Renovascular Hypertension and Ischemic Nephropathy

Clippers II III
Blood pressure
Renin
Change in blood pressure on removing clip

FIGURE 3-10
Sequential phases in two-kidney, one-clip (2K,1C) experimental renovascular hypertension. The schematic representation of renovascular hypertension depicted in Figure 3-9 is an oversimplification. In fact, the course of experimental 2K,1C hypertension may be divided into three sequential phases. In phase I, renal ischemia and activation of the renin angiotensin system are of fundamental importance, and in this early phase of experimental hypertension, the blood pressure elevation is renin- or angiotensin II-dependent. Acute administration of angiotensin II antagonists, administration of angiotensin-converting enzyme (ACE) inhibitors, removal of the renal artery stenosis (ie, removal of the clip in the experimental animal or removal of the “stenotic kidney”) promptly normalizes blood pressure. Several days after renal artery clamping, renin levels fall, but blood pressure remains elevated. This second phase of experimental 2K,1C hypertension may be viewed as a pathophysiologic transition phase that, depending on the experimental model and species, may last from a few days to several weeks. During this transition phase (phase II), salt and water retention are observed as a consequence of the effect of hypoperfusion of the stenotic kidney; augmented proximal tubular reabsorption of sodium and water and angiotensin II-induced stimulation of aldosterone secretion contribute to this sodium and water retention. In addition, the high levels of angiotensin II stimulate thirst, which further augments expansion of the extracellular fluid volume. The expanded extracellular fluid volume results in a progressive suppression of peripheral renin activity. During this transition phase, the hypertension is still responsive to removal of the unilateral renal artery stenosis, to angiotensin II blockade, or unilateral nephrectomy, although these maneuvers do not normalize the blood pressure as promptly and consistently as in the acute phase.

After several weeks, a chronic phase (phase III) ensues wherein unclipping the renal artery of the experimental animal does not lower the blood pressure. This failure of “unclipping” to lower the blood pressure in this chronic phase (III) of 2K,1C hypertension is due to widespread arteriolar damage to the “contralateral kidney,” consequent to prolonged exposure to high blood pressure and high levels of angiotensin II. In this chronic phase of 2K,1C renovascular hypertension, extracellular fluid volume expansion and systemic vasoconstriction are the main pathophysiologic abnormalities. The pressure natriuresis of the “contralateral kidney” blunts the extracellular fluid volume expansion caused by the “stenotic kidney;” but as the contralateral kidney suffers vascular damage from extended exposure to elevated arterial pressure, its secretory function diminishes and extracellular fluid volume expansion persists. In this third phase of experimental 2K,1C hypertension, acute blockade of the renin angiotensin system fails to lower blood pressure. Sodium depletion may ameliorate the hypertension but does not normalize it. The clinical surrogate of phase III experimental 2K,1C hypertension is duration of hypertension. Widespread clinical experience indicates that major improvements in blood pressure control or cure of the hypertension following renal revascularization or even removal of the kidney ipsilateral to the renal artery stenosis are rarely observed in patients with a long duration (ie, >5 years) of hypertension.

(Adapted from Brown and coworkers [3]; with permission.)

FIGURE 3-11
Schematic representation of two types of experimental hypertension. The discussion so far of the pathophysiology of renovascular hypertension has focused on the two-kidney, one-clip model of renovascular hypertension (“two-kidney hypertension”), wherein the artery to the “contralateral kidney” is patent and the “contralateral” nonaffected kidney is present. Elevated peripheral renin activity, normal plasma volume, and hypokalemia are typically associated with the elevated arterial pressure. There is another type of “renovascular hypertension” known as “one-kidney” hypertension, wherein in the experimental model, one renal artery is constricted and the contralateral kidney is removed. Although there is an initial increase in renin release responsible for the early rise in blood pressure in “one-kidney” hypertension as in “two-kidney” hypertension, the absence of an unclipped contralateral kidney allows for sodium retention early in the course of this one-kidney, one-clip (1K,1C) model. Renin levels are suppressed to normal levels in conjunction with high blood pressure which is maintained by salt and water retention. Thus, extracellular fluid volume expansion is a prime feature of “one-kidney” hypertension.
A. LESIONS PRODUCING THE SYNDROME OF RENOVASCULAR HYPERTENSION (“TWO-KIDNEY HYPERTENSION”)*

