ARTERIOSCLEROTIC RENAL ARTERY STENOSIS: CONSERVATIVE VERSUS INTERVENTIONAL MANAGEMENT

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Renal artery stenosis is the most common cause of secondary hypertension. Over 90% of renal artery stenoses are caused by arteriosclerosis, the remainder resulting from fibromuscular dysplasia which usually does not lead to progressive azotemia and end stage renal disease. Renal angioplasty is the treatment of choice for fibromuscular dysplastic disease and has the potential of curing hypertension if performed early.

The situation is quite different for arteriosclerotic renal artery disease which generally occurs in older patients with longstanding hypertension. The stenotic lesions are typically localised at the ostium of the renal artery, respectively in the aortic wall. Reconstructive surgery has been the classical treatment for these lesions,[1] particularly since the initial experience with renal artery angioplasty for arteriosclerotic ostial lesions was disappointing. However, a prospective randomised study has demonstrated that reconstructive surgery offers no definite advantage over interventional treatment of renal artery stenosis.[2] Since most patients with arteriosclerotic renal artery disease have coronary and cerebral atherosclerosis and other significant comorbid conditions which increase the risk of surgery, the interventional treatment of renal artery stenosis has become the preferred method of renal revascularisation in many centres. This development has been reinforced by the more recent introduction of renal arterial stent implantation, which may improve the outcome of renal artery interventions, although there have been no randomised prospective comparisons between renal artery stenting and other forms of treatment. Most reports on renal angioplasty with stent implantation have been based on relatively few patients with only a short follow up period. However, a recently published paper from a multicentre registry of 1058 patients reports a benefit from renal artery stenting on both blood pressure control and renal function after four years of follow up.[3]

The treatment of renal artery disease has recently been reviewed.[4] The present paper summarises the arguments and evidence for interventional versus conservative treatment of arteriosclerotic renal artery disease, focusing on the indications for interventional treatment to provide interventional cardiologists with criteria for patient selection.

RENAL ARTERY STENOSIS: WHY IS IT IMPORTANT FOR THE CARDIOLOGIST?

Renal artery stenosis is a particularly relevant comorbid condition in cardiological practice, since the risk factors for coronary artery disease and renal artery disease are identical. Consequently both vascular beds are commonly affected by atherosclerosis in the same patient.[5] Renal artery stenosis causes or aggravates hypertension and/or interferes with its treatment. Renal artery stenosis therefore has a negative impact on both primary and secondary prevention of coronary heart disease. In patients undergoing cardiac catheterisation renal artery stenosis is an independent risk factor for mortality which correlates with the severity of the renal artery disease.[6] Moreover, ischaemic renal disease is the most rapidly increasing cause of end stage renal disease in the USA.[7] Renal failure impairs the outcome of coronary artery bypass grafting and percutaneous coronary interventions.

Because of the interrelation between arteriosclerotic renal and coronary artery disease cardiologists are frequently confronted with "cardiorenal" problems. They are not only experts in the conservative treatment of atherosclerosis, but they also have the expertise necessary for interventional treatment of the complications of atherosclerosis. The angioplasty/stent implantation of ostial renal artery lesions can be performed effectively with equipment adapted from coronary artery interventions (fig 1). Indeed, the largest single centre series on primary renal artery stenting comes from a group of cardiologists.[8] This team treated 363 renal artery stenoses in 300 patients between 1993 and 1998 with stent implantation. The procedural success rate was 100% without procedural deaths or emergency surgical procedures. The overall restenosis rate during a median follow up of 16 months was 21%, 12% in renal arteries with a diameter > 4.5 mm These results show that primary renal artery stenting can be performed safely and effectively.

