Effect of renal denervation on left ventricular mass and function in patients with resistant hypertension: data from a multi-centre cardiovascular magnetic resonance imaging trial

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Aims

Sympathetic stimulation induces left ventricular hypertrophy and is associated with increased cardiovascular risk. Catheter-based renal denervation (RDN) has been shown to reduce sympathetic outflow and blood pressure (BP). The present multi-centre study aimed to investigate the effect of RDN on anatomic and functional myocardial parameters, assessed by cardiac magnetic resonance (CMR), in patients with resistant hypertension.

Methods and results

Cardiac magnetic resonance was performed in 72 patients (mean age 66 ± 10 years) with resistant hypertension (55 patients underwent RDN, 17 served as controls) at baseline and after 6 months. Clinical data and CMR results were analysed blindly. Renal denervation significantly reduced systolic and diastolic BP by 22/8 mm Hg and left ventricular mass index (LVMI) by 7.1% (46.3 ± 13.6 g/m² vs. 43.0 ± 12.6 g/m², P < 0.001) without changes in the control group (41.9 ± 10.8 g/m² vs. 42.0 ± 9.7 g/m², P = 0.653). Ejection fraction (LVEF) in patients with impaired LVEF at baseline (≤50%) significantly increased after RDN (43% vs. 50%, P < 0.001). Left ventricular circumferential strain as a surrogate of diastolic function in the subgroup of patients with reduced strain at baseline increased by 21% only in the RDN group (14.8% vs. 17.9% P = 0.001) and not in control patients (15.5% vs. 16.4% P = 0.508).

Conclusions

Catheter-based RDN significantly reduced BP and LVMI and improved EF and circumferential strain in patients with resistant hypertension, occurring partly BP independently.

Keywords

Resistant hypertension • Left ventricular hypertrophy • Circumferential strain • Cardiovascular magnetic resonance • Renal nerve ablation

Introduction

Hypertension is the most popular cardiovascular risk factor worldwide being closely associated with stroke and heart failure.1 Resistant hypertension is defined as blood pressure (BP) above goal despite the concurrent use of three or more different antihypertensive drugs, one ideally being a diuretic, with all agents prescribed at maximum or maximum tolerated doses.2 Patients with resistant hypertension are at high risk for cardiovascular events, in particular when hypertensive end organ damage is present.3 Hypertension induces left ventricular hypertrophy (LVH) and predicts incident chronic heart failure.4 Regression of LVH has been associated with favourable

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outcomes and varies between different antihypertensive drug classes.\textsuperscript{5} Sympathetic activation promotes hypertension and induces cardiac hypertrophy.\textsuperscript{6–8} Catheter-based renal denervation (RDN) in patients with resistant hypertension decreases BP and central sympathetic activity.\textsuperscript{9,10} Two recently published pilot studies demonstrated reductions in left ventricular mass and intraventricular septum thickness following RDN.\textsuperscript{11,12} Given the limited reproducibility of echocardiography these studies were of borderline power to assess changes in cardiac systolic and diastolic function and volumes.\textsuperscript{13} Cardiac magnetic resonance (CMR) is more precise and sensitive than echocardiography and provides highly reproducible assessments of cardiac volumes, function, and mass.\textsuperscript{14–16} allowing a considerable reduction in the patient numbers compared with echocardiography to prove changes in remodelling parameters after RDN.\textsuperscript{13} Therefore, the present multi-centre, blinded, controlled CMR study aimed to investigate the effects of RDN on myocardial parameters in 72 patients with resistant hypertension.

**Methods**

**Study population and design**

The present study was designed as a prospective, multi-centre study and was implemented at two investigational sites in Germany and one in Australia. Patients underwent RDN and received CMR at baseline and after 6 months. The study was approved by the local ethics committee and was conducted in accordance with the ethical standards defined by local law. All patients provided written informed consent.

