STUDIES ON RENAL VASOCONSTRICTOR RESPONSES

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A high incidence of postoperative renal dysfunction was observed during our early experience with excision of abdominal aortic aneurysms under conventional anesthesia. Further experience has shown that this complication can be prevented by the administration of a ganglionic blocking agent during the period of aortic occlusion. The possibility that the prevention of some vasoconstrictor phenomena might be responsible for this occurrence was supported by experimental reports that a pathologic picture similar to the one we observed may be secondary to local vascular disturbances. Further, the high incidence of renal dysfunction seen after body trauma and the generalized vasoconstrictor response to experimental and clinical trauma suggested that vasoconstriction may be the underlying factor common to both entities.

A laboratory investigation was undertaken in an attempt to evaluate the role of renal vasoconstrictor responses in the production of renal pathologic changes.

METHODS

Fifty-two adult, mongrel, dogs selected at random from the existing stock and weighing between 10 and 16 kg. were used for this experiment. Anesthesia was induced by intravenous pentobarbital 30 mg./kg. and maintained by additional small doses of the same drug, administered via a jugular vein. A patent airway was provided by endotracheal intubation. Continuous aortic pressure was measured by a long catheter inserted via the carotid artery and connected to a Statham strain gauge and a Sanborn preamplifier and recorder. Renal blood flow measurements were obtained by the direct technique because it was believed that the validity of clearance methods might be questioned in the presence of renal ischemia.

A special brass "T" cannula inserted through a slit in the left renal vein allowed blood to enter the inferior vena cava or to be diverted into a graduate cylinder for direct renal blood flow measurements. In the first group of experiments, the renal vein was approached posteriorly through a paraspinal incision. In the second and third group the anterior approach, through a standard flank incision, was used. The renal pedicle was visualized in all cases and the renal vein mobilized for a distance of not more than 3 cm., care being taken not to disturb the delicate nerve fibers which run along the renal arteries. Mechanical denervation, if desired, was accomplished by mobilization of the kidney, transection of the pedicle and immediate reanastomosis. Ganglionic blockade was induced by the intravenous administration of a slow drip of trimethaphan camphorsulfone 0.1 mg./ml. (Arfonad) via the jugular cut-down.

At the conclusion of each experiment, the cannulated kidney was removed and the wound closed. Two to four days later, the animal was killed and the previously undisturbed kidney removed and studied. Three groups of experiments were performed.

GROUP A: In this group the effects of clamping the abdominal aorta distal to the renal arteries were investigated. The basic preparation was the same as described above. The clamp employed was a conventional vascular clamp borrowed from the operating room for this purpose. Seventeen dogs were used.

GROUP B: The effects of trauma were studied in 23 dogs. Trauma was produced by the administration of 450 to 550 blows to one hind limb with a light leather mallet. In 6 of these animals, flow studies were carried out immediately after traumatization. In some cases renal oxygen consumption was calculated from the measured renal blood flow and the renal
arteriovenous oxygen difference as measured by the spectrophotometric technique.8

Group C: The reliability and reproducibility of blood flow measurements by this technique as well as the influence of splenectomy on renal oxygen consumption after trauma were investigated in this portion of the experiment. Twelve dogs were used; they were all splenectomized one week to ten days prior to the experiment and were in apparent good health at this time.

RESULTS

Group A: Five animals were subjected to clamping of the aorta only. In all cases the arterial pressure did not change appreciably but the renal blood flow fell to values below 50 per cent of control in a period varying from 15 to 105 minutes. A typical pattern is shown in figure 1. The calculated renal vascular resistance rose in every case. Histologic sections of the kidneys removed at the time of the initial insult showed only hydric changes. The untouched kidneys, removed at the time of sacrifice showed changes consistent with a diagnosis of tubular necrosis (fig. 2 A).

The control group consisted of 4 animals in which the experiment was repeated in all details except the clamping of the aorta. Renal blood flow did not change noticeably even after 48 hours of observation. The untouched kidney, removed at sacrifice two days later, did not show histological evidence of tubular degeneration (fig. 2 B).

Acute mechanical denervation was produced in 2 animals immediately prior to clamping of the aorta. The renal blood flow paralleled the mean arterial pressure in both cases and the calculated renal vascular resistance did not show gross changes. The contralateral, normally innervated kidneys removed two days later did show appreciable signs of tubular degeneration.

The induction of ganglionic blockade alone in the remaining 6 animals resulted in falls in the arterial blood pressure and renal blood flow (fig. 3). In this case the falls were roughly parallel and the calculated renal vascular resistance did not show an appreciable change. Application of the aortic clamp, after ganglionic blockade, failed to alter this pattern except in one case where a significant reduction in renal vascular resistance with a proportional increase in renal blood flow was observed. We have no explanation for this isolated occurrence. Cross tubular degeneration was not observed in these animals (fig. 2 C).

