Atherosclerotic renovascular disease in chronic heart failure: should we intervene?

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Renal artery stenosis (RAS) is most commonly caused by atherosclerosis, which is also the most common cause of chronic heart failure (CHF). One-third of patients with CHF are reported to have significant renovascular disease. The presence of RAS confers a worse outcome in studies of hypertension and coronary disease, though data are lacking for patients with CHF. As the kidney is intricately involved in the fluid retention that occurs in CHF, an adverse effect of RAS on outcome would be expected. Presentations of RAS in CHF include flash pulmonary oedema, hypertension, worsening of CHF, and worsening renal function. RAS commonly progresses and may cause worsening of renal function in patients with CHF and previously stable renal function. A variety of investigations that can safely and accurately identify RAS in CHF are available, although none is recommended in current guidelines for the management of CHF. Treatment for RAS, whether for hypertension, for renal dysfunction, or for pulmonary oedema, is at the discretion of the physician due to the lack of adequate randomized controlled trials demonstrating the efficacy and safety of intervention. As it is not clear how RAS should be managed in CHF, screening cannot be advocated. Currently, a multicentre randomized outcome trial, which includes a cohort of patients with RAS and CHF, is in progress to provide answers in this area of uncertainty.

KEYWORDS
Heart failure; Renovascular disease; Intervention

Introduction

Atherosclerosis is a common cause of chronic heart failure (CHF). It can affect both the coronary and renal arteries. It is possible that renal artery stenosis (RAS) caused by atherosclerosis plays a significant role in the pathophysiology and progression of CHF in some patients. RAS can cause pulmonary oedema and clinical CHF in the absence of obvious, major cardiac dysfunction. Benefit from renal revascularization in this setting, using either percutaneous or surgical techniques, has been suggested in case reports, but such treatment is not mentioned in the guidelines of heart failure. No randomized studies addressing the role of renal revascularization in patients with CHF and RAS exist. This review outlines the epidemiology, clinical presentations, and management strategies currently adopted for patients with atherosclerotic renovascular disease (AVRD), with a particular emphasis on patients with coexistent heart failure. We will discuss why prospective randomized studies in this setting are important.

Sources and selection criteria

We performed literature searches using MEDLINE, Embase, and the Cochrane register from inception to November 2004 using keywords such as 'renal artery stenosis', 'atherosclerotic renovascular disease', and 'ischaemic nephropathy', alone and in combination with 'heart failure' and 'flash pulmonary oedema'. Review articles, randomized controlled trials, major observational trials, and original work published in peer reviewed journals were accessed. In addition, the reference lists of the articles accessed were scrutinized to identify further papers not identified by the original search strategy.

Presentations of ARVD

Renovascular disease is often asymptomatic. Clinical presentations include hypertension, progressive renal dysfunction, a marked rise in serum creatinine with therapeutic blockade of the renin–angiotensin–aldosterone system (RAAS), atheroembolic disease, proteinuria, flash pulmonary oedema, and CHF. It is possible that the majority of patients with ARVD will present with heart failure, in turn taken as a manifestation of coronary artery disease and
chronic hypertension. It may be difficult to distinguish such patients from those with heart failure but without ARVD.

Case reports and small series suggest that patients with RAS may also present with flash pulmonary oedema or CHF without coronary disease, although no large case-series exist. Patients with flash pulmonary oedema present with sudden onset of acute pulmonary oedema (APO) associated with acute systemic and pulmonary hypertension. These are often elderly patients and may be less likely to be investigated for underlying RAS. The electrocardiogram and renal function, as indicated by serum creatinine, are often normal and left ventricular systolic function is often preserved. Other patients with bilateral ARVD may present with CHF and left ventricular systolic dysfunction without evidence of coronary disease, or with diastolic ventricular dysfunction in the presence of hypertension and impaired renal function.3