Enrolled subjects were aged \(\geq 18\) years with an office systolic blood pressure (SBP) above goal (\(\geq 140\) mm Hg) or mean ambulatory 24-h SBP \(\geq 135\) mm Hg despite the use of \(\geq 3\) antihypertensive agents of different classes, including a diuretic at maximum or highest tolerated doses.\textsuperscript{6} Office BP readings were taken in a seated position with an automatic oscillometric Omron HEM-705 monitor (Omron Healthcare, Vernon Hills, IL, USA) after 5 min of rest according to the Standard Joint National Committee VII Guidelines.\textsuperscript{17} At baseline, BP was measured at each arm and the arm with the higher BP was used for all subsequent readings. Averages of the triplicate measures were calculated and used for analysis. According to recent recommendations on RDN,\textsuperscript{18,19} patients with pseudo-resistant hypertension defined as mean ambulatory 24-h SBP \(< 130\) mm Hg were excluded.\textsuperscript{2} Patients with GFR \(< 45\) mL/min/1.73 m\(^2\) and patients on haemodialysis were excluded. All patients underwent a complete history and physical examination, assessment of vital signs, and review of medication.

**Magnetic resonance imaging**

Cardiac magnetic resonance images were performed in all subjects before and 6 months after RDN using a 1.5 T Achieva MRI scanner (Philips Healthcare, Best, the Netherlands) or 1.5 T Siemens Symphony or a 1.5 T Siemens Aera MRI system (Siemens Healthcare Sector, Erlangen, Germany). Cine images were acquired using a balanced steady-state free precession sequence during breath-holds of \(\approx 10–15\) s using VCG gating with patients being positioned in supine position. Whole-heart coverage from apex to base was performed as previously reported.\textsuperscript{21} Additionally, late gadolinium enhancement (LGE) has been performed in a subgroup of 24 patients to evaluate the impact of RDN on scar tissue and 16 control patients. Late gadolinium-enhanced imaging was performed 10–15 min after injection of 0.2 mmol/kg gadolinium DTPA using an inversion-recovery 3D spoiled gradient echo sequence. The pre-pulse delay was individually adjusted according to a pre-pulse-delay finder (Look-Locker sequence). All CMR examinations were performed by operators, who were blinded to patient’s treatment and time of the measurement (pre- or post-RDN).

**Cardiac magnetic resonance analysis**

**Left ventricular mass measurements**

Cardiac magnetic resonance image analyses were performed according to the recommendations of the task force for post-processing of the Society for Cardiovascular MR.\textsuperscript{22} Offline CMR analyses were performed using the software Qmass MR Enterprise Solution (version 7.4, Medis, the Netherlands). Endocardial and epicardial borders were traced automatically and corrected manually at end-diastole and end-systole, while the papillary muscles were excluded from LVM to achieve better reproducibility.\textsuperscript{23} Left ventricular volumes and mass were calculated using the summation of slices method.\textsuperscript{24} Left ventricular end-systolic (LVESVI) and end-diastolic volume index (LVEDVI) were normalized in every patient for sex, age, height, and weight, and LVESVI and LVEDVI have been assessed.\textsuperscript{25} Left ventricular mass was then normalized indexing to body surface area and height (g/m\(^1.7\)).\textsuperscript{26} Left ventricular measurements including wall thickness and internal dimensions were obtained using the SAX view basal to the tips of the papillary muscles. Wall thickness was defined as the radial distance between endocardium and epicardium for septum and lateral wall on basal short-axis, end-diastolic cine images.\textsuperscript{28} In addition, relative wall thickness has been calculated as \(2 \times \) posterior wall thickness divided by LV internal diameter at diastole.\textsuperscript{29}

Left ventricular wall stress was evaluated using the Laplace equation relating wall stress to intracavitary pressure, wall curvature, and wall thickness as follows: \(S = \frac{P(r)2h}{r}\), where \(S\) is wall stress, \(P\) is LV pressure, \(r\) is a radius of curvature, and \(h\) is wall thickness (modified by using brachial BP measurements from Yin\textsuperscript{30} and Grossman\textsuperscript{31}). These non-invasively assessed parameters have been demonstrated to be highly comparable with measurements using invasive hemodynamics.\textsuperscript{32}

**Feature tracking**

Analysis of myocardial circumferential strain (Ecc) was performed using the software Image Arena 4.6 (TomTec). The mid-ventricular SAX slice containing both papillary muscles was chosen, and endocardial borders were manually drawn by setting six to eight contour points beginning clockwise from the anterior septum. A reference point was set on the anterior interventricular septum to allow segmentation according to standard model.\textsuperscript{33} Circumferential strain and peak systolic strain rate was calculated for each myocardial segment.

