Postocclusive reactive hyperemia in the rabbit kidney

NISHIO HONDA, CHIKARA AIZAWA, AND YAWARA YOSHITOSHI
First Department of Medicine, University of Tokyo School of Medicine,
Tokyo, Japan

Honda, Nishio, Chikara Aizawa, and Yawara Yoshitoshi. Postocclusive reactive hyperemia in the rabbit kidney. Am. J. Physiol. 215(1): 190-196. 1968.—Postocclusive hyperemia was studied in the intact rabbit kidney. Characteristically, two phases of hyperemia were revealed after release of the arterial occlusion: an initial phase of overshoot of flow and a succeeding decrement below the preclosure level, and a second phase of gradual flow increase. The duration of the initial phase averaged 8 sec following a 1-min occlusion and increased with longer occlusion periods. The initial overshoot was not demonstrated in the kidney exhibiting control high vascular resistance and in the chronically ureterally obstructed kidney, in which the Bayliss myogenic response appeared to be diminished. The second flow increase was slower in development and more persistent than the initial flow increase. Its magnitude rose with progressively longer occlusions. Venous pressure elevations induced by simple venous occlusion or arterial-venous occlusion suppressed the development of the second flow increase. On the contrary, renal vein pressure elevation produced by infusion of unoxygenated dextran into the renal vein failed to suppress the appearance of the second phase. The findings suggest that myogenic and metabolic factors may both be involved in the mechanisms of reactive hyperemia in the kidney.

renal reactive hyperemia; Bayliss myogenic mechanism; renal arterial occlusion; renal vein pressure elevation; ureteral obstruction

CIRCULATORY autoregulation is most prominent in the mammalian kidney (4, 16, 17). Postocclusive reactive hyperemia, apparently similar to the autoregulatory phenomenon, is not as obvious in the kidney (5, 6, 10, 11, 13, 15, 18). Both ischemic and hyperemic responses in the renal vascular bed have been observed after a sudden release of renal arterial occlusion. The mechanisms responsible for reactive hyperemia still remain unsettled. The following mechanisms have been proposed to account for reactive hyperemia in the kidney: 1) a decrease in intravascular pressure with resultant relaxation of the arteriolar smooth muscle through the Bayliss myogenic mechanism (13), 2) a predominant decrease in intrarenal venous segment resistance due to diminished tissue pressure (6), and 3) a production of vasodilator substances in the ischemic tissues during the arterial occlusion (6, 12, 13).

The purpose of the present work was to study the possible mechanisms for postocclusion hyperemia in the kidney of rabbits. The results suggest a contribution of both myogenic and metabolic factors to the production of renal reactive hyperemia.

METHODS

Experiments were carried out on 45 rabbits weighing from 2.5 to 3.5 kg, anesthetized with 25-30 mg/kg sodium pentobarbital given intravenously and heparinized with 1,000 U/kg. The left kidney area was exposed through a midabdominal incision. The kidney vessels on the left side were cleared of all surrounding tissues. The renal nerve was left intact whenever possible. A T cannula was inserted into the renal vein. Renal venous blood was drained through a flowmeter into a blood reservoir. Heparinized blood collected in the reservoir was pumped back to the right femoral vein by a roller-type pump through a heating unit to maintain blood temperature at 39 C. The volume of blood returned to the femoral vein was controlled so that it was almost equal to the renal venous outflow volume. Pressure-flow measurements were made in each experiment before and after renal arterial occlusion ranging from 1 to 5 min. Renal arterial occlusion was produced by clamping the artery, with care taken to leave the nerve outside a clamp.

