Central arteriovenous anastomosis for patients with uncontrolled hypertension (the ROX CONTROL HTN Study): a randomised controlled trial

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Abstract

Background

Hypertension contributes to cardiovascular morbidity and mortality. We evaluated the safety and effectiveness of a 4 mm central iliac arteriovenous anastomosis to reduce blood pressure in patients with uncontrolled hypertension.

Methods

In this open-label, multicentre, prospective, randomised trial, patients with a baseline office systolic blood pressure ≥ 140 mmHg, average daytime systolic ambulatory blood pressure ≥ 135 mmHg, and diastolic ambulatory blood pressure ≥ 85 mmHg were randomly allocated in a one-to-one ratio to undergo implantation of an arteriovenous (AV) coupler device with previous treatment, or to maintain previous treatment alone (control group). The co-primary effectiveness endpoint was change in mean 24-hour systolic ambulatory blood pressure and office-based measurements of systolic blood pressure at six months as compared to baseline. Primary analysis included all patients remaining in follow-up at six months by intention to treat.

ClinicalTrials.gov, number NCT01642498.

Findings

Eighty-three (43%) of 195 patients screened for eligibility were randomly allocated to arteriovenous coupler therapy (n=44) or control (n=39) groups. Office-based systolic blood pressure measurements reduced by 26·9 ±23·9 mmHg (baseline 175

±18 mmHg, p<0·0001) in the AV Coupler group, and by 3·7 ±21·2 mmHg (baseline 171 ±22 mmHg, p=0·31 systolic) in the control group. Mean systolic 24-h ambulatory blood pressure reduced by 13·5 mmHg (±18·8; p<0·0001), in AV Coupler patients. Control patients did not change significantly in 24-h ambulatory blood pressure (-0·5 mmHg ±15·8; p=0·86). The AV Coupler was associated with the development of late ipsilateral venous stenosis in twelve (29%) of patients. There was significant reduction in high blood pressure-related events with the coupler compared to control.

Interpretation

Office and ambulatory blood pressure were significantly reduced following creation of an iliac AV anastomosis compared to control patients receiving pharmacotherapy. The intervention was associated with a reduction of hypertensive complications. These findings suggest an iliac AV anastomosis might provide valuable adjunctive therapy for patients with uncontrolled hypertension.

Funding

ROX Medical

Introduction

Hypertension remains a major cause of morbidity and mortality worldwide, being associated with coronary artery disease,[1] stroke,[2] chronic kidney disease,[3] and heart failure.[4] In clinical environments, only 48% of treated patients achieve optimal blood pressure control, the majority failing long-term persistence and adherence,[5-7] leaving them at increased cardiovascular risk.[8-10] Failure of polypharmacy to attain adequate blood pressure control may also be due to physiologic unresponsiveness to current pharmacotherapeutic strategies.

Even small increments in blood pressure (BP) are clinically relevant, as a 2 mmHg increase in systolic BP is associated with a 7% increase in mortality from coronary artery disease and a 10% increase in stroke.[11] This highlights the need for acceptable treatment strategies, and the potential utility of a safe and effective medical device causing a significant and immediate fall in arterial BP addresses an unmet clinical need of patients with drug-resistant hypertension as well as those who are unable or unwilling to maintain adherence to lifelong antihypertensive medication.

Arterial hypertrophy in response to chronic hypertension is associated with a loss of compliance. The central aorta and iliac vessels serve as conduits for blood, but their elasticity also buffers the pulsatile energy generated by the heart and cardiac cycle, decreasing cardiac afterload and myocardial stroke work and buffering highly pulsatile energy to end organs. Aortic stiffening is associated with increases in BP

variability, rises in pulse pressure, and end organ damage.[12] Arterial stiffness is independently associated with both adverse cardiovascular events and mortality.[13-16,20,30]

A novel device technology (ROX Arteriovenous (AV) Coupler, ROX Medical Inc, San Clemente, CA, USA) has been developed that causes an immediate, significant, and sustained reduction of BP by exploiting the mechanical effects of adding a low-resistance, high-compliance venous segment to the central arterial tree. [17-19] We report the results of a prospective, multicenter, international, randomised, blinded endpoint clinical trial, which aimed to show that creation of a central iliac AV anastomosis could safely reduce blood pressure in patients with uncontrolled hypertension.

