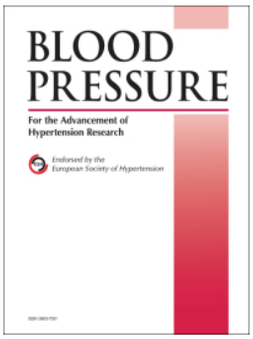

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RESEARCH ARTICLE

Echocardiographic findings following renal sympathetic denervation for treatment resistant hypertension, the ReShape CV-risk study

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ABSTRACT

Objective: The aim of this study was to describe and compare echocardiographic findings before renal sympathetic denervation (RDN) and 6 and 24 months after the procedure.

Materials and methods: Patients with treatment resistant hypertension (TRH) were included in this non-randomised intervention study. RDN was performed by a single experienced operator using the Symplicity Catheter System. Echocardiographic measurements were performed at baseline, and after 6 and 24 months.

Results: The cohort consisted of 21 patients with TRH, with a mean systolic office blood pressure (BP) of 163 mmHg and mean diastolic BP 109 mmHg. Mixed model analysis showed no significant change in left ventricular (LV) mass index (LVMI) or left atrium volume index (LAVI) after the RDN procedure. Higher LVMI at baseline was significantly associated with greater reduction in LVMI ($p < 0.001$). Relative wall thickness (RWT) increased over time (0.48 mm after two years) regardless of change in BP. There was a small but significant reduction in LV end-diastolic (LVIDd) and end-systolic (LVIDs) diameters after RDN, with a mean reduction of 2.6 and 2.4 mm, respectively, after two years. Progression to concentric hypertrophy was observed only in in patients who did not achieve normal BP values, despite BP reduction after RDN.

Conclusion: There was no reduction of LV mass after RDN. We found a small statistically significant reduction in LVIDd and LVIDs, which together with increase in RWT can indicate progression towards concentric hypertrophy. BP reduction after RDN on its own does not reverse concentric remodelling if target BP is not achieved.

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Echocardiography; hypertension; resistant hypertension; renal denervation; RDN; ventricular hypertrophy

Introduction

Hypertension is a leading risk factor for disease and mortality globally. According to the Global Burden of Disease Study, high blood pressure (BP) was accountable for 10.8 million deaths in 2019 alone [1]. Vast evidence shows that lowering BP leads to reduction of cardiovascular risks, and still, BP control worldwide remains unsatisfactory [2]. The structural changes due to pressure overload in the hypertensive heart include both concentric and eccentric myocardial remodelling in response to a chronically increased afterload, leading to left ventricular (LV) hypertrophy (LVH) and myocardial fibrosis, resulting in diastolic dysfunction, atrial enlargement and aortopathy [3]. LVH has been independently linked to adverse outcomes including myocardial infarction, stroke, chronic kidney disease, systolic heart failure, atrial and ventricular arrhythmias and premature death [4,5]. LVH can be prevented or reversed by normalising BP using antihypertensive therapy [6]. Thus, LVH is considered one of the markers in the management of hypertension [7]. Regression of LVH has been associated with reduced risk of cardiovascular death, myocardial infarction, stroke and all-cause mortality [8].

Diastolic dysfunction in hypertensive heart disease [9] may lead to heart failure with preserved ejection fraction (HFpEF). HFpEF prevalence is growing worldwide due to hypertension, population ageing

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and successes in treatment of coronary artery disease. HFpEF presents challenges for clinicians since the condition has few treatment options and has prognosis similar to heart failure with reduced ejection fraction. Effective antihypertensive treatment, however, may reduce the prevalence of HFpEF due to reduction in LVH [9]. Diastolic dysfunction in hypertension has been independently associated with poor prognosis [10]. In diastolic dysfunction, reduction in early diastolic LV filling is compensated by forceful atrial contraction. Elevation of LV filling pressures over time leads to pressure overload of the left atrium, resulting in atrial fibrosis and enlargement, which results in increased risk of atrial fibrillation [11]. Left atrial dilatation is an independent determinant of stroke, cardiovascular disease and death [12].

It is estimated that among medically treated hypertensive adults in the high-income countries, about one-half do not achieve desired therapeutic BP values [13]. In most of these patients uncontrolled hypertension is due to clinical inertia or poor therapy adherence. The prevalence of true treatment resistant hypertension (TRH) is likely to be 5–10% [2,14] of medically treated hypertensive patients.

Upregulation of renal sympathetic nerve activity is considered one of the main mechanisms involved in the development of hypertension, as well as cardiac remodelling [15]. Increased renal sympathetic nerve activity has been demonstrated to increase renal tubular reabsorption of urinary sodium and water, release of renin from the juxtaglomerular apparatus, thereby activating the renin–angiotensin–aldosterone cascade [15]. A pronounced increase in sympathetic nerve traffic and cardiac norepinephrine spill-over rate is documented in patients in whom hypertension is complicated by LVH or LV diastolic dysfunction [16].

Several adequately designed, randomised, sham-controlled trials [17–20] have demonstrated safety and clinically significant reduction of BP after catheter based renal sympathetic denervation (RDN). Recently the European Society of Hypertension stated that RDN is an effective and safe device-based technique for treatment of hypertension [21,22]. Furthermore, several clinical studies have demonstrated beneficial effects of RDN on LVH and cardiac function [23–26].

