

## The heart in atherosclerotic renovascular disease

Darren Green<sup>1</sup>, Philip A Kalra<sup>1</sup>

<sup>1</sup>Salford Royal Hospital, Stott Lane, M6 8HD, UK

### TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Epidemiology
4. Cardiac structure and function in ARVD
  - 4.1. Pathophysiology of myocardial remodeling in ARVD
5. "Flash" pulmonary oedema
  - 5.1. Pathophysiology of acute decompensated heart failure in ARVD
  - 5.2. Neurohormonal dysregulation in acute cardiac failure
6. Cardiovascular effects of renal artery revascularisation
  - 6.1. Hypertension
  - 6.2. Heart failure
  - 6.3. Cardiac Remodelling
7. Conclusion
8. References

## 1. ABSTRACT

Atherosclerotic renovascular disease (ARVD) is associated with a high rate of cardiovascular disease and mortality. ARVD is an independent risk factor for adverse outcome in coronary artery disease and there is a correlation between the presence of ARVD and severity of cardiovascular disease. ARVD is the most common cause of secondary hypertension and can be found in up to half of elderly patients with chronic heart failure. Abnormal cardiac structure and / or function will be present in 95% of ARVD patients, with left ventricular hypertrophy (LVH) and diastolic dysfunction the predominant abnormalities. These are likely to be due in part to over-activity of the renin-angiotensin pathway. Up to now, randomised trials have shown no benefit of renal artery revascularisation over medical therapy in terms of cardiovascular events but small case series clearly demonstrate situations where cardiac structure and function respond to revascularisation. Future strategies must focus on accurately identifying sub-groups of ARVD patients for whom revascularisation should be first line therapy.

## 2. INTRODUCTION

Atherosclerotic renovascular disease (ARVD) is associated with a poor cardiovascular outcome and an overall mortality rate 2.6 times higher than the similarly aged general Medicare population [1]. The incident rate of ARVD in this general population is approximately 3.7 per 1000 patient years seems low. ARVD co-exists with extensive generalised atheromatous disease affecting other major vascular branches. It is associated with abnormalities of cardiovascular structure and function and is an independent predictor of adverse cardiovascular outcome in the presence of other vascular disease. The purpose of this review is to outline the epidemiology of ARVD in relation to cardiovascular disease, to discuss how ARVD can invoke changes in cardiac morphology, and to review whether renal artery intervention can improve cardiovascular outcome.

## 3. EPIDEMIOLOGY

At the time of diagnosis, patients with ARVD have a higher prevalence of hypertension (Hazard ratio

## The heart in ARVD

**Table 1.** Cardiovascular event rate in ARVD compared to the 'general' population in Medicare

|               | Event rate (per 1000 patient years) |                    |
|---------------|-------------------------------------|--------------------|
|               | ARVD                                | General population |
| CAD           | 304                                 | 74                 |
| Heart failure | 259                                 | 52                 |
| Death         | 166                                 | 63                 |

Adapted with permission from (2)

**Table 2.** Comparison of structural and functional abnormalities in CKD patients with and without ARVD.

|                                  | ARVD   |        | P <sup>a</sup> |
|----------------------------------|--------|--------|----------------|
|                                  | No     | Yes    |                |
| Age (years)                      | 69±7   | 71±7   | 0.2            |
| Male (%)                         | 62.0   | 58.2   | 0.9            |
| Diabetes (%)                     | 30.0   | 24.1   | 0.7            |
| CAD (%)                          | 22.0   | 32.9   | 0.4            |
| eGFR (mL/min)                    | 33±16  | 36±19  | 0.8            |
| LVMI (g/m <sup>2</sup> )         | 116±33 | 183±74 | <0.001         |
| LVEF <sup>b</sup> (%)            | 57±12  | 53±12  | 0.16           |
| DD                               | 12.0   | 40.5   | 0.001          |
| LVEDV index (mL/m <sup>2</sup> ) | 34±16  | 82±35  | <0.001         |

Adapted with permission from (8) (a = adjusted for age, gender, eGFR, BP, anaemia and co-morbidities, b = measured by Simpson's method, DD = diastolic dysfunction defined as 2 or more abnormal of E:A, IVRT and EDT)

[HR] = 2.42), coronary artery disease (HR 1.70) and other macrovascular diseases than Medicare patients of similar age (1). Other investigators have shown that as many as 45% of cases of ARVD will have co-existent coronary artery disease (CAD) (2) and 90% will have hypertension (3). These data are summarised in Table 1.

