Dear Sir / Madam,

Please will you consider the enclosed manuscript entitled ‘The Haemodynamic Effects of a Central Iliac Arteriovenous Anastomosis at 6 Months in Patients with Resistant and Uncontrolled Hypertension’ for publication in your excellent journal.

We confirm that it is not under consideration for publication elsewhere. We look forward to hearing from you in the near future.

Yours sincerely,

William Eysenck, Jet van Zalen, Nick Freemantle, Paul Sobotka, Guy Lloyd, Stephen Furniss and Neil Sulke

TITLE PAGE

American Heart Journal

ORIGINAL RESEARCH ARTICLE

The Haemodynamic Effects of a Central Iliac Arteriovenous Anastomosis at 6 Months in Patients with Resistant and Uncontrolled Hypertension

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Declaration of interest:

WE has nothing to disclose

JvZ has nothing to disclose

NF has nothing to disclose

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ABSTRACT

BACKGROUND: A central iliac arteriovenous anastomosis, termed the 'coupler' (ROX Medical, California, USA) results in a significant reduction in blood pressure (BP) in hypertensive patients. This study assessed functional and haemodynamic changes induced by the device.

METHODS: Twenty-one patients with resistant and/or uncontrolled hypertension underwent stress echocardiography and cardiopulmonary exercise testing (CPET) at baseline and 6 months post coupler implantation. Endpoints were selected to best evaluate cardiac function including Doppler stroke volume (SV), septal and lateral E/E' and right ventricular systolic velocity S' (RV S'). CPET VO_2 peak demonstrated total cardiopulmonary performance.

RESULTS: SV increased from 76.4 SD12.2 mls to 92.1 SD22.7 mls 6 months post coupler; p=0.002. No changes in RV S', septal or lateral E/E', or VO_2 peak were observed. Five patients experienced increased diuretic requirement ≥3 times baseline. RV S' fell from 19.0 SD1.87 cm/s to 16.80 SD3.43 cm/s in these patients (p>0.05).

CONCLUSIONS: A significant increase in SV 6 months post coupler insertion was observed. In patients with increased diuretic requirement the device was associated with a lower RV S' suggesting occult RV dysfunction as the mechanism of this pre-specified adverse outcome.

Hypertension is the leading cause of cardiovascular comorbidity and mortality and is a risk factor for coronary heart disease, stroke, chronic kidney disease, and heart failure.[1,2] A central iliac arteriovenous anastomosis has been shown to alter mechanical arterial properties and reduce blood pressure (BP) in patients with resistant and/or uncontrolled hypertension.[3] The coupler was first used to treat hypertension in 2012 and adds a low-resistance, high-compliance venous segment to the central arterial tree.[4,5] The device is associated with an immediate and significant reduction in BP and reduces the risk of hospitalised hypertensive crises.[3]

The device has predictable effects on preload (increase) and afterload (significant sustained reduction) which affect cardiac size and volumes.[6,7] Some patients require increased oral diuretics due to volume changes induced by the coupler. Identification of such patients is useful in their management. The combination of cardiopulmonary exercise testing (CPET) and stress echocardiography (echo) concurrently assesses both exercise performance and functional myocardial changes, filling pressure and symptoms in an objective and reproducible manner.[8]

Methods

Study design and participants

This study was performed at Eastbourne General Hospital, East Sussex Healthcare NHS Trust and was approved by the national ethics committee. Twenty-one consecutive participants with resistant and/or uncontrolled hypertension taking part in the ROX Control Hypertension Registry (RH-03) NCT01885390 were included.[9] The rationale and design of the RH-03 registry have been described previously.[9] Inclusion criteria were patients aged 18 to 85 years with a diagnosis of resistant or uncontrolled hypertension made on the basis of office and 24 hour BP monitoring, medical history and physical examination. Patients were

excluded if they had any serious medical condition that might have adversely affected the patient's safety, limit the subject's ability to participate in the registry, comply with follow-up requirements, or impact the scientific integrity of the study. In addition, patients were excluded if found to have a baseline pulmonary capillary mean wedge pressure > 15mm Hg at right heart catheterisation. Written informed consent was obtained from all participants. All 21 participants underwent baseline and 6-month post coupler stress echo CPETs.

