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Atherosclerotic Renal Artery Stenosis

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Abstract

Atherosclerotic Renal Artery Stenosis is a form or peripheral arterial disease that tends to affect older subjects with hyperlipidemia, history of tobacco use, and who have other coexistent forms of vascular insufficiency. An abdominal bruit on physical exam can be a helpful clue. Slowly progressive, it can lead to critical narrowing of the renal arteries which creates a cascade of events such as renin-angiotensin-aldosterone activation (RAAS), hypertension, acute pulmonary edema, and renal fibrosis. The hypertension is considered a secondary form and can even be resistant to multiple antihypertensives. The diagnosis can be made with imaging (duplex ultrasound CT scans, MRA, or angiography). Because of the unique circulation to the kidney, stenting and angioplasty are rarely curative. This was confirmed in three recent large clinical trials. Therapy consists of lipid and blood pressure control, and dual anti-platelet agents. Because the disease activates the RAAS system, ace inhibitors and angiotensin receptor blockers can be useful agents but carry the risk of ischemic nephropathy, a form of acute kidney injury related to reduced renal blood flow after challenge with these agents. As such these agents are used with caution. Little is known about optimal blood pressure agents or the effect of lifestyle modification.

Keywords

Hypertension • Peripheral arterial disease • Stenosis • Hyperlipidemia • Acute pulmonary edema • Renin-angiotensin-aldosterone • Ischemic nephropathy • Abdominal bruit

1 Introduction

Atherosclerotic Renal Artery Stenosis is a common finding in secondary hypertension

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evaluations. Many clues can lead to its diagnosis including an abdominal bruit, history of tobacco use, peripheral arterial disease, flash pulmonary edema, and the development of acute kidney injury on agents blocking the renin-angiotensin system. It is an unusual form of peripheral arterial disease in that stenting and angioplasty do not seem to alter the clinical course of the disease as compared with peripheral interventions elsewhere (i.e. carotid and iliac arterial disease). This chapter will focus on the diagnosis of the disease and the therapeutic considerations in light of the vast array of available clinical trial data.

2 Epidemiology

Atherosclerotic renal artery stenosis (ARAS) commonly complicates chronic kidney disease (CKD) and end-stage renal disease (ESRD). As many as 5–15 % of patients who develop ESRD and 5–22 % of patients with CKD over 50 years old may have ARAS. It has an even higher prevalence in patients with other forms of atherosclerotic vascular disease. Among those with non-ESRD CKD, the absolute risk of cardiovascular outcomes is greater than the risk of developing ESRD. In the ESRD population the mortality rate is up to 50 % at 3 years (Rimmer 1993).

The degree of stenosis correlates inversely with survival. Patients with incidentally found moderate ARAS by angiogram often maintain stable renal function and may not be at any higher risk of ESRD than the general population up to 10 years after diagnosis (Leertouwer et al. 2001). Patients who go on to develop ESRD were generally diagnosed later in the course of the disease with worse renal function and had a faster rate of decline in their remaining renal function (Baboolal et al. 1998).

3 Pathogenesis

ARAS is due to atherosclerosis of the main blood vessels to the kidneys, the left and right renal arteries. Slowly developing, it follows the same mechanisms of other atherosclerotic vascular diseases such as coronary artery disease, carotid stenosis, and peripheral arterial disease. ARAS more commonly affects the proximal renal artery or the ostium and the aortic take-off, versus another form of renal arterial disease, fibromuscular dysplasia (FMD). FMD tends to occurs in younger patients, predominantly women, and affects the middle portion of the renal artery (Olin et al. 2012).

In ARAS over time the atherosclerotic plaques impair blood flow to the kidney. Only the renal cortex, the site of the glomerulus, appears to undergo significant ischemia (Gloviczki et al. 2011). Autoregulation, an early compensatory mechanism, sustains renal blood flow to a degree, but begins to fail once the stenosis reaches roughly 60 % (Herrmann et al. 2016). At this point, declining renal blood flow and tissue hypoxia leads to renin release and activation of the renin-angiotensin-aldosterone system (RAAS) causing retention of sodium and water and also peripheral vasoconstriction (Ritchie et al. 2014). This all leads to hypertension associated with ARAS. This cascade of events also leads to local release of cytokines, inflammation, and eventually fibrosis and deterioration of renal function (Gloviczki et al. 2011).

