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

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Summary

Background Hypertension contributes to cardiovascular morbidity and mortality. We assessed the safety and efficacy of a central iliac arteriovenous anastomosis to alter the mechanical arterial properties and reduce blood pressure in patients with uncontrolled hypertension.

Methods We enrolled patients in this open-label, multicentre, prospective, randomised, controlled trial between October, 2012, and April, 2014. Eligible patients had baseline office systolic blood pressure of 140 mm Hg or higher and average daytime ambulatory blood pressure of 135 mm Hg or higher systolic and 85 mm Hg or higher diastolic despite antihypertensive treatment. Patients were randomly allocated in a 1:1 ratio to undergo implantation of an arteriovenous coupler device plus current pharmaceutical treatment or to maintain current treatment alone (control). The primary endpoint was mean change from baseline in office and 24 h ambulatory systolic blood pressure at 6 months. Analysis was by modified intention to treat (all patients remaining in follow-up at 6 months). This trial is registered with ClinicalTrials.gov, number NCT01642498.

Findings 83 (43%) of 195 patients screened were assigned arteriovenous coupler therapy (n=44) or normal care (n=39). Mean office systolic blood pressure reduced by 26·9 (SD 23·9) mm Hg in the arteriovenous coupler group (p<0·0001) and by 3·7 (21·2) mm Hg in the control group (p=0·31). Mean systolic 24 h ambulatory blood pressure reduced by 13·5 (18·8) mm Hg (p<0·0001) in arteriovenous coupler recipients and by 0·5 (15·8) mm Hg (p=0·86) in controls. Implantation of the arteriovenous coupler was associated with late ipsilateral venous stenosis in 12 (29%) of 42 patients and was treatable with venoplasty or stenting.

Interpretation Arteriovenous anastomosis was associated with significantly reduced blood pressure and hypertensive complications. This approach might be a useful adjunctive therapy for patients with uncontrolled hypertension.

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Introduction

Hypertension remains a major cause of morbidity and mortality worldwide, and is 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 optimum blood pressure control, but most of these do not maintain long-term adherence,[5–7] which leaves them at increased cardiovascular risk.[8–10] The failure of polypharmacy to attain adequate control of blood pressure might also be due to physiological unresponsiveness.

Even small increments in blood pressure are clinically relevant: a 2 mm Hg increase in systolic blood pressure is associated with a 7% increase in risk of dying from coronary artery disease and a 10% increase in risk of stroke.[11] Acceptable and effective treatment strategies are, therefore, required. A safe and effective medical device that leads to an immediate and substantial fall in arterial blood pressure would address the unmet clinical needs of patients with drug-resistant hypertension and those who are unable or unwilling to adhere to lifelong antihypertensive medication.

Arterial hypertrophy in response to chronic hypertension is associated with a loss of arterial compliance. The central aorta and iliac vessels serve as conduits for blood, but their elasticity also acts as a buffer to end organs against the highly pulsatile energy generated by the heart and cardiac cycle, which decreases cardiac afterload and myocardial stroke work. Aortic stiffening is associated with increases in blood pressure variability, pulse pressure, and end organ damage,[12] and is independently associated with adverse cardiovascular events and mortality.[13–18]

The novel arteriovenous ROX Coupler (ROX Medical, San Clemente, CA, USA; figure 1) leads to an immediate, substantial, and sustained reduction of blood pressure by adding a low-resistance, high-compliance venous segment to the central arterial tree to exploit the natural mechanical effects.[19–21] We report the results of a prospective, multicentre, international, randomised, clinical trial, in which we investigated whether creation of a central iliac arteriovenous anastomosis could safely reduce blood pressure in patients with uncontrolled hypertension.

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Methods

Study design and patients

The ROX CONTROL HTN study is an international, open-label, multicentre, prospective, randomised, controlled trial investigating the safety and efficacy of an arteriovenous coupler in the treatment of patients with uncontrolled hypertension. Between October, 2012, and April, 2014, patients were screened at 16 centres in Europe, of which six were certified as hypertension centres of excellence by the European Society of Hypertension or the British Hypertension Society. Eligible patients were aged 18–80 years and had office systolic blood pressure 140 mm Hg or more and average daytime ambulatory blood pressure 135 mm Hg or higher systolic and 85 mm Hg or higher diastolic while taking an antihypertensive drug regimen of three or more medications of different classes, including a diuretic, unchanged in dose for at least 2 weeks.