- Unilateral atherosclerotic renal arterial disease
- Unilateral fibrous renal artery disease
- Renal artery aneurysm
- Arterial embolus
- Arteriovenous fistula (congenital and traumatic)
- Segmental arterial occlusion (traumatic)
- Pheochromocytoma compressing renal artery
- Unilateral perirenal hematoma or subcapsular hematoma (compressing renal parenchyma)

*Implies contralateral (nonaffected) kidney present.

B. LESIONS PRODUCING THE SYNDROME OF RENOVASCULAR HYPERTENSION (“ONE-KIDNEY HYPERTENSION”)*

- Stenosis to a solitary functioning kidney
- Bilateral renal arterial stenosis
- Aortic coarctation
- Vasculitis (polyarteritis nodosa and Takayasu’s arteritis)
- Atheroembolic disease

*Implies total renal mass ischemic.

FIGURE 3-12
Lesions producing the syndrome of renovascular hypertension. A. Two-kidney hypertension. The most common clinical counterpart to “two-kidney” hypertension is unilateral renal artery stenosis due to either atherosclerotic or fibrous renal artery disease. Unilateral renal trauma, with development of a calcified fibrous capsule surrounding the injured kidney causing compression of the renal parenchyma, may produce renovascular hypertension; this clinical situation is analogous to the experimental Page kidney, wherein cellophane wrapping of one of two kidneys causes hypertension, which is relieved by removal of the wrapped kidney.

B. One-kidney hypertension. Clinical counterparts of experimental one-kidney, one-clip (“one kidney”) hypertension include renal artery stenosis to a solitary functioning kidney, bilateral renal arterial stenosis, aortic coarctation, Takayasu’s arteritis, fulminant polyarteritis nodosa, atheroembolic renal disease, and renal artery stenosis in a transplanted kidney. In some parts of the world, e.g., China and India, Takayasu’s arteritis is a frequent cause of renovascular hypertension.

FIGURE 3-13
Steps in making the diagnosis of renovascular hypertension (RVHT). With the exception of oral contraceptive use and alcohol ingestion, RVHT is the most common cause of potentially remediable secondary hypertension. RVHT is estimated to occur with a prevalence of 1% to 15%. Some hypertension referral clinics have estimated a prevalence of RVHT as high as 15%, whereas other prevalence data suggest that less than 1% to 2% of the hypertensive population has RVHT.

Although elderly atherosclerotic hypertensive individuals often have atherosclerotic renal artery disease, their hypertension is usually essential hypertension, not RVHT. On balance, the prevalence of RVHT in the general hypertensive population is probably no more than 2% to 3%. The particular appeal of diagnosing RVHT centers around its potential curability by an interventional maneuver such as surgical revascularization, percutaneous transluminal renal angioplasty (PTRA), or renal artery stenting. Whether or not to use these interventions for the goal of improving blood pressure depends on the likelihood such intervention will improve the blood pressure.

The overwhelming majority of patients with RVHT will have this syndrome because of main renal artery stenosis. Therefore, the first step in making the diagnosis of RVHT is to demonstrate renal artery stenosis by one of several imaging procedures and, eventually, by angiography. The second step in establishing the probability that the renal artery stenosis is instrumental in promoting hypertension is to determine the pathophysiologic significance of the stenotic lesion. Finally, the hypertension, presumed to be renovascular in origin, is proven to be RVHT when the elevated blood pressure is cured or markedly ameliorated by an interventional maneuver such as surgical revascularization, PTRA, renal artery stent, or nephrectomy.
Renovascular Hypertension and Ischemic Nephropathy

