Preglomerular and postglomerular blood flow: relationship to kidney disease and treatment

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■ **BACKGROUND** In the kidney, the afferent and efferent arterioles normally constrict or dilate in response to changes in systemic blood pressure to maintain glomerular filtration while protecting the glomerulus from excessive pressure. In diabetes mellitus and hypertension, the two most common causes of kidney failure, sustained hypertension within the glomerulus damages the glomerular membrane and eventually results in loss of kidney function.

■ **SUMMARY** Techniques developed in the last 10 years allow direct study of the glomerulus and the glomerular circulation. In both diabetes and hypertension, the afferent vessels may dilate, resulting in excessive pressure in the glomerulus. Calcium antagonists, angiotensin-converting enzyme inhibitors, and cyclosporine have direct effects on the preglomerular and postglomerular vessels, and the afferent and efferent arterioles may respond differently to the same agent.

■ **CONCLUSIONS** Techniques for studying afferent and efferent arteriolar changes and glomerular filtration rate may provide important insights into the actions of drugs and into renal diseases. Clinicians are beginning to be able to select drugs that have desired effects on the renal microcirculation.

■ INDEX TERMS: KIDNEY GLOMERULUS; GLOMERULAR FILTRATION RATE; KIDNEY DISEASES ■ CLEVE CLIN J MED 1994; 61:179–185

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DIABETES MELLITUS and hypertension account for approximately two thirds of the 45 000 cases of kidney failure in the United States each year. In both of these diseases, damage occurs as the result of sustained hypertension within the glomerular capillaries. Research techniques developed in the last 10 years are shedding light on how the kidney regulates pressure within the glomerulus, how regulation is altered in diseases such as hypertension and diabetes, and how various drugs affect the renal microcirculation. Thanks to this increasing knowledge, clinicians are beginning to be able to select drugs that have desired effects on the renal circulation and, perhaps, to prevent or slow the progression of kidney failure.

GLOMERULAR FILTRATION

Within the glomerulus, hydrostatic pressure forces approximately 20% of the plasma through microscopic pores in the capillary membrane (*Figure 1*). The rate of