Systemic arterial pressure was measured just below the origin of the left renal artery with a Statham pressure transducer (P23AA), connected to a catheter inserted into the abdominal aorta through the right femoral artery. Renal vein pressure was measured by a Statham pressure transducer (P23BB) connected to the sidearm of the T cannula. All pressure transducers were connected to appropriate amplifiers in a pen-writing recorder (WI-180M, Nihon Koden Kogyo Co., Japan). Renal venous outflow was measured with a photoelectric drop rate meter incorporated with a blocking oscillator, which is a modification of Lindgren’s technique (8). A direct electric current proportional to the number of drops per second was recorded. In calculating venous outflow volume from the number of drops per unit
RENAL REACTIVE HYPEREMIA

FIG. 1. Alterations in renal vein pressure (RVP), abdominal aortic pressure (AP), renal venous outflow (RBF), and renal vascular resistance (RVR) following release of renal arterial occlusions (thick lines) ranging from 1 to 5 min.

RESULTS

1) Patterns of renal vascular responses following renal arterial occlusion. Renal arterial occlusion resulted in a drop in renal vein pressure (Fig. 1). Abdominal aortic pressure decreased transiently and then increased to or above the preocclusion level. Small venous blood runoff occurred during the occlusion. After sudden release of the occlusion aortic pressure was apt to decrease, usually accompanying a concomitant increase of the venous outflow. This outflow pattern, known as reactive hyperemia, showed the following characteristic two phases: an initial phase of overshoot of flow and a succeeding decrement below the preocclusion level, and a second phase of gradual flow increase.

Figure 2 illustrates recovery patterns of the outflow resulting from the release of 1-min arterial occlusion. The patterns were grouped into the following four types: type 1 with both the initial and second phases, type 2 with the initial overshoot alone, type 3 with a gradual flow increase, and type 4 with an ischemic response (Fig. 2, from top to bottom). Type 1 was the most typical vascular pattern seen after release of the arterial occlusion. The vascular responses of types 1 and 3 appear to meet the criterion of reactive hyperemia, but the type 2 does not meet it because of its fleeting flow increase. Ischemic...

...the error due to drop volume variation with drop rate was corrected by using a drop volume-drop frequency curve. Renal vascular resistances before and after the occlusion were calculated from the data obtained.

Effects on reactive hyperemia of venous pressure elevations obtained by the following procedures were studied on eight kidneys, in order to determine if intravascular pressure alteration may participate in the production of reactive hyperemia: 1) simple venous occlusion, 2) arterial-venous occlusion, and 3) infusion of unoxygenated dextran solution, warmed to body temperature, into the renal vein during the arterial occlusion. Renal vein was occluded by applying a clamp on the rubber tube placed distal to the T cannula. The arterial and venous occlusions were released simultaneously.

Alterations in the patterns of reactive hyperemia by ureteral obstruction were also studied in 16 kidneys. The ureteral obstruction or ureteral pressure elevation was obtained by doubly ligating the ureter or opening a ureter catheter connected to a pressure bottle. Ureteral pressure was measured by a Statham pressure transducer (P23BB) connected to the catheter. The duration of the ureteral pressure elevation and obstruction ranged from several minutes to 14 days.
Renal vascular resistance decreased during both the initial and second phases of the flow increase, except that there was a transient increase at the transitional point from the initial phase to the second phase (Fig. 1).

Denervation of the renal nerve did not qualitatively affect the vascular response pattern following release of the occlusion.

2) Effects of venous congestion on reactive hyperemia. Simple venous occlusion and arterial-venous occlusion in six kidneys resulted in an increase in renal vein pressure, but did not affect aortic pressure (Fig. 4, B-D). Venous pressure elevation was more conspicuous during simple venous occlusion than during simultaneous arterial-venous occlusion. The initial flow overshoot following release of venous occlusion and arterial-venous occlusion was large when compared with that which followed an equivalent period of simple arterial occlusion. By contrast, the magnitude of the second flow increase following venous occlusion and arterial-venous occlusion was less than that following simple arterial occlusion. This suppression of the second flow increase was most marked in the simple venous occlusion experiment (Fig. 4B). However, renal vein pressure elevation obtained by the infusion of unoxygenated dextran solution into the renal vein during arterial occlusion in five kidneys failed to suppress the second flow increase, despite a venous pressure equivalent to that in the simultaneous arterial-venous occlusion (Fig. 5).