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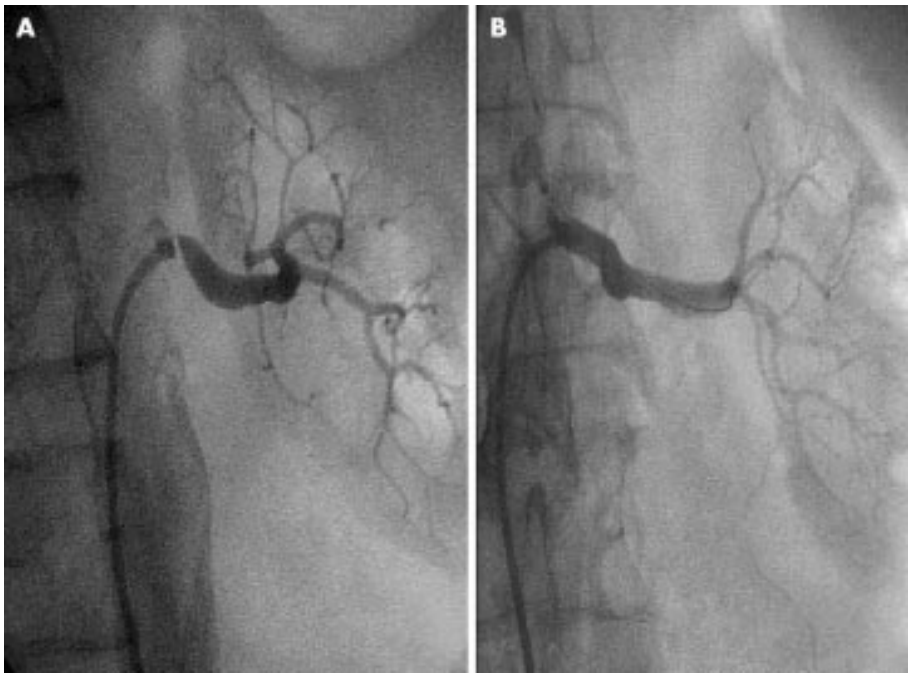

Figure 1 Arteriosclerotic renal artery stenosis in a 69 year old male patient. (A) Subtotal occlusion of the ostium of the left renal artery. (B) After percutaneous angioplasty with stent implantation. A guiding catheter (FR 3.5, 7 French) and a steerable 0.014 inch guidewire were used to advance a 12 mm balloon expandable stent over the lesion. The stent was deployed by inflating the balloon (6 mm diameter) for 30 seconds.

However, what is the evidence that percutaneous renal revascularisation benefits patients? This central question is particularly pertinent as recent studies suggest that blood pressure can be controlled conservatively in most patients with arteriosclerotic renal artery stenosis. What is the evidence that renal revascularisation improves/preserves renal function? Who should undergo renal revascularisation? What are the most effective methods for diagnosis and follow up?

RENAL ARTERY INTERVENTION FOR THE TREATMENT OF HYPERTENSION

Most patients with arteriosclerotic renal artery disease do not have renovascular hypertension. Rather they have essential hypertension that has been complicated by atherosclerosis and the development of a stenotic renal artery lesion. Therefore the correction of renal artery stenosis is unlikely to cure the hypertension, since the exposure of the non-stenotic kidney to the increased blood pressure results in (subclinical) renal injury. Such subtle renal damage is increasingly recognised as an important cause of persistent hypertension.[9] Nevertheless the data from a multicentre registry on renal artery stenting in 1058 patients over a four year period show a beneficial effect of renal revascularisation on blood pressure control.[3]

The indication of renal artery intervention for blood pressure control has been challenged. A randomised study comparing medical treatment with angioplasty in 55 patients with atheromatous renal artery stenosis showed a mild reduction of blood pressure after angioplasty only in patients with bilateral disease without improvement in renal function, but with a significant complication rate.[10] Another study involving 49 patients with unilateral renal artery stenosis showed a similar reduction in blood pressure in patients treated with renal angioplasty compared with conservative management.[11] A larger multicentre randomised trial in 106 patients with arteriosclerotic renal artery stenosis compared pharmacological treatment with renal angioplasty (only two patients received a stent). Twenty two patients initially assigned to drug treatment underwent renal angioplasty after three months. After 12 months the blood pressure was not significantly different between the two treatment groups, but the interventionally treated patients required fewer drugs. The authors concluded that angioplasty offers little advantage over antihypertensive drug treatment alone.[12]

In an individual patient the blood pressure response to renal revascularisation is uncertain. However, most published studies and the data from the large registry[3] are in agreement that blood pressure is better controlled with fewer medications after successful angioplasty.

