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Review Article

Revascularization in Resistant Hypertension Due to Renal Artery Stenosis

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ABSTRACT

Background: Renal artery stenosis (RAS) is a significant cause of resistant hypertension, especially in patients presenting with comorbidities. Revascularization has been initially recommended to treat resistant hypertension due to RAS. However, recent studies have shown modest benefits for blood pressure control over medical therapy only. There is limited data on revascularization in patients with resistant hypertension and RAS, particularly in patients with a high cardiovascular risk profile.

Materials and methods: A systematic review of case reports was conducted to summarize the outcomes of revascularization in patients with resistant hypertension and RAS. The search was conducted through the Medline database (2013–2023) and was able to identify nine relevant reports documenting ten cases. Data on patient characteristics, blood pressure (BP), renal function, and antihypertensive medications before and after revascularization were extracted and analyzed descriptively.

Results: The average age of patients was 60.4 years, with an equal distribution of male and female cases. Following revascularization, systolic BP decreased from 170 mmHg (± 29.69) to 126 mmHg (± 3.53), and diastolic BP from 96 mmHg (± 16.97) to 74 mmHg (± 7.07). The average number of antihypertensive medications reduced from four to two. Renal function also improved in all cases where creatinine and eGFR data were reported.

Conclusion: Revascularization in RAS showed its benefit in lowering BP and medication burden, along with improving renal function in select cases. Decision for revascularization should be tailored to each patient while considering its potential risks and benefits.

Keywords: Renal Artery Stenosis, Resistant Hypertension, Revascularization, Blood Pressure

INTRODUCTION

Renal artery stenosis (RAS) is defined as an increase in luminal diameter more than 60%, commonly caused by atherosclerosis or fibromuscular dysplasia[1,2]. Renal artery stenosis resulting from atherosclerotic disease is common in individuals with preexisting coronary artery disease (18% to 20%)[3]. RAS increases mortality, especially if associated with end-stage renal failure[4]. RAS is associated with hypertension and renal impairment, and was found in 24% patients with resistant hypertension[4,5]. It was previously recommended for RAS patients with resistant hypertension to undergo revascularization[6]. Renal artery stenting is considered appropriate for hemodynamically significant atherosclerotic RAS when there is accompanying cardiac destabilization syndromes (recurrent heart failure, sudden pulmonary

edema, or acute coronary syndrome), resistant hypertension, or progressive ischemic nephropathy in patients with bilateral disease or a solitary functioning kidney[7]. However, recent studies showed that revascularization only give modest effect on blood pressure control and antihypertensive treatment score compared to medication therapy alone[8]. Therefore, revascularization is not routinely recommended for RAS secondary to atherosclerosis in patients with hypertension[9]. Limitation of those studies was it had not included patients with resistant hypertension due to its higher cardiovascular risk. Consequently, the benefit of revascularization in this specific population has not been thoroughly investigated.

This systematic review of case reports was conducted in order to summarize existing evidence regarding revascularization procedure in a specific population. The objective of this review was to identify the characteristics of patients with coexisting RAS and resistant hypertension who underwent renal revascularization and their response after follow up.

MATERIALS AND METHODS

Data sources and searches:
We searched the Medline electronic database from 2013 to 2023 to identify case reports of patients with renal artery stenosis and resistant hypertension who underwent renal revascularization. Article search was limited to available English abstracts.

Study selection:
The screening of identified publications was conducted independently by two reviewers. First, the titles and abstracts of all citations were reviewed. Then, the full text of suitable citations was reviewed. Discrepancies were discussed. Cases were included if they reported patients with persistent hypertension ≥140/90 currently treated with ≥3 medications in its optimal dosage, and renal stenosis was discovered. Studies were excluded if they reported pediatric or pregnant patients.

Data extraction and quality assessment:
Data was extracted by one reviewer and checked by another. Extracted data was divided into before and after revascularization, including blood pressure, medications, and laboratory result of creatinine and eGFR to illustrate renal function (depicted in Table 3, Table 4, Table 5 and Table 6)

Modified version of a tool for quality appraisal of case reports was used. The assessment was carried out by one reviewer and checked by another. Four items of appraisal were used: provided in Table 7.

i) patient was described adequately (chief complaint, history, clinical and laboratory evaluations, treatments), ii) an accurate diagnosis was provided, iii) convincing evidence in support of the diagnosis was presented, and iv) alternate explanations were considered and refuted. Possible item ratings were yes, partially, or no. Quality appraisal are provided in Table 8.

