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Red cell trapping and postischemic renal blood flow. Differences between the cortex, outer and inner medulla

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Red cell trapping and postischemic renal blood flow. Differences between the cortex, outer and inner medulla. The distribution of blood flow in the rat kidney after 60 minutes of renal ischemia was studied by single-fiber laser-Doppler flowmetry. Blood flow in superficial cortex and inner medulla was measured with a probe directed towards the kidney surface and exposed papilla, respectively. Outer medullary blood flow was measured with a probe introduced through the renal core. After ischemia the blood flow decreased to 60% of the pre-ischemic value ($P < 0.01$) in superficial cortex and to 16% ($P < 0.01$) in outer medulla, while inner medullary blood flow increased paradoxically to 125% ($P < 0.01$). There was extensive trapping of red blood cells (RBC) in the outer medulla, but not in the inner medulla or cortex. The fractional RBC volume as measured by radiolabeled RBCs was 21% in the inner stripe of the outer medulla, but 2% in this area in a normal kidney. To investigate the influence of RBC trapping on intrarenal distribution of blood flow after ischemia, the hematocrit was reduced from 46% to 31% by isovolemic hemodilution. When performed before ischemia, this maneuver almost completely abolished RBC trapping. In this group blood flow in both outer and inner medulla was almost unchanged after ischemia, while superficial cortical blood flow decreased to 66% ($P < 0.01$) of the pre-ischemic value. It is concluded that RBC trapping in the outer medulla causes a large decrease in blood flow in this area and, at the same time, shunting of blood to the inner medulla. In the absence of RBC trapping, blood flow of both outer and inner medulla is well preserved after ischemia.

Despite several decades of debate, the distribution of the blood flow in postischemic acute renal failure (ARF) remains controversial. This is probably due to the lack of methods for measuring the blood flow in the renal medulla in general, and in the outer medulla in particular [1]. A preferential reduction of the cortical blood flow after ischemia has been proposed from studies with tracer wash-out techniques [2, 3]. In sharp contrast, microsphere studies have indicated a reperfusion deficit in the renal medulla, on the basis of the finding of a greater reduction in the perfusion of juxtamedullary than of superficial glomeruli [4, 5]. Other methods, including studies of the distribution of contrast media [6], determination of tracer extraction rates [7], and measurement of the distribution of fluorescein-globulin [8], have pointed to a large decrease in medullary blood flow. On the other hand, direct measurements of the blood flow in single capillaries of the exposed renal papilla have shown an increase in blood flow after ischemia [9, 10].

However, just as the cortical blood flow may not reflect the perfusion of the renal medulla, so may the inner medullary blood flow not reflect the blood flow of the outer medulla. The vascular arrangement [11] and the metabolic demand [12] differ substantially between the outer and inner medulla. Furthermore, morphological signs of ischemic injury are sparse in the inner compared with the outer medulla [13].

Laser-Doppler flowmetry (LDF) permits measurement of the relative blood flow in the superficial tissue layer [14–16], and has previously been used to measure the blood flow in the superficial cortex and in the exposed papilla in the rat kidney [17, 18]. Contrary to various techniques of measuring the blood flow in a single capillary [9, 10], LDF measures the average blood flow in a large number of capillaries, including those in the slightly deeper tissue compartments, which excludes the possibility of bias capillary selection.

Recently, a single-fiber laser probe, which transmits laser light both to and from the monitored tissue volume, has been developed [19]. These small probes can be introduced into the tissue with a minimum of traumatic injury and permit measurement of blood flow in deeper tissue compartments [20]. In the present study a three channel, single-fiber laser-Doppler flowmeter was used to measure the change in relative blood flow in the cortex, outer medulla and inner medulla resulting from renal ischemia.

It has been proposed that the trapping of red blood cells (RBC) in the microvasculature of the outer renal medulla causes delayed reperfusion in the renal medulla [5, 7, 21–25]. This RBC trapping can, however, be effectively prevented by reducing the hematocrit before reperfusion [22, 24, 25]. Thus, to evaluate the influence of RBC trapping on the intrarenal distribution of blood flow in ischemic ARF, hemodilution was performed in rats and the distribution of blood flow after ischemia in these animals was compared with that in animals with an unaltered hematocrit.

