Effect of variations of blood flow on renal oxygen extraction

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Temperature gradients have been established in the isolated kidney of the dog in an attempt to ascertain the changes in oxygen extraction of the cortical and medullary regions of the kidney in response to reductions of blood flow. Cooling of the saline bath in which the kidney was immersed resulted in hypothermia of an external zone of cortex. Consequently, the rate of O₂ consumption of the medulla plus a zone of juxta-medullary cortex was relatively exaggerated. Cooling the renal arterial blood, on the other hand, rendered the deeper regions hypothermic, and the relative role played by the external zone of cortex was enhanced. Under either set of conditions, reduction of the renal blood flow resulted in only slight changes in O₂ extraction which were not significantly different from the behavior of the entire kidney. It is concluded that the superficial and deeper regions of the kidney extract O₂ in a similar fashion in response to moderate reductions of blood flow.

It has recently been demonstrated that oxygen diffuses from the arterial to the venous segments of renal capillaries (1). It was conjectured that this phenomenon may, at least in part, account for the flow-limited behavior of the kidney, that is, the dependence of oxygen consumption upon the blood flow. If this were true, then it would be reasonable to postulate that the renal cortex and medulla would respond quite differently to reduction in blood flow, since the circulatory arrangements are so dissimilar in these two regions. The postglomerular capillaries in the cortex from a reticular network, while the medullary capillaries, the so-called vasa recta, are arranged in the form of hairpin capillary loops, with the arterial and venous limbs often lying in close apposition to each other (2). Furthermore, Longley, Lassen and Lilienfield (3) have observed that the highly diffusible gas, krypton₁₆, was incorporated very slowly in the renal medulla. This suggested to them that the vascular countercurrent exchange must be highly efficient in this region.

When the medullary blood flow is retarded, therefore, it may be postulated that the venous oxygen tension equilibrates more completely with the arterial oxygen tension; that is, the arteriovenous oxygen difference actually diminishes when renal blood flow is reduced. In the reticular capillary networks of the renal cortex, on the other hand, it may be conjectured that decreased renal blood flow leads to a more complete extraction of oxygen from each unit volume of blood, similar to the response observed in most other vascular beds. The appropriate combination of reduced A-V oxygen difference in the medulla and augmented A-V oxygen difference in the cortex might then account for the overall absence of any appreciable change in the total renal A-V oxygen difference during moderate reductions of renal blood flow.

This is the working hypothesis which the present series of experiments was designed to test. The marked depressant effect of cold upon both renal oxygen consumption and renal blood flow (4-7) has been employed to minimize the influence of the cortical or medullary regions of the isolated kidney of the dog, while the changes in oxygen utilization of the remaining normothermic portion of the kidney have been ascertained during alterations of the renal blood flow.

METHODS

Mongrel dogs weighing between 11.3 and 31.6 kg (mean 18.4 kg) were anesthetized with sodium pentobarbital, 30 mg/kg, administered intravenously. The left kidney was exposed through a transperitoneal incision, and dissected free from the surrounding connective tissue. Bleeding points on the renal capsule were cauterized. After heparin (generously donated by Dr. W. R. Kirtley, Lilly Research Laboratories) was injected to prevent blood coagulation, the ureter and renal vessels were ligated and transected, and the kidney was transferred quickly to a perfusion system. Circulation was re-established after a period of from 107 to 296 seconds (mean, 185 sec.).
The perfusion system was identical with that which has been previously described (7). The kidney was suspended in a thermostated saline bath. Blood was conducted to it from the femoral artery of the experimental animal. In its passage to the renal artery, the arterial blood passed through a coil-type condenser. The temperature of the water circulating through the jacket of this condenser was controlled. The temperature at points 4, 10 and 15 mm beneath the renal capsule, as well as that of the kidney bath and of the arterial blood at its point of entry into the renal artery, were recorded from thermistor probes. These temperatures were recorded sequentially by means of a motor-driven selector switch. The complete cycle of temperature measurements was repeated every 20 seconds. Cooling of the superficial regions of the kidney was accomplished simply by replacing the saline in the kidney bath with refrigerated saline (approx. 20°C). Simultaneously, the temperature recorded by the deepest probe was observed, and the relatively slight tendency for this temperature to decline was countered by making an appropriate elevation (usually 1° or 2°C) of the temperature in the water jacket surrounding the arterial blood. Cooling of the deeper regions of the kidney, on the other hand, was achieved by running cold tap water through the condenser jacket. The temperature at the probe 4 mm below the capsule was held constant by elevating slightly the saline bath temperature.

