Impact of renal sympathetic denervation on cardiac magnetic resonance-derived cardiac indices in hypertensive patients – a meta-analysis

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Abstract

Background: Renal sympathetic denervation (RDN) is a safe device-based option for the treatment of hypertension although current guidelines do not recommend its use in routine clinical practice. In this meta-analysis, we investigated the effects of RDN in cardiac magnetic resonance (CMR)-derived cardiac indices.

Methods: This meta-analysis was performed in accordance with the PRISMA statement. A comprehensive systematic search of MEDLINE database and Cochrane library through to January 2021 was performed. The inclusion criteria were studies that enrolled patients undergoing RDN in whom CMR data were provided for left ventricular end-diastolic volume indexed to body surface area (BSA) (LVEDVI), left ventricular end-systolic volume indexed (LVESVI), left ventricular mass indexed (LVMI), and left ventricular ejection fraction (LVEF) pre and post RDN. A random effects model was used for the analyses.

Results: Our search strategy revealed 9 studies that were finally included in the meta-analysis (n=300 patients, mean age: 60 years old, males: 59%). Compared to control group, RDN patients showed significantly lower values in the attained volumes (LVEDVI: -6.70 ml/m^2, *p*=0.01; LVESVI: -3.63 ml/m^2, *p*=0.006). Moreover, RDN group achieved a statistically significant higher attained LVEF (3.49%, *p*=0.01). A non-significant difference was found in the attained LVMI between RDN and control groups (-2.59 g/m^2, p=0.39). Compared to pre-RDN values, RDN reduces significantly the LVMI, the LVEDVI, and the LVESVI while a non-significant change of LVEF was found.

Conclusions: In conclusion, the current study demonstrates the potential beneficial role of RDN in CMR-derived cardiac indices that reflect adverse remodeling. However, large, randomized studies are needed to elucidate the role of RDN in cardiac remodeling in hypertension, heart failure, and other clinical settings.

Introduction

Elevated blood pressure (BP) is a leading contributor to premature death, accounting for almost 10 million deaths in 2015 [1]. In most cases, antihypertensive medications are effective in controlling hypertension [2]. Although various device-based therapies have emerged in cases of hypertension, their routine use in clinical practice is not recommended until further evidence regarding the efficacy becomes available [3]. Renal sympathetic denervation (RDN) is a safe device-based option for the treatment of hypertension with conflicting results regarding the BP lowering effects [4-9]. Beyond hypertension, decrease in sympathetic activity associated with RDN, may influence different clinical settings. For example, RDN has been found to have a beneficial role in atrial and ventricular arrhythmias [10-13]. Furthermore, the role of RDN in other clinical scenaria (obstructive sleep apnea, myocardial ischemia, heart failure, and chronic kidney disease) has also been studied [14]. Experimental models have demonstrated the beneficial role of RDN to the improvement of cardiac remodeling following myocardial infarction [15, 16]. In addition, RDN has been reported to attenuate left ventricular hypertrophy in hypertensive rats by suppressing the Raf/MEK/ERK signaling pathway [17].

In patients with resistant hypertension, RDN can improve left ventricular hypertrophy while this improvement can be partially explained by the direct effect of altered sympathetic activity [18, 19]. Cardiac magnetic resonance (CMR) data are less prone to measurement errors compared to echocardiographic data [20, 21]. This meta-analysis aims to summarize the data regarding the impact of RDN in CMR-derived cardiac indices in hypertensive patients.

Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22].

Search strategy

Two independent investigators (G.B. & G.T.) performed a comprehensive systematic search in MedLine database and Cochrane library through to January 2021 without any limitations. Furthermore, the reference lists of the relevant research studies as well as the relevant review studies and meta-analyses were manually searched. The keywords that were used to retrieve all relevant studies were: “cardiac magnetic resonance”,

"cardiovascular magnetic resonance", "CMR", "renal denervation". We first screened the titles and abstracts of each study and in case of considering a study as relevant then we went through the full text. Disagreements were resolved by a third investigator (C.T.)

