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Hypertension: An Open Access

Research Article

Michels da Silva D, et al. Hypertens Open Access 2: 104.
DOI: 10.29011/HTOA-104.000104

The Effect of Renal Denervation on Cardiovascular Risk Factors and Individual 10-Year Cardiovascular Risk in Patients with Resistant Hypertension

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Citation: Michels da Silva D, Weil J, Graf T (2019) The Effect of Renal Denervation on Cardiovascular Risk Factors and Individual 10-Year Cardiovascular Risk in Patients with Resistant Hypertension. Hypertens Open Access 2: 104. DOI: 10.29011/HTOA-104.000104

Received Date: 12 February, 2019; **Accepted Date:** 22 February, 2019; **Published Date:** 28 February, 2019

Abstract

Background: Few Renal Denervation (RDN) studies have analysed changes in cardiovascular risk factors beyond blood pressure or the impact on cardiovascular risk. This study aimed to evaluate the effect of RDN on four major risk factors and the subsequent change in estimated 10-year cardiovascular risk.

Methods and results: 67 patients (36 responders, 31 non-responders) receiving RDN within one of two single-centre registries and offering sufficient data to calculate at least one of three cardiovascular risk scores (Framingham Cardiovascular Risk Score 2008, Heartscore or Reynolds Risk Score) were included in this study. The primary endpoint consisted of between-group changes in four major risk factors (Office Systolic Blood Pressure (OSBP), total cholesterol, HDL cholesterol and C-reactive protein) and in the aforementioned risk scores from Baseline (BL) to 12 months after RDN. Amongst responders OSBP decreased significantly by 33.0±23.3 mmHg ($p<0.001$ vs. BL), whereas non-responders suffered a significant increase of 8.2±15.7 mmHg ($p=0.007$ vs. BL). There were no changes in total cholesterol, HDL cholesterol or C-reactive protein in either group. Risk scores were significantly reduced by 20% to 36% in the responder group: Framingham General Cardiovascular Risk Score 2008 (-8.2±11.0 percentage points; $p=0.008$ vs. BL), Heartscore (-2.6±2.1 pp; $p=0.011$ vs. BL) and Reynolds Risk Score (-3.7±4.1 pp; $p=0.016$ vs. BL). Non-responders by contrast experienced a non-significant increase in estimated 10-year risk.

Conclusion: This study supports the assumption that RDN is capable of significantly improving estimated 10-year cardiovascular risk. This is achieved solely by the extent of systolic blood pressure reduction.

Abbreviations

BL: Baseline; CRP: C-Reactive Protein; OSBP: Office Systolic Blood Pressure; ODBP: Office Diastolic Blood Pressure; RDN: Renal Denervation

Introduction

Over the past century cardiovascular diseases have become the leading cause of death worldwide [1,2]. The focus of scientific research has therefore shifted to identifying and analysing predisposing cardiovascular risk factors in order to prevent cardiovascular events. Major cardiovascular risk factors include age, blood pressure, diabetes, cholesterol, smoking and a positive family history.

Elevated blood pressure is undoubtedly the leading contributor to cardiovascular diseases and therefore morbidity and mortality worldwide [3]. In 2015 roughly 10 million deaths and over 200 disability adjusted life years were attributed to hypertension alone [4]. Despite advances in diagnosis and therapy prevalence of hypertension has increased by 40% since 1990 [4]. Based on ageing demographics, especially in industrialised countries, the global prevalence of hypertension is expected to rise by 15-20% from currently 1.13 [5], to 1.56 billion by 2025 [6].

