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Central iliac arteriovenous anastomosis for uncontrolled hypertension: 1 year results from the ROX CONTROL HTN trial

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ABSTRACT

Creation of a central iliac arteriovenous anastomosis using a novel nitinol coupler device results in an immediate, significant reduction of blood pressure. We present efficacy and safety findings at 12 months post coupler insertion. This open-label, multicenter, prospective, randomized trial, enrolled patients with a baseline office systolic blood pressure ≥ 140 mmHg and average daytime ambulatory blood pressure ≥ 135/85 mmHg. Subjects were randomly allocated to coupler implantation and continuing previous pharmacotherapy, or to maintain previous treatment alone. At 12 months, 39 patients who had coupler therapy were included in the intention to treat analysis. Office-based systolic blood pressure reduced by 25.1±23.3 mmHg (baseline 174±18 mmHg, p<0·0001) post coupler placement, and office diastolic blood pressure reduced by 20.8±13.3 mmHg (baseline 100±13 mmHg, p<0·0001). Mean 24-hour ambulatory blood pressure reduced by 12.6±17.4/ 15.3±9.7 mm Hg (p<0·0001 for both). In a pre-specified subset of patients who failed to respond adequately to prior renal denervation, coupler therapy led to highly significant reduction in office systolic/diastolic blood pressure (30.7/24.1 mm Hg) and significant reduction in 24-hour ambulatory systolic/diastolic blood pressure (12.4/14.4 mm Hg) at 12 months (n=9). Following coupler therapy, 14 patients (33%) developed ipsilateral venous stenosis; all were treated successfully with venous stenting. These findings confirm the importance of arterial mechanics in the pathophysiology of hypertension and support the clinical utility of a central iliac arteriovenous anastomosis.

Key Words

Blood pressure

Hypertension

Arteriovenous anastomosis

Nitinol

Blood pressure monitoring, Ambulatory

Prospective Studies

Clinical Trial Registration

ClinicalTrials.gov, number NCT01642498

https://clinicaltrials.gov/ct2/show/NCT01642498

Introduction

Uncontrolled hypertension is the most important cause of global cardiovascular morbidity and mortality, and is a major risk factor for coronary heart disease[1], stroke[2], chronic kidney disease[3], and heart failure[4]. Whilst most patients who choose to be compliant with life long polypharmacy will respond to lifestyle measures or drug therapy or a combination of the two, a proportion of patients remain uncontrolled due to treatment resistant hypertension (TRH)[5]. Estimates of the prevalence of TRH vary considerably depending on the cohorts examined but there is broad agreement that up to 10% of all hypertensive patients have TRH[6].

An important but overlooked cause of resistance to conventional antihypertensive regimens is underlying arterial stiffness. Moreover, arterial stiffness itself is an independent risk factor associated with both adverse cardiovascular events and mortality[7-9]. Loss of elastic aortic function is an impediment to the usual dual function of the aorta both as a major arterial conduit, and in its role of buffering of the pulsatile energy generated by each cardiac cycle. This results in an increase in cardiac afterload and myocardial stroke work with concomitant increases in average blood pressure (BP) levels, peak BP and BP variability, rises in pulse pressure, and ultimately end organ damage[10]. Measures of arterial stiffness can be altered by some antihypertensive drugs with effects that vary over time, and the adverse effects of drugs for patients whose hypertension is largely attributable to abnormalities in arterial stiffness remain high; it remains unclear if there is a successful pharmacological strategy for this particular form of uncontrolled hypertension[11].

We previously investigated the use of a novel implantable device (ROX Anastomotic Coupler, ROX Medical Inc, San Clemente, CA, USA) that exploits the haemodynamic effects of the creation of a low-resistance, high-compliance venous segment adjoined to the central arterial tree[12, 13] We undertook a prospective, multicenter, international, randomized, blinded endpoint clinical trial, the ROX CONTROL HTN Study (clinicaltrials.gov identifier NCT01642498), to examine the effects of this central iliac arteriovenous (cAV) coupler device in patients with uncontrolled hypertension taking 3 or more drugs[14]. At 6 months patients randomized to cAV coupler therapy demonstrated substantial and highly significant reduction in both BP and 24-hour ambulatory blood pressure (ABP) levels compared to control patients managed with usual medicines alone. There was also a striking reduction in hypertensive complications. We now report the 1 year follow up results from the ROX Control HTN Study for patients randomized to the active cAV coupler treated group.

