The right diagnostic work-up: investigating renal and renovascular disorders

Jörg Radermacher and Hermann Haller

Renovascular disease is present in about 10–40% of patients with end-stage renal disease, and constitutes the fastest-growing group of end-stage renal disease patients. The unselective correction of renal artery stenosis has led to disappointing results. Most studies that have compared conservative treatment with angioplasty have found only modest or no beneficial effects of angioplasty on renal function and blood pressure. It is therefore mandatory to evaluate the functional significance of a stenosis before intervention. Patients most likely to respond favourably to revascularization should be identified. Factors that affect outcome include the severity of renal artery stenosis, type of treatment of renal artery stenosis and, most importantly, underlying renal disease, which prevents a favourable response even after successful correction of renal artery stenosis. Doppler ultrasonography to evaluate the renal resistance index [1 – (end diastolic velocity/maximum systolic velocity) × 100] or captopril scintigraphy are the best methods by which to classify patients as responders or non-responders to intervention. In patients with a renal resistance index ≥80%, improvement of renal function or blood pressure is highly unlikely, despite successful correction of renal artery stenosis. The value of the renal resistance index can also be extended to patients with non-stenotic renal diseases. Identifying patients at risk for irreversible loss of renal function and who may benefit from intervention is a high research priority. *J Hypertens* 21 (suppl 2):S19–S24 © 2003 Lippincott Williams & Wilkins.

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Pathophysiology of renal artery stenosis

End-stage renal disease requiring renal replacement puts a major economic burden on the healthcare system. Renovascular disease is the most common cause of secondary hypertension and the most common cause, next to diabetic nephropathy, of renal insufficiency, and can lead to difficult-to-control hypertension [1]. The prevalence of renovascular disease in the general population is relatively small. In patients with essential hypertension, the prevalence is about 1–5% [2]. In certain patient populations, such as those with severe hypertension, refractory hypertension or those undergoing diagnostic coronary arteriography, the prevalence is much higher at 20–40% [3,4].

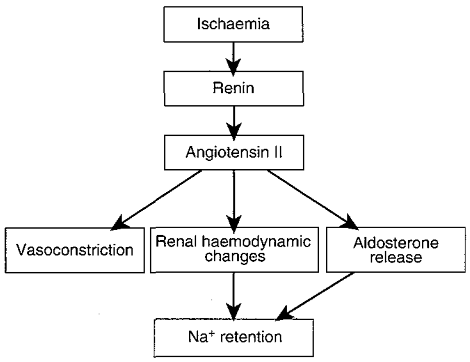
Renovascular hypertension is the clinical consequence of activation of the renin–angiotensin–aldosterone system (Fig. 1). Renal artery stenosis leads to renal ischaemia, which causes the release of renin from the juxtaglomerular cells of the kidney and a secondary increase in blood pressure. The release of renin activates a cascade system in which renin promotes the conversion of angiotensin I to angiotensin II and increases aldosterone release from the adrenal gland. Increased renin secretion increases angiotensin II and aldosterone release, which causes severe vasoconstriction and sodium and water retention. In unilateral stenosis, the normal contralateral kidney may compensate for the sodium and water retention by increasing filtration, but this compensatory mechanism does not occur in bilateral stenosis.

Diagnosis of renal artery stenosis

Early diagnosis and treatment of renovascular disease may help to prevent or improve hypertension and renal impairment due to renal artery stenosis. The clinical signs that suggest renovascular disease include an abdominal bruit, difficult-to-control hypertension (requiring ≥3 antihypertensive drugs), accelerated or essential hypertension that was previously well controlled, atherosclerosis in other vascular beds, and otherwise unexplained azotaemia. The onset of hypertension before the age of 30 years (from fibromuscular renal artery disease) or after the age of 55 years (from atherosclerotic renal artery disease) is another sign of renovascular disease. Differences in the sizes of the two kidneys also suggest renovascular hypertension.

It is important to identify the clinical signs of renovascular disease. Once renal artery stenosis is suspected, a screening test is used to confirm its presence. Although angiography remains the gold standard for diagnosing renal artery stenosis, it is an invasive procedure that does not adequately assess the functional importance of the stenotic lesion. It may also cause atheromatous embolization of the kidneys or renal impairment due to radiocontrast nephrotoxicity [2]. Selecting the appropriate

Fig. 1



Pathophysiology of renovascular hypertension.