Eligibility criteria

We included studies that enrolled patients who underwent RDN and CMR data [mean values ± standard deviation (SD)] were provided for left ventricular end-diastolic volume indexed to body surface area (BSA) (LVEDVI), left ventricular end-systolic volume indexed (LVESVI), left ventricular mass indexed (LVMI), left ventricular ejection fraction (LVEF) pre and post RDN. We excluded studies written in a language other than English, case reports, reviews, studies that provided only echocardiographic data for the outcomes of interest, studies about surgical denervation, and studies not providing indexed values. In case of duplicate cohorts, we kept the study with the longest follow-up and if it was similar, the cohort with the greater sample size.

Data collection process

The following data were extracted for each included study: First author, journal of publication, year of publication, study design (randomized controlled trials-prospective-retrospective), duration of follow-up, number of patients, gender, age, mean ± SD of systolic/diastolic blood pressure (SBP/DBP) (office or 24-h ambulatory blood pressure monitoring, ABPM) as well as the mean ± SD of the following CMR data: LVEDVI, LVESVI, LVMI, LVEF pre and post RDN. Furthermore, in case of randomized trials, we extracted the outcomes of interest for both the RDN and control groups. The data extraction was performed by two independent investigators (G.B. & G.T.).

Synthesis of results

Data analysis was performed by using the Review Manager software (RevMan), version 5.3. We performed separate analyses for SBP/DBP (office or 24-h ABPM) changes following RDN. Furthermore, we performed an analysis regarding attained

post RDN LVEDVI, LVESVI, LVEF, LVMI difference between RDN and control groups. Continuous outcome variables were pooled as mean difference with 95% confidence intervals (CI). The proportion of heterogeneity across studies not explained by chance was assessed by the I-squared index. A random effects model was used for the analyses. A *p*-value of less than 0.05 (two-tailed) was considered statistically significant.

Risk of bias across studies

The Newcastle–Ottawa Quality Assessment Scale (NOS) was used for quality assessment of the observational studies [23] and Cochrane collaboration's tool for assessing risk of bias in randomized trials [24]. Funnel plots were constructed using RevMan software to assess publication bias. The leave-one-out method was used in case of high heterogeneity.

Results

Studies and patients – quality assessment

The search strategy identified 42 possible relevant studies (Fig. 1). Of those, 19 studies were excluded at the title/abstract level while 14 studies were excluded at the full-text level. As a result, 9 studies (n= 300 patients, mean age: 60 years old, males: 59%) [25-36] were included for further analysis (Table 1). Regarding the quality assessment, of the eight cohort studies included, two were rated as high quality (9 stars in the NOS bias assessment) while the remaining studies were rated with 6 stars due to the lack of non-exposed cohort. The included randomized controlled trial was rated as low risk in all assessed domains while the other one was classified as high risk regarding the performance bias due to the open label design of the study. More details are provided in the supplementary material.

Synthesis of results

Effects of RDN on LV indices in sham-operated trials

Left ventricular mass indexed to BSA

Four studies [27, 28, 34, 36] provided comparative data for at least one of the outcomes of interest between RDN and control groups. Our analysis showed no significant difference in the attained LVMI between RDN and control groups [3 studies: -2.59 g/m^2 (-8.51, 3.34), I^2 34%, p=0.39] (Fig. 2).

Left ventricular volumes indexed to BSA

Regarding left ventricular volumes, significantly lower values in the attained volumes in the RDN group were found [LVEDVI: 2 studies, -6.70 ml/m^2 (-11.87, -1.53), I^2 0%, p=0.01 (Fig. 3); LVESVI: 2 studies, -3.63 ml/m^2 (-6.22, -1.05), I^2 0%, p=0.006] (Fig. 4).

Left ventricular ejection fraction

The quantitative synthesis of studies provided data about the LVEF outcome showed that RDN group achieved a statistically significant higher attained LVEF [2 studies, 3.49 % (0.76, 6.22), I^2 0%, p=0.01] (Fig. 5).

