Antihypertensive Effects of a Central Arteriovenous Anastomosis Are Mediated Through Profound Reduction in Systemic Vascular Resistance

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Device-based therapies increase therapeutic options for the treatment of hypertension for patients who fail polypharmacy because of adverse reactions or choice. Here we report the physiology related to a device, which uniquely addresses the structural pathogenesis of hypertension. Creation of a fixed-size central arteriovenous anastomosis mechanically causes an immediate and significant reduction of blood pressure (BP).[1] We present the first detailed hemodynamic findings before and after implantation of the ROX Coupler.

Case

A 74-year-old white female with longstanding isolated systolic hypertension complicated by multiple drug intolerances was referred for treatment of her hypertension. She could only tolerate liquid furosemide 20 mg daily, which lowered her office BP from 220/100 mm Hg to 190/90 mm Hg. She exhibited features of raised arterial stiffness with increased pulse pressure and pulse wave velocity, and it was felt that sympathomodulation would not be beneficial for BP control. An arteriovenous anastomosis was created using the ROX coupler, inserted in a standard catheterization laboratory setting under fluoroscopic guidance via an endovascular approach through the femoral vessels (Figure 1).[2] In situ, the coupler creates a fixed-caliber 4 mm conduit between the external iliac artery and vein, transferring 0.8 L/min of blood from the arterial to the venous compartment. The hemodynamic changes in relation to coupler placement were evaluated with left and right heart catheterization, pulse wave velocity, office BP, and ambulatory BP measurement (Tables 1–3). The opening of the arteriovenous coupler immediately leads to a large reduction in mean arterial pressure of 13% because of a profound reduction in systemic vascular resistance (SVR) by 38% on the table (Figure 2). In tandem, there are increases in stroke volume (24%), cardiac output (39%), and HR (14%) because of the proximal arteriovenous shunt. Of note, pulmonary vascular resistance was seen to immediately decline (−46%), despite an increase in pulmonary flow possibly because of improved central oxygenation. At 6-months post anastomosis formation, repeat catheterization demonstrated greater reductions in SVR (−50%) and mean arterial pressure (−24%) compared with baseline, accompanied by further increase in cardiac output (46%), stroke volume (67%), and pulmonary vascular resistance (53%). There were also large, immediate (1-day post-coupler) and durable (6-months post-coupler) reductions in office BP and ambulatory BP parameters at 6-months, with no change to the baseline medication regimen and no change in exercise capacity. The reduction in weight of 1 kg (2%) suggests that total body volume is largely unchanged after central arteriovenous anastomosis.

Discussion

The opening of the 4-mm, fixed diameter, central arteriovenous conduit leads to utilization of a proximal, low resistance, high compliance central venous segment in parallel with the aorta and results in an immediate and significant reduction in SVR (−38% with coupler opening and −50% at 6-months). The lowering of SVR in part arises because of creation of the low-resistance parallel circuit. Furthermore, the reduction in serum renin/aldosterone postcoupler, indicating reduced activation of the renin–angiotensin system, suggests a sympathoinhibitory component to the mechanism of action. Other hemodynamic and neurohumoral factors likely to facilitate reduction in SVR are mentioned in Figure 3. The increase in cardiac output immediately after coupler (38%) and at 6-months (46%) is due in part to coupler-mediated venous filling of 0.8 L/min and is also facilitated by the hemodynamic unloading of the left ventricle, consequent on a large reduction in afterload. The reduction and change in the aortic stress–strain relationship results in lower pulse wave velocity, reducing aortic augmentation. This physiology is in part appreciated in patients receiving peripheral arteriovenous fistula for dialysis, with a reduction in SVR of 17% soon after fistula formation.[3] Antihypertensive drug therapy has disparate effects on hemodynamics depending on drug class

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used, but no single drug therapy has caused reduction in SVR >15%. Furthermore, after sympathomodulatory therapy, such as renal denervation, lowering of SVR of only 19% has been demonstrated with ambulatory BP reduction of 10/5 mm Hg.[4] The central iliac arteriovenous anastomosis is a unique solution to hypertension in patients with reduced aortic compliance, a situation where neurohormonal interventions would not be anticipated to have substantial impact. The reduction in BP and SVR that we report is immediate and far greater in magnitude than alternative treatment strategies.