Temperatures were recorded on one channel of a four-channel Sanborn recorder. Pressure at the renal artery was registered on a second channel by means of a strain gauge. The oxygen content of renal arterial and venous blood was recorded alternately on a third channel by means of a cuvette densitometer (8). The densitometer was calibrated over a range of deflections by analysis of the corresponding blood samples for oxygen content by the method of Roughton and Scholander. The densitometer is sensitive to changes in hemoglobin concentration as well as to variations in oxygen content. Hematocrit ratio measurements throughout each experiment revealed only slight changes. Although such variations do alter the densitometer deflections corresponding to the absolute levels of arterial and venous blood oxygen contents, in the small range of hematocrit variations encountered in any given experiment, the A-V oxygen difference so determined is virtually unaffected. The arterial blood was kept fully saturated by mechanically hyperventilating the animal slightly with room air at a constant rate throughout each experiment.

The fourth channel was employed for the registration of the renal venous outflow. The technique has been described in detail previously (7), and involved collection of the renal venous outflow in a short, vertical tube which was, in turn, connected to a femoral vein by means of tygon tubing. This tubing was alternately obstructed and reopened by means of a stainless steel solenoid valve. During the occlusion phase of the cycle, the blood accumulated in the vertical cylinder. The rise of hydrostatic pressure was recorded during this phase of the cycle by means of a strain gauge, and the slope was proportional to the renal blood flow.

Since the arterial blood pressure tended to be somewhat variable from one experiment to the next, greater reproducibility was achieved in 5 of the 12 experiments by incorporating a perfusion pump in the line between the femoral artery and the coil-type condenser. This pump (9) was self-regulating, and automatically held the renal arterial pressure at any preset level, despite any variations in renal vascular resistance, such as those which were occasioned by temperature changes.

The experiments were conducted in five stages. A) With both the kidney bath and water-jacket temperatures at, or slightly above, the normal range, renal blood flow and renal arterial and venous oxygen contents were recorded at the control arterial pressure (or at 150 mm Hg in the experiments in which the perfusion pump was used). The pressure was then dropped suddenly by constricting the tubing leading from the femoral artery (or by resetting the pump), and the changes in flow and oxygen content were usually assessed after 2 or 3 minutes at two different levels of blood pressure reduction. The arterial pressure was then allowed to return to its original level, and the recovery values were obtained. B) Next, the temperature of the kidney bath was lowered. After renal temperatures, flow and oxygen contents had stabilized, the above sequence of pressure reductions was repeated. C) The temperature of the kidney bath was then raised to its original value. After a sufficient period for equilibration, the pressure reduction sequence was again performed. D) A fourth set of data was then obtained after the temperature of the arterial blood bath was lowered. E) Finally, a fifth set of values was recorded after the entire kidney was again warmed. In alternate experiments, the priority of performing stages B and D was reversed.

