Arteriovenous Anastomosis
Is This the Way to Control Hypertension?

Amy E. Burchell, Melvin D. Lobo, Neil Sulke, Paul A. Sobotka, Julian F.R. Paton

One in 4 people will develop hypertension, and there are estimated to be ≈1 billion patients with hypertension worldwide.[1] Hypertension confers an incremental cardiovascular risk; with each 20 mm Hg rise in systolic blood pressure (BP) or 10 mm Hg rise in diastolic BP >115/75 mm Hg giving a doubling in the risk of death from cardiovascular disease in adults aged 40 to 69 years.[2] Financial estimates indicate that if BP could be reduced to <140/90 mm Hg, the National Health Service in the UK could save ≈£97.2 million from reduced complications such as stroke, heart failure (HF), and renal failure.[3] With increasing longevity, the number of people with hypertension is predicted to reach 1.5 billion by 2025.[1] Despite the availability of a plethora of medications designed to treat hypertension, nearly half remain above target BP, leaving them at risk of cardiovascular, renal, and neurological morbidity and mortality. Recently, it has been suggested that as many as 14% of patients with hypertension on medication will develop resistance to current drug therapy.[4,5] Moreover, patients fail to sustain concordance to lifelong polypharmacy for numerous reasons, including real or perceived drug-related side effects or intolerance, cost, inconvenience, or lifestyle decision. Thus, there remains a substantial unmet clinical need to find new treatment strategies that efficiently enable patients to obtain target BP without side effects that exceed the estimated clinical benefits associated with attaining optimal BP control. Here, we look at the ROX Coupler, a device currently undergoing trials for the control of arterial hypertension, which proposes to fill this treatment gap by providing an immediate and sustained reduction in BP with a device using a mechanism substantially different from the current raft of devices that target the neurohumoral and sympathetic regulatory systems.

Device and Approach

The ROX Coupler creates a 4-mm anastomosis between the iliac artery and vein, diverting a calibrated amount of arterial blood into the venous system (≈800 mL/min). The anastomosis reduces vascular resistance and increases arterial compliance, resulting in immediate and substantial reduction of both systolic and diastolic BP. The ROX Coupler is available commercially in Europe under Conformité Européenne mark and is an intuitive, minimally invasive, quick (1 hour) procedure. It differs from predicate fistula forming procedures by targeting a central vein and strictly controlling the shunt volume by deliberate sizing of an anastomotic stent. The anastomosis may be repeatedly upsized to a maximum of 6 mm, and its effects may be reversed with a covered stent.

The ROX arteriovenous (AV) anastomosis was originally investigated in 2004 by researchers at Stanford University interested in using such a procedure for the treatment of chronic obstructive pulmonary disease.[6] In retrospective analysis of these ill patients, investigators identified significant reductions in arterial BP. The observation led to a brief safety trial in patients with resistant hypertension, and now a prospective, multicenter, randomized trial, anticipating completion later in 2014.

Reduction of BP Accompanying the Creation of an AV Anastomosis May be a Consequence of Several Classical Hemodynamic Mechanisms

The reduction in systemic BP seen after establishing a proximal AV anastomosis in patients with chronic obstructive pulmonary disease (COPD) was a serendipitous finding, but it should not have come as a significant surprise to the investigators because this effect can be predicted from several classical hemodynamic mechanisms. In 1965, Holman considered the creation and maintenance of an arteriovenous fistula (AVF) as 2 circuits running in parallel; a low resistance circuit via the fistula shunt and a high resistance circuit via the tissue capillary beds.[7] For circuits in parallel, the total resistance (R_{total}) will always be less than the value of the lowest resistance, this is in keeping with the equation for calculating resistance in parallel shown below, and so the addition of a shunt via the AVF will reduce overall systemic vascular resistance (SVR).

$$\frac{1}{\text{Rtotal}} = \frac{1}{\text{R1}} + \frac{1}{\text{R2}} + \ldots + \frac{1}{\text{Rn}}$$

The blood flow through the low resistance AV anastomosis permits blood to bypass the peripheral capillary beds and

