Abstract—Experimental narrowing of the main renal artery to produce hypertension increases the aorta-glomerular capillary pressure difference and vascular resistance. This article examines the hypothesis that hypertension also may be caused by structural changes that narrow intrarenal blood vessels, similarly increasing preglomerular vascular resistance and the aortic-glomerular capillary pressure gradient. There is evidence of both wall hypertrophy and lumen narrowing of the preglomerular arteries in spontaneously hypertensive rats, with increased preglomerular resistance and aortic-glomerular capillary pressure difference. We have also attempted to induce structural changes in renal-preglomerular vessels experimentally by infusing angiotensin II at low doses (0.5 to 4.5 ng/kg per minute) into the renal artery of Sprague-Dawley rats and greyhound dogs for up to 4 weeks. This angiotensin II infusion produced apparent dose-related effects on preglomerular vessel structure and hypertension. The possibility that hypertension may be induced by structural changes in preglomerular resistance vessel walls, by simulation of the hemodynamic effects of main renal artery stenosis, deserves further investigation. (Hypertension. 2000;36:648-652.)

Key Words: angiotensin II ■ arterioles ■ glomerular filtration rate ■ rats, spontaneously hypertensive ■ renal artery hypertrophy ■ hypertension, renal

More than 150 years ago, Richard Bright first linked the kidney to high blood pressure, but it was another 100 years before Goldblatt firmly established the potential of the kidney to cause hypertension. Goldblatt et al produced the first reliable form of experimental hypertension with the remarkably simple intervention of narrowing the main renal artery to perturb renal hemodynamics. Since then, interest in the kidney in the development of essential hypertension has waxed and waned, with considerable debate on whether the kidney is the initiator, potentiator, and/or victim of essential hypertension. Most investigators currently believe that the abnormalities and damage seen in the kidney in hypertension are entirely secondary. In particular, hypertrophy of the renal vessel walls is thought to be part of a response common to all systemic arterial vessels during sustained elevation of arterial pressure.

The main argument in recent years for the importance of the kidney in hypertension has come from Hall et al, Guyton, and Cowley. This work is widely accepted as showing the pivotal role of the arterial pressure/Na⁺ excretion rate relation in long-term blood pressure control. However, the mechanisms responsible for shifting this relation toward the right—that is, toward a prohypertensive situation in humans—remain unknown. In this article, we argue that primary changes in the structure of the preglomerular vessel walls may be one key mechanism responsible for a right shift of the pressure/Na⁺ excretion relation in hypertension. Using the simple situation of main renal artery stenosis as a background, we examined evidence for structurally based narrowing of the preglomerular vasculature as a possible underlying initiating cause of hypertension rather than as a secondary reaction to the hypertension in some situations.

Prohypertensive Hemodynamics of Main Renal Artery Stenosis

The extent of hypertension developed from main renal artery narrowing (stenosis) is related closely to the extent of increase that the stenosis produces in renal vascular resistance upstream from the glomerulus. We studied this in a series of experiments in which graded progressive stenoses were produced over a period of 2 to 3 days in conscious dogs. This allowed study of a wide range of degrees of narrowing of the main renal artery walls. The results, reproduced in Figure 1, show that there was a close relation between the extent of hypertension and the resistance to renal artery blood flow exerted by the stenosis itself.

These measurements were made in the acute phase of production of renal stenosis. However, measurements made in longer-term steady-state renal artery stenosis show that there is increased vascular resistance of the...
stenotic kidney. This measured resistance is attributable almost entirely to the stenosis itself. In dogs, we measured pressure distal to the stenosis and documented both the resistance of the stenosis and the downstream vasculature.8–12 We found that the stenosis itself increased the resistance of the kidney by up to 50% in marked, sustained hypertension. Indeed, the stenosis resistance accounted for almost all the increase in total renal vascular resistance, whereas the renal resistance of the entire renal vasculature downstream to the stenosis was not significantly different from values measured before the induction of the stenosis.8–12 In stable renal artery stenosis, even when the hypertension is significant, pressure in the distal renal artery beyond the stenosis may be near normal.8–12 Furthermore, when glomerular capillary pressure itself has been measured (estimated from stop-flow pressure), it has been found to be normal,13 as is glomerular filtration rate (GFR).11,12

As a corollary, stenoses that are not severe enough to increase renal vascular resistance do not cause hypertension.11 The resistance to blood flow of a narrowing of ≤70% of the lumen diameter exerts little resistance to blood flow.11 Even greater degrees of narrowing may not produce hypertension, in part because the renin-angiotensin system acts intrarenally to minimize the physiological effects of the stenosis.5,11 Although such a stenosis may initially lower pressure distally during acute induction experimentally (rather than a slow progressive event as in humans), intrarenal events occur that result in a marked lessening of the hemodynamic effects of the stenosis. These events appear to be mediated by angiotensin (Ang) II–induced vasoconstriction, which restores pressure distal to the stenosis, which in turn reduces the hemodynamic severity of the stenosis itself.11