Hypertension is the most common presentation of RAS. One to five per cent of all patients with hypertension will have RAS.9 Renovascular hypertension carries a worse cardiovascular prognosis than other hypertensive conditions.10 A renovascular cause for hypertension is suggested by many features, although none is diagnostic.11,12 These include a younger age of presentation in the absence of a positive family history, resistant hypertension, deteriorating blood pressure control in compliant patients, presence of atherosclerosis in other vascular trees, reversible early deterioration of renal function following initiation of angiotensin converting enzyme (ACE)-inhibitors with reversal on subsequent withdrawal, renal impairment with minimal proteinuria, and >1.5 cm difference in kidney size on ultrasonography.13 Clinical prediction rules have been devised to identify hypertensive patients who have a high probability of having RAS,14,15 and simple and readily determined clinical and laboratory patient characteristics are associated with severe RAS in populations at risk.16

Renal dysfunction is another common manifestation of RAS. Six per cent of all patients entering a dialysis program and 14% of those over the age of 50 had RAS as the cause of their renal failure.17 Other data suggest that RAS may be the underlying cause of renal failure in up to 25% of patients over the age of 60.18 A rapid increase (e.g. a rise in serum creatinine >44 μmol/L (0.5 mg/dL) if the initial serum creatinine is <177 μmol/L (2.0 mg/dL) or a rise in >88 μmol/L (1.0 mg/dL) if the baseline creatinine exceeds 177 μmol/L (2.0 mg/dL)), or >20% increase in serum creatinine following introduction of an ACE-inhibitor are both markers of underlying RAS.19

**Epidemiology of ARVD**

**Aetiology**

ARVD accounts for 90% of RAS.20 As coronary disease also accounts for most cases of heart failure due to left ventricular systolic dysfunction,21,22 it is likely that atherosclerosis is the most common cause of coexistent RAS in patients with heart failure. Ischaemic heart disease may make a less important, and hypertension a greater, contribution to the development of heart failure in patients with preserved left ventricular systolic function.23,24 However, the aetiology of RAS in such cases is also likely to be atherosclerotic. Other less common aetiologies of RAS include fibromuscular dysplasia, aortic or renal artery dissection, non-specific aortoarteritis, thrombotic or cholesterol embolization, collagen vascular disease, neurofibromatosis, trauma, post-transplantation stenosis, and post-radiation fibrosis.12

**Prevalence**

The prevalence of RAS increases with age,25 diabetes,26 aortoiliac occlusive disease, and hypertension,27 though no population-based estimates currently exist.28 Prevalence rates of 5, 10, 24, and 30% have been reported in patients with hypertension,29,30 stroke,31 peripheral vascular disease,31 and coronary artery disease,32,33 respectively. The only published study to our knowledge reporting the prevalence of RAS in CHF involved an elderly population with heart failure in which 86 patients over the age of 70 years (mean 77.5 years, 49% women) were investigated. Previous therapy with ACE-inhibitors and a serum creatinine level >300 μmol/L (3.4 mg/dL) were exclusion criteria. However, a selection bias existed in this study as all patients were screened using captopril renography and only 53 patients underwent magnetic resonance angiography. RAS >50% was present in 29 (34%) of the patients studied.

**Prognosis**

RAS augurs a worse outcome in studies of hypertension and coronary disease, predominantly due to coronary and cerebrovascular events rather than renal failure, but data are lacking in patients with heart failure. In patients with essential hypertension, 5-year mortality in two prospective studies was 7% higher in patients with RAS than in well-matched patients5 and 23% higher than in the general population.36 In patients investigated for coronary artery disease with angiography, 4-year survival was 21% higher in patients without renal artery involvement than in the group with RAS.37 In another study, patients with peripheral vascular disease and coexisting RAS of >50% at angiography had a 2-year mortality of 33%.37 Patients with CHF and renal dysfunction do have a worse prognosis38,39 but it is not clear whether renal dysfunction is a useful marker of RAS in this setting or that the presence of RAS itself alters outcome.