The aim of this study was to describe and compare echocardiographic findings (LV mass, LV mass index (LVMI), left atrium volume index (LAVI) and diastolic parameters) before RDN and 6 and 24 months after the procedure in a cohort of patients with TRH.

Materials and methods

Patient selection

The patients were recruited from the ReShape CV-risk study, which aimed to examine changes in insulin sensitivity after RDN, in patients with TRH [25].

Patients aged 18–68 years with TRH were eligible for inclusion and invited to participate in this non-randomised intervention study. Patients were recruited at the University Hospital of North Norway, Norway. TRH was defined as an office systolic BP > 140 mmHg despite four or more antihypertensive drugs. The presence of TRH was verified by ambulatory BP monitoring (ABPM) after witnessed intake of the prescribed antihypertensive drugs. The exclusion criteria included known diabetes mellitus, a positive pregnancy test, cancer, hemodynamically significant heart valve disease, pacemaker or implantable cardioverter defibrillator, renal artery stenosis and estimated glomerular filtration rate (eGFR) ≤ 45 mL/min/1.73 m^2.

The baseline echocardiography was performed in average 26 days before the RDN procedure. Bilateral RDN was performed by one trained senior interventional cardiologist (TKS), with the Symplicity Catheter System [27]. Details about the selection criteria and study procedure have been published previously and the study is registered in clinical.trials.gov [27] (clinical trial reg. no. NCT01630928). The study complied with the Declaration of Helsinki and the research protocol was approved by the Regional Committee for Medical Research Ethics (2011/1296/REK Nord). All study patients gave written informed consent. Data collection and storage were in accordance with the internal storage policy of research data and were approved by the Data Protection Officer at the University Hospital of North Norway.

Echocardiography

Transthoracic echocardiography with two-dimensional and Doppler measurements was performed at baseline and at 6 and 24 months after RDN by one single experienced cardiologist (ES). All echocardiographic measurements were made end-expiratory on a Siemens Sequoia 512 model No 10044692 (Siemens Medical Solutions USA, Inc.).

Echocardiographic measurements were available for 21 patients at baseline and at six months follow-up, and for 18 patients at 24 months. LV mass was calculated from M-mode measurements from measurements of interventricular septum diameter in diastole (IVSd), LV internal diameter in diastole (LVIDd),

posterior wall diameter in diastiole (LVPWd) using the formula: LV mass (g) = (1.04 (IVSd + LVIDd + LVPWTd)^3 − LVIDd^3) + 0.6 g [11].

LV mass was indexed by height, using the formula LVMI = LVmass/height(m)$^{2.7}$ [28]. In addition, we calculated LVMI using body surface area (BSA) indexing (du Bois formula) to facilitate comparisons with other studies. Only height indexing was included in further statistical analysis, as recommended [28]. LVH was considered present if the LVMI was over 50 g/m$^{2.7}$ for men and over 47 g/m$^{2.7}$ for women, according to the definition of the European Society of Cardiology [2]. Relative wall thickness (RWT) was calculated using the formula RWT = 2 * LVPWd/LVIDd. LVMI and RWT were used to estimate geometry of the left ventricle (Figure 1).

LV systolic function was measured by mitral annular plane systolic excursion (MAPSE), and by systolic tissue-Doppler velocities measured at the medial and lateral mitral annulus. Left atrial volume was calculated by the area length method indexed for BSA as LAVI [29]. LV diastolic function was assessed by pulsed-wave Doppler of mitral inflow and tissue Doppler imaging of the mitral anulus [30]. Aorta diameter was measured by M-mode method.

Statistical analysis

Data analysis was performed using Stata version 17 software (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Data were presented as means ± standard deviation.

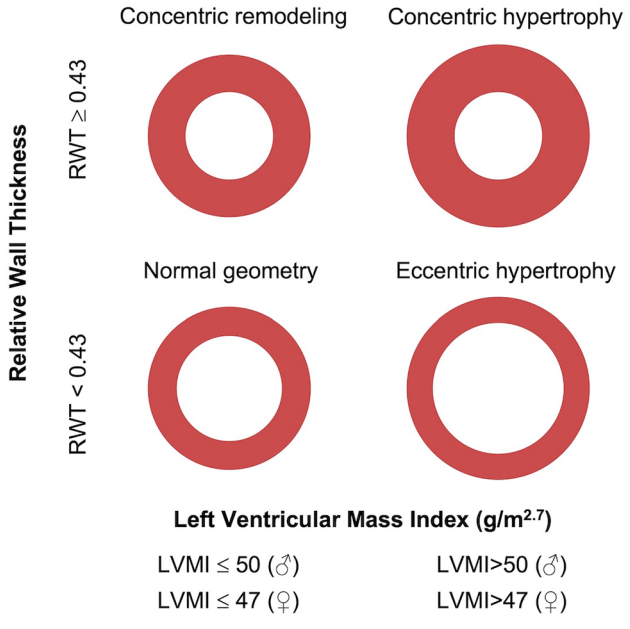

Figure 1. Left Ventricular geometry.

Data were checked for the normality of distribution graphically and using Shapiro–Wilk test for normality. Student's t-test was used for comparison of means where appropriate. Individual progression in echocardiographic measurements by time from RDN was explored using mixed model linear regression with random slope and intercept. To assess whether the effect of RDN on echocardiographic parameters was dependent of BP reduction, including ambulatory systolic and diastolic ABPM as a predictor and an interaction factor in a model. To compare differential effects of RDN on echocardiographic parameters based on response, we divided the whole cohort of patients in groups based on whether they: (1) responded to RDN with a decrease of systolic ABPM of 10 mmHg or more 6 months after RDN, and (2) had systolic ABPM < 140 mmHg at 6 months control. Differences in echocardiographic progression among the groups were explored using an interaction term with time. Repeated measures GEE model with ordinal dependent variable was used to assess time change in distribution of LV geometry pattern.