Data synthesis and analysis:
Data were summarized using descriptive statistics, with means for continuous variables and frequencies and percentages for dichotomous variables.

RESULTS

Publication characteristics:
A total of 31 citations were initially retrieved. Fourteen citations were regarded as suitable and reviewed for its full publication. Five were excluded; 1 was unretrievable, 3 was not giving adequate data, and 1 was excerpted from an interview session. Nine citations were included, reporting on 10 cases and was described separately.

PRISMA flow diagram is provided in Figure 1.

Patient characteristics:
The mean age of the cases was 60.4 years (standard deviation, 8.48 years) and was equal between male and female.

The most common comorbidities were hyperlipidemia (20%) and smoking (15%), followed by diabetes mellitus (10%), aneurysm (10%), heart disease (10%), and chronic kidney disease (5%)(depicted in Table-2). Some cases also include patients with a history of cervical cancer, gastrointestinal bleeding, rheumatoid arthritis, hepatitis B infection, and latent tuberculosis.

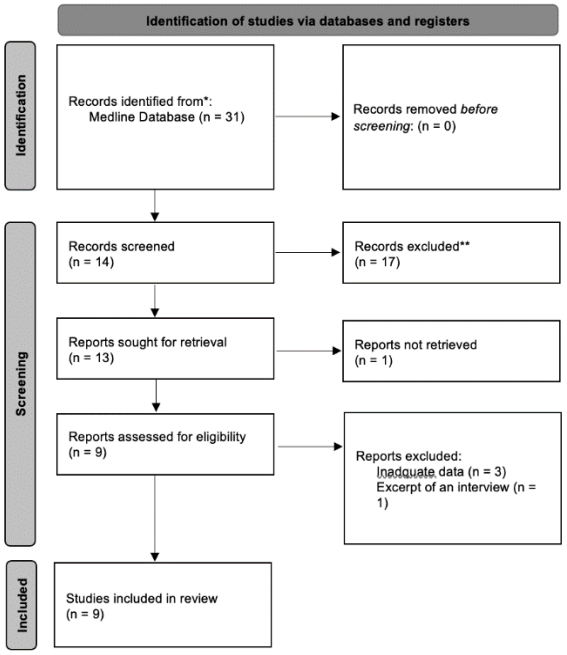

Figure -1: PRISMA flow diagram

Table-1:Patient characteristics

	Age	Gender
Chen, 2021	69	Male
Cianci, 2021	65	Male
Debiase, 2014	45	Male
Douvris, 2014	69	Female
Mishima, 2018 (1)	63	Female
Mishima, 2018 (2)	74	Female
Namazi, 2015	32	Female
Sarafidis, 2015	69	Male
Sasaki, 2021	57	Male
Wolfmueller, 2019	61	Female

Before revascularization:

The mean initial systolic blood pressure before revascularization was 170mmHg (standard deviation, 29.69) and diastolic blood pressure was 96 mmHg (standard deviation, 16.97). On average, 4 maintenance medications were taken. All cases reported the use of calcium channel blockers. Other commonly used drugs were ACE inhibitors/ARBs (70%), beta blockers (70%), and diuretics (60%). Some cases also added alpha blocker (40%), second diuretics (20%), alpha agonists (30%) and direct vasodilator (10%) to their regimen.

Table-2:Patient comorbidities

Diabetes mellitus	2	10.00%
Hyperlipidemia	4	20.00%
Smoking	3	15.00%
Aneurysm	2	10.00%
Heart disease	2	10.00%
Chronic kidney disease	1	5.00%
Others	6	10.00%

After revascularization:

The mean systolic blood pressure after revascularization was 126mmHg (standard deviation, 3.53) and diastolic blood pressure was 74mmHg (standard deviation, 7.07). The amount of maintenance medication used was 2-3 drugs averagely.