Lowering blood pressure with any medication reduces renal perfusion pressure and can cause a deterioration of renal function. This is particularly true for drugs that interfere with the renin angiotensin system because of their specific effects on the regulation of glomerular haemodynamics. The reduced renal perfusion pressure distal of a stenotic renal artery is counterbalanced by a decreased tone of the afferent glomerular arteriole and an increased tone of the efferent vessel. This results in an increased filtration pressure which maintains the glomerular filtration rate at a higher filtration fraction (fig 2). The increased resistance of the efferent arteriole is mediated by angiotensin II. Thus, angiotensin converting enzyme (ACE) inhibitors can cause a deterioration of renal function, particularly in patients with severe bilateral disease or a high grade stenosis of an artery supplying a single functioning kidney. On the other hand, ACE inhibitors are highly effective in the treatment of renovascular hypertension, particularly when combined with a diuretic. Therefore they are the treatment of choice for renovascular hypertension provided patients do not develop rapidly worsening azotemia. By extrapolation, the same should apply for angiotensin II receptor blockers, but there are fewer published data. Close monitoring of the serum creatinine concentration is essential upon initiation of ACE inhibitor treatment in patients with renal artery stenosis. During maintenance treatment periodic measurement of renal size and ("split" renal) function is prudent for the early detection of atrophy of the post-stenotic kidney under ACE inhibition. This should be regarded as an indication to proceed with revascularisation of the stenotic kidney.

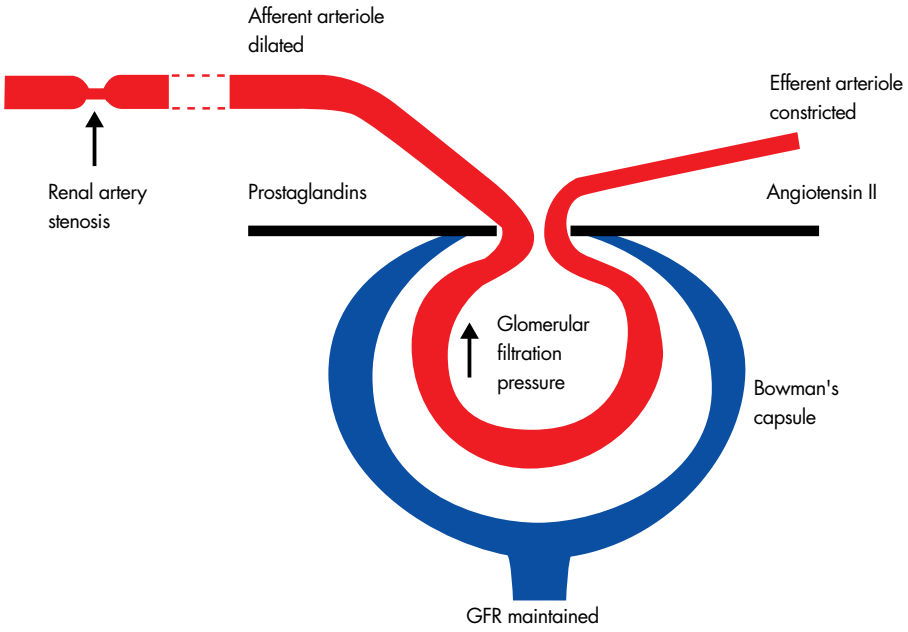

Figure 2 Regulation of glomerular haemodynamics. Reduction of the glomerular perfusion pressure behind a stenosis of the renal artery induces dilatation of the afferent arteriole and constriction of the efferent arteriole. The decreased resistance of the afferent arteriole is mediated by vasodilatory prostaglandins, the constriction of the efferent vessel by angiotensin II. These changes result in the increase of the filtration pressure. The higher filtration fraction maintains the glomerular filtration rate despite the lower perfusion pressure.