Procedure

Placement of the arteriovenous coupler was accomplished in the cardiac catheterisation laboratory in Eastbourne General Hospital under fluoroscopic guidance, and has been described in detail previously.[3] With a modified Seldinger technique, a short 4 F introducer sheath was placed into the right common femoral artery. An 11 F customised venous introducer was placed in the right common femoral vein 2 cm inferior to the arterial sheath. The target for the coupler was between the distal external iliac vein and artery, above the level of the femoral head and ischial spine. A crosshair wire was advanced through the arterial introducer to mark the target location. The coupler delivery system was advanced over the crossing wire from vein to artery. The 'arms' of the device were deployed. Finally, a 4 mm balloon catheter was advanced over the crossing wire within the coupler and the anastomosis was dilated to a final diameter of 4 mm.

24 hour blood pressure assessment

Twenty-four hour BP monitors (Spacelabs Healthcare, Snoqualmie, Washington, USA) were applied to all patients at baseline, day 1, 3 and 6 months post procedure as part of the RH-03 protocol.[9]

Cardiopulmonary exercise testing

See figure 1. CPET was performed by two experienced investigators (WE and JZ). A semi-recumbent tilting cycle ergometer (ERG 911 S/L, Schiller, Baar, Switzerland) was used. At the start of the test a 1-2 minute rest period was included followed by a 3 minute unloaded warm up period. Exercise protocols were individually determined based on the patient's functional status. Work rate (10, 15 or 20 Watt) increased every minute until voluntary exhaustion aiming for 8-10 minutes of exercise. Patients were asked to continue to take their medication as usual. Heart rate (HR), BP and oxygen saturations were monitored throughout. Oxygen uptake (VO_2), carbon dioxide production (VCO_2) and ventilation (V_E) were continuously measured and derived using a calibrated breath-by-breath analyser (Quark, Cosmed, Italy). Patients were verbally encouraged to exercise until maximal exertion. All tests were performed according to exercise testing guidelines.[10] VO_2 peak was expressed as the highest value from an average of 30 seconds during the final stage of the exercise test.

Echocardiography protocol

Echocardiography was performed using a GE Vivid 9 platform (Vingmed-General Electric, Horten, Norway) equipped with a phased-array 3.5 MHz transducer. All patients underwent a full British Society of Echocardiography (BSE) minimum dataset echo[11] by a BSE accredited physiologist. Two experienced BSE accredited physiologists (blinded to the patient and timing of the scan) performed offline echo measurements for each patient.

We prospectively selected 3 parameters to represent the principle facets of cardiac performance: SV to represent cardiac systolic function, E/E' to represent left atrial pressure / left ventricular (LV) filling, and RV S' to represent right ventricular systolic function. Parameters were selected based on two criteria: a) they are readily measured in all patents

with a high reproducibility and b) they represent an independent aspect of cardiac performance.

Doppler stroke volume

SV was calculated by multiplying the cross-sectional area of the left ventricular outflow tract (LVOT) (obtained in the parasternal long axis view) with the velocity time integral (VTI) of the LVOT (obtained in the 5-chamber view).

RV systolic velocity S'

For RVS' the apical 4-chamber window was used with a tissue spectral Doppler mode region of interest highlighting the right ventricular free wall. The pulsed Doppler sample volume was placed at the tricuspid level of the right ventricular free wall. Tricuspid annular motion was assessed by pulsed tissue Doppler to measure the longitudinal velocity of excursion. This velocity was taken to be the systolic excursion velocity or RV S'.