Methods

Study Design and Patients

The ROX CONTROL HTN study was the first randomized controlled study using a fixed calibre percutaneously placed iliac cAV anastomosis to treat hypertension. In this international multicenter, prospective, open-label randomized study we evaluated the safety and effectiveness of the ROX Coupler in patients with TRH. We included patients aged 18-80 years with office systolic BP ≥ 140 mmHg and average daytime systolic ABP ≥ 135 mmHg and diastolic ABP ≥ 85 mmHg despite taking three or more anti hypertensive medications. Exclusion criteria were as follows: secondary hypertension (other than sleep apnoea), recent renal denervation (within the previous six months), reduced renal function with estimated glomerular filtration rate (eGFR) (based on the modification of diet in renal disease criteria) < 30 ml/min per 1.73 m^2, type 1 diabetes, unstable cardiac disease requiring intervention, a prior 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, active and symptomatic peripheral arterial or venous disease. Detailed methods are described in the online supplement (please see http://hyper.ahajournals.org).

Statistical analysis

Categorical medication data were analysed using a 2-tailed Fisher's Exact Test (Graph Pad software). For within-group paired data, a paired t test was used unless otherwise specified. Steering committee pre-specified analyses included analysis of blood pressure changes in

patients who had prior renal denervation. Statistics were completed using Microsoft Excel 10 and a two-sided alpha level of 0.05 was used for statistical significance.

Role of the funding source

The steering committee designed the study in conjunction with advisers, including local investigators, and the sponsor (ROX Medical). Data monitoring and collection were managed by the sponsor. The corresponding author and all site PIs had full access to all of the data in the study and have final responsibility for the decision to submit this manuscript for publication.

This trial is registered with ClinicalTrials.gov, number NCT01642498.

Results

In total 83 patients were randomized in the study of whom 42 cAV coupler-treated patients were included in the intention to treat analysis at 6 months for the co-primary efficacy endpoints. At 12 months follow up, 39 patients have been included in the intention to treat analysis as 3 patients missed their 12-month follow up visit (Figure 1). Baseline characteristics and medications of the 39 cAV-coupler treated patients are shown in Table 1 and 2 respectively and demonstrate that this was a severely hypertensive group despite multiple antihypertensive drugs.

Anti-hypertensive medication usage

Diuretic therapy was appropriately used in nearly all cAV coupler-treated patients at baseline and follow up (>90% of patients); mineralocorticoid receptor antagonists (MRA) were prescribed in 1/3 of patients (Table 2). At 12 months follow up, 14 patients (36%) had reduced antihypertensive medications (tablets or doses) due to symptomatic hypotension and 6 patients (15%) had increased their anti-hypertensives due to worsening hypertension. In 19 patients (49%) there was no net change in medication use.

Overall changes in antihypertensive medication numbers were not significant ($p=0.26$) compared to baseline therapy and there were no significant differences in use of individual antihypertensives between baseline and 12 months.

Changes in Office BP

At 6 months post-randomization, the cAV coupler group exhibited large reduction in office systolic and diastolic BP (26.9 and 20.1 mm Hg respectively, $p<0.0001$ for both) by intention to treat analysis (Figure 2). In contrast there was no change in BP noted in the control patients at 6

months (data previously published). These reductions persisted to 12 months follow up (25.1 and 20.8 mm Hg respectively, $p<0.0001$ for both) in the 39 patients for whom data were available. In addition we have analysed a consistent cohort for whom data were available at both 6 and 12 months and found no difference in the degree of office BP reduction, which remained highly significant (Figure 2).