Results

The cohort consisted of 21 patients with TRH, 17 men and four women, aged 33–66 years, treated with four or more antihypertensive drugs, including a diuretic. Mean systolic office BP was 163 mmHg and mean diastolic BP 109 mmHg. All but one patient had body mass index (BMI) over 25 kg/m^2, 12 of the patients had BMI over 30 kg/m^2, all with metabolic syndrome [31] (Table 1).

Table 1. Baseline characteristics of patients (n = 21).

Age, years, mean ± SD	53.6 ± 8.7
Sex, male, *n* (%)	17 (81)
BMI, kg/m^2 ± SD	32.1 ± 5.0
Egfr ± SD, mL/min/1.73 m^2	79.7 ± 24.4
Total serum cholesterol, mmol/L	4.9 ± 1.1
Current smoker, *n* (%)	3 (14)
Previous smoker, *n* (%)	9 (43)
Coronary artery disease, *n* (%)	2 (9)
History of heart failure, *n* (%)	1 (5)
Stroke, *n* (%)	3 (14)
Atrial fibrillation, *n* (%)	1 (5)
Number of antihypertensive drugs, mean ± SD	4.9 (1.1)
Calcium channel blocker, *n* (%)	18 (86)
Beta-blocker, *n* (%)	17 (81)
ACEI, *n* (%)	8 (38)
ARB, *n* (%)	12 (57)
Loop diuretic, *n* (%)	14 (67)
Thiazide diuretic, *n* (%)	9 (43)
Aldosterone receptor blocker, *n* (%)	11 (52)
Central alpha2 sympatholytic, *n* (%)	7 (33)

Values are presented as mean ± SD or number (%).
ACEI: angiotensin-converting enzyme inhibitor; ARB: aldosterone receptor blocker; BMI: body mass index; eGFR: estimated glomerular filtration rate

As previously reported by Miroslawska et al. [27], we observed a significant reduction in the mean systolic ABPM from 156 ± 20 to 145 ± 16 mmHg at six months, which sustained at 145 ± 14 mmHg at 24 months. There was no statistically significant change in mean ABPM from 6 to 24 months. There was a statistically significant decrease in the mean number of BP lowering medications in use from 4.9 at baseline to 4.3 at 6 months (Table 2).

Patients who responded to RDN with systolic ABPM reduction of 10 or more mmHg after 6 months (n = 9) had significantly higher baseline systolic (168 ± 23 *vs.* 146 ± 10 mmHg, p = 0.007) and diastolic ABPM (107 ± 9 *vs.* 91 ± 9 mmHg, p < 0.001) than patients who had not responded to RDN. In responders, systolic ABPM decreased by 28 ± 20 mmHg after six months and 25 ± 28 mmHg at 24 months control, while in non-responders, mean systolic ABPM increased by 2 ± 8 mmHg on six months control, and decreased by 2 ± 7 mmHg compared to baseline at 24 months control.

Despite a significant mean systolic ABPM reduction of 11 mmHg after six months and 12 mmHg after 24 months in the whole cohort of patients, 67% and 63% of patients, respectively, had systolic BP over 140 mmHg at six months as assessed by ABPM.

Higher BP at baseline was significantly associated with greater reduction of systolic (p < 0.001) and diastolic (p = 0.008) ABPM at six months control (Figure 2).

Table 2. Comparison of patients grouped after whether they (1) had ≥ 10 mmHg reduction in systolic ABPM 6 months after RDN (n = 12) or not (n = 9), (2) achieved systolic ABPM (SABPM) < 140 mmHg 6 months after RDN (n = 14) or not (n = 7).

	Baseline	6 months	24 months
Systolic ABPM, mmHg	156 ± 20	145 ± 16*	145 ± 14*
≥10 mmHg	168 ± 23	140 ± 7	147 ± 6
<10 mmHg	146 ± 10	149 ± 3	144 ± 3
p Value	0.007	0.239	0.643
SABPM < 140 mmHg	150 ± 22	128 ± 9	132 ± 10
SABPM ≥ 140 mmHg	159 ± 18	154 ± 10	151 ± 11
p Value	0.366	n.r.	0.002
Diastolic ABPM, mmHg	98 ± 12	89 ± 11*	90 ± 11*
≥10 mmHg	107 ± 9	88 ± 4	93 ± 3
<10 mmHg	91 ± 9	89 ± 3	88 ± 3
p Value	<0.001	0.756	0.287
SABPM < 140 mmHg	97 ± 14	81 ± 14	83 ± 5
SABPM ≥ 140 mmHg	99 ± 12	93 ± 11	93 ± 11
p Value	0.807	0.020	0.035
Number of drugs	4.9 ± 1.1	4.3 ± 1.2*	4.2 ± 1.5
≥10 mmHg	4.8 ± 0.3	4.5 ± 0.4	4.5 ± 0.6
<10 mmHg	5.0 ± 0.4	4.1 ± 0.4	4.0 ± 0.4
p Value	0.739	0.398	0.502
SABPM < 140 mmHg	4.9 ± 1.2	4.2 ± 1.1	4.1 ± 1.6
SABPM ≥ 140 mmHg	5.0 ± 0.8	4.4 ± 1.5	4.3 ± 1.6
p Value	0.785	0.717	0.822