**Left atrium**

The size of the left atrium (LA) was assessed by four-chamber planimetry with Qmass software, using a four-chamber view at the level of the membranous septum. Endocardial contour was drawn manually at an end-systolic phase and a size of \(\geq 24\) cm\(^2\) was recognized as dilated.\textsuperscript{34}
Scar tissue
To evaluate the impact of RDN on myocardial fibrosis LGE MRI was applied using the inversion-recovery gradient-echo sequence. Late gadolinium-enhanced images were scored visually by two experienced observers (blinded to other MRI and clinical data) at the time of the acquisition using a 17-segment model. Each segment was graded using following -point score: 0, absence of enhancement; 1, enhancement of 1–25% transmurality; 2, enhancement of 26–50% transmurality; 3, enhancement of 51–75% transmurality, and 4, enhancement of 76–100% transmurality. The score per segment was then calculated by dividing total score by 17 referring to the 17-segment model.

Statistical analysis
All data are presented as mean ± SD. Differences in mean values were compared using a χ² test for unpaired tests and McNemar’s for paired comparisons. For the evaluation of intra- and interobserver variability, 12 measurements (for LVM, myocardial strain, and LA size) were repeated both by the first observer and a second observer after 3 months. Intra- and interobserver variability is displayed in Bland-Altman Plots. Additionally, the intraclass correlation coefficient (ICC) were considered as good with a value of >0.6 and excellent with a value of >0.7. All P-values of <0.05 were considered as statistically significant. Both, the regression to the mean phenomenon and the confounding by indication issue were addressed by general linear models for repeated measurements including covariates (ANCOVA) using SPSS Version 21. The treatment modality was investigated as an intergroup factor. Serial BP measurements (with LV mass at baseline as covariate) and serial LV mass determinations (with SBP at baseline as covariate) were explored separately. Moreover, a model including two inner-subject factors LV mass and SBP was implemented. Further covariates included in the analysis were age, diabetes, prevalence of coronary artery disease, number of antihypertensive drugs, weight, and height.

Results

Study population
Seventy-two patients with resistant hypertension were enrolled in the study. Fifty-five subjects were treated with RDN and 17 subjects served as controls (medical treatment only). No patient was lost to follow-up during the study period of 6 months. All clinical data are presented in Table 1.

Blood pressure
Office systolic and diastolic BP decreased significantly from 170/90 ± 21/15 mm Hg at baseline to 148/82 ± 19/14 mm Hg (P = 0.001) 6 months after RDN. SBP/diastolic BP (DBP) in the control group did change during follow-up (156/84 ± 17/11 vs. 145/77 ± 23/15 mm Hg; P = 0.044 for SBP and P = 0.034 for DBP).

Antihypertensive drugs
Patients and physicians were instructed not to change antihypertensive medication during the study period. The average number of antihypertensive drugs remained constant in the RDN group (4.6 ± 1.6 separately. Moreover, a model including two inner-subject factors LV mass and SBP was implemented. Further covariates included in the analysis were age, diabetes, prevalence of coronary artery disease, number of antihypertensive drugs, weight, and height.

<table>
<thead>
<tr>
<th>Variables</th>
<th>RDN (n = 55)</th>
<th>Control (n = 17)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 ± 10 (67)</td>
<td>70 ± 9 (74)</td>
<td>0.058</td>
</tr>
<tr>
<td>Male (%)</td>
<td>39 (71%)</td>
<td>10 (59%)</td>
<td>0.350</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.2 ± 4.3 (29)</td>
<td>28.6 ± 5.3 (28)</td>
<td>0.646</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (13%)</td>
<td>4 (24%)</td>
<td>0.279</td>
</tr>
<tr>
<td>Stroke</td>
<td>7 (13%)</td>
<td>2 (12%)</td>
<td>0.946</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>26 (47%)</td>
<td>7 (41%)</td>
<td>0.659</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>34 (62%)</td>
<td>13 (76%)</td>
<td>0.578</td>
</tr>
<tr>
<td>Smoking</td>
<td>9 (16%)</td>
<td>2 (12%)</td>
<td>0.645</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of antihypertensive drugs</td>
<td>4.6 ± 1.6 (4)</td>
<td>4.5 ± 1.2 (4)</td>
<td>0.704</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>49 (89%)</td>
<td>17 (100%)</td>
<td>0.763</td>
</tr>
<tr>
<td>Direct renin inhibitors</td>
<td>14 (26%)</td>
<td>1 (6%)</td>
<td>0.082</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>48 (87%)</td>
<td>16 (93%)</td>
<td>0.433</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>41 (75%)</td>
<td>15 (88%)</td>
<td>0.235</td>
</tr>
<tr>
<td>Diuretics</td>
<td>46 (84%)</td>
<td>17 (100%)</td>
<td>0.642</td>
</tr>
<tr>
<td>Sympatholytics</td>
<td>21 (38%)</td>
<td>5 (29%)</td>
<td>0.477</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>170.0 ± 21.4 (170)</td>
<td>157.4 ± 15.3 (159)</td>
<td>0.027</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>89.9 ± 14.8 (90)</td>
<td>83.8 ± 10.9 (82)</td>
<td>0.117</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>79.6 ± 15.0 (77)</td>
<td>74.6 ± 14.6 (72)</td>
<td>0.225</td>
</tr>
</tbody>
</table>