Table 1 Sensitivity and specificity of screening methods for renal artery stenosis

Screening method	Sensitivity/ specificity (%)	Disadvantage
Duplex ultrasonography	92/95	Investigator dependent Technical failure due to Obesity Excessive bowel gas Poor blood flow in main renal artery
Captopril scintigraphy	86/93	Less accurate in patients with: Renal impairment Bilateral stenosis or unilateral stenosis in a single functioning kidney
Magnetic resonance angiography	96/74	High cost Claustrophobia in 10% patients
Spiral computed tomography	98/94	High cost Radiocontrast toxicity

technique as a first-line screening test depends on the patient's risk of renovascular hypertension.

Screening for renal artery stenosis

If renal artery stenosis is suspected, an inexpensive, accurate (i.e. with a low rate of technical failure and high sensitivity and specificity) and non-invasive screening test should be considered [5]. Spiral computed tomography (CT) and magnetic resonance imaging (MRI) are non-invasive imaging techniques that have high sensitivity and specificity for detecting renal artery stenosis [1,6,7] (Table 1). These techniques are limited, however, by their high costs and, in the case of spiral-CT, the use of contrast agents. MRI is not suitable for patients with claustrophobia, certain types of metallic implants, or those who are seriously ill. The conventional renal angiogram currently remains the standard test for the definitive diagnosis of renal artery stenosis.

Measurement of the concentrations of renin in the renal vein can be used to predict the potential success of surgical revascularization. False-negative and false-positive results are common with this technique, and it is therefore not recommended as a reliable screening test for renal artery stenosis. The accuracy may be enhanced by using an angiotensin converting enzyme (ACE) inhibitor (captopril scintigraphy), which increases renin secretion, blocks the vasoconstrictive effect of angiotensin II on the efferent arteriole of the renal glomerulus, and reduces filtration on the side of the stenosis [1]. The captopril test, which measures plasma renin activity after a dose of 25–50 mg of captopril, is a simple technique but also has low specificity and sensitivity [8]. Antihypertensive drugs that interfere with plasma renin activity, however, limit all tests that rely on the measurement of plasma renin activity.

Captopril scintigraphy can detect renal artery stenosis with high sensitivity and acceptable specificity, and has also been shown to be of value in identifying patients whose blood pressure will improve after correcting the stenotic lesion [9]. This test, however, has not been shown to predict an improvement in renal function after correction of renal artery stenosis and it cannot locate the stenosis or determine its severity [1]. Furthermore, the sensitivity of this test is reduced in patients with renal insufficiency and in patients with bilateral stenoses or a stenosis in a single functioning kidney [1,10]. It is particularly important to identify these patients because the major rationale for performing surgery or angioplasty is to preserve renal function.

Doppler ultrasonography may be a good screening method to detect renal artery stenosis. Previous studies using this procedure have reported high rates of technical failure [2,11], excluded patients with impaired renal failure [12] or have not reported data on renal function [2]. Many of these studies have relied on either direct visualization of the renal arteries or measurement of various intrarenal haemodynamic properties to detect renal artery stenosis. With duplex Doppler ultrasonography, peak-systolic velocity and renal–aortic or renal–renal ratio can be measured and used to estimate the severity of a focal arterial stenosis [13]. It can detect both unilateral and bilateral renal artery stenosis and be used to detect recurrent stenoses in patients who have been treated with angioplasty or surgery [13]. In experienced hands, this technique is highly sensitive and specific for detecting renal artery stenosis, and is rapid and inexpensive [5]. Doppler ultrasonography is an ideal screening technique for detecting a renal artery stenosis ≥50% [5]. Two main approaches are used to detect a significant renal artery stenosis of 50–70% [5,14]. The first approach is a direct one that looks at flow acceleration at the site of the stenosis. This approach has good sensitivity and specificity for detecting stenoses ≥50%. Obesity, excessive bowel gas or poor blood flow in the main renal artery can, however, interfere with direct visualization of the renal arteries [5]. The second approach is an indirect one that looks at post-stenotic flow phenomena. This approach can be used in nearly all patients but will only detect severe stenoses of 60–70%. We have now combined the two parameters to provide an assessment of the anatomy of the renal arteries and to optimize the technical success of the procedure [5]. In patients with normal or impaired renal function, we reported no technical failure with duplex Doppler ultrasonography, and showed high sensitivity (96.7%) and specificity (98.0%) for detecting renal artery stenosis ≥50% compared with angiography [5].