Exclusion criteria were secondary hypertension other than that related to sleep apnoea, renal denervation within the previous 6 months, an estimated glomerular filtration rate (based on the modification of diet in renal disease criteria) of less than 30 mL/min per 1·73 m², type 1 diabetes mellitus, current diagnosis of unstable cardiac disease requiring intervention, history of heart failure, myocardial infarction, unstable angina, coronary angioplasty, or bypass surgery within the previous 6 months, current severe cerebrovascular disease or stroke within the previous year, and severe peripheral arterial or venous disease. Patients randomised to the treatment group with pulmonary arterial hypertension (mean pulmonary artery pressure higher than 25 mm Hg), raised pulmonary capillary wedge pressure (higher than 15 mm Hg), or both at the time of coupler implantation were also excluded.

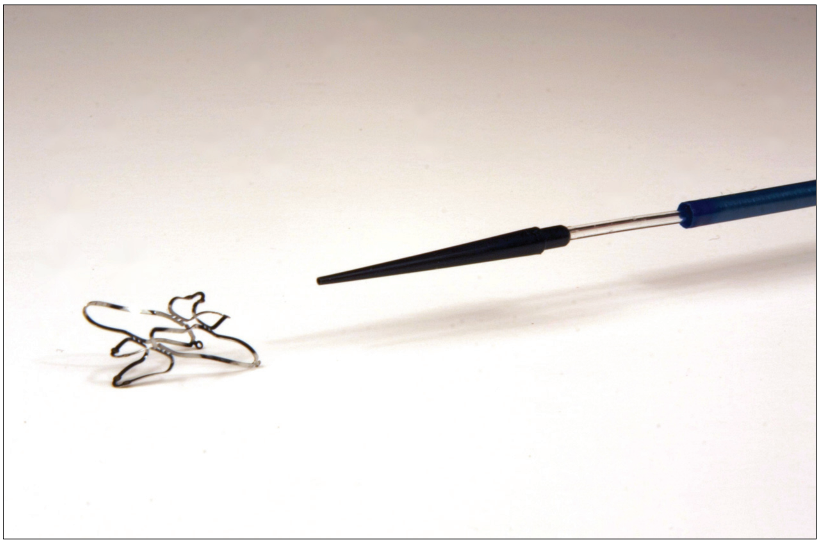

Figure 1: **Arteriovenous ROX Coupler and deployment catheter**
Reproduced by permission of ROX Medical, San Clemente, CA, USA.

The study was approved by the ethics committees at every participating site. All patients provided written informed consent.

Randomisation

Patients were randomly assigned in a 1:1 ratio to undergo creation of a central iliac arteriovenous anastomosis by placement of the ROX Coupler plus continuation of current pharmaceutical treatment or to maintain current treatment alone (control group). The randomisation schedule was computer generated, centrally allocated via email, and was stratified by study site and previous treatment with renal denervation.

Procedures

Placement of the arteriovenous coupler was accomplished in a standard cardiovascular catheterisation laboratory setting under fluoroscopic guidance. With a modified Seldinger technique, a short 4 F introducer sheath was placed into the left or right common femoral artery. An 11 F customised venous introducer was placed in the ipsilateral common femoral vein approximately 2 cm inferior to the arterial sheath insertion site. Target placement of the anastomotic coupler was between the distal external iliac vein and artery, above the level of the femoral head and ischial spine. A crosshair wire (ROX Medical) was advanced through the arterial introducer to mark the target location, after which a precurved, 21 gauge retractable micropuncture crossing needle was advanced through the venous introducer to the crosshair position. The needle was advanced out of the sheath and through the adjacent venous and arterial walls. A straight floppy-tipped nitinol 0·018 inch crossing wire was advanced through the crossing needle and into the common iliac artery. After removal of the crossing needle, the ROX Coupler delivery system was advanced over the crossing wire from vein to artery. The arterial coupler arms were deployed first, followed by the venous arms, and the delivery catheter was removed, leaving the crossing wire in situ. Lastly, a 4 mm balloon catheter was advanced over the straight crossing wire, positioned within the coupler, and the anastomosis was dilated to a final diameter of 4 mm. Femoral artery and vein haemostasis after the procedure was achieved with simple manual compression of the arterial and venous puncture sites.