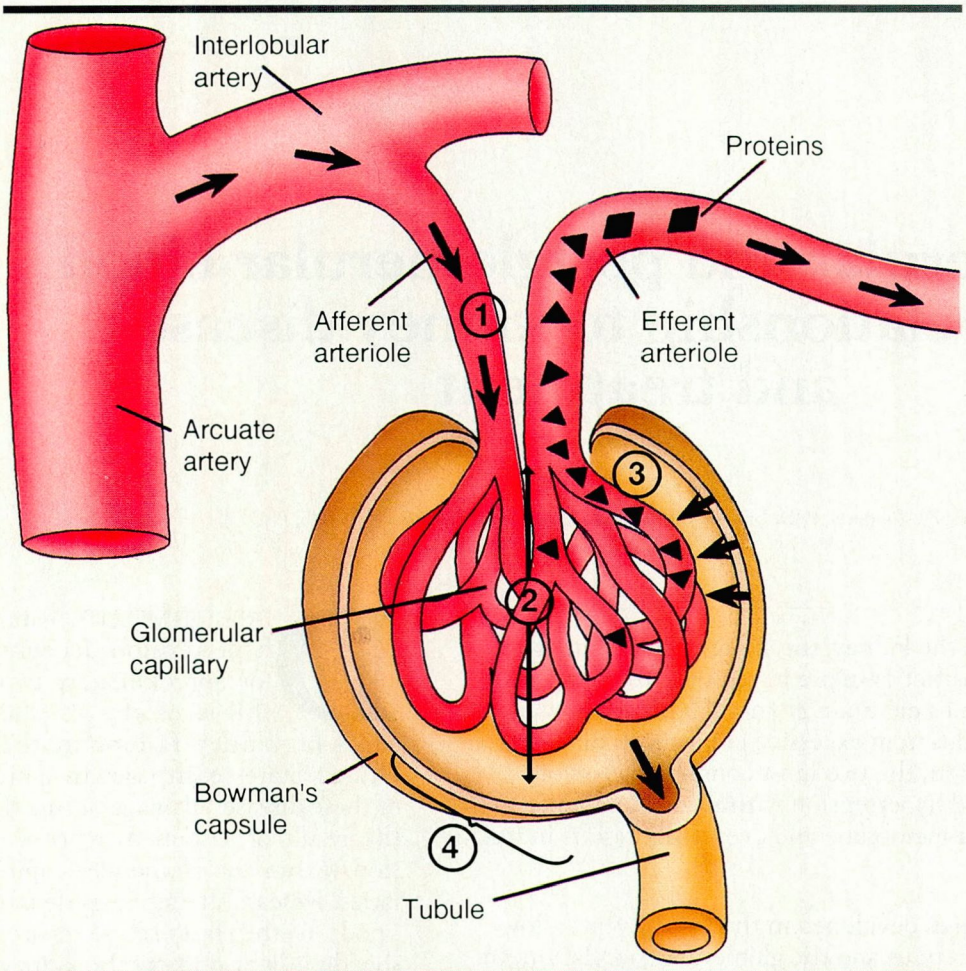

FIGURE 1. The renal microcirculation, highlighting factors that influence glomerular filtration. The rate of fluid flow = Kf × (blood pressure — oncotic pressure); Kf is the ultrafiltration coefficient, reflecting surface area and permeability of the glomerular membrane filtering surface. The glomerular filtration rate depends on (1) blood flow, (2) blood pressure, (3) oncotic pressure, and (4) surface area and surface permeability.

glomerular filtration thus depends primarily on the glomerular capillary pressure and on the surface area and permeability of the capillary; the oncotic pressure of the blood opposes this process. In clinical practice, the glomerular filtration rate is usually estimated from the concentration of serum creatinine, or more precisely calculated from the clearance of endogenous creatinine. One can also use exogenous substances such as inulin or iodine 125 iothalamate. Renal blood flow can also be measured with radionuclides or clearance techniques, and it can be measured experimentally using an electromagnetic or pulsed-Doppler probe placed on the renal artery.

The interlobar, arcuate, and interlobular arteries and afferent arterioles leading to a glomerulus and the efferent arterioles emerging from it can dilate or constrict independently to regulate pressure within and flow through the glomerulus, and thus, the glomerular filtration rate. If the systemic blood pressure falls, the afferent arteriole usually dilates to maintain the glomerular filtration rate; conversely, if the systemic blood pressure rises, the afferent arteriole should constrict to protect the glomerulus. The effects of changes in the diameter of the afferent and efferent arterioles on the glomerular filtration rate and renal blood flow are shown schematically in *Figure 2*.

Changes in glomerular filtration rate characterize renal disease. For example, in the early stages of diabetic nephropathy, increased pressure within the glomerulus causes the glomerular filtration rate to rise. Later in the disease process, the glomerular filtration rate progressively declines, and once it begins to do so, the process is irreversible.

Many drugs can also affect glomerular pressure and renal blood flow, and thus, glomerular filtration. For example, the immunosuppressive agent cyclosporine and some blood pressure-lowering agents including the calcium antagonists alter renal blood flow and the glomerular filtration rate in addition to their other systemic effects.

EXPERIMENTAL TECHNIQUES

Because changes in afferent and efferent vascular tone can markedly influence the glomerular filtration rate, experimental techniques to assess changes in glomerular hemodynamics have evolved over the past 30 years.

In the mid 1960s, micropuncture techniques were introduced that allowed for measurement of pressure and calculation of resistance within various segments of the renal circulation.[1] This involved inserting an extremely fine pipette into the vessel to be studied. By the late 1960s and early 1970s, researchers were using radiolabeled microspheres and tracers to determine the intrarenal distribution of blood flow and factors that change it.[2,3] The diameter of the preglomerular vessels could also be determined by delivering microspheres of a known size into the renal artery and observing where they become trapped. One can also use microspheres to measure the velocity of the blood in different vessels.

The micropuncture and microsphere techniques are limited in that they provide only indirect measurements of pressure and flow within the glomerulus. In addition, the structure of the kidney and the thickness of the tissue preclude using these techniques to study directly the afferent and efferent arterioles.

In the 1980s, innovative techniques emerged that allow us to directly study the glomerulus and the glomerular circulation. In 1984, Casellas and Navar[4] introduced the juxtamedullary perfused nephron technique whereby a kidney is removed, perfused, and dissected to isolate a single juxtamedullary nephron. (The juxtamedullary nephrons are located deep inside the kidney next to the medulla; the cortical nephrons lie in the outer renal cortex.) A video camera attached to the microscope displays a magnified image on a monitor, and the experiment is recorded on video tape. One can observe changes in vessel diameter as they happen and later obtain precise measurements of the diameters of the various vessels, using special programs that run on personal computers. This is known as videomicroscopy. In this preparation, one can also measure blood flow using a velocimeter attached to the microscope, and pressure using micropuncture techniques.

