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DOI:

[10.1111/nep.13038](https://doi.org/10.1111/nep.13038)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Green, D., Ritchie, J. P., Chrysochou, C., & Kalra, P. A. (2017). Revascularization of Atherosclerotic Renal Artery Stenosis for Chronic Heart Failure Versus Acute Pulmonary Oedema. *Nephrology*.
<https://doi.org/10.1111/nep.13038>

Published in:

Nephrology

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Revascularization of atherosclerotic renal artery stenosis for chronic heart failure versus acute pulmonary oedema

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Running title: RAS revascularization in HF

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/nep.13038

Abstract

Aim: To determine whether the apparent benefit of revascularization of renal artery stenosis for “flash” pulmonary oedema extends to heart failure patients without a history of prior acute pulmonary oedema.

Methods: A prospective study of patients with renal artery stenosis and heart failure at a single centre between 1st January 1995 and 31st December 2010. Patients were divided into those with and without previous acute pulmonary oedema / decompensation. Survival analysis compared revascularization versus medical therapy in each group using Cox regression adjusted for age, eGFR, blood pressure, and co-morbidities.

Results: There were 152 patients: 59% male, 36% diabetic, age 70 ± 9 years, eGFR 29 ± 17 mL/min/1.73m². 52 had experienced previous acute pulmonary oedema (34%), whereas 100 had no previous acute pulmonary oedema (66%). The revascularization rate was 31% in both groups.

For heart failure without previous acute pulmonary oedema, the hazard ratio for death after revascularization compared to medical therapy was 0.76 (0.58-0.99, $p=0.04$). In heart failure with previous acute pulmonary enema, the hazard ratio was 0.73 (0.44-1.21, $p=0.22$).

For those without previous acute pulmonary oedema, the hazard ratio for heart failure hospitalization after revascularization compared to medical therapy was 1.00 (0.17-6.05, $p=1.00$). In those with previous acute pulmonary oedema, it was 0.51 (0.08–3.30, $p=0.48$).

Conclusions: The benefit of revascularization in heart failure may extend beyond the current indication of acute pulmonary oedema. However, findings derive from an observational study.

Keywords: atherosclerosis, chronic kidney disease, heart failure, hypertension, renal artery stenosis

Introduction

The co-existence of cardiac and renal disease is common, and associated with poorer prognosis¹. Fifty-five percent of chronic heart failure patients have stage 3, 4, or 5 chronic kidney disease (CKD)², and both mortality and cardiovascular events increase as estimated glomerular filtration rate (eGFR) declines. One cause of concurrent CKD in heart failure is atherosclerotic renovascular disease causing renal artery stenosis (RAS)^{3,4}. 34% of patients suffering acute decompensation of heart failure requiring hospital admission have RAS⁵, 38% of RAS patients have heart failure⁶, and 12% of all RAS diagnoses present with “flash pulmonary oedema”⁷. Flash pulmonary oedema is a poorly defined term and the clinical presentation is no different to that of acute pulmonary oedema (APO) in decompensation of heart failure in other settings⁴. Indeed, “flash” pulmonary oedema was not a term used when this phenomenon was first described in association with RAS⁸.

Animal models of RAS have demonstrated a potential causative mechanism in which renal artery ligation leads to over-activation of the renin-angiotensin pathway, and consequent salt and water retention⁹. The earliest clinical case series of revascularization of RAS as therapy for APO noted that profound weight loss of up to 4kg, due to diuresis after revascularization, was a common feature^{8,10,11}. A more recent case report found a drop in circulating angiotensin 2 levels from 0.61ng/mL before to 0.16ng/mL one day post-revascularization¹². Up to 75% of RAS patients have echocardiographic evidence of left ventricular hypertrophy, often with significant diastolic dysfunction¹³. This presents a case for RAS playing a significant role in inducing cardiac remodelling with subsequent development of heart failure, rather than the relationship being simply limited to co-incidental renal atheroma alongside ischaemic cardiomyopathy.