Disclosures

Dr Sobotka reports personal fees and other from ROX Medical. Dr Lobo reports personal fees from ROX Medical. The other authors report no conflicts.

References

1. Lobo MD, Sobotka PA, Stanton A, Cockcroft JR, Sulke N, Dolan E, van der Giet M, Hoyer J, Furniss SS, Foran JP, Witkowski A, Januszewicz A, Schoors D, Tsioufis K, Rensing BJ, Scott B, Ng GA, Ott C, Schmieder RE; ROX CONTROL HTN Investigators. Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial. *Lancet*. 2015;385:1634–1641. doi: 10.1016/S0140-6736(14)62053-5.
2. Foran JP, Jain AK, Casserly IP, Kandzari DE, Rocha-Singh KJ, Witkowski A, Katzen BT, Deaton D, Balmforth P, Sobotka PA. The ROX coupler: creation of a fixed iliac arteriovenous anastomosis for the treatment of uncontrolled systemic arterial hypertension, exploiting the physical properties of the arterial vasculature. *Catheter Cardiovasc Interv*. 2015;85:880–886. doi: 10.1002/ccd.25707.
3. Korsheed S, Eldehni MT, John SG, Fluck RJ, McIntyre CW. Effects of arteriovenous fistula formation on arterial stiffness and cardiovascular performance and function. *Nephrol Dial Transplant*. 2011;26:3296–3302. doi: 10.1093/ndt/gfq851.
4. Ewen S, Cremers B, Meyer MR, Donazzan L, Kindermann I, Ukena C, Helfer AG, Maurer HH, Laufs U, Grassi G, Böhm M, Mahfoud F. Blood pressure changes after catheter-based renal denervation are related to reductions in total peripheral resistance. *J Hypertens*. 2015;33:2519–2525. doi: 10.1097/HJH.0000000000000752.

KEY WORDS: arteriovenous fistula ■ blood pressure ■ hemodynamic ■ hypertension ■ pulse wave velocity

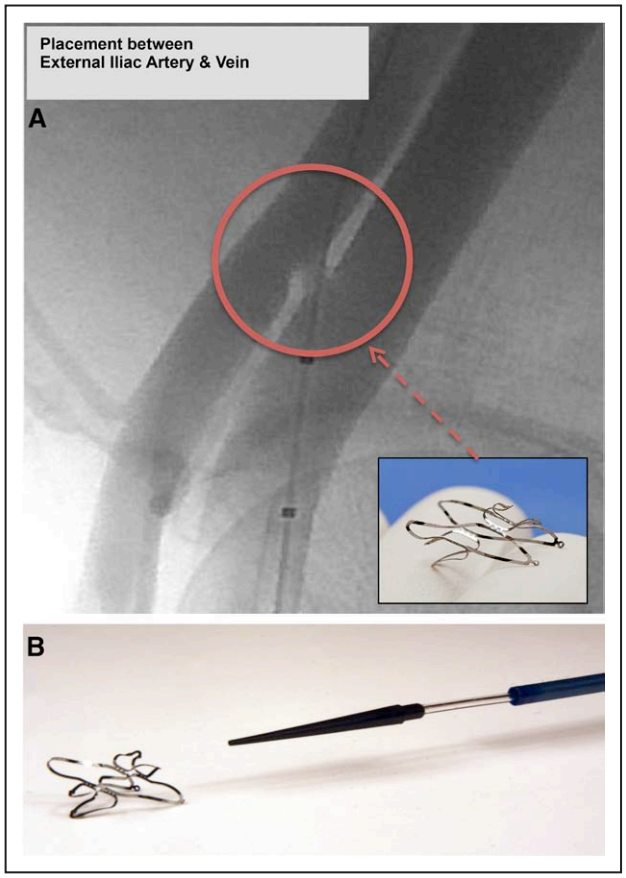

Figure 1. A, Arteriovenous coupler and introducer. The ROX coupler is a self-expanding nitinol stent-like device inserted in the catheterization laboratory in a procedure lasting 40 minutes. Reproduced with permission of ROX Medical Inc. **B**, Fluoroscopically guided arteriovenous (AV) coupler placement. This results in creation of a fixed caliber central anastomosis between external iliac artery and vein.