Changes in Ambulatory BP

At 6 months the cAV coupler group demonstrated a large reduction in 24-hour systolic and diastolic ABP by intention to treat analysis (13.5 and 13.5 mm Hg, $p<0.0001$ for both). No changes in ABP were observed in the control group at 6 months (data previously published). At 12 months there were persistent reductions in 24-hour systolic and diastolic ABP (12.6 and 15.3 mm Hg, $p<0.0001$ for both) and these changes were identical for the consistent cohort (Figure 3A). The extent of BP reduction seen with cAV coupler therapy was remarkably similar during both daytime and night-time (Figure 3B) and were highly significant. The changes in ambulatory BP noted for the intention to treat cohort (data not shown) were also similar to the consistent cohort and were also highly significant.

Changes in pulse pressure (PP) from office BP

Mean PP showed improvement; however, changes were not statistically significant at 12 months. In the consistent cohort with data at 6 and 12 months (n=39) the PP was 74.6 mm Hg at baseline, 68.44 mm Hg at 6 months ($p=0.0337$) and 70.4 at 12 months ($p=0.14$). While more than half of the subjects (22/39, 56%) experienced no change or a decrease in PP, 17 of the 39 (17/39, 44%)

experienced an increase in PP. Of these, 17 subjects 14 (14/17, 82.4%) had experienced a decrease in both systolic and diastolic office BP.

Subjects with an increase in PP had a lower office systolic BP at baseline (166.5 mm Hg for those who increased PP at 12 months vs 180.5 mm Hg for those who decreased PP at 12 months) and were significantly less likely to have a net decrease in antihypertensive medication regimen at 12 months (17.6% vs 50.0%, p=.0490).

We previously demonstrated that patients with isolated systolic hypertension (ISH: office systolic BP ≥ 140 and diastolic BP < 90 mm Hg) experienced similar BP reduction to those with combined hypertension (CH: office BP ≥140/90 mm Hg)[15]. At 12 months these reductions were unchanged in both groups suggesting that cAV implantation is equally efficacious for patients with CH and ISH (data not shown).

Subjects without BP improvement at 12 months

Of the 39 subjects, 2 (2/39, 5.1%) did not demonstrate a decrease of ≥ 5 mm Hg in either office systolic BP or 24-hour systolic ABP at 12 months. One of these two subjects had pre-existing chronic atrial fibrillation which was noted to be restored to sinus rhythm at 12 months. This subject reported a greater than 25 mm Hg decrease in home systolic BP at 24 months. Therefore, one subject (1/39, 2.6%) did not experience improvement in office BP or ABP.

Changes in heart rate

Mean heart rate from 24-hour ambulatory monitoring showed no change at 12 months. In the consistent cohort with data at 6 and 12 months (n=38) the heart rate was 70.9 beats per minute at baseline, 73.4 at 6 months (p=0.16) and 71.0 at 12 months (p=0.94).

New York Heart Association (NYHA) Functional Class

NYHA functional scoring demonstrated no mean change between baseline and 12 months (baseline mean NYHA 1.33 ± 0.48 and 12 month mean NYHA 1.33 ± 0.53, p=1.0000).

Changes in renal function

At the 12-month follow-up visit, serum testing showed a statistically significant change in mean eGFR of -6.8 ± 12.9, p=0.0026, n=38) with no subject having a reduction in eGFR greater than 50%. In subjects with eGFR less than 60 at baseline (n=9), there was no significant change at 12 months (baseline mean 49.0 ±8.8; 12 month mean 45.4 ±9.6; change in mean -3.6 ± 8.2; p=0.2281). There was no relation between fall in BP and changes in eGFR over the course of the trial.

Safety

There have been no unanticipated device related adverse events reported in the ROX Control HTN trial. Safety analysis is based on the as treated population and includes all subjects who underwent placement of the ROX Coupler. Following randomization, the cAV coupler was successfully placed in 42 patients with 32 (76%) patients having implantation on the right side

which was at the discretion of the proceduralist. Procedural complications were previously reported (13 in total) and all resolved without sequelae[14].

At 6 months 12 (29%) patients had presented with ipsilateral lower limb oedema due to iliac vein stenosis upstream from the coupler. At 12 months follow up, a further 2 patients had presented with venous stenosis (14/42 in total, 33.3%). For the 32 patients with right cAV implant, 9 (28%) developed venous stenosis within the 12 month follow-up period and for the 10 patients with left implant, 5 (50%) developed venous stenosis by 12 months. All patients were treated successfully with venoplasty and stenting. Four subjects reported ongoing oedema post-treatment for venous stenosis and were prescribed continued use of compression stockings. There have been no reports of subsequent restenosis.