Two features which may affect the validity of LDF in ischemically injured tissue, that is, postischemic edema and red cell trapping, were also considered in the present study.

Methods

Animals

All experiments were carried out on male DA Lewis rats with a body weight of 210 to 260 g. The animals had free access to tap

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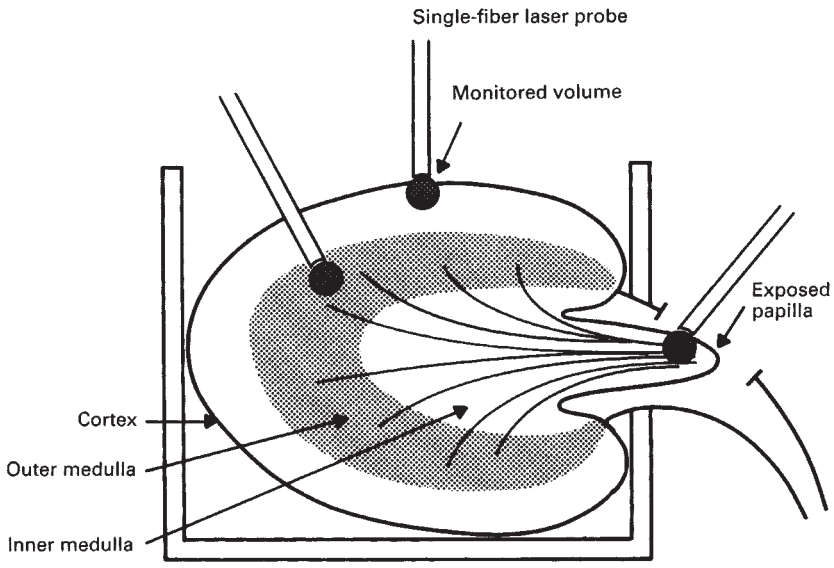

Fig. 1. *Cross section of the kidney supported in a Lucite cup.* The renal papilla was exposed through an incision in the pelvic ureter. The single-fiber laser probes were either directed towards the renal cortex, inserted through the cortex towards the outer medulla, or directed towards the exposed papilla.

water and standard rat chow R3® (Ewos, Södertälje, Sweden). Anesthesia was induced by an intraperitoneal injection of Inactin® (Byk Gulden, Konstanz, Germany) in a dose of 120 mg · kg^{-1} · body wt. The animals were placed on a servo-controlled heating pad, which stabilized the body temperature at 37.5°C, and were tracheostomized. Catheters were inserted into the left femoral artery and vein, the former for continuous measurement of blood pressure and the latter for infusion of Ringer solution containing 120 mM NaCl, 25 mM $NaHCO_3$, 2.5 mM KCl and 0.75 mM $CaCl_2$ at a rate of 5 ml · hr^{-1} · kg^{-1} body wt. The left kidney was exposed through a flank incision and immobilized in a Lucite cup. By excising the overlying pelvic ureter the papilla was visualized. The kidney was then bathed in mineral oil.

Experimental groups

After completion of the surgical procedures the animals were divided into two groups with seven in each. In the control group the hematocrit (Hct) was left unaltered and in the other one (low-Hct group) it was reduced by hemodilution. For this purpose 5 ml of a 5% albumin-Ringer solution (Human albumin, Kabi, Sweden) was injected into the femoral vein over a period of 10 minutes, while at the same time an equal volume of whole blood was withdrawn from the femoral artery.

Laser-Doppler flowmetry

A single fiber, multichannel laser-Doppler flowmeter SMULA III® (Department of Biomedical Engineering, University of Linköping, Linköping, Sweden), which permits simultaneous use of three single-fiber probes, was used. The diameter of the probes was 0.5 mm and to allow precise movements they were fixed in micromanipulators.

Values for relative blood flow (LDF signals) under pre-ischemic control conditions were obtained as follows: The superficial cortical blood flow was measured by scanning six to ten spots in each animal. The papillary blood flow was measured by placing the probe on the exposed papilla six to ten times in each animal; the position of the probe and its angle to the papilla differed slightly between each measurement.

The outer medullary blood flow was measured by introducing the probe through the renal cortex to a depth of 2 mm, which meant that the probe would monitor the outer medulla (Fig. 1). In the first few animals the location of the probe aperture in the outer medulla was verified by dissecting the kidney and observing the channel caused by the probe insertion. The outer medullary blood flow was estimated from four different punctures in each animal. In most cases there was little, if any, bleeding on retraction of the probe.

