperemia, and neither dose of aspirin nor heparin resulted in any significant improvement in renal function.

The frequency of each degree of medullary hyperemia observed after acutely raising perfusion pressure just after ischemia (delayed neck surgery or aortic declamping), and after lowering the number of erythrocytes before ischemia (heparin plasma or citrate plasma) is given in Figure 2. The two methods of raising perfusion pressure were equally effective in significantly reducing the degree of medullary hyperemia, and both shifted the frequency distribution of medullary hyperemia away from the severe and towards the light form. Lowering arterial hematocrit with either type of plasma was even more effective in reducing medullary hyperemia, because it shifted the frequency distribution of medullary hyperemia more towards the light form and prevented the development of hyperemia in some kidneys.

The corresponding values of renal function obtained after acutely raising perfusion pressure (delayed neck surgery or aortic declamping) or lowering the number of erythrocytes (citrate plasma) are listed in Table 2. Each of the treatment procedures improved renal function to the same extent. Filtration rate and tubular reabsorption were significantly raised from 20% of control in untreated kidneys to 60% of control, and both urinary concentrating power and free water removal were considerably improved. Renal blood flow, measured only when perfusion pressure had been acutely raised (delayed neck surgery), was elevated from 40% of control in untreated kidneys

Table 2. Values of renal function in untreated kidneys and those exposed to heological procedures

	μl/min/100 g			Reabs	U_{osm}	$^{-}C_{H_2O}$	RBF	Resist
	GFR	V̇	Reabs	%	*mOsm/kg*	*μl/min/100 g*	*ml/min/100 g*	*x*
Normal kidneys	407 ± 28 (9)	3.3 ± 1.1 (9)	396 ± 30 (9)	99.2 ± 0.3 (9)	1273 ± 186 (9)	6.3 ± 0.6 (9)	2.79 ± 0.33 (9)	43 ± 4 (9)
2–3 hr after ischemia								
untreated ischemia	86 ± 11 (10)	5.3 ± 1.0 (10)	81 ± 11 (10)	93.4 ± 1.3 (10)	465 ± 42 (10)	2.9 ± 0.9 (10)	1.25 ± 0.14 (9)	90 ± 8 (9)
delayed neck surgery	253 ± 30[a] (12)	8.1 ± 1.3 (12)	245 ± 30[a] (12)	95.7 ± 1.1 (12)	625 ± 84[a] (12)	5.7 ± 0.9[a,b] (12)	2.86 ± 0.27[a,b] (8)	40 ± 4[a,b] (8)
aortic declamping	255 ± 51[a] (8)	5.5 ± 1.2 (8)	250 ± 51[a] (8)	96.8 ± 1.1 (8)	567 ± 59[a] (8)	4.1 ± 0.8[a] (8)	—	—
lowered hematocrit	247 ± 58[a] (9)	5.2 ± 0.8 (9)	242 ± 58[a] (9)	95.8 ± 1.5 (9)	625 ± 90[a] (9)	4.8 ± 0.6[a,b] (9)	—	—
18 hr after ischemia	213 ± 42 (7)	1.7 ± 0.3 (7)	212 ± 42 (7)	98.9 ± 0.3[b] (7)	789 ± 36 (7)	2.7 ± 0.5 (7)	2.53 ± 0.28[b] (8)	59 ± 7 (8)

[a] At 2–3 hr, values differ significantly between the treated group and the untreated group.
[b] Values are the same in the treated group as normal kidney at 2–3 and 18 hr.
Resistance is in arbitrary units of mm Hg · 100 g/ml.

Table 3. Degree of medullary hyperemia at two to three hours after ischemia

	None	Light	Moderate	Severe	
GFR *μl/min/100 g*	301 ± 42	225 ± 33[a]	157 ± 29[a]	—	treated ischemia
	—	120 ± 17	68 ± 13	21 ± 4	untreated ischemia [1]
Capillary volume *% of inner stripe*	6.2 ± 0.5	8.8 ± 1.6[b]	21.0 ± 1.6[b]	—	treated ischemia
	—	12.0 ± 1.5	18.3 ± 3.4	21.2 ± 2.8	untreated ischemia [1]

[a] Values in treated group differ statistically from those in untreated group.
[b] Values in treated group do not differ from those in untreated group.

to 102% of control. Correspondingly, renal vascular resistance, more than twice normal in untreated kidneys, returned to normal after treatment. Glomerular blood flow, depressed to 68 ± 7, 41 ± 5, 35 ± 4 and 34 ± 4 nl/min/100 g in surface, superficial, middle, and deep nephrons after ischemia (55, 46, 45 and 32% of control values) was returned to 123 ± 12, 93 ± 10, 75 ± 7, and 114 ± 11 nl/min/100 g by treatment (108, 103, 95 and 107% of control values).