ARVD is said to be the cause of hypertension in up to 2% of cases. It is the most common cause of secondary hypertension and is also likely to exacerbate essential hypertension. There are no refs for this. Furthermore, ARVD is a very common underlying precipitant or concurrent finding in cardiovascular disease. 15% of patients undergoing diagnostic coronary artery angiography will have ≥50% stenosis in one or both renal arteries and patients with ARVD are more likely to have multiple-vessel CAD (4). CAD and ARVD have a common underlying pathology and so their co-existence is not surprising. What is noteworthy however is that the presence of ARVD is an independent predictor of adverse outcome in angiographically proven CAD. Four year survival with CAD is 65% in the presence of ARVD compared to 86% in patients without ARVD and risk increases with increasing severity of degree of renal artery stenosis (RAS). Patients with ≥95% renal stenosis suffer the greatest cardiovascular burden and those with bilateral disease fare worse than those with unilateral disease (5).

ARVD is a common finding in chronic heart failure (CHF). 54% of patients in an outpatient heart failure setting with left ventricular ejection fraction <40% have RAS. The presence of ARVD is associated with a greater rate of hospitalisation and higher mortality compared to those CHF patients without ARVD (Hazard ratio for mortality in ARVD = 2.99, 95% CI 1.17 to 7.54, p = 0.022)(6). Conversely, the clinical heart failure diagnosis in patients with ARVD increases risk of mortality of these already high-risk patients by almost 3 fold (7).

## 4. CARDIAC STRUCTURE AND FUNCTION IN ARVD

ARVD is associated with major cardiac abnormalities. In a cross-sectional study of 79 patients with ARVD (age = 70.7 ± 7.5 years, eGFR = 36 ± 19 mL/min, mean arterial pressure = 96 ± 14 mmHg), Wright *et al* described the pattern of structural cardiac abnormalities as found on echocardiography (8). Only 4 patients (5%) had a structurally normal heart, though overall left ventricular (LV) systolic function was surprisingly well preserved in a population with such a pronounced cardiovascular risk (mean LV ejection fraction = 53%). Regional wall motion abnormalities were found in 59.5% and LV hypertrophy (LVH) in 78.5%. Diastolic function was abnormal in 74.6% when defined as an abnormality of any of mitral E:A reversal, E wave deceleration time (EDT) or isovolumetric relaxation time (IVRT). All three were abnormal in 10% of patients. These findings are summarised in Table 2 alongside a control group of patients with chronic kidney disease (CKD) from other causes matched for age and estimated glomerular filtration rate (eGFR) just say (Table 2). In a prospective study, repeat echocardiography was undertaken at 12 months with management of the ARVD being determined by clinical need (what is 'clinical need' in a condition with no objectively defined criteria for intervention?). Compared to baseline there was no significant difference in either LV mass or function at 12 months but a significant increase in LV dilatation was noted. This latter finding was, however, significantly correlated with a fall in eGFR over the same period and may therefore be a reflection of CKD rather than ARVD (9).