A combination of both approaches is the most suitable technique for accurate detection of renal artery stenosis.

Index of clinical suspicion

The primary determinant of the work-up for renal artery stenosis, as has been stated before, is the index of clinical suspicion, and there are good screening methods to detect the anatomical presence of renal artery stenosis. Not every patient with a renal artery stenosis, however, will benefit from intervention. Correction of renal artery stenosis in unselected patients will improve renal function and blood pressure in only 60–80% of patients [14]. In patients with azotaemia, the percentage of patients who will achieve substantial recovery of renal function may be as low as 25–30% [15]. Most studies that have compared conservative treatment with angioplasty in unselected patients have reported only slight or no beneficial effects of angioplasty on renal function and blood pressure [16]. It is therefore important to identify those patients who will benefit from revascularization. There are various risk factors that have been shown to be useful in identifying patients who are unlikely to respond favourably to intervention. These factors include a urinary protein excretion of at least 1 g/day, hyperuricaemia, creatinine clearance of <40 ml/min, age of >65 years, pulse pressure of at least 70 mmHg, the absence of nocturnal fall in blood pressure, and the presence of coronary artery disease, arterial occlusive disease of the legs, or cerebrovascular disease [16].

Patients who are considered for revascularization to preserve or restore renal function include those with recent deterioration in renal function, advanced chronic renal failure, end-stage renal disease, bilateral renal artery stenosis or stenosis to a single functioning kidney, those with recurrent flash pulmonary oedema or reversible azotaemia during treatment with an ACE inhibitor, and those with resistant or poorly controlled hypertension [15,17]. None of these factors, however, is specific enough to predict in which patients blood pressure or renal function will be improved after a successful intervention. More reliable predictive tests are needed.

Choosing the optimal treatment and predicting the outcome of intervention

The decision to recommend revascularization depends on a balance between the risks and costs of treatment and the benefits obtained if renal function is successfully improved. Although surgery has long been considered the standard procedure for revascularization, it is invasive, requires prolonged hospitalization and is associated with complications, such as permanent renal failure, cholesterol embolism and mortality [9]. The overall complication rate for percutaneous transluminal renal angioplasty is low [9]. Stenoses <50% tend not to require invasive treatment because they generally do not cause hypertension or impaired renal function [9]. Stenoses >50%, however, can cause both hypertension and renal impairment [18].

Table 2 Factors associated with a reduced likelihood of improving blood pressure or renal function after successful correction of renal artery stenosis

Factor
Older age >65 years
Male sex
Severe atherosclerotic disease
Proteinuria >1 g/day
Severely impaired renal function (GFR <40 ml/min)
No abrupt onset or worsening of hypertension
Duration of hypertension >10 years
DBP <80 mmHg
SBP <160 mmHg
Diabetes mellitus
No smoking
Renal artery stenosis <70%

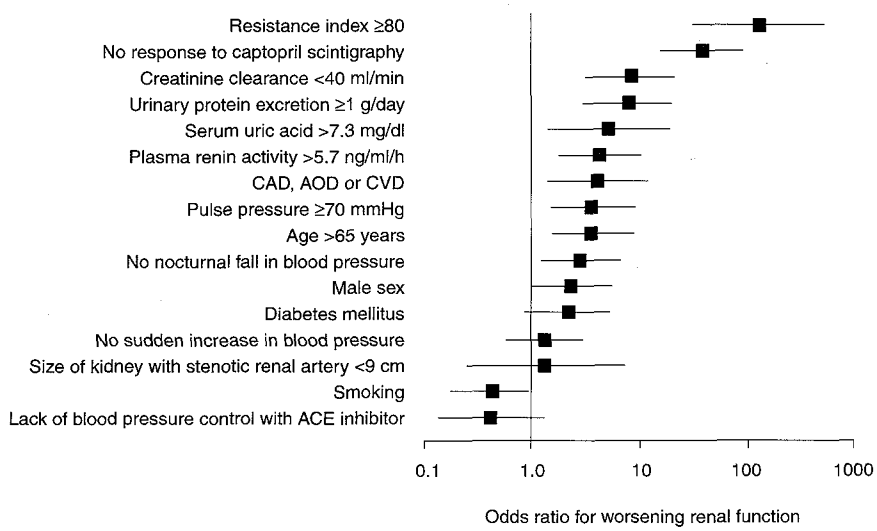
DBP, diastolic blood pressure; GFR, glomerular filtration rate; SBP, systolic blood pressure. Data from Radermacher *et al.* [9].