Statistical analysis

For each CPET and echo parameter, the difference between the pre- and post-value was calculated in a generalised mixed model, with two observations for each subject (pre and post), linked within patients with generalised random intercept term. The degrees of freedom from the analysis were derived from the number of subjects (rather than observations). The parameterisation of the model identified the pre- and post-values. In addition, for each analysis, a post treatment identifier for increased diuretic requirement was utilised to identify the interaction between post treatment values. This was done separately for each parameter of interest in an exploratory manner, and no multivariable analysis was conducted owing to the

modest number of patients included in the study and thus the limited degrees of freedom. A p value of <0.05 was considered significant.

Results

Participants with mean age of 67 years (range 48 to 81 years), 43% female had multiple comorbidities (including 48% with paroxysmal atrial fibrillation) (table 1a). Indications for coupler insertion were resistant hypertension (in 76% of study participants) and uncontrolled hypertension (in 24%). Patients were taking a mean of 3.19 (median of 3) anti-hypertensive medications and had a mean of 0.52 (median of 1) drug intolerances each, see table 1b. All patients were on diuretics at baseline (15 patients were taking loop diuretics and 6 patients were taking thiazide diuretics). All study participants had a baseline EF of >50% and a pulmonary capillary mean wedge pressure < 15mm Hg at right heart catheterisation.

Implantation of the ROX Coupler was successfully performed in all participants without procedural complications.

At 6 months follow-up five of the 21 patients had experienced a suboptimal response to the coupler requiring increased diuretic dose ≥ threefold compared to baseline.

Change in blood pressure

See figure 2. There was a significant reduction in systolic BP (SBP) (145.39±6.12 mmHg vs. 132.22±12.996; p=0.001) and diastolic BP (DBP) (79.22±9.039 mmHg vs. 68.11±9.209; p=0.0001) 1 day post procedure. There was a significant reduction in 3 month SBP (149.38±9.179 vs. 138.69±15.660; p=0.017) and DBP (83.38±7.377 vs. 71.92±9.106; p=0.0001). There was a significant reduction in 6 month DBP (80.33±9.063 vs. 68.86±11.168; p=0.0001), see figure 1.

Echocardiography

Results are displayed in table 2a. A significant increase in Doppler SV was seen from 76.4±12.2mls at baseline to 92.1±22.7mls at 6 months; p=0.002. There were no significant changes in RV S', septal E/E' or lateral E/E'.

Cardiopulmonary exercise testing

See table 2b. No difference in VO_2 peak, power reached or VE/VCO_2 were observed in the overall study population.

Predictors of increased diuretic requirement post coupler

See table 3. There were no significant differences in baseline echo and CPET parameters between those patients requiring increased diuretics and those who did not; p>0.05. Patients with increased diuretic requirement reached a significantly lower peak power on CPET 6 months post-coupler implant; -22.50W (95% CI -36.12 to -8.88W; p=0.003). RV S' was noted to reduce in patients with increased diuretic requirement (RV S' reduction of -3.14 cm/s, 95% CI -6.88 to -0.601; p = 0.096).

Discussion

The study was designed to test the hypothesis that implantation of a central iliac arteriovenous anastomosis results in important haemodynamic changes and detailed assessment of these with CPET stress echo predicts patients at risk of increased diuretic requirement post-coupler. The trial partly met its primary effectiveness end point, with a statistically significant increase in SV observed post coupler in the overall population.

SV is determined by three factors: i) preload: the filling pressure of the heart at the end of diastole ii) contractility: the vigour of contraction of the heart muscle during systole

and iii) afterload: the pressure against which the heart must work to eject blood during systole.[12] The flow of blood across the coupler from the arterial system to the venous system increases the volume and speed of venous return. According to the Frank-Starling law of the heart, this increase in preload will lead to an increase in SV.[13] In addition, the reduction in aortic pressure in systole predicts a reduction in afterload. By reducing the pressure against which the heart must work to eject blood during systole an increase in SV is hypothesised. It is likely that a combination of these factors result in the increase in SV observed. The SV does not increase to a significant degree in the patients with increased diuretic requirement because these patients cannot accommodate the increased preload induced by the coupler.