Group B: The effects of trauma alone were investigated in 17 dogs. Four died too early to furnish satisfactory results. The remaining 13 were killed at intervals varying from 48 hours to seven days. Of these dogs, 10 showed renal parenchymal damage such as seen in figure 2 A and 3 were free of disease. Continuous blood pressure measurements in these 13 dogs, at the time of the initial traumatization, had failed to show falls in systemic pressure to “shock” levels.

On the basis of these findings we decided that 450 to 550 blows to one hind limb and a waiting period of 48 to 72 hours would yield the best results. Accordingly the effects of such procedure upon renal blood flow and renal vascular resistance were studied in 6 dogs. In 2 of these 6 animals mechanical denervation was accomplished immediately prior to the administration of trauma. In both cases the renal blood flow and arterial pressure followed roughly parallel patterns (fig. 4).
Fig. 2. (A) Histologic picture from specimen removed at sacrifice 48 hours after aortic clamping of two hours duration. Notice loss of cellular structure, separation from the basement membrane and early cast formation. (B) Kidney removed at sacrifice 48 hours after sham experiment. Notice preservation of structure and staining properties. (C) Histologic picture from specimen removed at sacrifice 48 hours after aortic clamping of two hours duration during ganglionic blockade. Notice preservation of cellular architecture, and absence of separation from basement membrane.

The calculated renal vascular resistance showed minimal changes from control values. In 2 animals traumatization produced a fall in renal blood flow which was not matched by a proportional fall in blood pressure (fig. 5 A). The calculated renal vascular resistance showed a two fold increase and the contralateral kidney removed at sacrifice showed histological damage (fig. 6 A). In the last two animals ganglionic blockade was induced immediately after trauma. We observed that blood pressure and renal blood flow followed roughly parallel patterns (fig. 5 B). The calculated renal vascular resistance did not show significant changes and the contralateral kidney removed at sacrifice failed to show gross abnormalities (fig. 6 B).

The studies of renal oxygen consumption done in these animals were difficult to interpret because, immediately after trauma, the blood oxygen carrying capacity changed conspicuously, and adequate readings could be obtained only by repeated resetting of the slit.

Fig. 3. Arterial blood pressure and renal blood flow changes during the administration of a ganglionic blocking agent. Notice how the two parameters follow roughly parallel patterns. Occlusion of the abdominal aorta after ganglionic blockade did not alter this course of events.
Fig. 4. Arterial blood pressure and renal blood flow changes after single leg trauma in a denervated kidney. In (A) the blood pressure fell because of persistent hemorrhage. In (B) no blood loss was present. Notice how the blood pressure and renal flow follow roughly parallel patterns.

Fig. 5. (A) Arterial blood pressure and renal blood flow after single leg trauma. Notice the fall in renal blood flow unmatched by a proportional fall in pressure. (B) Arterial blood pressure and renal blood flow after single leg trauma followed by ganglionic blockade of two hours duration. Notice the fall in pressure and the roughly parallel fall in renal blood flow. For calculated renal vascular resistances in both cases see text.
Fig. 6. (A) Histologic picture from specimen removed at sacrifice 48 hours after single leg trauma. Notice early cast formation, pyknosis of nuclei, moderate loss of cellular architecture.

(B) Histologic picture from specimen removed at sacrifice 48 hours after single leg trauma followed by ganglionic blockade of two hours duration. Notice preservation of cellular architecture and absence of detachment from basement membrane.
Fig. 7. (A) Renal vascular resistance and renal oxygen consumption after single leg trauma followed by ganglionic blockade. There is an initial fall in resistance with return to control values within one hour. The oxygen consumption increases at first and then falls.

width of the spectrophotometer. Previous experience having shown that splenectomy could obviate this inconvenience\(^\text{10}\) we decided to repeat some of these experiments in splenectomized dogs.

**Group C:** Renal blood flow was measured in 8 dogs. All measurements were repeated for accuracy; then the kidney was removed, trimmed and weighed, the cannula inspected for clots. The flows expressed in ml./gm./m. are given in table 1. It is apparent that this technique yields reproducible and satisfactory results.

In 2 splenectomized animals, renal oxygen consumption was studied after trauma alone and in 2 after trauma and ganglionic blockade. The renal blood flow, the arterial blood pressure and the pathologic changes observed in these 4 dogs were similar to those observed in the nonsplenectomized dogs (group B). However, there were no appreciable changes in the blood oxygen carrying capacity throughout the course of these experiments.

In the traumatized untreated animals the renal vascular resistance increased and the renal oxygen consumption fell after trauma (fig. 7 A). The data obtained in the treated animals show an erratic pattern. In figure 7 B, it is seen that in one dog the renal vascular

<table>
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<th>Dog No.</th>
<th>Kidney Weight (Gm.)</th>
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Notice the highly consistent yield of this direct technique of renal blood flow measurement. With one exception all figures are between 3.3 and 4.1 ml./Gm./m.
resistance is decreased although in an irregular fashion. The oxygen consumption after an initial rise falls to levels below control. In the second dog, not shown here, the renal vascular resistance increased but the oxygen consumption remained close to control levels throughout the experiment.

