Kidney and Hypertension – Causes

Update 2003

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Abstract
Renal disease is closely associated with hypertension. On the one hand, kidney disease provokes hypertension. On the other hand, hypertension aggravates the progression of renal dysfunction.

The pathomechanisms through which the kidney raises blood pressure have been considerably clarified in recent years. In experimental and clinical studies, it could be shown that “hypertension goes with the kidney”. This suggests that some renal abnormalities predispose to hypertension. Recently, it could be shown that the kidneys of individuals with so-called essential hypertension have less glomeruli than the kidneys of control individuals.

In renal patients the kidney raises blood pressure through several mechanisms. First, the pressure-natriuresis relationship is shifted to the right, i.e., sodium excretion requires higher renal perfusion pressures. Second, there is inappropriate activation of the renin-angiotensin system. Third, as only recently documented in detail, renal injury raises the sympathetic tone, even when whole kidney glomerular filtration rate (GFR) is unchanged. This results from stimulating afferent signals emanating from the kidney. Fourth, there is evidence of impaired endothelial cell-dependent vasodilatation even in very early stages of renal dysfunction. Fifth, the pulse pressure profile is altered as a consequence of premature and accelerated aging causing stiffening of the aorta.

Knowledge of these pathomechanisms is important for selection of appropriate antihypertensive treatment.

Key Words: Hypertension · Kidney · Renal disease · Sodium retention · Renin-angiotensin system · Sympathetic nervous system · Endothelial cell dysfunction

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Zusammenfassung


Die Kenntnis dieser Pathomechanismen ist wichtig für die rationale Auswahl der Antihypertensiva bei Nierenpatienten.

Schlüsselwörter: Hypertonie · Niere · Nierenerkrankung · Salzretention · Renin-Angiotensin-System · Sympathisches Nervensystem · Endothelzelldysfunktion

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The Role of the Kidney in the Genesis of Hypertension

Decades ago, Guyton [1] had proposed the hypothesis that a disturbance of the blood pressure-natriuresis relationship (“renal function curve”) is responsible for the blood pressure elevation that occurs when renal function is impaired. According to this concept, because the “gain” of the blood pressure-natriuresis relationship overrides that of all other regulatory systems, the ultimate determinant of blood pressure must be renal handling of sodium. This statement does not imply that hypertension is a renal disease, but it indicates that a functional abnormality of the kidney, i.e., a disturbed blood pressure-natriuresis relationship, is a sine qua non condition for the development of hypertension of any type.

To what extent is this hypothesis today supported by evidence?

Early studies by Bianchi et al. [2] and more definite well-controlled experimental studies by Rettig et al. [3] and Patschan et al. [4] showed that “blood pressure goes with the kidney”. Transplantation of the kidney from a genetically hypertension-prone donor rat, even when it had been kept normotensive from weaning by antihypertensive medication, caused a progressive increase of blood pressure in a recipient animal which had been immunologically manipulated to prevent a rejection reaction. By contrast, and quantitatively less impressive, transplantation of a kidney graft from a donor rat which was genetically programmed for normotension, provoked normotension in the recipient.

Apart from such experimental data, there is also convincing information in humans undergoing renal transplantation. Recipients of renal grafts coming from hypertensive donors require more antihypertensive medication [5], and recipients of kidneys from donors dying from cerebral hemorrhage, presumably because of hypertension, had also a higher risk to develop hypertension [6]. These observations are not entirely convincing, however, because it is not excluded that hypertension of the donor had damaged the kidney. More impressive are the findings in the converse situation: black patients who had become dialysis-dependent because of hypertension-induced renal injury remained persistent normotensive even 4 years after transplantation, when the kidney had been obtained from a normotensive donor and when graft function was excellent [7].

Recently, Keller et al. [8] pursued a hypothesis which had originally been proposed by Brenner et al. [9]. They had postulated that so-called nephron underdosing, i.e., a low number of nephrons and glomeruli, predisposed to hypertension and to progressive renal disease. We examined ten hypertensive victims of accidents and ten matched controls. The number of glomeruli in the kidney were counted by stereological techniques according to Gundersen. The surprising result was that there was a highly significant decrease of the number of glomeruli in hypertensive as compared to normotensive individuals and this was accompanied by a (compensatory?) increase in glomerular volume as indicated in Table 1. Although it is not absolutely excluded that glomeruli may have been lost as a consequence of hypertension, appropriate studies suggested that this was not the case.

How could a low number of nephrons arise? There are some indications that rat strains with low nephron numbers are more predisposed to hypertension and progressive renal disease [10]. While this argues for a genetic predisposition, there are also experiments that maternal malnutrition during pregnancy reduces the number of nephrons in the kidneys of the offspring [11]. These findings are definitely reminiscent of the Barker hypothesis [12] according to which fetal malnutrition predisposes to many problems in adult life including hypertension.

Pathomechanisms through which the Kidney Raises Blood Pressure

Several studies documented in a certain proportion of patients with primary (or essential) hypertension and definitely in patients with renal disease that the pressure-natriuresis relationship [1] is shifted to the right, i.e., that the kidney has difficulties in getting rid of sodium unless the

Table 1. Number of glomeruli and glomerular volume in middle-aged victims of fatal accidents in whom hypertension and/or left ventricular hypertrophy were present compared to normotensive controls of the same age, sex, and body mass index (after [8]).

<table>
<thead>
<tr>
<th>Description</th>
<th>Hypertensive Individuals (n = 10)</th>
<th>Normotensive Individuals (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of glomeruli</td>
<td>890,869 ± 156,110</td>
<td>1,666,805 ± 411,690*</td>
</tr>
<tr>
<td>Mean glomerular volume (10^-3 mm^3)</td>
<td>5.67 ± 0.85</td>
<td>2.41 ± 0.71*</td>
</tr>
</tbody>
</table>

*p < 0.001 versus hypertensive individuals