Effects of RDN on LV indices (uncontrolled data)

Our analysis showed that RDN reduces significantly the LVMI [8 studies, -4.15 g/m^2 (-6.80, -1.49), I^2 0%, p=0.002] (Online Fig. 1), LVEDVI [6 studies, -3.47 ml/m^2 (-6.17, -0.77), I^2 0%, p=0.01] (Online Fig. 2) and LVESVI [6 studies, -3.04 ml/m^2 (-4.48, -1.60), I^2 0%, p<0.001] (Online Fig. 3). By contrast, no significant change of LVEF was observed following RDN [7 studies, 1.27 % (-0.66, 3.20), I^2 20%, p=0.20] (Online Fig. 4).

Sensitivity analysis

We performed a sensitivity analysis by including only studies that enrolled resistant hypertension patients. As a result, we removed Patel et al. [36]. which included heart failure with preserved ejection fraction patients and Kiuchi et al. [34], which included patients with premature ventricular complexes. Regarding the effects of RDN on LV

indices in controlled trials, a quantitative synthesis for the attained values could not be performed due to insufficient data. On the other hand, comparing to baseline, RDN led to a significant reduction regarding the LVMI [6 studies, -4.39 g/m^2 (-7.84, -0.94), I^2 0%, p=0.01], whilst no significant change was observed for LVEDVI [5 studies, -1.65 ml/m^2 (-6.29, 3.00), I^2 0%, p=0.49], LVESVI [5 studies, -2.80 ml/m^2 (-5.97, 0.38), I^2 0%, p=0.08] and LVEF [6 studies, 0.76 % (-1.44, 2.96), I^2 18%, p=0.5].

Secondary analyses - Effects of RDN in office and 24-h SBP and DBP

Finally, we analyzed the impact of RDN on office and 24-h SBP and DBP as depicted in the included studies. All studies that provided office BP data enrolled resistant hypertension patients. We found that both office SBP and DBP were significantly reduced following RDN [SBP: 5 studies, -23.86 mmHg (-32.75, -14.96), I^2 63%, p<0.001 (Online Fig. 5); DBP: 5 studies, -9.78 mmHg (-16.13, -3.43), I^2 72%, p=0.003] (Online Fig. 6). A sensitivity analysis was performed to evaluate the heterogeneity in the office SBP/DBP outcome. Regarding office SBP outcome, Tahir et al. [32], had a significant impact on heterogeneity. This finding could be attributed to the fact that this study provided 12-month follow-up data while the remaining studies provided 6-month follow-up data. On the other hand, regarding the office DBP outcome, Palionis et al. [29], had a significant impact on the observed heterogeneity while no heterogeneity was observed by removing both Palionis et al. [29] and Tahir et al. [32] studies (data with 12-month follow-up).

By contrast, three studies provided data in useful format about the impact of RDN in 24-h ABPM. Specifically, we found a small but statistically significant reduction of 24-h SBP [3 studies, -3.20 mmHg (-6.04, -0.35), I^2 0%, p=0.03] (Online Fig. 7) but no significant change of 24-h DBP [3 studies, -1.53 mmHg (-3.66, 0.61), I^2 4%, p=0.16] (Online Fig. 8). By excluding Kiuchi et al. [34] that included non-resistant hypertension patients (patients with premature ventricular contractions) a non-significant reduction of 24-h SBP following RDN was found while 24-h DBP remained non-significant.

Publication bias

Funnel plots revealed no significant publication bias for all the mentioned analyses.

Discussion

The main findings of this meta-analysis are the following:

a) Compared to control group, RDN patients showed smaller attained volumes in the follow-up. However, no significant difference was found between the two groups regarding the LVMI outcome;
b) The RDN group showed significantly greater attained LVEF in the follow-up compared to the control group;
c) Compared to pre-RDN values, RDN significantly reduced LVMI, LVEDVI, and LVESVI but no significant change in LVEF was observed;
d) RDN was found to significantly reduce both office SBP/ DBP and 24-h SBP but no change in 24-h DBP was revealed;
e) By including only resistant hypertension patients, compared to the pre-RDN values, RDN showed a significant reduction of LVMI but no change in LVEF, LVEDVI, and LVESVI.