Values are given either as total number, percentage or mean ± SD; median is given in parenthesis. BMI, body mass index; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure.
vs. 4.5 ± 1.7; P = 0.287) and the control group (4.5 ± 1.2 vs. 4.3 ± 1.3; P = 0.395).

**Cardiac magnetic resonance variables**

**Left ventricular measurements**

No significant changes between baseline and 6 months were evident for LVEF, however for LVEDV, LVEDV: 177 ± 54 mL vs. 176 ± 53; P = 0.246 and LVEF: 81 ± 40 mL vs. 77 ± 35 mL; P = 0.038). No significant changes between baseline and 6 months were evident for LVEF and LVEDV in the controls (EDV: 172 ± 42 vs. 172 ± 29 mL, P = 0.795 and ESV: 78 ± 31 mL vs. 78 ± 27 mL, P = 0.868). Normalized LVEF and LVEDV are given in Table 2. There were no significant changes of LV internal dimension measures in both groups.

Ejection fraction increased significantly after RDN (55.7 ± 11.1 vs. 57.6 ± 9.3%, P = 0.048) and remained unchanged in the control group (55.5 ± 8.2 vs. 55.5 ± 8.4%, P = 0.723). In patients with reduced systolic LVEF at baseline (defined as ≤ 50%, n = 19) LVEF significantly increased by 7.3% after RDN (43.2 ± 5.5 vs. 50.5 ± 7.0%, P < 0.001). There was no improvement in the control group (42.9 ± 5.7 vs. 44.3 ± 8.4%, P = 0.537; n = 3) (Figure 1).

Left ventricular mass indexed (LVMi) to height $^{1.7}$ significantly decreased by 7.1% 6 months after RDN (from 46.3 ± 13.6 to 43.0 ± 12.6 g/m$^{2.7}$, P < 0.001) (Table 2, Figure 2). In the control group, LV mass remained unchanged (41.9 ± 10.8 vs. 42.0 ± 9.7 g/m$^{2.7}$, P = 0.653) (Figure 2). In total, 18 (33%) patients after RDN showed a SBP reduction of < 10 mm Hg and were subsequently defined as ‘non-responders’. Interestingly, in 15/18 (83%) non-responders LVMi significantly decreased from 52.1 ± 14.9 vs. 47.8 ± 14.4 g/m$^{2.7}$ (P = 0.001) (Figure 3, Table 3). Left ventricular wall stress was reduced after RDN (105 ± 46 vs. 95 ± 43 dyn/mm$^{2}$, P = 0.033), whereas no changes occurred in the control group (120 ± 44 vs. 105 ± 38 dyn/mm$^{2}$, P = 0.149).

**Circumferential strain**

Mean values of Ecc remained constant in both study groups (Table 2). Patients were segregated in two subgroups depending on their contractile function at baseline. A circumferential strain of ≥ − 20% was
considered as a contractile dysfunction. In the subgroup of patients with reduced myocardial contractility at baseline (diastolic dysfunction, \( n = 27 \)), Ecc improved after RDN by 21% (\(-14.8 \pm 3.9 \) to \(-17.9 \pm 4.6\%\), \( P = 0.001 \)). In the control group (\( n = 10 \)), Ecc remained unchanged (\(-15.5 \pm 4.3 \) vs. \(-16.4 \pm 5.0\%, \ P = 0.508 \)) (Figure 4).

