Unusual case of recurrent renal artery stenosis: lessons to learn

Thomas J. Kiernan¹, Bryan P. Yan¹, Vishal Gupta¹ and Joseph M. Garasic¹

¹Department of Interventional Cardiology and Vascular Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA

CASE PRESENTATION

A 39 year old male chef with previous right aorto-renal artery surgical reimplantation at age 8 for reported congenital renal artery stenosis presented to an outside hospital with gastroenteritis including symptoms of abdominal pain, nausea, diarrhea and vomiting. Past medical history apart from previous surgery for congenital renal artery stenosis was unremarkable. He was an active tobacco user of one pack per day for the previous 20 years. There was no family history of premature coronary disease. Examination revealed a blood pressure of 210/100 mmHg, heart rate of 88 beats per minute and respiratory rate of 16 per minute. Blood pressure recordings were equal in both upper limbs. The radial, brachial, femoral and distal lower limb pulses were symmetrical and of normal volume. No bruits were audible over the carotid, subclavian or femoral arteries. The remainders of the cardiac, respiratory and abdominal examinations were unremarkable apart from a surgical scar as a result of previous renal artery surgery. Medications included nifedipine 90 mg and enalapril 20 mg had been started one month earlier for worsening hypertension. Laboratory profile on admission is shown in (Table 1).

His blood pressure was controlled on oral and intravenous antihypertensive therapy and his serum creatinine decreased to 1.4 mg/100 ml after discontinuation of the angiotensin-converting enzyme inhibitor and i.v. fluid replacement for dehydration. Evaluation of his renal arteries by magnetic resonance angiography and duplex ultrasound revealed high-grade stenosis in the right renal artery (RA) to a normal-sized right kidney (13 cm) and a small patent left RA to an atrophic left kidney (6.9 cm). A technetium renogram established that the right kidney accounted for 85% of the total renal function and the left kidney 15%.

The patient was subsequently referred to our institution for RA angiography. He received intravenous pre-hydrated and oral n-acetylcysteine pre-procedure for renal protection. Creatinine pre-procedure was 1.2 mg/100 ml. Angiography revealed a 70– 80% tubular stenosis in the right RA to aortic anastomosis (Figure 1). A small patent left RA to an atrophic left kidney was also visualized. A baseline pressure gradient of 100 mm Hg across the right renal artery stenosis (RAS) was obtained. The lesion was dilated with a 4.5 × 20 mm Ultrasoft balloon (Boston Scientific, Natick, MA, USA). This resulted in a 460% residual stenosis and therefore a 6.0 × 24 mm Genesis balloon expandable stent (Cordis, J&J, Miami, FL, USA) was implanted. The stent was post dilated with sequential 5.0, 6.0, and 7.0 mm balloons with a residual 30% stenosis and a translesional gradient of 20 mm Hg (Figure 2).

The patient did well for 5 months on nifedipine 120 mg qd before he presented with recurrent uncontrolled hypertension (systolic blood pressure 190 mm Hg). A duplex ultrasound of the right RA revealed a peak systolic velocity of 429 cm/sec, end diastolic velocity of 206 cm/sec, and a resistive index of 0.52. Repeat angiography was performed in view of poorly controlled blood pressure and duplex ultrasound findings. This revealed a right RA in-stent restenosis (ISR) of 50% with a translesional gradient of 55 mm Hg. Percutaneous angioplasty with a 6.0 mm balloon was performed at high pressures with 30% residual stenosis (Figure 3).

After 6 months, the patient’s systolic blood pressure became uncontrollable once again despite Toprol XL 100 mg qd and Norvasc 10 mg qd. Renal arterial duplex ultrasonography revealed a peak systolic velocity of 476 cm/sec in the proximal stented segment of the right RA with a renal-to-aortic ratio of 3.0, suggestive of significant recurrent
restenosis. Subsequent right RA angiography revealed a 50% long segment tubular ISR with a translesional gradient of 80 mm Hg (Figure 4).

A decision was made to seek a vascular surgical opinion at this stage. The patient underwent surgical bypass 2 months later with a reverse saphenous graft from the aorta to the right RA. He made an excellent postoperative recovery and his blood pressure remains well controlled on Toprol XL 100 mg qd, Norvasc 10 mg qd, and Diovan 80 mg qd.