4 Clinical Presentation

The presentation of ARAS is often chronic and insidious. As the ARAS progresses past the critical threshold from moderate to severe, the renal function will be compromised. The glomerular filtration rate (GFR) falls out of proportion to an expected age-related decline. Urinalysis is usually bland (no hematuria nor proteinuria) as ARAS has an initial pre-renal effect and subsequent renal dysfunction occurs due to hypertensive changes and fibrosis which has an intrinsic renal effect. Hypertension that was once easily controlled but now resistant or acutely worsening can be a sign of worsening RAS and should be considered during work up for secondary hypertension (Rimmer 1993).

Classically, ARAS may present with hypertensive crisis and associated flash pulmonary edema. Worsening renal function after starting RAAS blockade, ischemic nephropathy, or renal function that is excessively sensitive to intravascular volume may be clues to the diagnosis (Textor and Wilcox 2000). Many advocate stopping RAAS blockade if the serum creatinine rises by more than 30 % after use of such agents. ARAS is almost always associated with other forms of atherosclerotic diseases. Common risk factors are hyperlipidemia, smoking, and age over 50. On physical exam it may be possible to auscultate an abdominal bruit due to turbulent flow past a stenosis in a renal artery. Imaging of the kidneys is especially useful as it may reveal asymmetric or smaller than expected kidneys (Rimmer 1993). Table 1 lists common attributes of ARAS.

5 Diagnosis

A hallmark of ARAS is an elevated plasma renin assay and serum aldosterone concentration. Once suspected, duplex ultrasonography, magnetic resonance angiography (MRA) and computed tomography angiography (CTA) can aid in diagnosis (Rimmer 1993).

Duplex ultrasonography is the least sensitive and specific modality but is a safe and reasonable first test. It is labor-intensive, time-consuming, operator dependent, and in certain patients, particularly the obese, it is of limited utility. The resistive index ([peak systolic velocity – end-diastolic velocity] divided by peak systolic velocity) when added to duplex Doppler ultrasonography may aid in diagnosing RAS. A higher resistive index is indicative of more extensive atherosclerotic burden distal to the main renal arteries. Controversy exists as to whether a lower resistive index (i.e. < 80 %) represents an opportunity for revascularization resulting in lowering blood pressure (Williams et al. 2007).

MRA confers the risk of gadolinium-induced nephrogenic systemic fibrosis, a syndrome linked to individuals with a GFR <30 ml/min. Using arteriography as the gold standard, MRA had excellent sensitivity and specificity (100, 96 % respectively) for the detection of stenosis of the main renal arteries, but was less helpful in accessory renal arteries (Textor 2004).

CTA requires a significant volume of contrast and may be contraindicated in those with advancing CKD. Multidetector, spiral CTA can provide excellent sensitivity (96 %) and specificity (97 %), but is probably just a bit inferior to MRA (Crutchley et al. 2009). Conventional intra-arterial angiography can confirm the diagnosis but also carries a contrast nephropathy risk as well as that of atheroemboli. Blood oxygen level-dependent MRI which can identify renal ischemia in a non-invasive way may be a promising imaging modality (Gloviczki et al. 2011).

6 Treatment

Several recent clinical trials have addressed the role of interventional therapies versus medical management. The success of percutaneous

Table 1 Features of atherosclerotic renal arterial disease (ARAS)

Age of onset (years)	50–60
Common lab findings	AKI after RAAS agent usage.
Preferred BP agents	Unknown but caution with RAAS agents.
Location of lesion	Typically ostial, proximal 1/3 of renal artery versus Fibromuscular Dysplasia which affects middle portion of renal artery
How diagnosed?	Duplex ultrasound, CT Angiography, MR Angiography
Risk factors	Hyperlipidemia, Age > 50, Tobacco use

Rimmer (1993), Ritchie et al. (2014) and Textor and Wilcox (2000)

interventions in other peripheral arterial sites has not been demonstrated in RAS. Three randomized trials, ASTRAL, CORAL, and STAR compared standard medical therapy to the same therapy plus intervention (stenting/angioplasty) (Levy and Creager 2009; Cooper et al. 2014; Bax et al. 2009). The trials found no improvement in renal function, clinically significant reduction in antihypertensive requirements, nor mortality benefit, while morbidity was not trivial among those stented. Percutaneous interventions are no longer the standard of care in the management of ARAS following these trials and as such Medicare claims data for such procedures fell dramatically following the publication of these trials (Bax et al. 2009). While there may be a benefit to revascularization in a smaller population of patients with recurrent flash pulmonary edema, severe resistant hypertension, or rapidly progressive CKD, this has been poorly studied.