Methods

Study Design and Patients

The ROX CONTROL HTN study is an international, open-label, multicentre, prospective, randomised trial of the safety and effectiveness of an AV Coupler in patients with uncontrolled hypertension. Patients aged 18-80 years with an office systolic blood pressure (OSBP) of 140 mmHg or more and average daytime ambulatory systolic blood pressure (ASBP) ≥ 135 mmHg and ambulatory diastolic blood pressure (ADBP) ≥ 85 mmHg while adhering to a stable antihypertensive drug regimen of three or more medications of different classes, including a diuretic, unchanged in dose for at least two weeks were eligible for inclusion.

Exclusion criteria included secondary hypertension other than sleep apnoea, renal denervation within the previous six months, an estimated glomerular filtration rate (eGFR) (based on the modification of diet in renal disease criteria) of less than 30 ml/min per 1·73 m^2, type 1 diabetes, current diagnosis of unstable cardiac disease requiring intervention, history of heart failure, recent myocardial infarction, unstable angina, coronary angioplasty or bypass surgery within last six months, current severe cerebrovascular disease or stroke within the previous year, significant peripheral arterial or venous disease.

Patients randomised to the treatment group with pulmonary arterial hypertension (mean pulmonary artery pressure >25 mmHg) and/or elevated pulmonary capillary wedge pressure (>15mmHg) were also excluded.

Screening was completed at 16 centres in Europe of which six were certified as hypertension centres of excellence as designated by the European Society of Hypertension or by the British Hypertension Society. The study was approved by the ethics committees at every participating site, and all patients provided written informed consent.

Randomisation

Patients were randomly assigned in a 1:1 ratio to undergo placement of the AV Coupler or to the control group. Randomisation, centrally allocated and provided

via email, was stratified by study site and previous treatment with renal denervation.

Procedures

For patients randomly assigned to undergo creation of a central iliac arteriovenous anastomosis via placement of the AV Coupler (Figure 1), the procedure is accomplished within a standard cardiovascular catheterization laboratory setting under fluoroscopic guidance. Using a modified Seldinger technique, a short 4F introducer sheath is placed into the left or right common femoral artery. An 11F customized venous introducer is placed in the ipsilateral common femoral vein approximately 2 cm inferior to the level of the arterial sheath insertion site. Target placement of the anastomotic coupler is between the distal external iliac vein and artery above the level of the femoral head and ischial spine. A Crosshair wire (ROX Medical, Inc.) is advanced through the arterial introducer to mark the target arterial crossing location. Thereafter, a pre-curved, 21-gauge retractable micropuncture crossing needle is advanced through the venous introducer to the level of the arterial crosshair wire. The needle is then advanced out of the sheath and through the adjacent venous and arterial walls. A straight floppy tipped Nitinol 0·018-in. crossing wire is advanced through the crossing needle and into the common iliac artery. Following removal of the crossing needle, the AV Coupler delivery system is advanced over the 0·018-in. wire from vein to artery. The arterial coupler arms are initially deployed, followed by the venous arms and the delivery catheter removed, leaving the 0·018-in. guide wire in situ. Lastly, a 4-mm balloon catheter is advanced

over the straight 0·018-in. guide wire, positioned within the coupler and the anastomosis dilated to a final diameter of 4-mm. Femoral artery and vein haemostasis is achieved post-procedure with simple manual compression of the arterial and venous puncture sites. Anticoagulation was determined on an individual basis by the interventionalist.[20]

Post-procedure care included wearing graduated surgical compression stockings on the treated limb for a minimum of two weeks, as deemed appropriate by the study physician.

