Are Renal Hemodynamics a Key Factor in the Development and Maintenance of Arterial Hypertension in Humans?

Luis M. Ruilope, Vicente Lahera, Jose L. Rodicio, J. Carlos Romero

Abstract The kidney plays a key role in the control of body fluids and blood pressure. Evidence has shown that impairment of renal function can lead to the development of arterial hypertension. The regulation of renal blood flow appears to be a key element in the pathophysiology of the hypertensive process, because multiple evidence suggests the existence of a functional enhancement of renal vascular tone in this disorder. The existence of renal vasoconstriction and of an inherited defect in the regulation of renal blood flow has been proposed in the prehypertensive stage. The mechanisms responsible for this alteration include a lack of modulation of the renal vasculature to angiotensin II, increased sympathetic activity, or suppressed renal dopaminergic activity. Established hypertension is characterized by elevated renal vascular resistance, decreased renal blood flow, sustained glomerular filtration rate, and increased filtration fraction. The increase in renal vascular resistance is initially due to elevations in renal vascular tone and is reversible, whereas later it becomes irreversible because of structural changes involved in nephrosclerosis. Antihypertensive drugs are able to decrease blood pressure and to prevent the development of further renal vascular damage independently of variable effects on renal hemodynamics. (Hypertension. 1994;23:3-9.)

Key Words • hemodynamics • glomerular filtration rate • sodium • hypertension, arterial • antihypertensive agents

It has long been known that the kidney plays a central role in the control of body fluids and blood pressure and that a derangement of renal function could lead to the development of hypertension. Furthermore, several theories have been proposed as to which specific hemodynamic or tubular alterations could induce an elevation of blood pressure. In this review, the clinical studies investigating changes in renal function accompanying the development and maintenance of essential hypertension are critically examined. The studies indicate that the common manifestation of hypertension is an increase of intrarenal vascular resistance; however, the manner in which this single alteration could trigger all the pathophysiological alterations responsible for hypertension is not completely known.

Renal Hemodynamics in the Prehypertensive State in Humans

The role of the kidney in the development of essential hypertension has been examined in studies of control and experimental subjects with a family history of hypertension. These studies have revealed conflicting results. Bianchi et al found that renal blood flow and glomerular filtration rate were elevated in offspring of hypertensive parents, whereas filtration fraction remained normal. On the other hand, Hollenberg et al and Uneda et al reported that renal plasma flow and glomerular filtration rate were normal in the offspring of both normotensive and hypertensive parents; however, renal vascular resistance was increased. Van Hooft et al reported that renal blood flow was reduced and renal vascular resistance and filtration fraction were elevated in young people at risk for hypertension. The apparently contradictory results were explained by van Hooft et al as perhaps being a consequence of the methodology used for the determination of renal plasma flow and glomerular filtration rate that could have artificially created the differences in renal blood flow. These publications suggest that an abnormal renal vasoconstriction exists in the prehypertensive state. Offspring of hypertensive parents have shown an exaggerated renal vasodilation in response to calcium channel blockers and converting enzyme inhibitors. This vasodilation suggests the existence of functional renal vasoconstriction in subjects at risk of developing hypertension.

The mechanisms underlying the inherited renal defects in essential hypertension remain to be elucidated. Plasma renin activity and plasma aldosterone levels are normal or reduced in the offspring of hypertensive patients. Nevertheless, an increased sensitivity of the renal vasculature to the infusion of angiotensin II as well as a renal vasoconstrictor response to intravenous infusion of saline have been described in these subjects. A subset of essential hypertensive patients has a decreased capacity to excrete a sodium load, suggesting a lack of modulation of the renal vasculature in response to a fall in intrarenal angiotensin II levels.

Another component of the renal hemodynamic defect in essential hypertension may be linked to the control of renal tone. Evidence supporting this possibility is (1)
the abnormal sympathetic response to a high sodium intake in young prehypertensive individuals; (2) an increased renal vasoconstriction and sodium retention in response to stress; (3) the relation between sympathetic tone, sodium intake, and blood pressure in the general population; and (4) the higher plasma levels of norepinephrine found in sons of hypertensive parents. Limura et al suggested suppressed renal dopaminergic activity in the prehypertensive stage, as they found a decrease in urinary dopamine excretion and increased urine volume and urinary sodium excretion in response to dopamine infusion.

Borderline hypertension has been suggested to represent the early phase of essential hypertension. Borderline hypertension is a condition in which a subject's blood pressure is above the normal range but is not sufficiently high to require antihypertensive therapy. Renal blood flow tends to be normal or slightly reduced in these patients, and renal vascular resistance is elevated. They also exhibit an enhanced renal vasoconstrictor response to infusion of norepinephrine and to postural changes. The renal vasoconstrictive response to upright posture is more pronounced when these patients are placed on a high salt diet.