Ischemia was then induced by occluding the left renal artery with a ligature for 60 minutes. During this time the flank incision was kept closed to ensure that the body temperature was maintained in the kidney.

After 30 minutes of reperfusion LDF was repeated for about one hour as described above. For measurements in the outer medulla, the probe was first inserted into the same holes as were used before the ischemia, and four to six new punctures were then made in each animal.

Assessment of RBC trapping

The intrarenal distribution of ^{51}Cr-labeled RBCs was measured essentially as described by Karlberg et al [21]. Briefly, 0.2 ml of ^{51}Cr-labeled RBCs (equivalent to 5 μCi), was injected intravenously before induction of ischemia. After completion of LDF a 100 μl reference blood sample was drawn. Both the postischemic (left) and the intact (right) kidney were removed and dissected into specimens of cortex, outer and inner stripe of outer medulla, and inner medulla. The volumes of the specimens were determined by weighing, assuming a density of 1. The radioactivity in reference blood samples and in kidney specimens was measured in a gamma-spectrophotometer (Nucab AB, Göteborg, Sweden). The fractional red cell volume (RBC%) in the different areas of the kidney was then calculated as:

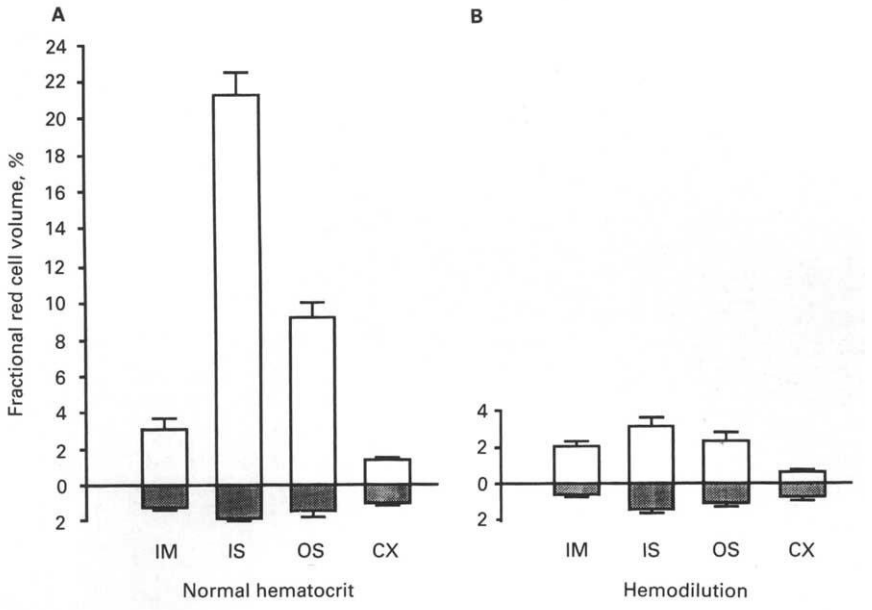

Fig. 2. *Fractional red cell volume in the renal cortex (CX), the outer stripe (OS) and inner stripe (IS) of the outer medulla, and the inner medulla (IM) in animals with a normal hematocrit (46 ± 1%)* (**A**)*, and a low hematocrit (31 ± 1%)* (**B**). Bars above the baseline refer to the post-ischemic kidney (□) and those below to the normal (■) contralateral kidney. Values are means ± 1 SE.

$$RBC\% = Cpm_{tissue} \cdot Hct \cdot Cpm_{blood}^{-1} \cdot \text{tissue weight}^{-1} \cdot 100$$

Depth sensitivity of LDF in normal and postischemic renal tissue

Since the presence of stagnant RBCs in the postischemic kidney may cause a decrease in the depth of penetration of the laser beam and hence in the monitored volume, with underestimation of the blood flow as a consequence, the following experiment was performed.

Two normal kidneys and two kidneys subjected to ischemia and reperfusion were excised and fixed for 24 hours in 2.5% glutaraldehyde (Kebo Lab AB, Stockholm, Sweden) dissolved in a phosphate buffer solution (pH 7.4). Thin sections (40 to 500 μm) of renal tissue were cut by means of an Oxford vibratome and put in saline. Before the sectioning the kidneys were placed in 1% osmium tetroxide (Expectron Man., AB, Stockholm, Sweden) for five minutes. By this procedure a frame was obtained around the sections, facilitating their handling.