The role of RDN is not limited to the BP-lowering effects. RDN has also been found to significantly reduce cardiac sympathetic activity demonstrating a direct impact to the heart independently of the BP effect [37]. This is consistent with the pathophysiologic basis for the observed pleiotropic effects of RDN and its role in cardiovascular remodeling, arrhythmogenesis, and heart failure [38-41]. Our study confirms the role of RDN in the regression of the measured cardiac indices as depicted from CMR data. Although our analysis showed a significant reduction of both SBP/ DBP following RDN, we cannot conclude that this is the only mechanism for the observed outcomes. Indeed, a non-significant association between the regression of echocardiographic derived LVMI and BP reduction was found in a previous meta-analysis [42]. In our meta-analysis, we included studies which provided CMR data that are less prone to measurement errors compared to echocardiographic data [20, 21]. However, a previous meta-analysis showed a regression of echocardiographic calculated LVMI as well as an improvement of E/Em but not in E/A following RDN in the estimation of diastolic function [43]. In the same study, a statistically significant regression of the indexed left

atrial volume (LAVI) was found in the quantitative synthesis of studies provided 6-month follow-up data [43]. In addition, in another meta-analysis, a significant reduction of echocardiographic measured LAVI was reported but CMR data did not show a significant reduction in LA area [42]. A significant regression of both echocardiographic and CMR-derived LVMI was also reported [42]. The CMR reference ranges for LV volumes in Caucasians are: LVEDVI: 60-110 ml/m^2 for men and 54-94 ml/m^2 for women while for LVESVI: 21-49 ml/m^2 for men and 19-40 ml/m^2 for women. Regarding LVMI the CMR reference range is 35-70 g/m^2 for men and 29-55 g/m^2 for women [44]. The LV mass can be calculated by multiplying the myocardial volume obtained by the myocardial density of 1.05 g/ml [45].

In our meta-analysis, we were unable to perform a quantitative synthesis for LAVI due to lack of sufficient CMR data. However, Delacroix et al. reported a non-significant change in CMR derived LAVI following RDN procedure [25]. Regarding the LVEF outcome, we did not find a statistically significant increase. However, all included studies that provided LVEF CMR-derived data, had a preserved LVEF at baseline. RDN has been found to significantly increase the LVEF in heart failure patients with reduced ejection fraction [39], although further data are required to delineate the specific role of RDN.

Except for the aforementioned outcomes, CMR studies have also demonstrated the role of RDN in other major outcomes. RDN has been reported to improve aortic distensibility as well as myocardial perfusion reserve index [25, 37]. The beneficial role of RDN in aortic distensibility has been found to be more pronounced in younger patients and in responders to RDN [31]. Furthermore, a decrease of arterial markers (carotid-femoral pulse wave velocity and the augmentation index) and a significant decrease of CMR retrograde flow volume in the ascending aorta has also been reported [29].

By contrast, RDN seems to improve interstitial myocardial fibrosis. Specifically, a significant decrease of extracellular volume (ECV) following RDN has been reported [25]. The beneficial role of RDN in absolute ECV reduction has also been demonstrated in a prospective study while a nonsignificant increase was observed in

the control group [26]. The importance of these findings can be attributed to the fact that the regression in LVMI cannot be explained only in terms of reversion of myocyte hypertrophy but additionally to a reduction in myocardial interstitial fibrosis. McLellan et al. reported a significant reduction of diffuse ventricular fibrosis as depicted by T1 partition-coefficient following RDN while another interesting finding was the improvement of atrial conduction properties [35]. Finally, the CMR-based hemodynamic effects following RDN have also been studied. Although there are not enough data, a significant reduction in stroke volume index has been reported following RDN while cardiac index and stroke work index tended to be reduced [27]. The reduction in stroke work index can be interpreted as a sign of beneficial remodeling and has been associated with a reduced myocardial oxygen consumption [27, 46].