A comparison between the degree of medullary hyperemia as assessed subjectively by grading and as determined morphometrically as the percentage of the inner stripe occupied by capillaries is shown in Table 3 in kidneys subjected to ischemia and one of the treatment procedures. In kidneys assessed as having no hyperemia, capillaries occupied exactly the same percentage of the inner stripe as reported previously for normal kidneys [1]. In kidneys assessed as having a light or moderate hyperemia, there was no difference in the percentage of the inner stripe occupied by capillaries, compared to that reported previously [1]. For all kidneys subjected to one of the treatment procedures the percentage of the inner stripe occupied by capillaries averaged 8.9 ± 1.3%, significantly less than the average value of 16.5 ± 1.7% observed in untreated kidneys, but still significantly more than the 6.2 ± 0.3% seen in normal kidneys.

The degree of tubular damage was assessed in kidneys subjected to these three treatment procedures and compared to that found in untreated kidneys. There was no difference in the incidence of epithelial flattening in either the proximal convoluted or straight tubule or in the occurrence of blebs in the proximal part of the nephron. In the proximal convolution and thick ascending limb of Henle, necrobioses were mild in degree and relatively infrequent, with an occurrence of approximately 20%, which was not reduced by treatment. In the proximal straight tubule, however, necrobioses were also mild in degree but much more frequent, with an occurrence of approximately 50%, which fell significantly to only 5% after treatment.

Eighteen hours after ischemia

In kidneys exposed to a lowered arterial hematocrit the previous day, subjective assessment of medullary hyperemia showed 56% to have no hyperemia and 44% to have only the light form, much as seen three hours after ischemia, and quite in contract to the 33% mild and 67% more severe forms seen previously in untreated ischemia at 18 hours [1]. The values of renal function measured at this time in kidneys exposed to a lowered hematocrit before ischemia are summarized in Table 2. The improvement in filtration rate and tubular reabsorption, now at 50% of control, had been largely preserved, and was in striking contrast to the 20% that was measured earlier in the one–third non-anuric kidneys of untreated animals [1]. Although urine concentration had improved further, free water removal had fallen. Renal blood flow, at 90% of control, had been maintained but renal resistance had risen with borderline significance. Glomerular blood flow to surface, superficial, middle, and deep nephrons, at 114 ± 15, 81 ± 8, 72 ± 7 and 91 ± 14 nl/min/100 g, was still normal at this time (100, 89, 91 and 86% of control values).

The degree of tubular damage was assessed and compared to that of untreated kidneys. There was no difference in the incidence of debris and hyaline cylinders in the proximal part of the nephron. In the proximal convoluted and straight tubule necrosis, which was mild to severe in degree and diffuse or

segmental in nature, occurred with a frequency of approximately 80% and was similarly unaltered by treatment. In the thick ascending limb of Henle, however, necrosis was also mild to severe in degree, but less frequent, with an occurrence of 42% which fell significantly to 0% after treatment. Although there was no indication of necrosis in these cells after treatment, cytoplasmic swelling was present to a variable degree in all kidneys, suggesting a functional impairment that may explain the decrease in free water extraction at this time.

Discussion

The current experiments further support the contention that the formation of medullary hyperemia does not involve hemostatic mechanisms, such as thrombocyte aggregation or fibrin deposition, but is caused by erythrocyte aggregation. Administration of acetyl salicylic acid or of heparin prior to ischemia had no influence on the development of medullary hyperemia, as would be expected if hemostatic mechanisms participated. In contrast, suddenly increasing renal perfusion pressure after ischemia or lowering the number of circulating erythrocytes before ischemia either reduced the severity of medullary hyperemia or even eliminated it completely. The influence of other factors, such as raised systemic arterial pressure or the neck surgery used to induce it, as well as pharmacological effects or endocrinological changes accompanying volume expansion, could all be excluded. Thus, the antihyperemic and anticongestive action of these procedures is most probably explained by their ability to disperse aggregated erythrocytes. Erythrocyte aggregates are known to dissipate when exposed to a pressure wave sufficient to overcome their high yield stress or when their internal stress is lowered by reducing the hematocrit. Thus, everything known about vascular obstruction so far, its rheological behaviour, its appearance under the light microscope [1] or the electron microscope [4], and its capability for spontaneous reversal [1] indicates that it is not caused by blood clotting but by erythrocyte sludging.