3.9

**DIAGNOSIS OF RENAL ARTERIAL STENOSIS**

<table>
<thead>
<tr>
<th>Clinical clues</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age onset of hypertension &lt;30 y or &gt;55 y</td>
<td>Duplex ultrasonography</td>
</tr>
<tr>
<td>Abrupt onset of hypertension</td>
<td>Radionuclide renography</td>
</tr>
<tr>
<td>Acceleration of previously well-controlled hypertension</td>
<td>Captopril renography</td>
</tr>
<tr>
<td>Hypertension refractory to an appropriate three-drug regimen</td>
<td>Captopril provocation test</td>
</tr>
<tr>
<td>Accelerated retinopathy</td>
<td>Intra-venous digital subtraction angiography</td>
</tr>
<tr>
<td>Systolic-diastolic abdominal bruit</td>
<td>Rapid sequence IVP</td>
</tr>
<tr>
<td>Evidence of generalized atherosclerosis obliterans</td>
<td>Magnetic resonance angiography</td>
</tr>
<tr>
<td>Malignant hypertension</td>
<td>Spiral CT angiography</td>
</tr>
<tr>
<td>Flash pulmonary edema</td>
<td>CO\textsubscript{2} angiography</td>
</tr>
<tr>
<td>Acute renal failure with use of angiotensin-converting enzyme inhibitors or angiotensin II receptor-blockers</td>
<td>Conventional (contrast) angiography</td>
</tr>
</tbody>
</table>

**FIGURE 3-14**

Diagnosis of renal artery stenosis. Clinical clues suggesting renal artery stenosis, some of which suggest that the stenosis is the cause of the hypertension, are listed on the left. The well-documented age of onset of hypertension in an individual under the age of 30 or over age 55 years, particularly if the hypertension is severe and requiring three antihypertensive drugs, is a strong clinical clue to renal artery stenosis and predicts that the stenosis is causing the hypertension. The patient with a long history of mild hypertension, easily controlled with one or two drugs, who, particularly in older age, develops severe and refractory hypertension, is likely to have developed atherosclerotic renal artery stenosis as a contributor to underlying longstanding essential hypertension. Grade III hypertensive retinopathy, malignant hypertension, and flash pulmonary edema all suggest renal artery stenosis with or without renovascular hypertension. The observation of a diastolic bruit in the abdomen of a young white woman suggests fibrous renal artery disease and, further, is a reliable clinical clue that the hypertension will be helped substantially by surgical renal revascularization or percutaneous transluminal renal angioplasty.

The diagnostic tests listed along the right side are used mainly to detect renal artery stenosis (ie, the anatomic presence of disease). Captopril renography is also used to predict physiologic significance of the stenotic lesion. The popularity of these diagnostic tests in detecting renal artery stenosis varies from institution to institution; correlations with percent stenosis by comparative angiography are widely variable. A substantial fall in blood pressure following initiation of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker suggests RVHT. With the exception of a diastolic abdominal bruit and accelerated retinopathy, no clear-cut physical findings definitely discriminate patients with RVHT from the larger pool of patients with essential hypertension.

**FIGURE 3-15**

Renal duplex ultrasound for diagnosis of renal artery stenosis. Duplex ultrasound scanning of the renal arteries is a noninvasive screening test for the detection of renal artery stenosis. It combines direct visualization of the renal arteries (B-mode imaging) with measurement of various hemodynamic factors in the main renal arteries and within the kidney (Doppler), thus providing both an anatomic and functional assessment. Unlike other noninvasive screening tests (eg, captopril renography), duplex ultrasonography does not require patients to discontinue any antihypertensive medications before the test. The study should be performed while the patient is fasting. The white arrow indicates the aorta and the black arrow the left renal artery, which is stenotic. Doppler scans (bottom) measure the corresponding peak systolic velocities in the aorta and in the renal artery. The peak systolic velocity in the left renal artery was 400 cm/s, and the peak systolic velocity in the aorta was 75 cm/s. Therefore, the renal-aortic ratio was 5.3, consistent with a 60% to 99% left renal artery stenosis. (From Hoffman and coworkers [4]; with permission.)