The prevalence of arterial hypertension increases with age, and the incidence rises above 50% in people older than 65 years in Western societies. This increased prevalence may be due to the decline in renal function in older patients. There is a progressive decrease in renal plasma flow and glomerular filtration rate and an increase in filtration fraction due to a proportionately greater fall in renal plasma flow. The decrease in renal plasma flow has been attributed to the development of renal vasoconstriction with age, and this view is supported by the evidence that renal vascular resistances are higher in older versus young hypertensive individuals. McDonald et al observed a greater pyrogen-induced renal vasodilation in old versus young subjects as well as the disappearance of any age-related differences in filtration fraction, suggesting that the renal vasoconstriction is reversible. The relevance of endothelial function on renal function has been suggested, and the data from McDonald et al point to a progressive decrease in endothelial function with age. Hollenberg et al showed that the renal vasoconstriction similar to that observed in the offspring of hypertensive parents seems to occur in the general population with aging.

Renal Hemodynamics in Established Essential Hypertension

Most patients with established essential hypertension exhibit increased renal vascular resistance, decreased renal blood flow, normal glomerular filtration rate, and increased filtration fraction. The maintenance of glomerular filtration rate within normal limits has been attributed to increased efferent resistance. The reduction in renal blood flow seems to occur preferentially in the outer cortex. The degree of renal blood flow reduction correlates directly with the degree of hypertensive vascular damage and inversely with mean blood pressure values. Various antihypertensive agents exhibit different effects on renal hemodynamics (Table 2).

### Table 1. Factors That Can Influence Renal Hemodynamics and Function in Established Hypertension

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of renal vascular tone (angiotensin II, sympathetic activity?)</td>
</tr>
<tr>
<td>Level of mean blood pressure</td>
</tr>
<tr>
<td>Severity and duration of the disease</td>
</tr>
<tr>
<td>Structural changes in renal vasculature</td>
</tr>
<tr>
<td>Age of the patient</td>
</tr>
<tr>
<td>Sodium and protein intake</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
</tr>
<tr>
<td>Concomitant medications</td>
</tr>
</tbody>
</table>

Hollenberg et al showed that the renal vasoconstriction seen in established essential hypertension is reversible. They also demonstrated that the renal vasodilator response to acetylcholine, dopamine, and phenolamine was increased in two thirds of mild essential hypertensive individuals. The response to these three drugs was abolished in patients with advanced nephrosclerosis, chronic pyelonephritis, and polycystic kidney disease. The observed renal vasoconstriction may also be attributed to an abnormal renal response to prevailing intrarenal levels of angiotensin II or increased sympathetic activity. These alterations could contribute to the development of salt sensitivity by impeding the renal vasodilation that normally accompanies a high sodium intake. Variability in renal hemodynamics and function has been described in established essential hypertension. Renal blood flow measurements of patients with essential hypertension compared with healthy volunteers may vary by 2.2-5-fold. A summary of factors that can influence renal hemodynamics in established hypertension is provided in Table 1.

In recent years, the importance of arterial hypertension and various renal diseases on glomerular hemodynamics has been established. Whereas ischemia may mediate renal damage, recent studies in experimental models have also suggested that glomerular capillary hyperperfusion and hypertension, secondary to the transmission of the elevated systemic pressure, can contribute to the progressive decline in renal function. However, estimations of glomerular capillary pressure in essential hypertensive patients using the formula of Gomez suggest that it is not increased because of elevated afferent arteriolar resistance.

The findings discussed above suggest that the most probable hemodynamic alterations in the development of hypertension are an increase in preglomerular resistance and a dysfunction of the pressor systems' control of fluid volume. The pathogenic significance of these alterations is discussed later in this review.

### Renal and Hemodynamic Effects of Antihypertensive Medication

In the last two decades, knowledge of the effects of antihypertensive agents on renal hemodynamics and function in humans has increased sharply. Various antihypertensive agents exhibit different effects on renal hemodynamics (Table 2).
TABLE 2. Effect of Different Groups of Antihypertensive Drugs on Renal Plasma Flow, Glomerular Filtration Rate, Renal Vascular Resistance, and Sodium Excretion

<table>
<thead>
<tr>
<th>Antihypertensive Agent</th>
<th>RPF</th>
<th>GFR</th>
<th>RVR</th>
<th>U_{Na}V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>α-Blockers</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Centrally acting sympatolytic agents</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Nonspecific vasodilators</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

RPF indicates renal plasma flow; GFR, glomerular filtration rate; RVR, renal vascular resistance; U_{Na}V, urinary sodium excretion; ACE, angiotensin converting enzyme; ↑, no effect; ↓, reduction; and ↑, increase.