Antihypertensive Medication Regimens

For both treatment and control groups, changes to baseline doses of all antihypertensive drugs were not allowed for at least six months, unless judged medically necessary.

Blood Pressure Monitoring: Office and Ambulatory

Blood pressure was measured at baseline prior to randomisation and at the six-month follow-up according to protocol-specified guidelines based on the Standard Joint National Committee VII, European Society of Hypertension and European Society of Cardiology recommendations.[21-22]

Office blood pressure was an average of triplicate measurements in the arm with the higher readings. BP was repeated when SBP measures were more than 15 mmHg apart and the last 3 consecutive consistent readings were recorded.

Twenty-four hour ambulatory blood pressure (ABP) was measured primarily with an oscillometric Spacelabs 90207-1Q monitor (Spacelabs Healthcare Ltd, Hertford, United Kingdom) with readings recorded at least every 30 minutes during the day and hourly at night. Ambulatory measures required a minimum of 70% reading success rate over the course of 24 hours, or alternatively a minimum of 14 daytime and 7 nighttime readings.

Endpoints

The co-primary effectiveness endpoint was change in mean 24-h ASBP and OSBP at six months as compared to baseline. Secondary endpoints were change in mean 24-h ADBP and office-based measurements of DBP (ODBP) at six months, and incidence of complications directly associated with delivery and/or use of the AV Coupler. Additional analysis specified by the Safety Committee and principal investigators included any clinical complications associated with hypertension. All adverse events were reviewed by an independent data and safety monitoring board.

Statistical analysis

With a sample size of 82 patients, we calculated that the study would have at least 90% power to show benefit of the AV Coupler over control, with respect to the

primary endpoints, assuming at least a 5 mmHg difference between groups and a 7 mmHg standard deviation in SBP. Analyses using SAS version 9.3 were completed with available data for all patients randomised. We assessed continuous variables between groups, with Student's two-sample t test. The Fisher's exact test was used to compare categorical variables. For within-group changes, a paired t test was used. Changes in pressure between groups utilized least squares (LS) means from ANCOVA model. A two-sided alpha level of 0·05 was used for all superiority testing. Data were analysed using modified intent-to-treat reporting no data on patients lost to follow-up. In the analyses of co-primary endpoints the p-values are reported without multiplicity adjustment.

Role of the funding source

The study was designed by the steering committee and advisers, including local investigators and the sponsor (ROX Medical, Inc.). Data were monitored, collected, and analysed by the sponsor and an independent statistician under the direction of MDL, PAS and DSMB. The corresponding author and all site PIs had full access to all of the data in the study and have final responsibility for the publication.

Results

From October 2012, to January 2014, 83/195 (43%) of patients screened were eligible for study inclusion. Patients were randomly allocated to the AV Coupler or control group (Figure 2). Evaluation of baseline characteristics demonstrates well

matched groups in regards to baseline systolic and diastolic blood pressures (Table 1). Observed differences in demographics are not statistically significant, likely clinically insignificant, yet too infrequent to assure the absence of associations. No statistically significant differences were observed in the number and type of antihypertensive medications between both groups (Table 2) with the exception of dihydropyridine calcium channel blockers, which was significantly lower in the AV Coupler group. Diuretics, including aldosterone antagonists, were used in 78 (94%) patients.

Of 83 patients randomised into the trial, 44 were allocated to the AV Coupler and 39 allocated to control. The modified intent-to-treat analysis at six months included 42 AV Coupler patients and 35 control patients. One AV Coupler patient withdrew consent prior to the procedure and one patient has not returned for six-month follow-up. Three control patients were lost to follow up. One control patient was exited for safety reasons; the patient was hospitalised twice for hypertensive crisis necessitating more aggressive treatment options.

