

Management of Renal Artery Stenosis - an Update

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Abstract: The role of the renal vasculature in eliciting renovascular hypertension (RVH) was established in 1934, when Goldblatt et al. [1] in a classical experimental study demonstrated that partial obstruction of the renal artery increased mean arterial blood pressure (BP). The pathophysiology of renal artery stenosis (RAS) is incompletely understood but has been postulated to be related to increased afterload from neurohormonal activation and cytokine release [2]. Atherosclerotic RAS (ARAS) is increasingly diagnosed in the expanding elderly population, which also has a high prevalence of arterial hypertension. There is still considerable uncertainty concerning the optimal management of patients with RAS. Many hypertensive patients with RAS have co-existing essential hypertension and furthermore, it is often difficult to determine to what degree the RAS is responsible for the impairment of renal function. There are three possible treatment strategies: medical management, surgery, or percutaneous transluminal renal angioplasty (PTRA) with or without stent implantation. The use of stents has improved the technical success rate of PTRA and also led to lower risk of restenosis, in particular for ostial RAS. PTRA with stenting has therefore replaced surgical revascularisation for most patients with RAS and has led to a lower threshold for intervention. The treatment of choice to control hypertension in fibromuscular dysplasia (FMD) is generally accepted to be PTRA [3]. In ARAS, on the other hand, the benefits with PTRA are less clear [4] and the challenge to identify which patients are likely to benefit from revascularisation remains unknown.

Key words: Renal artery stenosis, percutaneous transluminal renal angioplasty, blood pressure, renal function.

Etiology of renal artery stenosis

RAS may be caused by different conditions, but about 90% of all cases are accounted for by ARAS (Fig. 1), mostly in patients over the age of 50 years. FMD of the renal artery accounts for about 10% of RAS. Patients are regarded as having atherosclerotic lesions when the characteristic irregular shape of the lesions is seen on angiography and/or in the presence of obvious atherosclerosis of the aorta. ARAS usually affects the proximal part of the main renal artery or the aortorenal orifice. This is in contrast to FMD, which often affects the distal main renal artery or the segmental branches, with a typically beaded, aneurysmal appearance on angiography.

Rare causes of RAS are arteritis, Takayasu's arteritis and giant cell arteritis. Takayasu's arteritis affects the aorta and its major branches. It is typically a disease of women in their second to fourth decades and is more common in Asia than in Europe. Giant cell arteritis tends to primarily involve carotid artery branches of Northern Europeans older than 50 years. Both Takayasu's arteritis and giant cell arteritis feature acute inflammation and subsequent fibrosis, leading to stenoses, which may cause aortic coarctation, aneurysmal dilatation and distal ischaemia. Both conditions can cause RAS, RVH and ischaemic renal injury, but Takayasu's arteritis is a more common etiology than giant cell arteritis.

RAS has also been reported in patients with the antiphospholipid syndrome and in patients with autoimmune diseases, such as systemic lupus erythematosus. Other rare causes of RVH include polyarteritis nodosa, embolism and dissection of the renal artery, extrinsic compression bands, tumours adjacent to the renal artery, retroperitoneal fibrosis, primary arterial tumours, and iatrogenic reasons.

ies. Also, some patients may refuse surgical treatment and demand only the extraction of the affected tooth. Such patients were not included in this study. Conversely, patients with cystic lesions are more likely to be treated at

the dental school and inclusion of data from private clinics could actually lower the observed prevalence rate. Knowledge of the relative frequencies and sites of presentation of odontogenic cysts in different ethnogeographic backgrounds is an essential step in the early diagnosis and management of these benign yet potentially destructive lesions.



Figure 1. Angiogram showing atherosclerotic RAS

Fibromuscular dysplasia (FMD)

FMD is a non-atheromatous, non-inflammatory, multifocal segmental angiopathy of uncertain aetiology (Fig. 2). Mechanically, both the internal carotid and the renal arteries are subjected to repeated stretching during motion and respiration, which may induce injury. This hypothesis is supported by the observation that renal FMD is more prevalent on the right side, on which the renal artery is longer making the right kidney more subject to renal ptosis than the left one [5]. FMD should be excluded in young people presenting with acute carotid artery dissection or occlusion.

In vitro studies have demonstrated increased production of collagen, hyaluronate, and

chondroitin sulphate in arteries exposed to cyclical stretching [6]. Mural ischaemia caused by functional defects in the vasa vasorum, possibly in association with de-velopmental renal malposition, has also been postulated as a cause of FMD. FMD is common among women, 75% of patients are female. The higher prevalence of disease among women implies that hormonal factors are important [7]. Patients are usually aged 15–50 years. Middle-aged individuals with renal FMD develop hypertension more of-ten than age-matched controls. The profound arterial BP response to treatment and re-current arterial hypertension with restenosis supports the high probability of a reno-vascular origin of arterial hypertension in FMD patients [8].