Limitations

A major limitation of this meta-analysis is the inclusion of observational studies and the small number of studies that were included in the analysis. Although all observational studies had a prospective study design, most of them did not include a control group to estimate the comparative impact of RDN on the measured outcomes. Our findings show that there is a non-significant difference in the attained LVMI values between RDN and control groups but the analysis including only RDN patients revealed a significant decrease of LVMI from baseline following RDN. As a result, we cannot extract a safe conclusion regarding the impact of RDN on LVMI because uncontrolled data analysis has several limitations. In addition, we refrained from considering differences from baseline (for both RDN and control groups), because this type of approach introduces two types of outcome (measurement) bias. First, the initial (baseline) levels of each indexed measure (e.g. LVMI) were not identical between the two arms in each separate study and second because differences from baseline are related to the Wilder's principle [47]. A subgroup analysis based on the follow-up duration or other binary variables could not be performed due to the small number of the included studies. Similarly, a meta-regression analysis to estimate the impact of attained SBP/ DBP or other continuous variables-modifiers on the measured outcomes could not be performed. A comparative analysis regarding the impact of RDN on SBP

and DBP between RDN and control groups could not be performed due to the small number of studies and the provided data in either office or ABPM. Finally, a quantitative synthesis regarding the impact of RDN on stroke volume index, cardiac index and stroke work index cannot be performed due to lack of enough data.

Conclusions

The current study demonstrates the potential beneficial role of RDN on CMR-derived LV mass and volumes. However, large, randomized studies are needed to elucidate and contextualize the role of RDN in cardiac remodeling in other clinical settings including resistant hypertension and heart failure.

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Disclosures

The authors declare no conflicts of interest

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Figure legends

Figure 1 Flow diagram of the search strategy.
BSA, body surface area.

Figure 2 Effects of RDN on attained left ventricular mass indexed (RDN vs. control groups).
RDN, renal sympathetic denervation.

Figure 3 Effects of RDN on the attained left ventricular end-diastolic volume index (RDN vs. control groups).
RDN, renal sympathetic denervation.

Figure 4 Effects of RDN on the attained left ventricular end-systolic volume index (RDN vs. control groups).
RDN, renal sympathetic denervation.

Figure 5. Effects of RDN on the attained left ventricular ejection fraction (RDN vs. control groups).
RDN, renal sympathetic denervation.

Table 1 Baseline characteristics and reported outcomes of the included studies.

F author	Number of patients	Age (years)	Males (%)	Follow-up (months)	Indication for RDN / RDN system used	Complications	Blood pressure/heart rate outcomes	CMR outcomes
Delacroix S	12	N/A	N/A	6	Resistant HTN / EnligHTN Renal Denervation System	No major complications reported	Significant reduction of mean office BP at 6 months follow-up	• Improvement in regional aortic distensibility • Trends of improved myocardial perfusion reserve index Left ventricular end systolic volume index reduction • No significant change in left ventricular end diastolic volume index Improvement in mean left ventricular ejection fraction Reduction of extracellular volume percent • No significant change in left ventricular mass or in left atrial volumes indexed to BSA No significant change in native T1 relaxation • No change in overall myocardial strain or in strain rate
Kiuchi MG	34 (20 RDN, 14 controls)	52	25 (74%)	12	Polymorphic PVCs / N/A	No major complications reported	No significant change in 24-h ABPM in both groups A significant reduction in HR was observed at 6 months of f/u in the RDN group but was not maintained at 12 months of f/u A significant reduction in HR was observed at 12 months of f/u in control group. A significant decrease in PVCs was observed at 12 months of f/u in RDN groups compared to control group.	A significant reduction in LVEDVI, LVESVI, LV mass/BSA was observed in RDN group but not in control group. A significant increase in LVEF was observed in RDN group but not in control group.

