International Journal of Cardiology 202 (2016) 322–327

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

# Renal sympathetic denervation in uncontrolled arterial hypertension after successful repair for aortic coarctation

Philipp Lurz [a,*], Thomas Okon [a], Thomas Riede [b], Robert Wagner [b], Gerhard Schuler [a], Ingo Daehnert [b], Steffen Desch [c]

[a] Dept. of Internal Medicine/Cardiology, University of Leipzig-Heart Center, Leipzig, Germany
[b] Dept. of Paediatric Cardiology, University of Leipzig-Heart Center, Leipzig, Germany
[c] Medical Clinic II, University Heart Center Luebeck, Luebeck, Germany

ARTICLE INFO

*Article history:*
Received 18 June 2015
Received in revised form 14 September 2015
Accepted 19 September 2015
Available online 21 September 2015

*Keywords:*
Coarctation of the aorta
Congenital heart disease
Arterial hypertension
Renal nerves
Renal sympathetic denervation

ABSTRACT

*Background:* Uncontrolled arterial hypertension is a frequent problem after successful repair of CoA and has been attributed to increased central sympathetic drive as well as a blunted baroreceptor reflex. RSD is a promising therapy to reduce central sympathetic drive and improve baroreflex sensitivity.
*Methods:* 8 patients (age: 27 ± 6 years) with previous surgical and/or percutaneous repair of CoA, absence of any relevant restenosis (invasive gradient across the site of previous treatment 3 ± 4 mm Hg) and resistant arterial hypertension (daytime SBP ≥ 140 mm Hg on 24 hour ambulatory blood pressure measurements [ABPM] in spite of the concurrent use of 3 antihypertensive agents of different classes or intolerance to BP medications) were included. Bilateral RSD was performed using the Symplicity Flex™ catheter (Medtronic, MN, USA).
*Results:* RSD was successful in all patients with no procedural complications and no evidence for renal artery stenosis 6 months post procedure. From baseline to 6 month follow-up, RSD was followed by a significant reduction in average daytime systolic BP (150.4 ± 7.8 to 143.1 ± 8.0 mm Hg; p = 0.0117) as well as systolic BP throughout 24 h (146.8 ± 7.3 vs. 140.5 ± 7.8, p = 0.04).
*Conclusion:* The BP reductions observed in these patients justify engaging in a larger clinical trial on the efficacy of RSD in this specific type of secondary hypertension and bares the hope that RSD might extend the currently very limited armory against arterial hypertension in young adults with previous repair of CoA.


## 1. Introduction

Coarctation of the aorta (CoA) occurs with a prevalence of 5% in children with congenital heart diseases [1]. Late after successful treatment of the anatomical pathology, uncontrolled arterial hypertension represents a major clinical problem in these patients and responds poorly to medical treatment [2,3]. Even in the context of optimal hemodynamic results at the site of previous interventions, the incidence of arterial hypertension in this population is reported to exceed 30%[4]. Late morbidity and mortality after repair of CoA has been associated to uncontrolled hypertension in this patient population [5]. This type of secondary hypertension has been attributed to generalized arterial wall abnormalities and cystic medial necrosis [6,7]. Consequently, formation of intracranial aneurysms is not uncommon in this patient cohort. Late arterial hypertension after successful repair of CoA has also been attributed to increased central sympathetic drive as well as a blunted baroreceptor reflex [2,3,8–12].

Renal sympathetic nerve denervation (RSD) therapy has been introduced as a potentially successful treatment strategy in patients with therapy-resistant essential arterial hypertension [13–16]. Analysis of mechanisms involved in lowering arterial pressures suggests that this transcatheter based treatment might lead to reduced central sympathetic drive and improvements in baroreflex sensitivity [17].

We speculated that RSD could potentially improve blood pressure control not only in patients with essential hypertension but also in young adults with previous repair of CoA and uncontrolled arterial blood pressure [18].

Thus, the aim of this study was to assess the safety and efficacy of RSD in a series of patients with this specific type of secondary hypertension.