Data presented as means ± SE. Difference between groups assessed by Student's t-test.
*Significant difference when compared to baseline, p < 0.05.
n.r.: not relevant

LV remodelling patterns

At baseline, 40% of patients had normal LV geometry while 60% had eccentric LVH, with a mean LVMI of 56.2 ± 15.6 g/m$^{2.7}$ (123.8 ± 27.7 g/m^2) for men and 46.4 ± 16.1 g/m$^{2.7}$ (92.0 ± 19.5 g/m$^{2.7}$) for women. Mean MAPSE at baseline was greater than 10 mm, indicating normal systolic LVEF. Mean LAVI was 33.7 ± 6.5 mL/m^2, with seven of 21 of patients having mildly abnormal LAVI, one moderately abnormal and one severely abnormal LAVI at the baseline.

After 24 months, only 30% of patients still had normal geometry, 40% had eccentric LVH and 15% developed concentric LVH (measurements on the rest 15% were missing) (p = 0.22). When the distribution of the geometric patterns was compared between the patients who responded to RDN with systolic ABPM reduction of 10 mmHg or more and the patients who did not, three patients who responded to RDN developed concentric hypertrophy, while in the group of patients who did not respond to RDN no one developed concentric hypertrophy (Figure 3).

On the other hand, when patients were divided in two groups based on whether they achieved BP goal of under 140 mmHg, we found out that none of patients in a group of BP < 140 mmHg developed concentric hypertrophy, and more than half still had normal geometry.

LVMI at baseline was lowest at the lower tertile of systolic AMBP, mean LVMI was 42 ± 7 g/m$^{2.7}$, medium 59 ± 12 g/m$^{2.7}$ and upper tertile 59 ± 20 g/m$^{2.7}$ (linear regression p < 0.05).

There was no significant difference between LVMI at baseline or at controls between the patients who responded to RDN with systolic ABPM reduction of 10 mmHg or more, and non-responders (Supplementary Table 1s). RWT was significantly higher in responders (0.42 ± 0.06 *vs.* 0.36 ± 0.03, p = 0.036).

Change in LVMI was not significantly associated with the total number of ablations.

Mixed model analysis

In mixed model analysis, there was no significant change in LVMI or LAVI after the RDN procedure

