Renal revascularization for heart failure in patients with atherosclerotic renovascular disease

Philip A. Kalra

Salford Royal Hospital, Salford, UK, and University of Manchester, Manchester, UK

Correspondence and offprint requests to: Philip A. Kalra; E-mail: Philip.kalra@srfht.nhs.uk

Elsewhere in this issue, Kane et al. [1] report the Mayo Clinic experience of patients with both atherosclerotic renovascular disease (ARVD) and heart failure, providing important insights into the epidemiology of this common disease association as well as the benefits of undertaking renal revascularization procedures in improving clinical outcomes.

All nephrologists are well aware of the high prevalence of ARVD, especially in older populations, its association with extrarenal atherosclerotic disease and its high mortality. Data from US Medicare show that patients with ARVD have an ~3-fold increased mortality compared to those Medicare recipients without the condition [2], and that over the 12-year period, 1992–2004, there was an ~4-fold increase in the diagnosis of ARVD [3], with approximately one-sixth of the patients likely to be treated with renal revascularization. Co-morbid cardiovascular disease is very common, and there is a strong association with ARVD and coronary artery disease (CAD) [4], peripheral vascular disease [5] and stroke [6]. As would be expected, heart failure is also common in patients with ARVD, although it was not systematically studied until the report provided by Kane et al. [1]. We studied this association from a different angle and our data showed that ARVD was detectable in approximately one-third of elderly patients presenting acutely to a hospital with heart failure [7]. In addition, 54% of a UK outpatient cardiac failure population had renal artery stenosis (RAS) >50% [8].

Kane et al. examined the prevalence and associations of heart failure in 163 patients with ARVD who had significant (>70%) RAS, chronic kidney disease (creatinine >2 mg/dl or 176 umol/l) and hypertension, all of whom underwent percutaneous renal revascularization [1]. Heart failure, ascertained by clinical diagnosis and the presence of Framingham heart failure criteria, was present in 31%, a figure similar to that observed in the ARVD patients within the Medicare population (37.6%) [2]. Interestingly, although clinical CAD was evident in approximately 70% of patients, echocardiography showed that left ventricular (LV) systolic function was relatively well preserved in the ARVD patients with heart failure, and in those without [LV ejection fraction (LVEF) 47% and 55%, respectively]. However, those with heart failure had a greater left ventricular mass index (LVMI; 130 vs. 112 g/m²), a higher prevalence of moderate or severe diastolic dysfunction (93% vs. 46%) and higher filling pressures than those without heart failure. Although no coronary angiographic validation was available, the authors reasonably speculated that the high rate of diastolic heart failure in the patients was likely to have resulted from the long-standing or severe hypertension which invariably was present. The presence of these echocardiographic abnormalities and of the clinical heart failure diagnosis was associated with a 2.9 increased risk of mortality compared to patients without heart failure, with 1- and 5-year mortality being 23% vs. 8%, and 73% vs. 35%, respectively, and heart failure conferred a doubling of the risk of progressing to end-stage renal disease (ESRD). The only systematic echocardiographic studies in ARVD have been performed by our own group, and these showed similar results; Wright et al. prospectively studied 79 ARVD patients and compared the findings with 50 patients with CKD from other causes, both groups having similar estimated glomerular filtration rate (eGFR) (36 ml/min) and blood pressure control [9]. The prevalence of LV hypertrophy was almost twice as great in the ARVD patients, of whom only 5% were found to have structurally normal hearts, and increased LVMI, parameters of diastolic dysfunction and LV volume overload were all more frequent in the ARVD group than in the control CKD patients. A longitudinal study of a subgroup of these ARVD patients showed that the cardiac changes worsened over time, but very few of them received revascularization therapy [10].

So what is the evidence that revascularizing patients with heart failure associated with RAS actually leads to clinical improvement? Current guidance from the American College of Cardiology (ACC)/American Heart Association (AHA) is that recurrent and unexplained heart failure and/or sudden onset of pulmonary oedema in the presence of haemodynamically significant RAS is a class I indication for revascularization therapy [11]. However, the evidence upon which this recommendation is based is largely derived from expert opinion and assimilation of the outcomes of small uncontrolled case series that show an overall improvement in various clinical outcomes with intervention (see Table 1, adapted from de Silva et al., [12]) [13–20]. To summarize the study results, the four studies, which concerned patients presenting with acute, presumably sometimes ‘flash’, pulmonary
Table 1. Reports of renal revascularization for CCF and/or acute pulmonary oedema in the presence of RAS (adapted from de Silva et al. [12])

