Role of the renal microcirculation in antihypertensive therapy

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■ **BACKGROUND** The renal circulation plays a central role in regulating blood pressure and glomerular filtration.

■ **OBJECTIVE** To examine the effects of the various classes of antihypertensive agents on the renal microcirculation.

■ **SUMMARY** Peripheral vascular resistance is generally increased in hypertension, and the microcirculation makes the major contribution to resistance. In the kidney, the preglomerular and postglomerular vessels constrict to protect the glomerular capillary from increased hydrostatic pressure, further increasing peripheral resistance. Because the renal microcirculation adjusts to maintain glomerular filtration and blood flow, antihypertensive agents that can normalize the pressure and blood flow in these vessels may help prevent the long-term consequences of hypertension. Angiotensin-converting enzyme inhibitors directly affect preglomerular and postglomerular resistance, but they further decrease postglomerular resistance. Calcium antagonists selectively decrease preglomerular resistance. The diuretics, vasodilators, alpha blockers, and beta blockers may also cause changes in preglomerular and postglomerular resistance; however, compensatory reflex responses may mitigate their direct effects.

■ **CONCLUSION** Some antihypertensive agents have unique actions on the renal microcirculation that better maintain renal function. A basic understanding of the physiologic action of these agents on the microcirculation may help in their selection.

■ INDEX TERMS: ANTIHYPERTENSIVE AGENTS; RENAL CIRCULATION; MICROCIRCULATION ■ CLEVE CLIN J MED 1994; 61:356–362

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HYPERTENSION is characterized by an increase in peripheral vascular resistance, generally in proportion to the elevation in blood pressure. In the early stages of hypertension, the increase in resistance is limited to the kidney; in the later stages the increase is shared by most organ systems.[1] This response is thought to occur in the resistance vessels [2,3]; the largest, rather than the smallest arterioles, make the greatest contribution to resistance,[4] both in hypertension and in normal blood pressure.

The increase in peripheral vascular resistance in hypertension serves several purposes. It protects structures distal to the resistance vessels from excessive hydrostatic pressure and maintains a normal or slightly elevated pressure in the capillaries to drive the Starling forces necessary for the proper exchange of oxygen, nutrients, and metabolic products between the blood and the tissue parenchyma. Adjustments in the renal microcirculation also help regulate renal blood flow, glomerular filtration, and salt and water excretion

(*Figure*). Unfortunately, the increase in resistance tends to drive the systemic blood pressure up further. Later in hypertension, glomerular hydrostatic pressure increases and causes glomerular damage, at least in various experimental situations.[5,6]

This review focuses on the effect of antihypertensive agents on the renal microcirculation, how these effects may contribute to the antihypertensive action of various drugs, and how antihypertensive agents that can normalize renal microvascular pressure and blood flow may help prevent the long-term consequences of hypertension.

EFFECTS OF HYPERTENSION ON THE KIDNEY

Hypertension may alter three regulatory mechanisms that control the renal microcirculation.[7] First, there may be morphologic changes within the renal microvasculature, in which hypertrophy of the vessel wall reduces the lumen diameter and decreases the ability of the vessel to dilate.[8] This results in an increased resistance to flow, further exacerbating the elevated peripheral resistance.

Second is a change in the kidney's ability to autoregulate in response to alterations in systemic arterial pressure. Renal autoregulation is thought to include two components: an intrinsic myogenic component and the tubuloglomerular feedback mechanism.[9] The myogenic response causes the vessels to dilate when perfusion pressure declines and to constrict when perfusion pressure increases. In experimental models of hypertension, this intrinsic myogenic response is either abolished or reset to a greater pressure.[10–12]

Tubuloglomerular feedback is the relationship between the glomerular filtration rate (GFR) and the flow of sodium chloride past the macula densa. When renal perfusion increases, so does the GFR. The increased flow of sodium chloride past the macula densa initiates the tubuloglomerular feedback response—an afferent vasoconstriction that returns the GFR to normal. In hypertension, tubuloglomerular feedback is thought to be impaired.[13] Angiotensin II also modulates tubuloglomerular feedback.[14]

The third altered mechanism in hypertension is a change in vascular responses to vasoactive hormones.[7] Renal vascular responses and the afferent and efferent arteriolar responses to vasoconstrictors such as angiotensin II, norepinephrine, and thromboxane are exaggerated in hypertensive animals compared with normotensive animals.[15–17] This may contribute to increased renal vascular resistance.