Figure 2. Angiogram showing fibromuscular RAS.

Prevalence of RAS

The prevalence of renovascular disease in the general population is difficult to map, as there are no easily applicable screening tests. The true prevalence of RVH is also unknown, but it may account for 1-5% of all cases of hypertension in adults, and is more likely present in patients with resistant or malignant phase hypertension. The prevalence data are derived mostly from autopsy studies, which indicate a greater prevalence of RAS because of difficulties to estimate the significance of stenosis. The large majority of patients with atherosclerotic disease have preexisting hypertension, which is an independent predictor of the presence of renal arterial disease in most series [9]. RAS prevalence continues to increase with increasing age.

Pathology and pathophysiology of renovascular hypertension (Fig. 3)

The term RAS refers to the narrowing of the renal artery lumen, and does not imply the presence of physiologic consequences. In contrast, both RVH and ischaemic nephropathy are clinico-pathologic entities. RVH is defined as hypertension that develops as a direct consequence of RAS. Most agree that a stenosis narrowing the luminal diameter by 75% is almost certainly of hemodynamic significance. The physiologic significance of lesser degrees of stenosis, however, may depend on the resistance of the peripheral renal vasculature or the condition of the renal autoregulatory system [10].

Animal studies of ARAS suggest that injury to the endothelium in an atherosclerotic milieu of hyperlipidemia and hypertension is required for the development of ARAS [11].

In unilateral disease, the arterial perfusion pressure in the stenosed kidney is reduced, leading to activation of the renin-angiotensin-aldosterone (RAA) system. Angiotensin II-dependent hypertension results in a pressure natriuresis through the contralateral kidney. In bilateral stenoses, there is RAA activation with volume expansion and hypertension, which ultimately leads to feedback inhibition of the RAA system. Most patients with RAS have essential hypertension complicated by the renovascular disease, and hypertension at this chronic stage is no longer directly dependent on a general effect of the RAA-system, but on local vasoconstrictive proliferative effects in the arterial wall, gradually leading to therapy-resistant hypertension [12]. In experimental models, systemic RAA activation is not sustained and several proposed mechanisms, including increased endothelin (ET) production, local RAA activation, arterial wall re-modeling and oxidative stress are responsible for maintaining the hypertension. Excessive oxidative stress is at least in part involved in the impaired endothelium-dependent vasodilatation in addition to the effects of the hypertension itself [13] which may also contribute directly to renal injury.

When hypertension is sustained, plasma renin activity decreases, referred to as "reverse tachyphylaxis", partially explaining the limitations of renin measurement for identifying patients with RVH.

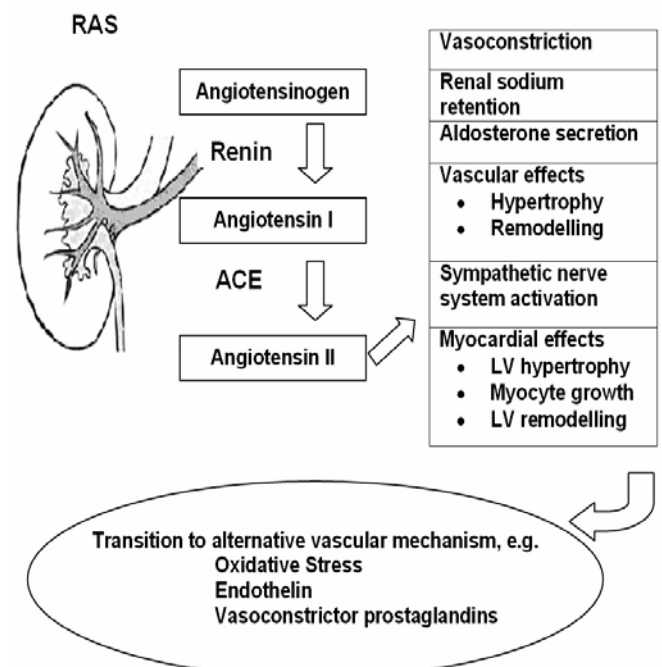


Figure 3. Patophysiology in RAS. Modified from: Garovic VD et al

It is important to evaluate progression of luminal narrowing and the extent of renal parenchymal damage when considering the natural history of ARAS. In ARAS, both kidneys are at risk of parenchymal damage, irrespective of the stenosis being unilateral or bilateral. This is well illustrated by doppler ultrasound findings of

bilateral abnormal renal haemodynamics in patients with unilateral ARAS. Electron beam CT confirms reduced renal cortical blood flow in ARAS compared to FMD [15]. This is further supported by measurements of individual kidney function in patients with ARAS, showing significant correlations between the degree of stenosis and GFR in the stenotic kidney. However, in patients with unilateral stenosis, there is no difference in GFR between the stenosed and the unstenosed kidneys [16], emphasizing that ischaemia from proximal stenosis is not the only cause of parenchymal injury in ARAS.