One of the major reasons for treatment failure, despite the successful correction of renal artery stenosis ≥50%, is renal failure [9]. The most common diseases responsible for renal failure are hypertensive nephrosclerosis and diabetic nephropathy with glomerulosclerosis. Patients with nephrosclerosis or diabetic glomerulosclerosis would therefore be expected to have an unfavourable outcome after correction of renal artery stenosis. Several factors must therefore be considered when recommending revascularization to patients with renal artery stenosis, including the severity of the stenosis, the procedure used to treat the stenosis, and most importantly, underlying renal disease [9,16,19]. Giroux *et al.* [20] have suggested that some easily obtainable clinical and angiographic criteria are the best predictors of success after revascularization (Table 2). These criteria, however, are insufficiently sensitive or specific to predict those patients who are most likely to benefit from intervention. More accurate techniques, such as measuring the renal resistance index with Doppler ultrasonography, are more reliable for predicting outcome.

Renal resistance index

The renal resistance index is an indicator of the amount of renal arterial impedance. The renal resistance index can be calculated as [1 – (end diastolic velocity/maximum systolic velocity) × 100]. The value of the renal resistance index in predicting the clinical success of

Fig. 2



Univariate odds ratio for worsening renal function after correction of renal artery stenosis (with 95% confidence intervals). The absence of a nocturnal fall in blood pressure was determined from measurements of 24-h ambulatory blood pressure. The odds ratio for captopril scintigraphy was calculated from published data (Fernandez *et al.* [21], Fommei *et al.* [22]). A sudden increase in blood pressure refers to recent worsening of hypertension. To convert the value for serum uric acid to µmol/l, multiply by 59.5. ACE, angiotensin converting enzyme; AOD, arterial occlusive disease of the legs; CAD, coronary artery disease; CVD, cerebrovascular disease. Reproduced with permission from Lippincott Williams & Wilkins [9].

intervention in patients with renal artery stenosis or non-stenotic lesions is currently a subject of investigation.

Patients with renal artery stenosis

Captopril scintigraphy or evaluation of renal resistance index using Doppler ultrasonography are effective methods of classifying patients as either responders or non-responders to intervention [9]. We have shown that, in patients with renal artery stenosis, an increase in renal resistance index ≥80% in either kidney was associated with poor outcome after revascularization and identified patients at risk of progressive renal disease. After intervention, mean arterial blood pressure was not reduced by at least 10% in 97% of patients whose renal resistance index was ≥80%. Renal function was reduced in 80% of patients, 46% required dialysis and 29% died during follow-up. In contrast, in patients with a low renal resistance index <80%, correction of renal artery stenosis with revascularization reduced mean arterial blood pressure by at least 10% in 94% of patients, 3% required dialysis and 3% died. After both uni- and multivariate analysis, only a renal resistance index ≥80% reliably predicted progression of renal disease in patients with renal artery stenosis, and identified those whose blood pressure or renal function was unlikely to improve with intervention (Fig. 2) [16,21,22].