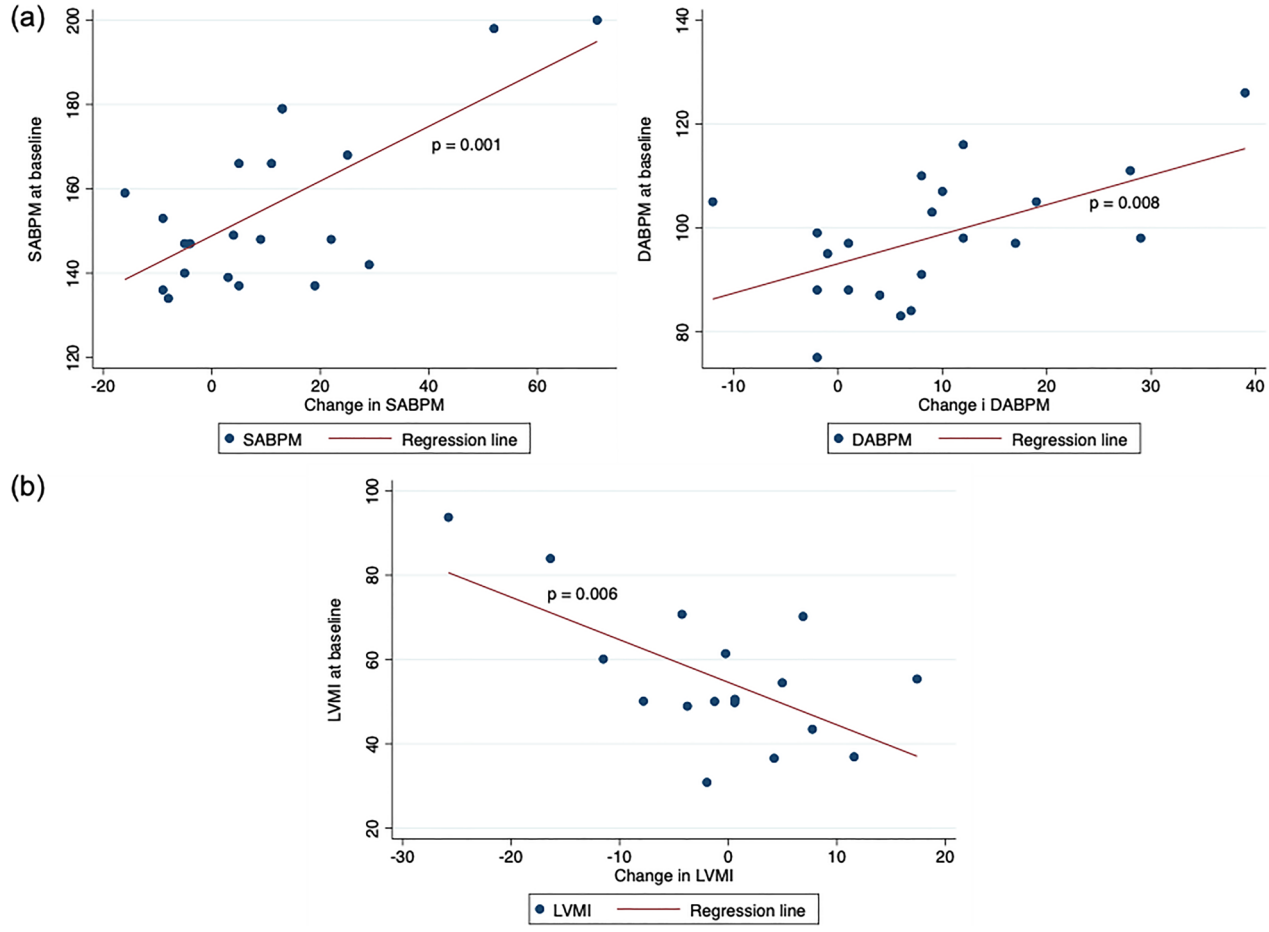

Figure 2. (a) Association of systolic and diastolic ABPM at baseline with reduction at six-months control (p value from linear regression). (b) Association of baseline LVMI with reduction to 24 months control (p value from linear regression).

(Table 3). Higher LVMI at baseline was significantly associated with greater reduction in LVMI ($p < 0.001$).

For the whole cohort of patients, mixed model analysis showed that RWT increased over time (0.048 after two years). We observed a small but significant reduction in LVIDd and LVIDs after RDN, with a mean reduction of 2.6 and 2.4 mm, respectively, after two years. In group comparison, significant increase of RWT and decrease of LVIDd and LVIDs was found in patients who responded to RDN with systolic ABPM reduction of 10 mmHg or more (Table 1s).

On the contrary, when patients were divided according to systolic ABPM level six months after RDN, significant increase in RWT and decrease in LVIDd and LVIDs was observed only in patients who still had systolic ABPM > 140 mmHg (Table 3).

Analysis showed a statistically significant increase in MAPSE with the absolute value of increase of one mm over two years for the whole cohort (Tables 1s and 3).

Discussion

In this study on 21 patients with TRH, the ambulatory and office BP were significantly reduced six months and 24 months after RDN. Higher baseline systolic and diastolic ABPM was associated with more pronounced BP reduction after RDN.

We did not observe a reduction of LV mass after RDN. There was no significant difference in effect of RDN on LVMI in responders and non-responders. However, higher LVMI at baseline was significantly associated with greater reduction in LVMI. In the subgroup of patients who did not achieve systolic ABPM of less than 140 mmHg, we observed a significant reduction in LVIDd and LVIDs, as well as increase of RWT, which indicate progression to concentric hypertrophy.

The method of renal denervation has a solid physiological rationale, and in animal models inhibition of the renal sympathetic activity has favourable effects on BP as well as effect on cardiac remodelling and function [32–38]. Several recent, adequately designed,