Kane *et al* undertook echocardiography on 163 patients referred for revascularisation of ARVD and divided the group into those with clinical heart failure (ascertained by clinical diagnosis and the presence of

Framingham heart failure criteria; 31%) and those without. Although clinical CAD was evident in approximately 70% of all patients they found that LV systolic function was not significantly worse in the heart failure group (LV ejection fraction 47% compared to 55% in non-heart failure patients), but that there was a greater level of LV hypertrophy (LV mass index (LVMI) 130 vs. 112 g/m<sup>2</sup>), diastolic dysfunction and LV dilatation among the patients with CHF (7). There is evidence that increase in LV mass predisposes to development of CHF in CKD from any cause, and this has been shown in a dialysis cohort by Foley *et al* (10). Like the Kane *et al* study, Wright *et al* demonstrated that morphological changes are independent of blood pressure (BP), there being no significant difference in blood pressure between the study and control groups (8). However, this observation needs to be interpreted with caution as neither study examined the possible impact of previous duration or severity of hypertension or of anti-hypertensive treatments.

In the general population, 91% of patients who develop heart failure will have a preceding diagnosis of hypertension (11). In determining whether hypertension is the primary cause of heart failure in ARVD, Zeller *et al* compared LV mass index (LVMI) in ARVD patients with an age-matched group with essential hypertension (12). Despite a lower blood pressure in the ARVD group (mean arterial pressure, ARVD = 99 mmHg, 95% CI: 97 to 101, Essential hypertension = 102mmHg, CI: 99 to 105. P = 0.04) there was a significantly greater LVMI in these patients (ARVD = 136g/m<sup>2</sup> [129 to 143], essential hypertension 117 g/m<sup>2</sup> [111 to 124], p = 0.001). This indicates that hypertension alone does not explain the cardiovascular structural changes seen in ARVD. This is likely to be at least in part due to over-activation of the renin-angiotensin-aldosterone system (RAAS)(13) as discussed in the following paragraphs – say it later when the argument is expanded.

### 4.1. Pathophysiology of myocardial remodeling in ARVD

There is some evidence for a role of neurohormonal activation in the evolution of cardiovascular changes in ARVD. As early as 1934 the role of renal ischaemia in the development of hypertension was described (14) and the full RAAS system was understood by the mid 1970s (15), with the systemic effect of RAAS over-activity in ARVD, particularly that of angiotensin II, being clarified. Angiotensin II is a potent systemic vasoconstrictor, leading to LVH. It also increases production of pro-inflammatory cytokines, notably fibroblast growth factor (FGF), platelet-derived growth factor (PDGF) and transforming growth factor-beta<sub>1</sub> (TGF-β<sub>1</sub>). These are associated with myocyte fibrosis causing abnormal cardiac remodelling, but they also lead to vascular endothelial dysfunction and risk of CAD.

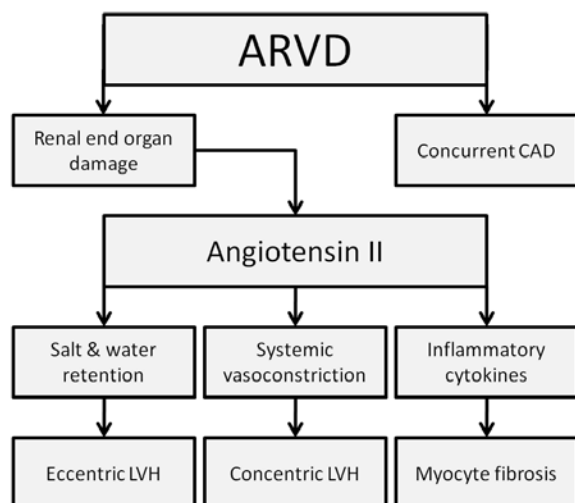
CKD itself is associated with both neurohormonal activation and the development of LVH, independent of underlying cause. This has been demonstrated in an ARVD population in which the presence of eccentric LVH was associated with reduced

GFR (16). Hence, abnormal cardiac remodelling in ARVD can be viewed as an accelerated process exacerbated both by the underlying pathology but also by renal end organ damage. Add in the effects of hypertension with increased afterload induced concentric LVH, as well as eccentric LVH associated with volume overload, then it is clear why patients with ARVD have 58% greater LVMI than matched non-renalovascular CKD patients (8).