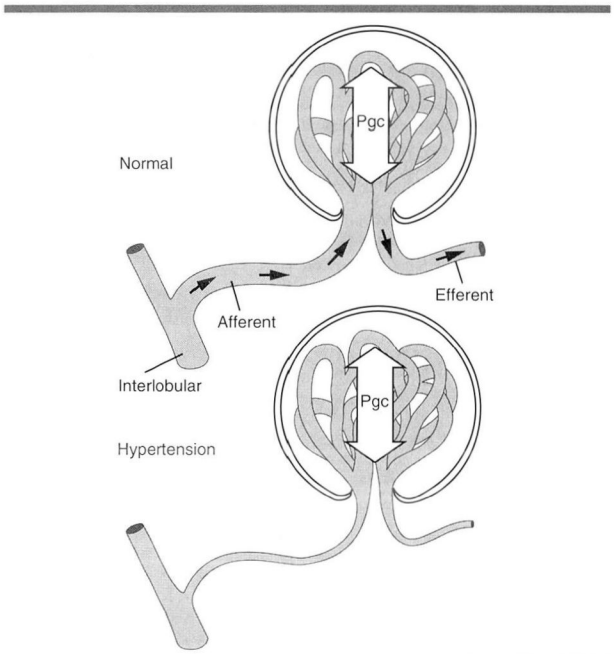

FIGURE. Effect of hypertension on glomerular capillary pressure (P_{gc}). The afferent and efferent vessels normally constrict or dilate in response to variations in blood pressure to keep the P_{gc} constant. In early hypertension, P_{gc} remains constant, but later in the disease P_{gc} tends to rise. The glomerular filtration rate is influenced by the P_{gc}, the hydrostatic pressure within Bowman's capsule, the oncotic pressures within the capillary and within the capsule, and the permeability of the capillary membrane.

ANTIHYPERTENSIVE AGENTS

Our understanding of the pharmacologic effects of antihypertensive agents is based to a certain extent on experimental studies and indirect assumptions. This section will discuss the major classes of antihypertensive agents and their proposed mechanisms of action on the renal microcirculation.

Angiotensin-converting enzyme inhibitors

Because angiotensin II constricts both afferent and efferent arterioles,[18–20] angiotensin-converting enzyme (ACE) inhibitors should therefore interfere with the effect of angiotensin II at both sites. Data from micropuncture experiments substantiate this.

Anderson et al[5] confirmed that an ACE inhibitor could preserve renal structure and function. They

produced systemic and glomerular hypertension in rats by performing "5/6 nephrectomies" (removing one whole kidney and two thirds of the other). One group was treated with an ACE inhibitor (enalapril), and the other group was treated with a combination of reserpine, hydralazine, and hydrochlorothiazide. Both regimens effectively reduced systemic blood pressure; however, the rats treated with enalapril had lower glomerular pressures and less proteinuria and glomerulosclerosis. This suggests that ACE inhibitors dilate both afferent and efferent arterioles; the efferent arteriolar dilation reduced the glomerular capillary pressure and thus protected against further structural damage.

Efferent arterioles may be more sensitive to angiotensin II than are interlobular arteries and afferent arterioles. Thus, the inhibition of converting-enzyme activity may be manifested by a greater decrease in efferent than in afferent resistance. Although it is difficult to show experimentally that ACE inhibitors have a greater effect on the efferent arteriole,[21] this is the commonly proposed site of their action.

