LEARNING THE ROPES

Atherosclerotic Renal Artery Stenosis

A common cause of secondary hypertension

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Renal artery stenosis (RAS) is a common cause of secondary hypertension and mainly due to atherosclerotic renal artery disease (ARAS) and less frequently due to fibromuscular dysplasia (FMD). A hemodynamically relevant RAS predominantly activates the renin-angiotensin-aldosterone system and can present clinically in form of hypertension, ischemic nephropathy, and cardiac destabilization syndromes. Advances in imaging techniques and interventional approaches have led to improved detection of RAS and more widespread use of renal artery revascularization strategies. While revascularization appears as an obvious therapeutic choice, data from three larger randomized controlled clinical trials (RCTs) failed to demonstrate convincing clinical benefit, although their design and selection of patients have been discussed controversially in the literature. Current therapeutic management is predominantly based on conventional antihypertensive and anti-atherosclerotic treatment and identification of subgroups of patients with a hemodynamically significant RAS in the context of worsening hypertension, progressive renal insufficiency and/or cardiac destabilization syndromes.

RAS is defined as a vascular lesion that results in narrowing of the renal artery. As a consequence, a reduction in renal blood flow to the affected kidney can occur. Atherosclerotic renal artery disease (ARAS) is the most common primary disease affecting the renal arteries accounting for ~90% of lesions typically occurring at the ostium and the proximal third of the renal artery. The prevalence of ARAS increases with increasing age and presence of cardiovascular (CV) risk factors including diabetes, hypertension, ischemic heart

disease and peripheral arterial disease¹. The presence of RAS is associated with poorer clinical outcomes².

Advancements in non-invasive diagnostic imaging and interventional techniques have led to the improved detection of RAS and the widespread use of endovascular revascularization strategies in the management of ARAS. However, a number of prospective RCTs have failed to demonstrate clear clinical benefits from revascularization compared to medical therapy³⁻⁵. These trials have been discussed controversially regarding flaws in study design and inherent bias, making their interpretation challenging and causing uncertainties amongst clinicians on appropriate management of affected patients. Optimal medical therapy and selection of patients likely to benefit from revascularization strategies seems essential and can be guided by the clinical presentation.

Clinical manifestations of ARAS

ARAS is implicated in the pathophysiology of three clinically distinct syndromes including hypertension, ischemic nephropathy, and cardiac destabilization syndromes.

Hypertension: In patients with acute, severe, or refractory hypertension, the prevalence of RAS is reported to be as high as 10-40%. RAS causes a reduction in renal perfusion pressure that results in the activation of the renin-angiotensin-aldosterone system. Renovascular hypertension is most profound in patients with bilateral RAS or RAS affecting a solitary kidney. In these patients rapid worsening of hypertension control

and recurrent sudden onset (flash) pulmonary oedema may occur¹. Longer term consequences can include congestive heart failure, hypertensive encephalopathy, intra-cerebral bleed, end-stage kidney disease and aneurysms¹.

Ischaemic Nephropathy: The exact pathophysiology of ischemic nephropathy remains uncertain. Although an association is seen between the severity of RAS and hypoperfusion leading to ischemic nephropathy and kidney atrophy, this is thought to be insufficient to explain deterioration of kidney function. Recurrent microembolisms may also be implicated in the loss of kidney filtration capacity¹. Ischaemic nephropathy most commonly occurs in the context of severe bilateral RAS or unilateral RAS in a solitary functioning kidney.

Cardiac Destabilization Syndromes: Uncontrolled HTN and volume retention mediated by RAAS activation associated with ARAS play an important role in the destabilization of patients with acute coronary syndromes (ACS) or congestive heart failure (CHF). Sudden onset “flash” pulmonary edema (*Pickering syndrome*) is a recognized destabilization syndrome resulting from ARAS⁶. Sustained excess of aldosterone promotes myocardial fibrosis and left ventricular remodelling thereby contributing to aggravation of CHF. The presence of these syndromes should prompt an investigation for RAS.

Diagnosis

Diagnosis of RAS may include non-invasive and invasive imaging studies to evaluate the degree of stenosis and renal function, physiological studies to assess the renin-angiotensin system; and perfusion scanning to evaluate differential renal blood perfusion. The choice of imaging modality is largely determined by patient factors, as well as the local availability of tests and expertise. Doppler ultrasound, CT angiography (CTA) and magnetic resonance angiography (MRA) are useful first-line investigations. If clinical suspicion for severe RAS is high and non-invasive tests are inconclusive, catheter angiography including pressure measurements or IVUS should be considered. Although catheter angiography is the gold-standard test, it is invasive and therefore carries a risk of access site complications, contrast

induced nephropathy and thrombotic and embolic events that need to be taken into account.

Medical therapy

As with all forms of hypertension, the overall therapeutic goal is to reduce the morbidity and mortality associated with elevated BP. In the context of RAS, a second goal is to protect the circulation and function of the kidneys. Guideline recommended principles of hypertension treatment generally apply also to patients with RAS. Due to the pivotal role of RAAS activation in the development of renovascular hypertension, it seems intuitive that RAAS inhibitors should be preferred therapy. Indeed, several prospective, randomized trials utilizing ACE/ARB therapy for patients with atherosclerotic disease elsewhere indicate a mortality benefit during long-term therapy, particularly for those with reduced estimated GFR (eGFR). RAAS blockade is frequently used as part of the medical regimen, particularly with unilateral renovascular disease. Close monitoring of renal function is important and if unexplained loss of GFR develops, cessation of RAAS blockade, at least temporarily is appropriate.