What is unclear is where the point lies at which the degree of RAS becomes clinically significant. Though it is likely to vary from patient to patient, studies will most often use 50% and 75% luminal narrowing as cut of points when defining ARVD. This point is demonstrated in 2 studies by Conlon *et al* in which hypertension was shown to be associated with ARVD when defined as luminal narrowing of ≥75% but not ≥50% (5, 17). In a dog model of renal artery stenosis (RAS) using inflatable cuffs, mean flow and pressure gradient across the stenosis were measured at varying degrees of stenosis. Stenosis between 30% and 80% had some effect on early but not mid-systolic peak flow and stenosis of >90% was required before a significant drop in mid-systolic flow was observed. This change was abrupt however, with a shift from 80 – 90% stenosis being associated with a fall from no haemodynamic change in flow to a 50% flow rate reduction (18). This would suggest that only near occlusive disease should be associated with significant cardiovascular morbidity split all this up, sentences are too long and hard to read. but the echocardiographic data from Wright *et al* above shows that this is not the case and the work by Conlon *et al* shows that hypertension is present at lesser degrees of stenosis (5, 8). However, caution should again be used with interpretation of the animal data. The kidneys beyond the RAS in the canine model will have been healthy, which is rarely the case in ARVD, in which kidneys usually have been injured by prior hypertension, atheroma and ischaemic insults. Hence, the haemodynamic effects of a given RAS in the two situations may well be different, as the co-existence of CKD in human RAS will have an effect upon intra-renal resistance. Figure 1 gives a simplified schematic of the possible interaction of factors in abnormal cardiac remodelling in ARVD.

## 5. “FLASH” PULMONARY OEDEMA

The term “flash pulmonary oedema” (FPO) has become synonymous (insert the word WRONGLY ?) with the occurrence of acute decompensated heart failure in patients with or subsequently found to have ARVD. Don’t agree - it can occur in the absence of ARVD, and can also be caused by transient cardiac ischaemia – with or without chest pain. Approximately 5-10% of all ARVD presentations are thought to be with this condition. (what evidence ?) Previously unpublished data from our own database supports this with 7.1% of 621 consecutive ARVD cases having acute pulmonary oedema as the presenting symptom. The characteristic phenotype is one of bilateral RAS or RAS with renal artery occlusion (RAO) in patients with stiff and hypertrophied left ventricles. In one early epidemiological study, 13 of 55 ARVD patients undergoing revascularisation had a history of recurrent



**Figure 1.** Schematic representation of factors that may interact in producing abnormal myocardial remodelling in ARVD.

pulmonary oedema, of whom 12 had bilateral disease (19). This finding was mirrored in a later cohort study of 90 patients undergoing renal artery angioplasty in which 23 of 27 patients with a history of pulmonary oedema had bilateral disease (20). In contrast, of 94 consecutive patients diagnosed with ARVD (but not necessarily undergoing angioplasty) in a third study, there was no difference in the prevalent rate of recurrent pulmonary oedema between bilateral and unilateral disease (7% and 5% respectively) in patients presenting with non-occlusive ARVD. However, in the same study recurrent pulmonary oedema was present in 41% of patients with occlusive disease of one or both renal arteries (21). Although the relationship between flash pulmonary oedema and RAS is thought to be due to the neurohumoral effects and impaired natriuresis caused by the latter, we also know that patients with more severe ARVD also have more severe CAD, which is the most common cause of heart failure in the general population.

### 5.1. Pathophysiology of acute decompensated heart failure in ARVD

What would seem to differentiate flash pulmonary oedema from decompensated heart failure in other settings is the apparent rapidity of onset. However, this temporal data is only anecdotal and many of the early studies from which the rationale for renal revascularization for flash pulmonary oedema has been derived actually describe “recurrent” or “acute” pulmonary oedema. Indeed, the only clear distinction in the relationship between ARVD and heart failure is that of chronic and decompensated events. A globally accepted definition of FPO has never made its way into mainstream clinical practice and so use of the term may be redundant. Furthermore, acute decompensated and de novo heart failure events may present more rapidly in any patient if precipitated or confounded by myocardial ischaemia, mitral valve disease or arrhythmia (as said above). The fact that coronary ischaemia and structural heart disease are particularly highly prevalent in patients with ARVD may