Use of anticoagulation was decided on an individual basis by the treating physician.[17] Patients wore graduated surgical compression stockings on the treated limb for a minimum of 2 weeks after coupler placement, as deemed appropriate by the study physician. For patients in the treatment and control groups, changes to baseline doses of all antihypertensive drugs were not allowed for at least 6 months unless judged medically necessary.

Blood pressure monitoring

Blood pressure was measured at baseline before randomisation and at the 6-month follow-up visit, in line

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with the Standard Joint National Committee VII, European Society of Hypertension and European Society of Cardiology recommendations.[22,23]

Office blood pressure was the average of triplicate measurements in the non-dominant arm. If systolic blood pressure values were more than 15 mm Hg apart, measurement was repeated and the final value based on the last three consecutive consistent readings.

24 h ambulatory blood pressure was measured primarily with an oscillometric Spacelabs 90207-1Q monitor (Spacelabs Healthcare, Hertford, UK), with readings recorded at least every 30 min during the day and every 60 min at night. Measurements were deemed acceptable if at least 70% of readings over 24 h or 14 daytime and seven night-time readings were successfully recorded.

Outcomes

The primary endpoint was mean change in office systolic and 24 h ambulatory systolic blood pressure at 6 months from values at baseline. Secondary endpoints were mean change in office and 24 h ambulatory diastolic blood pressure at 6 months and any complications directly associated with delivery, use, or both, of the arteriovenous coupler. An additional outcome, specified by the independent data safety monitoring board and principal investigators, was any clinical complications associated with hypertension. All adverse events were reviewed by the data and safety monitoring board.

Statistical analysis

We calculated that the study would have at least 90% power with a sample size of 82 patients to show benefit of the ROX Coupler over control, with respect to the primary endpoints, assuming at least a 5 mm Hg difference between groups (SD 7 mm Hg) in systolic blood pressure. We assessed continuous variables between groups, with Student's two-sample *t* test. Fisher's exact test was used to compare categorical variables. For within-group changes we used a paired *t* test. Changes in blood pressure between groups were assessed with least squares means from an ANCOVA model. A two-sided α level of 0·05 was taken as the significance threshold for all superiority testing. Data were assessed with a modified intention-to-treat analysis in which no data were included from patients lost to follow-up. In the analyses of the primary endpoint, the p values are reported without adjustment for multiplicity. Analyses were done with SAS (version 9.3). This study is registered with ClinicalTrials.gov, number NCT01642498.

Role of the funding source

Data were monitored, collected, and analysed by the funder and an independent statistician under the direction of MDL, PAS, and the data safety monitoring board. The funder had no role in study design. PAS participated in the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