## 2. Methods

### 2.1. Patient population and study protocol

In this prospective study, young adults with uncontrolled resistant arterial hypertension late after successful surgical and/or interventional treatment of aortic CoA were included. Uncontrolled resistant arterial hypertension was defined by a mean daytime systolic blood pressure (SBP) of ≥140 mm Hg or diastolic blood pressure (DBP) of

* Corresponding author at: Department of Internal Medicine/Cardiology, Struempellstrasse 39, 04289 Leipzig, Germany.
*E-mail address:* Philipp.Lurz@gmx.de (P. Lurz).

http://dx.doi.org/10.1016/j.ijcard.2015.09.034
0167-5273/

≥90 mm Hg on ambulatory blood pressure measurements (ABPM) despite being treated with ≥3 antihypertensive drugs (including 1 diuretic) at maximum tolerated doses or patients with intolerance to antihypertensive drug treatment. Additionally, medications should not have been changed for a minimum of 4 weeks before enrolment. To rule out isolated brachiocephalic hypertension due to significant re-coarctation, patients were considered for RSD and inclusion into the study only if the invasively measured peak gradient across the previous site of coarctation repair/treatment was less than 10 mm Hg. Excluded were patients with renal artery anatomy not suitable for RSD [13], impaired renal function with an estimated glomerular filtration rate (eGFR; based on the modification of diet in renal disease criteria [19]) of less than 45 mL/min per 1.73 $m^2$, type 1 diabetes, substantial stenotic valvular heart disease, pregnancy or planned pregnancy during the study, a history of myocardial infarction, or unstable angina.

Potential candidates for inclusion into the study were identified from our grown up congenital heart disease (GUCH) clinic database. Patients with previous surgical and/or interventional treatment of coarctation at our institution and known arterial hypertension were considered for initial screening. These patients underwent ABPM. Those with a mean daytime SBP of ≥140 mm Hg or DBP of ≥90 mm Hg underwent further workup including magnetic resonance angiography for assessment of renal artery anatomy and blood tests to assess for renal function. After enrolment, patients underwent cardiac catheterization including angiography and measurement of the pull-back gradient at the site of previous treatment of aortic coarctation. After exclusion of any relevant re-coarctation, RSD was performed in all renal arteries suitable (as described below).

Other secondary forms of hypertension were excluded by pre-procedural angiography (exclusion of renal artery stenosis), laboratory testing (exclusion of hyperthyroidism and renal parenchymal disease) as well as physical examination and by taking patients history.

Approval of this study was given by the institute's ethics committee. All patients provided written informed consent.

### 2.2. 24-Hour-blood-pressure-measurement

ABPM was performed using an oscillometric Spacelabs monitor 90207 (Spacelabs Healthcare, Issaqua, WA). The cuff was positioned at the right arm as recommended in patients with coarctation [20]. The used cuff size was adapted to the extent of the right upper arm. All ambulatory readings were performed with the display monitor off to avoid expectations of the blood pressure registration. The ambulatory blood pressure monitor was programmed to record the blood pressure every 15 min at daytime and every 30 min at nighttime according to the latest guidelines [21]. All patients kept an activity diary which included marking out the sleeping time. Patients were encouraged to keep their normal daily activity, work and sleeping routine. The software program Del Mar Reynolds Medical CardioNavigator Version 2.4.13 (Hertford, UK) was used to analyze the blood pressure recordings.

### 2.3. Catheterization and renal sympathetic denervation

The femoral artery was accessed by standard catheterization techniques. An angiogram at the site of previous coarctation repair was performed using a 6 F Pigtail catheter (Cordis, CA, USA) The pullback gradient across the site of repair was recorded to exclude relevant re-coarctation. Renal sympathetic denervation was performed with the Symplicity™ catheter (Medtronic, MN, USA) as previously described [13,14]. In brief, 4 to 8 ablation points were applied over the whole length of the all renal artery meeting morphological suitability criteria (≥4 mm in diameter). Continuous intravenous administration of remifentanil was used for pain relief during energy delivery.

### 2.4. Endpoints and statistical analysis

The primary endpoint was defined as the change in mean daytime SBP on ABPM recordings between baseline to 6 month follow-up. Data were tested for normal distribution by the D'Agostino & Pearson omnibus normality test. Normally distributed data are expressed as mean ± SD, not normally distributed data as median and range. Proportions are expressed as number of patients and percentages. A paired samples t-test was used for continuous variables. A two-tailed probability-level value of $p < 0.05$ was accepted as significant. Statistical testing and data analysis was performed with GraphPad Prism version 5.0b (Graphpad Software, San Diego, CA, USA).