Although two recent randomized controlled trials (RCT) of >800 patients, as well as meta-analyses, have failed to show a benefit of renal artery revascularization over medical therapy for RAS as first line therapy in allcomers¹⁴⁻¹⁶, patients with HF were in the minority in the RCT and those with APO non-existent in at least one trial which excluded patients with a previously described indication for intervention¹⁴. Nevertheless, flash pulmonary oedema remains a documented indication for revascularization¹⁷. This is based on historical case series, and is supported by a recent observational study in which the hazard ratio for death in patients with flash pulmonary oedema undergoing revascularization was 0.4 (95% CI, 0.2-0.9; $P = 0.01$) compared to treatment with medical therapy⁷.

Whether the apparent benefit of renal artery revascularization over medical therapy extends to heart failure without APO (*i.e.* without previous acute decompensation) is uncertain, but a similar theoretical benefit of revascularization exists as that for APO. Given the high prevalence of atherosclerotic RAS in heart failure – both are diseases of ageing - this is a potentially valuable therapeutic option. In a case series of 100 patients with heart failure, RAS, and hypertension, those who underwent revascularization suffered fewer hospitalizations and lower NYHA scores than gender matched controls managed medically¹⁸. However, this study did not adjust for statistical and numerical differences in age and co-morbidities between the groups, nor whether APO was a presenting feature in any or all of the revascularized cases.

The intention of this study was to compare adjusted outcomes for renal artery revascularization versus medical therapy for RAS in the setting of heart failure, in a large prospectively collected dataset. More uniquely, patients with heart failure were sub-divided into those with and without prior APO to determine whether the benefit of revascularization for APO patients noted previously may also be seen in chronic heart failure without previous

APO. Also, phenotype data were compared between revascularized and medically managed patients to determine whether these groups were comparable.

Such a comparison is potentially viable in an observational setting because of variation in clinical practice associated with RAS management¹⁹. This is based to some extent on the lack of randomized trial data to underpin generally acknowledged indications for revascularization including “flash” pulmonary oedema, as well as hypertension and rapid decline in renal function. For example, in 2010 in the United States fewer than half the number of renal revascularization procedures for RAS were performed compared to the year 2000.

The primary aim of the study was therefore to investigate whether patients with ARVD and chronic heart failure without any previous episode of APO may benefit from renal revascularization. A secondary aim was to compare outcome and the relative impact of revascularization in ARVD-HF with and without previous APO.

Materials and Method

This was retrospective analysis of a prospectively collected observational study of adult patients with unilateral or bilateral RAS $\geq 50\%$ managed in a single nephrology secondary care centre between January 1995 and December 2010. Ethical approval was granted by the local Research Ethics Committee, and the study complied with the Declaration of Helsinki. A diagnosis of RAS was made by CT, MR or direct angiography. Non-atherosclerotic causes of RAS were excluded. Decisions to treat for both medical and revascularization groups were made by the attending physician based upon prevailing opinion (as opposed to being protocol driven), or in some cases randomization of patients into

contemporary RCT. All revascularization procedures were by angioplasty $\pm$ stenting. There were no surgical interventions.

Data were recorded for degree of stenosis (patency score), indication for revascularization, laboratory data from the date of patient entry into the study, prescribed medication at baseline, and cardiovascular co-morbidities. A diagnosis of heart failure was based on the clinical history including that of previous hospitalization, physical examination and radiographic evidence, with echocardiographic evidence of diastolic dysfunction or left ventricular ejection fraction (LVEF) $<50\%$. Diastolic dysfunction was defined as abnormalities in at least 2 of: Transmitral E:A velocities ratio; mitral flow E wave deceleration time; and isovolumetric relaxation time. APO was defined as hospitalization for acute pulmonary oedema in the presence of atherosclerotic RAS and irrespective of aetiology i.e. including decompensation of heart failure. Whether patients had previous APO events was determined from history taking, hospital medical records (ours is a secondary care centre for cardiology as well as nephrology), and primary care records where available. RAS patency score was defined as % diameter right renal artery patent + % diameter left renal artery patent, and occlusive RAS was defined as unilateral or bilateral RAS where all lesions demonstrate complete luminal occlusion.