Interventional therapy

The development and refinement of endovascular interventional techniques has been a major advance in managing vascular disease. Restoring vessel patency is now possible in the majority of patients with high-grade ARAS. Stent placement is associated with greater long-term patency than angioplasty alone. Complication rates from atheroembolic disease have fallen with improvements in peri-interventional management. However, prospective randomized trials have failed to identify additional benefits from endovascular stent revascularization for ARAS when added to medical therapy³⁻⁵. These studies were systematically reviewed at the request of the Agency for Health Care Quality Research (AHCQR)⁷. The aforementioned trials were found to suffer from limited recruitment, partly due to reluctance from clinicians to randomize patients with severe disease that are known to benefit from treatment in some cases. The effects of revascularization on relevant outcome parameters including BP response and renal function are summarized below.

Effect of Renal Revascularization on Hypertension:

The CORAL study published in 2014, is the largest randomized control trial to date evaluating renal artery stenting versus medical management (Table 1)³. In this study, a consistent but only modest difference in systolic blood pressure favoring the stent group was reported. Notably, 40% of patients in this study had a RAS of <60% on duplex measurements and the frequency of bilateral renal artery stenosis was also low. Moreover, 29% of patients had a systolic BP of <140mmHg which could be one of the explanations why no significant changes in BP following revascularization were seen. Similarly, in the ASTRAL⁴, STAR⁵ and DRASTIC⁸ studies, no significant differences in blood pressure between groups was observed over the follow-up period, however, the daily drug dose was reduced in both the ASTRAL and DRASTIC studies^{4,8}.

A subsequent meta-analysis of 8 studies including 2,223 patients did not demonstrate any change in systolic blood pressure from baseline with revascularization when compared to medical therapy alone⁹.

Effect of Renal Revascularization on Renal Function:

In the ASTRAL trial, 59% of the patients had a RAS >70 %, and 60 % had a serum creatinine of $\geq 150\mu\text{mol/L}$ (4). At a mean follow-up of 33.6 months (range 1-4 years) differences in renal function, kidney and cardiovascular events were not significant, even in the highest risk groups, which included patients with global ischemia or impaired or rapidly decreasing kidney function. The primary study end-point, the decline in renal function over time, was marginally slower in the revascularization group, but this was not statistically significant. The STAR multicenter trial enrolled 140 patients to detect a 20% or greater decrease in creatinine clearance⁵. At 2 years, the primary end point was reached in 16% of patients in the stented group and 22 % of patients in the medical treatment group; although the difference was not statistically significant, more than 50% of patients randomized to the stenting arm had a <70% RAS and 28% of patients did not receive a stent. In the DRASTIC study, GFR increased by 15 ml/min in the balloon angioplasty group whereas it slightly decreased by 1 ml/min in the control arm. However, the study was not powered adequately to show a significant difference⁸. In the CORAL Trial³, progressive renal insufficiency was defined

as a reduction from baseline of 30% or more in the estimated GFR. No significant improvement in renal function was seen in the follow-up period.

Which Patients should be considered for revascularization therapy?

The decision to perform RAS revascularization should involve a thorough review of the patients' co-morbidities, quality of blood pressure control and status of renal function. In light of the current available evidence, renal revascularization should be considered in patients with anatomically significant bilateral RAS who present with 'flash' pulmonary oedema, congestive heart failure with preserved left ventricular function or acute oligo-anuric renal failure with global kidney ischemia.

Conclusions

RAS is a common cause of secondary hypertension and associated with adverse outcomes. Modern imaging techniques combined with physiologic measures allows assessment of the degree of stenosis and hemodynamic relevance. Medical therapy with guideline recommended antihypertensive therapy including RAS blockers are usually effective in lowering BP while maintaining renal function. Benefit from revascularization therapy is likely to occur where there is a hemodynamically significant RAS, in the context of deteriorating arterial hypertension, progressive renal insufficiency, and cardiac destabilization syndromes.

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Table 1: Summary of most relevant RCTs comparing renal artery revascularization with medical therapy (from (10) with permission)

Trial	STAR	ASTRAL	CORAL
Year	2009	2009	2014
Number of patients	140	806	947
Inclusion criteria	Impaired renal function (CrCl <80) Ostial ARAS of ≥50% (CTA, MRA, DSA) Controlled BP <140/90 mm Hg	Renal artery atherosclerotic disease in ≥1 renal artery amenable to revascularization Clinician unsure if revascularization would provide clear benefit	Severe RAS angiographically defined as ≥60% but <100%, and hypertension with systolic BP ≥155 mm Hg on ≥2 agents or CKD defined as GFR <60 ml/min/1.73 m ²
Exclusion criteria	Renal size <8 cm Renal artery <4 mm CrCl <15 Diabetes with proteinuria >3 g/day Malignant hypertension	Disease needing surgical revascularization High likelihood of needing revascularization in 6 months Nonatheromatous disease Prior RAS revascularization Lack of informed consent	FMD CKD from causes other than ischemic nephropathy Cr >4 Kidney size <7 cm Lesions that could not be treated with 1 stent
Primary endpoint	Worsening renal function >20% decrease of CrCl	Slope of the reciprocal of Cr over 5 yrs	Time to major renal or cardiovascular event (stroke, heart attack, CHF hospitalization, progressive renal insufficiency, need for dialysis)
Limitations	Patients had controlled BP Considerable number of participants had <50% stenoses	Rate of complications much higher than reported Smaller number of antihypertensive agents used in intervention group Diagnosis of RAS made with noninvasive imaging without functional studies Patients with kidney size <6 cm included in study Patients with insignificant lesions included	Patients were not optimized on antihypertensive therapy Inclusion of patients with mild stenosis Only moderate correlation between angiography and hemodynamically significant stenoses

Figure 1: Illustration of a clinical pathway to optimize identification and management of patients with RAS and relevant associated clinical syndromes (from (10) with permission).

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