partly explain why they are prone to acute pulmonary oedema. In a cohort of 86 elderly patients (>70 years) admitted to hospital with heart failure, 33.7% had evidence of ARVD on magnetic resonance imaging of the renal arteries (22). The patient characteristics from this study are summarised in Table 3. In contrast to the study by Wright *et al* (Table 2) which examined the hearts of an ARVD population regardless of presenting illness (8), the patients found to have ARVD and heart failure by MacDowell *et al* had severe LV dysfunction, a very high rate of CAD, but less pronounced hypertension (perhaps in part due to the poor LV function in this group). However, in the latter study there was no difference in these characteristics between heart failure patients with and without ARVD, suggesting that heart failure in ARVD is largely caused by the same pathological precipitants as in the general population as a whole. Given the propensity for hypertension and CAD in patients with ARVD we should perhaps not be surprised by this.

### 5.2. Neurohormonal dysregulation in acute cardiac failure

Neurohormonal dysregulation provides a further explanation for why ARVD itself may precipitate heart failure and PFOpo. As already mentioned ARVD is associated with increased circulating levels of RAAS hormones. In a dog experimental model, Lohmeier *et al* infused physiological and supra-physiological amounts of Angiotensin 2 into animals with pacing induced heart failure (23). They found that salt and water retention and drinking was significantly increased in animals treated with supra-physiological therapy compared to control animals and those receiving physiological doses of angiotensin 2. They also had a disproportionate increase of sympathetic activation as assessed by plasma noradrenaline levels. However, there was no noteworthy effect on renal haemodynamics compared to control dogs. There are case reports which probably reflect similar neurohormonal effects in clinical practice, for example, those patients who present with rapid onset hypertensive heart failure in pheochromocytoma (24). An earlier experimental model, also in dogs, had used implanted modifiable occlusive aortic balloons to vary renal artery pressure, thereby mimicking the haemodynamic effects of RAS. By semi-occluding the renal arteries to reduce renal artery pressure, and infusing angiotensin 2, the authors were able to cause salt and water retention to the point of pulmonary oedema in some dogs. Upon release of the occlusion, renal artery pressure was able to rise to systemic levels and a natriuresis occurred with relief of the pulmonary oedema (25). What this series of experiments tells us is that there is both a theoretical causative pathway from RAS to acute decompensated heart failure, and also a reduced ability of the ischaemic kidney to respond with necessary homeostatic changes to relieve the effects of heart failure. Hence, ARVD may independently cause and / or exacerbate heart failure in patients who are already at high risk of cardiac failure. The animal models also provide an insight into why renal revascularization can bring dramatic relief from heart failure in humans with atherosclerotic RAS (26).

**Table 3.** Comparison of baseline characteristics in heart failure patients with and without ARVD

|                           | ARVD   |        | P      |
|---------------------------|--------|--------|--------|
|                           | No     | Yes    |        |
| Age (years)               | 77±5   | 80±6   | <0.01  |
| Male (%)                  | 56     | 41     | 0.3    |
| Cause of HF CAD (%)       | 77     | 72     | 0.8    |
| Hypertension (%)          | 19     | 24     | 0.8    |
| Serum creatinine (μmol/L) | 136±40 | 201±56 | <0.001 |
| Hypertension (%)          | 32     | 35     | 0.98   |
| LVEF <sup>a</sup> (%)     | 30±15  | 28±13  | 0.6    |

Adapted with permission from (22) (a = method of assessment not defined).