**Figure 2** Left ventricular mass index at baseline and 6-month follow-up in patients undergoing renal denervation (\( n = 55 \)) and controls (\( n = 17 \)), depicted as individual changes and average values ± standard deviation.

**Figure 3** Correlation of absolute change in systolic blood pressure and left ventricular mass index after renal denervation. Response to renal denervation was defined as a ≥10 mm Hg decrease in systolic blood pressure.

**Figure 4** Subgroup of patients with reduced myocardial contractility (diastolic dysfunction, renal denervation; \( n = 27 \); control; \( n = 10 \)) at baseline and 6-month follow-up evaluated by measurements of circumferential strain. Values are given as mean ± standard deviation.

**Left atrium**
Mean values of LA size did not significantly change (Table 2). However, following RDN the number of patients with left-atrial enlargement (LAE) was decreased from 62 to 55% and increased from 47 to 53% in the control group. Notably, in the subgroup of patients with LAE at baseline (\( n = 34 \); 62%) RDN resulted in a significant reduction of LA size from 29.7 ± 5.8 to 28.6 ± 5.3 cm\(^2\) (\( P = 0.026 \)).

**Late gadolinium enhancement**
There was no significant difference in LGE score between RDN patients and controls at baseline (0.22 ± 0.6 vs. 0.25 ± 0.8;
Table 3  Comparison of baseline and 6-months follow-up parameters in patients undergoing renal denervation divided in responder (systolic blood pressure reduction at 6 months follow-up ≥ 10 mm Hg) and non-responder (systolic blood pressure reduction at 6 months < 10 mm Hg)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Responder (n = 37)</th>
<th>Non-responder (n = 18)</th>
<th>Responder vs. non-responder at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 months</td>
<td>P-value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 ± 11 (66)</td>
<td>67 ± 15 (69)</td>
<td>0.268</td>
</tr>
<tr>
<td>Number of antihypertensive drugs</td>
<td>4.7 ± 1.4 (5)</td>
<td>4.3 ± 1.8 (4)</td>
<td>0.388</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.9 ± 4.6 (29)</td>
<td>29.8 ± 3.6 (29)</td>
<td>0.455</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>174 ± 21 (171)</td>
<td>161 ± 21 (163)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>92 ± 16 (90)</td>
<td>86 ± 12 (89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>82 ± 14 (81)</td>
<td>75 ± 17 (73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anatomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVSTd (mm)</td>
<td>12.1 ± 3.5 (12)</td>
<td>11.8 ± 3.3 (12)</td>
<td>0.481</td>
</tr>
<tr>
<td>LVIDd (mm)</td>
<td>56.1 ± 5.7 (56)</td>
<td>55.7 ± 5.8 (57)</td>
<td>0.683</td>
</tr>
<tr>
<td>PWTd (mm)</td>
<td>8.6 ± 1.9 (8)</td>
<td>8.4 ± 2.3 (8)</td>
<td>0.313</td>
</tr>
<tr>
<td>LVEDVI (mL/m³)</td>
<td>81.1 ± 19.7 (84)</td>
<td>81.9 ± 22.3 (79)</td>
<td>0.783</td>
</tr>
<tr>
<td>LVESVI (mL/m³)</td>
<td>35.6 ± 13.0 (35)</td>
<td>35.1 ± 14.5 (31)</td>
<td>0.226</td>
</tr>
<tr>
<td>LV mass/height¹⁷ (g/m¹⁷)</td>
<td>43.4 ± 12.1 (44)</td>
<td>41.7 ± 11.2 (38)</td>
<td>0.001</td>
</tr>
<tr>
<td>LA size (cm²)</td>
<td>24.1 ± 6.4 (24)</td>
<td>23.6 ± 5.9 (23)</td>
<td>0.280</td>
</tr>
<tr>
<td>Myocardial scar score</td>
<td>0.32 ± 0.8</td>
<td>0.05 ± 0.14</td>
<td>0.311</td>
</tr>
<tr>
<td>Function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>56.2 ± 10.2 (56)</td>
<td>57.7 ± 8.6 (56)</td>
<td>0.151</td>
</tr>
<tr>
<td>Circumferential strain (%)</td>
<td>-21.5 ± 7.2 (-21)</td>
<td>-21.8 ± 7.0 (-22)</td>
<td>0.489</td>
</tr>
<tr>
<td>Peak systolic strain rate (s⁻¹)</td>
<td>-1.34 ± 0.47 (-1.32)</td>
<td>-1.38 ± 0.40 (-1.42)</td>
<td>0.112</td>
</tr>
</tbody>
</table>