Of particular interest is the trend in renal arteriovenous-oxygen difference. In the traumatized and untreated dogs, it increases slightly while in the treated animals, its increase is five to six times the initial value.

**DISCUSSION**

The results in the first group of experiments indicate that clamping of the abdominal aorta near the renal arteries produces an increase in renal vascular resistance associated with a reduction in renal blood flow. These changes are followed by histologic alterations which may be ascribed to anoxia.2 Denervation of the kidney, mechanical or pharmacological, modifies the immediate hemodynamic alterations in the sense that gross changes in the calculated renal vascular resistance are not seen or are less. In the case of pharmacological denervation, one observation should be emphasized; that is, no histologic changes are seen for absolute flows equal, or even lower, to those after simple aortic occlusion without ganglionic blockade.

The most important conclusion drawn from these experiments is that it is possible to elicit a vasoconstrictor response which cannot be related to obvious systemic hypotension or shock and which is in itself capable of producing anoxic tissue damage. On the strength of these observations, we undertook the second and third group of experiments in an attempt to estimate the role of a generalized vasoconstrictor response as opposed to what might be considered a vicinity or proximity response to intense vascular stimulation.14

The results from the second and third group of experiments show that it is possible for a generalized vasoconstrictor response, which is not correlated with an obvious clinical picture of "shock," to produce local tissue damage, presumably ischemic. One should note the important role that these hemodynamic alterations may play in the pathogenesis of renal failure after trauma. However, for the present time, we would like to confine ourselves to the basic problem of the consequences of these responses upon the tissues which are thereby affected. An increase in local vascular resistance with a reduction in over-all oxygen consumption associated, at a later stage, with anoxic tissue damage seems to be the rule (figs. 5 A, 6 A and 7 A).

The modifications that ganglionic blockade have upon these events are the prevention of tissue damage (fig. 6 B) possibly through the maintenance of an adequate local oxygen uptake (fig. 7 B) and a normal or close to normal local vascular resistance (figs. 5 B and 7 B), though the latter does not seem to be an absolute requisite. We have been puzzled by this fact and we think the answer may be that our figures for resistance are only relative. The following explanation is offered: given a general equation for flow $F_i - P_0 = F - R$, where $P_i - P_0$ is the difference in pressure between any two points of the system, $F$ is the flow and $R$ the total of the resistances between the two points, it is obvious that for any pressure difference an infinite set of paired values for flow and resistance will satisfy the equation. For practical purpose, the viscosity of the fluid, the friction against the walls and the total number of channels which may be developed will limit the range of values for resistance. Thus, a fall in pressure does not necessarily mean a fall in flow, though once the lowest possible resistance is reached a fall in pressure necessarily would entail a fall in flow, hence a relative increase in resistance. This seems to be the case, as figure 8 shows. After ganglionic blockade the relative values for peripheral resistance increase below a critical pressure.

Reconsidering the data which have been presented two fundamental questions appear justified. First, how do these stimuli arise and how are they carried to the intrarenal vasculature? Second, are the circulatory modifications that they induce always beneficial?

Answering the first question, we may say that constrictor impulses travel along nerve fibers which accompany the renal artery. Electrical stimulation of these fibers in the renal pedicle results in a fall in renal blood flow.12 Conversely, in our experiments, interruption of
of maximal vasoconstriction by means of exogenous pressor substances.\textsuperscript{14-17} The experimental evidence in the laboratory points out that their use does not increase the survival rate.\textsuperscript{16, 19} Furthermore, when an attempt is made at suppressing the vasoconstrictor response to hemorrhage, an increase in survival rate is observed.\textsuperscript{10}

On the basis of the experimental evidence presented so far, it is legitimate to wonder whether or not the same should not apply to trauma.

\section*{Summary}

Under the conditions of the experiment clamping the abdominal aorta just distal to the renal arteries produces a decrease in renal blood flow associated with an increase in renal vascular resistance. These immediate changes are associated with late histopathologic changes compatible with an acute ischemic episode and morphologically similar to human, distal tubular necrosis.

Acute mechanical denervation of the kidney prevents immediate renal hemodynamic alterations, and pharmacological denervation (ganglionic blockade) modifies favorably the immediate changes and late histopathologic manifestations.

Under the conditions of the experiment limited trauma to one hind-limb produces immediate and late renal manifestations similar to those observed after aortic clamping. Ganglionic blockade administered immediately after trauma favorably modifies immediate and late renal changes.

A review of available data suggests that in the kidney it is possible to produce vasoconstrictor responses which result in histologic damage. Prevention of the constrictor response modifies favorably this course of events.

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\section*{References}