The most common drugs prescribed were identical, though the numbers have lowered; calcium channel blockers (66.67%), ACEi/ARBs (55.56%), and beta blockers (44.44%). Other drugs included were diuretics (33.33%), alpha blockers (22.22%), alpha agonists (22.22%), direct vasodilator (11.11%). One case includes an aldosterone antagonist. One study did not state its regimen after revascularization. Five studies stated laboratory results before and after revascularization. Overall, renal improvement was seen in all studies. Creatinine levels were decreased and eGFR was increased.

Table-3:Blood pressure measurement before and after revascularization

	Before Revascularization		After Revascularization	
	SBP (170.4 ± 29.69)	DBP (96.6 ± 16.97)	SBP (126.5 ± 3.53)	DBP (74.5 ± 7.07)
Chen, 2021	200	100	130	75
Cianci, 2021	170	100	145	80
Debiase, 2014	210	100	130	80
Douvris, 2014	150	80	135	85
Mishima, 2018 (1)	140	90	120	70
Mishima, 2018 (2)	142	94	110	60
Namazi, 2015	160	100	120	70
Sarafidis, 2015	174	96	120	70
Sasaki, 2021	200	130	120	70
Wolfmueller, 2019	158	76	135	85

Table-4: Antihypertensive medications before and after revascularization

	Before Revascularization (mean= 4)	**After Revascularization (mean= 2.67)**
Chen, 2021	4	2
Cianci, 2021	3	0
Debiase, 2014	5	5
Douvris, 2014	4	4
Mishima, 2018 (1)	3	2
Mishima, 2018 (2)	3	0
Namazi, 2015	4	n/d
Sarafidis, 2015	5	4
Sasaki, 2021	3	4
Wolfmueller, 2019	6	3

Table-5:Renal functions before and after revascularization

	Creatinine (in mg/dl)		eGFR (in ml/min/1.73m^2)	
	B	A	B	A
Chen, 2021	1.38	1.08	51.80	69.21
Cianci, 2021	1.85	1.47	37	48
Douvris, 2014	1.75	1.13	n/d	n/d
Sarafidis, 2015	5	2.99	12.3	22.2
Sasaki, 2021	1.1	1.2	n/d	n/d

DISCUSSION

This review showed that renal revascularization demonstrated its benefit to control blood pressure and reduce antihypertensive medication burden in cases of resistant hypertension. These findings were consistent with other observational studies in similar population[2,10]. Current recommendation has limited the indication for revascularization to a small group of patients with severe clinical presentations such as recurrent episodes of acute heart failure, oligo-anuric renal failure or acute increase in creatine concentration after the introduction of a RAS blocker[11-13]. Only two studies in this review presented those conditions[14,15]. Several studies reported new onset hypertension or sudden deterioration of blood pressure[14,16,17]. This highlights the importance that decision for revascularization should be made individually despite the absence of severe clinical presentations. It had been suggested that worsening hypertension and treatment resistant hypertension would benefit from revascularization. RAS due to fibromuscular dysplasia with hypertension should also be considered for revascularization[18], as it was found in one study in this review[19].

Table-6:Types of antihypertensive medications before and after revascularization

	CCB		BB		D1		D2		Acei/Arb		AB		AA		VD		Ald A	
	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
Chen, 2021	•		•	•	•		•			•								
Cianci, 2021	•		•						•									
Debiase, 2014	•	•	•	•	•	•			•	•	•	•						
Douvris, 2014	•	•	•	•		•			•				•	•				
Mishima, 2018 (1)	•	•							•	•	•							
Mishima, 2018 (2)	•				•				•									
Namazi, 2015	•	n/d	•	n/d	•	n/d		n/d	•	n/d		n/d		n/d		n/d		n/d
Sarafidis, 2015	•	•	•	•	•						•	•	•	•				
Sasaki, 2021	•	•				•				•	•		•					•
Wolfmueller, 2019	•	•	•		•		•		•	•					•	•		