## 6. CARDIOVASCULAR EFFECTS OF RENAL ARTERY REVASCULARISATION

There have now been 5 published randomised control trials (RCTs) that have examined the clinical effects of renal revascularization in patients with ARVD (27-31). None of these have shown any significant benefit to accompany intervention in terms of blood pressure control, improvement of renal function, cardiovascular events or mortality. However, this data must be considered in the light of the clinical characteristics of patients entered into the trials – very few patients would have been entered on the basis of having cardiac failure together with RAS. There have been several case reports and case series demonstrating that revascularization is beneficial for patients with heart failure, particularly those with acute heart failure or pulmonary oedema (19, 20, 32-34), but these publications are inevitably limited by positive reporting bias. Despite this, current guidelines in a collaborative report from the American College of Cardiology and American Heart Association state that revascularization is indicated for cardiovascular reasons when patients with haemodynamically significant RAS present with malignant, refractory or accelerated hypertension, recurrent, unexplained congestive heart failure or sudden, unexplained pulmonary oedema or unstable angina (35).

### 6.1. Hypertension

The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial randomized 806 patients with ARVD to receive either medical therapy alone or medical therapy plus revascularization. This study found that both medically managed patients and those who underwent intervention had a significant improvement in blood pressure control during the five year follow up period. There was no difference in blood pressure control between the two arms (31). The three earliest RCTs showed that both medical therapy and intervention were associated with an improvement in blood pressure control (27-29). However, a meta-analysis of these RCTs suggested that the degree of systolic blood pressure control may have been better in the intervention arm (blood pressure reduction intervention = 6.3mmHg vs. medical therapy = 3.3mmHg,  $p = 0.02$ ,  $n = 210$ ) (36), and the greatest difference was noted in patients with bilateral RAS in one of the studies (27). The difference between patients recruited into these studies and those in ASTRAL is that in the meta-analysis the patients were specifically those with ARVD and poorly

controlled hypertension compared to the unselected and more clinically heterogeneous ARVD population found in ASTRAL.

These findings were also supported by a non-randomised observational study involving two centres, one in Germany the other in the UK. The German centre revascularised all ARVD patients with Doppler assessed haemodynamically significant RAS, whereas the other centre used medical therapy only unless revascularisation was indicated according to the above guidelines (which ones?). No difference in blood pressure control was observed between the two groups (37).

Although this data suggests little clinical benefit to blood pressure control should be anticipated with revascularization, it is again important to consider the enrolled population. None of these studies set out to examine patients with accelerated or extremely severe hypertension, and well-designed studies in these sub-populations are lacking. Structure of paragraph should separate results and conclusions more clearly.

### 6.2. Heart failure

Pickering *et al* were the first group to describe the effective use of revascularisation to treat acute pulmonary oedema associated with ARVD. They describe a case series of 11 such patients in whom 10 suffered no further episodes of pulmonary oedema after intervention. Ten of the 11 patients had “diffuse severe atherosclerotic disease” and although the follow up period ranged from 8 to 78 months with a mean of 28 month there was no mortality data in this study. Furthermore, there was no control group of aggressive medical therapy (20). However, this study has become a landmark in management of RAS which heralded a trend for such case series to be published. There have been 9 further case series published of ≥ 5 patients. Four include patients with ARVD and CHF (33, 38-40), two include ARVD patients with acute pulmonary oedema (APO) (32, 41), and three refer to patients with either CHF or APO (7, 19, 34). There are 16 further small case series (<5 patients) or individual case reports. All of these studies report a trend towards clinical improvement after revascularisation, be it improvement in NYHA class or a reduction in hospitalisation for either CHF or APO (26, 42). Two of the larger case series also indicate an improvement in angina symptoms in patients with unstable CAD (19, 39). While the anecdotal evidence is persuasive in this subgroup, there is no controlled data.

## The heart in ARVD

A secondary end-point of ASTRAL was major cardiovascular events which included heart failure and fluid overload as well as myocardial infarction, cerebrovascular accident and cardiovascular death. Worth explaining that patients with prior severe acute heart failure were probably not randomised into ASTRAL – because of the preconception of benefit. There was no difference in cardiovascular outcome between the medical treated and revascularised patients (31). The unselected nature of large randomised trials does not mean that their findings can be extrapolated down to the level of all individual subjects, and small sub-groups who benefit from treatment can usually be identified. Though post-hoc analysis is of limited value, further sub-group analysis of heart failure in ASTRAL may shed further light on the question of who to revascularise, or at least guide the design of further randomised trials.