**CLINICAL DIAGNOSIS**

Recurrent RAS and resultant hypertension in a young male patient with previous history of RA bypass to the same kidney as a child.

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**Table 1 | Laboratory parameters of the index patient at the time of admission**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Result (reference range)</th>
</tr>
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<tbody>
<tr>
<td><strong>Serum chemistry</strong></td>
<td></td>
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<tr>
<td>Sodium</td>
<td>133.0 mmol/l (136–142 per liter)</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.9 mmol/l (3.5–5.0 mmol/l)</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.3 mmol/l (8.8–10.5 mmol/l)</td>
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<tr>
<td>Creatinine</td>
<td>5.5 mg/100 ml (0.7–1.3 mg/100 ml)</td>
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<tr>
<td>Blood urea nitrogen</td>
<td>79.0 mg/100 ml (9–25 mg/100 ml)</td>
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<tr>
<td>Blood glucose</td>
<td>87.0 mg/100 ml (54–118 mg/100 ml)</td>
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<tr>
<td>HgbA1C</td>
<td>4.9% (4.2–5.8%)</td>
</tr>
<tr>
<td><strong>Blood count</strong></td>
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</tr>
<tr>
<td>Hemoglobin</td>
<td>15.2 g/100 ml (13.5–18 g/100 ml)</td>
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<td>WBC</td>
<td>8.27 k/μl (4–10 k/μl)</td>
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<td>Platelets</td>
<td>235.0 k/μl (150–450 k/μl)</td>
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<td>Hematocrit</td>
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<td>Triglycerides</td>
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<tr>
<td>LDL</td>
<td>97 mg/100 ml (50–129 mg/100 ml)</td>
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<tr>
<td>HDL</td>
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HDL, high-density lipoprotein; HgbA1C, hemoglobin A1C; LDL, low-density lipoprotein; WBC, white blood cell.

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**Figure 1 | Initial renal artery angiography showing severe proximal right renal artery stenosis (arrow).**

**Figure 2 | Renal artery angiography showing residual 30% renal artery stenosis (arrow) after balloon angioplasty and stent implantation.**

**Figure 3 | Duplex ultrasound findings of Doppler waveform spectral broadening, high peak-systolic and end-diastolic velocities suggestive of high-grade restenosis of the right renal artery.**

**Figure 4 | Renal artery angiography showing recurrent right renal artery in-stent restenosis (arrow).**
CLINICAL FOLLOW-UP
The patient is currently 1-year post-surgical revascularization of his RA and his blood pressure is adequately controlled on Toprol XL 100 mg qd, Norvasc 10 mg qd, and Diovan 80 mg qd.

DISCUSSION
Percutaneous transluminal angioplasty with stent implantation has been shown to be effective in the treatment of atherosclerotic RA stenosis. Analogous to stenting in the coronary artery, long-term efficacy of RA stenting is limited by ISR in up to 20% of patients. We describe an interesting case of recurrent RAS in a young man with surgical revascularization of RAS as a child, which highlights the potential limitations of percutaneous RA interventions.

Renal artery stenosis
The differential diagnosis of RAS in a young male patient includes RA atherosclerosis, fibromuscular dysplasia, and indeed possibly connective tissue disease such as Wegener’s granulomatosis. RA atherosclerosis tends to occur in older patients than the case presented and also associated with risk factors, such as diabetes, smoking, hyperlipidemia, associated coronary or peripheral vascular disease, and family history. Fibromuscular dysplasia, formerly called fibromuscular fibroplasia, is a group of nonatherosclerotic, noninflammatory arterial diseases that can affect almost any artery, but most commonly involves the renal arteries and usually occurs in young female patients. Wegener’s granulomatosis is an inflammatory vasculitis of medium-to-large arterial vessels that can also cause RAS.