Similarly, single vessels can be isolated and perfused for study; this method was introduced in 1983 by Edwards.[5] However, the isolated perfused vessel technique and the juxtamedullary nephron technique both require dissection of the nephron unit, causing trauma to the blood vessels, kidney, and renal nerves, and therefore potentially affecting the physiologic and pharmacologic properties of the microvessels.

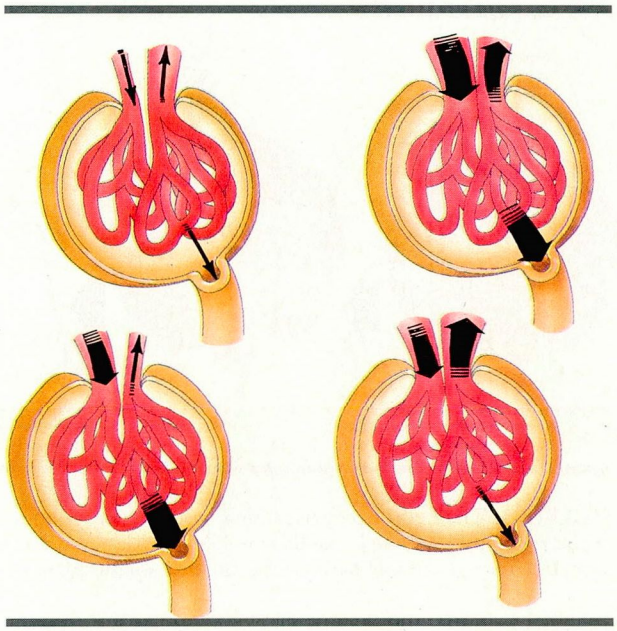

FIGURE 2. Effects of changes in diameter of the afferent and efferent arterioles on glomerular filtration and renal blood flow. Top, constriction of the afferent arteriole decreases renal blood flow and glomerular filtration; dilation of the afferent arteriole increases filtration and blood flow. Bottom, constriction of the efferent arteriole decreases blood flow but increases filtration; dilation of the efferent arteriole increases flow but decreases filtration.

The hydronephrotic kidney preparation

The hydronephrotic kidney preparation allows one to directly view the renal microcirculation without microdissection of the glomerular network. Introduced by Steinhausen in 1983,[6] this preparation is unique in that one can directly observe the preglomerular and postglomerular vessels with their nerves and blood supply intact. The arterioles contain their normal renin-secreting cells, and the vasculature autoregulates and responds normally to vasoactive agents.[7]

The kidney is first prepared by ligating one ureter in young rats that weigh about 130 g. After 4 to 6 weeks, the resulting hydronephrosis thins the renal cortex so that light easily passes through it and the glomerular circulation can be seen. The renal mi-

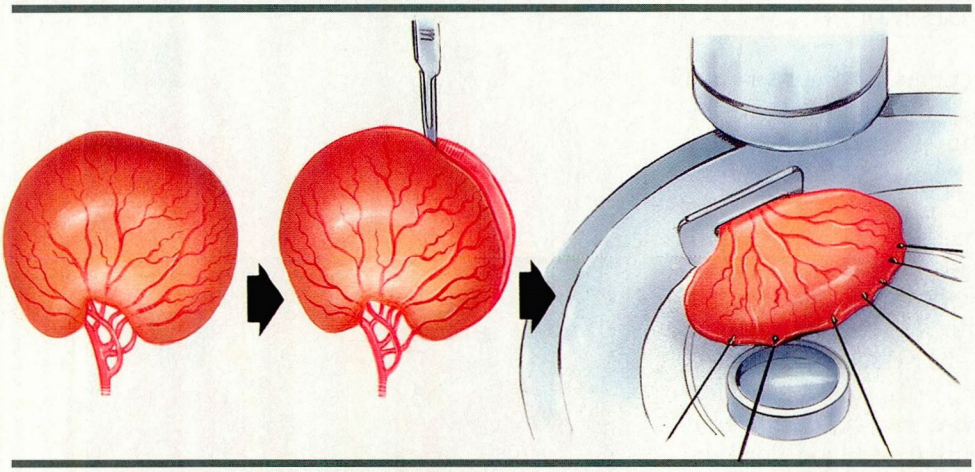

FIGURE 3. The hydronephrotic kidney preparation, used to observe changes in diameter of the renal microvessels. The hydronephrotic kidney is cut along its longitudinal curvature and placed in an isotonic bath on the stage of a light microscope.