Tricuspid annular motion can be assessed by pulsed tissue Doppler to measure the longitudinal velocity of excursion. This velocity has been termed the RV S' or systolic excursion velocity. RV S' has been shown to be highly reproducible and was the chosen echo parameter for assessment of right heart function[14]. Prior to the study it was hypothesised that the RV S' would increase due to the extra circulatory volume imposed upon the right ventricle. A nonsignificant increase in RV S' was observed in the overall study population. However, with a larger population, the increase may have reached statistical significance. There was a nonsignificant reduction in RV S' in the patients requiring increased diuretics. This finding provides an explanation for the mechanism of increased diuretic requirement. Patients who are unable to cope with the increased volume load on the right heart, might require increased diuretic doses post coupler insertion, whilst those who accommodate the increased right heart volume loading do not.

Invasive cardiac catheterisation is the gold standard in LV filling pressure assessment. However, recent echocardiographic studies have identified no difference in outcome between the invasive measurement of filling pressure using Swan-Ganz catheter insertion and non-invasive echocardiography.[15] E/E' is generally the most feasible and the most reproducible

method for estimation of filling pressure[16] and is proportionate to left atrial pressure. No significant differences between lateral or septal E/E' were observed post-coupler but a larger sample size may have revealed a significant change in this parameter. It is possible that with increased right heart filling pressures and reduced arterial stiffness the E/E' could decrease and a larger sample may have provided evidence for this hypothesis.

VO_2 peak is determined by cellular oxygen demand and equates to maximal rate of O_2 transport. No significant change in this end-point was observed confirming no detrimental effect of the iliac anastomosis upon this key CPET parameter. VO_2 peak has been shown to have high prognostic value in cardiac patients and healthy individuals.[17] This negative finding provides reassurance that the previously described significant increase in SV does not cause significant detrimental effects to the rate of O_2 transport.

The minute ventilation/carbon dioxide production (VE/VCO_2) slope reflects the increase in ventilation in response to CO_2 production, and thus shows increased ventilatory drive[18]. Changes in the VE/VCO_2 slope may be induced by increased chemoreceptors, the peripheral ergoreceptor response, the ventilator dead-space and also by the muscle mass engaged in exercise.[19] No significant differences in the VE/VCO_2 slope were observed confirming no detrimental effect of the iliac anastomosis upon this important CPET parameter.

The power reached during CPET is an objective measure of the amount of work done during the test.[20] The power reached on the cycle ergometer did not change pre- and post-coupler. This is despite a degree of diversion of leg arterial blood flow. Potentially a vascular steal syndrome could arise with this device as has been reported in between 5-15% of brachio-cephalic/basilic fistulae used for haemodialysis.[21] The findings that there were no significant changes in power reached alleviates this concern. The reason for this is that the

diversion of blood flow induced by the coupler is small (0.8L/min) compared to arterial capacity and the increased SV would tend to ameliorate this change in leg perfusion.

A significant reduction in power was noted in patients with increased diuretic requirement and confirms that this pre-defined clinical adverse effect is an important outcome measure in patients who have a suboptimal response to the coupler. It should be noted that the baseline power reached on the CPET was almost 30W less for the patients who required significant increases in diuretic dose. This suggests that patients with lower baseline exercise capacity have a greater risk of right heart decompensation.

Study Limitations

A larger study population would have improved the statistical power of the study and may have provided evidence for the hypothesized reduction in E/E' and increase in RV S'. The detected nonsignificant reduction in RV S' in patients with increased diuretic requirement might explain the mechanism of this undesirable outcome but will need an increased number of patients to provide robust evidence required to confirm this finding.

Five patients (24%) experienced a change in medication with a significant increase in diuretic dose required for clinical reasons, and likely to have affected the echo and CPET parameters studied. Keeping pharmacological therapy unchanged would not have been ethical in this cohort.

