



SYSTEMATIC REVIEW AND CASE REPORT

Mineralocorticoid Receptor Antagonists for Recurrent Hypertensive Emergency due to Bilateral Renal Artery Stenosis

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Abstract

Introduction: Bilateral renal artery stenosis (RAS) causing recurrent hypertensive emergency and pulmonary oedema is difficult to manage. Use of angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) is usually contraindicated. We present a systematic review of literature and a case vignette which highlights the useful properties of mineralocorticoid receptor antagonists (MRAs) in this scenario.

Methods: Medline, EMBASE, and the Cochrane Central Register of Controlled Trials were searched. Online searches were also conducted. Eligible studies involved the use of MRAs in bilateral RAS. Our search included case reports, case series, case-controls, cohort studies, randomised controlled trials, and systematic reviews. Consensus guidelines on the management of bilateral RAS were also included.

Results: 354 abstracts were screened. One case report was included for review. This reported successful use of eplerenone in bilateral RAS following unilateral renal artery stenting. Online search yielded one international guideline for inclusion. This did not mention the use of MRAs in bilateral RAS.

Discussion and conclusion: There is no evidence or recommendations from controlled trials, cohort studies, or consensus guidelines to inform clinicians on the use of MRAs in bilateral RAS. One case report describes successful use of eplerenone for management of refractory hypertension secondary to bilateral RAS. We describe our experience of the successful addition of spironolactone to an anti-hypertensive regimen which prevented recurrence of hypertensive emergency and pulmonary oedema in a patient with multiple previous hospital admissions. We feel that MRAs offer an effective and relatively safe but underused option in this condition.

Keywords

*KDIGO: Kidney Disease Improving Global Outcomes; Hypertension; Renal Artery Stenosis; Mineralocorticoid Receptor Antagonists; Pulmonary Oedema

Case Vignette

A 75-year-old woman with severe bilateral renal artery stenosis (RAS) not amenable to stenting or surgery presented to the emergency department with hypertensive emergency and acute pulmonary oedema on 3 separate occasions. On each admission electrocardiogram and echocardiogram demonstrated acute left ventricular strain and diastolic dysfunction related to severe hypertension. Each admission required admission to the intensive care unit (ICU) for invasive monitoring and treatment with intravenous diuretics and vasodilators, with subsequent improvement and ultimate discharge from hospital. On each occasion, she was discharged on at least 4 oral antihypertensives, which included combinations of a loop diuretic, calcium channel blocker (CCB), a beta blocker, an alpha blocker, and hydralazine. Her antihypertensive regimen excluded angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), and mineralocorticoid receptor antagonists (MRA).

Despite good compliance with medications, she was readmitted with similar episodes again requiring parenteral treatment and invasive monitoring in the ICU. Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) were

considered contraindicated due to severe bilateral RAS and concerns for acute kidney injury.

Following the third admission with acute pulmonary oedema and hypertensive emergency she was commenced on a combination of 75 mg of spironolactone, in addition to slow release indapamide 1.5 mg and amlodipine 10 mg. With this regimen, she did not suffer another episode of pulmonary oedema or hypertensive emergency.

Introduction

Renal artery stenosis (RAS) involves narrowing of one or both renal arteries [1]. RAS is present in 1% of mildly hypertensive patients, and up to 40% of patients with refractory hypertension [1,2]. The most common aetiology is atherosclerosis, which accounts for 90% of cases [2]. This is associated with typical risk factors such as smoking, diabetes mellitus, hyperlipidaemia, and raised BMI [3]. The second commonest cause of RAS is fibromuscular dysplasia (FMD), and this should be considered in female patients under age 55 years [3,4]. Rare causes include arterial dissection, aneurysms, vasculitis, connective tissue disease, post-radiation effects, trauma, neurofibromatosis, and congenital bands [4].

RAS may cause secondary hypertension, ischemic nephropathy, acute kidney injury, and chronic kidney disease (CKD) [5]. In cases of bilateral RAS, unilateral RAS with solitary kidney, or rarely unilateral RAS with a normal contralateral kidney, a combination of sudden severe fluid overload, heart failure severe hypertension, and acute onset 'flash' pulmonary oedema may occur [6]. This is known as Pickering Syndrome [6].

The usual management of RAS involves aggressive blood pressure control, cardiovascular risk factor modification, and in some cases revascularisation [7]. There is no firm evidence from randomised controlled trials to favour revascularisation over medical treatment in the prevention of major cardiac or renal outcomes at 5 years, but this remains a controversial topic [8-10]. However, expert opinion and cohort studies support endovascular intervention in cases of recurrent pulmonary oedema and heart failure [10]. Comorbidities may preclude patients from invasive management. In addition, the presence of diffuse bilateral RAS or the presence of accessory renal arteries may make angioplasty technically impractical [10]. It is important to offer these patients combinations of medications which reliably control hypertension and prevent pulmonary oedema.