The study start date was taken as date of first clinic visit for medically managed patients, or date of attempted revascularization. Analysis was performed on an intention to treat basis. Patients with a diagnosis of heart failure were selected for this analysis and were divided into those with and without a previous episode of APO.

End points were time to: 1) all-cause mortality; 2) hospitalization for heart failure including for APO, and; 3) fatal or non-fatal cardiovascular event (myocardial infarction, coronary revascularization, hospitalization for acute pulmonary oedema or other management of heart failure, hospitalization with arrhythmia, stroke, or non-traumatic intracranial bleed).

Comparisons of baseline patient characteristics were made using chi square tests for binary variables and unpaired t-tests for continuous variables. Survival analyses were performed using a Cox proportional hazard model, adjusted for age, eGFR, systolic blood pressure, coronary artery disease (previous myocardial infarction, coronary revascularisation or bypass, or medically managed angina), smoking, diabetes mellitus, and RAS patency score. Significance was set at $p \leq 0.05$ (2-sided).

To test the existence of selection bias for revascularization procedures in influencing outcome, we also determined the adjusted hazard ratio (HR) for mortality in patients without heart failure who had not been randomized into the ASTRAL or CORAL trials who had undergone revascularization compared to medical therapy. We then compared the HR here with data from a recent meta-analysis of mortality outcomes in revascularization versus medical therapy for RAS. This meta-analysis showed no difference in outcome between treatment arms²⁰. Therefore, any difference in outcome between treatments in non-heart failure patients in our study would likely reflect bias, whereas if our findings were consistent with those of the meta-analysis it would argue in favour of the variation in clinical practice and our statistical adjustments overcoming such bias.

Results

There were 152 heart failure patients with RAS. 59% were male, 36% diabetic, the mean age was 70 ± 9 years, eGFR 29 ± 17 mL/min/ 1.73m^2 . 52 had previous APO at presentation (34%). Comparisons with a statistical difference were as follows: patients without previous APO who were revascularized had a lower patency score than those managed medically (73 ± 50 versus 94 ± 46 , $p = 0.04$), and patients with previous APO who were revascularized were younger than those managed medically (64 ± 7 versus 72 ± 7 years, $p = 0.01$). Table 1 shows phenotype data and a full breakdown of between group comparisons for revascularization versus medical therapy in each of heart failure patients with and without previous APO.

The proportion of patients undergoing revascularization was 31% for patients with heart failure but not APO ($n=31$), and also 31% for heart failure patients with APO ($n=16$). There were 5 failed procedures (HF no APO $n=3$ [10%], HF with APO $n=2$ [13%]). For patients with heart failure but no APO, the most common indications for revascularization were hypertension (32%) and heart failure (19%). For patients with APO, the APO was the indication for revascularization in the majority. Table 2 shows a full list of primary indications for revascularization for each patient group.

The mean follow up time was 52 ± 42 months during which there were 118 deaths (78%), and 59 cardiovascular event end points (39%), of which 13 (22% of cardiovascular events) were hospitalization for heart failure. For heart failure without APO the HR for death compared to heart failure with APO was 1.91 (1.55 – 2.54, $p < 0.001$).

For heart failure patients without previous APO, the adjusted HR for death in those revascularized compared to receiving medical therapy was 0.76 (0.58 -0.99, $p = 0.04$). This was numerically similar in patients with APO (HR 0.73 [0.44 - 1.21], $p=0.22$) but non-significant. Survival curves for these data are shown in figure 1.

For patients without previous APO, the adjusted HR for future heart failure hospitalization in revascularized compared to medically treated patients was 1.00 (0.17 -6.05, $p=1.00$). For patients with previous APO the HR was 0.51 (0.08 – 3.30, $p=0.48$).