Patients with non-stenotic lesions

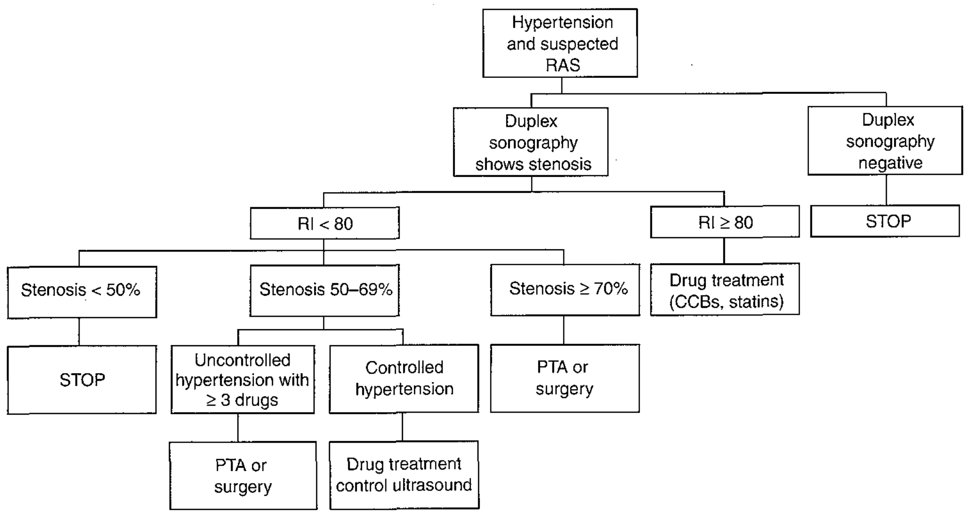
We have also investigated the predictive value of renal resistance index in patients with non-stenotic renal disease [19]. In patients with newly diagnosed renal disease, renal resistance index was measured in the segmental arteries of both kidneys. The combined endpoint was a decrease of creatinine clearance by ≥50%, end-stage renal disease with replacement therapy, or death. At baseline, 15% of patients had a renal resistance index ≥80%. Of these, 76% had a decline in renal function ≥50%, 64% progressed to dialysis and 24% died. In patients with a renal resistance index <80%, 9% had a decline in renal function, 5% progressed to dialysis, and 1% died. The renal resistance index was a specific prognostic indicator with a high positive and negative predictive value. After univariate analysis, only impaired creatinine clearance had a predictive value as high as the renal resistance index, which is shown by the odds ratio for the prediction of worsening renal function (Table 3). After multivariate analysis, the renal resistance index predicted the odds ratio for worsening renal function or death more reliably than proteinuria >1 g/day or

Table 3 Risk factors and odds ratios for worsening renal function or death

	Odds ratio for worsening renal function or death[a]	
	Univariate	Multivariate[b]
Resistance index ≥80	110 (23–519)	211 (10–4269)
Proteinuria >1 g/day	77 (23–259)	46 (4–481)
Creatinine clearance <40 ml/min	121 (35–423)	4.3 (0.7–24)

Worsening renal function means decrease in creatinine clearance of at least 50% or dependence on dialysis. [a]Odds ratio with 95% confidence intervals in parentheses. [b]Stepwise logistic regression analysis was used. Only findings that remained independent predictors after stepwise forward logistic regression analysis are listed. Reproduced with permission from Lippincott Williams & Wilkins [19].

Fig. 3



Pathway for evaluation of renovascular disease. CCB, calcium channel blocker; PTA, percutaneous transluminal angioplasty; RAS, renal artery stenosis; RI, resistance index (Pourcelot index); stenosis, percent diameter reduction. Reproduced with permission from Lippincott Williams & Wilkins [9].

creatinine clearance <40 ml/min. The only independent variables that indicated progression were a resistance index ≥80% and proteinuria >1 g/day.

The renal resistance index may prove to be a valuable tool in evaluating the therapeutic effects of drugs on renal function. We are currently investigating the effect of the angiotensin II type 1 receptor antagonist olmesartan medoxomil on renal haemodynamics in patients with type 2 diabetes with or without mild-to-moderate hypertension. By using renal Doppler ultrasonography, we aim to examine the effect of olmesartan on the primary endpoint of change in renal resistance index from baseline. We hypothesize that olmesartan will have a beneficial effect on the renal vasculature and will improve the renal resistance index.

Summary

Renal artery disease is the most common cause of secondary hypertension and an important cause of end-stage renal failure. It is important to identify patients with renal artery stenosis and to determine those who will benefit from correction of renal artery stenosis. Clinical signs and symptoms associated with renovascular disease, such as refractory hypertension, abdominal bruit or proof of atherosclerosis in other vascular beds, should be identified first. If such signs are present, an inexpensive, accurate (i.e. low rate of technical failure and high sensitivity and specificity) and non-invasive screening test should be considered. In general, stenoses with a diameter reduction >70% should be corrected and stenoses of 50–70% should only be corrected if blood pressure cannot be controlled with antihypertensive treatment (Fig. 3). Possible predictors of a favourable response to revascularization are a renal resistance index <80%, as measured by Doppler ultrasonography, or a positive captopril scintigraphy test.

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