Ischaemic nephropathy is defined as an obstruction of renal blood flow that leads to ischemia and excretory dysfunction.

Autoregulation of blood flow in the kidney is ineffective when systolic BP (SBP) falls below 70 or 80 mm Hg, and factors such as reduced shear stress and decreased production of nitric oxide, increased production of ET, and activation of the RAA-system may create localized areas of ischemia, tubular injury, endothelial cell disruption, and interstitial fibrosis [17]. Progressive loss of renal structure and function occurs with histological features of focal glomerular sclerosis with ischaemic tuft retraction and peri-glomerular fibrosis. Renal parenchymal damage also results from small vessel atherosclerosis and atheroembolism of platelet and cholesterol thrombi derived from unstable atherosclerotic plaques. Functionally, there is a progressive decrease in GFR with proteinuria, hypertension and sodium retention. In severe cases, end-stage renal failure with uraemia may occur [18].

A syndrome of acute pulmonary oedema - with or without renal failure - has been described in patients with either high-grade stenosis of a single kidney or with bilateral disease, often with one renal artery occluded and the other stenosed. The symptoms of these patients with severe and rapid onset "flash" pulmonary oedema, often with associated renal dysfunction, may be confused with coronary syndromes [19]. When acute renal failure and oliguria are caused by bilateral occlusion of the renal arteries, urinary findings may mimic those of acute tubular necrosis. Deterioration of the renal function in a patient with ARAS of one renal artery usually suggests the development of bilateral stenosis, parenchymal disease, or both.

The consequences of high grade RAS can be dramatic and severe and include accelerated or malignant hypertension, acute or chronic renal impairment, acute left ventricular failure and hypertrophy, nephrosclerosis and small vessel cerebral ischemia. At this stage, the opposite kidney may also be damaged by exposure to hypertension. Intervention, before occlusion or atrophy of the affected kidney occurs, can reverse these acute changes, underlining the need for early detection of RAS to allow treatment while duration of hypertension is short.

Inflammation and oxidative stress in RAS

Despite beneficial effects on BP with endovascular treatment, the prognosis remains ominous in patients with RAS because of increased cardiovascular mortality. In patients with atherosclerotic RAS, the mortality is

increased 6-fold compared with an age-matched population [20]. We might speculate that this high cardiovascular mortality in patients with RAS may be explained by increased inflammatory activity caused by activation of the RAA system.

Several inflammatory mediators such as interleukin 6 (IL-6), tumour necrosis factor (TNF) [21], neopterin, and CD40 ligand are involved in atherogenesis. In particular, increased levels of IL-6 and high-sensitivity C-reactive protein (hs-CRP) have been shown to predict cardiovascular disease. ET-1, a vasoconstrictor peptide produced by the endothelium promoting initiation and progression of atherosclerosis, is also involved in the pathogenesis of atherosclerosis [22].

Angiotensin II can cause inflammation and in animal trials it is the main pressure-peptide inducing oxidative stress in the arterial wall and kidney tissue through the formation of superoxide. This leads in turn to consumption of nitric oxide and formations of new oxidants resulting in further tissue injury. The superoxides act as vasoconstrictors and stimulate the growth of the smooth muscle cells [23]. Although PTRAs, with or without stenting, is a commonly used treatment for RAS, little is known regarding potential systemic inflammatory responses following such intervention. Recently, we reported beneficial effects on the systemic inflammatory mediators with decreasing ET-1 and IL-6 after one month of PTRAs [24].

The natural history of RAS

It is important to understand the natural history of RAS to enable appropriate decisions concerning indications and timing of renal artery interventions. Previous studies summarised in Table I have shown that RAS progression in small series occurs in about 35 % of patients at 3 years and in 50 % at 5 years. RAS has been shown to progress to occlusion in around 3-7 % of patients per year. The risk of progression to complete occlusion has been shown to be particularly great in renal arteries with greater than 60 % stenosis on the initial angiogram, and the greater the degree of stenosis, the more quickly total occlusion occurs (Table I). However, these studies probably overestimated the rate of progression, as the decision to carry out angiography was likely to have been influenced by clinical deterioration.

Declining overall renal functions, estimated by creatinine (Cr) concentration, and decreases in kidney size, were more common in patients with progressive disease [25,26].

While medical therapy usually controls hypertension, progression of the underlying RAS and renal atrophy frequently occurs despite antihypertensive therapy. On the other hand, bilateral cortical thinning in unilateral RAS disease [27] can be stabilized by renal revascularization [27]. At 19 months follow-up, reduction in kidney length > 1 cm occurred in only 8 of 33 treated patients [28].

