Midterm complications of ROX arteriovenous coupler device, managed by targeted endovascular repair: a case report

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Background
Resistant and uncontrolled hypertension prominently amplifies the risk of end-stage renal disease and fatal cardiovascular events. Therapeutic inertia, despite maximum tolerated anti-hypertensive medications, puts patients at high risk, thus non-pharmacologic therapies have been proposed. The ROX arteriovenous coupler (ROX, Medical Inc., San Clemente, CA, USA), initially developed for treatment of chronic obstructive pulmonary disease, exploits the biomechanical effects of diverting arterial blood into a low-resistance, high-compliance venous segment, thereby decreasing arterial vascular resistance and blood pressure (BP).

Case summary
A 76-year-old male, non-smoker and non-diabetic with resistant primary hypertension presented to our institution with disabling claudication, lower limb swelling and right hip pain. He had concomitant saccular abdominal aortic and right iliac aneurysms. He had previously undergone renal denervation on two separate occasions yet continued to require increasing anti-hypertensive medications. He subsequently had an insertion of an ROX coupler device between his right external iliac artery and vein after failure of insertion into his left iliac system. He developed right hip and buttock pain and consequently underwent a total hip replacement and subsequent revision, which did not alleviate his symptoms. Ankle-brachial indices were reduced to 0.70 on the right limb and normal on the left. Insertion of the ROX coupler device was reversed with concomitant endovascular aortic repair.

Discussion
There is no clear consensus on reversal of the ROX coupler device. Endovascular aortic repair reversal of the ROX coupler device in this case was safe, effective, and improved symptoms including patient’s BP control and limb symptoms.

Keywords
Resistant hypertension • ROX arteriovenous coupler • DVT • Claudication • EVAR • Case report

Learning points
• Endovascular aortic repair reversal of ROX in this case was safe, effective, and improved symptoms.
• A multidisciplinary approach is beneficial for ROX reversal and management of resistant hypertension patients.

Introduction
Resistant hypertension has a 25% augmented risk of progression to end-stage renal disease or cerebrovascular accidents over 5 years.1–3 ROX is a self-expanding, stent-like device (Figure 1),4 which was investigated for treatment of chronic obstructive pulmonary
disease and investigators identified reductions in arterial blood pressure (BP).\(^5\)

The ROX CONTROL HTN trial\(^6,7\) showed positive initial results, with venous stenosis the major reported adverse event.\(^5,6\)

We report a rare case of ROX device failure with disabling right lower limb claudication, deep venous thrombosis (DVT), congestive heart failure, and augmented resistant hypertension.

### Timeline

| Timeline | Event | Result |
|---------|-------|--------|
| 2010    | Renal magnetic resonance angiography (MRA) | Excluded renal stenosis or pheochromocytoma |
| 2012    | Renal denervation using paradise renal denervation system (ReCor Medical, Palo Alto, CA, USA) | Continued to require increasing doses of antihypertensives |
| 2013    | Renal denervation using simplicity spyral multielectrode catheter (Medtronic, MN, USA) | Continued to require increasing doses of antihypertensives |
| 2014    | ROX coupler device inserted between the right external iliac artery and vein, following failure of insertion into left iliac system. | Claudication of right leg beginning on day of procedure and swelling both lower limbs. |
| 2015    | Ongoing buttock claudication and hip pain | Total right hip replacement of right hip joint (Dupuy) |
| 2018    | Continuous hip pain | Revision of hip surgery |
| 2018    | Referral to vascular surgery for right lower limb claudication. Ankle-brachial indices (ABIs) and CT angiogram performed | Right Lower Limb ABI reduced to 0.77 CT Angiogram demonstrated two saccular aneurysms, one in the intrarenal aorta and one in the right common iliac |
| 2018    | Reversal of ROX coupler with a concomitant endovascular aortic repair | Patient’s blood pressure and limb symptoms improved |

### Case presentation

We report a case of a 76-year-old male, non-smoker and non-diabetic with resistant primary hypertension. He was on four different anti-hypertensive medications; direct renin inhibitor, potassium-sparing diuretic, beta-blocker, and calcium-channel blocker. His average systolic pressure was consistently above 150 mmHg. A renal magnetic resonance angiography (MRA) (Figure 2) performed in 2010 excluded renal artery stenosis or pheochromocytoma. He underwent renal denervation in 2012 and 2013 in different institutions; first with the Paradise renal denervation system (ReCor Medical, Palo Alto, CA, USA), and then with Simplicity Spyral multielectrode catheter (Medtronic, Minneapolis, MA, USA). After both procedures, he continued to require increasing doses of antihypertensives.

In 2014, he had an ROX inserted between his right external iliac artery and vein after failure of insertion into his left iliac system. Postoperatively he experienced disabling claudication of his right leg beginning on the day of the procedure, and swelling of both lower limbs. Despite therapeutic interventions, his BP increased with systolic readings between 190 and 200 mmHg. Following this, he was diagnosed with right superficial femoral vein and left common iliac vein DVT and was managed with elastic stockings, clopidogrel, and apixaban daily.

His ongoing buttock claudication and hip pain were mistaken for osteoarthritic hip pain. After review by several orthopaedic specialists, he underwent total hip replacement of his right hip joint in 2015, which unsurprisingly did not alleviate his symptoms. He subsequently went on to have revision hip surgery following a product recall from Dupuy (DePuy Orthopaedics, Inc, Warsaw, IN, USA).

Throughout all of this period, his BP remained uncontrolled.