RAS has become increasingly recognized as a contributing factor to resistant hypertension, deterioration in renal function, recurrent ‘flash pulmonary edema’, and long-term ill effects of poorly controlled hypertension. RAS is prevalent in patients with atherosclerotic vascular disease affecting other vascular territories. In one series of 395 arteriograms performed in patients with abdominal aortic aneurysms, aortoiliac atherosclerosis, or infrainguinal atherosclerosis, 33–50% had an RAS of >50%. In a prospective study of 1302 patients undergoing coronary arteriography, concurrent abdominal aortography demonstrated significant RAS in 15% of patients. More recent prospective data using duplex ultrasonography to assess RA patency demonstrated that 48% of renal arteries whose baseline stenosis was <60% progressed to >60% stenosis after 36 months, compared with only 8% in vessels with no stenosis at baseline.

Older comparative trials have shown that stenting and surgery are more effective than balloon angioplasty in restoring RA patency, but neither resulted in better clinical outcomes. A meta-analysis (Table 2) has demonstrated that balloon angioplasty is more effective than antihypertensive drug therapy in reducing blood pressure among hypertensive patients with atherosclerotic RAS. The magnitude of the difference, however, is modest, and it remains to be determined whether this benefit will persist in the longer term and improve clinical outcomes. In the pooled analysis using the 12-month instead of the 3-month follow-up data for the Dutch Renal Artery Stenosis Intervention Cooperative trial, angioplasty was still favored, although the difference for systolic blood pressure was no longer statistically significant.

CORAL is an ongoing randomized clinical trial of patients with RAS contrasting optimum medical therapy alone to stenting with optimum medical therapy on a composite cardiovascular and renal end point: cardiovascular or renal death, myocardial infarction, hospitalization for congestive heart failure, stroke, doubling of serum creatinine, and need for renal replacement therapy. The secondary end points will evaluate the effectiveness of revascularization in important subgroups of patients and with respect to all-cause mortality, kidney function, RA patency, microvascular renal function, and blood pressure control. The results will provide a greater understanding of RA revascularization versus medical therapy.

RA stenting has emerged as the preferred endovascular therapy for patients suffering from RAS. This procedure is largely performed with very good technical results, good anatomical results, and a low complication rate. By and large, endovascular therapy has supplanted open RA reconstruction in the United States secondary to the perceived lower morbidity and mortality by referring physicians and patients. The beneficial short- and long-term results of RA stent placement have resulted in a rapid increase in stent use in the treatment of RAS. Unfortunately, the long-term beneficial effect of RA stent placement is limited by a restenosis rate of between 9 and 25%. Recent data in relation to blood pressure control concluded that patients with resistant or difficult-to-control hypertension showed the greatest improvement in blood pressure control after RA stenting. However, results to date have been less favorable in terms of improving associated renal insufficiency. This may be secondary to procedure-related atheroembolization or perhaps shortcomings in study design and power, inadequate to demonstrate such a benefit.

Monitoring after RA intervention is extremely important and probably best served by duplex ultrasound in terms of cost effectiveness and lack of burden for the patient. Mahler and colleagues have previously shown in a prospective clinical study that 73% of renal arteries were patent 12 months after primary RA intervention. With consistent

<table>
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<th>Study</th>
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<th>Medical therapy</th>
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<td>DRASTIC</td>
<td>56</td>
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</tr>
<tr>
<td>EMMA</td>
<td>23</td>
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<tr>
<td>SNRASCG</td>
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DRASTIC, Dutch Renal Artery Stenosis Intervention Cooperative trial; EMMA, Essai Multicentrique Medicaments vs Angioplastie trial; SNRASCG, Scottish and Newcastle Renal Artery Stenosis Collaborative Group trial.
duplex ultrasound follow-up and catheter reintervention in cases of restenosis, the 12 month patency rate was increased to 94% overall.

Renal artery in-stent restenosis
RA ISR, similar to coronary artery ISR, is due to neointimal hyperplasia, a pathological process where stent placement disrupts the intima of the artery and acts as a stimulus for neointimal proliferation. Histologically, this process is due to smooth muscle cell proliferation and migration and abnormal endothelial remodeling. The optimal treatment of RA ISR is not well established as there is currently a paucity of data regarding which strategy is best. Treatments for ISR of renal arteries include percutaneous transluminal renal angioplasty (PTRA), repeat stent placement (bare metal stents (BMSs), drug eluting stents (DESs), or covered stents), brachytherapy, and cutting balloon angioplasty.