Diagnostic methods

Diagnosis of RAS should always be considered in patients with hypertension resistant to pharmacological therapy, although hypertension is not always the

presenting symptom of RAS. The diagnosis may also be suggested by a rise in Cr level (or rarely, acute renal failure) after the introduction of an ACE inhibitor or ARB. Other patients with RAS may present with progressive renal insufficiency, proteinuria, and nephrotic syndrome [38], or renal asymmetry.

Congestive cardiac failure or episodes of 'flash' pulmonary oedema, occurring in the absence of an acute coronary event, can also be the presenting complaint.

An ideal investigation for RAS in the above-mentioned patients would be noninvasive, accurately quantify the stenosis, provide functional information and identify those stenoses that are likely to benefit from intervention.

Creatinine (Cr) and glomerular filtration rate (GFR)

They are methods of functional assessment and outcome assays of renal interventions. Significant unilateral RAS is often associated with a reduction in GFR in one kidney, but there may be no change in the Cr concentration until 50% of the total renal mass is lost. Thus, the Cr level is a poor index of the function of individual kidneys and renal mass does not perfectly reflect the GFR. In addition, an improvement in GFR of the post-stenotic kidney after angioplasty is offset by a decline in GFR of the contralateral kidney that limits the beneficial effects on overall GFR [39]. However, with increasing renal dysfunction, the Cr becomes more concordant with the GFR and with renal function.

Estimating GFR by creatinine based formula like; Cockcroft-Gault, MDRD or measuring GFR by iohexol clearance are more accurate than serum creatinine.

Ultrasonography

Ultrasonography is able to detect renal asymmetry that may be due to RAS. An increased renal resistance index suggests structural abnormalities in the small blood vessels of the kidney. Such small-vessel disease has been documented in longstanding hypertension associated with nephrosclerosis or glomerulosclerosis. Patients likely to benefit from renal revascularisation can be identified by a resistance index of <80. Resistance index was calculated as $[(I - (\text{end diastolic velocity cm/s})/\text{maximal systolic velocity cm/s})] \times 100$ [40].

Limitations of renal artery duplex ultrasonography include its absolute dependency on operator skill and that it may still be unsuccessful in about 20% of the patients because of problems with visualization of accessory renal arteries, and the difficulty or inability to image obese patients or patients with intervening bowel gas [41].

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Table I: Progression of atherosclerotic renal artery stenosis (ARAS) and fibromuscular dysplasia (FMD) - follow-up studies of untreated cases.

ARAS	Progression	Follow-up
Renal angiogram		
Meaney1968 [28] N = 39	36%	6 months - 7 years
Wollenweber1968 [29] N = 30	63%	28 months
Pohl 1985 [24] N = 85	44% 16% occlusion	3 - 172 months
Schreiber 1984 [30] N = 85	44% 16% occlusion	52 months
Duplex scan		
Caps 1998 A [31] N = 170	35% 51% 3% occlusion	3 years 5 years 33 months
Zierler 1994 [32], 1996 [33] N = 156	30% 44% 48% 5% occlusion	1 year 2 years 3 years 1 year
FMD		
Renal angiogram		
Schreiber 1984 [30] N = 66	33% No complete occlusion	45 months
Pohl 1985 [24] N = 66	33% No complete occlusion	3 - 172 months
Renal atrophy (RAS greater than 60% and reduction in renal length of >0.5 cm)		
Caps 1998 B [25] (duplex) N =122 ARAS	16%	33 months
Guzman 1994 [34] (duplex) N =54 ARAS	19%	Per year
Tollefson 1991 [35] (renal angiogram) N =48 ARAS	53%	7.3 years
Goncharenko 1981 [36] (renal angiogram) N =42 FMD	62%	1 month – 11.5 years

Captopril renography

It is a functional test used to detect the angiotensin II dependence of GFR. In a positive test, the pre-administration of oral captopril 25–50 mg delays the uptake of tracer, reduces peak uptake, prolongs parenchymal transit and slows excretion, as well as affecting divided function in unilateral disease. The sensitivity and specificity of captopril renography decrease in the presence of azotemia, bilateral disease and in a solitary functioning kidney. Its most useful role is probably in predicting the benefit from revascularization of a stenosed kidney. However, captopril renography cannot be recommended for assessing RAS [42].