In Germany developments are following global trends. A study from Neuhauser, et al. [7] evaluating adult health in the German population calculated a prevalence of 32% which equals that of other central and eastern European countries (~30-45%) [8]. Apart from the detrimental impact on individual health, hypertension also poses a substantial burden to national economies. According to the German Federal Statistic Office and the Robert Koch Institute direct costs from hypertension regardless of its influence on cardiovascular diseases amounted to ~8,6 billion Euros, equalling 3.6% of all healthcare expenditures [9]. Additionally, indirect costs arising from disability, invalidity and premature death of gainfully employed persons must be taken into account. Hence, prevention and control of hypertension require particular attention, especially in the light of rising numbers of uncontrolled hypertension over the past decades (from 605 to 978 million from 1980 to 2008 [10]). To this end effective means of treatment for true-resistant hypertension must also be found. A systematic review and meta-analysis from 2018 including 91 studies reporting data of a pooled sample of over 3 million patients with hypertension on antihypertensive drugs estimated a prevalence of 10.3% and 12.3% in the general and elderly population [11]. Percentages were especially high in patients with chronic kidney disease (22.9%) and renal transplant (56%) [11]. An analysis of the population studied in the German Health Interview and Examination Survey for Adults in 2008-2011 (DEGS1) put prevalence of uncontrolled hypertension at 37.9% and true-resistance at 6.8% [12].

Catheter-based percutaneous Renal Denervation (RDN) has been shown to reduce blood pressure in patients with resistant hypertension [13-22]. Latter is defined as blood pressure above goal despite a stable drug regime of at least three drugs, one being a diuretic, at maximum or maximally tolerated doses. Previous studies have offered varying results regarding the potency of long-term blood pressure reduction after RDN and therefore bring the efficacy of this minimal-invasive therapy into question [23]. Furthermore, very few studies have examined the effect of RDN on other cardiovascular risk factors or cardiovascular risk. One underlying problem has been the lack of tools for risk stratification. In recent years though, algorithms incorporating central cardiovascular risk factors have been developed in order to predict short- and long-term cardiovascular risk. Therefore, this study aimed to investigate the effect of RDN on four modifiable cardiovascular risk factors included in validated risk scores and the subsequent change in individual estimated 10-year cardiovascular risk.

Methods

This study was designed as a prospective, open-label, unblinded pilot study, whereby patients were required to have undergone RDN within one of two single-centre registries at the Universitätsklinikum Schleswig-Holstein Lübeck or Sana Klinikum Lübeck. Enrolled patients were at least 18 years old, consistently showed an Office Systolic Blood Pressure (OSBP) of ≥160 mmHg (≥150 mmHg for type 2 diabetics) despite a stable drug therapy comprising ≥3 drugs, including a diuretic, at maximum or maximally tolerated doses, and had no indication of pseudo-resistant or secondary hypertension. Furthermore, only patients with sufficient data to calculate at least one of three selected cardiovascular risk scores (Framingham General Cardiovascular Risk Score 2008 [24], Heartscore [25], and Reynolds Risk Score [26]) at both dates were suitable for inclusion. Patients with renal artery malformations, a GFR ≤45 ml/min/1,73m^2 or on haemodialysis were excluded. In total 67 patients were enrolled and divided into responders (36 patients) and non-responders (31 patients) according to the response criterion declared in the SYMPLICITY HTN studies: reduction of OSBP ≥10 mmHg at 12 months. Non-responders were regarded as the control group.

Four major cardiovascular risk factors (blood pressure, total cholesterol, HDL cholesterol and C-reactive protein) and all further variables (age, sex, smoking status, diabetes, positive family history) required for the calculation of the afore-mentioned cardiovascular risk scores were recorded at Baseline (BL) and after 12 months and compared between groups.

Office blood pressure was measured in accordance to the JNC VII [27] and ESC/ESH Guidelines [28]. Readings were taken in a seated position with automatic oscillometric monitors – either the Omron 705 IT^{TN} (Omron HealthCare, Vernon Hills, IL, USA) or Visomat® comfort eco (UEBE Medical GmbH, Wertheim, Germany) - after 3-5 minutes rest. The average of triplicate measures was used for analysis. All patients underwent a medical evaluation including complete medical history, physical examination with assessment of vital signs, a review of medication and further diagnostic evaluation (e.g. ECG, 24-hour-ECG, echocardiography, ergometry, duplex sonography or CT/MRI) depending on preceding findings. Patients and physicians were instructed not to change antihypertensive medication during the study unless medically required. Drug compliance was evaluated through patient interviews.