Drug eluting stents have significantly reduced the incidence of ISR in coronary arteries. Recently, a nonrandomized prospective study evaluated the efficacy of sirolimus DES compared to BMS in the treatment of atherosclerotic RAS. This small study with 105 patients concluded that the angiographic outcome at 6 months did not show a significant difference between BMS and DES. However, RA stenting with both types of stent was associated with significantly improved blood pressure. Future studies with a larger patient population and longer angiographic follow-up are warranted to determine the efficacy of DES in the treatment of RAS.

Repeat RA stenting is thought preferably to PTRA alone for RA ISR as the 6-month results of standalone PTRA for RA ISR are disappointing with significant restenosis rates between 36 and 67%. By comparison, DES was associated with superior 6-month patency in a recent case report. A recent prospective study concluded that balloon angioplasty and the implantation of a BMS, a covered stent, or a DES seemed to offer favorable long-term patency compared to cutting balloon angioplasty in the treatment of recurrent RA ISR. There are no large series of patients or randomized trials using brachytherapy for ISR of renal arteries although case reports have shown patency at 22 months and 4 years.

Congenital renal artery stenosis
Severe arterial hypertension in neonates is often due to RAS. Other causes include RA hypoplasia, abdominal aortic atresia, co-arterialization of the aorta, cystic kidney disease, and reflux nephropathies. Fibromuscular dysplasia is the most frequent cause of isolated RAS in this circumstance. Occasionally, accessory stenotic renal arteries exist. In neonates, umbilical artery catheter placement is the most frequent cause of RA thrombosis resulting in renovascular hypertension. It must be stated that unilateral RAS in a single functioning kidney in neonates or infants is potentially a harmful condition associated with severe hypertension, progressive renal failure, and a high risk of morbidity and mortality.

To date, medical therapy remains the initial treatment for neonatal hypertension with nephrectomy reserved in cases of severe renal hypertension refractory to medical therapy. Although blood pressure may be controlled in such cases, follow-up imaging often shows severe atrophy of the affected kidney. In infants with RAS, it was historically thought necessary to manage the child medically until they are older and open repair of the vascular abnormalities was deemed feasible. Surgical reconstructive procedures include surgical dilatation, RA resection and reanastomosis, and autologous or synthetic bypass grafts, and autotransplantation have had good long-term results in many patients, but may sometimes result in primary or secondary nephrectomy.

Medical therapy of hypertension in congenital RAS is extremely important especially in patients with congenital RAS in a solitary functioning kidney. In the latter type of patients however, refractoriness to medical therapy is common. Its pathogenesis can be explained by the model of one-kidney, one-clip Goldblatt hypertension, in which renal hypoperfusion leads to hyperactivation of the renin–angiotensin-aldosterone system with a consequent circulatory volume expansion that cannot be modulated by pressure natriuresis by means of the unaffected kidney. Pharmacological blockade of the renin–angiotensin-aldosterone system may result in acute renal failure. Therefore, medical therapy accompanied by little compensatory renin release and minimal effect on glomerular filtration rate, such as labetalol and a-adrenergic blocking agents, is preferred.

Currently, percutaneous transluminal angioplasty with or without stent implantation is considered the first-line treatment for RAS in adults and in adolescents. Overall, good results from endovascular treatment appear to outweigh the risks of recurrent stenosis and rare but severe complications such as RA dissection, rupture, or occlusion, retroperitoneal bleeding or aneurysmal formation. In infants, the utility of endovascular technique may be limited due to small vessel size and the overall experience in small children is limited.

CONCLUSION
This difficult case highlights some important clinical issues regarding RAS. Despite the lack of randomized data, there is still nonetheless good evidence to suggest that RA stenting is technically feasible and safe, improves renovascular hypertension, and to a lesser degree improves renal function. ISR remains a significant limitation to endovascular techniques, especially when PTRA and or stenting fail to achieve optimal vessel dilatation, as in our case with previous RA bypass surgery. Surgical treatment is still important in the management of RAS, particularly in patients that have failed percutaneous treatment.

REFERENCES