Change at six months in mean OSBP for AV Coupler patients was -26·9 mmHg (±23·9; $p<0·0001$), and -20·1 mmHg (±14·0; $p<0·0001$) for ODBP. In contrast, change at six months in mean OSBP for control patients was -3·7 mmHg (±21·2; $p=0·31$), and -2·4 mmHg (±12·1; $p=0·26$) for ODBP (Figure 3). The net difference in mean office BP was -23·2/-17·7 mmHg in favor of the AV Coupler group ($p<0·0001/p<0·0001$) at six months follow-up.

In the AV Coupler group, change at six months in mean 24-h ASBP was -13·5 mmHg (±18·8; p<0·0001), and -13·5 mmHg (SD ±9·5; p<0.0001) for ADBP. Change at six months for control patients was -0·5 mmHg for ASBP (±15·8; p=0·86), and -0·1 mmHg (±9·7; p=0·96) for ADBP (Figure 3). At the six-month follow-up, the difference in mean 24-h ABP between the AV Coupler group and control group was -13·0/-13·4 mmHg (p=0·0020/p<0·0001).

Furthermore, the six-month ABP data show clinically and statistically meaningful drops in daytime -13·9/-14·7 mmHg (±20·0/±9·8; p<0·0001/p<0·0001), and nighttime -11·5/-10·0 mmHg (±17·6/±9·7; p=0·0001/p<0·0001) BP in AV Coupler patients. Control patients did not change significantly in daytime -1·5/-1·1 mmHg (±16·7/±10·5; p=0·60/p=0·56), or nighttime ABP +3·0/+2·5 mmHg (±16·8/±9·7; p=0·30/p=0·14). Comparing the groups revealed statistically significant net differences in favor of the AV Coupler group for both daytime -12·4/-13·6 mmHg (p=0·0038/p<0·0001) and nighttime -14·5/-12·5 mmHg (p=0·0010/p<0·0001) ABP.

Seventeen patients (n=10 AV Coupler; n=7 control) underwent renal denervation (RDN) no less than 6 months prior to enrollment (Figure 4). AV Coupler patients with previous RDN reduced mean OBP at six months by 34·3/21·6 mmHg (±25·9/±14·6; p=0·0024/p=0·0012), and mean 24-h ABP by 13·6/14·6 mmHg (±12·2/±8·8; p=0·0066/p=0·0006). Control patients with previous RDN

experienced a mean change in OBP of +3·2/-4·6 mmHg (±18·7/±11·9; p=0·70/p=0·39), and mean change in 24-h ABP of +5·2/+5·2 mmHg (±18·5/±12·6; p=0·52/p=0·36). Comparing the groups revealed statistically significant net differences between patients with previous RDN in favor of the AV Coupler group for both OBP -37·5/-17·0 mmHg (p=0·0029/p=0·0041) and ABP -18·8/-19·8 mmHg (p=0·0368/p=0·0086).

Eleven AV Coupler patients reduced hypertension medications during the six-month follow up, as compared to only two control patients (p=0·0303). Four AV Coupler patients increased antihypertensive medications compared to ten control patients (p=0·0382).

There was no statistically significant mean change in eGFR (ml/min per 1·73 m^2) within the treatment (-1·8 ±9·0), or the control group (+1·9 ±7·6) at six months as compared to baseline.

The AV Coupler was successfully placed in 42/43 (98%) patients. The side of implantation was at the discretion of the investigator, and 32/42 (76%) were implanted on the right side. No patient had more than one anastomosis created. Placement was not attempted in one patient due to unsuitable anatomy. Arterial deployment occurred in 3/42 (7%) procedures. In these cases the coupler was retrieved with a snare, removed via the arterial access sheath, and a second coupler was deployed as intended. One patient with arterial deployment, who was on

anticoagulants, experienced a hematoma and hemoglobin drop. Other procedural complications consisted of intimal dissection of the external iliac artery (n=1) with prophylactic covered stent placement, transient bradycardia (n=1), and contrast reaction (n=1); all complications resolved without sequelae (Table 3).