It was previously reported that through the six month follow-up, there were no hospitalizations for hypertensive crisis for patients treated with the cAV coupler as compared to five hospitalizations in the control group ($p=0.0225$). As of the 12 month follow-up, there continued to be no hospitalizations for hypertensive crisis in the cAV coupler group and none of the patients required reversal of the coupler (achieved using a covered stent) due to adverse effects such as heart failure.

Discussion

Extended follow up of patients with uncontrolled hypertension treated with a iliac cAV anastomosis in the ROX CONTROL HTN study has demonstrated durable office and ambulatory BP reduction with no newly identified safety reports. The magnitude of office BP reduction that was observed at 6 months follow up was greater than that reported following use of renal denervation in TRH and also use of spironolactone as a fourth line anti-hypertensive drug strategy for TRH[16]. However the degree of ABP reduction in this study was striking and much larger than that reported following renal denervation at both 6 and 12 months and establishes a genuine, significant and durable antihypertensive effect.[17]

All the patients were recruited from experienced hypertension centers of excellence and managed by accredited hypertension specialists. The fact that baseline BP was uncontrolled despite use of ~5 medications therefore indicates a particularly challenging phenotype who are at very high risk of cardiovascular events[18]. Although baseline usage of spironolactone was limited to 1/3 of patients, this reflects real life use of such drugs which are well recognized to be poorly tolerated and frequently discontinued within 6-12 months of first prescription due to side effects.[19, 20]There were unavoidable medication adjustments during the course of the study with the majority of changes arising due to symptomatic hypotension in the Coupler treated patients, affecting 36% of patients. Such changes outweigh the medication increases observed in 15% of patients such that the overall BP-lowering effect of cAV coupler therapy would have been masked to some extent in this study.

In the subgroup of patients with prior renal denervation, substantial and sustained office and ABP reduction was identified at 12 months (please see http://hyper.ahajournals.org). We have previously demonstrated that patients with isolated systolic hypertension have a similar response to cAV coupler therapy as those with systodiastolic hypertension[15]. Taken together, these findings suggest that the improvement in BP that was seen may be attributable to mechano-circulatory improvement rather than through sympathomodulation. Furthermore the finding that cAV therapy was equally beneficial in patients with CH and ISH in our study is in marked contrast to the attenuated effect of renal denervation in patients with ISH and mandates further scrutiny of the role of structural hypertension and how best it may be treated.[21, 22]

The creation of a cAV anastomosis was associated with the development of venous stenosis upstream from the conduit and was associated with symptoms of ipsilateral lower limb swelling and an increase in the BP levels. This complication was observed in 14 patients (33%) at 12 months, 12 of whom were identified in the first 6 months. The marked difference in the incidence of venous stenosis arising from left sided coupler implantation (50%) compared to right sided (28%) is likely to be due to left sided predominance of May-Thurner sydrome[23].

In all cases, venous stenosis was resolved with a self-expanding venous stent with no subsequent complications. Data from the renal haemodialysis population have demonstrated that venous stenosis occurs in up to 46% of patients following upper limb arteriovenous fistula creation and thus the rates of venous stenosis we have observed post cAV anastomosis are lower than what is predicted for this treatment modality[24]. Future iterations of the cAV coupler should result in an improved safety profile with a lower incidence of venous stenosis either due to adaptation of the

device/implantation procedure or through peri-procedural prophylactic stenting of the iliac vein or a combination of these approaches. At present it has not been determined whether anticoagulant or antiplatelet therapy might beneficially impact upon the incidence of venous stenosis.

Limitations

The limitations of study include lack of an explicit sham-control group ; however, we acknowledge that the dramatic immediate reduction of BP following the shunt opening in the treatment group may render a sham effort futile. We deliberately limited the duration of the drug stationary control group to 6 months, sacrificing control data, because of our concerns that exposing these patients to a longer duration of substantially elevated BP would be unethical and actually increases the incidence of cardiovascular complications[25].