R E S U L T S

Representative records from a typical experiment are presented in figure 1. Each segment shows blood pressure (P) in the renal artery, blood oxygen content (O), renal venous outflow (F), and temperature (T) of the kidney bath, renal arterial blood, and of the kidney at depths of 4, 10 and 15 mm beneath the capsule. This experiment was one of the five in which a perfusion pump was installed between the femoral artery and the coil-type condenser. The initial pressure was set at 150 mm Hg, as shown in segment a. The renal blood flow was 155 ml/min, or 236 ml/min/100 gm kidney weight (represented by the upward slope on the flow channel, corrected for the rate of withdrawal of blood through the densitometer cuvette). The oxygen content of the renal arterial blood is illustrated on the left side of the oxygen content channel of segment a; the renal venous content is shown on the right side of this segment. The arteriovenous oxygen difference amounted to 3.0 vol. %.
renal oxygen extraction

perature was 39°C, and the renal arterial blood was 37°C. The temperature at the most superficial probe in the kidney (4 mm below the capsule) was 38°C, while the two deeper probes (10 and 15 mm) were at 37°C. Segments b and c show the effects of reduction of pressure to 90 and 60 mm Hg, respectively. The corresponding flow rates were 141 and 119 ml/min. It is evident from the oxygen tracings that the saturation of the renal venous blood was not appreciably affected by these degrees of flow restriction. After segment c was recorded, the arterial pressure was returned to 120 mm Hg, and the recovery values (not shown in the figure) were essentially the same as those observed during control period a.

Segments d, e and f illustrate the effects of replacing the warm saline in the kidney bath with refrigerated saline (21°C). The probe 4 mm deep registered 23°C, while the two deeper probes remained at 37°C. The tracings show the oxygen content as renal arterial pressure is diminished. Measurements were made under conditions in which renal temperatures (T) were homogeneously normothermic (W/W), when the kidney bath was cooled (C/W), or when the arterial blood was cooled (W/C). The arterial oxygen content is shown on the left half of these same segments. Each subdivision on the oxygen scale (O) represents an increment of 1 ml O₂/100 ml blood. Each subdivision on the flow scale (F) represents an increment of 10 ml blood in the vertical reservoir. Since the sensitivities of the five temperature probes were different, the individual calibration scales were not incorporated in the figure.

![Fig. 1](image)

**Fig. 1.** Segments of original records from a typical experiment, showing changes in renal blood flow (F) and in arterial and renal venous oxygen content (O) as renal arterial pressure (P) is diminished. Measurements were made under conditions in which renal temperatures (T) were homogeneously normothermic (W/W), when the kidney bath was cooled (C/W), or when the arterial blood was cooled (W/C). The arterial oxygen content is shown on the left half of segments a, d and g. The renal venous oxygen content is recorded on the right half of these same segments, as well as throughout the entire extent of the remaining segments. Each subdivision on the oxygen content scale (O) represents an increment of 1 ml O₂/100 ml blood. Each subdivision on the flow scale (F) represents an increment of 10 ml blood in the vertical reservoir. Since the sensitivities of the five temperature probes were different, the individual calibration scales were not incorporated in the figure.

The composite data from the five experiments (including that shown in fig. 1) in which a pump was employed in the perfusion system are presented in figure 2. In the three periods marked 'W/W,' the temperatures of all strata of the kidney were 38°-40°C. In the first of these periods, the renal blood flow was 266 ± 45 (mean ± S.E.) ml/min/100 gm kidney weight at a mean renal arterial pressure of 119 ± 0.7 mm Hg. In the second and third W/W periods, at the initial arterial pressures of 120 mm Hg, renal blood flows were 299 ± 24 and 211 ± 16 ml/min/100 gm, respectively. Thus, over the course of the experiment, there was gradual increase in renal vascular resistance. The changes in flow in response to pressure reductions were quite similar in all cases, however. Furthermore, the A-V oxygen differences were very similar during the three W/W periods, and in each case remained quite constant during the periods in which pressure and flow were reduced.