RENAL ARTERY INTERVENTION FOR PRESERVATION OF RENAL FUNCTION

There is increasing consensus that blood pressure can be managed medically in most patients with renal artery stenosis. Therefore the preservation/improvement of renal function has become the most important indication for renal revascularisation. Patients with generalised atherosclerosis may have a variety of conditions causing renal failure including (essential) hypertension, renal hypoperfusion due to congestive heart failure, atheroembolic disease, diabetes mellitus, radiocontrast nephrotoxicity from (repeat) percutaneous coronary interventions, and ischaemic nephropathy from arteriosclerotic renal artery disease. Recently it has been argued that many patients with renal artery stenosis do not have critical ischaemia/hypoxia of the renal parenchyma, but rather a relative hypoperfusion which limits the glomerular filtration rate without causing true tissue ischaemia. Therefore, the more appropriate term "chronic azotemic renovascular disease" has been proposed.[13]

Compared with the excellent procedural results of renal artery stenting[8] the clinical outcome of this procedure is less certain. In particular, the impact on renal function is complex; in addition to the general risks of invasive arterial procedures, renal artery interventions themselves carry a significant renal risk, mainly related to radiocontrast nephropathy and cholesterol embolisation from atheromatous plaques. Hence it is not surprising that renal function often fails to improve, despite technically successful revascularisation; in a substantial portion of patients it may even deteriorate. The registry report on renal artery stenting in 1058 patients showed overall a significant reduction of the mean (SD) serum creatinine concentration from 1.7 (1.1) mg/dl (150 (97) μmol/l) to 1.3 (0.8) mg/dl (115 (71) μmol/l) over a four year follow up period, suggesting that renal artery revascularisation is beneficial in the long term in the majority of patients.[3]

However, there are no published randomised controlled studies in which the effect of renal artery stenting is compared to optimal conservative treatment with modern antihypertensive agents. Such studies are very difficult to conduct, as patients with advanced renal dysfunction are more likely to die of other (cardiovascular) causes before a potential benefit of the renal revascularisation can be detected. On the other hand, patients with normal or only mild renal dysfunction may require very long follow up periods to show a significant benefit.

The functional results of 10 descriptive studies have been reviewed by Isles and colleagues: renal function improved in 26%, remained stable in 48%, and deteriorated in 26% of stented patients.[14] In the large single centre series on primary renal artery stenting by Lederman and colleagues, renal function improved in 19% of patients with renal insufficiency before the intervention, remained stable in 54%, and decreased in 27%.[8] Thus, despite the 100% procedural success rate reported by this group, from the renal function point of view the procedure was detrimental in more patients than it was beneficial; in most patients it was inconsequential.

Watson and associates published the results of a prospective study on renal artery stenting in 33 patients with deteriorating renal function before the intervention.[15] Stenting was technically successful in all patients. During 20 (11) months of follow up, renal function improved in 18 patients and the deterioration of renal function was stopped or slowed in the remainder of the patients. The preservation/improvement of renal function was accompanied by a preservation of renal size. Another recent prospective study on the effect of renal artery stenting on renal function in 63 patients with renal insufficiency is consistent with these results, demonstrating that patients with declining renal function, but not with stable renal dysfunction, benefit from stenting.[16] However, in this study five patients reached end stage renal failure within six months of stent implantation, in two cases because of stent implantation. Patients with stable renal insufficiency derived no benefit from stenting during a median follow up period of 23 months.

Taken together these studies suggest that renal revascularisation is most beneficial in patients with progressive renal failure. Its overall usefulness in patients with stable renal (dys)function is less certain, since the procedure itself is not innocuous and can cause a rapid deterioration of renal function. Hence, careful patient selection and meticulously documented informed consent are important.