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From the CardioNomics Research Group, Clinical Research & Imaging Centre-Bristol, Bristol Heart Institute, University Hospitals Bristol NHS Foundation Trust (A.E.B., J.F.R.P.) and School of Clinical Sciences (A.E.B.), University of Bristol, UK; William Harvey Heart Centre, NIHR Cardiovascular Biomedical Research Unit, Centre for Clinical Pharmacology, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, UK (M.D.L.); Barts Hypertension Clinic, Department of Clinical Pharmacology, Barts Health NHS Trust, London, UK (M.D.L.); Eastbourne DG Hospital, Kings Drive, Eastbourne, East Sussex, UK (N.S.); Rox Medical Inc. & The Ohio State University, St Paul, MN (P.A.S.); and School of Physiology & Pharmacology, Bristol CardioVascular, Medical Sciences Building, University of Bristol, UK (J.F.R.P.).

Correspondence to Julian F.R. Paton, School of Physiology & Pharmacology, CardioNomics Research Group, Medical Sciences Building, University of Bristol, Bristol, BS8 1TD, UK. E-mail Julian.F.R.Paton@Bristol.ac.uk

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increases venous return. An increase in right atrial pressure and cardiac volumes thus results in myocardial stretch with activation of the Frank–Starling mechanism with an increase in cardiac output (CO). Increases in right atrial pressure, stroke volume, CO, and cardiac work have been documented in patients implanted with the ROX device.[8,9]

The vascular system obeys an adaptation of Ohms law, known as Darcy law, where the flow through a tissue bed (Q) is proportional to the ratio between the pressure differential (ΔP) across the vascular bed and the resistance to flow (R), this can be expressed as Q=ΔP/R. In the normotensive setting, a reduction in SVR is compensated by an increase in CO, and BP is preserved. For the ROX Coupler to be effective in reducing BP in individuals with hypertension, it follows that the increase in CO after device deployment does not overcompensate, and that BP falls. This concept explains the instantaneous reduction in BP seen after ROX deployment because of the reduction in SVR via flow through the fistula circuit. However, BP does not seem to drop further after the immediate reduction and thus the immediate fall could also be because of the multiple mechanisms outlined below (Table). The maintenance of this hypotensive effect, despite the compensatory increase in CO and sympathoexcitatory inputs triggered in response to a sudden fall in pressure via the arterial baroreceptors, could be explained by a reduction in afterload and improved vascular compliance, and by the recruitment of the other neurohumoral mechanisms. We next consider these potential hypotheses for BP reduction via the ROX Coupler device.

Reduction of Total SVR

The mechanism underlying reduction of total SVR, described above, relates to blood flow through a low resistance anastomosis seated in parallel to the peripheral vasculature. The flow through the anastomotic circuit will be dependent on the size of the fistula and its location, with more proximal fistulae having relatively lower resistance as blood only need to travel a short distance through large caliber veins and arteries when compared with distal fistulae circuits that must include more distant flow through increasingly small caliber vessels. This is in keeping with Poiseuille Law that relates the rate at which blood flows through a small blood vessel (Q) with the difference in blood pressure at the 2 ends (P), the radius (a) and the length (L) of the artery, and the viscosity (n) of the blood:

$$Q = \frac{\pi \alpha^4 P}{8 L \eta}$$

Given this difference and the fact that the ROX Coupler gives a fixed diameter anastomosis rather than traditional hemodialysis (HD) fistulae, which slowly dilate under pressure with time, data from dialysis cohorts must be applied to the ROX population with caution. However, it has been demonstrated that, in predialysis patients, AVF formation led to a sustained reduction in both BP and arterial stiffness up to 3 months postfistula formation.[10]

Table. Potential mechanisms that may be engaged after installation of the ROX Coupler

- reduction of total SVR
- reduction of effective arterial volume
- increase in arterial compliance with reduction of reflected pulse wave
- increased oxygen delivery to tissues
  - – suppression of chemoreceptor activity in association with increases in arterial oxygen contact
  - – suppression of sympathoexcitatory drive secondary to cerebral/renal hypoperfusion
- reduced renal ischemia with decreased sympathoexcitation
- increased right atrial pressure with atrial natriuretic peptide release
- increased right atrial filling triggering the Bainbridge reflex, producing peripheral sympathoinhibition
- activation of venous baroreceptors
- activation of pulmonary arterial mechanoreceptors
- venous oxygenation and increased pulmonary blood flow.