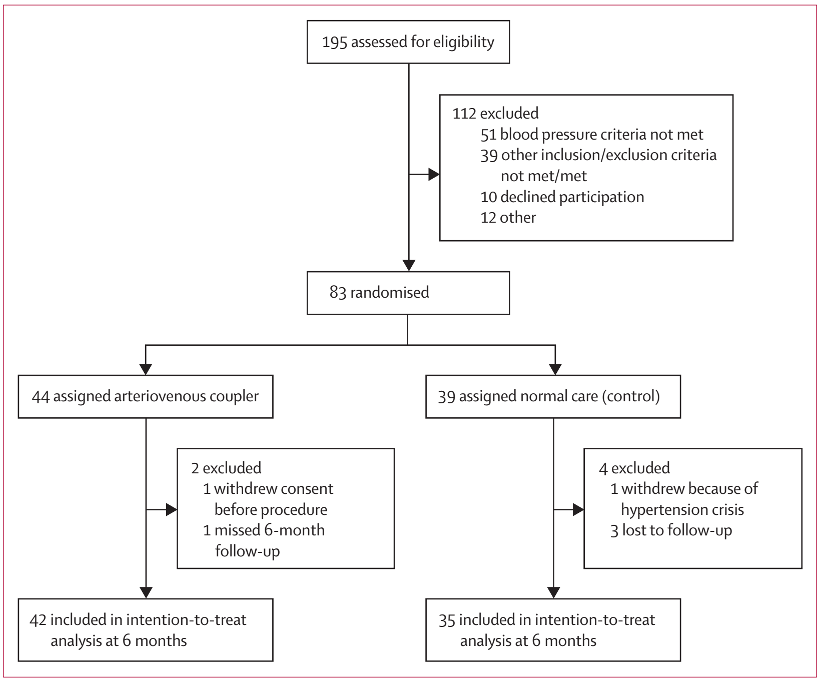

Figure 2: **Trial profile**

Results

Of 195 patients screened, 83 (43%) were eligible for inclusion (figure 2). Baseline blood pressure characteristics were well matched in the two groups (table 1). Differences between groups were seen for some demographics; these were not significant and probably have no clinical relevance, but were not infrequent enough to assure the absence of associations. No significant differences were seen between groups in the number and type of antihypertensive medications (table 2), except for dihydropyridine calcium-channel blockers, for which use was significantly lower in the arteriovenous coupler group. Diuretics, including aldosterone antagonists, were used in 78 (94%) patients.

42 patients in the arteriovenous coupler group and 35 in the control group were included in the modified intention-to-treat analysis (figure 2). Mean changes in office and 24 h ambulatory systolic blood pressure at 6 months were significantly greater in the arteriovenous coupler group than in the control group (figure 3). Net mean differences were all in favour of the arteriovenous coupler group (office blood pressure –23·2 mm Hg systolic and –17·7 mm Hg diastolic, both p<0·0001, and ambulatory blood pressure –13·0 mm Hg systolic, p=0·0020, and –13·4 mm Hg diastolic, p<0·0001). Daytime and night-time ambulatory blood pressure values also decreased significantly in the arteriovenous coupler group (daytime: systolic –13·9 [SD 20·0] mm Hg and diastolic –14·7 [9·8] mm Hg, both p<0·0001; night-time: systolic –11·5 [17·6] mm Hg, p=0·0001, and diastolic –10·0 [9·7], p<0·0001), compared with no

	Arteriovenous coupler group (n=44)	Control (n=39)
Age (years)	59 (9)	58 (9)
Female	11 (25%)	14 (36%)
White ethnic origin	40 (91%)	31 (79%)
Body-mass index (kg/m²)	30 (4)	30 (5)
eGFR (mL/min per 1·73 m²)*	76 (20)	77 (18)
Previous renal denervation	10 (23%)	7 (18%)
Coronary artery disease	7 (16%)	10 (26%)
Type 2 diabetes mellitus	9 (20%)	5 (13%)
Previous cerebrovascular events	5 (11%)	8 (21%)
Baseline office blood pressure (mm Hg)		
Systolic	175 (18)	171 (22)
Diastolic	100 (13)	100 (18)
Baseline ambulatory blood pressure (mm Hg)		
24 h systolic	157 (15)	156 (14)
24 h diastolic	93 (11)	93 (13)
Daytime systolic	160 (15)	160 (14)
Daytime diastolic	95 (11)	95 (13)
Night-time systolic	149 (18)	146 (18)
Night-time diastolic	85 (13)	84 (14)

Data are mean (SD) or number (%). eGFR=estimated glomerular filtration rate. *Modification of diet in renal disease calculation.

Table 1: **Demographics and baseline characteristics**

	Arteriovenous coupler group (n=44)	Control group (n=39)
Mean (SD) number of antihypertensive medications	4·6 (1·5)	5·0 (1·6)
Patients taking ≥5 medications	21 (48%)	23 (59%)
Diuretics	41 (93%)	37 (95%)
Thiazide	26 (59%)	24 (62%)
Loop	13 (30%)	10 (26%)
Aldosterone antagonist	16 (36%)	14 (36%)
Potassium-sparing	0	1 (3%)
ACE inhibitors	18 (41%)	13 (33%)
Angiotensin-receptor blockers	25 (57%)	23 (59%)
Direct renin inhibitors	3 (7%)	2 (5%)
β blockers	31 (70%)	24 (62%)
Calcium-channel blockers	31 (70%)	36 (92%)
Dihydropyridine	27 (61%)	33 (85%)
Non-dihydropyridine	4 (9%)	4 (10%)
α blockers	16 (36%)	17 (44%)
Centrally acting sympatholytics	5 (11%)	8 (21%)
α adrenergic agonists	6 (14%)	8 (21%)
Vasodilators	1 (2%)	2 (5%)
Nitroglycerin or nitrates	4 (9%)	4 (10%)

