Autoregulation of Renal Circulation

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An attempt was made to investigate the mechanism of autoregulation of renal circulation in 19 canine kidneys perfused in situ with the donor's blood.

It was found that the rate of renal blood flow was increased proportionately less than the rise in perfusion pressure within a range of approximately 70–200 mm.Hg. This pressure-flow regulation was not deteriorated by either pharmacological denervation or infusion of regitine, but disappeared during the administration of papaverine hydrochloride, a known direct smooth muscle relaxant. Thus, the presence of autoregulation of renal circulation, the mechanism of which being ascribed to the myogenic nature of the renal vasculature, was confirmed.

During the direct infusion of high concentration of norepinephrine, renal blood flow was reduced to subnormal value and autoregulation disappeared. This fact suggests that autoregulation is not a participant of maintaining sufficient renal blood flow in circulatory emergency which being intensely influenced by humoral factors.

In some kidneys, renal venous pressure was successively increased, maintaining arterial pressure constant. Renal vascular resistance decreased according as the venous pressure rose, i.e., as the arterio-venous pressure difference decreased. It is therefore suggested that the mechanism of autoregulation in the renal blood flow is related to the arterio-venous pressure difference rather than to the absolute level of arterial pressure.

MANY investigators have found that the renal blood flow tends to remain relatively constant in spite of changes in renal arterial pressure within a range of approximately 70–200 mm.Hg.^{1)–12)} Since the mechanism of this pressure-flow regulation is generally accepted as an intrinsic property of the kidney, not due to nervous or humoral control from outside, it is termed autoregulation.¹³⁾ However, there still remain several conflicts concerning in the precise mechanism residing in the kidney. Indeed, Langston et al.^{14)–17)} reported that this phenomenon was an artefact caused by experimental procedures and the normal kidney did not manifest autoregulation.

The present study was conducted to demonstrate the presence of autoregulation of renal circulation in the normal kidney and to investigate the

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mechanism of it, and further the effects of norepinephrine and elevated venous pressure on renal circulation were also studied.

MATERIALS AND METHODS

A total of 19 perfused kidneys in situ from mongrel dogs weighing from 6 to 11 Kg. were used in this study. Weights of the kidneys widely ranged from 16 to 54 Gm. (average 36 Gm.). Animals were anesthetized with a combination of subcutaneous morphine hydrochloride (6 mg./Kg.) and intravenous chloralose (70 mg./Kg.). The left hilum area of the recipient dog was exposed by a retroperitoneal flank incision and then the renal artery and vein were cannulated respectively, without disturbing the renal nerve supply. The spermatic or ovarian vein was ligated. Immediately after cannulation, perfusion of the kidney was commenced with blood from the femoral artery of the donor dog through a pump-perfusion apparatus (Fig. 1). The procedures interrupted the renal blood flow supply for 2-3 min. The perfusion circuit was primed with fresh blood from 1 or 2 additional dogs prior to the perfusion. Heparin sodium was employed as an anticoagulant. The donor dog was inspired with 100% oxygen via tracheal intubation during the experiment. Perfusion pressure was regulated by means of a Starling resistance device and was recorded by an electric manometer through the T-tube placed near the tip of the arterial cannula. Distal end of the venous tube was placed at the height of renal hilum and venous pressure was monitored by another electric manometer. When elevated venous pressure was needed, another Starling resistance was set in the venous circuit. An electro-magnetic flowmeter was employed for recording either renal blood inflow or outflow. Venous blood was once collected in a venous reservoir and returned into the femoral vein of the donor dog through a venous pump. The

Fig. 1. Diagram of perfusion apparatus employed. 1: Femoral artery, b: Femoral vein, c: Electro-magnetic flowmeter, d, e: Electric manometer, f: Left renal artery, g: Left renal vein.

blood in the circuit was always kept at about 38°C. Drugs dissolved in normal saline was directly infused into the arterial circuit by a constant infusion machine at the rate of 1.45 ml./min.