Reduction of Effective Arterial Volume

Although overall blood volume must be preserved, at least in the short-term, preferential arterial blood flow via an AV anastomosis or shunt may reduce effective arterial volume. This manifests as a reduction in arterial volume and afterload, helping to reduce cardiac work in the context of increased cardiac volumes and output. Conversely, transfer of blood into the proximal venous circulation could result in impaired venous return distal to the anastomosis and hence venous congestion and edema. Localized thigh peripheral edema has been seen in patients treated with the ROX Coupler and compression stockings are therefore advised for all patients.[8,9,11]

Increase in Arterial Compliance

Arterial compliance (C) is defined as the ratio between the change in volume of the vessel (V) and the change in pressure (P):

$$C = \frac{\Delta V}{\Delta P}$$

This relationship is nonlinear (vessels under greater pressure are stiffer) and, therefore, if ROX deployment reduces BP and SVR, the volume/pressure relationship will be shifted and compliance should improve. Increased vascular stiffness can be seen as an increase in the reflected pulse wave, which acts to augment central arterial pressure; this may improve after ROX because of a reduction in arterial vascular resistance. Peripheral pulse wave analysis is a well validated, noninvasive method for assessing this reflected wave, often expressed as the augmentation index. Pulse wave analysis has been used to demonstrate reduced vascular compliance in patients with hypertension and an elevated augmentation index is a risk factor for cardiovascular complications.[12]

Increased Oxygen Delivery to Tissues

Studies using the ROX Coupler in patients with COPD have shown no increase in arterial oxygen saturation[8,9]; however, in the pilot study of Bertog et al,[9] there was an increase in arterial oxygen content (CaO_2) which, in combination with increased CO and blood flow, gave an increase in tissue oxygen delivery or DO_2.[6]

$$DO_2 = CO * CaO_2$$

One concern with a decrease in BP and preferential blood flow via a low resistance AV shunt is engagement of central and peripheral neurohormonal mechanisms that increase BP. This could include sympathoexcitation (and elevated arterial pressure) via central pathways (triggered by reduced cerebral perfusion, the selfish brain, Cushing response), reflex activation of renal afferents via renal hypoperfusion, and unloading of arterial baroreceptors.[13] Likewise, peripheral hypoperfusion could activate hormonal mechanisms including the renin–angiotensin–aldosterone axis causing vasoconstriction and salt and fluid retention. Ori et al[14] reported a reduction in plasma renin activity, although no change in aldosterone levels, after AVF formation before HD. However, if the creation of a moderate AV shunt improves tissue oxygen delivery, the activation of many pathways driving up BP may be blunted. Moreover, an increase in arterial oxygen content may also suppress peripheral chemoreceptor activity, which seems to be tonically hyperactive in patients with hypertension,[15] and may further reduce sympathoexcitatory drive and baroreflex suppression.

Faul and Sievert[16] go one step further and hypothesize that an increase in stroke volume after AVF formation will allow for a greater increase in CO in response to an increase in heart rate.

$$CO = SV * HR$$

They suggest that this effect may be particularly beneficial during exercise, when an amplified increase in CO because of tachycardia with an increased stroke volume in the context of a fixed flow shunt (no change in shunt flow between rest and exertion) will give a relative increase in systemic blood flow and therefore oxygen delivery during exercise.

Increased Cardiac Output

AVF formation is known to be accompanied by an increase in filling volumes and heart rate, resulting in improvements in stroke volume and CO. Interestingly, the reduction in total SVR that accompanies the creation of an anastomosis also reduces cardiac afterload and hence decreases myocyte work and improves stroke volume thus, in theory, reducing myocardial oxygen demand. This was first shown by Guyton and Sagawa who used a canine model to demonstrate that with the creation of an AVF the CO increased almost instantly, and the arterial pressure and total peripheral resistance fell, presumably because of baroreflex unloading.[17] They also showed that the mechanisms to accommodate the increased fistula flow are increased heart rate (Bainbridge reflex, see below) and myocardial contractility (including Starling's mechanism). Thus, the improvement in contractility and reduction of vascular resistance both contribute to improve emptying and higher COs.[18] In individuals with hypertension, the reduction of vascular resistance and improvement of arterial compliance is expected to significantly reduce myocardial work, even at higher heart rates and heart volume.