Three different catheters were used for RDN: radiofrequency ablation with the single-electrode Symplicity Flex^{TM} system (Ardian Medtronic, Palo Alto, California, USA) or the multi-electrode Symplicity Spyral^{TM} system (Ardian Medtronic, Palo Alto, California, USA) or ultrasound ablation with the Paradise® system (Recor Medical, Palo Alto, California, USA).

The study was approved by the local ethics committee and was conducted in accordance with the local, juridically defined ethical standards. All patients provided written informed consent.

Cardiovascular risk factors

For all 67 patients changes in Office systolic and Diastolic Blood Pressure (ODBP), total cholesterol, HDL cholesterol and

C-Reactive Protein (CRP) from baseline to 12 months after RDN were calculated and compared between responders and non-responders.

Cardiovascular risk scores

Three internationally validated scoring systems were selected in order to estimate individual 10-year cardiovascular morbidity and/or mortality. Cardiovascular risk scores were calculated using web-based calculators on the official websites: http://www.framinghamheartstudy.org under "risk functions" and "cardiovascular disease (10-year risk)"; https://escol.escardio.org under "Online Version" and "Heartscore Germany" (equals SCORE model recalibrated using German mortality risk); http://www.reynoldsriskscore.org.

Variables had to be adjusted in accordance to predefined limit values. If continuous variables were above or below the limit, the highest or lowest possible value was filled in. Variables also needed to be rounded off to whole or decimal numbers depending on particular score specifications.

The Framingham General Cardiovascular Risk Score 2008 was issued as a decimal number, the Heartscore and Reynolds Risk Score as whole numbers. Risk categories were then assigned based on the absolute risk score.

Because patients were only required to provide sufficient data for at least one risk score, risk score groups varied in size: Framingham General Cardiovascular Risk Score 2008 (18 responders/18 non-responders), Heartscore (10 responders/ 18 non-responders), Reynolds Risk Score (9 responders/ 18 non-responders).

Statistical analysis

Discrete variables are presented with absolute and relative frequencies, continuous variables as mean±standard deviation. Changes in values were calculated as absolute and relative differences with indication of the 95% confidence interval. Differences in means were compared using the two-sample t-test for unpaired tests or the repeated measures test (if normally distributed) or Wilcoxon-Test (if not normally distributed) for paired samples. Level of significance was set at $p<0.05$, whereby $p<0.01$ was considered as highly significant. Differences between times of examination and between groups are depicted in bar charts with whiskers indicating 95% confidence interval.

Results

Study population

67 patients with resistant hypertension were enrolled in the study. 36 subjects experienced a systolic blood pressure reduction of ≥10 mmHg at 12 months and were defined as responders, while 31 non-responders served as controls. The risk score subgroups were smaller in size due to further selection based on availability of score variables and patient history (see methods and Figure 1).

Baseline characteristics

Both response groups were similar in regard to most characteristics (Table 1), but responders were significantly older (66.8±8.9 vs. 60.9±10.6 years, p=0.019) and showed a higher proportion of type 2 diabetes (44 vs. 16.1%, p=0.013), renal insufficiency (55.6 vs. 29.0%, p=0.029) and use of cholesterol-lowering agents (52.8 vs. 29.0%, p=0.049). Furthermore, OSBP was significantly higher amongst responders (181.3±21.4 vs. 150.9±19.7 mmHg, p<0.001). Mean total cholesterol, HDL cholesterol and CRP did not differ between groups. Most patients were treated with radiofrequency ablation and a single-electrode catheter. There was no significant difference regarding the ratio of single-, multi-electrode and ultrasound procedure between groups.