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

Table 2: **Antihypertensive medications**

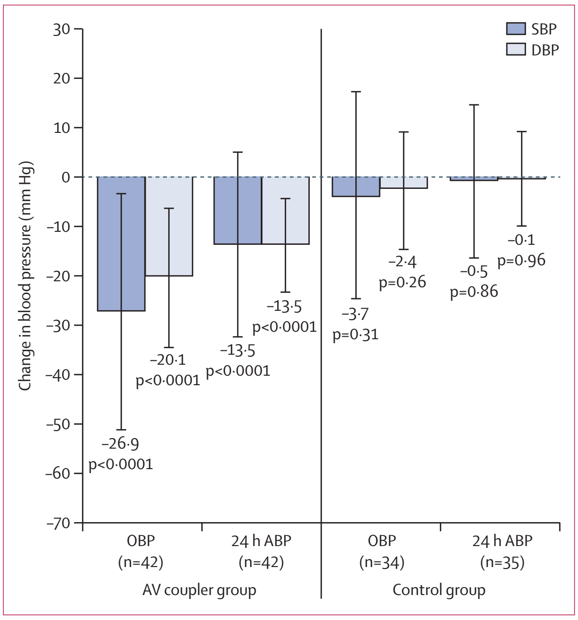

Figure 3: **Change from baseline in blood pressure at 6 months**
Data are mean (SD). SBP=systolic blood pressure. DBP=diastolic blood pressure. OBP=office blood pressure. ABP=ambulatory blood pressure. AV=arteriovenous.

significant change in the control group (daytime: –1·5 [16·7] mm Hg systolic, p=0·60, and –1·1 [10·5] mm Hg diastolic, p=0·56; night-time: 3·0 [16·8] mm Hg systolic, p=0·30, and 2·5 [9·7] mm Hg diastolic, p=0·14).

17 patients (n=10 in the arteriovenous coupler group and n=7 in the control group) had previously undergone renal denervation within 6 months of enrolment. Those in the arteriovenous coupler group had significant mean reductions in systolic and diastolic office blood pressure and systolic and diastolic mean 24 h ambulatory blood pressure at 6 months (figure 4). In contrast, mean changes in the control patients who had undergone renal denervation were not significant for office or 24 h ambulatory blood pressure (figure 4). Net mean differences were all in favour of the arteriovenous coupler group (office blood pressure –37·5 mm Hg systolic, p=0·0029, and –17·0 mm Hg diastolic, p=0·0041, and ambulatory blood pressure –18·8 mm Hg systolic, p=0·0368, and –19·8 mm Hg diastolic, p=0·0086).

11 patients in the arteriovenous coupler group had the number of hypertension medications reduced during the 6-month follow-up, compared with only two in the control group (p=0·0303), while four and ten, respectively, had the number of antihypertensive medications increased (p=0·0382). No significant mean change from baseline was seen in estimated glomerular filtration rate in the arteriovenous coupler (–1·8 [SD 9·0] mL/min per 1·73 m²) or control group (1·9 [7·6] mL/min per 1·73 m²) at 6 months.

The arteriovenous coupler was successfully placed in 42 (98%) of 43 patients. The side of implantation was at the discretion of the investigator; 32 (76%) of 42 were

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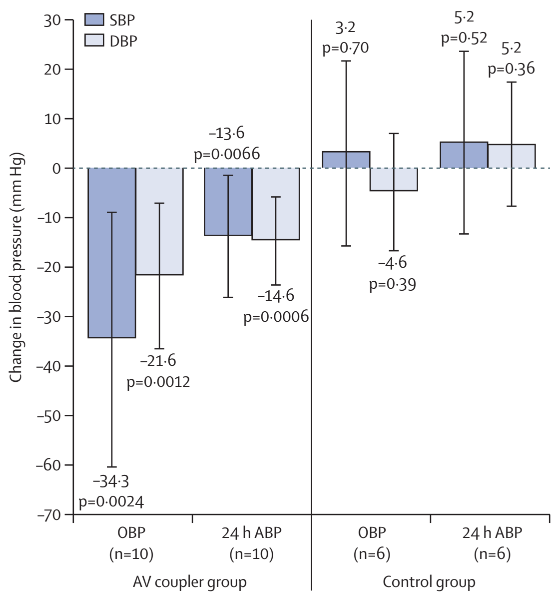

***Figure 4:* Change from baseline in blood pressure at 6 months in patients with previous renal dernervation**

Data are mean (SD). SBP=systolic blood pressure. DBP=diastolic blood pressure. OBP=office blood pressure. ABP=ambulatory blood pressure. AV=arteriovenous.