In unilateral RAS, medical management with ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs) is indicated. This aims to offset renin-angiotensin-aldosterone system (RAAS) overactivation [10]. In contrast to this, ACEi and ARBs are relatively contraindicated in bilateral RAS or high-grade unilateral

stenosis [10]. This is based on the risk of inducing efferent arteriole dilation and reduced glomerular hydrostatic pressure [10]. This may lead to a severe acute kidney injury. An unexpectedly large rise in creatinine following initiation of ACEi or ARBs may be the first indication that undiagnosed bilateral RAS is present [10].

There has been almost no research on the use of mineralocorticoid receptor antagonists (MRAs) in cases of bilateral RAS. We present a case report on successful use of spironolactone in a patient who presented with recurrent pulmonary oedema and severe hypertension associated with bilateral RAS. Since commencing this drug, the patient has remained well and required no further hospitalisations. This poses the question - are MRAs an underused option in bilateral RAS associated with recurrent hypertensive emergency and pulmonary oedema?

Search Methods for Literature Review

Systematic review methodology was used according to PRISMA guidelines. Medline, EMBASE, and the Cochrane Central Register of Controlled Trials were chosen search databases. This search included studies published up until December 2022. There was no limitation on the earliest date of publication. Results were limited to the English language or English translation. Online searches using Google were also conducted, specifically looking for relevant guidelines, studies, or case reports. Relevant nephrology textbooks, review articles, and case reports were also searched. Institutional approval was not required for this study.

The inclusion criteria are outlined in Table 1. Included articles were limited to those which assessed the use of MRAs in bilateral RAS, or guidelines which outlined management approaches for bilateral RAS. No age limits were set on included populations. An exclusion criterion was the use of MRAs in unilateral RAS.

Table 1: Inclusion criteria for systematic review.

Study type: Case report, case series, case-control, cohort study, RCT, systematic review, expert guideline.
Population: Human populations; no age limit; patients with bilateral renal artery stenosis.
Intervention: Use of MRAs in patients with bilateral RAS.

Table 2: Search terms used.

1. Renal artery stenosis AND Diuretic
2. Renal artery stenosis AND potassium-sparing diuretic
3. Renal artery stenosis AND Mineralocorticoid receptor antagonist
4. Renal artery stenosis AND Aldosterone antagonist
5. Renal artery stenosis AND MRA
6. Renal artery stenosis AND Spironolactone
7. Renal artery stenosis AND Eplerenone
8. Renal artery stenosis AND Finerenone

The search strategy is outlined in [Table 2](#) and included the following: (I) Renal artery stenosis AND Diuretic (147 results; 1 relevant); (II) Renal artery stenosis AND potassium-sparing diuretic (1 result; 0 relevant); (III) Renal artery stenosis AND Mineralocorticoid receptor antagonist (13 results; 1 relevant); (IV) Renal artery stenosis AND Aldosterone antagonist (0 results); (V) Renal artery stenosis AND MRA (183 results; 0 relevant); (VI) Renal artery stenosis AND Spironolactone (10 results; 1 relevant); (VII) Renal artery stenosis AND Eplerenone (1 result; 1 relevant); (VIII) Renal artery stenosis AND Finerenone (0 results).

Following detailed searches 2 reviewers (MH and DS) independently conducted a screening of abstracts and then full text articles.

Statistical analysis

Only 1 case report and 1 guideline were included and contained heterogeneous outcomes, therefore meta-analysis was not feasible. A descriptive report of each paper is provided.

Search Results

Our database search results are outlined in a PRISMA flow diagram in [Table 3](#). Individual results are described in [Table 4](#). Our search yielded 1 case report [11]. This described a 29-year-old female with refractory hypertension and previous subarachnoid haemorrhage. Imaging showed bilateral RAS secondary to FMD. Due to technical challenges, bilateral revascularisation

Table 3: PRISMA flow chart of database search results.

I: 147 results; 1 relevant case report.
II: 1 result; 0 relevant.
III: 13 results; 1 relevant case report.
IV: 0 results.
V: 183 results; 0 relevant.
VI: 10 results; 1 relevant case report.
VII: 1 result; 1 relevant case report.
VIII: 0 results
Online Google search: 1 evidence-based guideline.

was not feasible, and unilateral renal artery balloon angioplasty was performed. Hypertension persisted due to persistent hyperaldosteronism presumably from the remaining unilateral renal artery stenosis. Eplerenone was added, and normotension was achieved without any decline in renal function. This case is not entirely reflective of our research question, as unilateral revascularisation was done in advance of commencing spironolactone, therefore removing the challenge of dealing with bilateral stenosis.

An online search using Google yielded one relevant guideline: the KDIGO* guideline on the management of renovascular hypertension, 2021 [12]. This makes no mention of the use of MRAs in RAS, however it does stress that ACEi and ARBs are not *absolutely* contraindicated in bilateral RAS, and may be considered.