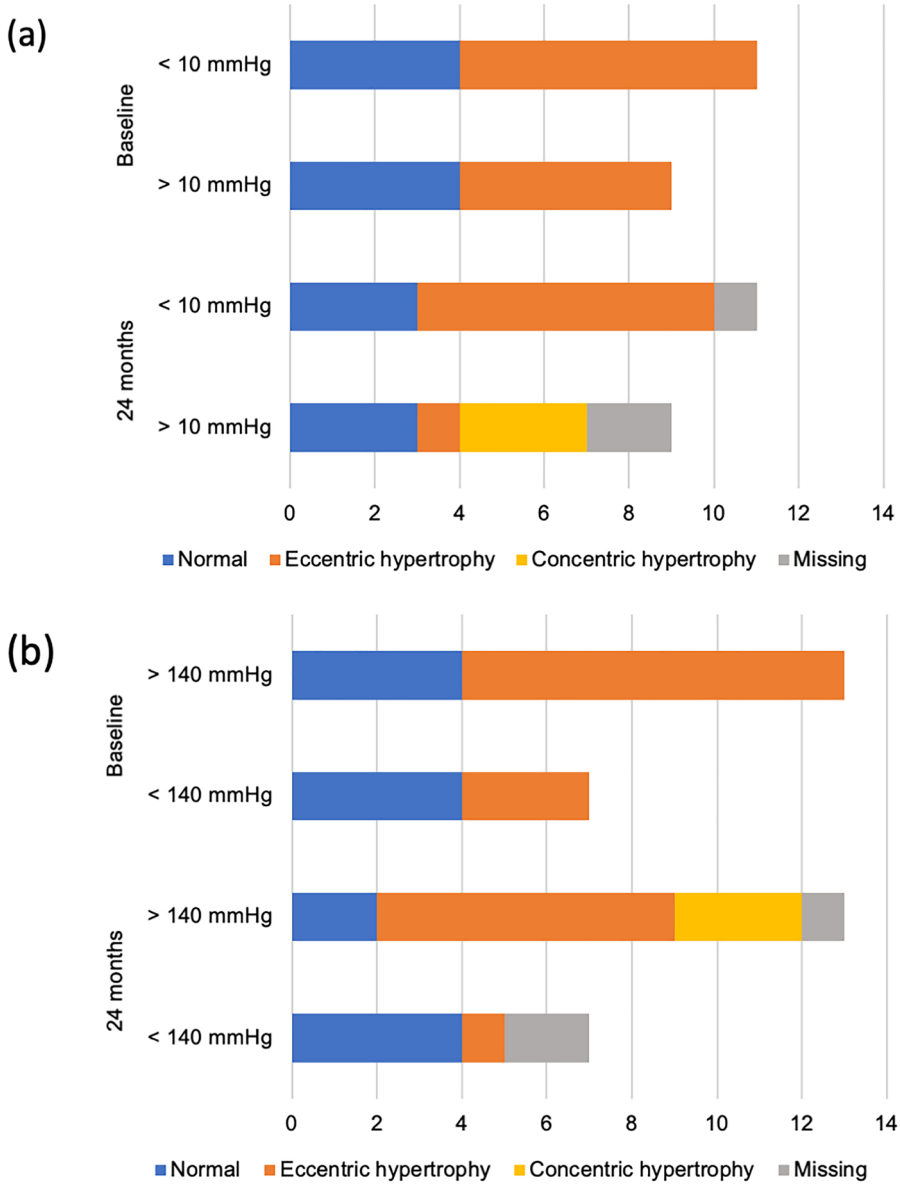

Figure 3. Geometric pattern distribution at baseline and at 24 months control. Horizontal axis shows the number of patients.

randomised, sham-controlled trials have demonstrated that RND is a safe procedure which leads to clinically relevant reduction in BP [17–20]. Clinical studies have demonstrated beneficial effects of RDN on LVH and cardiac function [23–26]. A meta-analysis of 17 RDN studies including a total of 698 patients with TRH has shown that RDN led to a regression of LVMI assessed by both echocardiography and MR, and a significant decline in E/e' ratio, the effect of RDN being independent of baseline BP and BP reduction [39].

BP reduction after RDN demonstrated in our study is in line with the results published from other RDN studies. Still, as opposed to our results, most studies examining effects of RDN on LV mass and other echocardiographic parameters, show positive effect of RDN. It is plausible that our group of patients is different to those in which the favourable effect of BP reduction was demonstrated.

Although we demonstrate a statistically significant increase in MAPSE over time, the absolute value of the increase is small, about one mm over two years. Compared to previously published data, patients in our study were relatively young, and the higher MAPSE, lower LVMI, and the absence of septum hypertrophy observed at baseline in our group of patients is likely to indicate that the hypertensive heart disease was less advanced. We included relatively young patients (mean age 53.6 ± 8.7), hypothesising that the renin–angiotensin–aldosterone system (RAAS) and volume overload as well as hormonally induced vasoconstriction dominate in less advanced

Table 3. Echocardiographic measurements, means with standard deviation, for patients who had normal BP levels at 6 months control (systolic ABMP < 140 mmHg) and patients who were still hypertensive (systolic ABMP ≥ 140 mmHg), at baseline, at 6-month and 24-month control.