ACE inhibitors slow the progressive loss of renal function in hypertensive patients with diabetic nephropathy. In a randomized, double-blind study, 409 insulin-dependent diabetic patients with kidney disease were given either an ACE inhibitor (captopril) or placebo for 3 years. By the end of the study, patients taking the ACE inhibitor had better renal function than those receiving placebo. Regardless of the stage of kidney disease, captopril treatment doubled the amount of time before a patient needed dialysis.[22] The investigators speculated that captopril reduced the high pressure within the glomerulus by preventing angiotensin II from constricting the efferent arteriole, thus reducing intraglomerular pressure.

Angiotensin II antagonists

Angiotensin II antagonists, introduced in the early 1970s, were also hoped to be effective in treating hypertension. Unfortunately, these peptides have intrinsic agonistic properties that make them difficult to use for this purpose. More recently, specific nonpeptide angiotensin II receptor antagonists have been developed and have allowed for the discrimination of two types of angiotensin II receptors, type 1 (AT1) and type 2 (AT2).[23]

The AT1 receptor is thought to be involved in vasoconstriction, as its antagonist blocks renin-dependent hypertension.[24,25] Selective AT1 blockade is as effective as ACE inhibition in preventing glomerulosclerosis in spontaneously hypertensive rats with reduced renal mass.[26] The role of AT2 receptors is less well defined. The AT2 receptors are found in large preglomerular vessels.[27] Vasoconstriction in the larger interlobular artery is mediated by both AT1 and AT2 receptors, but AT1 receptors have greater influence. The afferent and efferent arteriolar responses to angiotensin II are mediated predominantly by AT1 receptors.[28]

From these recent findings one can infer that AT2-receptor antagonists produce their greatest effects in the large preglomerular vessels. Because of the prominent role of AT1 receptors in the renal microvasculature, blockade of these receptors will reduce intraglomerular pressure by reversing the angiotensin II-induced postglomerular vasoconstriction. Several angiotensin II receptor antagonists provide the opportunity for a more specific blockade of the renin-angiotensin system at peripheral receptor sites, thus obviating the adverse effects associated with bradykinin accumulation that occur with ACE inhibitors.

Calcium antagonists

Calcium antagonists lower peripheral resistance by preventing calcium from entering vascular smooth-muscle cells. The calcium antagonists have a very specific effect on microvascular resistance in the kidney: they preferentially dilate preglomerular vessels and have little or no effect on the efferent arteriole.[29] This has been tested in vessels constricted in response to norepinephrine or angiotensin II[29,30] and, in studies of diltiazem and nitrendipine in the hydronephrotic kidney preparation, in vessels not pretreated with vasoconstrictors.[31]

All three classes of calcium antagonists (dihydropyridines, diphenylalkylamines, benzothiazepines) dilate blood vessels by blocking the voltage-gated L-type channels in vascular smooth muscle.[32] In the kidney, L-type channels are predominantly located on the preglomerular vessels, with a very small number on the efferent arteriole.[29,31] Because the calcium antagonists dilate the constricted afferent arteriole in hypertension, they decrease renal vascular resistance and increase renal blood flow and glomerular filtration. Calcium antagonists should have greater effect if basal vascular tone is increased and thus would be ideal agents in reducing renal vascular resistance in hypertension.

Diuretics

Diuretics produce effects in the kidney that appear to both increase and decrease renal blood flow. For example, the loop diuretics furosemide and ethacrynic acid increase renal blood flow and redistribute blood flow from the medulla to the cortex to cause diuresis.[33] These agents block tubuloglomerular feedback,[34] possibly by blocking the transduction of chloride at the macula densa. Inhibition of tubuloglomerular feedback in the presence of natriuresis and diuresis would further enhance the natriuresis. On the other hand, because diuretics decrease vascular volume, they increase plasma renin activity,[35] which activates the renin-angiotensin system and should result in a diminution of total renal blood flow.