Revascularization appeared to have little impact on overall cardiovascular events outside of the numerical difference in heart failure hospitalization. For patients without previous APO, the adjusted HR for cardiovascular events in revascularized compared to medically treated patients was 0.98 (0.44 -2.18, $p=0.96$). For patients with previous APO the HR was 0.62 (0.31 - 1.27, $p=0.19$). A summary of the HR for this and other end points is shown in table 3. A breakdown of all causes of death in different patient groups and the diagnoses for cardiovascular event end points is shown in table 4. In patients without prior APO who were managed medically, 39% of patients died from cardiac causes during follow up compared with 16% in revascularized patients. In patients with prior APO, there was a similar difference of 35% versus 17%. There was no reduction in death due to other cardiovascular or non-cardiovascular causes in either of the revascularized groups. The numerical differences described did not reach statistical significance. The numerical differences described did not reach statistical significance.

In order to provide some external validation to our non-randomised observational study, the adjusted HR for all-cause mortality in revascularized patients in non-HF patients was compared with that in a previous meta-analysis²⁰. There were 459 non-heart failure RAS patients with a mean age of 70 ± 9 years. 56% were male, with eGFR 35 ± 19

mL/min/1.73m². In our study the HR was 0.92 (0.62 – 1.14, p=0.66) compared with 0.91 (0.75 – 1.11, p=0.98) in the meta-analysis.

Discussion

In this study of 152 patients with co-existent heart failure and RAS, the phenotype of patients undergoing revascularization was broadly comparable to those managed medically. This reflects the variation in practice between clinicians for such patients given that evidence for management of RAS in heart failure and APO was not based on RCT data^{17,19}, and also reflecting the long duration of this prospective study. Nonetheless, despite these similarities, the presented analyses were adjusted for demographic and co-morbid data in an attempt to minimise the effect of hidden bias in observational studies such as this. Our efforts are supported by the comparison of mortality in our non-HF patients with meta-analysis of RCT. However, the possibility of bias in HF sub-groups remains and this is the main limitation affecting interpretation. The analyses were performed in a patient group in whom detailed clinical and laboratory data have been prospectively and studiously collected over 15 years. Whilst the single centre patient management, rigor of data collection, and real-life setting are strengths, the lack of true randomization of patients for revascularization is a weakness that cannot be overcome outside of an RCT.

The key finding in this study was the significant reduction in all-cause mortality for patients with heart failure who had never had a previous presentation with APO. Table 4 demonstrates that this appears to be due to a reduction in death due to cardiac causes. However, this improved survival was not associated with an overall reduction in cardiovascular events.

In this study, all episodes of acute pulmonary oedema in the setting of co-existent RAS were considered to be comparable to “flash pulmonary oedema” described in other studies given that there is no clear diagnostic difference between “flash” and “acute” pulmonary oedema. This contrasts with our previous analysis in which the term flash pulmonary oedema excluded episodes in those patients with established severe systolic impairment⁷. In that study, patients with occlusive disease were also excluded, and revascularization was associated with a greater reduction in mortality (HR = 0.4 [0.2-0.9], $p = 0.01$) compared to the present analysis, and the mortality advantage was statistically significant. That only 31% of acute pulmonary oedema patients in this study were revascularized serves to demonstrate the differences in clinical practice associated with RAS, and the partial randomization effect this produces.

There was also a numerical reduction in hospitalization due to heart failure, specific to patients with previous APO. This is consistent with previous studies. Kane *et al* found a five-fold reduction in heart failure hospitalizations amongst 50 patients who were revascularized versus 50 gender matched medically managed controls with heart failure and RAS¹⁸. However, in that study, there was no difference in mortality between arms. Another small RCT has shown reduction in left ventricular mass after 12 months following revascularization in a cohort of 84 RAS patients with coronary artery disease²¹. Despite some differences in the outcomes measured, this and other studies provide support for, or at least do not counter, the possibility that revascularization for RAS in the presence of heart failure leads to improved outcome irrespective of the presence of APO. The mechanistic theory behind this beneficial clinical outcome is provided by the association of RAS with excess circulating angiotensin²¹² and salt and water retention in both animal models and cases in man^{9,10}, and evidence of progressive abnormal cardiac remodelling in patients with RAS^{13,22}. These pathological

changes have been shown to regress, at least partially, after revascularization, albeit in selected case series^{12,21,23}.