	Number (%) of adverse events (n=42)
Procedural complication	
Arterial deployment*	3 (7·1%)
Intimal dissection iliac artery	1 (2·4%)
Transient bradycardia	1 (2·4%)
Contrast reaction	1 (2·4%)
Urinary retention	1 (2·4%)
Anaemia	1 (2·4%)
Transient or localised pain	2 (4·8%)
Nausea or lethargy	1 (2·4%)
Deep venous thrombosis	1 (2·4%)
Lower limb pain	1 (2·4%)
Device-related event	
Venous stenosis	12 (28·6%)

*Coupler retrieved via arterial sheath and second coupler successfully deployed.

***Table 3:* Adverse events related to arteriovenous coupler placement or device**

implanted on the right side. No patient had more than one anastomosis created. Placement was not attempted in one patient because of unsuitable anatomy. 25 procedure-related or device-related adverse events were reported (table 3). Two of the events were serious (urinary retention and anaemia) and occurred during the periprocedural period (within 48 h). Three events were minor events (transient localised or limb pain and nausea or lethargy). Late events (more than 7 days after surgery) were classified as probably or possibly related to the procedure and comprised deep venous thrombosis, deemed provoked by instrumentation of the venous system and a highly prothrombotic state due to severe contrast allergy in one patient and lower-limb pain in one patient. All events resolved without sequelae. 12 (29%) of patients presented with clinically identifiable symptoms of unilateral lower-extremity oedema between 2·3 and 8·7 months after procedure and were subsequently diagnosed as having iliac vein stenosis proximal to the anastomosis. Stenosis was treated with venoplasty alone in one patient or stenting with venoplasty in the remaining 11 patients without further complications.

Reductions in antihypertensive medications due to hypotension were reported in eight (19%) of 42 patients in the arteriovenous coupler group and none in the control group (p=0·0056). In relation to worsening of hypertension, five hospital admissions for hypertensive crisis were reported in three (8%) of the 39 control patients, compared with none in the arteriovenous coupler group (p=0·0225), and antihypertensive therapy needed to be increased in four (10%) of 39 patients in the control group and one (2%) of 42 patients in the arteriovenous coupler.

Discussion

In this study of the use of an arteriovenous anastomotic coupler to alter the mechanical arterial properties contributing to chronic hypertension, we found significant reductions in blood pressure could be achieved in patients with uncontrolled essential hypertension, despite inadequate response to multiple antihypertensive drugs (panel). Incorporating a segment of vein in the central arterial circuit to restore the Windkessel model[24] is expected to cause an immediate reduction of blood pressure through improved arterial compliance and lowering of vascular resistance, and our findings support this theory. We found concordance in office and 24 h ambulatory blood pressure measurements at 6 months after the procedure.

Patients in the arteriovenous coupler group who had previously undergone renal denervation had significant reductions in office and 24 h ambulatory blood pressures compared with control patients with previous renal denervation, in whom no significant changes were seen. These reductions in the arteriovenous coupler group patients were not different from those experienced by patients in this group who had not undergone renal denervation (change in office blood pressure p=0·47 and 24 h ambulatory blood pressure p=0·95). This finding suggests that inadequate response to renal denervation might be due partly to arterial stiffness, which is not targeted by sympathomodulation, but would need to be investigated in future studies.

The observed reduction of blood pressure does not reflect the differences in use of antihypertensive medication between the arteriovenous coupler and control groups at 6 months. Significantly more patients in the arteriovenous coupler group received reduced numbers of antihypertensive medications than those in

Panel: Research in context

Systematic review

Creation of an iliac arteriovenous anastomosis is a novel technique for lowering of blood pressure. We searched PubMed for clinical trials and case reports, published between 1900 and 2014 in English, with the terms "arteriovenous anastomosis", "arteriovenous fistula", "hypertension", and "blood pressure". We identified one observational study[17] that showed blood pressure was lowered in hypertensive patients with chronic obstructive pulmonary disease after this treatment was used to improve oxygen delivery.