The disappointing results in intervention trials have paved the way toward a newer paradigm in therapy of ARAS. In the absence of compelling data regarding who will respond to vascular interventions, we reserve stenting and angioplasty for those who have failed medical therapy and develop resistant or refractory hypertension and/or pulmonary edema. At that point there is little else to offer and we feel the risks of the procedure are justified.

Now, the most important goal is to optimize any potential risk factors present. This includes a comprehensive effort to control hypertension, hyperlipidemia, and limit platelet aggregation. Hyperlipidemia can be managed with a statin. Dual antiplatelet therapy may be employed depending on risk factors for bleeding (Cooper et al. 2014).

The control of hypertension associated with ARAS is complicated. As noted above, ARAS leads to increased activation of the RAAS system making it is a logical target to guide therapy. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARB) are key components for controlling the hyperactivation of the RAAS system, but confounded by the potential for ischemic nephropathy. About 20 % of patients with ARAS will have an unacceptable deterioration in renal function (>30 % rise in serum creatinine) following initiation of RAAS blockade (Franklin and Ronald 1985). We do not advocate the use of RAAS agents without nephrology consultation. A subject with ARAS and treated with RAAS agents must have regular bloodwork (creatinine, blood urea nitrogen, and potassium) and must strictly avoid nonsteroidal agents that alter renal hemodynamics, as well as be mindful of developing volume depletion. Still, the benefits of RAAS blockade in delaying the progression of CKD and their particular mechanism of action make these agents a potentially valuable option.

Little data exists about the best agents to control blood pressure, but we can use the experiences in STAR, ASTRAL, and CORAL (Levy and Creager 2009; Cooper et al. 2014; Bax et al. 2009). Table 2 highlights the features of the trials and agents used. RAAS blocking agents were used quite commonly if not outright mandated for use. The CORAL trial provided an ARB (Candesartan) to all patients and also mandated the use of Hydrochlorothiazide, and the combination pill of Amlodipine and Atorvastatin. RAAS agents were used to a lesser degree (40–60 %) in the other trials. Both STAR and ASTRAL emphasized lipid control and antiplatelet agents as well.

As with all forms of resistant hypertension (RH), focusing on modifiable factors should supplement pharmacologic and/or interventional

Table 2 Clinical trials in renal artery stenosis (RAS)

Trial	Coral	Star	Astral
Year	2014	2009	2009
Number of patients	921	140	806
Mean age (Yrs)	69	69	70
Mean BP or SBP (mm Hg)	150	150	150/76
Primary endpoint P value	NS	NS	NS
Baseline GFR (ml/min)	58	46 (CrCl)	40
Mean # Drugs	*	2.9	2.8
% Taking ACEI or ARB	100	56–60	38–47

Levy and Creager (2009), Cooper et al. (2014) and Bax et al. (2009)

* Implies no data available on that parameter

therapies. The effect of lifestyle modification on RH is being investigated across a broad class of hypertensive diseases in the upcoming Triumph Trial and may shed light on the role of weight loss, sodium restriction, and exercise on the progression of ARAS (Blumenthal et al. 2015). In the CORAL trial some of the reassuring renal outcomes were attributed to addressing smoking, diabetes, and other non-hypertension factors.

7 Conclusions

ARAS is frequently identified in patients with high risk for peripheral arterial disease, diagnosed by duplex ultrasonography, CT angiography, MR angiography, or direct visualization. Therapy addresses blood pressure control, lipids, and utilizing anti-platelet therapy. The approach to interventional therapies is complex and we advocate a case-by-case basis to determine how to proceed. Modifying risk factors such as smoking, diabetes, sedentary lifestyle, and use of confounding agents like non-steroidals and sodium are non-pharmacologic adjuncts we expect to play a bigger role in the future.

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