Variables	Responder (n=36)	Non-responder (n=31)	p-value
Characteristics			
Age (years)	66.8 ±8.9	60.9±10.6	0.019
Male	24 (66.7)	20 (64.5)	0.853
Cardiovascular risk factors			
Body Mass Index (kg/m^2)	29.9±5.9	31.5±4.6	0.219
Office systolic blood pressure (mmHg)	181.3±19.8	150.9±19.7	<0.001
Office diastolic blood pressure (mmHg)	91.5±17.6	90.3±14.4	0.759
Total cholesterol (mmol/l)	5.2±1.4	5.4±1.2	0.507

HDL cholesterol (mmol/l)	1.4±0.5	1.5±0.7	0.656
Hypercholesterolaemia (≥6.19 mmol)	6 (16.7)	6 (19.4)	0.775
Smoker	3 (8.3)	4 (12.9)	0.696
C-reactive protein (mg/l)	3.3±2.8*	4.6±4.3	0.181
Positive family history			
Arterial hypertension	20 (55.6)	18 (58.1)	0.836
Myocardial infarction < 60 years	3 (8.3)	1 (3.2)	0.618
Myocardial infarction ≥ 60 years	5 (13.9)	5 (16.1)	0.798
Stroke	6 (16.7)	4 (12.9)	0.666
Pre-existing conditions			
Type 2 diabetes	16 (44.4)	5 (16.1)	0.013
Angina pectoris	1 (2.8)	0 (0.0)	1
Coronary heart disease	14 (38.9)	9 (29.0)	0.397
Myocardial infarction	3 (8.3)	2 (6.5)	1
Congestive heart failure	2 (5.6)	3 (9.7)	0.656
Stroke	6 (16.7)	3 (9.7)	0.489
Peripheral arterial disease	5 (13.9)	4 (12.9)	1
Renal insufficiency (GFR 45-89 ml/min/1,73 m^2 calculated with MDRD formula)	20 (55.6)	9 (29.0)	0.029
Medication			
Antihypertensives	5.6±1.5	5.2±1.8	0.241
Cholesterol-lowering agents	19 (52.8)	9 (29.0)	0.049
Renal denervation catheter			
Radiofrequency	33 (91.7)	28 (90.3)	1
Single-electrode	29 (80.6)	24 (77.4)	1
Multi-electrode	4 (11.1)	4 (12.9)	1
Ultrasound	3 (8.3)	3 (9.7)	1

Values are given either as total number or mean±SD. Percentages are stated in parenthesis. GFR: Glomerular Filtration Rate; CPAP: Continuous Positive Airway Pressure. *Extreme value of 91.1 mg/l was excluded.

Table 1: Patients' baseline characteristics.

Antihypertensive and cholesterol-lowering drugs

Patients and physicians were instructed not to change antihypertensive or cholesterol-lowering medication during the study period unless medically required. The mean number of antihypertensive drugs remained mainly constant amongst responders (5.6±1.5 vs. 5.3±1.8, p=0.074) and non-responders (5.2±1.8 vs. 4.8±1.8, p=0.062). However, overall 58.3% of the responders and 61.3% of the non-responders underwent a change in number or dosage of their antihypertensive medication (responders: 41.7% reduction, 16.7% increase; non-responders: 41.9% reduction, 19.4% increase).

The number of responders taking cholesterol-lowering drugs remained the same (19 vs. 19), while one non-responder stopped due to normalised cholesterol levels.

Blood pressure

While responders experienced a highly significant reduction in office systolic and diastolic blood pressure (OSBP -33.0±22.3 mmHg, p<0.001; ODBP -8.9±13.4 mmHg, p<0.001), non-responders suffered a significant increase in OSBP (8.2±15.7 mmHg, p=0.007) and no change in ODBP (0.9±8.4 mmHg, p=0.613) (Table 2). At baseline and 12 months OSBP differed significantly between groups, whereby responders showed an average OSBP below that of non-responders 12 months after RDN (148.3±19.2 vs. 159.1±19.1 mmHg, p=0.024) (Table 2). Likewise, ODBP was significantly lower in the responder group at 12 months (82.6±15.1 mmHg vs. 91.2±12.8 mmHg, p=0.014) (Table 2). Interestingly, it was observed that response rates and absolute reduction of OSPB increased with higher pre-procedural hypertension. While patients with stage 1 hypertension showed a response rate of 21.1% and an average absolute reduction of 14 mmHg, 66.7% of patients with stage 2 and 94.7% with stage 3 showed mean reductions of 24 mmHg and 44 mmHg respectively. Lastly, OSBP decreased by at least 20 mmHg in 61.1% of responders.