Conclusions

SV significantly increases in hypertensive patients treated with a coupler. SV does not increase to a significant degree in the patients with increased diuretic requirement, probably as these patients cannot accommodate the increased preload increased by the device. Likewise, right ventricular function did not augment in this population. Despite this, the

coupler was not associated with any significant change in exercise performance. A mechanism of reduced recruitability of the right and left ventricles was shared by patients requiring increased diuretics. This study confirms the safety of the coupler and its neutral impact on exercise performance in this group of patients likely to be sensitive to preload.

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Table 1a. Baseline demographics of the study participants

	Number (± SD)
Female Gender, n (%)	**9/21 (43)**
COPD	**2 (30.78)**
Diabetes	**6 (47.02)**
CVA/TIA	**1 (22.36)**
Vascular disease	**5 (44.43)**
Hypercholesterolaemia	**9 (51.04)**
Chronic kidney disease	**6 (47.02)**

Table 1b. Baseline medications of the study participants

	Mean	SD
ACE-i/ARB	0.86	0.359
Beta blocker	0.76	1.091
Loop diuretic	0.71	0.463
Thiazide diuretic	0.24	0.436
Aldosterone antagonist	0.19	0.402
Calcium antagonist	0.43	0.507
Centrally acting anti-hypertensive	0.24	0.436

Figure 1. Change in 24h BP throughout the study period. Error bars represent the standard error of mean.