BMI, body mass index; BP, blood pressure; IVSTd, interventricular septal thickness at diastole; LVIDd, left ventricular internal diameter at diastole; PWTd, posterior wall thickness at diastole; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LV, left ventricle; LA, left atrium; EF, ejection fraction.
Reproducibility

Bland-Altman plots and ICC analysis are shown in Supplementary material online, Figure S1A–E and Table S1 for intra- and interobserver variability measurements for LVMI, myocardial strain, and LA size. The intra- and interobserver concordance (95% confidence interval) for LV mass, circumferential strain, and LA size were 0.95 (0.53–0.99), 0.61 (−0.04–0.90), and 0.99 (0.96–0.99) as well as 0.91 (0.72–0.97), 0.65 (0.04–0.91), and 0.90 (0.66–0.98), respectively, indicating good or excellent consistency of repeated evaluations.

Discussion

Renal denervation offers a novel approach to effectively reduce BP and sympathetic activity by selectively interrupting renal sympathetic fibres. It has been demonstrated to reduce LVM and improve diastolic function measured by echocardiography. Cardiac magnetic resonance is more sensitive and highly reproducible in assessing cardiac function and morphology and allows a considerable reduction in the patient numbers to prove changes in remodelling parameters after RDN when compared with echocardiography. The results of the present prospective, multi-centre, blinded study demonstrated that RDN in patients with resistant hypertension significantly decreases BP and LVMI, improves EF and circumferential strain in patients with impairments at baseline and reduces the number of patients with LAE. Interestingly, the structural and functional cardiac changes occurred partly BP independent, pointing towards a direct role of modulating sympathetic nervous system activity.

Left ventricular hypertrophy represents a strong, independent predictor of increased cardiovascular morbidity and mortality and reflects the long-term effects of hemodynamic and non-hemodynamic factors. Hypertensive LVH has been associated with increased sympathetic activity to the heart as measured by NE spillover and plasma NE concentrations. Regression of LVH by different pharmacological regimens is an accepted treatment target in patients with hypertension that drives beneficial effects on LV function and prognosis independent of other risk factors. Renal denervation decreases both BP and LVMI in patients with resistant hypertension. Pilot clinical data indicated that RDN could reduce echocardiography-derived LVMI by 17% (33.9 ± 15.6 g/m² vs. 44.7 ± 14.9 g/m², n = 46, P < 0.001) 6 months after treatment. Herein, the effect of RDN on LVMI was less pronounced (−7.1%), which might be related to the more precise assessment of cardiac mass using CMR and the blinded investigation. Indeed, repeated measures of the CMR-derived parameters revealed good or excellent reproducibility on intra- and interobserver levels. Recently, a meta-analysis with 6000 patients investigated the effect of different antihypertensive drugs on LVH. The LVMI regression ranged between 7.6 and 12.6%, however, only patients with monotherapy and not treatment resistant patients were included. Interestingly, LVMI was reduced in 15 of the 18 patients with a change in SBP of <10 mm Hg 6 months after RDN, supporting the notion of BP-independent effects of RDN on LVH. This finding is interesting because experimental data indicate that sympathetic nerve fibres directly mediate hypertension-induced LVH by stimulation of cardiomyocyte alpha-adrenergic receptors. In line, clinical and experimental data using the combined alpha- and beta-receptor blocker carvedilol indicate an alpha receptor-mediated effect of anti-sympathetic treatment on LVH, which might also underlie the herein observed effects of RDN. Furthermore, a BP independent effect of sympathetomy on LVH has been described in an animal model of abdominal aortic banding, when BP was unaffected by sympathetomy but LVH decreased significantly.

Besides the reductions in BP and LVMI also LVEF and circumferential strain improved after RDN. Left ventricular wall stress defined as a function of chamber size and configuration, thickness of the ventricular wall, and intraventricular pressure significantly decreased after RDN. Although LGE reliably detects localized fibrosis, this technique is limited in the assessment of diffuse myocardial fibrosis.