	Responder (n = 36)			**Non-responder (n = 31)**				
	baseline	12 months	p-value	baseline	12 months	p-value	p-value R vs NR at BL	p-value R vs. NR at 12 months
OSBP (mmHg)	181.3±19.8	148.3±19.2	<0.001	150.9±19.7	159.1±19.1	0.007	<0.001	0.024
ODBP (mmHg)	91.5±17.6	82.6±15.1	<0.001	90.3±14.4	91.2±12.8	0.613	0.759	0.014
Total cholesterol (mmol/l)	5.2±1.4	5.1±1.1	0.48	5.4±1.2	5.5±1.2	0.652	0.507	0.194
HDL cholesterol (mmol/l)	1.4±0.5	1.4±0.5	0.318	1.5±0.7	1.4±0.4	0.374	0.656	0.977
CRP (mg/l)*	3.3±2.8	4.0±3.9	0.131	4.6±4.3	3.8±3.1	0.291	0.181	0.801

Values are given as mean±SD. P value for comparison between baseline and 12 months within a response group or between responders and non-responders. OSBP: Office Systolic Blood Pressure; ODBP: Office Diastolic Blood Pressure; CRP: C-Reactive Protein; R: Responder; NR: Non-responder; BL: Baseline. *calculated with data from 33 responders (one with extreme value at 12 months and two with missing data at baseline or twelve months were excluded) and 30 non-responders (one with missing data at twelve months was excluded).

Table 2: Cardiovascular risk factors at baseline and after 12 months and comparison between response groups.

Total cholesterol, HDL cholesterol and CRP

No significant change between baseline and 12 months was evident for total cholesterol in both groups (responders: 5.2±1.4 vs. 5.1±1.1 mmol/l, p=0.480; non-responders: 5.4±1.2 vs. 5.5±1.2 mmol/l, p=0.652) (Table 2). Likewise, HDL cholesterol remained constant amongst responders (1.4±0.5 vs. 1.4±0.5 mmol/l, p=0.318) and non-responders (1.5±0.7 vs. 1.4±0.4 mmol/l, p=0.374) 12 months after RDN (Table 2).

Neither responders nor non-responders showed significant changes in mean CRP after 12 months (responders: 3.3±2.8 vs. 4.0±3.9 mg/l, p=0.131; non-responders: 4.6±4.3 vs. 3.8±3.1 mg/l, p=0.291) (Table 2). Also, there were no significant differences between groups regarding total cholesterol, HDL cholesterol and CRP at both dates of examination (Table 2).

Cardiovascular risk scores

All 67 patients fulfilled the requirements to calculate at least one cardiovascular risk score, but only few were eligible for all three. Therefore, the number of responders and non-responders in each risk score subgroup were overall smaller and varied (see methods and Figures 1-3). Furthermore, the patient population for the Heartscore and Reynolds Risk Score only differed due to exclusion of one responder missing a CRP value.

Group characteristics at baseline and 12 months were mostly similar for all risk scores. The only difference was OSBP, whereby responders showed a significantly higher OSBP at baseline and significant reductions in OSBP at 12 months. There was no significant change in OSBP amongst non-responders. Also, responders eligible for the Framingham General Cardiovascular

Risk Score 2008 suffered from type 2 diabetes more often than non-responders. Total cholesterol, HDL cholesterol and CRP did not differ between groups and remained constant over 12 months.