In the first series of this study, changes in renal blood flow during alterations of perfusion pressure were investigated, while venous pressure remained at near the atmospheric pressure.

Perfusion pressure was initially adjusted to the 120–140 mm. Hg range for 20–30 min. until the renal blood flow was adequately stabilized. Thereafter, perfusion pressure was reduced to about 40 mm. Hg from the initial control pressure and then it was increased successively by 20–30 mm. Hg steps to about 240 mm. Hg. The renal blood flow was measured at each perfusion pressure level 1–2 min. after the pressure change. Perfusion pressure was again adjusted to the initial control pressure for approximately 20 min. Denervation was then accomplished by a combination of injection of 2% procain into the renal hilum area and painting phenol on the tissues surrounding the renal vessels, following which there occurred no change in renal blood flow by an electrical stimulation of the splanchnic nerve of the recipient (Fig. 2). After denervation, the procedure of changing pressure was repeated. Thereafter, dibenamine hydrochloride (200 μ g./min.) or regitine (100 μ g./min.) was infused in order to inactivate circulating catecholamine (Fig. 3) and then papaverine hydrochloride (20 mg./min.) was also administered in order to relax the smooth muscle of the renal vasculature directly.

E. S. : Electrical stimulation.

Fig. 2. Response in renal blood flow to the electrical stimulation of the left splanchnic nerve of the recipient (20 cps., 20 msec., 10 mV.).

A: Innervated kidney. B: Denervated kidney.

Fig. 3. Response in renal blood flow of the recipient to a single injection of epinephrine directly into the arterial circuit. A: Before the infusion of regitine. B: During the infusion of regitine (100 μ g./min.).

Transient pattern of the pressure-flow relation was also studied. A partial occlusion of the arterial channel produced by a clamp was suddenly released and the changes in renal blood flow were continuously recorded during the procedure.

In 2 kidneys, 4% polyvinylpyrrolidone (PVP) in normal saline was used for the perfusate.

In the second series of this study, norepinephrine was directly infused at various concentrations into the arterial circuit of denervated preparations and the effect of norepinephrine on renal autoregulation was investigated.

In the third series of this study, renal venous pressure was increased in stepwise fashion to about 40 mm. Hg and the effect of elevated venous pressure on renal circulation was studied.

RESULTS

Relationship of renal blood flow to perfusion pressure: Fig. 4 A represents the pressure-flow relations in 7 innervated kidneys perfused with blood. The pressure-flow curve was of a sigmoid shape, being concave to the pressure axis over the lower range of perfusion pressure and convex to the pressure axis over the higher range of perfusion pressure. The rate of renal blood flow was increased proportionately less than the rise in perfusion pressure within a range of approximately 70–200 mm.Hg, so that the calculated vascular resistance was increased as a function of elevated perfusion pressure within this range of pressure. This pressure-flow relationship remained essentially unchanged after the pharmacological denervation was accomplished (Fig. 4 B). The infusion of regitine or dibenamine hydrochloride also failed to affect this pressure-flow relationship (Fig. 4 C).

On the contrary, renal blood flow was markedly increased during the infusion of papaverine hydrochloride and renal blood flow was increased proportionately or more than the rise in perfusion pressure, so that the pressure-

flow curve became linear (Fig. 4 D).

During the perfusion with PVP solution, the pressure-flow curve was linear (Fig. 5).

Fig. 4. Relationship of renal blood flow to perfusion pressure in the kidneys perfused with blood. Abbreviations in Fig. 4 C are as follows ;

D : Dibenamine hydrochloride, R : Regitine.

Fig. 5. Relationship of renal flow to perfusion pressure in the kidneys perfused with PVP solution.