## 3. Results

### 3.1. Study population

A total of 104 adult patients (≥18 years of age) with surgical and/or interventional repaired CoA were screened. Arterial hypertension (office SBP >140 mm Hg or DBP >90 mm Hg) was present at previous visits to our GUCH clinic in 67 patients (64.4%). 41 of these 67 hypertensive patients were treated with three or more drugs or had a history of antihypertensive drug intolerance. ABPM measurements were performed in 31 and revealed therapy resistant arterial hypertension as defined above in 10 patients. One patient declined inclusion into the study. Another patient was excluded after invasive assessment demonstrated a peak pullback gradient at the site of previous repair of 23 mm Hg and subsequently underwent stenting of the re-stenosed aorta. Therefore, eight patients were included into this study (Fig. 1).

### 3.2. Patient characteristics

Patient characteristics are shown in Table 1. The mean age at the time of RSD was 27 ± 6 years, and 7/8 were male. The majority of patients (5/8) had surgery for primary repair of CoA, the mean age at primary repair was 12 ± 9 years. Patients were on 2.9 ± 1.8 antihypertensive drugs, two patients refused intake of any (patient number 2) respectively more than one (patient number 5) antihypertensive drugs due to multiple side effects in the past. During the follow-up period, regular intake of medication was assessed by patients' medication diaries, which were assessed 1, 3 and 6 months at follow-up visits. There were no changes in antihypertensive medication.

### 3.3. Catheterization and renal denervation

Fig. 2 depicts individual aortic angiograms of all eight patients, demonstrating adequate results after repair of CoA. A gothic arch geometry was observed in 1 patient. The mean peak pressure gradient across the site of previous repair of CoA was 2.6 ± 3.0 mm Hg. RSD was uncomplicated in all patients. RSD was performed successfully (completed run for 2 min) at 6.1 ± 0.6 spots in the right and 5.5 ± 0.9 spots in the left renal artery. The procedure time was 75 ± 12 min with a fluoroscopy time of 12 ± 3 min. The total amount of contrast agent including aortic angiograms was 158 ± 71 ml.

### 3.4. Blood pressure control

The daytime SBP as the primary endpoint decreased significantly from 150.4 ± 7.8 to 143.1 ± 8.0 mm Hg ($p = 0.0117$). The percentage of daytime SBP recordings ≥ 140 mm Hg was reduced from 78 ± 13 to 56 ± 20% ($p = 0.004$). There was a non-significant trend towards improved daytime DBP (from 77.1 ± 16.1 to 73.8 ± 3.1 mm Hg; $p = 0.075$) and a significant reduction in maximal daytime DBP (from 103.1 ± 15.6 to 98.4 ± 14.6 mm Hg; $p = 0.0475$).

During nighttime, changes in SBP were not significant (pre RSD 135.4 ± 10.6 vs. post RSD 131.3 ± 10.7 mm Hg; $p = 0.31$), whereas DBP fell from 68.6 ± 13.3 mm Hg to 64.6 ± 12.6 mm Hg ($p = 0.04$). In addition, the maximal nighttime DBP decreased from 89.3 ± 13.9 to 79.0 ± 11.0 mm Hg ($p = 0.027$) as well as the percentage of DBP readings > 80 mm Hg (25 ± 29 vs. 16 ± 31%; $p = 0.047$). All other blood pressure changes during night time were non-significant.

Considering blood pressure recordings throughout 24 h, the mean SBP and DBP was reduced significantly 6 months after RSD (146.8 ± 7.3 vs. 140.5 ± 7.8, $p = 0.04$; and 75.4 ± 15.1 vs. 71.9 ± 12.9 mm Hg, $p = 0{,}0358$; respectively).

On office blood pressure measurements, the SBP fell from 163.3 ± 12.1 to 139.5 ± 12.1 mm Hg ($p = 0.002$), and the DBP from 91.3 ± 21.7 to 75.5 ± 15.6 mm Hg ($p = 0.0134$).

Results of blood pressure measurements are summarized in Table 2 and Fig. 3. Individual results of the mean daytime systolic BP are illustrated in Fig. 4.

### 3.5. Safety

There were no deaths, other serious adverse events or vascular complications. Kidney function as estimated by the glomerular filtration rate and creatinine remained unchanged at 6 months after the procedure (Table 3).