3) Effects of ureteral pressure elevation on reactive hyperemia. An acute transient elevation in ureteral pressure for less than 1 hr in nine animals produced an increase in renal venous outflow and a decrease in renal vascular resistance (Fig. 6). When ureteral pressure was lowered to the initial level again, venous outflow returned to the control value after a transient increase. The characteristic pattern of reactive hyperemia was not qualitatively affected by ureteral pressure elevation of less than 60 mm Hg. The magnitude of both the initial and second phases in excess of the preocclusion level decreased with progressively elevated ureteral pressure (Fig. 6, lower right). A chronic ureteral obstruction over 3 days in seven animals resulted in a decrease in renal venous outflow and an increase in renal vascular resistance. Ureteral pressure ranged 13-46 mm Hg. Following release of the ureteral blockade renal venous outflow increased. In these chronic obstruction animals, the initial flow overshoot following release of the arterial occlusion was not observed before and after release of the ureteral obstruction (Fig. 7). All reactive hyperemia elicited in 75% of the chronic obstruction experiments showed a pattern of gradual flow increase after release of the arterial occlusion. Even 1 hr after release of the ureteral obstruction, a brief ureteral pressure elevation did not result in the increase of flow and the decrease of vascular resistance seen in the acute occlusion group (Fig. 7).
FIG. 3. Interrelation of initial overshoot of flow ($F_d/F_a$), duration of overshoot ($t_1$), flow level in second phase ($F_d/F_a$), duration of second phase ($t_2$), and percent of repayment of blood flow debt produced during occlusion (B/A) with arterial occlusion period ($t_1$). Each point indicates average value in 26 experiments on 8 kidneys.

Discussion

The phenomenon of reactive hyperemia following release of arterial occlusion, commonly observed in other tissues (4), was also demonstrated in the intact rabbit kidney. The characteristic pattern of reactive hyperemia in the kidney revealed two phases as described by other investigators (11, 13): an initial overshoot of flow and a slowly developed flow increase. This vascular response is not of neurogenic origin, because it was not abolished by denervation. Also it was not directly related to alterations in aortic pressure.

The height of initial overshoot remained relatively constant despite longer duration of the arterial occlusion. Its duration averaged 8 sec after 1-min occlusion and increased with longer occlusion periods. Subsequent to the overshoot, a transient decrement of flow below the preocclusion level was observed. The overshoot was not produced in the kidney exhibiting control high vascular resistance. These findings appear to meet the criteria of a Bayliss myogenic response (1). Reduction in the vascular transmural pressure gradients during arterial occlusion may have resulted in active arteriolar dilation and, then, restoration of the transmural pressure gradients after release of the occlusion may have produced arteriolar constriction.

The increase in renal blood flow and the decrease in renal vascular resistance during acute ureteral pressure elevation also have been thought to be the result of an active myogenic vascular response of the arterioles to the reduced vascular transmural pressure gradients due to tissue pressure elevation (3, 9, 16, 17, 19). Chronic ureteral obstruction resulted in a decrease of renal blood flow and an increase of renal vascular resistance, despite less ureteral pressure elevation than that produced in the acute experiment. The decrease in prevenous segment resistance, seen during acute ureteral pressure
HONDA, AIZAWA, AND YOSHITOSHI

FIG. 5. Vascular responses after releases of simple arterial occlusion (left), simultaneous arterial-venous occlusion (middle), and venous congestion obtained by infusion of unoxegenated dextran solution into renal vein during arterial occlusion (right).