The antihypertensive effect of diuretics is initially mediated by a natriuresis and diuresis that acutely reduce cardiac output. This is followed by a sustained reduction in peripheral resistance. These drugs reduce both renal plasma flow and glomerular filtration rate, and renal vascular resistance is increased because of the stimulation of the sympathetic nervous system and renin-angiotensin system.

The antihypertensive effect of β-adrenergic blocking agents is through the attenuation of the effects of sympathetic tone (competitive antagonism of catecholamines at β-adrenergic receptors). The net systemic effects are a reduction of heart rate, cardiac output, central sympathetic discharge, and peripheral norepinephrine release. This is accompanied by an acute increase in total peripheral vascular resistance that may return toward pretreatment levels with prolonged therapy. Changes in cardiac output and systemic vascular resistance are paralleled by changes in renal blood flow and renal vascular resistance. The renal effects of β-blockers are variable depending on the drug used. For example, propranolol decreases both renal plasma flow and glomerular filtration rate after acute and chronic administration and increases renal vascular resistance without influencing renal sodium handling. On the other hand, nadolol and tertatolol can acutely increase both renal plasma flow and glomerular filtration rate.

The renal vasodilation is maintained during long-term oral therapy with tertatolol but not with nadolol. Nonselective β-blockers with intrinsic sympathomimetic activity and selective β-blockers with or without intrinsic sympathomimetic activity also exhibit conflicting effects on renal function in acute studies. In general, they do not alter renal plasma flow, glomerular filtration rate, or sodium excretion during long-term therapy. The presence of intrinsic sympathomimetic activity contributes to diminished peripheral and renal vascular resistances. β-Blockers with vasodilating properties, such as labetalol, cilazopril, and carvedilol, do not alter renal hemodynamics.

α-Adrenergic blocking agents are selective α_1-adrenergic receptor antagonists that induce a fall in blood pressure by lowering peripheral vascular resistance. They do not alter renal hemodynamics because they also decrease renal vascular resistance. This renal vasodilator effect, characterized by an increase in renal plasma flow and glomerular filtration rate, during the administration of this type of drug has been described. On the other hand, there are reports of salt and water retention with the use of prazosin and terazosin in hypertensive patients.

Calcium antagonists represent a diverse group of compounds that inhibit calcium entry into cardiac cells and smooth muscle cells of the coronary and systemic circulation, reducing peripheral vascular resistance. These drugs dilate the renal vasculature and increase both renal plasma flow and glomerular filtration rate depending on the preexisting degree of vascular tone. They also increase sodium excretion during long-term therapy.

Agents that inhibit angiotensin converting enzyme produce a decrease in angiotensin II formation and a corresponding reduction in systemic vascular resistance. Their effects on renal hemodynamics and function depend on the state of sodium balance and vascular tone. In essential hypertensive patients, converting enzyme inhibitors decrease renal vascular resistance and increase renal plasma flow and glomerular filtration rate. The short-term administration of converting enzyme inhibitors also has been shown to produce natriuresis.

Centrally acting antiadrenergic blockers, such as clonidine, methyl dopa, guanabenz, and guanfacine, diminish sympathetic nerve activity and reduce systemic vascular resistance. These agents have been shown to reduce renal vascular resistance in the absence of changes or with minimal changes in renal plasma flow and glomerular filtration rate.

Nonspecific vasodilators relax vascular smooth muscle through a direct action that lowers both systemic and renal resistances; however, any increase in renal plasma flow depends on how much renal perfusion pressure was decreased. If renal blood flow falls, they generally produce salt and water retention. This phenomenon serves to illustrate that a given therapeutic effect could correct hypertension by acting on peripheral resistance (vasodilators) or on fluid volume (diuretics) without necessarily modifying the initial defect that generated hypertension. Moreover, the initial preglomerular vasoconstriction could be aggravated by pharmacologic interventions effective in normalizing blood pressure. This has significant therapeutic implications for designing tools to correct renal alterations facilitating the development and maintenance of hypertension.

Despite the varied renal effects of antihypertensive drugs, it is generally accepted that treatment of arterial hypertension protects the kidney from the vascular injury induced by the sustained elevation of blood pressure, especially in the malignant and severe forms of the disease. Nevertheless, several studies have shown that the protection of the kidney may be insufficient and progressive deterioration of renal function may occur during traditional antihypertensive therapy. Indeed, the incidence of end-stage renal failure attributable to nephrosclerosis has continued to increase despite widespread use of antihypertensive therapy over the last decade.