Table 1 Factors influencing the treatment decision of renal artery stenosis

- Favouring renal revascularisation:
  - Refractory hypertension despite >3 drugs
  - Progressive azotemia
  - Acute renal failure on ACE inhibitors (angiotensin II receptor blockers)
  - Recurrent "flash" pulmonary oedema
  - "Salvage" therapy in recent onset end stage renal disease
- Favouring conservative treatment/watchful waiting:
  - Hypertension controlled on <3 drugs
  - Normal renal function
  - Stable mild/moderate renal insufficiency
  - Advanced renal atrophy (<7.5 cm)
  - Doppler ultrasonographic renal resistance index >80
  - History or clinical evidence of cholesterol embolisation

ACE, angiotensin converting enzyme.

Arteriosclerotic renal artery stenosis: key points

- Arteriosclerosis is the most common cause of renal artery stenosis
- Hypertension can be treated safely and effectively with antihypertensive drugs in most patients with renal artery stenosis
- The treatment of arteriosclerotic renal artery stenosis with angioplasty and stenting is safe and effective with a low risk of restenosis
- Correction of arteriosclerotic renal artery stenosis generally fails to cure hypertension, but control of blood pressure requires fewer drugs
- The preservation of renal function through the interventional treatment of arteriosclerotic renal artery stenosis is less certain; patients with deteriorating renal function seem to derive greater benefit than patients with stable renal insufficiency

WHO SHOULD BE EVALUATED FOR RENAL ARTERY STENOSIS?

General screening of hypertensive patients for the presence of renal artery stenosis is not indicated for two reasons: (1) the prevalence of renal artery stenosis in the general hypertensive population is too low; and (2) even if renal artery stenosis is present, this finding does not need to influence patient management provided blood pressure is controlled by medication and renal size and function remain stable. Therefore only patients who potentially benefit from renal revascularisation should be worked up for renal artery revascularisation. There are several clinical clues to identify these patients (table 1). Unusually severe hypertension or hypertension refractory to more than three medications should prompt an evaluation for renal artery stenosis, especially if a renal ultrasound shows asymmetric and/or small kidneys. Patients with hypertension, other arteriosclerotic manifestations, and renal failure should have a work up for renal artery stenosis, particularly if the renal insufficiency is progressive and/or aggravated by ACE inhibitors or angiotensin II antagonists.

Patients with severe hypertension, good systolic left ventricular function, and recurrent "flash" pulmonary oedema are a distinct subgroup in whom it is important to exclude renal artery stenosis.[17] This clinical syndrome of recurrent episodes of sudden onset non-ischaemic pulmonary oedema can be caused by severe bilateral renal artery stenosis or a critically stenosed artery to a single functioning kidney. Because of the compromised renal perfusion a rise in blood pressure is not accompanied by a pressure natriuresis. The ensuing hypertensive crisis induces pronounced diastolic dysfunction and pulmonary oedema. Correction of the stenosis permits the excretion of sodium and prevents the hypertensive crisis and the recurrence of the pulmonary oedema.

The renal risk of angioplasty is increased in proportion to the severity of the renal insufficiency because of the greater susceptibility to radiocontrast nephropathy and possibly the greater arteriosclerotic burden, adding to the risk of cholesterol embolisation. This increased risk has to be taken into account when obtaining informed consent, and patients should be warned that the interventional procedure can hasten the course towards dialysis. On the other hand, there are several anecdotal reports that even patients with severe renal failure on dialysis may recover sufficient renal function from renal "salvage" revascularisation to discontinue renal replacement therapy. Therefore, treatment of renal artery disease should not be denied simply because a patient is on dialysis, particularly if kidney size is relatively preserved and renal replacement therapy has just begun.

Since renal atrophy is irreversible, no significant functional improvement can be expected in atrophic kidneys, and patients with renal artery stenosis in kidneys < 7.5 cm should be treated conservatively (or by nephrectomy, if blood pressure cannot be controlled pharmacologically).[13] Recently Doppler ultrasound has been proposed as a valuable tool to discriminate between patients who benefit from renal revascularisation and those who can be spared this potentially dangerous and expensive procedure.[18] However, the discriminating value of the Doppler sonographic renal resistance index in routine clinical practice is still uncertain. Other indicators of parenchymal renal disease, including a urinary protein excretion > 1 g/day, hyperuricaemia, and a creatinine clearance < 40 ml/min, may identify a subgroup of patients who are less likely to benefit from renal revascularisation.