CT angiography (CTA) and MR angiography (MRA)

They are noninvasive imaging techniques of renal arteries. A meta-analysis has showed the superiority of these techniques over both captopril renography and ultrasonography [43]. However, MRA imaging may overestimate the degree of RAS [44]. Recently, Eklöf M et al. reported that MRA and CTA were significantly better than duplex ultrasonography and captopril renography in detecting hemodynamically significant RAS [42]. CTA is as accurate as MRA, but has the disadvantages of the radiation dose and infusion of a potentially nephrotoxic contrast substance. A negative contrast-enhanced MRA probably excludes significant RAS but false-positive results due to turbulence are common. Five to ten percent of all cases have been reported as false negative. Unfortunately, there are, since 1997, reports of cases of nephrogenic systemic fibrosis in patients with $GFR < 30$ [45] which has limited the use of MRA. Currently in most centers, MRA or CTA is at least in low GFR patients used as a second-line test after a positive screening test with duplex ultrasonography or captopril renography when the index of clinical suspicion is high. As its availability increases it is likely that MRA will become the screening test .

Spiral CT

Spiral CT has, in a recent study, showed cortical thinning in unilateral fibromuscular RAS and cortical imaging is probably important to identify haemodynamically significant stenoses [27]. Its use as a potential screening method for RAS should be investigated further.

Contrast arteriography

Contrast arteriography remains, with aortography and selective renal artery cannulation, the 'gold standard' in assessing renal artery anatomy. It is sufficiently sensitive and specific to confidently exclude renovascular disease. It is particularly useful in the early detection of FMD, in the diagnosis of intrarenal branch artery stenoses and in kidneys with complex anatomy, including multiple accessory arteries. Disadvantages of this technique include significant interobserver variation in assessing the degree of stenosis [46], the absence of functional information, and the risks of contrast nephropathy and cholesterol embolisation syndrome. Contrast arteriography is used routinely before PTRAs or surgical intervention, but its role as a diagnostic test is being re-defined with the increased availability of MRA. Catheter-directed angiography should be performed only to identify a RAS that would be treated if found.

Selective renal vein renin analysis

It is another invasive test that can lend support to the clinical significance of a RAS of borderline hemodynamic significance [47]. This test however is seldom used nowadays. .

Management of RAS

Pharmacological treatment

The benefit of intervention must include not only preservation of renal function and improved control of hypertension, but also a reduction in the overall cardiovascular risk.

Reversible causes of renal failure should always be sought and treated as stated in The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [48], and they endorse the approach of minimal to no investigation for the cause of well-controlled hypertension.

All patients with ARAS should receive anti-platelet agents as they reduce morbidity and mortality in cardiovascular disease. Dyslipidemia is often present in patients with ARAS, although the severity does not predict the progression of ARAS [49]. There are no studies specifically reporting the use of statins in ARAS, although their benefit in improving cardiovascular outcome in high-risk patients is well-established. Reports indicate that aggressive lipid reduction may lead to regression of atherosclerotic disease, also in the renal arteries [50]. In addition to lowering lipids, statins are anti-inflammatory and stabilize atherosclerotic plaques.

Calcium-channel blockers, which maintain renal perfusion by reducing afferent arteriolar tone and beta-blockers by lowering renin, are also established options for patients with renovascular disease. However, there is little research comparing the efficacy of these antihypertensive agents in RVH.

Many patients with renovascular disease will be candidates for ACE inhibitor and/or angiotensin receptor blockade (ARB). Clinical data suggest that survival of patients with RVH is better when ACE inhibitors are part of therapy than when they are not [52]. ARBs can be used safely in patients at risk of ARAS. In a prospective study examining the safety of ACE inhibitors in ARAS, 69 of 108 patients showed $> 20\%$ rise in Cr levels, and of these 52 had bilateral disease or stenosis of a single kidney. No patient developed oliguric renal failure and Cr levels returned to baseline after stopping the drug [53]. However, concurrent diuretic therapy should be initially avoided. In low doses and without diuretics, captopril has

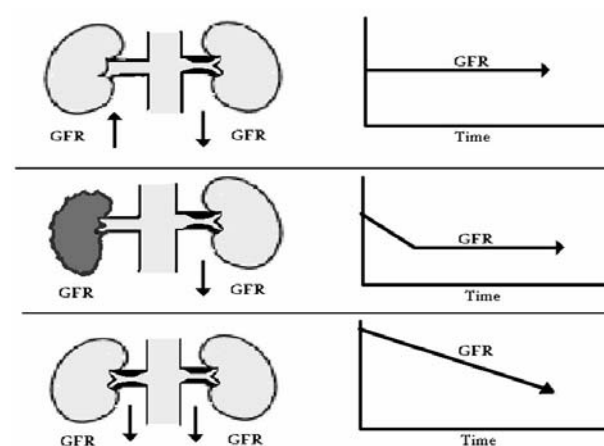


Figure 4. Potential effects of ACE inhibition on GFR (renal function) in patients with hemodynamically significant RAS. Upper: The effect in the setting of unilateral stenosis with a normal contralateral kidney. Middle: The effect in the setting of unilateral stenosis with contralateral parenchymal disease (gray). Lower: The effect in the setting of bilateral stenosis (Modified from Rimmer JM and Gennari FJ) [51].

never been reported to induce functional acute renal failure [54]. The drug should be stopped, however, if there is > 20% rise in Cr levels and such patients should be considered for revascularisation. In bilateral disease or stenosis of a single kidney, specific caution is recommended with ACE inhibitors, as renal function can be compromised due to dilatory drug effect on the efferent arterioles. This can reduce the capillary pressure within the glomerulus to below the critical perfusion pressure and acute renal failure can occur 1 to 14 days after the initiation of treatment with ACE inhibitors [55].