Table 1. Hemodynamic Changes in Relation to Coupler Placement Determined by Left and Right Heart Catheterization

Left and Right Heart Catheters	Baseline On-Table Precoupler Opening	Immediately Postcoupler Opening	6 mo FU	Change From Baseline Postcoupler Insertion (% Change vs Baseline)	Change at 6 mo FU vs Baseline (% Change vs Baseline)
Heart rate (baseline), bpm	70	80	58	10 (14)	–12 (–17)
Aorta systolic pressure, mm Hg	240	216	190	–24 (–10)	–50 (–21)
Aorta diastolic pressure, mm Hg	96	80	69	–16 (–17)	–27 (–28)
MAP, mm Hg	144	125	109	–19 (–13)	–35 (–24)
LV systolic pressure—mean, mm Hg	230.0	196	190	–34 (–15)	–40 (–17)
LV diastolic pressure—mean, mm Hg	19	24	20	5 (26)	1 (5)
RA pressure—mean, mm Hg	6	7	8	1 (17)	2 (33)
RV systolic pressure—mean, mm Hg	32	34	35	2 (6)	3 (9)
RV diastolic pressure—mean (mm Hg	3	5	8	2 (67)	5 (167)
PA systolic pressure—mean, mm Hg	30	33	32	3 (10)	2 (7)
PA diastolic pressure—mean, mm Hg	12	13	17	1 (8)	5 (42)
PA mean pressure, mm Hg	18	21	26	3 (17)	8 (44)
PAWP mean pressure, mm Hg	14	18	17	4 (29)	3 (21)
Cardiac output (mean), L/min	4.1	5.7	6.0	1.6 (39)	1.9 (46)
Systolic pressure variation	25	6	15	–19 (–76)	–10 (–40)
Stroke volume, mL	51	63	86	12 (24)	35 (67)
Cardiac index, L/min/m^2	2.5	3.4	3.6	0.9 (36)	1.1 (44)
Stroke volume index, mL/m^2	30	38	51	8 (24)	21 (70)
Systemic vascular resistance, dyn·s/cm^5	2693	1661	1346	–1032 (–38)	–1347 (–50)
Pulmonary vascular resistance, dyn·s/cm^5	78	42	119	–36 (–46)	41 (53)
LV stroke work, g m/beat	90	92	108	2 (2)	18 (20)
RV stroke work, g m/beat	8	12	21	4 (50)	13 (163)
Coronary artery perfusion pressure, mm Hg	82	62	52	–20 (24)	–30 (37)

FU indicates follow up; LV, left ventricle; MAP, mean arterial pressure; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; RA, right atrium; and RV, right ventricle.

Table 2. Oscillometric Office BP and Ambulatory BP Measurement Changes in Relation to Coupler Placement

	Baseline	1-Day Postcoupler	6 mo Postcoupler	Change at Day 1 vs Baseline (% Change vs Baseline)	Change at 6 mo vs Baseline (% Change vs Baseline)
Weight, kg	60.3	60	59.3	–0.3 (–0.5)	–1 (–2)
Office blood pressure					
Systolic BP, mm Hg	179	128 (28)	147 (18)	–51 (–28)	–32 (–18)
Diastolic BP, mm Hg	82	60	61	–18 (–22)	–19 (–23)
HR, bpm	73	82	67	9 (12)	–6 (–8)
Ambulatory BP					
24-h systolic BP, mm Hg	147	138	131	–9 (–6)	–16 (–11)
24-h diastolic BP, mm Hg	78	69	56	–9 (12)	–22 (–28)
24-h MAP, mm Hg	103	94	83	–9 (–9)	–20 (–19)
24-h HR, bpm	72	75	68	3 (4)	–4 (–6)

BP indicates blood pressure; HR, heart rate; and MAP, mean arterial pressure.

Table 3. Pulse Wave Velocity Changes in Relation to Coupler Placement

Pulse Wave Velocity	Baseline	Day 3	6 mo FU	Change at Day 3 vs Baseline (% Change vs Baseline)	Change at 6 mo vs Baseline (% Change vs Baseline)
Pulse wave velocity, m/s	12.1	7.8	10.8	–4.3 (–36)	–1.3 (–11)
Augmentation index, %	0.43	0.36	0.38	–0.07 (–16)	–0.05 (–12)

FU indicates follow up.