The site of action within the renal microvasculature of the various diuretic agents has not been delineated. It is not known whether thiazides or the potassium-sparing diuretics have any direct effect on tubuloglomerular feedback. Acetazolamide is not thought to have a direct effect on the renal microcirculation other than through changes in systemic pressure and volume. The benzothiazides may reduce glomerular filtration by a direct action on the renal vasculature. Neither the aldosterone antagonist spironolactone nor amiloride have any direct effect on the renal microcirculation.

Vasodilators

Arterial vasodilators are used as antihypertensive agents when an immediate reduction in blood pressure is required.[36] Their effects are present only as long as the drug is administered. The direct vasodilators lower systemic pressure by reducing total peripheral resistance. Sodium nitroprusside dilates the preglomerular and postglomerular vessels. Diazoxide and hydralazine cause arterial dilation with little effect on capacitance vessels.[33] Greater reductions in vascular resistance occur in the renal, portal, and coronary circulations than in the brain, muscle, or skin, resulting in compensatory reflex responses that include an increase in plasma renin activity.

Beta blockers can attenuate the cardiac stimulation caused by vasodilators and further decrease systemic vascular resistance by decreasing renin release. Minoxidil, a renal vasodilator and a potent stimulator of renin secretion, has a much greater vasodilatory effect than hydralazine does. Prazosin has potent phosphodiesterase-inhibiting activity that may prevent the degradation of cyclic adenosine monophosphate, thereby causing vasodilation. Diazoxide directly relaxes arterial smooth muscle but has little effect on the veins. Nitroglycerin predominantly dilates the venous capacitance vessels but causes arterial dilation at higher infusion rates.[33]

The direct renal vasodilatory effects of these agents are sometimes blocked by other compensatory cardiovascular responses to the decrease in blood pressure, ie, salt and water retention and reflex tachycardia. These effects make it appropriate to concomitantly use a natriuretic diuretic to prevent salt and water retention and a beta blocker or other sympathetic inhibiting agents to blunt the tendency for reflex increases in heart rate.

Alpha blockers and beta blockers

The adrenergic nervous system, because of its ubiquitous distribution within the vasculature, has a direct influence on peripheral vascular resistance. This influence extends to the renal microcirculation, where norepinephrine release increases renin release, salt and water excretion, and prostaglandin release; as a result, the glomerular blood flow and GFR decrease.

Norepinephrine is the major neurotransmitter of renal nerves and also the catecholamine that circulates in the highest concentration under most conditions. It can bind to four different receptor types: alpha-1, alpha-2, beta-1, and beta-2. The renal vasculature and all portions of the renal tubules receive innervation. Norepinephrine released from renal nerves reacts primarily with alpha-1 receptors to cause vasoconstriction.

In hypertensive animals, the number of adrenergic receptors in the kidney increases. Alpha-1 and alpha-2 receptors are found in the arterioles, glomeruli, proximal tubules, and collecting tubules of rats; beta receptors have been found in the glomeruli, thick ascending limb, distal tubule, and collecting tubule.

Alpha-1 receptors are the major adrenergic regulators of renal resistance in response to renal nerve stimulation in rats. Alpha-2 agonists are potent vasoconstrictors in isolated perfused rat kidneys, and alpha-2 receptors respond to circulating catecholamines.[37] The alpha-2 and beta receptors located on the glomeruli may play a role in controlling blood flow through the glomerulus via mesangial contraction.

Beta-1 receptors are also known to increase the release of renin from the juxtaglomerular apparatus,

TABLE
EFFECT OF HYPERTENSION AND ANTIHYPERTENSIVE AGENTS ON THE KIDNEY

	Hypertension	Angiotensin-converting enzyme inhibitors	Calcium antagonists	Diuretics	Vasodilators	Alpha blockers	Beta blockers
Renal blood flow	NC or ↓*	NC or ↑	↑	NC or ↑	↑	NC or ↑	NC or ↓
Renal vascular resistance	↑	↓	NC or ↓	↓	↓	↓	NC or ↓
Afferent resistance	↑	NC or ↓	↓	↓	↓	↓	NC or ↓
Efferent resistance	↑	↓	NC	NC	↓	↓	NC or ↓
Glomerular capillary pressure	↑	↓	↑	↑	NC or ↑	NC or ↓	NC
Glomerular filtration rate	NC or ↓	NC or ↑	NC or ↑	NC or ↑	NC or ↑	NC or ↓	NC

*↑ increase; ↓ decrease; NC no change

which can influence tubuloglomerular feedback. There is no evidence of beta receptors on renal arterioles.