Mahfound F	72 (55 RDN, 17 controls)	66,2	49 (68,1%)	6	Resistant HTN / Symplicity Flex System (Medtronic,Minneapolis, MN, USA)	N/A	• Significant decrease in office systolic and diastolic BP following RDN	A significant reduction in LVESVI, LV mass/BSA, LV wall stress, left atrial size (in the subgroup with left atrial enlargement) and LVMI (in the subgroup of nonresponders) were observed following RDN A significant incease in LVEF and myocardial circumferential strain (in the subgroup with reduced myocardial contractility) was reported following RDN Non-significant changes in LVEDVI, left atrial size, IVSTd, LVIDd, PWTd, RWT, circumferential strain, peak systolic strain rate and late gadolinium enhancement per segment were noticed following RDN Non-significant changes in any of the mentioned parameters were reported in the control group
McLellan AJA	14	64	10 (67%)	6	Resistant HTN / N/A-Symplicity catheter	N/A	• Significant reduction of mean 24-h ABPM • No significant change in HR	Significant reduction in LV mass-LVMI, RA area and diffuse ventricular fibrosis Non-significant changes in LVEDV, LVESV, LVEF, LA area, atrial T1 relaxation time
Patel HC RDT-PEF	25 (17 RDN, 8 controls)	74,3	15 (60%)	12	HFpEF / Symplicity catheter	• There were no deaths, strokes, or myocardial infarctions • No femoral artery complications. • Intense renal artery spasm/oedema (2 patients)	No significant difference between groups at 12 months with respect to change in 24-h ambulatory systolic blood pressure or 24-h mean heart rate	• No significant difference in the change from baseline for left atrial volume and LV mass between RDN and controls • No significant difference in the change from baseline for aorta PWV and aorta distensibility between RDN and controls
Stoiber L	58	64,4	42 (72%)	6	Resistant HTN / Symplicity Flex system	N/A	Significant decrease of SBP, DBP and pulse pressure	**Data from 50 patients**

					catheter (Medtronic, Minneapolis, MN, USA)			Significant reduction in LVESVI and LV mass/BSA No significant change in LVEDVI, LVEF, IVSTd, LV internal diameter in diastole, LA size and GLS **Data from 58 patients** • Significant increase of aortic distensibility and maximum aortic area
Tahir E	16	64	10 (62,5)	12	Resistant HTN / SymplicityTM Renal Denervation System (Medtronic, Dublin, Ireland)	N/A	• No significant difference in heart rate, ambulatory and office SBP/DBP at the 12 months follow-up	Compared to the baseline values: Significant decrease in LV mass/BSA • No significant difference in the indexed values of LVEDV, LVESV, LVEF, LV stroke volume, RVEDV, RVESV, RV stroke volume and RVEF • Significant increase in radial and longitudinal strain and non-significant difference in circumferential strain
Verloop WL	54	58	27	12	Resistant HTN / Symplicity Flex device (Medtronic, Minneapolis, MN, USA) [94,4%], EnligHTN system (St Jude, St Paul, MN, USA) [3,7%], OneShot system (Covidien, Mansfield, MA, USA) [1,9%]	N/A	In the subgroup of 34 standardized patients: No significant change in 24-h SBP/DBP or heart rate	In the subgroup of 46 patients who underwent CMR: • No significant change in LVMI Significant increase in PWV in the standardized subgroup
Palionis D	15	54	8 (53,3%)	6	Resistant HTN / Symplicity catheter and	No periprocedural complications reported	Significant decrease in office SBP/DBP and heart rate	• Significant decrease in PWV and aortic augmentation index

					radiofrequency generator (Medtronic)			Significant decrease in LV mass, LV mass/BSA Non-significant change in LVEF, LVEDV/BSA, LVESV/BSA, LV stroke volume, LA area,

BSA, body surface area; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LV, left ventricle; EF, ejection fraction; HR, heart rate; BP, blood pressure; HTN, hypertension; SBP, systolic blood pressure; f/u, follow up; CMR, cardiac magnetic resonance; RDN, renal denervation; PVCs, premature ventricular contractions; SVI, stroke volume index; SVRI, systemic vascular resistance index; SWI, stroke work index; RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; N/A, not available; IVSTd, interventricular septal thickness at diastole; LVIDd, left ventricular internal diameter at diastole; PWTd, posterior wall thickness at diastole; RWT, relative wall thickness; ABPM, ambulatory blood pressure monitoring; LA, left atrial; RA, right atrial; LVMI, left ventricular mass indexed to BSA.

*Data about SVRI and SWI were retrieved from 95 patients while data about LVEDVI, LVESVI, LVEF, RVEDVI, RVESVI, RVEF were retrieved from 46 patients.