### Differential diagnosis

- Post Thrombotic Syndrome secondary to DVT.
- Arterial stenosis due to iatrogenic or arteriosclerotic aetiologies.
- Steal from his right iliac arteriovenous fistula (AVF).

An early and late phase CT-Angiogram (CTA, Figure 3) was performed at our institute to investigate right leg disabling claudication. The CTA showed two saccular aneurysms in his infra-renal aorta and right common iliac artery, and no evidence of renal artery stenosis or dissection.

His right leg claudication was deemed secondary to steal from the AVF, as no stenotic lesions were identified on CTA and his ankle-
brachial indices (ABIs) were 0.77 on the right and 1.17 on the left lower limbs. A decision was made to reverse the ROX with a concomitant endovascular aortic repair (EVAR). However, the physician who had inserted the ROX warned of the risks of reversal, which include brain haemorrhage, sudden cardiac failure, and life-threatening arrhythmias.

Percutaneous bilateral common femoral artery cannulations were performed under duplex ultrasound guidance. Pre-closure was achieved with Proglide devices (Abbott Laboratories, Chicago, IL, USA). On-table angiogram (Figure 4) allowed us to intentionally occlude the AVF by ballooning the right common iliac and external iliac arteries with a 16 x 4 mm balloon for 60 min. During that time, he had transoesophageal echo and we monitored his cardiac index, heart rate, and BP. There was no change in any of these parameters, which allowed us to deploy an Endurant II stent graft system (Medtronic, Minnesota, USA). We continued intraoperatively measuring his cardiac haemodynamic status without change. He was transferred to the intensive care unit (ICU) postoperatively, where he remained for 72 h. His postoperative ABIs were 1.31 on the right and 1.25 on the left, and he was discharged home without pain in his right hip.

Post-reversal, the patient had significant improvement in BP, with average readings of systolic BP of 135 mmHg. The EVAR device patency, absence of endoleak, and sustained occlusion of the ROX.

![Figure 2](image2.png) Magnetic resonance angiography with gadolinium, done in 2010 to investigate hypertension, found no evidence of renal artery stenosis or pheochromocytoma. The aortic diameter is 28 mm in diameter and right common iliac is 17 mm in diameter.

![Figure 3](image3.png) 3D reconstruction of early and late phase CT-Angiogram performed at our institute to investigate right leg disabling claudication.

![Figure 4](image4.png) Arterial intra-operative digital subtraction image, delineating the functioning fistula.
were demonstrated on 6 (Figure 5) and 18 months follow-up scans (Figure 6). Furthermore, the patient did not require use of elastic compression stockings and reported significant reduction in pain and improved mobility.

Discussion

The 1-year follow-up of the ROX trial reported that the principal complication was venous stenosis in 33% of patients who had ROX; all were managed with venous stenting.

ROX CONTROL HTN-1 trial authors indicated if clinical necessity required, this device can be reversed, by the implantation of a nitinol stent graft. This seems ambitious and overly simplistic, as the haemodynamic changes that this can induce on the heart require targeted slow occlusion of AVF. Our patient posed the additional challenge of abdominal aortic and right common iliac artery aneurysms.

The ROX CONTROL HTN Trial Investigators suggest that the high-velocity arterial jet that traverses the ROX creates turbulence in the contralateral venous wall and that this turbulence incites a hyperplastic response. Moreover, pre-existing arterial compression of the vein due to tortuosity and poor arterial compliance, will further increase turbulence, resulting in a pronounced venous wall injury and hyperplastic tissue response. The authors suggested that deployment of the ROX exclusively to the right arteriovenous iliac tree will reduce the incidence of venous stenosis compared to deployment in the left external artery and vein, presumably due to avoiding upstream May–Thurner Syndrome effects. Accordingly, ROX deployment was confined to the right side in the ROX CONTROL HTN-2 trial.

Lobo et al. in their safety and efficacy assessment of ROX, included 20% of patients with previous renal denervation. They reported 13 procedure-related and 12 device-related adverse events, with no adverse events reported in the control group, and all ROX patients remained hypertensive.

Hensey et al. reported a case of a lady on 11 anti-hypertensive medications with aortic dissection. She had a ROX insertion with minimal improvement; however, the underlying mechanism was believed to be due to manipulation of the Windkessel effect in blood haemodynamics, which was facilitated by the aortic graft. Our case showed a contradicting outcome as the EVAR stent reversed the AVF but reduced the elastic Windkessel effect of arterial bed. Yet, the patient showed undoubted improvement in his BP control.

Faul et al. reported 10 cases, with major adverse clinical events in 50% of patients, and 25% had early adverse events, including femoral pseudoaneurysm, myocardial infarction, and DVT. Late adverse events were reported in the remaining, all of which were device-related: DVT, closure of the shunt due to lack of clinical improvement and venous stenosis of the iliac vein. Worryingly, in their series, all patients remained hypertensive.

We believe that more transparency in the reporting of the time course of venous stenosis and occlusions and the durability of the BP effect after implantation requires further elucidation.
Conclusion

The ROX coupler device has been removed from the market. However, there remain a substantial number of patients who still have this device implanted. Endovascular targeted ROX reversal can be successful without negative impact on cardiac haemodynamic function.

Lead author biography

Prof Sherif Sultan is a pioneering vascular and endovascular senior surgeon at the Saolta Hospital group in Galway, Ireland, serving a population of more than 1 million people.

Supplementary material

Supplementary material is available at European Heart Journal - Case Reports online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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