**Pathophysiology**

Experiments conducted by Goldblatt et al.40 on the effects of renal-artery constriction in animals led to the recognition that RAS may cause hypertension. A haemodynamically significant unilateral stenosis increases renin secretion from the juxta-glomerular apparatus (JGA), causing sodium and water retention by the ipsilateral kidney, both through direct actions of angiotensin II and via aldosterone synthesis.41 The ischaemic kidney also acts as a direct stimulus to the sympathetic nervous system (SNS) with subsequent release of norepinephrine.42 A normal contralateral kidney suppresses its renin secretion and a pressure natriuresis occurs, restoring intravascular volume. Natriuresis fails to occur in the presence of bilateral RAS or abnormal contralateral kidney function43 (Figure 1). Volume overload can occur due to kidneys ‘protected’ by bilateral stenosis failing to mount a pressure natriuresis to high arterial pressures.1,44 It is possible that in heart failure, a condition often...
associated with reduced arterial pressure, failing baroreflexes, and altered renal pathophysiology, there is also a failure of pressure-natriuresis, making such patients more susceptible to salt and water retention. This may manifest as recurrent episodes of flash pulmonary oedema, characterized by hyper-reninaemia, which may occur in the presence of normal left ventricular systolic function. However, diastolic dysfunction may be a contributing factor. Other mechanisms may contribute to the progression of CHF in patients with significant ARVD (Table 1).

The pathophysiology of the renal impairment in patients with RAS is multifactorial. Intrarenal atheroma, cholesterol embolization, hypertensive damage, and ischaemic damage all contribute. An abnormal serum creatinine value reflects loss of 50–60% of functioning nephrons. As the kidneys are a paired organ system, an abnormal serum creatinine in a patient with unilateral RAS suggests concomitant dysfunction of the contralateral kidney. Possible causes include renal parenchymal damage, atheroembolic renal disease, and hypertensive nephrosclerosis (intrarenal artery stenosis), which is a more common manifestation of ARVD than involvement of the extra-renal vasculature.

Natural history of ARVD

ARVD tends to progress from unilateral to bilateral, from stenosis to occlusion, and from normal to elevated serum creatinine concentrations. In one study using duplex ultrasound, 23% of subjects with <60% unilateral stenosis had progressed to >60% at the end of 1 year; in patients with >60% stenosis, 5% developed total occlusion at 1 year and 10% developed total occlusion at 2 years. A prospective study in patients with hypertension and/or renal insufficiency showed that arteries classified as normal at baseline had progressed to a high-grade stenosis (>60%) in one-third of cases after 5 years. Patients with unilateral disease have a 49% risk of developing bilateral disease within 2 years. However, the use of treatments and life-style modifications proved to reduce the progression of atherosclerosis were not uniform in these observational reports. The natural history of RAS in patients with CHF is unknown. Progression of RAS may be truncated by the demise of the patient and it

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**Figure 1** Pathophysiology in the development of pulmonary oedema. Failure of pressure natriuresis occurs in the presence of significant contra-lateral renal artery stenosis or a diseased kidney.

**Table 1** Mechanisms that may contribute to the progression of CHF in ARVD

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced cardiac baroreceptor reflex sensitivity</td>
<td>48</td>
</tr>
<tr>
<td>Increased sympathetic nerve activity</td>
<td>49</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>50</td>
</tr>
<tr>
<td>Attenuation of nitric oxide induced endothelium-dependent vasodilation</td>
<td>51</td>
</tr>
<tr>
<td>Increased oxidative stress</td>
<td>52</td>
</tr>
<tr>
<td>Excess production of endothelin and vasopressin</td>
<td>53</td>
</tr>
<tr>
<td>Low density lipoprotein oxidation</td>
<td>54</td>
</tr>
</tbody>
</table>
is unclear to what extent progression of RAS may be responsible for this.

**Investigations for RAS**

As it is often not clear that diagnosis of RAS will alter management, investigation of suspected RAS is not always mandatory. When investigations are planned, information about the site, degree, and haemodynamic significance of the lesion is required to try to ensure that treatment is worthwhile. However, no universally accepted definition for significant RAS exists, as anatomical narrowing does not necessarily correlate with functional impairment. Lesions causing <50% stenosis are probably haemodynamically insignificant, lesions that are 50% are likely to have only minor haemodynamic effects, and lesions between 50 and 70% are probably haemodynamically significant. A stenosis between 50 and 80% is thought to be significant if a translesional peak pressure gradient of >20 mmHg or a mean of 10 mmHg is found using Doppler wire interrogation of the lesion.