In the period (C/W) in which the kidney bath temperature was diminished, the temperature recorded by the most superficial probe averaged 23°C, while the two deeper probes were 37°-38°C. Cooling the renal surface produced moderate reduction in renal blood flow. At the initial pressure of 120 mm Hg, the flow was 218 ± 27 ml/min/100 gm. The A-V oxygen difference was somewhat less than during the W/W periods, but the oxygen difference was not significantly affected by reduction of arterial pressure.

Cooling the renal arterial blood (W/C) resulted in renal medullary temperatures (two deeper probes) in the range of 24°-27°C, while the midcortical temperature (superficial probe) was maintained at 40°C. This had a much more profound influence upon renal blood flow. At the initial pressure of 121 ± 0.5 mm Hg, renal blood flow amounted to only 125 ± 22 ml/min/100 gm. Reduction of pressure to 91 ± 3 mm Hg resulted in a fall in renal blood flow to 91 ± 17 ml/min. The A-V oxygen difference increased very slightly from a value of 1.8 ± 0.2 vol. % to 1.9 ± 0.4 vol. %. Further reduction of flow to 62 ± 10 ml/min, however, was attended by a rise in A-V oxygen difference to 2.5 ± 0.6 vol. %.

With the exception of this augmentation of A-V oxygen difference at the lowest arterial pressure levels when the deeper regions of the kidney were depressed by cooling, the results of the experiments in which an accessory pump was not employed in the perfusion system were quite similar to the preceding results. Since the initial control blood pressures at the renal artery varied in individual animals from 90 to 120 mm Hg, the experiments could not be conducted in as uni-
In five experiments in which a perfusion pump was included in the arterial line, temperatures (T) were indicated at depths of 4 (circles), 10 (squares), and 15 (triangles) mm below the renal capsule. The mean thickness of the kidney used in this study was 58.3 mm. The mean weight of the kidneys was 58.3 g. The mean thickness of the cortical region was 7.6 mm, of the medulla, 14.5 mm. Cooling of the renal arterial blood resulted in a temperature distribution within the kidney in which the greatest rate of temperature change of temperature as a function of distance from the renal capsule occurred at a depth somewhere between 4 and 10 mm.

In the experiments depicted in figure 3, however, when the kidney bath temperature was reduced (C/W), the initial renal blood flow at an arterial pressure of 120 mm Hg was 218 ± 27 μl/min/100 gm. When the renal arterial blood was cooled (W/C), on the other hand, a much more drastic reduction in flow (125 ± 22 ml/min/100 gm) was obtained at an equivalent pressure. Since the arteriovenous oxygen differences were quite similar (1.70 ± 0.18 and 1.75 ± 0.24 vol. %, respectively), the rate of oxygen consumption was proportional to the difference in oxygen tension across the renal vessels and remained essentially constant during the experiments. In a previous study (7) from this laboratory, in which the experimental conditions were virtually identical with those of the present study, a homogeneous reduction of temperature of the entire kidney to 25°C resulted in a decrease of flow to approximately 45% and of oxygen consumption to about 28% of the normothermic values. In the present study, therefore, it may be presumed that when one region of the kidney was rendered hypothermic, its contribution to the total rate of oxygen utilization was markedly reduced. Accordingly, the relative role played by the remaining normothermic region was considerably enhanced. Therefore, by cooling either the more superficial or deeper zones of the kidney, the response of the remaining normothermic region to reductions of blood flow may be deduced.

Cooling the renal arterial blood exerted its most profound effects upon the deeper zones of the kidney. The more superficial regions were influenced principally by the temperature of the saline bath in which the kidney was immersed. The averaged weight of the kidneys used in this study was 58.3 g. The mean thickness of the cortex was 7.6 mm, of the medulla, 14.5 mm. These values are quite similar to those published by Janssen and Grupp (10, 11). The most superficial temperature probe, inserted into the kidney 4 mm beneath the capsule, was therefore located quite centrally in the cortex, while the probes 10 and 15 mm deep were both situated in the medulla. Cooling of the kidney bath or of the renal arterial blood resulted in a temperature distribution within the kidney in which the greatest rate of change of temperature as a function of distance from the renal capsule occurred at a depth somewhere between 4 and 10 mm.