Increased Right Atrial Pressure With Natriuretic Peptide Release

Increased venous return because of flow via the AV anastomosis will result in an increase in right atrial pressure, which has already been demonstrated after the deployment of the ROX Coupler in patients with COPD.[8,9] Creation of an AV anastomosis results in an elevation in plasma levels of both atrial and brain natriuretic peptide and a decrease in plasma renin,[14,19] which further contribute to the decrease in SVR. Atrial natriuretic peptide is a potent vasodilatory hormone. It acts on the kidney to increase both renal blood flow (this may also help suppress renal afferent discharge) and glomerular filtration rate. It also decreases sodium reabsorption, hence could reduce blood volume. All said, the latter will have a beneficial effect on BP lowering.

Cardiopulmonary Reflex Responses to Increased Venous Return

The following reflexes are likely to be stimulated with an increase in venous return after implantation of the ROX Coupler that could contribute to reducing arterial pressure:

1. Mechanoreceptors located at the junction of the right atrium and caval veins or at the junctions of the pulmonary veins and the left atrium are likely to be activated triggering the Bainbridge reflex comprising inhibition of renal sympathetic activity, reduction in vasopressin secretion causing a diuresis and tachycardia.[20,21]
2. Cardiac vagal mechanoreceptors: Any stretch of the left ventricle consequent of increased venous return will activate cardiac vagal mechanoreceptors causing vagal-mediated bradycardia and inhibition of sympathetic vasomotor tone leading to a decrease in arterial pressure.[20]
3. Coronary artery baroreceptors respond like arterial baroreceptors and may become activated by the elevation in CO to lower SVR.

In contrast to these arterial BP–lowering reflexes, activation of the pulmonary artery baroreceptors in response to the elevated CO would produce tachycardia and increases in both sympathetic nerve activity and arterial pressure.[22]

Venous Oxygenation and Increased Pulmonary Blood Flow

Shunting of oxygenated blood from the arterial circulation into the venous system, bypassing the peripheral capillary beds, will increase the mixed venous oxygen concentration.[9] Given that hypoxia is a major vasoconstrictor in the lungs, raising the oxygen content of pulmonary arterial blood could potentially dilate the pulmonary vascular bed to increase perfusion. There may be knock on adaptive changes to nitric oxide production and endothelial function. This increase will be further augmented by the increased CO from the right ventricle. The increased pulmonary blood flow may offset any ventilation:perfusion mismatch through recruitment and distension of the pulmonary vascular bed. This effect will contribute to increased arterial oxygen content (although not necessarily arterial oxygen saturation), thus improving tissue oxygen delivery, particularly during exercise, the potentially beneficial effects of which are discussed above. The increase in oxygen content may result in inhibition of the peripheral chemoreflex.

Improved Renal Oxygenation

The kidneys are innervated with chemoreceptors that send afferent signals to the brain to reflexly increase sympathetic tone.[23] These chemoreceptors are sensitive to hypoxia and local agents such as adenosine (generated in response to hypoxia). Reducing renal hypoxia and the afferent feedback from renal

chemoreceptors may provide a mechanism to lower arterial pressure. After all, renal denervation, an existing interventional antihypertensive therapy, aims to reduce this afferent signaling. If deployment of the ROX Coupler improved blood oxygen content, then the adverse effects of renal ischemia and sympathetic activation may be reversed.

Outcome of Using ROX in Patients With COPD

To date, 2 studies have been published on the use of ROX AV anastomosis in patients with COPD. In 2010, Faul et al[8] investigated the role of a central AVF to improve exercise capacity in 15 patients with severe hypoxic COPD. Fistulae were formed using a mix of surgical AVF (saphenous vein to superficial femoral artery, end-to-side anastomosis) and endovascular treatment with the ROX Coupler device. Creation of an iliofemoral fistula in this cohort improved 6-minute walking distance (6MWD). The patients showed an increase in CO and left ventricular (LV) stroke work, but no significant change in mean arterial pressure or SVR and a reduction in mean arterial oxygen content and hemoglobin. There was a trend toward a reduction in right atrial pressure and pulmonary vascular resistance.