Another study has reported reversible acute renal failure in several patients with hypertension shortly after the onset of captopril treatment. This has been attributed to a sudden decrease in renal perfusion due to the fall in BP, a direct toxic effect on the kidney, and to a hypersensitivity drug reaction in the form of acute interstitial nephritis [56].

Revascularisation Indications

Indications for angioplasty of a hemodynamically significant RAS are shown in Table II.

Percutaneous transluminal renal angioplasty (PTRA)

PTRA with or without stenting is a widely accepted treatment for RAS. In most series, about 30% of the patients show an improvement in renal function after PTRA with or without stenting, with the remainder equally divided between no improvement and deterioration.

Unfortunately, details about methods of measuring BP, length of follow-up, and medication dosage and class vary widely between studies, as has been reviewed [58]. Leertouwer et al. reported that after angioplasty, BP control improved in up to 49% of patients [59]. Several studies indicate that hypertension is only rarely cured in patients with ARAS, while improvement occurs in <10% to 75% of patients. Little or no change in either BP control or medication requirements has been reported in 30% (range 0% to 54%) of the treated patients [58]. Overall, BP changes commonly approach a reduction of 25/10 mm Hg [60].

Stenting

Endovascular stents have been recommended for failed PTRA (unsatisfactory results or complications) and for treatment of restenotic lesions.

Many cohort studies have been performed comparing PTRA with and without stenting, but there is only one single randomised controlled trial comparing 42 patients with RAS undergoing PTRA only with 45 undergoing PTRA and stenting [63]. The success and patency rates were significantly higher with stenting than with PTRA alone. However, renal function and BP were stable or unchanged in both groups at 6-month follow-up, with no significant difference between the PTRA and stent groups. The addition of stenting to PTRA added no incremental benefits on BP control in another study by Leertouwer et al. [59].

Cohort studies with sample sizes ranging from 100 to 200 patients examining the outcome of stenting have reported stabilisation of renal function and improvement in BP [64]. These studies all had a follow-up of 3 to 5 years. Many of these studies have limitations in sampling and analysis. Similar findings have been demonstrated in smaller scale cohort studies focusing on renal function alone, especially improvement of previously declining renal function and stabilised Cr levels. There are also data suggesting that angioplasty and stenting are associated with a reduction in cardiovascular mortality. Patients in whom renal function improved after stenting showed better survival than those without improved renal function (45% versus 0% cumulative survival) [65].

Table II: Indications for angioplasty of a hemodynamically significant RAS [57]

Control of hypertension

- a. A reasonable likelihood of cure of RVH.
 - i. Onset of hypertension before age 30
 - ii. Recent onset of hypertension after age 60
 - iii. Stenosis is caused by FMD
- b. Hypertension is "refractory" to medical control with at least three medications of different classes including a diuretic.
- c. Hypertension is "accelerated" (ie, there is sudden worsening of previously controlled hypertension).
- d. Hypertension is "malignant" (i.e., is associated with end-organ damage such as left ventricular hypertrophy, congestive heart failure, visual or neurological disturbance, grade III-IV retinopathy).
- e. The patient is intolerant to or noncompliant with antihypertensive medical treatment.

Renal salvage

- a. Unexplained worsening of renal function.
- b. Loss of renal mass, during antihypertensive treatment.
- c. Impairment of renal function or acute renal failure secondary to antihypertensive medication, particularly with an ACEi.
- d. Progression of a hemodynamically significant RAS.

Cardiac disturbance syndrome

- a. Recurrent "flash" pulmonary oedema secondary to impaired left ventricular function.
- b. Unstable angina pectoris.

Parameters predictive of successful renal revascularisation include function of the involved kidney, the state of arterioles distal to the RAS, and renal biopsy demonstrating minimal arteriolar sclerosis [61].

There is only one study that has evaluated the role of prophylactic treatment for hemodynamically significant RAS in patients with normal renal function who were either normotensive or had easily controlled hypertension. Chaikof et al. [62] revascularised 43 kidneys in 32 patients with RAS out of which 22% were normotensive and the rest only needed one drug to control the BP. The indication for angiography was abdominal aortic aneurysm or aortic occlusive disease. BP remained normal with a single drug or without medication in 75% of patients and there was no statistically significant deterioration in renal function in the 96% of patients available for late follow-up (median, 64 mo) [62].