The different sections were then placed between the probe and the surface of the exposed kidney immobilized in a Lucite cup. In each section five measurements were made by positioning the probe at five different points on the section. Care was taken to place the probe over the darkest regions, that is, those areas representing the outer medulla in the postischemic kidneys. All data were expressed as the fraction of the LDF signal obtained on the bare surface of the kidney. The baseline signal was determined from a 3 mm thick section placed on the kidney, and subtracted from all values. The origin of this baseline signal, which was approximately 1% of the LDF signal recorded from the cortex, is not completely understood. Slight movements of the kidney during measurement, and Brownian molecular movements, are probable sources [14].

The decrease in the LDF signal resulting from placement of tissue sections between the probe and the kidney may not be due solely to screening of the laser beam, but may also result from an increase in the distance between the probe and the illuminated kidney. To evaluate this possibility, the change in LDF signal caused by retraction of the probe from the kidney surface was investigated with saline in the interspace. For this purpose the lucite cup supporting the kidney was sealed with agarose gel and filled with saline.

Statistics

The variance within the animals compared to that among them was analyzed by one factor ANOVA. To compare pre- and post-ischemic values Student's *t*-test for paired samples were used. To compare the control and low-Hct groups, Student's *t*-test for unpaired samples was used. The mean value was calculated from all observations, while the degree of freedom was considered to be 13 (that is, the number of animals − 1). A P value of less than 0.01 was considered to be significant.

Results

Hemodilution resulted in a hematocrit of 31 ± 1%, as compared with 46 ± 1% in the control group. This decrease was accompanied by a reduction in mean arterial blood pressure to 109 ± 2 mm Hg versus 123 ± 2 mm Hg in the control group.

The intrarenal distribution of red blood cells resulting from ischemia is shown in Figure 2. It is clear that hemodilution reduced the RBC trapping substantially. The fractional red cell volume in the inner stripe of the outer medulla was 21.2 ± 1.3% in the control group and 3.1 ± 0.5% ($P < 0.01$) in the low-Hct group; the latter value was only slightly above the value of 1.6 ± 0.2% found in a normal kidney. In the inner zone of the medulla the RBC trapping was substantially less pronounced: 3.1 ± 0.6% in the control group and 1.94 ± 0.3% ($P < 0.01$) in the low-Hct group. It may be noted, however, that in the contralateral kidneys of low-Hct animals the RBC volume in all areas of the kidney decreased in proportion to the systemic hematocrit. In the renal cortex there was no evidence of RBC trapping in either of the groups.