In 2012, Bertog et al[9] used the ROX Coupler device to treat a further 15 patients with severe COPD. They report significant increases in CO, mixed venous oxygen saturation, and oxygen delivery and a statistically significant improvement in New York Heart Association class from III to II in a nonblinded feasibility trial. In contrast to Faul et al,[11] there was a NON-significant reduction in 6MWD, which the investigators postulate could relate to worsening cardiac function or steal with relative muscle tissue hypoperfusion, although the relative preservation of 6MWD in patients with severe COPD might alone be interpreted as clinical success. Unfortunately, the authors do not comment on the effect of AVF formation on systemic arterial pressure. The mean fistula diameter determined by ultrasound postprocedure was 3.8±0.36 mm (which is similar to the expected diameter proposed for the study of ROX in resistant hypertension), with no significant change at 12 weeks suggesting patency is maintained.

Is the ROX Coupler Safe?

Historically, physicians have sought to close spontaneous and traumatic AVF because of concerns about aneurysm formation, bleeding, infection, and high-output heart failure (HOHF). Given this convention, what are the risks associated with the elective creation of an AV anastomosis using a stent? We will review safety data from the 2 published cohorts treated with the ROX Coupler device[8,9] and differentiate the stent-based safety data from the existing group of patients undergoing the elective creation of an AVF for HD, recognizing that the latter group represents both technical differences and substantial differences in patient populations. The iatrogenic fistula for end-stage renal disease entrain multiple confounding factors, including chronic kidney disease, uremia, fluid shifts with dialysis, repeated vascular access via the fistula, and in some cases the uses of prosthetic graft material in the fistula formation. The ROX Coupler device creates a fixed anastomosis with a defined shunt size and is therefore not subject to the venous stretch and dilatation seen with conventional fistula formation techniques, and the site is not intended to be repeatedly invaded for dialysis.

In the study by Faul et al,[8] 15 patients with severe COPD underwent creation of an AVF, with a mix of surgical and endovascular ROX Coupler techniques. Of the 15 patients originally treated, 3 died during the first few months post-AVF formation (2 of pneumonia, 1 of lung cancer), and so their data are not presented. No significant adverse events were reported and, specifically, no patients developed clinical HF. All patients were treated with dual antiplatelet therapy (aspirin and clopidogrel) in the first instance and, of note, all patients were given graduated compression stockings, with mild leg edema reported as a minor side-effect because of passive congestion. Of note, the current ROX device has a 4-mm diameter (previously 5 mm in these earlier studies); a 36% reduction of shunt volume from this reported series. The adverse events were not different between those with stent anastomosis or biological fistula.

Bertog et al,[9] in a pilot study, examined patients with advanced chronic lung disease, some of which seem to have had antecedent right HF in hopes of improving symptomatic dyspnoea and exercise capacity. In this morbid patient population, the procedure was associated with severe adverse events, possibly or probably related to the AV anastomosis in this particular population. A patient with advancing right HF and a documented deep vein thrombosis experienced sudden death, which may be a consequence of a venous stenosis, thrombosis, and related pulmonary embolus. Eight patients required closure of the AVF because of ipsilateral external iliac vein stenosis and ipsilateral lower extremity edema, and a single patient developed right HF.

Further data are clearly required to formally assess the safety of the ROX Coupler in the resistant hypertensive population. The device aims to create a fixed shunt volume in a less morbid population; however, caution is required as with any new device. The ROX population will age and potentially develop vascular pathology, the effects of a chronic increase in CO should be considered, and although the procedure is potentially reversible with a covered stent, or amenable to subsequent dilatation or upsizing, these additional interventions in themselves may not prove completely benign. For this reason, and given the lack of data for the ROX device at this stage, we will address some of the potential complications of central AVF formation based on data from the HD population. Caution is required when extrapolating this to the resistant hypertensive population receiving ROX, but the risk factors identified will be helpful in evaluating which patients would be safe to receive this novel intervention.