More recent guidelines for novel anti-hypertensive strategies have recommended the use of drug adherence testing as well as ensuring stability of medications during studies of new device therapies[26, 27]. Although we did not undertake formal testing for adherence such as directly observed tablet taking or urinary drug metabolite screening our aim was to assess the efficacy and safety of the coupler device in a real world setting. It should also be highlighted that no strategy to improve medication adherence has demonstrated useful long term improvement in BP control[28]. Moreover, this device causes an immediate significant BP reduction, and experiments

reporting long term BP effects entrain the effects of home BP monitoring on patient decisions on both increasing and reducing drug adherence[29].

At present concerns about long term consequences of the cAV anastomosis remain to be fully documented. In contrast however to other interventional approaches such as renal denervation and carotid body ablation, this treatment is fully reversible as the coupler may be closed (with a covered stent), eliminating its clinical risks.

Perspectives

Targeting mechanical aspects of the circulation to improve BP control has been overlooked in the treatment of hypertension as the recent introduction of a number of devices primarily focused on sympathomodulation has demonstrated[30]. Whilst renal denervation has emerged as a frontrunner in this field, it has become increasingly apparent that sympathomodulation may be of limited benefit in the setting of a stiff circulation as commonly arises in drug refractory or resistant hypertension.

Furthermore clinical trials demonstrate wildly varying responses to renal denervation therapy with no on-table marker of procedural success[31]. Difficulty in assessing the benefit of device therapy also arises due to the ability of patients to measure their BP at home, and facilitating choices regarding their medications which may not be easily captured. This is less a Hawthorne effect and more the consequence of patients empowered to self-measure BP and choose adherence to drugs[32, 33]. With these issues to contend with, a pivotal US study is currently planned to start enrolment in early 2017 (ClinicalTrials.gov: .

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References

1. Kannel WB, Schwartz MJ, McNamara PM. Blood pressure and risk of coronary heart disease: The framingham study. *Diseases of the chest*. 1969;56:43-52

2. Kannel WB, Wolf PA, Verter J, McNamara PM. Epidemiologic assessment of the role of blood pressure in stroke. The framingham study. *JAMA : the journal of the American Medical Association*. 1970;214:301-310

3. Klahr S, Schreiner G, Ichikawa I. The progression of renal disease. *The New England journal of medicine*. 1988;318:1657-1666

4. Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for heart failure: A population-based case-control study. *The American journal of medicine*. 2009;122:1023-1028

5. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B, Carey RM. Resistant hypertension: Diagnosis, evaluation, and treatment a scientific statement from the american heart association professional education committee of the council for high blood pressure research. *Hypertension*. 2008;51:1403-1419

6. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, O'Connor PJ, Selby JV, Ho PM. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation*. 2012;125:1635-1642

7. Agabiti-Rosei E, Mancia G, O'Rourke MF, Roman MJ, Safar ME, Smulyan H, Wang JG, Wilkinson IB, Williams B, Vlachopoulos C. Central blood pressure measurements and antihypertensive therapy: A consensus document. *Hypertension*. 2007;50:154-160

8. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: An individual participant meta-analysis of prospective observational data from 17,635 subjects. *Journal of the American College of Cardiology*. 2014;63:636-646

9. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: The framingham heart study. *Circulation*. 2010;121:505-511

10. Coutinho T, Turner ST, Kullo IJ. Aortic pulse wave velocity is associated with measures of subclinical target organ damage. *JACC. Cardiovascular imaging*. 2011;4:754-761

11. Mahmud A, Feely J. Antihypertensive drugs and arterial stiffness. *Expert Rev Cardiovasc Ther*. 2003;1:65-78

12. 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. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions*. 2015;85:880-886

13. Fudim M, Stanton A, Sobotka PA, Dolan E, Krum H. The thrill of success: Central arterial-venous anastomosis for hypertension. *Current hypertension reports*. 2014;16:497

14. Lobo MD, Sobotka PA, Stanton A, et al. 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

15. Ott C, Lobo MD, Sobotka PA, et al. Effect of arteriovenous anastomosis on blood pressure reduction in patients with isolated systolic hypertension compared with combined hypertension. *Journal of the American Heart Association*. 2016;5