Figure 5. Placement of stent in an ostial RAS.

In FMD, the RAS tends to be post-ostial and highly amenable to PTRA alone. The mechanism by which balloon angioplasty enlarges the arterial lumen in FMD is by stretching of the adventitia beyond its elastic recoil. Subsequent changes include smooth muscle cell necrosis, fibrosis, and some degree of neointima formation. Although this method may completely relieve the stenosis and cure hypertension in FMD, most patients still require some antihypertensive medication, and up to 25% will have re-stenosed after one year [66]. Stenting seems not to give better results and normally not used. Surgical intervention may be more appropriate with complex stenoses.

Medical versus endovascular therapy

There are only three randomized controlled studies comparing medical therapy with PTRA, and these have not showed any differences in either BP control or preservation of renal function. In the largest of these studies, however, half of the patients assigned to medical therapy alone crossed over to receive PTRA for poorly controlled BP within 3 months [4]. These studies have been the focus of a Cochrane review in 2003 [67]. The primary outcome was BP. This meta-analysis of 210 patients recorded no statistically significant difference between PTRA and medical therapy in reducing SBP, although there was a difference in mean arterial BP of 7 mmHg (CI -12 to -1 mmHg) favouring PTRA.

There was no difference in renal function outcome between the groups after 12 months, despite the finding that PTRA resulted in improved patency of renal arteries [odds ratio (OR) 4.2 (CI: 1.8-9.8)]. PTRA did not significantly reduce the number of antihypertensive drugs required or complications of these agents (OR= 0.27, $p=0.09$). The review therefore concluded that there was some modest benefit of PTRA for reducing BP in these patients [67]. The problem with these studies is to ascertain selection bias. Did all patients included have a significant RAS?

Major cardiovascular and renovascular complications occurred in 10 of 104 patients undergoing PTRA (9.6%), compared to 26 of 106 patients (24.5%) treated medically [OR 0.32 (95% CI 0.15-0.70)].

The finding that there is no benefit on renal function from PTRA is supported by other investigators [68] who

demonstrated that single kidney GFR and the degree of renal artery narrowing are unrelated, with no improvement after PTRA, implying that the outcome is determined not by narrowing of large renal arteries, but rather by the reversibility of intra-renal small vessel disease.

Surgical revascularisation

The effectiveness of surgical revascularisation has been established in non-randomised retrospective studies, and only two randomised prospective studies are available. From our institution Weibull et al. published a prospective randomised study on 58 patients in 1993. They compared PTRA without stent and open surgery in patients with unilateral ARAS. The technical success rate was 83% in the PTRA group and 97% in the surgical group ($p=0.19$). The primary patency was better ($p=0.05$) in the surgical group (75% with PTRA and 96% with surgery), but secondary patency and effects on BP and renal function were the same in both groups. The authors concluded that PTRA is recommendable as initial therapy for unilateral ARAS causing RVH if combined with intensive follow-up and aggressive reintervention [69]. A second randomised study [70] in 52 patients with ARAS reported no statistically significant differences in survival, dialysis-free survival, BP control or GFR, but the power of the study was limited by the small sample size [70]. There are large retrospective studies comparing PTRA with surgery that report comparable outcomes on BP and renal function with PTRA and open surgery in mainly ARAS, but demonstrated better both short- and long-term survival after PTRA [71].

Predictors of success of revascularisation

The majority of patients with ARAS are identified during the investigation of hypertension or chronic renal impairment, whereas FMD rarely results in renal failure. Proposed clinical indicators of poor response to PTRA are small renal size (< 8 cm), proteinuria and degree of renal impairment, the more advanced, the lower the chance of success [40]. Radermacher et al. found that a renal artery duplex doppler resistance index value of ≥ 80 before revascularisation was a strong predictor of worsening renal function and lack of improvement in BP, despite the correction of RAS [40]. In this study intrarenal Doppler signals were obtained from segmental arteries and the resistance index values were the average of two to three measurements in segmental arteries from the upper, middle, and lower third of each kidney. Conversely, lower resistance indices were associated with improvements in both renal function and BP. This may indicate that non-reversible parenchymal injury, as a result of longstanding hypertension or other factors such as diabetes, nephrosclerosis, ischaemic fibrosis and focal glomerulosclerosis, is not reversible with interventions, irrespective of how significant the stenosis may be.

However, these data have been challenged by a prospective uncontrolled study of renal stent placement in 241 patients [72] in which also patients with an elevated resistance index achieved a favorable BP response and renal functional improvement after PTRA. Resistance index > 80 should therefore not prevent revascularization if clinical signs of RVH are strong [4]. Advanced age has been recognized as a negative prognostic factor for

beneficial clinical outcome. With increasing age, individuals with RAS lose the ability to reverse the structural vascular changes in the kidney associated with secondary hypertension [73].