Potential Procedural Complications

Bourquelot et al[24] published long-term follow-up data for 70 patients with surgically created femoral fistulae. These lower limb fistulae had higher flow than upper limb fistulae with a mean flow of 1529±429 mL/min (range, 700–3000 mL/min) and are substantially larger in diameter than the current ROX stent anastomosis, which has a 4-mm diameter and admits 800 to 1000/min. Thirteen patients (18%) required fistula ligation: 5 diabetic patients with peripheral arterial occlusive disease and high flow fistulae developed ischemic complications (1 major amputation included); 1 patient developed lower leg compartment syndrome (acute, required fasciotomies); 2 acute venous hypertension; 2 secondary major edema; 1 high-output cardiac failure (9 years after fistula creation, high-flow fistula); 2 major bleeding.[24] The group now excludes patients with diabetes mellitus and patients

with significant peripheral arterial occlusive disease from femoral vein transposition for AVF formation. Patients are investigated preoperatively via palpation of distal pulses, duplex ultrasound evaluation, and ankle-brachial pressure indices (although there is no established cutoff for ankle-brachial pressure indices that would indicate high risk for peripheral vascular complications post-AVF formation). Patients at risk of HOHF are also excluded and those with high-flow fistulae monitored with serial echo for development of ventricular dysfunction.

Periprocedural Vascular Complications

As with all angiographic procedures performed via the femoral approach, there is a risk of procedure-related vascular complications (≈2%); these include bleeding, hematoma formation, pseudoaneurysms, and retroperitoneal hemorrhage.[25] The ROX population will be at slightly increased risk of vascular complications because they will be significantly hypertensive.

Venous Hypertension, Edema, and Thrombosis

Raised central venous pressure or venous outflow obstruction could result in peripheral venous congestion with blood stagnation, edema, and thrombosis.[9,26,27] After AVF formation, patients do indeed demonstrate an increase in right atrial pressure. Faul et al[11] advise the routine long-term use of compression stockings and aspirin in all patients undergoing ROX Coupler, and report that venous congestion after deployment of the device is usually because of venous outflow stenosis, which is amenable to percutaneous intervention with a self-expanding stent rather than balloon angioplasty or fistula closure.

Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) occurs primarily because of an increased demand in LV work because of volume/flow and pressure overload. Two forms of LVH can occur: eccentric hypertrophy results from volume overload leading to cardiac myocyte dropout because of myocyte to arteriolar capillary mismatch; concentric hypertrophy results from pressure overload because of hypertension and increased afterload and is exacerbated by anemia, hyperparathyroidism, and high angiotensin II concentrations.[28]

Holman[7] demonstrated that the size of an experimental fistula correlated with LV mass. A possible concern therefore is that the ROX Coupler could cause or exacerbate LVH. Data from the HD population are conflicting with some studies reporting an increase in LV mass (Ori et al[14]), whereas De Lima et al[29] and Gorgulu et al[30] reported no change. There are also multiple studies showing that closure of an AVF after renal transplantation results in favorable cardiac remodeling and a reduction in LVH.[31–34] In animal models, Liu et al[35] demonstrated an adaptive effect on LV mass and myocyte function and morphology with time: the initial volume overloading from a large aortocaval fistula was characterized by depressed LV function and compensatory hypertrophy resolving to normal cardiac function at 1-month postfistula formation.[36]

Further research is clearly required to clarify the relationship between AVF with the ROX Coupler and LVH. If increased systemic filling pressure, a reduction in vascular resistance, and an improvement in arterial compliance are seen after the deployment of the ROX Coupler, then a reduction in myocardial work might be expected and thus limit or even reverse existing LVH. For an individual patient, it is likely that this balance between vascular offloading via the fistula and cardiac volume loading through increased venous return will be key. In patients with good myocardial reserve, a reduction in cardiac work and an improvement in LVH could be hypothesized, but, in patients with underlying cardiac ischemia or myocardial dysfunction, the increase in cardiac work required to maintain a higher CO may result in adverse cardiac remodeling and myocardial insufficiency.