Non-invasive tools used to diagnose ARVD include colour coded duplex sonography (CDS), captopril renography, computed tomographic angiography (CTA), and gadolinium enhanced magnetic resonance angiography (MRA). Digital subtraction, arterial-phase renal angiography remains the ‘gold standard’ for diagnosis, providing information about the site and severity of stenosis, and guiding appropriate revascularization strategies. It is, however, an invasive procedure with associated risks, and suggestions have been made that it should be restricted for angioplasty and stenting only, and not for confirming suspected ARVD.

CDS is operator dependent with sensitivity and specificity approaching 95% for the detection of lesions >50% in dedicated laboratories. A formula derived using Doppler ultrasound [the renal resistance-index calculated as follows: 1 – (end-diastolic velocity/maximal systolic velocity) × 100] may identify patients who will benefit from intervention. Administration of captopril reduces the angiotensin II dependent efferent arteriolar resistance that is increased in RAS to maintain glomerular filtration rate. This vasodilatation leads to a reduction of transcapillary forces, therefore reducing the glomerular filtration rate in the kidney. A substantial reduction in renal function following captopril administration with reversal of the effect on cessation of the drug indicates the presence of haemodynamically significant RAS. It is both sensitive (80–95%) and specific (50–94%) but does not provide information about the anatomy of the renal arteries. However, the sensitivity of the test is insufficient in the presence of renal failure, bilateral RAS and renin-independent hypertension. Other nuclear imaging techniques are used for evaluating total and single kidney glomerular filtration rates. They can be used to look for early manifestations of ischaemic nephropathy and to assess the functional significance of an anatomical lesion.

CTA has sensitivity and specificity rates of ~95%, and using techniques such as spiral CTA, it may be even superior to standard angiography. Functional information is available using faster scanners, with the ability to quantify renal perfusion and segmental renal function. However, a major limitation is the risk of nephrotoxicity from the use of contrast agents.

Gadolinium enhanced MRA has a 100% sensitivity and 89% specificity compared with conventional angiography. Detection rates for RAS are comparable to those for CTA. Future developments may allow dynamic assessment of the anatomy and functional effects of a lesion during the same assessment, and studies assessing aortic spiral blood flow may have a role in identifying those patients most suitable for renal revascularization. Major disadvantages of MRA are the cost and duration of the test, difficulty in visualizing the distal, intrarenal vessels, false-positive artefacts due to respiration, peristalsis and tortuous vessels, and overestimation of the severity of RAS. It is also not useful in monitoring patients following renal artery stenting due to stent artefact. Advantages include the high sensitivity of MRA, the lack of ionizing radiation and the ability for use in the presence of renal impairment, as the contrast agents are not nephrotoxic.

**Treatment of ARVD**

The rationale for intervention in patients with RAS is based on the progressive natural history of the condition. Despite little evidence, in the presence of significant RAS and normal sized ipsilateral kidneys, renal revascularization is conventionally offered in the following settings: severe hypertension resistant to medical therapy, rapidly progressive renal failure with no other obvious cause, recurrent flash pulmonary oedema, and worsening renal function (WRF) in the presence of ACE-inhibitors or angiotensin receptor blockers.

**Heart failure**

Anecdotal reports, case reports, and retrospective case series (Table 2) support a benefit of treating RAS in the presence of CHF or flash pulmonary oedema. The majority of reports involved patients with significant bilateral RAS or unilateral RAS with a non-functioning contralateral kidney. Whether revascularization will improve the symptoms of heart failure in a patient with unilateral disease and two functioning kidneys is unclear. No randomized or observational study has prospectively assessed the outcome of renal revascularization for RAS in patients with CHF.

**Hypertension**

Reversal of hypertension by nephrectomy for unilateral renal disease was first demonstrated in 1937. Vascular reconstruction was later found to have the same effect in selected cases. With the advent of percutaneous transluminal renal angioplasty (PTRA), revascularization has become an acceptable mode of treatment. However, interpretation of trials of percutaneous revascularization in hypertension is difficult, due to different selection criteria, different definitions of improvement and variable, often short, duration of follow up. The studies are also limited by small patient numbers, lack of control subjects and failure to standardize anti-hypertensive therapy or methods of blood pressure measurement.