<table>
<thead>
<tr>
<th>Authors and year of publication</th>
<th>Number of cases</th>
<th>Acute or chronic heart failure presentation</th>
<th>CAD</th>
<th>Left ventricular systolic dysfunction</th>
<th>RAS degree</th>
<th>CCF end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weatherford et al. 1997 [14]</td>
<td>5</td>
<td>Acute</td>
<td>Yes 2/5</td>
<td>No</td>
<td>1 severe bilateral, 4 severe unilateral to SFK</td>
<td>No APO over mean follow-up 57 months</td>
</tr>
<tr>
<td>Messina et al. 1992 [15]</td>
<td>17</td>
<td>Acute</td>
<td>Yes 11/17</td>
<td>Yes 6/17</td>
<td>Severe bilateral</td>
<td>No APO over mean follow-up 2.4 years</td>
</tr>
<tr>
<td>Pickering et al. 1988 [16]</td>
<td>11</td>
<td>Acute</td>
<td>Yes 5/11</td>
<td>No</td>
<td>7 bilateral, 2 unilateral to SFK, 2 unilateral</td>
<td>10/11 no further APO</td>
</tr>
<tr>
<td>Missouris et al. 2000 [17]</td>
<td>9</td>
<td>Chronic</td>
<td>Unknown</td>
<td>Unknown</td>
<td>4 severe bilateral, 5 severe unilateral</td>
<td>Echo normalized in one, free from heart failure in other</td>
</tr>
<tr>
<td>Khosla et al. 1997 [18]</td>
<td>28</td>
<td>Chronic</td>
<td>Yes 24/28</td>
<td>Yes 22/28</td>
<td>&gt;70% stenosis, 8 unilateral, 20 bilateral</td>
<td>16/28 improvement in NYHA class</td>
</tr>
<tr>
<td>Meissner et al. 1988 [19]</td>
<td>6</td>
<td>Chronic</td>
<td>Yes</td>
<td>Yes</td>
<td>Severe bilateral or unilateral to SFK</td>
<td>Undefined clinical improvement</td>
</tr>
</tbody>
</table>

The study of Kane et al. also has significant limitations with its retrospective and non-randomized design, but the comparison of outcomes between the 50 RAS patients with heart failure treated with revascularization and those of a one-to-one matched conservatively managed ARVD and heart failure ‘control’ group who had similar renal function, RAS severity, co-morbidity and heart failure severity does provide more systematic evidence suggestive of benefit [1]. Over follow-up, the revascularized patients had significantly better systolic blood pressure (decreased by 28 vs. 9 mm Hg) and heart failure control, with a 5-fold reduction in hospitalizations and reduced NYHA class (1.9 vs. 2.6). However, this did not translate into a survival advantage as mortality was not improved. This was also the case for the rate of decline of renal function and progression to ESRD, although significantly more revascularized patients (13 vs. 4) had a clinically worthwhile improvement in renal function during follow-up. It needs to be emphasized that, although not categorically stated, the heart failure diagnosis within the cohort of Kane et al. was most likely to be CHF, and not acute and/or recurrent pulmonary oedema, as all patients undergoing revascularization did so because of ACC/AHA class IIa indications (accelerated or resistant hypertension or ischaemic nephropathy, in the setting of bilateral significant RAS or RAS in a solitary kidney).

What can we conclude from these new findings, and what are the implications for the management of patients with RAS and CHF? Heart failure confers a poor outcome in all patient groups and not just ARVD, but the absence of a survival and overall renal functional benefit accompanying revascularization in this CHF cohort should not be surprising, especially in view of the limited study design, but also the extensive cardiovascular co-morbidities suffered by ARVD patients. In the recently published ASTRAL trial [21], in which 806 patients with anatomically significant ARVD were randomized equally between renal revascularization/medical therapy and medical therapy, revascularization was not associated with an improvement in renal function (the primary end-point) or blood pressure, cardiovascular events or survival. Although data regarding heart failure were not collected, almost half of the ASTRAL population had a prior clinical diagnosis of CAD. A cardiac substudy [22], which compares the cardiac structural and functional changes accompanying revascularization with those in medically treated patients, is due to report soon and should provide important insights regarding the effects of renal revascularization upon the heart. However, very few, if any, of these patients will have been entered into ASTRAL primarily because of heart failure. The CORAL study [23], which is due to finish recruitment at the end of 2009, is also unlikely to shed more light on the impact of revascularization in patients with heart failure as this co-morbidity was not a major part of the study design. Despite the results of ASTRAL, and of the four other previous but smaller randomized controlled trials (RCT) that essentially showed no benefit from revascularization in ARVD...
[24–27], there seems little doubt that specific subgroups of patients do benefit substantially from renal revascularization, and some patients with CHF may well fall into this category. The case for a RCT in patients with RAS and acute and/or recurrent pulmonary oedema, which can be life-threatening, appears rather limited on disease severity and ethical grounds. However, there is every reason to undertake an adequately powered RCT investigating whether renal revascularization improves survival, hospitalization and renal functional outcomes in patients presenting with clinical CHF in the setting of haemodynamically significant ARVD. Such a study should include assessments of cardiac structure and function, and also of the neuro-humoral axis, in order to further investigate the complex interplay between heart and kidneys, and to determine the characteristics of those highest-risk ARVD patients most likely to benefit from a treatment that is not without complications.

Conflict of interest statement. None declared.

References


Received for publication: 17.11.09; Accepted in revised form: 12.1.10