Kane *et al* compared outcome in 100 ARVD patients with heart failure, half of whom had undergone revascularisation, the other 50 being matched and treated medically. This was not a randomised study, but a retrospective cohort study. The revascularised group were younger (74±8 years vs. 78±7 years,  $p = <0.01$ ) but otherwise there was no difference in co-morbidities, hypertension, NYHA class, or echocardiographic parameters. The rationale for referral for revascularisation is therefore unclear, but the authors state that no cases were referred for heart failure alone. There was no difference in survival between the two groups and both groups showed an overall improvement in New York Heart Association (NYHA) class of heart failure. Patients who were revascularised did fare better in having a longer time to first hospital admission for heart failure and having a greater proportion of patients improve to NYHA class I or II CHF compared to the medically managed group. What this study tells us is that there is some benefit to revascularisation in some patients with both ARVD and CHF, but it does not delineate clearly who these patients are (7). Since it is all retrospective this tells us nothing applicable, and this should be said plainly.

In an early case series of 9 ARVD patients with hypertension and heart failure, all underwent renal revascularisation without concurrent changes in medical therapy. After revascularisation, there was a profound natriuresis, with a mean weight loss of 3.6kg in the 7 days after revascularisation. Alongside this, atrial natriuretic peptide levels fell, renal function and blood pressure improved and no patient had any symptoms of heart failure at an undefined “long term follow up” end point. This pattern seems to mimic exactly that seen in the dog models of ARVD that were described in an earlier section. However, yet again the rationale for intervention in these patients is not enunciated (33). Would this be better placed in 6.1 or 4.1 as an illustration of the relevance of the neurohumoral relationship?

### 6.3. Cardiac remodelling

Two studies have described changes in cardiac morphology following renal artery revascularisation, but neither were RCTs. Zeller *et al* showed an improvement in

LVMI of  $10\text{g/m}^2$  at a mean follow up of 24 months in 102 ARVD patients. This was compared to a group of 101 non-ARVD CKD controls with hypertension (mean baseline creatinine: ARVD group 1.46 mg/dL, control 1.01 mg/dL). In the control group there was an increase in LVMI of  $9\text{g/m}^2$  over the same period (12). Zeller However, the suitability of this control group can be questioned given that the likelihood that the pathophysiology of cardiac structural changes in ARVD may be different to that in other hypertensive CKD patients.

The second study undertook echocardiography at baseline and a mean of 7.7 months following revascularisation in 20 ARVD patients. They measured LV systolic and diastolic function as well as LV mass. They too found that there was a statistically significant improvement in LVMI after revascularisation, but no difference in cardiac function, and there was no control group (43).

Neither of these studies specified whether these improvements were independent of simultaneous or ongoing changes in concurrent medical therapy. Although these appear to be important reductions in LV mass, verification in studies including an appropriate control group is necessary, and two RCTs are due to report shortly, as will be described below. Chrysochou *et al* described the outcome of a single patient diagnosed with bilateral ARVD prior to elective coronary artery bypass grafting (CABG). He underwent pre-operative percutaneous renal artery revascularisation to minimise risk of peri-operative acute kidney injury. The patient underwent repeat echocardiography 8 weeks after revascularisation, but pre-operative to the CABG, having had no changes to medical therapy and with no change in blood pressure since revascularisation. A profound change in LV diastolic function had occurred over this short period. (echocardiography findings pre vs. post-revascularisation: Mitral E:A = 2.1 vs. 1.3, EDT = 111ms vs. 176ms, mitral E:E' = 18 vs. 10) (26). These reports all highlight an important link between renal and cardiac physiology in ARVD, and the case report shows that there are cases where improvement occurs after revascularisation which is independent of medical therapy and blood pressure. Theoretically these improvements must have been related to beneficial alterations in the neurohumoral profile of the patient, but this was not assessed in that case. In these non-trial scenarios we also do not know what the effect of aggressive medical therapy dose titration compared to intervention would have been, again highlighting the importance of control groups.