As some of the presently employed procedures were successful in reducing the incidence and severity of medullary hyperemia, it was possible to estimate to what extent vascular obstruction is responsible for the depression in renal function after ischemia. Successful treatment procedures raised filtration rate and tubular reabsorption from approximately 20% to approximately 60% of control three hours after ischemia, suggesting that almost half the loss in filtration rate and tubular reabsorption is attributable to vascular obstruction. They also raised renal blood flow from approximately 40% of control to completely normal, thereby fully restoring renal vascular resistance three hours after ischemia, suggesting that all the reduction in renal blood flow, as well as all the increase in renal vascular resistance can be explained by vascular obstruction. This implies that only half the loss in filtration and reabsorption and none of the loss in renal blood flow is caused by damage to the kidney *during ischemia*, and the remaining loss in filtration rate and all the loss in blood flow is due to poor perfusion *after ischemia*.

There is a considerable number of additional observations consistent with the contention that the reduction in renal blood flow after ischemia, is, indeed caused by vascular obstruction. First, there is a temporal association between the extent of renal perfusion and the degree of vascular obstruction. Renal blood flow in the rat is invariably depressed within the first hours following ischemia [1, 3–8], when medullary congestion is always present [1, 9], but is normal more that a day later [4, 5, 7], when medullary congestion is known to have disappeared [9, 10]. Second, a negative correlation between the degree of medullary congestion and the level of renal perfusion both early and later after ischemia can be demonstrated. Unpaired measurements of medullary congestion and of renal blood flow in the present and a previous study [1], suggest a negative relationship between the two, as indicated in Figure 3A, whose statistical significance was confirmed using the paired determinations available. This lends further support to the concept that it is vessel obstruction and not vessel constriction that reduces renal blood flow and increases vascular resistance after ischemia.

The question arises, however, as to whether the decrease in filtration rate seen after ischemia can be explained by the decrease in renal perfusion. Early after ischemia it seems that half the loss in filtration may be a direct result of poor perfusion. Unpaired determinations of renal blood flow and of glomerular filtration in the present and a previous study [1] suggest a positive relationship between the two, as indicated in Figure 3B, whose statistical significance was verified using the paired measurements available. Since this relationship is similar to that seen in normal kidneys when perfusion pressure is varied in the low range, it suggests that here too, renal blood flow determines filtration rate. Later after ischemia, however, none of the loss in filtration is caused *directly* by a decrease in renal perfusion, for the filtration rate remains depressed even after blood flow has almost normalized [1, 7]. However, it may be caused *indirectly* by the decrease in perfusion, whose degree and duration early on may determine the extent of renal damage and thus renal function at a late stage. When vascular congestion was reduced early by treatment, filtration rate at 18 hours was 50% of normal and histological damage minimal. Similarly, when it disappeared spontaneously within 18 hours, filtration rate was 40% and histological damage was modest [1]. However when it persisted at 18 hours filtration rate was less than 2% of normal and histological damage was considerable [1]. Thus, early restoration of perfusion can improve filtration at a later stage. Consequently, it is feasible that a decrease in renal blood flow may determine filtration rate both early and later after ischemia, even though by different mechanisms.

The finding that whole kidney blood flow and glomerular blood flow to each nephron type are completely normal after medullary hyperemia has been reduced, suggest that vascular obstruction is not just confined to the medulla but is also present in the cortex. There are several other observations that indicate the existence of vascular obstruction in the cortex. First, although a blockage of the cortical capillaries can only be detected histologically during or shortly after ischemia [1], a filling defect of the cortical labyrinth compared to that of control kidneys filled identically is often still apparent one hour after ischemia [1]. Second, studies using radiolabeled erythrocytes have shown the vessels in the cortex to contain considerable numbers of stagnant, non-circulating erythrocytes after ischemia [11]. Third, it seems that cortical and medullary congestion must be separate entities because filtration rate and medullary hyperemia respond differently to treatment, as indicated in Table 3. Whereas filtration rate increases as hyperemia