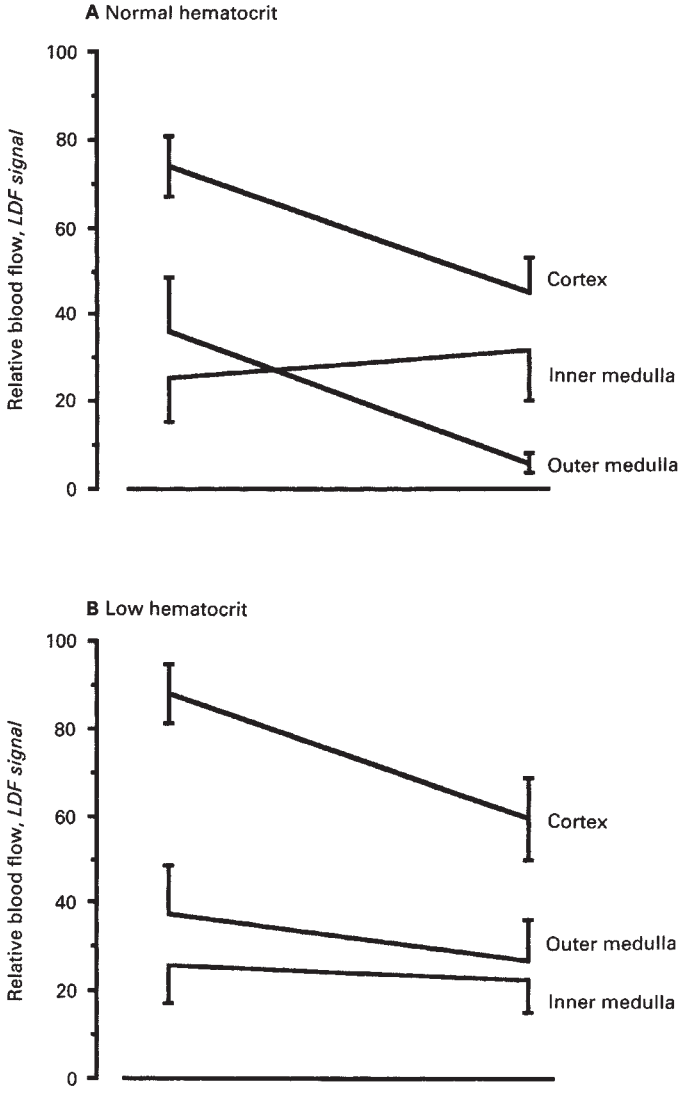

Fig. 3. *Relative blood flow (LDF signal) before and after 60 minutes of ischemia and 30 minutes of reperfusion in the cortex and the outer and inner medulla (papilla).* **A.** Animals with normal hematocrit (46%); **(B)** those with reduced hematocrit (31%).

The degree of postischemic edema was similar in the two groups, the wet weight of the ischemic relative to the contralateral kidney being 124 ± 4% in low-Hct animals and 127 ± 4% in the control group.

Laser Doppler flowmetry

Figure 3 summarizes the relative blood flow values (LDF signals), which are detailed in Table 1 before and after ischemia, in the superficial cortex, outer medulla and inner medulla (papilla). It should be emphasized that the LDF signal does not represent absolute blood flow. But it is the product of the number of erythrocytes and their linear velocity within the monitored volume. Thus, the change in LDF signal is proportional to the change in RBC flow, provided that the monitored volume is constant (see below, *Methodological considerations*).

In each animal there was good agreement between the values obtained when the probe was placed on different spots of the renal cortex, while the values for the outer medulla and papillary blood flow showed greater scatter. There was no difference, however, between the LDF signals obtained on insertion of the probe into the same holes as were used pre-ischemically, and those obtained by performing new punctures.

Under pre-ischemic conditions the LDF values for the superficial cortex were higher in the low-Hct group than in the controls, while in the outer and inner medulla there was no difference between the groups, thus indicating that hemodilution resulted in hyperperfusion preferentially of the outer cortex [26].

Ischemia caused an approximally equal decrease in superficial cortical blood flow in the control and low-Hct groups, to 60% and 66% of the pre-ischemic values, respectively.

After ischemia the outer medullary blood flow in the control group decreased to only 16% of the pre-ischemic value, while the inner medullary flow increased to 125% of the pre-ischemic values.

Both the marked decrease in outer medullary blood flow and the paradoxical increase in inner medullary blood flow after ischemia were prevented by hemodilution. Thus the LDF signals obtained from the outer and inner medulla in the low-Hct group showed reductions of borderline significance, to 83% ($P = 0.09$) and 86% ($P = 0.06$) of the pre-ischemic values, respectively.

Figure 4 shows the decrease in LDF signal caused by retraction of the probe from the kidney surface with saline in the interspace. Evidently the probe was rather insensitive in this respect. Hence, at a distance of 0.5 mm, which is a distance equal to the depth sensitivity in renal tissue (see below), the LDF signal was over 90% of that found when the probe was in close contact with the kidney.

The decreases in LDF signals resulting from the absorption of laser light in kidney slices placed between the laser probe and the kidney surface are shown in Figure 5; the upper panel refers to slices of normal parenchyma and the lower one to slices obtained from a postischemic kidney with a large number of trapped RBCs.