Transient pattern of the pressure-flow relationship: The suddenly raised perfusion pressure by a rapid release of the arterial occlusion produced an initial sharp rise in renal blood flow which was followed by a rapid reduction of renal blood flow towards the control value (Fig. 6 A, Fig. 6 B). Degree of the occlusion was the more severe, the greater became magnitude of the overshoot of the flow rate from the control value. After mild arterial occlusion, renal blood flow was stabilized within several seconds. Following severe arterial occlusion, renal blood flow was once reduced from its peak value down to the sub-control value and then the second small rise in the flow rate was prolonged for 1–2 minutes. On the other hand, the rapid reduction following the initial sharp rise in the flow rate was scarcely observed during the papaverine administration (Fig. 6 C).

Fig. 6. Transient changes in renal blood flow after the sudden release of the arterial occlusion. A: Denervated kidney. B: Innervated kidney. C: During the infusion of papaverine hydrochloride (20 mg./min.).

Effect of norepinephrine on the pressure-flow relationship: The denervated preparations employed here showed the sigmoid pressure-flow curves before the infusion of norepinephrine (Fig. 7). After the infusion of norepinephrine at the rate of 0.1 μ g./min., renal vascular resistance at the control pressure was slightly increased or remained unchanged. During the infusion of such a low

Fig. 7. Effect of norepinephrine on pressure-flow relationship.

concentration of norepinephrine, the pressure-flow curve remained essentially unchanged. However, when higher concentration of norepinephrine was infused, the pressure-flow curve became linear. The renal blood flow at normal pressure was extremely subnormal and the absolute value of change in renal blood flow was small. However, it was found that the increase in flow rate was nearly proportionate to the rise in perfusion pressure.

Effect of elevated venous pressure on renal circulation: Fig. 8 represents the effect of elevated venous pressure on renal blood flow, maintaining the perfusion pressure constant within the 140–160 mm.Hg range. Reduction of renal blood flow was found to be relatively small until venous pressure approached about 20 mm. Hg. Above this level of venous pressure, reduction of renal

Fig. 8. Effect of elevated venous pressure on renal circulation, maintaining perfusion pressure constant within the 140–160 mm.Hg range.

blood flow with increase in venous pressure was somewhat greater. However, decrease in renal blood flow was less than proportionate to the rise in venous pressure, so that the resistance to flow, i.e., arterio-venous pressure difference divided by flow rate decreased in some degree according as venous pressure rose, except in the kidney having a high resistance to flow. There was no detectable difference in pressure-flow relations between innervated and denervated kidneys.

DISCUSSION

This study was begun with confirming the presence of autoregulation of renal circulation, thereafter the effect of norepinephrine or elevated venous pressure on renal circulation was also investigated.

The pressure-flow relations in innervated kidneys perfused with blood depicted sigmoid curves shaping the plateaux to the pressure axis within a range of approximately 70–200 mm. Hg, since increase in renal blood flow was less than proportionate to the rise in perfusion pressure within this range of pressure.

This pressure-flow regulation was not deteriorated after pharmacological denervation, as reported by Haddy et al.³⁾ Procedures for inactivating the circulating catecholamine also failed to affect this pressure-flow regulatory mechanism, as observed by others.^{2), 3), 18)} Hence, the presence of renal autoregulation was demonstrated, confirming the works conducted by several investigators.^{1)–12)}

On the other hand, Langston et al.^{14), 15)} reported that renal autoregulation was absent in the normal kidney but present after perirenal tissue damage or after renal ischemia. However, it was pointed out that the rates of renal blood flow at normal perfusion pressure were extremely subnormal in their aortic cannulated preparations.^{18), 19)} de Wardener and Miles²⁰⁾ found that cannulation of the abdominal aorta often induced intense renal vasoconstriction and loss of autoregulation. It has been observed that renal vasoconstriction by any causes tends to impair the autoregulatory mechanism,^{8), 20)} although vasoconstriction is not the only factor for impairment of autoregulation.^{7), 20), 21)} Therefore, the observations of Langston et al. are not quite contrary to the fact that the normal kidney reveals autoregulation. Furthermore, Schmid²²⁾ recently suggested that the pressure-flow regulation was not an artefact caused by experimental procedures, using a non-cannulating electro-magnetic flow-meter probe.