Agents that block the synthesis or release of norepinephrine therefore can influence systemic blood pressure. Reserpine inhibits the binding of norepinephrine and dopamine in the storage granules and thereby minimizes its release and subsequent vasoconstrictor action. Guanethidine inhibits the reuptake of norepinephrine, which eventually depletes the storage granules of norepinephrine and prevents its release. Monoamine oxidase inhibitors prevent the release of norepinephrine by depleting the storage granules of it.

Alpha adrenergic agents attenuate sympathetic vasoconstriction in arteries and veins. Phenoxybenzamine is a long-acting alpha blocker with significant side effects. Phentolamine, a short-acting alpha blocker with fewer side effects, is the drug of choice for hypertensive crises involving sympathetic stimulation. Because these agents lack efficacy in chronic hypertension and have serious adverse effects, they are used primarily for diagnosing and treating pheochromocytoma.[38]

Clonidine and methyldopa, which block norepinephrine-induced vasoconstriction in the periphery, also act on the central nervous system to reduce blood pressure. Beta blockers such as propranolol exert their antihypertensive effects through a central nervous system effect and an inhibition of renin release.

Because of the many varied effects of the adrenergic nervous system on the kidney, it is difficult to clearly define the effect of many antihypertensive agents on the renal microcirculation; many of their direct effects may be masked by compensatory cardiovascular responses.

Catecholamines constrict preglomerular and postglomerular vessels,[16,39] and inhibition or blockade of alpha-1 or alpha-2 receptors should decrease the resistance if sympathetic tone is high. Beta blockers are thought to reduce renal blood flow in the short term.[33] This reduction may be due to an alteration in renin secretion or an action within the mesangium or both. Compensatory, systemic hemodynamic responses may mask the direct renal effect of alpha blockers or beta blockers. Nonetheless, an understanding of these direct renal effects may be useful when renal function is compromised.

Endothelial-derived factors

The recent discovery of endothelial-derived relaxing factor (EDRF) and constricting factor (endothelin) and the concomitant development of specific antagonists to these agents may provide a means of controlling the capability of the endothelium to influence peripheral resistance and systemic blood pressure. Because of the great surface area of the vasculature and the proposed importance of the local autocrine and paracrine agents, inhibition of vasoconstriction within the renal microcirculation could be very effective in selectively controlling hypertension.

SUMMARY

The *Table* summarizes the effects of the different classes of antihypertensive agents on the renal circulation. The ACE inhibitors have the most potential to affect the renal microcirculation, as it is regulated greatly by the renin-angiotensin system; they decrease efferent arteriolar resistance more than afferent resistance. The relatively new class of angiotensin II antagonists may also allow one to selectively

interfere with the renin-angiotensin system at the level of the renal microcirculation. In contrast, the calcium antagonists preferentially decrease afferent arteriolar resistance.

Diuretics by themselves have little if any direct effect on the renal microcirculation; the alterations caused by diuretics is a consequence of volume changes. Drugs that influence postganglionic neural transmission lower blood pressure by minimizing norepinephrine-induced vasoconstriction and the resulting consequences of norepinephrine-induced renin release. Thus, the alpha blockers and beta blockers would by themselves cause vasodilation within the renal microcirculation. However, compensatory reflex responses may mitigate the direct effects of these agents on the renal microcirculation.

Some agents are better than others at maintaining renal function. Although each drug may have specific actions on the renal microcirculation, compensatory cardiovascular responses may negate their effects. Consequently, it may be important to use a combination of drugs to achieve a beneficial effect on protecting renal function.

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