At baseline responders possessed a significantly higher Framingham General Cardiovascular Risk Score 2008 than non-responders (40.2±19.7 vs. 22.7±12.4%, p=0.003) (Figure 1). Due to a significant risk score reduction in the responder group (-8.2±11.0 percentage points (pp), relative reduction 20.5%, p=0.008) and no change amongst non-responders (2.0±10.1 pp, p=0.420) the difference between groups at 12 months was no longer significant (32.5±22.5 vs. 24.7±14.6%, p=0.280) (Figure 1).

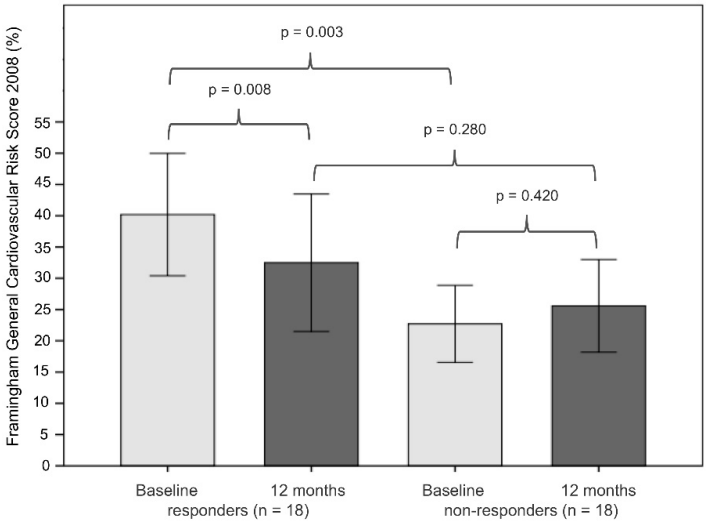

Figure 1: Framingham General Cardiovascular Risk Score 2008 at baseline and 12 months and comparison between groups. Light grey bar indicates risk at baseline, dark grey bar indicates risk at 12 months. Y-axis shows risk score in %. p indicates p-value for changes within and between response groups. n stands for number of patients.

The mean Heartscore did not differ between groups at baseline and 12 months (BL: 7.3±4.9% vs. 3.8±2.2%, p=0.065; 12 months: 4.7±3.4 vs. 4.4±3.5%, p=0.854), whereby the p-value at baseline was only slightly above level of significance Figure 2). More importantly, responders showed a significant reduction of their mean Heartscore 12 months after RDN (-2.6±2.1 pp, relative risk reduction 35.6%, p=0.011) in comparison to non-responders who showed no change (0.6±1.6 pp, p=0.854) (Figure 2).

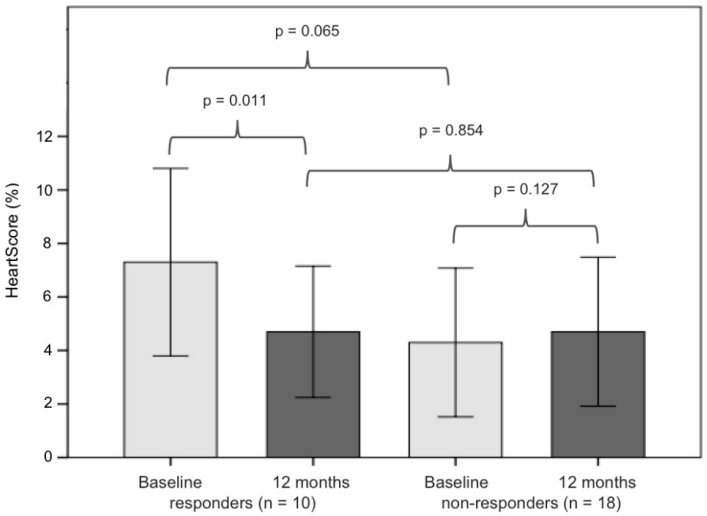

Figure 2: Heartscore at baseline and 12 months and comparison between groups. Light grey bar indicates risk at baseline, dark grey bar indicates risk at 12 months. Y-axis shows risk score in %. p indicates p-value for changes within and between response groups. n stands for number of patients.