Since the LDF signal, S(x), seems to decrease monoexponentially with the thickness, x, the experimental data were fitted to the equation

$$S(x) = S_0 \exp(-Kx), \quad (1)$$

where S_0 is the LDF signal from the uncovered kidney surface. K is a factor describing the reduction in LDF signal per unit length, which was estimated to be 27 μm^{-1} (K_{normal}) on insertion of slices of normal renal parenchyma and increased to 43 μm^{-1} ($K_{ischemic}$) when slices obtained from the postischemic kidney were inserted. This difference in K values would for obvious reasons also influence the signal obtained under the in vivo conditions investigated here. More precisely, the LDF signal, I(x), generated in a layer of unit thickness at a distance x, with absorption A will follow the relation

$$I(x) = I_0 \exp(-Ax), \quad (2)$$

and

$$\int_0^x I(x) \cdot dx = I_0/A \cdot \exp - Ax \quad (3)$$

Table 1. Relative blood flow (LDF signal) before and after 60 minutes of renal ischemia

	Cortex	Outer medulla	Inner medulla
Normal hematocrit (N = 7)			
Pre-ischemia	73.9 ± 7.0 (n = 40)	36.3 ± 12.2 (n = 28)	25.2 ± 10.1 (n = 57)
Postischemia	44.8 ± 8.33 (n = 42)[a]	5.8 ± 2.3 (n = 70)[a]	31.9 ± 12.0 (n = 57)[a]
Low hematocrit (N = 7)			
Pre-ischemia	87.8 ± 6.8 (n = 42)[b]	37.4 ± 11.2 (n = 28)	25.8 ± 8.6 (n = 58)
Postischemia	59.3 ± 9.5 (n = 43)[a]	26.9 ± 9.2 (n = 69)[b]	22.3 ± 6.9 (n = 60)[b]

Values are means ± 1 SD. N = number of animals, n = number of measurements
[a] $P < 0.01$ compared with the pre-ischemic value in the same animals
[b] $P < 0.01$ compared with the normal hematocrit group

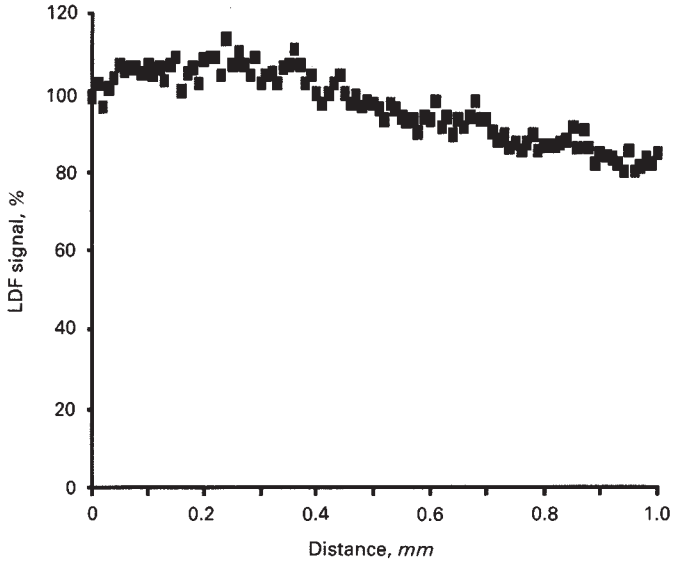

Fig. 4. *The decrease in laser-Doppler signal resulting from retraction of the probe from the renal surface with saline in the interspace.*