Only three randomized controlled trials comparing PTRA with medical therapy for the treatment of hypertension...
Table 2  Reports of renal revascularisation for chronic heart failure and/or acute pulmonary oedema in the presence of renal artery stenosis

<table>
<thead>
<tr>
<th>Authors and year of publication</th>
<th>Number of cases</th>
<th>Heart failure presentation</th>
<th>Coronary artery disease</th>
<th>Left ventricular systolic dysfunction</th>
<th>ACE-inhibitor use</th>
<th>Renal artery stenosis degree</th>
<th>Intervention</th>
<th>CHF endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pickering et al. 1988(^3)</td>
<td>11</td>
<td>APO</td>
<td>Yes 5/11</td>
<td>No</td>
<td>Yes 8/11 showed WRF(^a)</td>
<td>7 Bilateral, 2 unilateral to SFK, 2 unilateral Severe bilateral or unilateral to SFK</td>
<td>8 PTRA, 3 surgery</td>
<td>10/11 no further APO</td>
</tr>
<tr>
<td>Meissner et al. 1988(^3)</td>
<td>6</td>
<td>CHF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes with WRF(^a)</td>
<td>4 PTRA, 1 surgery, one none</td>
<td>PTRA</td>
<td>Undefined clinical improvement</td>
</tr>
<tr>
<td>Palmar et al. 1989(^5)</td>
<td>1</td>
<td>APO</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes with WRF(^a)</td>
<td>Severe unilateral to SFK</td>
<td>PTRA</td>
<td>No further APO before discharge</td>
</tr>
<tr>
<td>Messina et al. 1992(^6)</td>
<td>17</td>
<td>APO</td>
<td>Yes 11/17</td>
<td>Yes 6/17</td>
<td>Unknown</td>
<td>Severe bilateral</td>
<td>1 PTRA, 16 surgery</td>
<td>No APO over mean follow-up 2.4 years</td>
</tr>
<tr>
<td>Missouris et al. 1993(^7)</td>
<td>2</td>
<td>CHF</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes with WRF(^a)</td>
<td>Severe unilateral to SFK</td>
<td>2 PTRA, 1 surgery</td>
<td>Echo normalised in one, free from heart failure in other</td>
</tr>
<tr>
<td>Diamond 1993(^8)</td>
<td>3</td>
<td>APO</td>
<td>Yes 1/3</td>
<td>No</td>
<td>Yes 1/3 with WRF(^a)</td>
<td>2 Severe bilateral, 1 severe unilateral to SFK, 4 severe unilateral to SFK</td>
<td>Surgery</td>
<td>2/3 no further APO</td>
</tr>
<tr>
<td>Weatherford et al. 1997(^9)</td>
<td>5</td>
<td>APO</td>
<td>Yes 2/5</td>
<td>No</td>
<td>Unknown</td>
<td>Severe bilateral</td>
<td>Surgery</td>
<td>No APO over mean follow-up 57 months</td>
</tr>
<tr>
<td>Ducloux et al. 1997(^6)</td>
<td>1</td>
<td>CHF</td>
<td>No</td>
<td>Yes</td>
<td>Unknown</td>
<td>Severe bilateral</td>
<td>Bilateral PTRA</td>
<td>Undefined clinical improvement</td>
</tr>
<tr>
<td>Kwan et al. 1997(^10)</td>
<td>1</td>
<td>APO</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Severe bilateral</td>
<td>PTRA and bilateral stents</td>
<td>Unknown</td>
</tr>
<tr>
<td>Khosla et al. 1997(^11)</td>
<td>28</td>
<td>CHF</td>
<td>Yes 24/28</td>
<td>Yes 22/28</td>
<td>Unknown</td>
<td>&gt;70% Stenosis, 8 unilateral, 20 bilateral</td>
<td>28 PTRA with stent</td>
<td>16/28 improvement in NYHA class</td>