Interpretation

We did a prospective, randomised, controlled trial to assess the potential of iliac arteriovenous anastomosis to reduce blood pressure in patients with uncontrolled hypertension. Significant reductions were seen in office and ambulatory blood pressure 6 months after the procedure. These findings suggest that a strategy targeting mechanical characteristics of the arterial system could be an important component of successful hypertension control.

the control group, and significantly more in the control group received increased numbers of medications. These changes in medications might have masked the true magnitude of blood pressure reduction brought about by placement of the arteriovenous coupler.

Creation of the arteriovenous anastomosis was associated with late development of venous stenosis above the anastomosis. This complication is made clinically evident by signs of unilateral lower-extremity oedema, and in some cases simultaneously increased blood pressure. Treatment with self-expanding venous stents alleviated these symptoms in all 12 patients affected.

Either the immediate reduction of blood pressure[17] or the unique mechanism of blood pressure reduction[25] after placement of the arteriovenous coupler was associated with a significant reduction in hospital admissions for hypertension in the 6 months after the procedure. Repeat hospital admissions for acute severe hypertension occur in 29% of patients admitted with hypertensive crisis.[26] A reduction in hypertension-related admissions was noted after the use of baroreflex activation therapy,[27] but has not been reported in pharmacological trials of hypertension.

Our study has several limitations. The trial did not have an explicit sham-control group, which raises the possibility that knowledge of treatment allocation contributes to blood pressure reductions. In this trial, we saw no reductions in mean blood pressure in control patients, which is similar to the findings in the control group of Symplicity HTN-2,[28] which also had no sham-control group, but is in contrast to those of the Symplicity HTN-3 study,[29] which did. Furthermore, unlike Symplicity HTN-3, we recruited patients from hypertension centres of excellence, which ensured that only patients with established hypertension and stable antihypertensive regimens were included. Importantly, unlike renal denervation, technical success with the arteriovenous coupler is documented during the procedure and is associated with an immediate fall in blood pressure.[17] This difference eliminates the placebo effect and isolates the sham effect to an interaction between a patient's knowledge of treatment allocation with longer-term clinical behaviours.

We did not attempt to assess adherence to antihypertensive medications during the study because the primary aim was to determine whether or not treatment with the device lowered blood pressure. Furthermore, no strategy for improving adherence to medicines has been shown to sustain long-term control of hypertension.

Another limitation is that the cardiovascular consequences of the small shunt were not formally assessed and are unknown. Extensive experience in patients treated with similarly sized shunts created for dialysis access, however, suggests that the risk of cardiovascular decompensation is low. Short-term improvement in left ventricular function related to reduced peripheral and central blood pressure and in arterial compliance have been reported in predialysis patients who undergo peripheral arteriovenous fistula formation,[18,30] and seems likely to persist with the use of a fixed-calibre shunt.[21] In patients with end-stage renal disease, increased cardiac output immediately after creation of arteriovenous fistulae is offset by substantially reduced peripheral vascular resistance.[31] Furthermore, where high output cardiac failure does occur in these patients, shunt volumes exceed 30% of cardiac output[32] and flow rates of at least 2·0 L/min are necessary.[33] The fixed-calibre arteriovenous coupler we implanted only permits flow of 0·8–1·2 L/min.[17] Future studies will need to address predictors of response and non-response to this treatment and to investigate mechanisms of action and long-term safety of the device.

Creation of a small central arteriovenous anastomosis in patients with hypertension despite the use of multiple medications resulted in significantly reduced office and 24 h ambulatory blood pressure values. Subsequent studies are needed to investigate whether reported reductions in hypertension and related diseases, morbidity, and short-term risk of hospital admission can be replicated. If safety and efficacy are proven, arteriovenous anastomosis might be a useful option for patients who are unable or unwilling to persist with lifelong antihypertensive pharmacotherapy. The technique is associated with the development of symptomatic venous stenosis, but this complication can be managed with conventional strategies. This innovative mechanically based technique affirms the roles of arterial compliance and vascular resistance abnormalities in patients with arterial hypertension.

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Contributors

MDL was the principal investigator. All authors contributed to the writing of the report. MDL and PAS supervised the statistical analysis.

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