The precise mechanism of autoregulation still remains unsettled. Kinter and Pappenheimer^{5), 23), 24)} postulated that the mechanism underlying auto-

regulation was based on the process of separation of red cell from plasma in the renal arterial tree. On the other hand, Hinshaw et al.^{4), 25), 26)} and the others^{1), 27)} believed that renal tissue pressure increased with elevated arterial pressure. Hinshaw et al.⁴⁾ described that the mechanism of autoregulation could be explained on the basis of effects of increases in extravascular pressure. However, Miles and de Wardener,²⁸⁾ Gottschalk²⁹⁾ and the others^{3), 18)} reported that renal tissue pressure was hardly affected by elevation of arterial pressure alone. Waugh,^{12), 18)} and Thureau and Kramer¹¹⁾ postulated that renal autoregulation was dependent upon the myogenic nature of the intrarenal vasculature. Renal autoregulation has also been ascribed to the changes in tissue metabolites in response to changes in flow rate or pressure.^{30)–32)}

In this study, autoregulation was completely abolished by relaxation of the smooth muscle with papaverine hydrochloride, as reported by Thureau and Kramer.¹¹⁾ Similarly, it has been found that renal autoregulation was impaired by some agents, such as chloral hydrate,¹⁸⁾ cyanide^{6), 33)} or high concentration of procaine,¹⁸⁾ which had direct depressant effect upon smooth muscle. Since the procedures rendering the smooth muscle inactive easily affected autoregulation, it is strongly suggested that the mechanism of autoregulation is related to the myogenic nature of intrarenal vasculature rather than to the passive process. Also, the absence of autoregulation even during the perfusion with cell-rich blood is an indirect evidence against the cell separation process as a causal factor of autoregulation. The lack of autoregulation in the kidney perfused with PVP solution is probably due to the damage of renal vasculature. Haddy et al.⁸⁾ observed that autoregulation was absent even during the perfusion with whole blood when dextran solution was alternately used as the perfusate at each flow rate. Furthermore, fairly good autoregulation was still preserved in the kidney perfused with cell-free perfusate including plasma.¹⁸⁾ Thus, the cell separation process seemed to be unlikely as a causal factor of autoregulation.

Transient pattern of the pressure-flow relations provided a further support for the active myogenic process as a mechanism underlying the autoregulation. It is inferred that the initial sharp rise in renal blood flow after rapid rise in perfusion pressure is due to the passive dilatation of renal vasculature which is relatively relaxed in the lower level of perfusion pressure. The following reduction of renal blood flow towards the control value may be due to the reactive renal vasoconstriction in response to the rise in perfusion pressure. This reaction occurred rapidly as the smooth muscle contracted with direct or nervous stimulation.^{34), 35)} The second small rise in renal blood flow following the initial spike often observed after severe arterial occlusion is probably due to the reactive hyperemia.^{7), 22)} The rapid reduction following initial sharp

rise in renal blood flow was scarcely seen during the papaverine administration, as reported by Thurau and Kramer,¹¹⁾ similarly by Waugh.¹⁸⁾ It is difficult to explain these findings by the passive process. It also seems to be unlikely that changes in concentration of tissue metabolites take place within such a short period. Hence, it is concluded that active myogenic process of intrarenal vasculature is most suitable for the mechanism underlying the autoregulation. Bülbbring³⁶⁾ found that smooth muscle itself well responded to the mechanical stretch.