At the present time, insufficient data are available concerning the relative rates of blood flow through the renal cortex and medulla. It seems probable, however, that the cortical blood flow exceeds the medullary flow (12, 13). Furthermore, the heat production per unit mass of renal cortex is equal to (14) or twice as great as (10) that of the medulla. Since heat production in the kidney is closely correlated with its rate of oxygen consumption (15), and since the cortical mass is approximately twice that of the medulla (11), the oxygen consumption of the cortex is very probably significantly greater than that of the medulla.

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DISCUSSION

Previous studies have demonstrated that hypothermia elicits a rather marked reduction of renal blood flow and oxygen utilization (4-7). In the experiments illustrated in figures 2, the temperatures of the hypothermic region of the kidney were in the range of 23°-27°C. In a previous study (7) from this laboratory, in which the experimental conditions were virtually identical with those of the present study, a homogeneous reduction of temperature of the entire kidney to 25°C resulted in a decrease of flow to approximately 45% and of oxygen consumption to about 28% of the normothermic values. In the present study, therefore, it may be presumed that when one region of the kidney was rendered hypothermic, its contribution to the total rate of oxygen utilization was markedly reduced. Accordingly, the relative role played by the remaining normothermic region was considerably enhanced. Therefore, by cooling either the more superficial or deeper zones of the kidney, the response of the remaining normothermic region to reductions of blood flow may be deduced.

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to the flow under each set of conditions. Therefore, oxygen utilization was depressed to an appreciably greater extent when the deeper regions of the kidney were cooled.

A similar situation obtained in the experiments in which a perfusion pump was not used (fig. 3). When renal blood flow was not restricted by the arterial clamp, during cooling of the kidney bath (C/W), the renal blood flow was 228 ± 72 ml/min/100 gm compared to an average value of 285 ± 59 for the normothermic (W/W) periods preceding and following this procedure. On the other hand, cooling of the renal arterial blood (W/C) resulted in a much lower rate of flow, 133 ± 27, compared to an average of 273 ± 52 for the preceding and ensuing normothermic (W/W) periods.

Since current information suggests that the renal cortex is actually responsible for two-thirds or more of the total oxygen consumed by the kidney, it appears probable that lowering the temperature of the renal arterial blood must not only cool the renal medulla, but also a significant zone of the adjacent cortex as well. Similarly, decreasing the kidney bath temperature must not render the deeper strata of the cortex hypothermic. Thus, cooling the renal arterial blood while the kidney bath is at normothermic or slightly hyperthermic levels creates a situation in which only the outer zone of the renal cortex is metabolizing at an approximately normal rate. When the kidney bath is cooled, on the other hand, the medulla and the deeper portion of the cortex are consuming oxygen at a normal rate.

In the experiments depicted in figure 3, the oxygen extraction remained rather constant or increased somewhat when renal arterial pressure was diminished. The changes obtained when the role played by the superficial cortex was relatively exaggerated (W/C) are not obviously different from those observed when the renal medulla plus juxta-medullary cortex (C/W) were preponderant. Nor do the directional changes of oxygen extraction of these portions of the kidney differ from the response of the entire normothermic kidney (W/W).