High Output Heart Failure

HOHF is defined as symptoms of cardiac failure (eg, dyspnoea, orthopnoea, paroxysmal dyspnoea, pulmonary or peripheral edema) in the presence of a supranormal cardiac index (≥4.0 L/min per m^2).[18] Having a raised CO does not in itself lead to HOHF. Over time, because of the increase in blood volume and venous return, right atrial pressure, pulmonary artery pressure, and LV end-diastolic pressure gradually increase until the myocardium decompensates, the LV then dilates, the ejection fraction declines, and the patient has symptoms of HF.[18] Alternatively, patients with LVH and diastolic dysfunction can present with symptoms of HF with a preserved ejection (HFPEF), an increasingly recognized diagnosis.

The frequency of HOHF after AVF formation remains unclear, but it is rare. Currently, there are no guidelines as to the level of AVF flow that constitutes a potential cardiac risk for patients nor are there guidelines to define high-access flows.[18] Generally, forearm accesses have flow 400 to 800 mL/min and brachial accesses 800 to 1500 mL/min,[28] with the 4-mm ROX Coupler device estimated to have a flow of 800 to 1000 mL/min. It seems that patients with high-flow AVFs >1.5 l/min are at risk of developing HOHF with those with elevated access flow/CO ratios of >30% being at highest risk.[26] Reassuringly, surgical correction of high-flow fistulas resulted in notable improvement of cardiac failure in 13 of 14 patients. Also of note is the fact that the creation of dialysis access with normal flow volume (709±311 mL/min) leads to significant increase of brain natriuretic peptide, which is related to the rate of fistula flow.[37] It may be that this increase of brain natriuretic peptide mirrors the worsening of clinically silent HF, and this could provide a useful tool for monitoring patients at high risk of HOHF (ie, those with high-flow fistulae or pre-existing cardiovascular disease).

Pulmonary Vasodilation/Pulmonary Hypertension

The evidence for a clinically significant effect on pulmonary blood flow and the development of pulmonary arterial hypertension after AVF formation for HD is equivocal, with some studies showing no relationship between AVF creation and pulmonary artery pressure (PAP) or the development of pulmonary arterial hypertension.[38,39] The ROX device for symptomatic relief from COPD caused an increase in PAP and pulmonary capillary wedge pressure, but there was no change in pulmonary vascular resistance. The long-term clinical implications of ROX deployment on pulmonary pressures and pulmonary endothelial function are yet to be established.

Steal Syndrome/Ischemia

Steal syndrome is preferential blood flow via the low resistance shunt/ fistula circuit and hypoperfusion of the distal