Variable	Baseline	6 months	24 months	Progression rate/1 year (SE)	*p* for progression
Left ventricular mass indexed (by height), g/m$^{2.7}$	54.3 ± 15.8	54.2 ± 13.1	54.6 ± 12.8	−0.18 (1.10)	0.870
<140 mmHg	47.2 ± 7.7	45.2 ± 5.3	46.9 ± 4.0	−0.30 (1.24)	0.807
≥140 mmHg	58.1 ± 17.9	59.1 ± 13.5	57.8 ± 14.0	−0.07 (1.58)	0.964
p for interaction				0.887	
LV end-diastolic diameter, mm	**56.1 ± 5.2**	**55.7 ± 4.2**	**54.1 ± 4.7**	**−1.29 (0.39)**	**0.001**
<140 mmHg	53.6 ± 5.3	53.9 ± 2.8	55.4 ± 3.2	−0.01 (0.88)	0.986
≥140 mmHg	**57.5 ± 4.8**	**56.6 ± 4.6**	**54.3 ± 5.3**	**−1.81 (0.39)**	**<0.001**
p for interaction				0.072	
LV end-systolic diameter, mm	**34.8 ± 4.2**	**33.4 ± 4.7**	**32.4 ± 4.8**	**−1.20 (0.48)**	**0.013**
<140 mmHg	33.3 ± 3.9	33.6 ± 3.3	33.7 ± 2.5	−0.07 (0.60)	0.904
≥140 mmHg	**35.7 ± 4.2**	**33.3 ± 5.4**	**31.8 ± 5.5**	**−1.73 (0.63)**	**0.006**
p for interaction				0.094	
Interventricular septum (diastole), mm	9.3 ± 1.4	9.4 ± 1.2	9.6 ± 1.0	0.13 (0.13)	0.321
<140 mmHg	8.9 ± 0.9	8.6 ± 0.9	9.0 ± 0.8	−0.04 (0.17)	0.826
≥140 mmHg	9.5 ± 1.5	9.9 ± 1.1	9.8 ± 1.0	0.17 (0.18)	0.346
p for interaction				0.505	
Relative wall thickness	**0.33 ± 0.05**	**0.34 ± 0.05**	**0.38 ± 0.05**	**0.02 (0.01)**	**<0.001**
<140 mmHg	0.34 ± 0.04	0.32 ± 0.05	0.35 ± 0.01	0.01 (0.01)	0.412
≥140 mmHg	**0.33 ± 0.05**	**0.36 ± 0.05**	**0.40 ± 0.06**	**0.03 (0.01)**	**<0.001**
p for interaction				**0.028**	
LV fractional shortening (%)	37.9 ± 4.8	40.3 ± 5.4	40.7 ± 6.2	0.87 (0.83)	0.299
<140 mmHg	37.7 ± 6.4	37.7 ± 3.7	37.2 ± 4.9	0.58 (1.26)	0.215
≥140 mmHg	38.0 ± 4.0	41.5 ± 5.7	41.5 ± 6.4	1.05 (1.14)	0.356
p for interaction				0.380	
MAPSE ((sept+lat)/2), mm	**14.6 ± 2.1**	**16.5 ± 1.7**	**16.1 ± 2.3**	**0.50 (0.24)**	**0.038**
<140 mmHg	14.9 ± 2.5	16.9 ± 1.5	16.0 ± 1.4	0.32 (0.51)	0.537
≥140 mmHg	**14.5 ± 2.0**	**16.3 ± 1.9**	**16.2 ± 2.6**	**0.57 (0.27)**	**0.038**
p for interaction				0.618	
Left atrium volume index (LAVI), mL/m^2	33.7 ± 6.5	33.5 ± 5.8	34.8 ± 8.4	0.54 (0.75)	0.468
<140 mmHg	35.9 ± 7.2	33.9 ± 4.9	34.3 ± 7.3	−0.60 (1.34)	0.654
≥140 mmHg	32.5 ± 6.0	33.3 ± 6.5	35.0 ± 9.1	1.17 (0.95)	0.216
p for interaction				0.248	
E/A	0.95 ± 0.19	0.95 ± 0.25	0.96 ± 0.25	−0.01 (0.03)	0.978
<140 mmHg	0.99 ± 0.24	1.12 ± 0.14	1.03 ± 0.19	0.02 (0.07)	0.823
≥140 mmHg	0.93 ± 0.17	0.87 ± 0.25	0.93 ± 0.27	−0.01 (0.03)	0.952
p for interaction				0.954	
DT	222.6 ± 24.9	242.6 ± 61.1	254.2 ± 56.4	14.45 (7.75)	0.062
<140 mmHg	227.1 ± 33.4	199.4 ± 37.9	229.4 ± 35.4	4.84 (10.98)	0.659
≥140 mmHg	220.3 ± 20.6	264.1 ± 59.9	263.8 ± 61.1	17.3 (9.89)	0.079
p for interaction				0.483	
Mean é velocity, cm/s	8.9 ± 1.7	10.1 ± 1.9	9.6 ± 1.8	0.23 (0.22)	0.305
<140 mmHg	8.3 ± 2.3	11.2 ± 2.3	9.8 ± 1.7	0.51 (0.53)	0.338
≥140 mmHg	9.2 ± 1.2	9.4 ± 1.4	9.5 ± 1.9	0.08 (0.25)	0.737
p for interaction				0.359	
e' septal, cm/s	7.1 ± 1.2	7.8 ± 1.4	7.8 ± 1.7	0.27 (0.17)	0.115
<140 mmHg	6.9 ± 1.6	8.8 ± 1.3	8.2 ± 1.1	0.43 (0.36)	0.239
≥140 mmHg	7.2 ± 1.0	7.3 ± 1.3	7.6 ± 1.6	0.20 (0.23)	0.390
p for interaction				0.804	
Mean E/e'	7.7 ± 1.5	7.2 ± 2.2	7.3 ± 1.6	−0.21 (0.18)	0.252
<140 mmHg	8.3 ± 1.8	7.0 ± 1.7	7.3 ± 1.7	−0.52 (0.43)	0.226
≥140 mmHg	7.4 ± 1.3	7.3 ± 2.5	7.4 ± 1.7	−0.06 (0.21)	0.767
p for interaction				0.188	
PV S/D ratio	1.5 ± 0.3	1.6 ± 0.4	1.6 ± 0.7	0.01 (0.04)	0.792
<140 mmHg	1.6 ± 0.2	1.5 ± 0.2	1.6 ± 0.4	−0.02 (0.06)	0.399
≥140 mmHg	1.5 ± 0.3	1.7 ± 0.5	1.6 ± 0.2	0.07 (0.6)	0.705
p for interaction				0.680	
AR duration, ms	**137.3 ± 19.6**	**143.1 ± 18.8**	**149.3 ± 16.4**	**5.45 (2.43)**	**0.025**
<140 mmHg	136.8 ± 17.1	139.9 ± 17.4	148.9 ± 27.1	4.56 (4.68)	0.330
≥140 mmHg	137.6 ± 21.5	144.9 ± 19.9	149.5 ± 11.3	5.34 (3.20)	0.095
p for interaction				0.983	
AR-A duration, ms	6.6 ± 21.3	15.1 ± 16.2	12.1 ± 15.4	1.68 (2.58)	0.515
<140 mmHg	10.3 ± 9.9	12.3 ± 17.9	20.6 ± 16.4	5.25 (4.51)	0.246
≥140 mmHg	4.5 ± 26.0	16.6 ± 15.7	8.5 ± 14.2	0.05 (3.39)	0.989
p for interaction				0.366	
Aorta diameter, mm	35.7 ± 2.5	35.5 ± 2.9	36.0 ± 3.6	0.34 (0.43)	0.427
<140 mmHg	36.9± 2.7	36.3 ± 3.0	35.9 ± 4.7	−0.25 (1.06)	0.816
≥140 mmHg	35.1 ± 0.2	35.0 ± 2.8	36.0 ± 3.2	0.62 (0.47)	0.195
p for interaction				0.324	

Data presented as means ± SD. Progression rate and *p* values from mixed model analysis. Statistically significant parameters in bold.

hypertensive heart disease [40]. The fact that patients in our study had lower LV mass at baseline than in several other studies, thus, can be a reason for why we fail to show LV mass reduction. This explanation was proposed as well by Oliveras et al. who failed to demonstrate LVMI reduction in their trial either in RDN or spironolactone group [41].