crovasculature is visualized by "bivalving" the kidney—slicing it open along its longitudinal curvature—and placing half of it in a bath. The rat and kidney bath are placed on a light-microscope stage, and the glomerulus and vessels are viewed through a 40× water-immersible lens (*Figure 3*).

Agents to be studied can be given either intravenously, or, if one wishes to avoid systemic effects, topically to the kidney bath. Videomicroscopy provides precise measurements of the vessels studied and can provide a direct visualization of the sites where drugs exert their influence on the glomerular circulation. For instance, using this technique, it was determined that the neuromuscular blocking agent vecuronium exhibits a selective preglomerular vasoconstriction.[8]

Therefore, many techniques can be used to study the renal microcirculation. However, each technique represents a technical compromise, and each has its limitations. Nonetheless, these techniques have provided a basis for understanding the physiology of the renal microcirculation. Newer imaging techniques that obviate creating hydronephrosis, such as fluorescent dyes and intricate optics applied to both in vivo and in vitro preparations, should further enhance our understanding.

EFFECT OF DRUGS

The effects of various agents on the glomerular circulation have been directly studied using the newer techniques. Although both the afferent and efferent arterioles are anatomically closely associated with the glomerulus, these vessels have very different vasoactive properties. Specifically, some agents have preferential effects on the preglomerular or postglomerular vessels (*Table*) and thus have specific effects on pressure and flow within the glomerulus and on the glomerular filtration rate.

In general, most agents affect the afferent and efferent arteriole in the same manner. For instance, it has long been thought that angiotensin II constricts only the efferent arteriole. However, these techniques have shown that angiotensin II constricts both preglomerular and postglomerular vessels,[9–11] although some studies indicate it constricts the efferent arteriole more.[12] In contrast, atrial natriuretic factor, an endogenous peptide, increases glomerular filtration rate by dilating the afferent arteriole while concurrently constricting the efferent arteriole.[23]

The calcium antagonists nitrendipine and diltiazem selectively dilate the afferent arteriole,[17,18] resulting in greater glomerular blood flow and filtration. In chronic renal disease, glomerular blood flow is decreased; thus, a calcium antagonist could lower blood pressure without affecting glomerular filtration rate by causing afferent vasodilation. Because of the specific site of action of calcium antagonists, clinicians often use them to maintain glomerular filtration rate.[24]

In contrast, cyclosporine, an immunosuppressive agent, preferentially constricts the large preglomerular vessels, resulting in lower blood flow and pressure transmitted to the glomerular capillary.[21,22] These findings are consistent with the transient impairment in renal blood flow and glomerular filtration rate observed with cyclosporine. To counteract these effects, calcium antagonists are used concomitantly with cyclosporine.

DISEASE PROCESSES

Hypertension and diabetes mellitus are associated with disease processes of the kidney and abnormalities in the renal microcirculation. Hypertension can occur with or without concomitant increases in glomerular capillary pressure. Rats made hypertensive with deoxycorticosterone acetate (DOCA) and salt have systemic hypertension and increased glomerular capillary pressure, presumably due to afferent vasodilation.[25]

TABLE
RENAL MICROVASCULAR RESPONSES TO VASOACTIVE AGENTS

	Afferent arteriolar diameter	Efferent arteriolar diameter	Renal blood flow	Glomerular filtration rate	References
Angiotensin II	↓	↓↓	↓	↓	9,10,11,12
Captopril	↑	↑	↑	↑	13,14
Norepinephrine	↓	NC	↓	↓	14,15
Dopamine					
Low dose	↑	↑	↑	↑	16
High dose	↓	↓	↓	↓	16
Calcium antagonists					
Nitrendipine	↑	NC	↑	↑	17
Diltiazem	↑	NC	↑	↑	18
Verapamil	↑	↑	↑	↑	18
Arginine vasopressin	NC	↓	NC	NC	19,20
Cyclosporine	↓	↓	↓	↓	21,22