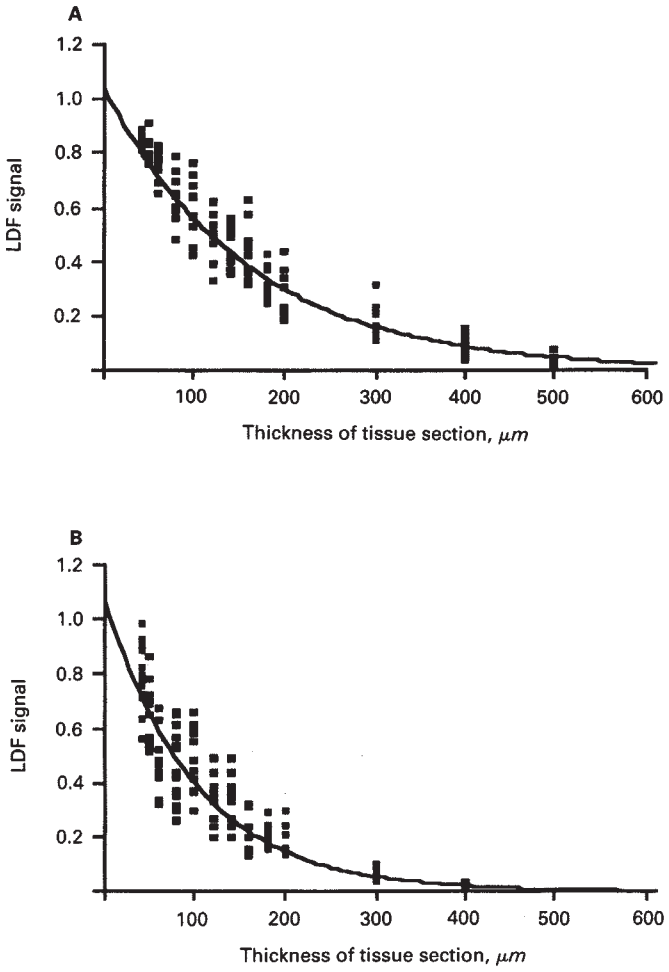

Fig. 5. *The decrease in the laser-Doppler signal resulting from placement of sections of renal tissue between the laser probe and the kidney surface.* **B.** Tissue sections from a normal kidney and (**A**) tissue sections from a postischemic kidney, containing a large volume of RBCs. By the least square method monoexponential curves were fitted according to the equations; $y = 1.04 \cdot 10^{(-0.0027x)}$ $R = 0.94$ (upper curve); and $y = 1.07 \cdot 10^{(-0.0043x)}$ $R = 0.96$ (lower curve).

Equation 3 should be identical to Equation 1, which means that $K = A$ and $S_0 = I_0/A$ or I_0/K.

Since I_0 at $x = 0$ will be the same in normal and ischemic tissue (that is, absorption will be zero in the first infinitely thin segment), the total LDF signal will be proportional to the reciprocal of the respective absorption coefficient, $A_{ischemic}/A_{normal}$. This means that the sensitivity of the LDF probe resulting from absorption of laser light in trapped RBCs would be reduced to 63%.

If this error is taken into account, the LDF signal obtained from the outer medulla in the control group should be 16.2/0.63 = 25.7% ($P < 0.01$) of the pre-ischemic value.

Discussion

There is still no general agreement as to whether the large number of RBCs in the outer medulla in ischemic ARF reflects an increase or a decrease in blood flow. For example, the phenomenon is sometimes referred to as hyperemia and sometimes as stasis. The latter opinion is supported by the observation of a postischemic perfusion deficit in the juxtamedullary glomeruli, from which the medullary capillaries derive [4, 5]. In contrast, direct measurement of the inner medullary blood flow on the exposed papilla has suggested that the perfusion in the inner medulla is well preserved or even increased after ischemia [9, 10]. The present study indicates that these results may not be contradictory. Thus after ischemia the outer medullary blood flow may be greatly reduced, while at the same time the inner medullary blood flow is paradoxically increased. It may be

noted here that although the vasa recta that supply the inner medulla run through the outer medulla, the distance between these vessels in the outer medulla is substantially longer than in the inner medulla, since the vasa recta converge towards the papilla. This will explain why a well preserved vasa recta blood flow yields low LDF values in the outer medulla and high ones in the inner medulla.

Vetterlein, Pethö and Schmidt [8] investigated the distribution of post-glomerular blood flow by means of fluorescein-globulin and found virtually no perfusion in the inner stripe of the outer medulla, except in spot-like areas which as a rule were seen in the region of the vasa recta. Scanning electron microscopy of the outer medulla has revealed that after ischemia RBC aggregates are present in considerable amounts in the tiny capillaries of the outer medulla, while the vasa recta generally exhibit no RBC trapping [24]. Both these observations support the present conclusion that the outer medullary blood flow may differ substantially from that in the inner medulla, which may actually be increased after ischemia. Furthermore, the present study has shown that this paradoxical postischemic increase in inner medullary blood flow may be due to RBC trapping in the capillaries of the outer medulla. The most probable explanation for this finding, we consider, is that RBC trapping will cause obstruction of outer medullary capillaries and shunting of blood through the outer to the inner medulla.

It may be considered that papillary exposure may cause hyperperfusion of the inner medulla [27, 28]. However, there seems to be no general agreement on whether papillary exposure *per se* affects the perfusion of the renal papilla. Hansell et al, using three different techniques to measure an index of medullary blood flow, found no increase in papillary plasma or RBC flow 15 to 120 minutes after papillary exposure [29], which is within the time course of the present study.