When we induced very severe renal artery narrowing to more than double the resistance of the narrowed main renal artery, blood pressure below the stenosis remained low and malignant hypertension developed without restoring blood pressure distal to the stenosis toward prestenosis levels.7

Thus, increased vascular resistance characterizes main renal artery stenosis, resulting in increased aortic-glomerular capillary pressure difference. The extent of hypertension directly related to the extent of increase in this resistance. Renal artery stenosis hypertension is a simple model whose initiating event is purely renovascular. Is there evidence for other renal vascular changes that might mimic the hemodynamic effects of main renal artery stenosis and thereby cause hypertension? Goldblatt14 himself suggested that this might be the case.

Spontaneously Hypertensive Rats

The spontaneously hypertensive rat (SHR) is a genetic model of hypertension in which there is definitive evidence for preglomerular vessel hypertrophy. Measurements of renal hemodynamics in vivo show increased renal vascular resistance as the hypertension develops while GFR and glomerular capillary pressure are normal, indicating that the increase in vascular resistance is preglomerular (eg, see References 15 and 16). Morphometric measurements have shown that there is hypertrophy of the arcuate and radial cortical arteries,17,18 and functional analyses have indicated that there is structurally based narrowing of the lumen of resistance vessels.17,19 Narrowing of the afferent arterioles has also been confirmed morphometrically.20 Furthermore, evidence of vascular hypertrophy and increased renal preglomerular vascular resistance has been found as early as 4 weeks of age in SHR, before the rapid rise in arterial pressure.16,17

Surprisingly, there has been relatively little study of the functional consequences of these structural changes in the vasculature of the kidney in the SHR. Studies are needed to confirm that in vivo, with the operation of all the normal control mechanisms, the renal preglomerular vessels act in a similar hemodynamic manner to main renal artery stenosis. However, there is considerable evidence that suggests this, including measurements of increased preglomerular resistance and normal blood flow and increased aortic-glomerular capillary pressure gradient.21 It would further be expected that the structural changes would augment the responses to circulating or local vasoconstrictors,22 thereby acting as an additional hypertensive stimulus by further increasing the aorta-Pgc gradient—equivalent to further tightening of a main renal artery stenosis.7

We have shown that renal arterial wall hypertrophy in the SHR does not appear to be reversed by antihypertensive treatment. We studied the effects of treating SHR from weaning until 10 weeks of age with either an ACE inhibitor18 or an angiotensin (AT)1 antagonist.23 Neither agent reduced the extent of wall hypertrophy, measured by careful stereological techniques. Previously, Smeda and colleagues24 had also shown that successful treatment of the SHR hypertension with hydralazine likewise had no significant effect on preglomerular arterial wall hypertrophy. In contrast, in other vascular beds, antihypertensive treatment of the SHR does reverse the hypertrophy of arterial vessel walls.25 It is therefore interesting to speculate whether the hypertrophy of the renal vasculature is under different cellular control mechanisms and whether
its development is the primary stimulus to SHR hypertension by progressively increasing the aorta-glomerular capillary pressure gradient.

It should be noted, however, that in contrast to the wall hypertrophy, Notoya et al.26 and Bergstrom et al.27 have shown that the remodeling of renal afferent arterioles is reversed by long-term ACE inhibition.

The presence of structural changes in preglomerular arteries and afferent arterioles before the development of hypertension and the persistence of these structural changes despite normalization of arterial pressure (with antihypertensive treatment) strongly suggest that these changes are not due to elevated arterial pressure but may instead be involved in the pathogenesis of hypertension. Consistent with this hypothesis, Norrelund et al.28 found a correlation between lumen diameter of the afferent arteriole at 7 weeks of age in an F2-generation SHR/Wistar-Kyoto cross and the extent of subsequent development of hypertension.

Thus, structural changes in the preglomerular vessel wall in the SHR, whether primary or secondary to the hypertension, may mimic hemodynamically main renal artery stenosis. If there is hypertrophy and lumen reduction in the SHR, is there any evidence for this in human essential hypertension?

**Human Hypertension**

Although marked changes occur in the renal vessels in long-term and severe human essential hypertension, there is no direct evidence that these are primary. Indeed, it is difficult to imagine how such evidence might be obtained ethically. However, Ruilope and colleagues29 have reviewed the evidence for early changes in renal hemodynamics in borderline and early hypertension and in the children of hypertensive parents. They concluded that there is commonly an early increase in renal vascular resistance in patients with essential hypertension and in their offspring but normal GFR,29 suggesting that the increase is preglomerular and that there is increased responsiveness to vasoconstrictor stimuli.29 There are many possible explanations for these early renal vascular changes, and it will be some time before we can tell whether they are due to structural changes in the renal vessels, as in the SHR, or due to intrarenal vasoconstriction.