* ↑increase; ↓decrease; NC no change

Elevated glomerular pressure and flow augment the flux of plasma protein across the glomerular membrane. As protein accumulates in the mesangium, the mesangium proliferates, and glomerulosclerosis ensues.[26] Reducing glomerular capillary pressure preserves renal function in this situation. Alternatively, in the spontaneously hypertensive rat, which is a model of systemic hypertension without glomerular hypertension, the glomerulus is protected from the high systemic blood pressure by a relative afferent arteriolar constriction.[27]

In theory, in systemic hypertension with intraglomerular hypertension, it would be optimal to constrict the dilated preglomerular vessels or dilate the postglomerular vessels and thus reduce the high pressure and flow in the glomerular capillary. In practice, however, there is still no convincing evidence in humans that any particular antihypertensive agent has an advantage over any other in preventing renal injury. Current guidelines from the National High Blood Pressure Education Program Working Group on Hypertension and Chronic Renal Failure call for controlling hypertension by any effective means to slow the progression of renal failure.[28] It is possible that, as we learn more about these drugs through utilization of these techniques, specific drugs may be chosen to alter the preglomerular and postglomerular resistances to protect the glomerulus from the elevated pressures.

Diabetic nephropathy is another example of altered renal microcirculation. Early in the course of the disease, the preglomerular and postglomerular resistances decrease. However, the afferent vessels dilate more than the efferent ones, resulting in increased blood flow, increased intraglomerular pressure, and an increased glomerular filtration rate. These early hemodynamic changes are thought to initiate an increase in mesangial matrix and ultimately cause glomerulosclerosis.

In a study of rats made diabetic with streptozotocin, Hostetter et al[29] found a 33% increase in glomerular filtration rate in rats with moderate hyperglycemia. Using micropuncture techniques, they also found a decrease in afferent and efferent arteriolar resistance, but the afferent arterioles dilated more than the efferent arterioles, resulting in increased glomerular capillary plasma flow and hydraulic pressure and accounting for the increased glomerular filtration rate. Numerous investigators have attempted to elucidate the mechanisms involved in the initial preglomerular and postglomerular vasodilation.

Because the renin-angiotensin system has been implicated in the altered microvascular reactivity observed in experimental diabetes, investigators have studied the responses to the vasoconstrictor angiotensin II in this model. In the early stages of diabetes, there is a blunted response to angiotensin II in both the preglomerular and postglomerular vessels. This is consistent with a relative dilation in these vessels, accounting for the hyperfiltration seen in early stages of diabetes. While the mechanism of the blunted response to angiotensin II is not known,

a reduction in the number of angiotensin II receptors is possible. With fewer receptors, the normal effect of circulating angiotensin II on maintaining preglomerular and postglomerular tone would be absent. This may account for the dilated status of the arterioles.

CLINICAL IMPLICATIONS

Angiotensin-converting enzyme inhibitors are beneficial in lowering intraglomerular hypertension in diabetic patients, presumably by dilating the efferent arteriole more than the afferent arteriole. A large-scale trial of captopril in patients with diabetic nephropathy has shown this agent slows the decline in renal function in this disease.[30] Studies need to be done to assess the effects of other antihypertensive drugs such as alpha blockers, beta blockers, and the newer calcium antagonists on glomerular hemodynamics. In addition, lipid-lowering agents, alone or in combination with ACE inhibitors or other drugs may also alter the hemodynamic changes observed in diabetes[31] and in the nephrotic syndrome.[32] Drugs that act on either the afferent or efferent arteriole can be chosen to minimize intraglomerular hypertension and hyperfiltration or, alternatively, to maintain glomerular pressure and filtration when the blood pressure is lowered.

SUMMARY

With new techniques to study the renal microcirculation directly, we now have the ability to assess the direct preglomerular and postglomerular actions of various agents. Changes in pressure and diameter can be measured, and the neural control of the renal vasculature both at the level of the renal nerve and the central nervous system can be studied. In addition, we can investigate abnormalities occurring at the level of the glomerulus in disease states. Therefore, techniques for studying afferent and efferent arteriolar resistances and thus glomerular filtration rate may provide important insights into the actions of drugs and into renal diseases to ensure the best possible treatment for patients.

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