16. Rosa J, Widimsky P, Tousek P, et al. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: Six-month results from the prague-15 study. *Hypertension*. 2015;65:407-413

17. Mahfoud F, Ukena C, Schmieder RE, et al. Ambulatory blood pressure changes after renal sympathetic denervation in patients with resistant hypertension. *Circulation*. 2013;128:132-140

18. Pierdomenico SD, Lapenna D, Bucci A, Di Tommaso R, Di Mascio R, Manente BM, Caldarella MP, Neri M, Cuccurullo F, Mezzetti A. Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. *Am. J. Hypertens.* 2005;18:1422-1428

19. Margolis J, Gerber RA, Roberts C, Gheorghiade M. Adherence to aldosterone-blocking agents in patients with heart failure. *Am J Ther*. 2010;17:446-454

20. Strauch B, Petrak O, Zelinka T, Rosa J, Somloova Z, Indra T, Chytil L, Maresova V, Kurcova I, Holaj R, Wichterle D, Widimsky J, Jr. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. *Journal of hypertension*. 2013;31:2455-2461

21. Ewen S, Ukena C, Linz D, Kindermann I, Cremers B, Laufs U, Wagenpfeil S, Schmieder RE, Bohm M, Mahfoud F. Reduced effect of percutaneous renal denervation on blood pressure in patients with isolated systolic hypertension. *Hypertension*. 2015;65:193-199

22. Brier TJ, Jain AK, Lobo MD. Central arteriovenous anastomosis for hypertension: It is not all about sympathomodulation. *Future Cardiol*. 2015;11:503-506

23. Carroll S, Moll S. Inferior vena cava filters, may-thurner syndrome, and vein stents. *Circulation*. 2016;133:e383-387

24. Roy-Chaudhury P, Spergel LM, Besarab A, Asif A, Ravani P. Biology of arteriovenous fistula failure. *J Nephrol*. 2007;20:150-163

25. Xu W, Goldberg SI, Shubina M, Turchin A. Optimal systolic blood pressure target, time to intensification, and time to follow-up in treatment of hypertension: Population based retrospective cohort study. *BMJ*. 2015;350:h158

26. Mahfoud F, Bohm M, Azizi M, et al. Proceedings from the european clinical consensus conference for renal denervation: Considerations on future clinical trial design. *European heart journal*. 2015;36:2219-2227

27. Zannad F, Stough WG, Mahfoud F, Bakris GL, Kjeldsen SE, Kieval RS, Haller H, Yared N, De Ferrari GM, Pina IL, Stein K, Azizi M. Design considerations for clinical trials of autonomic modulation therapies targeting hypertension and heart failure. *Hypertension*. 2015;65:5-15

28. Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev*. 2014:CD000011

29. Abdullah A, Othman S. The influence of self-owned home blood pressure monitoring (hbpm) on primary care patients with hypertension: A qualitative study. *BMC Fam Pract*. 2011;12:143

30. Lobo MD, Sobotka PA, Pathak A. Interventional procedures and future drug therapy for hypertension. *European heart journal*. 2017;38:1101-1111

31. Mahfoud F, Bhatt DL. Catheter-based renal denervation: The black box procedure. *JACC Cardiovasc Interv*. 2013;6:1092-1094

32. Azizi M, Sapoval M, Gosse P, et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (denerhtn): A multicentre, open-label, randomised controlled trial. *Lancet*. 2015;385:1957-1965

33. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. *The New England journal of medicine*. 2014;370:1393-1401

Novelty and Significance

What is new

Implantation of a nitinol coupler to create a fixed calibre (4mm) central iliac arteriovenous anastomosis represents a unique way to treat uncontrolled hypertension. As opposed to other device therapy of hypertension (including renal sympathetic denervation and baroreflex activation therapy), this novel approach targets mechanical aspects of the circulation although it is likely there are sympathomodulatory aspects to the mechanism of action which remain to be clearly elucidated.

What is relevant

Device therapy of hypertension is a more invasive means to control blood pressure and is rightly restricted to use in clinical trials/registries. Such approaches merit investigation given the increasing evidence for overt/covert non-adherence to polypharmacy in patients with uncontrolled/resistant hypertension. Unlike renal denervation, coupler therapy is entirely reversible using a simple procedure to close off the device with a covered stent.