These findings were essentially confirmed by the series of experiments in which a pump was employed (fig. 2). During the three normothermic periods (W/W), oxygen extraction remained constant as pressure and flow were decreased. When the medulla plus juxta-medullary cortex (C/W) were metabolizing at a normal rate, the oxygen extraction behaved in a similar fashion. In the case of the normothermic external cortical region (W/C), during the first pressure reduction (to 90 mm Hg), again no appreciable change in the A-V oxygen difference was evident. With a more severe restriction of flow, however, the A-V oxygen difference did increase to 2.5 ± 0.6 vol. %, as compared to 1.8 ± 0.2 during the initial, and 2.1 ± 0.4 vol. % during the succeeding 120-mm Hg period. The A-V oxygen difference during this lowest flow period was not significantly different statistically from the values obtained during the initial (P = 0.3) or the final (P = 0.5) 120 mm Hg period, however. It is possible that the absence of statistical significance in this case may be attributable to the small sample size (5 experiments). However, a larger series was not performed, but the finding was interpreted as having no true physiological import for the following reasons: a) no appreciable change in oxygen extraction occurred during the preceding 90-mm Hg period; b) similar changes were not observed under comparable conditions in the series in which the pump was not used (fig. 3); c) in other studies, with more severe reductions in flow, increases in oxygen extraction are regularly observed (16), and a pressure of 60 mm Hg is at the margin of the transition zone; and finally d) if this augmented oxygen extraction were physiologically significant, then one would expect to see some reduction in oxygen extraction when blood flow to the medullary and juxta-medullary region (C/W) was reduced to a comparable degree, in order to account for the constancy of oxygen extraction as a function of total renal blood flow.

The hypothesis advanced in the introduction to this paper, which predicted divergent directional changes in oxygen extraction in cortex and medulla in response to moderate reductions of renal blood flow, is therefore felt to be untenable. One of two major alternative conclusions may be drawn. It is possible that diffusion of oxygen from arterial to venous limbs of renal capillaries occurs almost exclusively in the vasa recta of the medulla, but the magnitude of this phenomenon is insufficient to account for the flow-limited behavior of the entire kidney. The second alternative is that such diffusion occurs in both divisions of the kidney. Current experimental evidence from this laboratory (in preparation) indicates that the second possibility is more likely. However, until precise quantitation of the rate of oxygen diffusion is achieved, its role in explaining the flow-limited behavior of the kidney cannot be assessed.

The observation made in this study upon the isolated
kidney that the arteriovenous oxygen difference remains rather constant as renal blood flow is moderately diminished is in accord with numerous investigations upon more intact preparations (16-25). The recent studies of Grupp and his collaborators (26) have questioned the validity of this finding. They claim that the true response to a reduction in renal blood flow is a proportionate increase in oxygen extraction, with the consequence that renal oxygen utilization remains virtually constant as a function of flow. They argue that their studies reveal the correct physiological response of the kidney because of several alleged improvements in experimental design and technic; namely, a) sufficient time was allowed for the kidney to recover from surgical trauma, b) incomplete saturation of the arterial blood was avoided by having the animal respire oxygen-enriched air, c) data from experiments in which the renal blood flow was less than 1.8 ml/min/gm were considered to be abnormal, and d) each experiment was considered individually, rather than included in a scatter diagram. In the present, as well as in a previous study from this laboratory (16), all of these precautions were observed, at least in certain groups of experiments. For example, at least 1 hour was allowed to elapse from the time of completion of the surgical procedures until any experimental observations were made in both studies from this laboratory. In the previous study, 95–100% oxygen was administered to one group of animals. In the remaining experiments, as well as in the experiments described in the present study, complete saturation of the arterial blood with oxygen was assured by slightly hyperventilating the animals with room air by means of an artificial respirator. The mean control values for renal blood flow in both studies were well above the minimum acceptable level cited by Grupp et al. Furthermore, in the previous study, there was a remarkable parallelism in other aspects of experimental design with the experiments of Grupp and his collaborators, including type of anesthesia, surgical approach, method of achieving acute reductions of renal blood flow, and the use of a venous outflow technic for assessing flow. Despite these similarities in design, reduction of renal blood flow was almost invariably attended by a proportionate diminution in oxygen consumption in the studies performed in this laboratory. Since this is in accord with the vast majority of previous reports, it is concluded that the reasons advanced by Grupp and his colleagues do not adequately account for their differences in experimental results.

REFERENCES