The Reynolds Risk Score was reduced significantly in the responder group (-3.7±4.1 pp, relative risk reduction -33.3%, p=0.016) and remained constant amongst non-responders (3.3±8.1. pp, p=0.100) (Figure 3). There was no significant between-group difference regarding the mean Reynolds Risk Score at baseline and 12 months (BL: 11.0±4.8 vs. 9.8±9.8%, p=0.667; 12 months: 7.3±4.8 vs. 13.1±14.0%, p=0.129) (Figure 3).

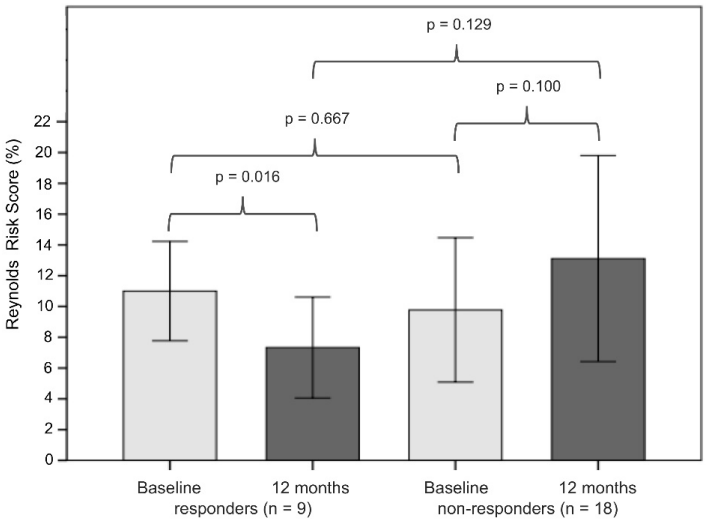

Figure 3: Reynolds Risk Score at baseline and 12 months and comparison between groups. Light grey bar indicates risk at baseline, dark grey bar indicates risk at 12 months. Y-axis shows risk score in %. p indicates p-value for changes within and between response groups. n stands for number of patients.

Discussion

Due to diverging results of past trials the effect of renal denervation on blood pressure in patients with resistant hypertension has not been conclusively clarified. Furthermore, its influence on other cardiovascular risk factors remains unknown. Should RDN be capable of improving multiple risk factors, then the question arises to which extent and how this may benefit cardiovascular risk. Up to date studies have mainly focused on proving a statistically significant absolute reduction of blood pressure in resistant hypertension, but no study to date has thoroughly determined the tangible clinical impact on rehospitalization, cardiovascular events, end organ damage or mortality. This study set out to show how a numerical improvement of risk factors could translate into clinical improvement. Validated score models represent reliable tools to predict future 10-year cardiovascular morbidity and mortality. The results of the present study strongly suggest that RDN significantly improves cardiovascular risk solely by means of systolic blood pressure reduction. RDN does not exhibit an antilipidemic or anti-inflammatory effect multiple studies [13-19], last of which being SPYRAL HTN ON/OFF-MED [20,21], and RADIANCE-HTN SOLO [22], have shown that renal denervation can achieve significant reductions in office and 24-hour blood pressure in patients with hypertension. This study supports these findings, whereby absolute change amongst responders was similar compared to the Symplicity HTN-2 trial [16] (-28/-10 vs. -33/-9 mmHg). Additionally, higher pre-procedural OSBP entailed higher response rates and absolute reduction of OSBP, which explains why responders showed a significantly higher baseline OSBP and reaffirms the role of baseline OSBP as a positive predictor of response as previously postulated in the Symplicity HTN-3 study [29]. Non-responders by contrast experienced an increase in blood pressure, a development that is to be expected in patients with resistant hypertension that remains uncontrolled.