FIG. 6. Reactive hyperemia during acute ureteral pressure elevation (UP). Thick line indicates renal arterial occlusion. S: elevation (19), was not observed in the chronic ureteral obstruction. These findings are in contrast to those observed in acute ureteral pressure elevation. Thus the apparent myogenic response appeared to be diminished in the kidney with chronic ureteral obstruction. The primary cause for the diminished myogenic response remains unknown. During prolonged ureteral obstruction states, the kidney volume significantly increased and edema occurred. Microscopic findings showed markedly distended tubular lumina, but no abnormal changes in the blood vessel. On the other hand, the initial flow overshoot following release of the arterial...
occlusion, usually demonstrated in the normal kidney, was not produced in the kidney with chronic ureteral obstruction. These findings support the possibility of the myogenic origin of the initial overshoot.

Some investigators have interpreted the initial overshoot of arterial inflow as a phenomenon resulting from the refilling of intrarenal blood vessels depleted by venous drainage during arterial occlusion (5, 11). This is not solely the case, for the initial overshoot was also observed in the venous outflow pattern. However, the increase in initial flow overshoot observed in the kidney with venous congestion may be due to a greater flow runoff downstream from the arterioles before the occlusion is removed.

Progressively longer arterial occlusion resulted in lengthening the duration of the initial phase and reduction of the flow decrement subsequent to the initial overshoot. This might have been due to the depressed myogenic response of the ischemic arteriolar smooth muscle.

The second phase of flow increase after release of the arterial occlusion resulted in development and more persistent than the initial phase. The increased flow level in the second phase rose with progressively longer periods of arterial occlusion, though its duration remained relatively constant. Thus, an increase in blood volume supplied during the second phase with longer occlusions was brought about by increasing the flow level. The increased magnitude of the second phase with longer arterial occlusions suggested the possibility of metabolic factors as the mechanism responsible for the second flow increase.

Renal vein pressure elevations elicited by the above-described procedures suppressed the development of the second flow increase in reactive hyperemia. The similar finding in the dog limb has been interpreted as evidence for a myogenic origin of reactive hyperemia (2, 7). The explanation for this effect of venous congestion was that the arteriolar smooth muscles retained most of their tone, in accordance with findings of Bayliss (1), since relatively high vascular transmural pressure gradients were maintained by reducing the fall in intravascular pressure during venous pressure elevation. In contrast to the dog limb, venous pressure elevation in the rabbit kidney resulted in decreases in both precapillary and venous segment resistances (20). Therefore the above-described explanation for the effect of the venous congestion is unreasonable in the rabbit kidney. The more attractive explanation, as speculated in the canine intestine by Selkurt (14), appears to be that erythrocytes are retained in the intrarenal blood vessels and thus supply a greater oxygen reserve for utilization during congestive venous occlusion or arterial-venous occlusion than during simple arterial occlusion. Also, the other finding, that elevated venous pressure obtained by infusion of unoxygenated dextran solution through the
renal vein during arterial occlusion failed to reduce the second flow increase, may rule out the Bayliss myogenic response and support the concept of liberation of vasodilator substances from the ischemic tissues as an important factor for production of the second flow increase, as suggested by other investigators (6, 12, 13).

Hinshaw et al. (6) have emphasized the predominant contribution of the decrease in resistance of the venous segment through a diminished tissue pressure in the production of reactive hyperemia. Reactive hyperemia was not produced in the isolated rabbit kidney perfused with whole blood, in which the postocclusive hyperemia was demonstrated in the control state, adrenaline infusion resulted in the postocclusive ischemic response. Thus the ischemic response might be partly related to liberation of vasoconstrictive substances from the kidney tissue during the occlusion period (6).

The authors thank Drs. L. D. Carlson, Chief of Div. of Sciences Basic to Medicine, University of California, Davis, Calif., and W. H. Waugh, Associate Professor of Dept. of Medicine, University of Kentucky, Lexington, Ky., for their kind criticisms and suggestions.

This work was supported in part by a research grant administered by the Educational Ministry of Japan.

Received for publication 11 December 1967.

REFERENCES