Patients who had previous APO events had a numerically higher LVEF and systolic blood pressure, but were less likely to have had a previous MI. We offer two possible explanations which may both contribute to this finding. Firstly, the history of fewer MIs and more preserved systolic function in those patients with previous APO may indicate a survival bias. Patients with heart failure who have coronary artery disease, systolic heart failure and previous decompensation are likely to die earlier and therefore be under-represented in the study. Second, the higher blood pressure and preserved systolic function in these APO patients may demonstrate a mechanistic association between the ARVD and APO. Patients with ARVD typically have preserved systolic function, diastolic dysfunction and hypertension¹³. Patients at extremes of this phenotype are likely to be those who suffer APO.

It is well established, albeit in observational settings such as this, that APO patients benefit from renal artery revascularization. We have previously shown reduction in both left ventricular hypertrophy on cardiac MRI after revascularization in such a patient, as well as concurrent lowering of circulating angiotensin II levels¹². It may also be that these effects contribute to the survival benefit in the chronic heart failure group without prior APO.

Chronic heart failure patients with AVRVD are also likely to demonstrate elevated angiotensin II levels and hypertrophic remodelling of the left ventricle. Reduction in these parameters may reduce the likelihood of future cardiovascular events. Supporting this, as seen in table 4, we note that fewer died from a cardiac cause (rather than specifically heart failure) in non-APO patients who were revascularized compared to those managed medically (16% versus 39%).

The more preserved LVEF in the APO patients highlights that there is often disconnect between severity of heart failure symptoms and LVEF, particularly with HFPEF (heart failure with preserved ejection fraction). NHYA score may provide useful information in ARVD-HF patients but was not recorded as part of this study.

Despite the inconsistency of its definition, flash pulmonary oedema is currently an agreed indication for revascularization for RAS based on data from very small cohorts and selective historical cases studies. Accepting the limitations of this study, this finding, coupled with the findings of other studies discussed above, make the case for further investigation into extending the renal revascularization indication to all RAS patients with heart failure, irrespective of presentation. However, given the potential cost implications of the high co-existent prevalence of heart failure and RAS, the neutral results of ASTRAL and CORAL making RAS screening less likely in heart failure, and the fact that revascularization can be associated with significant morbidity in some patients, revascularization in this clinical situation is unlikely to become routine. Perhaps, therefore, an RCT of renal artery revascularization versus medical therapy in heart failure must be pursued for a more conclusive guideline to be produced.

Acknowledgements

We thank the patients of Salford Royal Hospital for their participation in this study.

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Figure 1. Survival curves for all-cause mortality in patients with atherosclerotic renal artery stenosis and heart failure, comparing revascularization versus medical therapy divided into those with and without previous acute pulmonary oedema and adjusted for age, renal function, systolic blood pressure, coronary artery disease, smoking, diabetes mellitus, and patency score.

APO = acute pulmonary oedema, Revasc = revascularization.

Tables

Table 1. Baseline cohort characteristics.