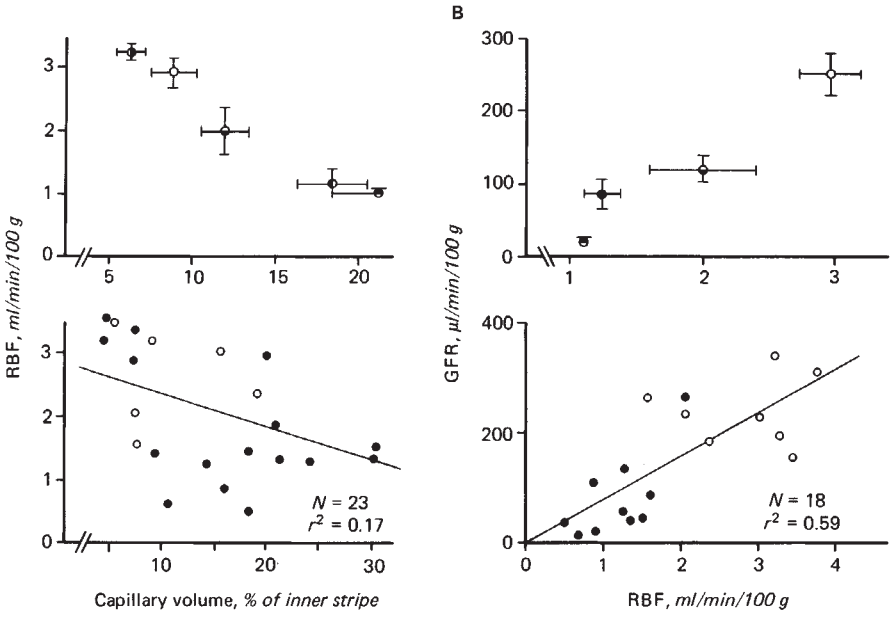

Fig. 3. *The relationship between renal blood flow, RBF, and capillary volume in the outer medulla in treated or untreated kidneys at 2–3 and 18 hr after ischemia.* The mean data from this and a previous study [1] is given above and the paired data with the regression line and the index of determination is given below. The vertically and horizontally divided circles indicate values at 2–3 and 18 hr after ischemia in untreated kidneys of an earlier study [1]. The open and closed circles indicate values at 2–3 hr after ischemia in treated or untreated kidneys in the present study.

decreases in both untreated [1] and treated kidneys, filtration rate is greater in treated kidneys than in untreated ones at each level of hyperemia. A false assessment of hyperemia cannot explain the dissociation between medullary congestion and cortical function, for quantification showed it to be the same in both groups. Since treatment procedures are able to improve cortical function independently of medullary congestion, it would seem that they are more effective in removing vascular obstruction from the cortex than from the medulla. That it is much easier to reverse vascular obstruction in the cortex than from the medulla is clear, because in the untreated kidney reperfusion alone causes most of the cortical capillary blockage to disappear, whilst medullary congestion remains [1].

Although vascular congestion in the medulla is unable to influence filtration rate directly, it may influence it indirectly by depressing tubular reabsorption in the thick ascending limb, thus increasing macula densa sodium chloride concentration and activating the tubuloglomerular feedback mechanism. This mechanism, long suspected of lowering filtration rate in ischemic renal failure, is still operational after ischemia [12], when the decrease in tubular diluting ability indicates that a macula densa signal may be available to activate it [13]. Nevertheless, in untreated ischemic kidneys there is no evidence that it is functional, for neither suppression of the feedback response by chronic renin depletion [14, 15], nor with high doses of furosemide [16] was able to improve renal function after ischemia. This could indicate that the reduction in filtration rate is sufficient to compensate for the decrease in tubular transport, so that a macula densa signal is simply not generated. This situation could easily be reversed in treated ischemic kidneys with little vascular obstruction, for here tubular reabsorption is still somewhat depressed but filtration rate is much higher. Under these circumstances it may indeed be tubuloglomerular feedback that keeps filtration rate at half normal and prevents the delivery of salt and fluid to an epithelium unable to reabsorb it adequately.

In conclusion, vascular obstruction that seems to be caused by the simple aggregation of erythrocytes during ischemia appears to play a decisive role in determining to fate of the kidney after ischemia. Vascular obstruction, which restricts renal perfusion, persists long after ischemia has ended and is responsible for much of the functional and structural defects that follow, for procedures that prevent or alleviate it provide considerable functional and morphological protection. Elimination of vascular obstruction, although not fully avoiding the loss of function nor completely preventing the development of tubular necrosis, does reduce both to such an extent that renal failure can be completely avoided.

Acknowledgments

This investigation was supported by the Deutsche Forschungsgemeinschaft. Grateful thanks are extended to Mr. Christian Kurz and Ms. Gisela Schubert for helping to complete one of the experimental series.

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