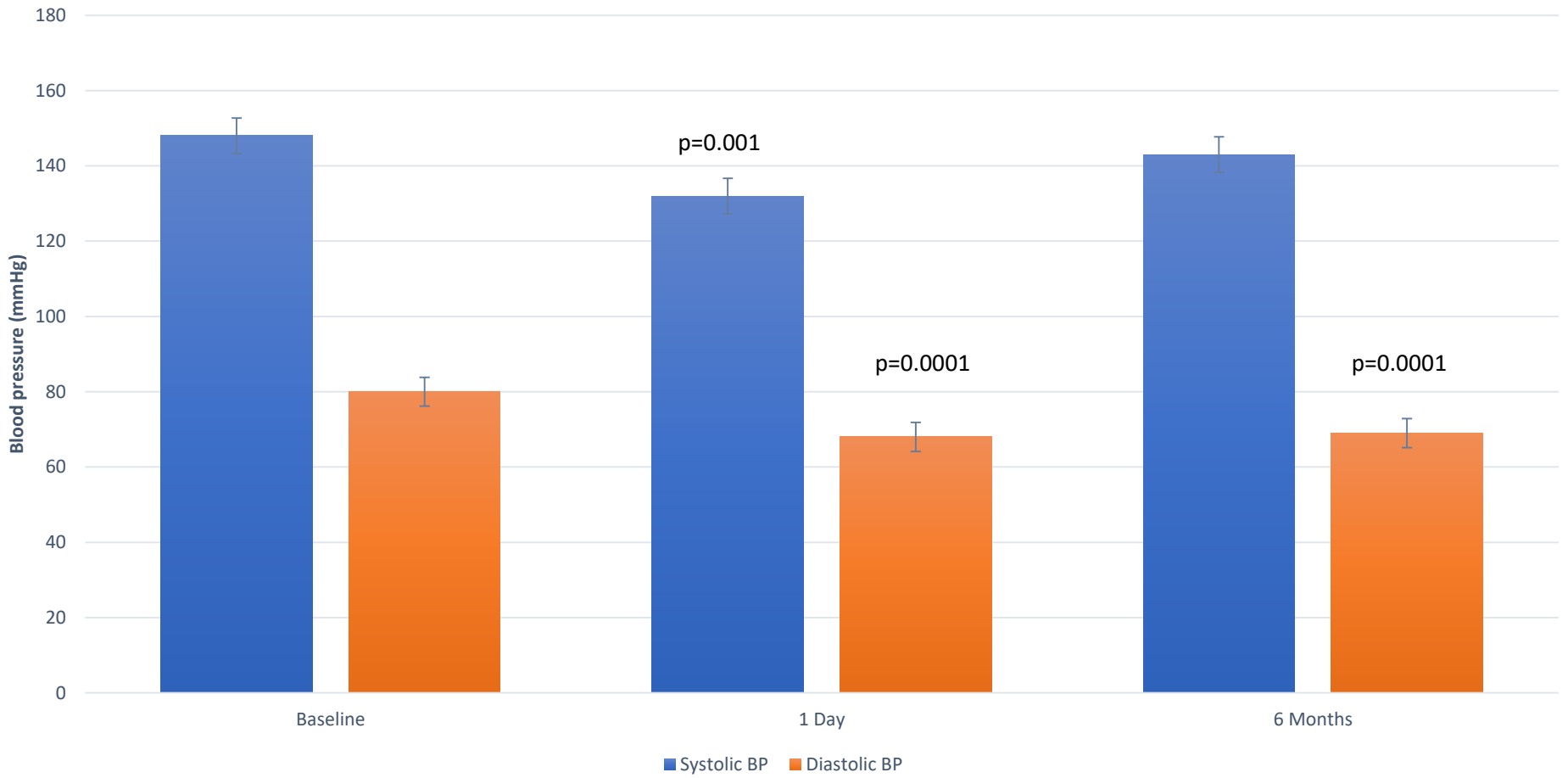

Table 2a. Echo parameters at baseline and 6 months post-ROX Coupler

	Baseline	6 Months Post-ROX	P Value
Doppler SV (mL)	76.4 (12.2)	92.1 (22.7)	0.002
RV S' (cm/s)	17.1 (3.9)	17.2 (4.0)	0.29
Septal E/E'	11.1 (3.2)	10.8 (3.7)	0.85
Lateral E/E'	13.0 (22.7)	8.5 (3.8)	0.91

Table 2b. CPET parameters at baseline and 6 months post-ROX Coupler

	Baseline	6 Months Post-ROX	P Value
VO_2 Peak	18.1 (4.7)	17.0 (4.8)	ns
Power (W)	113.6 (49.9)	105.8 (57.0)	ns
VE/VCO_2	33.9 (8.5)	37.1 (6.3)	ns

Table 3 Results of prespecified models by outcome

Name	Post	Increased diuretic requirement (baseline)	Increased diuretic requirement*Post
VO_2 peak	-0.588 (95% CI -2.123 to 0.948; p=0.433)	-1.909 (95% CI -6.912 to 3.094; p=0.434)	-2.213 (95% CI -5.359 to 0.934; p=0.157)
Power	-2.500 (95% CI -9.145 to 4.145; p=0.441)	-29.425 (95% CI -84.735 to 25.885; p=0.279)	-22.500 (95% CI -36.118 to -8.882; p=0.003)
VE/VCO2	2.488 (95% CI -1.469 to 6.444; p=0.203)	1.594 (95% CI -7.079 to 10.268; p=0.704)	2.812 (95% CI -5.857 to 11.481; p=0.504)
RV S'	0.938 (95% CI -0.890 to 2.765; p=0.296)	2.563 (95% CI -1.672 to 6.797; p=0.221)	-3.138 (95% CI -6.883 to 0.608; p=0.096)
Doppler SV	17.013 (95% CI 7.304 to 26.721; p=0.002)	-0.459 (95% CI -20.427 to 19.508; p=0.962)	-4.175 (95% CI -24.072 to 15.721; p=0.665)
E/E' lateral	-0.117 (95% CI -2.157 to 1.924; p=0.906)	2.911 (95% CI -1.047 to 6.868; p=0.140)	-1.690 (95% CI -5.872 to 2.492; p=0.408)
E/E' septal	-0.171 (95% CI -2.073 to 1.732; p=0.853)	0.142 (95% CI -3.643 to 3.926; p=0.938)	-0.631 (95% CI -4.530 to 3.269; p=0.739)