Regarding total RBF and GFR, RBC trapping seems to have little influence. In previous studies it was found that reduction of the hematocrit and thereby prevention of RBC trapping, and conversely an increase in the hematocrit, by which RBC trapping could be produced with a minimum of ischemia, had little if any preservative effect on postischemic RBF and GFR [25]. This lack of cause-effect relationship between RBC trapping and GFR is further supported by the observations that administration of osmolar diuretics such as mannitol [30], sucrose [31] or even contrast media [32] after ischemia caused an increase in inulin clearance, probably by wash-out of tubular casts, but no reduction in the RBC trapping in the outer medulla. Moreover, it is very probable that a reperfusion defect, restricted to the outer medulla, will have little influence on RBF and GFR. Nevertheless, RBC trapping may have a distinct pathophysiological relevance by causing secondary hypoxia in the outer medulla and thereby enhancing long-term kidney damage [24]. Thus, even if the vasa recta blood flow is well preserved, or even increased, it is probably insufficient to meet the high metabolic demand of the outer medulla [12]. In the inner medulla the distances between the vasa recta become shorter as they converge towards the papilla. The consequently better nutritive effect of the vasa recta flow in combination with a substantial anaerobic metabolism in the inner medulla might explain the sparse occurrence of morphological signs of injury in the inner medulla after renal ischemia [13].

Methodological considerations

Although the present small single-fiber probes may influence the whole organ blood flow to only a minor extent, they may affect the microcirculation near the probe. There is a high probability, however, that the probe intrusion will have the same effect in control and low-Hct animals, and the large decrease in outer medullary blood flow found only in the control group cannot be explained by such an artifact.

A possible source of error in LDF is the swelling of tubules and interstitial edema, which may separate the capillaries and hence reduce the number of vessels within the monitored tissue volume. However, with saline between the probe and the kidney surface over 90% of the LDF signal remained at a distance of 0.5 mm, which is equal to the maximal depth sensitivity of the laser probe in renal tissue as found in this study. Thus interstitial and tubular fluid most likely offer little restriction to the laser beam. Hence the number of vessels within the monitored volume would not be significantly influenced by edema. It may also be noted that the postischemic edema was of equal degree in animals with a normal and low hematocrit.

The presence of RBCs in tissue may, however, cause an increase in laser light absorption and hence lead to an underestimation of the blood flow. From the ratio between the absorption coefficients in normal and postischemic renal tissue the degree of underestimation was found to be 63%. However, this value represents a maximal error, as the absorption coefficient in normal renal tissue under the in vivo conditions would be higher than in the sections of a bled-out kidney, since not only stagnant but also moving RBCs will contribute to absorption of laser light. Nevertheless, even if we considered this underestimation at 63%, it could not explain the reduction in LDF signal to only 16% of the pre-ischemic value in the animals with RBC trapping.

Although in principal the LDF technique only provides values for relative blood flow, these have been shown to be linearly related to blood flow measured with other techniques [14–17]. Thus a comparison of the LDF signals obtained from the different regions of the kidney under pre-ischemic control conditions would seem valid. In the present study the LDF signals in the outer and inner medulla amounted to 49 and 29%, respectively, of the LDF signal in the cortex. The value for the inner medulla is in accordance with the report by Steinhausen et al [9, 33] that the blood flow per tissue volume in the exposed papilla was 24% of that in the kidney as a whole, since total renal blood flow mainly reflects the blood flow in the cortex.

Regarding the outer medulla, Wolgast, using intrarenal beta-sensitive detectors, found a red cell transit time in this area of the kidney of about 40% of that in the cortex [34]. This is in accordance with the present values of 49% and 43% in the control and low-Hct animals, respectively. Determinations of tracer extraction rates in the rat outer medulla have yielded similar values [7, reviewed in 1].

It is concluded from the present study that postischemic blood flow in the outer and inner medulla may differ substantially. The trapping of RBCs in the vasculature of the outer medulla causes a major reduction in the blood flow of this area of the kidney and a paradoxical increase in the inner medulla. By hemodilution RBC trapping can be effectively prevented

and, as a result, both the decrease in the outer and the increase in the inner medulla blood flow can be abolished. The decrease in cortical blood flow resulting from ischemia is not related to RBC trapping.

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