Selection criteria in our study were different from other studies. Patients were referred from hypertension outpatient clinics where specialists followed them and found them treatment resistant. The inclusion criterion in our study was true TRH despite four or more drug classes including a diuretic, while most of the studies in this field included patients treated with three drug classes or more. Half of our patients were treated with a mineral corticoid receptor antagonist. In a RCT by Rosa et al. where RDN was compared with spironolactone, the spironolactone group achieved better BP reduction [42].

Adjustment of antihypertensive therapy is a possible confounding factor in studies on effects of RDN. Some patients may require reduction of BP medication intensity due to marked BP reduction after the procedure, whereas others need maintained or intensified antihypertensive therapy adjusted during two years' follow-up. In our data, there was a small significant reduction in the mean number of BP lowering medications between baseline and six months control, which could not explain BP reduction after RDN.

Although our study showed a significant mean systolic ABPM reduction of 11 mmHg after six months and 12 mmHg after 24 months, about two-thirds of patients were still hypertensive 6 and 24 months after RDN, which can be one of the reasons why we did not observe a significant reduction in LV mass.

We describe a change in remodelling patterns in hypertension during the two years observational period. At baseline, 60% of patients had LV hypertrophy, all of them having eccentric hypertrophy geometry. This correlates well with previous epidemiological studies [9]. At 24 months, three patients had developed concentric LVH, while six patients had normal LV geometry and eight patients had eccentric LVH. A combination of high BP and obesity can have a pronounced impact on the development of LVH [43]. Progression of LVH can also be influenced by other related conditions such as chronic kidney disease, obesity or diabetes. Patients included in our study had normal or mildly reduced kidney function and did not have diabetes at baseline, but most of the patients were obese with a mean BMI of 32.1 kg/m^2 and insulin resistance, all having metabolic syndrome [44]. Hypertension and insulin resistance form a vicious cycle, sharing the same pathophysiologic mechanisms and leading to activation of the sympathetic system and inflammation [45]. Obesity, insulin resistance and hypertension present in the same patients lead to elevation of cardiac preload and afterload, resulting in LVH combining both concentric and eccentric patterns [46,47]. As opposed to our results, the study of de Sousa et al. included 31 patients with a mean BMI 31.8 kg/m^2, 71% with diabetes mellitus type two showed significant reduction of LV mass 12 months after RDN [48]. In the same study, no significant difference in geometric patterns was shown.

Strengths and limitations

Strengths andlimitations of the ReShape CV-Risk study were discussed previously [27,44,49,50]. The main strength of our study is that it was conducted on a highly selected group of patients with true resistant hypertension, as assessed by witnessed intake of BP medications before the ambulatory BP measurements. We are aware that witnessed drug intake is inferior to measurements of plasma or urine drug concentrations, but these measurements were not available. We followed the patients over a period of two years, which is a long follow-up period compared to most studies on RDN. The study was carried out several years back and utilised methodology that has since evolved. However, the equipment employed for RDN was the same that achieved proof of concept, leading to a notable reduction in BP, also in our cohort.

The main limitations are the small sample size, skewed gender distribution among our study patents, the non-randomised study design, and the lack of control group, which makes this study an observational one. Low number of patients limits the possibilities for subgroup analyses. Mixed model longitudinal analysis was therefore included to ensure enough statistical power despite small sample size. Another limitation of our study lies in the character of 2D echocardiography itself, as the measurements are highly dependent on the qualification of the echocardiographer, and have intrinsically lower reproducibility compared to cardiac magnetic resonance, which is a gold standard for LV mass measurements. Echocardiography is, however, an available technique that is widely used. Both baseline and follow-up echocardiographic measurements in this study were performed by one trained cardiologist (ES) to reduce variability in measurements.

Conclusions

In our non-controlled clinical study on 21 patients with resistant hypertension, we found reduction of systolic and diastolic ABPM 6 and 24 months after RDN. Different from other studies, we have not found a significant reduction of indexed LV mass after the procedure. Higher baseline systolic and diastolic BP was significantly associated with more pronounced effect of RDN. Further, higher LVMI at baseline was significantly associated with greater reduction in LVMI. Over time we observed progression to concentric hypertrophy in patients who did not achieve normal BP values, despite BP reduction after RDN. We conclude therefore that BP reduction after RDN *per se* does not reverse concentric remodelling of the left ventricle if target BP is not achieved. Our patients may be different from those included in other studies in terms of lower proportion of patients with LV hypertrophy at baseline and four or more classes of antihypertensive medications.

Author contributions

E.S., A.M., M.D.S. and T.S. contributed to the conception or design of the work. A.S., E.S., A.M., M.D.S. and T.S. contributed to the acquisition, analysis or interpretation of data. A.S. drafted the manuscript. All authors critically revised the manuscript, gave final approval and agreed to be accountable for all aspects of this work, ensuring integrity and accuracy.

Disclosure statement

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [A.S.], upon reasonable request.

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