The differential effects of antihypertensive agents on the progression of renal vascular injury have gained importance. Antihypertensive drugs not only may facil-
vascular resistance and even increase sodium retention. The efficacy of the antihypertensive medication may be decreased with time if the initial cause of the hypertension remains uncorrected.

**Significance and Consequences of Preglomerular Renal Vasconstriction**

Increased preglomerular vascular tone may be due to a generalized disturbance in peripheral resistance or to a localized alteration in the renal vasculature. The preglomerular vasculature is composed of resistance vessels and as such may be affected by the same alterations that affect peripheral vascular resistance. Therefore, renal vasconstriction could produce renal hypoperfusion and decrease sodium excretion even when blood pressure levels are elevated. Although this may be the case in some essential hypertensive patients, the clinical evidence we have reviewed indicates that an increase in renal vascular resistance constitutes an initial event that leads to an elevation of total peripheral resistance and blood pressure. Furthermore, the theory that the renal alterations are of primary importance in the genesis of hypertension has significant experimental support. For example, transplantation of a kidney from a Dahl salt-resistant rat into a salt-sensitive rat prevents the development of hypertension in the latter, whereas salt-resistant rats transplanted with a kidney from a salt-sensitive rat develop hypertension. Similar effects have been observed after cross-transplantations of kidneys in other models of genetically hypertensive rats. The relevance of these findings to the pathogenesis of human essential hypertension is supported by the observation of Curtis et al., who found that transplantation of kidneys from young normotensive donors into patients with essential hypertension who had their own kidneys removed led to complete normalization of blood pressure.

The mechanism by which elevations in preglomerular vascular resistance induce hypertension remains undefined. Hall has suggested that the systemic alterations are comparable to those produced experimentally by the constriction of the renal artery. In the one-kidney, one clip model of hypertension developed by Goldblatt et al., a decrease in renal perfusion pressure, which increases renin release and produces sodium retention, is responsible for the elevation in systemic arterial pressure. This hypertension restores renal perfusion distal to the clamp and normalizes renin release and sodium excretion. At this stage, the only detectable alteration, like in essential hypertension, is the increase in total peripheral resistance. It could be argued that this model implies a prehypertensive stage of hyper-reninism that has not yet been identified in essential hypertension. However, 45% of essential hypertensive patients have elevated levels of circulating renin that may be reflective of hyperperfusion created by an increase in preglomerular renal vascular resistance. The cause of the increased preglomerular renal vascular resistance has not been identified, but a possibility is an increased concentration of calcium in the cytosol of vascular smooth muscle cells. This could be the result of genetic alteration, because the administration of calcium antagonists produces a greater renal vasodilatation in normotensive offspring of hypertensive parents than in offspring of normotensive parents.

A second explanation of how the increase in preglomerular resistance is associated with hypertension is through a defect in the synthesis of a humoral factor that also mediates sodium excretion. Lahera et al. have shown that a partial reduction in the synthesis of nitric oxide could reproduce this situation. These investigators demonstrated that the administration of low doses of the nitric oxide synthesis inhibitor N^\text{G}-nitro-L-arginine methyl ester (L-NAME) simultaneously induced sodium retention and an increased renovascular resistance without altering mean arterial pressure. This creates a condition in which the level of blood pressure is determined by the degree of vascular volume, which is mainly influenced by sodium intake. This phenomenon was demonstrated by Salazar et al. in dogs in which the administration of a high salt intake produced hypertension in animals chronically treated with a non-hypertensive dose of L-NAME. It should be pointed out that the inhibition of nitric oxide produces not only an increase in intrarenal vascular resistance but a simultaneous enhancement of tubular sodium reabsorption due to the fall in cyclic GMP formation. Cyclic GMP inhibits sodium reabsorption through amiloride-sensitive channels. Furthermore, a decrease in the synthesis of nitric oxide could disturb the regulation of renomedullary circulation, which appears to play a critical role in the resetting of pressure natriuresis. These findings suggest that the increase in preglomerular resistance may not represent an isolated perturbation triggering antinatriuresis through renal hyperperfusion but a manifestation of a complex set of renal alterations that involves impaired sodium excretion. The inhibition of other intrarenal humoral factors such as prostaglandins, kinins, and dopamine does not lead to an increase in preglomerular resistance and sodium retention. However, no studies have been done to determine whether the regulatory role of these factors has an indirect participation in any of the situations mentioned above.

In summary, the ability of the kidney to regulate blood pressure by controlling both the amount of sodium excreted and the release of vasoactive hormones involves the participation of several processes, the failure of which could result in hypertension. However, the elucidation of the factors underlying the most prevalent alteration of renal function, that is, an increase in preglomerular renal vascular resistance, has obvious clinical and therapeutic importance.

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