</tr>
<tr>
<td>Planken et al. 1998(^12)</td>
<td>2</td>
<td>APO</td>
<td>Yes 1/2</td>
<td>Yes 1/2</td>
<td>Yes 1/2</td>
<td>1 Severe unilateral to SFK, 1 severe bilateral</td>
<td>2 PTRA</td>
<td>No recurrence of APO at follow-up</td>
</tr>
<tr>
<td>Farmer et al. 1999(^13)</td>
<td>1</td>
<td>APO</td>
<td>Unknown</td>
<td>No</td>
<td>No</td>
<td>Severe unilateral stenosis of vein graft to SFK</td>
<td>PTRA</td>
<td>No APO at 2-month follow-up</td>
</tr>
<tr>
<td>Bloch et al. 1999(^14)</td>
<td>25</td>
<td>19 APO, 6 CHF</td>
<td>Yes 15/25</td>
<td>Yes 4/25</td>
<td>Unknown</td>
<td>22 Bilateral, 3 unilateral</td>
<td>25 PTRA and stent</td>
<td>18/25 no recurrence, 3 with APO, 4 with CHF at 1 year</td>
</tr>
<tr>
<td>Bhardwaj et al. 2000(^15)</td>
<td>1</td>
<td>APO</td>
<td>Unknown</td>
<td>Yes</td>
<td>Unknown</td>
<td>Severe unilateral</td>
<td>PTRA</td>
<td>No symptoms at 1 month</td>
</tr>
<tr>
<td>Missouris et al. 2000(^16)</td>
<td>9</td>
<td>CHF</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes with WRF(^a)</td>
<td>4 Severe bilateral, 5 severe unilateral</td>
<td>8 PTRA, 1 surgery</td>
<td>Unspecified improvement</td>
</tr>
<tr>
<td>Walker et al. 2001(^17)</td>
<td>1</td>
<td>APO</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Severe unilateral</td>
<td>PTRA</td>
<td>No further APO</td>
</tr>
<tr>
<td>Holeggen et al. 2001(^18)</td>
<td>1</td>
<td>APO</td>
<td>Yes</td>
<td>Unknown</td>
<td>Yes with WRF(^a)</td>
<td>Bilateral</td>
<td>PTRA</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mansoor et al. 2001(^19)</td>
<td>1</td>
<td>APO</td>
<td>No</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Critical RAS</td>
<td>PTRA</td>
<td>No SOB at 3 years</td>
</tr>
<tr>
<td>Duclos et al. 2002(^20)</td>
<td>2</td>
<td>APO</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>18/39 Severe bilateral, 21/39 Severe unilateral to SFK</td>
<td>26 PTRA and stent</td>
<td>Symptom free at 6 months</td>
</tr>
<tr>
<td>Gray et al. 2002(^21)</td>
<td>39</td>
<td>CHF and APO</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes 6/39</td>
<td>Bilateral RAS</td>
<td>PTRA and stent</td>
<td>Reduction in hospitalization for heart failure</td>
</tr>
<tr>
<td>Basaria et al. 2002(^22)</td>
<td>1</td>
<td>APO</td>
<td>Unknown</td>
<td>No</td>
<td>Unknown</td>
<td>Bilateral RAS</td>
<td>PTRA and stent</td>
<td>No further APO at 3-year follow-up</td>
</tr>
<tr>
<td>Aslam et al. 2003(^23)</td>
<td>1</td>
<td>APO</td>
<td>Yes</td>
<td>No</td>
<td>Yes with WRF(^a)</td>
<td>Bilateral RAS</td>
<td>PTRA and stent</td>
<td>No further APO at 6-month follow-up</td>
</tr>
<tr>
<td>Brammah et al. 2003(^24)</td>
<td>1</td>
<td>CHF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes with WRF(^a)</td>
<td>Severe unilateral, occluded contralateral</td>
<td>Unilateral PTRA and stent</td>
<td>No further CHF</td>
</tr>
</tbody>
</table>