	Heart failure, no APO				Heart failure with APO			
	Overall	Medical	Revas	p	Overall	Medical	Revas	p
Demographics								
N	100	69	31	-	52	36	16	-
Age (years)	71 ± 9	72 ± 9	69 ± 9	0.22	70 ± 7	72 ± 7	64 ± 7	0.01
Male gender (%)	66	67	65	0.82	46	51	31	0.24
Cardiovascular co-morbidities								
LVEF (%)	42 ± 13	44 ± 12	39 ± 16	0.58	47 ± 12	47 ± 12	48 ± 13	0.86
Systolic BP (mmHg)	149 ± 32	146 ± 32	156 ± 32	0.17	158 ± 30	155 ± 30	165 ± 30	0.26
Previous MI (%)	50	54	42	0.28	26	24	31	0.74
Diabetes (%)	39	38	42	0.82	30	30	31	1.00
Smoker (%)	33	33	32	0.43	61	63	57	0.92
RAS severity								
eGFR (mL/min/1.73m ²)	27 ± 15	27 ± 16	27 ± 13	0.93	28 ± 19	27 ± 21	31 ± 15	0.54
Bilateral RAS (%)	55	51	65	0.38	52	51	56	0.75
Occlusive RAS (%)	33	35	29	0.85	31	35	19	0.49
Patency score	88 ± 47	94 ± 46	73 ± 50	0.04	89 ± 43	93 ± 40	78 ± 50	0.26
Concurrent medication								
RAAS use (%)	50	55	39	0.19	34	41	13	0.09
Statin use (%)	56	54	61	0.52	46	49	38	0.56
Anti-platelet use (%)	39	38	42	0.83	56	62	44	0.32

Key: APO = acute pulmonary oedema; revas = revascularization; LVEF = left ventricular ejection fraction; BP = blood pressure; MI = myocardial infarction; eGFR = estimated glomerular filtration rate; RAS = renal artery stenosis; RAAS = renin-angiotensin-aldosterone system.

Table 2. Primary indications for revascularization.

	Heart failure, no APO		Heart failure with APO	
	n	%	n	%
Hypertension	10	(32)	2	(12.5)
Acute pulmonary oedema	0	-	12	(75)
Heart failure	6	(19)	0	-
Decline in renal function	5	(16)	2	(12.5)
ACE inhibitor intolerance	5	(16)	0	-
Clinical trial	5	(16)	0	-
Total	31	(100)	16	(100)

Key: APO = acute pulmonary oedema

Table 3. Hazard ratio (HR) for outcome in patients undergoing renal artery revascularization versus medical therapy, adjusted for age, renal function, systolic blood pressure, coronary artery disease, smoking, diabetes mellitus, and concurrent medication.

	HR	95% CI	p	Events, n (%)	
				Medical	Revasc
All-cause mortality					
HF, no APO	0.76	0.58 – 0.99	0.04	57 (83)	22 (71)
HF with APO	0.73	0.44 – 1.21	0.22	30 (81)	10 (63)
Heart failure hospitalization					
HF, no APO	1.00	0.17 – 6.05	1.00	6 (9)	2 (6)
HF with APO	0.51	0.08 – 3.30	0.48	4 (11)	1 (6)
Fatal and non-fatal cardiovascular events					
HF, no APO	0.98	0.44 – 2.18	0.96	26 (38)	12 (39)
HF with APO	0.62	0.31 – 1.27	0.19	15 (41)	6 (38)

Key: HF = heart failure; APO = acute pulmonary oedema.

Table 4. Causes of death and cardiovascular events expressed as a percentage of patients in each category.

	Cause of death				Cause of cardiovascular event			
	No APO		APO		No APO		APO	
	Medical	Revasc	Medical	Revasc	Medical	Revasc	Medical	Revasc
Cardiac	39	16	35	17	33	29	32	27
CAD	17	8	0	17	22	23	14	20
Heart failure	17	8	29	0	9	6	16	7
Arrhythmia / SCD	6	0	6	0	3	0	3	0
Other cardiovascular	11	16	12	17	4	10	8	13
Other cause	33	39	29	32	-	-	-	-
Renal	8	8	0	0	-	-	-	-
Infection	17	8	29	32	-	-	-	-
Malignancy	8	16	0	0	-	-	-	-
Other	0	8	0		-	-	-	-

Key: APO = acute pulmonary oedema, CAD = coronary artery disease, SCD = sudden cardiac death.