Restenosis and complications of revascularisation

Over time there is an approximately 1-mm circumferential deposition of myointimal hyperplasia after PTRA with or without stenting, with resultant luminal narrowing. This neointimal hyperplasia and vascular remodeling are the main causes of restenosis, independently of the histopathologic nature of the initial lesions, whereas the excessive restenosis rate of ostial atherosclerotic lesions is to a large degree due to recoiling of aortic wall plaques [55,63]. FMD and non-ostial ARAS both have similar restenosis rates after PTRA; up to 25% will have re-stenosed after a year.

Two meta-analyses of renal artery intervention have demonstrated average restenosis rates of 16% and 17% after stent placement [59,60]. Other reports suggest that restenosis rates of less than 15% can be achieved with optimal stent deployment techniques [55]. Recurrent arterial hypertension has been shown to be a strong clinical indicator of restenosis ($p < 0.01$) [8].

Complications in general are divided into minor and major complications. Puncture site complications are hematoma, pseudoaneurysm or arteriovenous fistula formation. Brachial plexus damage might occur if haematoma formation occurs when the axillary artery approach is used. Renal artery related complications include dissection, thrombosis, rupture, atheroembolism and perinephric bleeding. Contrast related and systemic complications include acute renal failure, defined as a transient rise in Cr to $> 20\%$ above the baseline due to contrast medium toxicity, atheroemboli or intrarenal vasoconstriction [69]. Direct toxicity of iodinated contrast medium to nephrons appears to be related to its osmolality. Intrarenal vasoconstriction is a vascular response to contrast media, and possibly an organ response to cholesterol emboli. The overall risk of acute renal failure is approximately 20% in patients with diabetes and 13% in patients without diabetes undergoing renal angiography [74]. The use of distal intrarenal protection devices may limit the athero-embolic risk [75]. However, the incidence of acute renal failure leading to dialysis is low (0.5-2.0%).

Microshowers of cholesterol emboli occur in about 50% of percutaneous interventions where a guiding catheter is passed through the aorta [76]. Most cases are clinically silent, but in approximately 1% a cholesterol-embolic syndrome can develop, manifested by acute renal failure, mesenteric ischemia and decreased microcirculation to the extremities. Myocardial infarction and stroke are other systemic complications [63].

Complications to surgical revascularisation are bleeding, problems related to anaesthesia, wound infection and systemic complications such as myocardial infarction, stroke, and acute renal failure.

Ongoing studies

Several ongoing randomised studies will help to clarify effects of and indications for PTRA of RAS in the future. As the potential effects of PTRA on mortality are uncertain, a prospective trial, Cardiovascular Outcomes in Renal Artery Lesions (CORAL), evaluates the effect of intensive medical management with or without stenting on cardiovascular events.

The 3R Study (Renal outcome in Renal ischemia: Revascularisation or medical treatment), is a prospective controlled study comparing effects of PTRA versus medical therapy in 300 patients with RAS of 50 - 90% and Cr levels $< 352 \mu\text{mol/l}$.

The STAR-study (Benefit of STent placement and BP and lipid-lowering for the prevention of progression of renal dysfunction caused by atherosclerotic ostial stenosis of the renal artery) compares effects of renal artery stenting together with medication, versus medication alone on renal function in patients with ARAS of $\geq 50\%$ and renal failure. The primary outcome is a reduction in Cr of $> 20\%$ compared to baseline. Similarly, the ASTRAL (PTRA and stenting for renal artery lesions) trial aims to randomise up to 1000 patients between PTRA combined with medical treatment, versus medical treatment alone (<http://www.astral.bham.ac.uk/trial/protocol/>).

The problem remains to define when a stenosis is significant. Percentage stenosis may be less accurate and that may limit the value of ongoing studies. We have recently reported that PTRA has positive effects on BP and treatment in RAS patients with mean pressure gradient (MPG) $> 10 \text{ mmHg}$. Whether PTRA is indicated also with MPG $< 10 \text{ mmHg}$ requires further evaluation. Residual MPG post PTRA predicts re-do but not the outcome of the intervention [77].

Conclusion

In patients with RVH the likelihood of cure of hypertension is highest among those with FMD. In patients with ARAS, control of hypertension is facilitated by PTRA. Cure of hypertension is unusual. Improved control with fewer medications and preservation of renal function is a more realistic goal.

Renal artery surgery still offers major benefits for some patient groups such as patients undergoing surgical repair of the aorta and patients with complex disease of the renal arteries, e.g., associated renal artery aneurysm or failed endovascular procedures.

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