SFK, single functioning kidney; NYHA, New York Heart Association, SOB, shortness of breath.

\(^a\)Definition varies between case reports.
exist. A combined total of 210 patients were followed-up for a period of 6–12 months, and a meta-analysis of the trials has recently been published. In the majority of cases, the only advantage for patients treated with PTRA was a reduction in their drug regime, though this was not observed in patients with pre-existing renal failure. A subgroup of patients with bilateral RAS had better control of their blood pressure with PTRA. No long-term benefit on the preservation of renal function was demonstrated in these trials.

Renal disease

One study suggested that up to 15% of elderly hospitalized patients had ischaemic nephropathy leading to end stage renal disease often as a result of atherosclerotic extraparenchymal RAS. Another observational study suggested that revascularization prevented further decline in the function and size of kidneys with RAS. PTRA may also relieve severe proteinuria secondary to RAS. Observational trials of patients with renal dysfunction showed that PTRA may delay the need for renal replacement therapy or allow dialysis to be discontinued in some patients. However, revascularization can also be associated with a decline in renal function, and as noted earlier, randomized trials of hypertension failed to show any benefit on renal function.

Predicting outcome of treatment

Owing to the limited success of PTRA in treating both hypertension and renal impairment, it is important to identify patients whose blood pressure and/or renal function improve following successful correction of RAS. A shrunken kidney, a kidney with cortical necrosis or a kidney proven by biopsy to have irreversible damage will not benefit from revascularization. Factors that affect outcome include the severity of RAS, the procedure used to treat RAS, radiocontrast nephrotoxicity, atheroembolism and the presence of underlying renal parenchymal disease. Reasons for lack of benefit include long term exposure to the effects of high blood pressure leading to irreversible renal and vascular damage (hypertensive nephrosclerosis) and suboptimal vessel dilation when analysed using intravascular ultrasound.

Modern PTRA with stenting may be safer and more beneficial, but this cannot be assumed. PTRA with stenting has higher rates of procedural success and lower rates of restenosis than PTRA alone. A randomized comparison of PTRA and PTRA with stent placement for the treatment of atherosclerotic ostial RAS showed vessel patency rates of 57% vs. 88% and restenosis rates of 48% vs. 14%, respectively. However, there was no difference between the two groups in terms of blood pressure reduction or improvement of renal function.

Complications

Despite improvement in PTRA techniques, failure rates are still appreciable. A meta-analysis from the early 1990s showed an overall rate of residual stenosis >50% in 12% following PTRA. Another review of 1417 angioplasties carried out in 20 experienced centres showed an overall rate of technical failures of 30%, increasing to 45% for ostial lesions. Early complications include recoil of aorto-ostial plaques and dissections and late complications include persisting encroachment of aortic atheroma and restenosis. At 6–12 months, restenosis rates of 27–100% have been reported. A high incidence of technical failure occurs despite apparent visual success following PTRA. With the use of stents, complication rates range from 18 to 33%, and include dissections, sub-acute thrombosis, and restenosis. Restenosis rates of 11–39% occur at 1 year follow up. This is due to myointimal hyperplasia and is common with increasing age and ostial lesions. Treatment options for restenosis include PTRA with or without stent placement, excimer laser-assisted angioplasty, rotational atherectomy, brachytherapy, and surgical end-atherectomy. Technological advances such as the use of drug eluting stents and atheroembolic protection devices may reduce both the early and late complication rates associated with PTRA.

Surgery

Reconstructive surgery has similar effects to PTRA and stenting in lowering blood pressure, although the former may offer greater improvement in renal function, but with a higher mortality rate of 3–6%. Surgical revascularization is performed in patients with occluded renal arteries to functioning kidneys supplied by collaterals, and in the presence of aneurysmal or occlusive diseases of the abdominal aorta. Uncontrolled studies suggest that surgical intervention may reduce nephrotic range proteinuria and delay the need for renal replacement therapy. The management of hemodynamically insignificant lesions remains uncertain. It would appear logical to try to prevent the progression of atheroma using treatment that is believed to be effective for the coronary and cerebral circulation (e.g. smoking cessation, LDL-cholesterol <100 mg/dL, blood pressure <140/85 mmHg, ACE-inhibition if tolerated, low-dose aspirin, folate administration). A randomized trial is underway to determine the effects of statins, anti-hypertensive agents, and anti-platelet agents, with or without stent placement, upon the progression of renal dysfunction caused by ARVD.

CHF and renovascular disease

Should intervention be offered to CHF patients with atherosclerotic RAS?