Summary

We demonstrate substantial, durable reduction in office and ambulatory BP at 12 months post coupler implantation. One third of the patients developed an ipsilateral venous stenosis which was reversed using a venous stent. No other safety signal was noted up to the 12 month follow up period. Future iterations of the device should aim to minimise the incidence of venous stenosis and explore the utility of starting with a smaller conduit diameter.

Figure Legends

Figure 1: Trial Profile

Figure 2: Change from baseline in office blood pressure (OBP) at 6 and 12 months post central arteriovenous (cAV) coupler implant.

Data are mean (SD). SBP=systolic blood pressure. DBP= diastolic blood pressure.

Figure 3: Ambulatory BP (ABP) changes

3A. Change from baseline in 24 hour ABP at 6 and 12 months post cAV coupler implant.

3B. Change from baseline in daytime and nighttime ABP at 6 and 12 months post AV coupler implant.

Data are mean (SD). SBP=systolic blood pressure. DBP= diastolic blood pressure.

Table 1: Demographic and Baseline Characteristics for patients with 12 month data (n=39)

Characterstics	**Arteriovenous Coupler (n = 39)**
Age (years)	60 ± 9
Female	10 (26%)
White ethnic origin	35 (90%)
Body-mass index (kg/m^2)	30 ± 4
eGFR (ml/min per 1.73 m^2) MDRD Calculation*	74 ± 20
Previous renal denervation	9 (23%)
Coronary artery disease	7 (18%)
Type 2 diabetes mellitus	8 (21%)
Prior cerebrovascular events	5 (13%)
Baseline office systolic blood pressure (mm Hg)	174 ± 18
Baseline office diastolic blood pressure (mm Hg)	100 ± 13
Baseline 24-Hr ambulatory systolic blood pressure (mm Hg)	158 ± 15
Baseline 24-Hr ambulatory diastolic blood pressure (mm Hg)	93 ± 11
Baseline Daytime ambulatory systolic blood pressure (mm Hg)	160 ± 15
Baseline Daytime ambulatory diastolic blood pressure (mm Hg)	95 ± 11

Baseline Nighttime ambulatory systolic BP (mm Hg)	150 ± 19
Baseline Nighttime ambulatory diastolic BP (mm Hg)	85 ± 12

Data are mean ± Standard Deviation or number (%).

* eGFR=estimated glomerular filtration rate. MDRD=Modification of Diet in Renal Disease.

Table 2: Antihypertensive Medication Use Baseline vs 12 Months post ROX Coupler implant

Drug treatment	**Baseline (n = 39)**	**12 Months (n = 39)**
Mean (SD) number of antihypertensive medications	4.6 ± 1.6	4.5 ± 1.4
Patients on five or more medications	20 (51%)	17 (44%)
Diuretics	36 (92%)	37 (95%)
Thiazide	23 (59%)	21 (54%)
Loop	12 (31%)	15 (38%)
Aldosterone antagonist	14 (36%)	12 (31%)
Potassium-sparing	0 (0%)	0 (0%)
ACE inhibitors	17 (44%)	13 (33%)
Angiotensin receptor blockers	21 (54%)	23 (59%)
Direct renin inhibitors	3 (8%)	2 (5%)
β blockers	28 (72%)	27 (69%)*
Calcium-channel blockers	29 (74%)	32 (82%)
Dihydropyridine	25 (64%)	27 (69%)
Non-Dihydropyridine	4 (10%)	5 (13%)

Alpha-blockers	13 (33%)	10 (26%)[†]
Centrally acting sympatholytics	5 (13%)	4 (10%)
Alpha adrenergic agonists	6 (15%)	4 (10%)
Vasodilators	1 (3%)	1 (3%)
Nitroglycerin / Nitrates	4 (10%)	4 (10%)

Data are number (%) unless stated otherwise. ACE=angiotensin-converting enzyme.

[*]Not included: one subject with new prescription for Bisoprolol 2.5 mg/daily for rate control.

[†]Not included: two subjects with new prescription for Tamsulosin 400 mcg/daily for prostate enlargement/cancer.