During the direct infusion of relatively high concentration of norepinephrine, renal blood flow was considerably reduced to subnormal value and the pressure-flow curve became linear. Although the absolute value of increase in flow rate was small, increase in flow rate was nearly proportionate to the rise in perfusion pressure. Grupp³⁷⁾ also found the loss of renal autoregulation by the intravenous infusion of norepinephrine. This impairment of autoregulation suggests that autoregulation is not a participant of maintaining the sufficient renal blood flow in circulatory emergency which being intensely affected by humoral factors. The loss of autoregulation has been found in a hemorrhagic shock.^{8), 18), 20)}

Opinions regarding the effect of elevated venous pressure on renal circulation still remain unsettled.^{33), 38)–40)} In the present study, changes in renal blood flow was a little during the alterations of venous pressure within a range of about 0–20 mm. Hg. Among the possible factors operating on renal circulation in an elevated venous pressure,^{38), 41)} the effect of increased renal tissue pressure with increased venous pressure is thought to be most important.³⁹⁾ Gottschalk²⁹⁾ found that renal tissue pressure remained constant until venous pressure approached pre-existing tissue pressure (average 16 mm. Hg). Above this level of venous pressure, decrease in renal blood flow with increased venous pressure was somewhat greater. However, decrease in renal blood flow was less than proportionate to the rise in venous pressure, so that resistance to flow, i.e., arterio-venous pressure difference divided by flow rate, decreased as venous pressure rose. Thus, reduction of arterio-venous pressure difference solely produced by the elevation of venous pressure was also accompanied by reduction of resistance.

This suggests that autoregulatory mechanism is related to the arterio-venous pressure difference rather than to the absolute level of arterial pressure. Semple and de Wardener⁴²⁾ also reported that autoregulation was primarily dependent upon the arterio-venous pressure difference from the observations of transient patterns of pressure-flow relations. Gottschalk²⁹⁾ found that renal tissue pressure was increased together with increased venous pressure when venous pressure exceeded about 20 mm. Hg. Winton⁴³⁾ agreed with the fact

that when venous pressure exceeded pre-existing renal tissue pressure, both pressures were increased equally, although he obtained different control value for renal tissue pressure. From these findings, it is suggested that arterio-venous pressure difference, holding venous pressure within relatively higher range, is closely related to the transmural pressure of intrarenal vasculature.^{39), 42)} If this is correct, it is indicated that autoregulatory mechanism is attributed to the transmural vascular pressure rather than to the absolute value of intravascular pressure, as postulated by Waugh,¹⁸⁾ or Semple and de Wardener.³²⁾

SUMMARY

(1) A total of 19 canine kidneys were perfused in situ with the donor's blood or with PVP solution to demonstrate the presence of autoregulation of renal circulation and to investigate the mechanism of it.

(2) The rate of renal blood flow was measured at various levels of perfusion pressure. The rate of renal blood flow was increased proportionately less than the rise in perfusion pressure within a range of approximately 70–200 mm. Hg both in innervated and denervated kidneys. This pressure-flow regulation was not deteriorated by the infused dibenamine hydrochloride or regitine inactivating catecholamine, but it was completely abolished by the administration of papaverine hydrochloride, a known direct smooth muscle relaxant. Thus, the presence of autoregulation of renal circulation, the mechanism of which being ascribed to the myogenic nature of the renal vasculature, was demonstrated.

(3) Transient change in renal blood flow after the sudden release of arterial occlusion was composed of the initial sharp rise followed by the rapid reduction towards the control value. The time interval for this response was within several seconds. The rapid reduction following the initial sharp rise in renal blood flow disappeared during the papaverine administration. These findings provided a further support for the active myogenic process of intrarenal vasculature as a causal factor of autoregulation.

(4) During the perfusion with PVP solution, autoregulation was not evident. This is probably due to the damage of renal vasculature by the agent.

(5) During the direct infusion of high concentration of norepinephrine, renal blood flow was reduced to subnormal value and autoregulation disappeared. This fact suggests that autoregulation is not a participant of maintaining sufficient renal blood flow in circulatory emergency which being intensely influenced by humoral factors.

(6) In some kidneys, the effect of elevated venous pressure on renal cir-

culation was studied. Reduction of arterio-venous pressure difference solely produced by elevation of venous pressure was also accompanied by decrease in resistance. It is therefore suggested that the mechanism of autoregulation is related to the arterio-venous pressure difference rather than to the absolute level of arterial pressure.

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