The few randomized trials looking at cardiovascular outcomes in ARVD use blood pressure and renal function as endpoints. They were underpowered to determine whether revascularization improved cardiovascular outcomes. Anecdotal reports exist (Table 2) on the safety and efficacy of renal angioplasty for RAS in the presence of CHF and/or flash pulmonary oedema but randomized controlled trials are lacking. When the balance of risk and benefit is in doubt, randomized trials are required. Until the answers to the trials are known, it would seem appropriate to use renal revascularization as an intervention of last resort rather than a preferred treatment.
Should clinicians screen routinely for RAS in patients with CHF?

Before adopting a screening test, it is important to know the approximate prevalence of the condition to ensure that screening is a good use of resources and that detection will benefit patients by changing management. Neither of these conditions has been adequately fulfilled in patients with heart failure. Consequently, there is no clinical imperative to screen. However, clinical indicators, such as cardiac and renal failure in the presence of hypertension, presence of atherosclerosis in other vascular trees, reversible early deterioration of renal function following initiation of and subsequent withdrawal of ACE-inhibitors and >1.5 cm difference in kidney size on ultrasonography will make the diagnosis of RAS more likely.8,13

Should ACE-inhibitors be used in patients with heart failure and ARVD, and if so can high doses be tolerated?

ACE-inhibitors reduce morbidity and mortality in CHF143 with some evidence of a greater benefit with higher doses.144 Deteriorating renal function is an important cause for the under-use of ACE-inhibitors. Approximately 2% of patients entering randomized controlled trials will have ACE-inhibitors withdrawn for WRF.145 However, as patients with elevated serum creatinine were excluded and patients were younger than the epidemiological mean age, the true risk in the community may be higher. It is unclear what proportion of trial patients had ARVD or indeed whether the presence of ARVD predicts WRF when ACE-inhibitors are introduced.34 For the moment, it would seem appropriate to treat patients with heart failure and RAS with an ACE-inhibitor. If renal dysfunction develops, then trying to reduce treatments other than the ACE-inhibitor, in order to restore renal afferent arteriolar perfusion pressure, is the appropriate first response.146 If renal dysfunction continues to deteriorate the choices include renal revascularization,139,147 treatment with a combination of hydralazine and nitrates148 or withdrawal of the ACE-inhibitor. In patients with no prior diagnosis of RAS, recommendations that withdrawal of an ACE-inhibitor should occur only when the rise in creatinine exceeds 30% above baseline within the first 2 months of initiation have been made.149 However, a rise in serum creatinine that gradually improves with time is a normal haemodynamic response following the initiation of ACE-inhibitors in patients with heart failure. Successful stenting of the renal arteries may permit the use of high dose ACE-inhibitors provided renal function continues to be monitored closely150,151 though ‘prophylactic’ stenting of RAS to reduce the risk of ACE-inhibitor-induced renal dysfunction does not seem justified given the imperfect relationship between RAS and WRF.

Should we expect mortality and morbidity benefits from intervening?

WRF indicates a poorer prognosis in CHF38,39 but it is not clear that either renal function or outcome can be improved by renal revascularization either for unilateral or bilateral disease.103 The United Kingdom Medical Research Council’s ASTRAL (Angioplasty and Stent for Renal Artery Lesions) trial152 comparing revascularization (PTRA with or without stent insertion) and medical management and which includes patients with RAS requiring treatment, whether for renal dysfunction or for hypertension, may provide some answers. The study will investigate symptoms, renal and cardiac function and major morbidity and mortality and include a substantial subgroup of patients with heart failure. To date, however, there are no randomized controlled trials primarily designed to prospectively assess the outcome of renal artery revascularization in patients with significant ARVD and CHF.

Conclusion

Heart failure is a systemic disease caused by cardiac dysfunction. Sometimes the cardiac dysfunction may itself be secondary to disease in other organs, including the kidney. When cardiac dysfunction cannot be corrected, and even sometimes when it can, it is appropriate to identify other non-cardiac targets for therapeutic interventions. Successful management of heart failure requires a multidisciplinary approach making it one of the most interesting and fruitful areas of clinical research and practice. It is surprising that so little is known about the causes and management of renal dysfunction in heart failure. It is possible that ARVD plays an important role in both respects.

References