Left-atrial enlargement is an independent predictor of common cardiovascular outcomes such as atrial fibrillation, stroke, heart failure, and death. Increased LA volume usually reflects ventricular filling pressure, as it is exposed to LV pressure during ventricular diastole. Left-atrial enlargement may therefore represent the chronicity exposure of the LA to abnormal LV filling pressure, mainly by high arterial BP. The left atrium possesses structural features that contribute to the pathogenesis of atrial fibrillation. Reverse remodelling of the LA by controlling BP represents a treatment target in patients at risk. Treatment with RDN reduced the number of patients with LAE.

Late gadolinium enhancement has demonstrated to be a strong predictor of cardiovascular events at long-term follow-up, suggesting its incremental value for the assessment of long-term prognosis. In our subgroup analysis, LGE-score remained unchanged after RDN. Although LGE reliably detects localized fibrosis, this technique is limited in the assessment of diffuse myocardial fibrosis.

Multiple trials have proven that RDN lowers office and 24-h BP in patients with resistant hypertension. The average BP reduction in the present study was less pronounced compared with the Symplicity trials (−22/−8 vs. −32/−12 mm Hg). Baseline SBP has been identified as a predictor of response to treatment. The fact that baseline BP herein was lower compared with the Symplicity HTN-2 trial (170/90 vs. 178/97 mm Hg) might in part account for the smaller BP lowering effect. In line, non-responders had lower SBP at baseline compared with responders. Additionally, non-responders had larger ventricles indicated by higher LVEDVI and
LVESVI, dilated left atria and significantly increased LVMI, which potentially indicate longstanding resistant hypertension with severe structural hypertensive end organ damage. Blood pressure was also reduced in the control group (−11/−7 mm Hg; \( P = 0.044 \) for SBP and \( P = 0.034 \) for DBP), interestingly, this did not correspond to an improvement in LVMI or EF. Although, some reports suggest that diffuse renal artery constriction and local tissue damage at the ablation site with oedema and thrombus formation may occur after RDN, none of the patients included in the study developed a significant renal artery stenosis or clinical apparent renal embolism during follow-up of 6 months.

Limitations

The non-randomized study design and the small sample size are limitations of this study that might also limit the evaluation and interpretation of subgroups among the cohort, although it represents the largest cohort of patients undergoing RDN and followed by CMR. Furthermore, CMR is a highly reproducible method, resulting in a considerable reduction in sample sizes of 80–90% when compared with echocardiography. The control group consisted of 17 patients with resistant hypertension on stable antihypertensive medication, which were not anatomical eligible for the procedure or denied an invasive treatment. We carefully checked whether these patients were principally different from those treated with RDN. Except for SBP all other visible potential confounders have not reached statistical significance between both groups. Due to the relative small number of patients minor differences between the treatment group and the control group might not have reached statistical significance probably due to power. In consideration of the relatively small number of patients propensity score matching with respect to these characteristics was not done. However, general linear modelling was performed to assess the regression to the mean and the confounding by indication issue. The results are given in the statistical supplement. Future studies need to address the issue of imbalance between the groups in larger cohorts of patients. Patients with an SBP reduction of ≥10 mm Hg were subsequently defined as responders to RDN. Although this threshold was not provided by guidelines, it represents a clinically relevant BP reduction and was used in the trials. Patients and physicians were instructed not to change antihypertensive medication during the study period. However, antihypertensive drug regimen was reduced in one patient (1%), due to confirmed BP levels below respective target BP and the development of symptomatic hypotension. Antihypertensive treatment was increased in two patients (3%) who remained above target BP during follow-up. Censoring for these post-procedural medication changes did not affect the improvements in LVMI or function, making a relevant influence of treatment intensification unlikely. Furthermore, it is possible that patients changed their medication themselves, as non-adherence is a major problem in patients with resistant hypertension. Adherence to prescribed drug regimen was checked before study entrance and at each visit, making a self-reduction of drug treatment unlikely, although not impossible. However, urine or plasma toxicological analysis of antihypertensive drugs or corresponding metabolites was not part of the study protocol.

Conclusion

Renal denervation reduced BP and significantly improved LVH and myocardial function, as diagnosed by CMR, in patients with resistant hypertension. The beneficial effects of RDN on cardiac remodelling documented herein occurred partly BP independent, suggesting a prognostic benefit of RDN in patients at high cardiovascular risk. Randomized controlled studies are needed to investigate whether these changes correlate to improved outcomes.

Supplementary material

Supplementary material is available at European Heart Journal online.

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Conflict of interest:

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