There are two RCTs which have investigated the change in cardiovascular morphology or heart failure symptoms in ARVD, and these are due to report soon. The ASTRAL Heart sub-study, which undertook baseline and follow up echocardiography, cardiac magnetic resonance imaging and ambulatory blood pressure measurements in a cohort of patients from the main ASTRAL study, is due to report its findings in 2011(44). The RASCAD study (stenting of renal artery stenosis in coronary artery disease) randomised patients found to have ARVD during coronary

## The heart in ARVD

angiography to either medical therapy or medical therapy plus renal artery revascularization. The primary end-point examines progression of LV mass (45). An interim analysis of RASCAD has been released which actually showed comparable regression of LVMI between revascularised (n=35) and medically treated (n=38) patients ( $\delta$ LVMI = -4.9% Vs. -4.1% respectively, p=not significant). However, the full study was designed to show a 20% difference in LV mass on echocardiography between the groups and baseline power calculations suggested a cohort of 168 patients was required, so the study is currently underpowered (46).

## 7. CONCLUSION

Though there is some discordance between the studies discussed, what is emerging is a general picture of the heart in ARVD. These patients have a high rate of cardiovascular co-morbidities, namely CAD, hypertension and heart failure. These occur in the setting of LVH and poor diastolic function. Those at highest risk of cardiovascular mortality and hospitalisation with heart failure are those with poor LV systolic function and CAD, a pattern comparable to the general population. However, there also seems to be a specific sub-group of ARVD patients whose morbidity is driven in part by neurohormonal over-activation. It is unlikely that many patients with ARVD who develop acute decompensated heart failure will do so solely because of hypertension or CAD or diastolic dysfunction. Rather, each of these factors is so highly prevalent and occurs in the setting of abnormal neurohormonal activity that an interaction between them is likely to interplay in causing acute cardiovascular illness in ARVD.

Randomised trials have, up to now, shown only that the ARVD population as a whole do not benefit from revascularisation over medical therapy in terms of cardiovascular events. However, animal models and small case series have demonstrated a definite benefit of renal artery revascularisation in some circumstances. Up to now, there have been no studies specifically aimed at stratifying risk and identifying sub-groups of ARVD patients for whom revascularisation is clearly beneficial. The biggest problem that we face is trying to develop a study which can accommodate all the pathophysiological factors involved. Hence, although consensus guidelines do suggest that revascularization should be performed in certain high-risk cardiovascular ARVD phenotypes, there is, for now, no level 1 evidence to support them.

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**Abbreviations:** ARVD: atherosclerotic renovascular disease; HR: Hazard ratio; CAD: coronary artery disease ; RAS: renal artery stenosis; CHF: chronic heart failure; LV: left ventricular (LV) LVH: Left ventricular hypertrophy; FGF: fibroblast growth factor; PDGF: platelet-derived growth factor; TGF- $\beta_1$ : transforming growth factor-beta<sub>1</sub>; RAS: renal artery stenosis; EDT: E wave deceleration time; IVRT: isovolumetric relaxation time; LVMI: LV mass index; RAAS: renin-angiotensin-aldosterone system; RCT: randomised control trial; ASTRAL: the angioplasty and stenting for renal artery lesions trial; APO: acute pulmonary oedema; RASCAD: stenting of renal artery stenosis in coronary artery disease trial; NYHA: New York Heart Association; CABG: coronary artery bypass graft.

**Key Words:** Renal Artery Stenosis, Heart Failure, Revascularisation, Pulmonary Oedema, Cardiovascular, Chronic Kidney Disease, Review

**Send correspondence to:** Philip A Kalra, Department of Renal Medicine, Salford Royal Hospital, Stott Lane, M6 8HD, UK. Tel: 441612060509, Fax: 441612065342, E-mail: philip.kalra@srft.nhs.uk

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