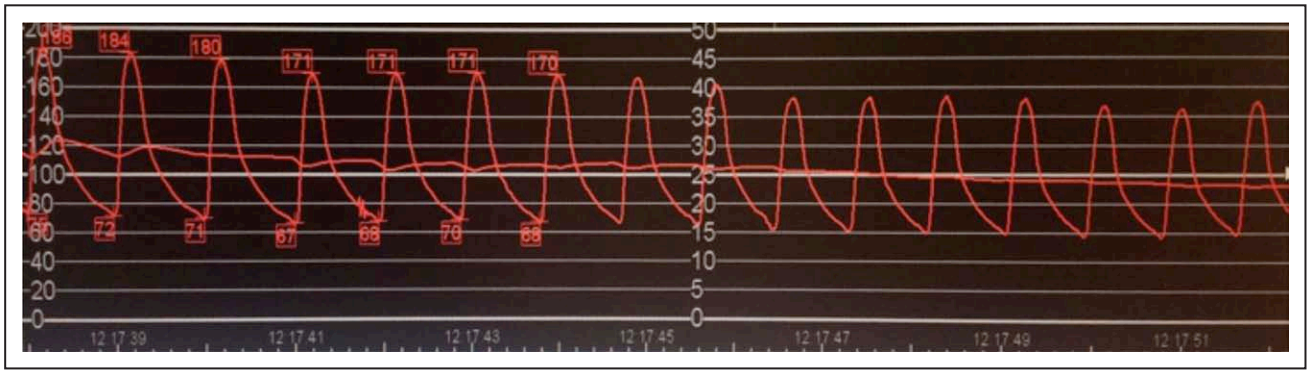

Figure 2. Immediate blood pressure (BP) reduction with opening of coupler. The on-table BP reduction is large and immediately follows opening of the anastomosis (verifying technical success of the procedure) and also is reversed with coupler closure.

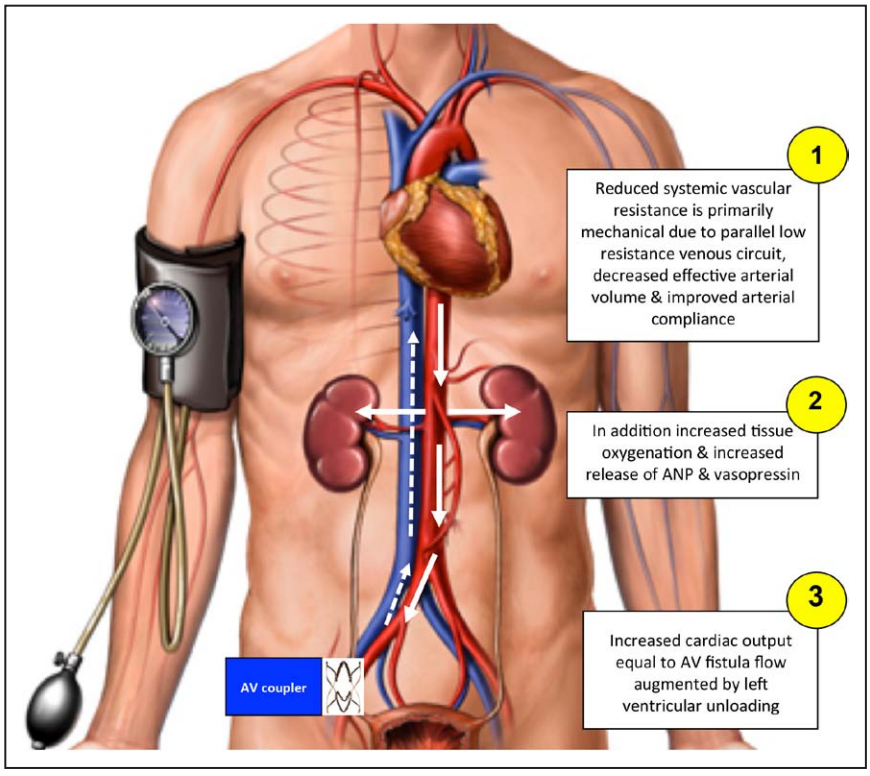

Figure 3. Central arteriovenous (AV) anastomosis effects. Dramatic reduction in invasively measured blood pressure immediately n opening of the coupler arises because of creation of a parallel low-resistance circuit and profound lowering of systemic vascular resistance. ANP indicates atrial natriuretic peptide.

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