During the periprocedural period (≤ 48 hours), two serious events (urinary retention and anemia), and three minor events (transient localized or limb pain n=2, nausea/lethargy n=1) were reported; all events resolved without sequelae (Table 3).

Two late events (> 7 days post procedure) were classified as probably/possibly related to the procedure and comprised deep venous thrombosis (DVT) and lower limb pain. The DVT was deemed provoked by instrumentation of the venous system and a highly prothrombotic state due to severe contrast allergy (Table 3).

Twelve (12/42, 29%) patients in the AV Coupler group presented with clinically identifiable symptoms of unilateral lower extremity edema between 2·3 and 8·7 months post procedure and were subsequently diagnosed with iliac vein stenosis proximal to the anastomosis. Venous stenosis was treated with venoplasty alone (n=1) or stenting with venoplasty (n=11) without further complication (Table 3).

Reduction in antihypertensive medication due to hypotension was reported for 8/42 (19%) AV Coupler patients, and 0/39 control patients (p=0·0056). Notable adverse events related to hypertension were 5 hospitalisations in 3/39 (8%) control

patients for hypertensive crisis, whereas 0/42 AV Coupler patients experienced such an event (this difference was statistically significant: p=0.0122). In addition, 4/39 (10%) control patients and 1/42 (2%) AV Coupler patient experienced worsening blood pressure requiring increase in antihypertensive medication (Table 4).

Discussion

Our study, the first targeting treatment of mechanical arterial properties contributing to chronic hypertension, showed that significant reduction in blood pressure can be achieved with catheter-based implantation of a central arteriovenous anastomotic coupler in patients with uncontrolled essential hypertension despite treatment with multiple antihypertensive drugs (panel). Incorporating a segment of vein in the central arterial circuit to restore the Windkessel model[23] is expected to cause an immediate reduction of BP through the improvement of arterial compliance and reduction of vascular resistance. This treatment strategy for hypertension is unique and highlights the critical importance of the mechanical properties of the arterial system in sustaining hypertension. The resulting reduction of BP was apparent by the concordance of measurements of OBP and the double blind measurement of 24-h ABP at six months post procedure. AV Coupler patients with prior RDN had a significant reduction of both OBP and ABP, compared to control patients with prior RDN, who experienced no significant changes. These blood pressure reductions in Coupler patients with prior RDN were

not different than those experienced by Coupler RDN-naive patients (OBP p=0·47; ABP p=0·95). This suggests that inadequate response to RDN may be due in part to arterial stiffness which is not targeted by sympathomodulation. This would need to be investigated in future studies.

The observed reduction of blood pressure does not reflect the differences in use of medication between the treatment and control groups at six months. Significantly more patients with the coupler reduced antihypertensive medications compared to controls, and significantly more controls increased medications compared to the AV Coupler group. These changes in medications would tend to mask the true magnitude of blood pressure reduction consequent to the placement of the coupler.

Creation of the AV anastomosis was associated with a significant late development of venous stenosis above the anastomosis. This complication is clinically evident with signs of unilateral lower extremity edema and in some cases a simultaneous increase in BP. Subsequent therapy with a self-expanding venous stent resulted alleviation of symptoms.