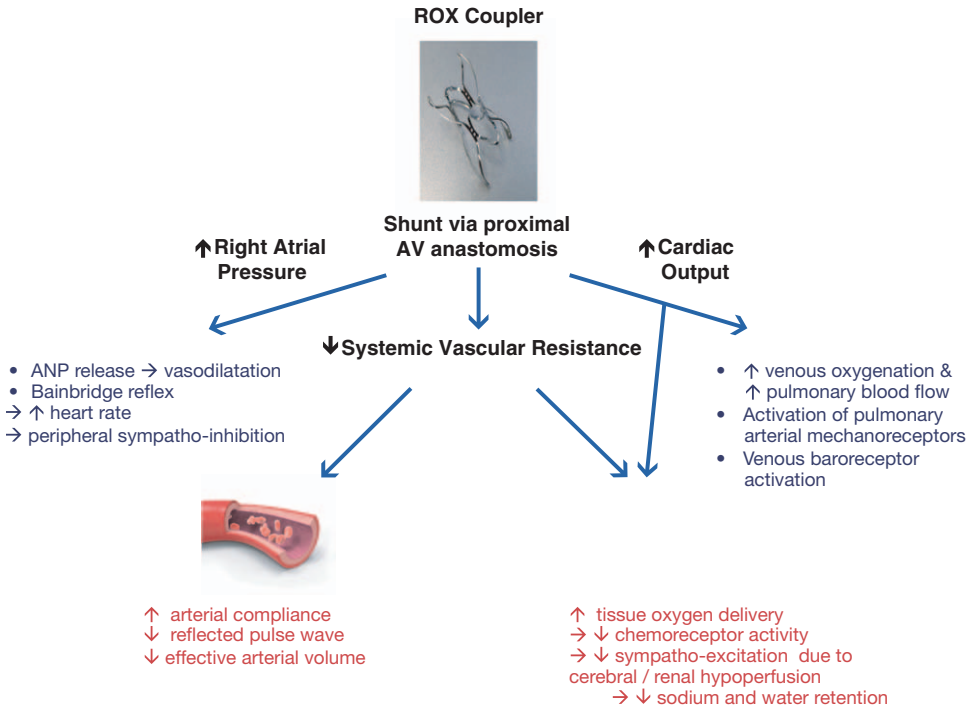

Figure. Potential mechanisms for the reduction in blood pressure seen after the creation of a fixed, central arteriovenous (AV) anastomosis using the ROX Coupler. See text for discussion. ANP indicates atrial naturetic peptide.

capillary bed and is of particular risk in those with underlying peripheral vascular disease or diabetes mellitus.[40–42] The condition worsens with a large proximal fistula and may present on increased metabolic demand such as during exercise.

Potential Additional Risk Factors

The recognized risk factors for steal syndrome such as diabetes mellitus and peripheral vascular disease and pre-existing pulmonary hypertension are already exclusion criteria for the current ROX clinical study, but there may be other potential factors that merit consideration:

- What happens during exercise? Will enough blood be available in the ipsilateral leg to maintain work output?
- In stress, what is the implication of the possible diversion of increased concentrations of circulating catecholamines into the venous circulation?
- What are the implications of increased oxygen content in arterial blood? Could this cause vasoconstriction via direct action on vascular smooth muscle or increase oxidative stress and endothelial dysfunction?

Risk–Benefit of Hypertension Treatment

The absolute reduction of cardiovascular risk with BP reduction is linear, so the magnitude of BP reduction after AV anastomosis establishes the baseline on which the noted theoretical risks can be compared. Clearly, if the ongoing trial demonstrates a significant reduction of BP after AV anastomosis, patients with hypertension would be expected to experience profound beneficial reductions of cardiovascular and stroke risk, whereas smaller reductions in BP or higher rates of irreversible adverse events would restrict clinical applications. Until full appreciation of the risk associated with the device is available, treatment of patients with modest elevation of BP or those making lifestyle decisions not to participate in poly pharmacy is ill advised.

Conclusions

The ROX Coupler device provides a novel approach in the management of patients with significant elevations of BP and those with drug resistance. Numerous beneficial autonomic mechanisms may be implicated in the potential therapeutic effect of the ROX anastomosis device, and we hypothesize that the key factors include a reduction in total SVR and an increase in cardiac volumes and reduction in afterload, resulting in an overall reduction in cardiac work despite increased CO. Improvements in arterial oxygen content may accompany this increase in CO; both acting to increase tissue oxygen delivery and thus reduce the hypertensive actions of a range of neurohumoral mechanisms including peripheral and renal chemoreceptors that drive sympathoexcitation. The reduction in SVR and decrease in effective arterial volume seen after ROX deployment will also likely result in improved vascular compliance with a reduction in the reflected pulse wave contributing to reducing cardiac work.

One fascinating question relates to the interaction between AV fistula formation and the sympathetic nervous system. It is well established that hypertension is related to sympathetic overdrive, and many current pharmacological and developing interventional therapies (eg, renal denervation, baroreflex stimulation) aim to achieve BP reduction via sympathoinhibition. It is not easy to predict what the net effect on sympathetic activity will be after ROX deployment because there are a gamut of reflexes that may be stimulated with some increasing and others decreasing sympathetic activity. The response of the sympathetic nervous system after an AV fistula should be a focus of future research.

The use of a fixed AV anastomosis is a completely novel approach for BP control in patients with elevated BP and those with drug-resistant hypertension. Its efficacy and safety in the treatment of hypertension, particularly in the long term, and the mechanisms underlying any hypotensive effect are yet to be established, but we have presented potential hypotheses

that we hope will guide further discussion and research. A European multicentre randomized study to evaluate the safety and efficacy of the ROX Coupler AV anastomosis for the treatment of resistant hypertension is already recruiting (ClinicalTrials.gov identifier: NCT01642498). The trial includes those who are renal denervation treatment failures.

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