Discussion

RAS should be considered in cases of recurrent hypertensive emergency and flash pulmonary oedema [13]. The pathophysiological mechanism for acute pulmonary oedema in this situation involves glomerular hypoperfusion, RAAS activation, sympathetic nervous system (SNS) activation, and subsequent hypervolemia. RAAS and SNS over-activation contribute to diastolic left side cardiac dysfunction and elevated left atrial pressure [13]. The combination of pressure and fluid overload manifests as pulmonary venous congestion [13]. Acute management strategies include volume control with loop diuretics, blood pressure reduction often with intravenous vasodilators, and in eligible patients, renal artery angioplasty and stenting [13,14]. In our case, acute management with intravenous agents was successful. Once discharged however, oral antihypertensive regimens which included loop diuretics, CCBs, alpha blockers, beta-blockers, and hydralazine proved unable to prevent recurrence of pulmonary oedema. The addition of spironolactone proved effective, and the patient has remained out of hospital.

ACE-inhibition seems mechanistically appropriate for management of RAS, but in cases of bilateral stenosis or high-grade unilateral stenosis there is a

Table 4: Relevant Results according to article type.

Systematic Review: 0	
RCTs: 0	
Cohort study: 0	
Case series: 0	
Case Reports: 1	Ibuki C, Kawamata H, Seino Y, Mizuno K. Successful blood pressure control with additive administration of eplerenone, an aldosterone receptor blocker, in a patient with bilateral renovascular hypertension treated with angioplasty. <i>Intern Med.</i> 2010; 49(22): 2455-9. doi: 10.2169/internalmedicine.49.4055. Epub 2010 Nov 15. PMID: 21088349.
Guidelines: 1	Hicks CW, Clark TWI, Cooper CJ, de Bhailís ÁM, De Carlo M, Green D, Matyszko J, Miglinas M, Textor SC, Herzog CA, Johansen KL, Reinecke H, Kalra PA. Atherosclerotic Renovascular Disease: A KDIGO (Kidney Disease: Improving Global Outcomes) Controversies Conference. <i>Am J Kidney Dis.</i> 2021 Aug 9:S0272-6386(21)00776-9. doi: 10.1053/j.ajkd.2021.06.025. Epub ahead of print. PMID: 34384806.

high dependence on angiotensin-II mediated efferent arteriole constriction to preserve glomerular hydrostatic pressure [14]. There is an inability for a contralateral 'normal' kidney to achieve a pressure natriuresis, and RAAS blockade of is therefore likely to result in significant renal dysfunction and potential dialysis dependence [14].

MRAs act through competitive antagonism of the aldosterone receptor in the distal tubule [15]. This promotes sodium and water loss without directly affecting intra-glomerular pressure [14]. In this scenario, MRA use achieved the goal of volume and blood pressure control without sacrificing renal function, and also without causing hyperkalaemia. Dosing guidelines on MRAs are mainly based on studies of cohorts with heart failure with reduced ejection fraction, refractory hypertension (add-on therapy), primary hyperaldosteronism (first-line therapy), and more recently diabetic chronic kidney disease [14-22]. There is no literature to guide dosing strategies for MRAs in cases of RAS where the goal is both control of blood pressure and avoidance of pulmonary oedema. There is also a lack of data to inform clinicians of the magnitude of risk of hyperkalaemia with MRA use in RAS patients. It is conceivable that the risk is lower compared to other patient cohorts, given the high degree of RAAS overactivation. Concomitant use of thiazide/thiazide-like diuretics may also reduce this risk.

In addition to controlling volume overload and hypertension, the use of MRAs in RAS patients may prove to have an extended benefit of slowing CKD progression and reducing primary cardiac events. The recent RCTs, FIGARO-CKD and FIDELIO-CKD, have shown that the use of finerenone (a novel non-steroidal MRA) is associated with lower rates of death due to cardiovascular events and renal disease, as well as lower rates of sustained eGFR decline in patients with type 2 diabetes mellitus and proteinuric CKD [20,21]. The FIDELITY study was a pooled analysis of these two RCTs which confirmed the promising results of each trial. It is anticipated that these benefits will extend to patients with non-diabetic proteinuric CKD, and possibly non-proteinuric CKD, but research is awaited before this is confirmed. Populations with RAS and CKD are likely to have high cardiac risk profiles, and therefore finerenone may be an appealing option in these patients due its dual cardiorenal protective effect [22].

Conclusion

The paucity of research and case reports on this topic suggests that MRAs may be an underused option for managing and preventing complications of bilateral RAS. This case report presents successful use of spironolactone, in addition to a thiazide-like diuretic and CCB, to prevent readmission to hospital due to RAS-associated pulmonary oedema. There was no accompanying acute kidney injury or hyperkalaemia.

Further research in this area would be of benefit to inform whether this drug class should be included in the standard of care for this patient cohort.

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