Table-7: RAS Causes, Clinical Presentation, and Complications

Author, Year	Causes of RAS	Clinical Presentation	Complications
Chen, 2021	Atherosclerosis	New resistant hypertension	None
Cianci, 2021	Atherosclerosis	History of resistant hypertension for 1 year	None
Debiase, 2014	Atherosclerosis	Resistant hypertension	None
Douvris, 2014	Atherosclerosis	New resistant hypertension, deterioration of kidney function after the addition of antihypertensive drugs	Renal hematoma
Mishima, 2018 (1)	Polycythemia vera	History of severe hypertension for 2 years with massive proteinuria	None
Mishima, 2018 (2)	Essential thrombocytopenia	History of new resistant hypertension for 1 year and thrombocytosis	None
Namazi, 2015	Sindroma antiphospholipid	New resistant hypertension	None
Sarafidis, 2015	Atherosclerosis	Deterioration of kidney function after the addition of antihypertensive drugs	Restenosis
Sasaki, 2021	Atherosclerosis	Sudden exacerbation of blood pressure	None
Wolfmueller, 2019	Displasia fibromuskular	History of resistant hypertension for 4 years	None

Table-8: Quality appraisal

Author	Year	Adequate description	Reliable outcome	Convincing evidence	Alternate explanation
Chen	2021	Yes	Yes	Yes	Yes
Cianci	2021	Yes	Yes	Yes	Yes
Debiase	2014	Yes	Yes	Yes	Yes
Douvris	2014	Yes	Yes	Yes	Yes
Mishima (1)	2018	Yes	Yes	Yes	Yes
Mishima (2)	2018	Yes	Yes	Yes	Yes
Namazi	2015	Yes	Yes	Yes	Yes
Sarafidis	2015	Yes	Yes	Yes	Yes
Sasaki	2021	Yes	Yes	Yes	Yes
Wolfmueller	2019	Yes	Yes	Yes	Yes

Revascularization should allow for more blood flow through the kidney and attenuate renin release which contribute to the decline of blood pressure and obtain hypertension control. This result may be more pronounced in conditions where hypertension is the main concern, rather than worsening renal function. This could be found in non-atherosclerotic causes of RAS, such as vasculitis or fibromuscular dysplasia[20]. Significant reduction of blood pressure and use of antihypertensive medication in those populations had been observed[21]. Two cases in this review also reported similar result regarding non-atherosclerotic RAS[22,23]. Other cases in this review reporting atherosclerotic RAS also showed reduction in blood pressure. Although all causes of RAS may benefit from revascularization in controlling blood pressure, revascularization may show variable result in
In this review, improvement of renal function was found in all cases that provided their laboratory values before and after revascularization. Among those cases, most were present with new onset hypertension and increased creatinine levels after introduction of RAAS inhibitors.

improving renal function. Another factor that should be considered in atherosclerotic RAS was duration of ischemia and degree of tissue injury. This would determine renal responsiveness to revascularization therapy, which would be reflected as renal function. It had been observed that kidneys with higher ratio of renal parenchymal volume to GFR would demonstrate increased renal function after revascularization. This ratio could imply salvageable renal parenchyma which not yet affected by stenosis[24]. Therefore, it should be addressed whether renal function is the end point for revascularization, as consideration for ischemia would be taken into account. Some measures had been tested to help predict the presence of salvageable renal tissue, such as doppler ultrasonography evaluation of renal resistance index[25].

Both conditions were suggested to benefit from revascularization[18,26]. New onset hypertension, in theory, translates to relatively shorter duration of ischemia, therefore revascularization would give its beneficial response accordingly.

Increased creatinine after consumption of RAAS inhibitors showed glomerular filtration dependency to angiotensin II. Initiating RAAS inhibitors would reduce renal blood flow and consequently reduce glomerular filtration rate, which presented as increased creatinine levels[27]. Revascularization would attenuate RAAS overactivity and enable the possibility to reintroduce RAAS to the medication regimen[26]. Revascularization did not come without risks. Two cases in this review reported restenosis and kidney hematoma separately. Both were resolved with corresponding therapy. Restenosis can occur, with rates between 13% and 39% by duplex ultrasound, often within a year[18]. Technical difficulty and potential procedural complication should always be addressed in order to prepare for its appropriate management.

CONCLUSIONS

Renal revascularization was able to provide its benefit in controlling blood pressure and reducing medication burden, especially in the occurrence of resistant hypertension. In select cases, it could also allow for further improvement of renal function.

We accept that this review is less than ideal to draw general conclusions due to its heterogenous circumstances. Therefore, decision for revascularization should be tailored to each patient while considering its potential risks and benefits.

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