**Ang II–Mediated Renal Hypertension**

Hypertrophy of the walls of preglomerular vessels could have a genetic basis (eg, in SHR) or be induced by exposure of normal vessel walls to hypertrophying agents. We have tested recently whether exposure of the renal vessels to high local levels of Ang II might induce wall hypertrophy. The growth-promoting effects of Ang II on vascular smooth muscle cells is well established in vitro,30,31 and Ang II is known to be elevated within the kidney in a number of forms of experimental and human hypertension.32–34

We have infused Ang II at low doses directly into the renal artery for up to 1 month in both Sprague-Dawley rats35 and greyhound dogs.36,37 The doses used cause no immediate changes in arterial pressure and were doses at which little spillover into the systemic circulation would be expected (confirmed in rats).35 In rats, Ang II infused into the right renal artery (0.5, 1.5, or 4.5 ng/kg per minute) for 14 or 25 days produced dose-related increases in arterial pressure.35 The hypertension occurred whether or not the left kidney was nephrectomized before or at the time of commencement of the Ang II infusion, but the extent of the hypertension was reduced by approximately one third when the left kidney was not removed but instead remained in situ. In dogs, infusion of Ang II at 0.5 ng/kg per minute produced a stable, long-lasting hypertension36,37 that was due to an increase in total peripheral resistance, as is also the case in the hypertension from renal artery stenosis. Despite the known effects of Ang II on renal Na+ handling, there was no evidence for marked salt and water retention, and the hypertension was not cardiac-output mediated.36 During the long-term Ang II infusion, renal blood flow and GFR were normal, but renal vascular resistance was elevated.36,37

We have also conducted preliminary studies on whether the long-term Ang II infusion had caused structural changes in the preglomerular resistance vessels by using the established in vitro assay of renal vessel structural changes developed by Gothberg et al.19 We have modified the technique and used it recently to study the effects of long-term ACE inhibition27 and of renal denervation in the developing SHR.38 In brief, kidneys are perfused at increasing pressure with an isotonic colloid perfuse, at maximal vasodilation, to produce pressure-flow and pressure-GFR relations, with changes in the slope and position of these relations taken to reflect structural changes in the vasculature.

We concluded from these experiments that the long-term Ang II infusions had caused structurally based increases in renal resistance (reduced lumen diameter; exemplified by reduced slope of the pressure-flow relationship), caused by an apparent increased pre– to post–glomerular resistance ratio (right shift of the pressure-GFR relation).35 That is, the results indicated that 25 days of Ang II infusion into the renal artery in rats had produced structural remodeling of the preglomerular vessels. In these experiments, the reduced preglomerular lumen diameter is demonstrated most directly by comparing, during the progressive increase in perfusion pressure in each kidney, the lowest perfusion pressure at which the oncotic pressure of the artificial plasma was overcome and ultrafiltration commenced.35 As can be seen from Figure 2, this pressure was ≈55 mm Hg in the vehicle rats (as expected) but was progressively higher in the kidneys of rats that had received increasing doses of Ang II infusion for the previous 25 days, indicating dose-related reductions in preglomerular resistance vessel diameter.35 Confirmation of these findings by stereological techniques (see Reference 18) is under way. At this time, we cannot say whether this is due to the direct effects of Ang II or is secondary to the hypertension.

**Conclusions**

This article has advanced the hypothesis that structural changes in the preglomerular vasculature, resulting in increased wall thickness and lumen narrowing, may cause...
hypertension by mimicking the hemodynamic effects of main renal artery stenosis. There is evidence compatible with this hypothesis in SHR, and there is preliminary evidence that experimentally increased intrarenal Ang II levels can cause structural changes in the walls of the preglomerular resistance vessels and hypertension. Other factors that deserve consideration for producing structural changes include overactivity of the renal sympathetic nervous system and endothelial cell dysfunction. Structurally induced increases in preglomerular resistance would be predicted to shift the pressure-natriuresis relation to the right and thus could be an additional factor responsible for such a prohypertensive change in the pressure-Na+ excretion relation of Hall et al., Guyton, and Cowley. However, it remains to be shown whether structural changes can occur primarily and drive an increase in arterial pressure or if they are always secondarily induced by elevation arterial pressure. In human hypertension, the hypothesis remains conjecture because the necessary measurements of renal vessel structure (resistance vessel wall dimensions, lumen dimensions) are not possible; however, renal hemodynamic changes in early and borderline human hypertension are compatible with early structural changes.

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