Either the immediate reduction of blood pressure[20], or the unique mechanism of blood pressure reduction[24] following creation of a central arterial-venous anastomosis is associated with a significant reduction of reported hospitalisations for hypertension or cardiovascular causes within the six months following the procedure. Repeat hospitalisation for acute severe hypertension occurs in 29% of

451 hospitalized hypertension patients[25] and a reduction in hypertension-related
452 admissions was recently noted following baroreflex activation therapy[26] but has not
453 been reported in pharmacological trials of hypertension.
454
455 Our study has several limitations. The trial did not have an explicit sham-control
456 limb, raising the possibility that knowledge of treatment allocation participates in
457 the observed blood pressure reduction. In this trial control patients demonstrated
458 no average reduction of blood pressure, similar to Symplicity HTN-2[27] and unlike
459 the reported significant fall in the sham-control arm of the Symplicity HTN-3
460 study.[28] Furthermore, recruitment from hypertension centres of excellence ensured
461 that only patients with established hypertension and stable anti-hypertensive
462 regimens were included different from the subjects in the Symplicity HTN-3 trial.
463 Critically, unlike renal denervation, technical success is intra-procedurally
464 documented and associated with immediate BP fall.[20] This eliminates placebo effect
465 and isolated sham effect to interaction of subject knowledge of treatment allocation
466 with longer-term clinical behaviors. Finally a sham procedure may not be feasible
467 also because patients have spontaneously reported a thrill in the groin region
468 following coupler implantation.
469
470 We did not attempt to assess compliance with antihypertensive medications in the
471 study as the primary aim was to determine whether or not a device therapy
472 addressing mechanical aspects of the circulation could be of benefit in lowering
473 blood pressure. Furthermore no strategy for improving medicines compliance has

been demonstrated to maintain long term control of hypertension.

Another limitation is that the cardiovascular consequences of the small shunt were not formally assessed in our study protocol and are not known. However, extensive experience in patients with similarly sized shunts created for dialysis access suggests a low risk for cardiovascular decompensation. Short term improvement in LV function related to reduced peripheral and central blood pressure and increased arterial compliance has already been demonstrated in pre-dialysis patients undergoing peripheral AV fistula formation[29,30] and is likely to persist with the use of a fixed caliber shunt.[19] In patients with end stage renal failure (ESRF), it has been demonstrated that immediately following AV fistula creation, an increase in cardiac output is offset by a substantial reduction in peripheral vascular resistance.[31] Furthermore where high output cardiac failure does occur post-AV fistula formation, shunt volumes exceed 30% of cardiac output[32] and flow rates of ≥ 2.0 L/min are necessary:[33] the fixed caliber AV coupler we have implanted only permits flow of 0.8-1.2 L/min.[20] Future studies will need to address predictors of response/non-response to this therapy and mechanisms of action and long-term safety of the device.

Creation of a small central arteriovenous anastomosis, performed in a multicenter, randomised trial in patients whose blood pressure is elevated despite multiple medications, resulted in significant reduction of both office and ambulatory BP. Subsequent studies need to replicate the reported reductions of hypertension-

related diseases and morbidity, as well as the reduction in the short-term risk of hospitalisation related to hypertension. It may ultimately prove to be safe and effective for patients who are unable or unwilling to persist with life-long antihypertensive pharmacotherapy. The technique is associated with the development of symptomatic venous stenosis, managed with conventionally available effective strategies. This mechanistically unique therapeutic innovation, affirms the role of arterial compliance and vascular resistance abnormalities in patients with arterial hypertension.

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Figure Legends:

Figure 1. AV Coupler

AV Coupler deployed from the delivery catheter.

Figure 2. Consort Diagram

42/43 (97.7%) subjects underwent successful coupler placement
1 Procedure not attempted due to tortuous vessels

Figure 3. Change at 6 months from baseline in mean office systolic and diastolic blood pressure and mean 24-hr ambulatory systolic and diastolic blood pressure.

Error bars are ± 1 Standard Deviation. ABP=ambulatory blood pressure. BP=blood pressure. OBP=office blood pressure.

Figure 4. Change at 6 months from baseline in mean office systolic and diastolic blood pressure and mean 24-hr ambulatory systolic and diastolic blood pressure in the subset of patients with previous renal denervation

Error bars are ± 1 Standard Deviation. ABP=ambulatory blood pressure. BP=blood pressure. OBP=office blood pressure.