HOW IS RENAL ARTERY STENOSIS DIAGNOSED?

The diagnosis of renal artery stenosis is established by functional and/or morphological studies. The current diagnostic gold standard is arterial digital subtraction angiography (DSA). Arterial DSA requires cannulation of the aorta and exposes the patient to potentially nephrotoxic iodinated radiocontrast agents. This is pertinent, since renal function is often compromised in these patients putting them at an increased risk of radiocontrast induced nephropathy.

Spiral computed tomographic angiography allows the three dimensional reconstruction of the abdominal aorta and its branches, including the renal arteries. However, it requires about the same volume of intravenous iodinated radiocontrast material as arterial DSA; therefore it also carries the risk of nephrotoxicity.

Nuclear magnetic resonance angiography is becoming increasingly popular for imaging renal arteries, since it is relatively non-invasive and does not require iodinated radiocontrast agents. In addition to imaging the renal arteries, enabling direct detection of a stenosis, this technique allows the evaluation of renal function and perfusion. Hence it can provide information on the haemodynamic relevance of the stenosis. The assessment of perfusion is potentially useful for follow up after stent implantation, since imaging by magnetic resonance is usually not possible after stent implantation because of the metal artefact.

A totally non-invasive tool for the diagnosis of renal artery stenosis is renal duplex ultrasonography. However, even under optimal circumstances this technique is time consuming and

in a substantial group of patients not satisfactory because of obesity, bowel gas, and other patient factors. Because duplex ultrasonography does not expose the patient to nephrotoxic contrast agents or ionising radiation it can be readily repeated and is the method of choice for follow up after renal artery interventions, including stent implantation in suitable patients.

Renal scintigraphy, especially in combination with the administration of captopril, is a standard technique to evaluate renal perfusion for the diagnosis of renovascular hypertension. The captopril challenge is based on the substantial reduction of the glomerular filtration rate in the post-stenotic kidney after reducing angiotensin II by blocking the angiotensin converting enzyme (fig 2). Renal scintigraphy can be useful not only for the estimation of the functional significance of the stenosis, but also for follow up after interventions to exclude a haemodynamically relevant restenosis. A disadvantage of the method is that it does not provide anatomical information and has only a limited diagnostic accuracy, even when used in combination with captopril.

Many patients with renal artery stenosis undergo coronary angiography. In selected patients it may be appropriate to proceed directly to renal arteriography after the coronary procedure with little additional risk, provided the radiocontrast volume stays within reasonable limits. However, most patients with morphological evidence of renal artery stenosis do not have renovascular hypertension and are not likely to benefit from angioplasty. Therefore the routine imaging of renal arteries during coronary angiography in all hypertensive patients as a screening tool for renal artery disease and especially immediate angioplasty/stenting is not indicated.

CONCLUSIONS AND OUTLOOK

Renal artery angioplasty with stent implantation has become a standard procedure in the management of patients with arteriosclerotic renal artery disease. The procedure is safe and effective and results in the reduction of blood pressure and/or medication requirement. With regards to renal function its benefit is less clear. Patients with progressive renal dysfunction appear to be more likely to benefit from the procedure than patients with stable renal failure. The procedure has a definite risk of worsening renal function through radiocontrast nephrotoxicity and/or atheroembolism. Therefore patient selection is critical (table 1). In appropriately selected patients the diagnosis and treatment of renal artery stenosis is not only clinically beneficial, but also cost effective.[19]

All patients with arteriosclerotic renal artery stenosis should be evaluated for coronary artery disease and most patients should receive an ACE inhibitor and a statin. The latter not only reduces cardiac risk but may induce a regression of renal artery stenosis.[20] The role of pharmacological treatment in the management of renal artery disease is likely to increase in the future.

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