It has been proven that elevated total cholesterol and CRP as well as low HDL cholesterol cause atherosclerosis and therefore increase the risk for ischaemic cardiovascular diseases by two- to fourfold in both sexes throughout all age groups [30-32]. In this study no changes in total cholesterol, HDL cholesterol or CRP were noted in both groups under stable cholesterol-lowering medication. This leads to the conclusion, that the inhibition of central sympathetic activity through RDN does not influence lipid metabolism or inflammatory processes.

National and international guidelines recognise cardiovascular risk scores as helpful tools to estimate short- and long-term cardiovascular morbidity and mortality and recommend their use in daily clinical routine. Despite being mathematical algorithms risk scores are based on data of genuine incidence of cardiovascular events in different populations and may therefore reliably predict clinical improvement. The three most validated risk models - the Framingham General Cardiovascular Risk Score 2008, the Heartscore (derived from SCORE) and Reynolds Risk Score - were applied in this study. At baseline responders showed higher mean risks, whereby between-group difference was only significant in regard to the Framingham General Cardiovascular Risk Score 2008. This can be attributed to a higher mean age, mean OSBP and number of diabetics. Amongst responders all three cardiovascular risk scores decreased significantly by 20-36%, meaning that around one fifth to one third of predicted cardiovascular events could be prevented in the next ten years. Non-responders on the other hand experienced a non-significant increase in cardiovascular risk. In all cases OSBP was the only score parameter to either be significantly reduced or whose increase came close to level of significance. These findings strongly suggest that any change in cardiovascular risk after 12 months must in most part be ascribed to the effect RDN has on blood pressure and that if RDN is successful in reducing blood pressure it not only averts the effect of ageing but moreover achieves a considerable improvement in estimated 10-year cardiovascular risk.

The study population consisted in most part of white Caucasians from Germany, a low-risk population. Therefore, some may question the validity of applying the Framingham General Cardiovascular Risk Score 2008 and Reynolds Risk Score, two risk models derived from American cohorts with high risk. In general, event and mortality rates for cardiovascular diseases within cohorts are used to calculate relative risk and risk coefficients of individual risk factors. The more incidence and mortality rates diverge, the more inconsistent weighting of one and the same risk parameter becomes [33]. Hence, risk scores might not be unconditionally applicable to all populations or subgroups. Research has shown that the Framingham Risk Score systematically overestimates absolute cardiovascular risk in high-risk populations and underestimates it in low-risk populations [33-35]. Moreover, the Framingham General Cardiovascular Risk Score 2008 demonstrates a lack of precision in multi-ethnic populations unlike the Reynolds Risk Score [36]. Likewise, the SCORE revealed inaccuracies in particular European populations [37,38]. This led to the recalibration of the SCORE algorithm based on national mortality rates. With this in mind, it is certainly legitimate to doubt the accuracy of absolute risks detailed in this study. However, a prospective study from Hense, et al. [33] validating the application of the Framingham risk function for coronary heart disease in the MONICA Augsburg and PROCAM cohort, determined that predicted risks for German cohorts were consistently overestimated by a factor of 2 to 3. This means that even if an over- or underestimation of absolute risk occurs, in does so to the same extent at both times of examination. Risk scores could therefore be easily adjusted using a correction factor. Granted, absolute risk may not be accurate, but the arithmetical ratio remains the same, wherewith the core statements of this study remain valid. In the future improved risk algorithms and

self-learning artificial neuronal networks [38], will greatly help to better determine the impact of RDN on cardiovascular risk.

In this study solely changes in estimated 10-year cardiovascular risk were evaluated. Therefore, no statement can be made regarding effects on long-term or lifetime risk. However, it is known that the cumulative damage caused by moderately or strongly elevated risk factors is often underestimated. Several publications have demonstrated that 10-year and lifetime cardiovascular risks may diverge substantially [40-42]. Hence, it can be assumed that the lifetime benefit of successful blood pressure reduction achieved by RDN is even greater than already the case for 10-year risk.

In order to fully grasp the potential of RDN to improve cardiovascular risk two further aspects must be addressed. Firstly, the effect of RDN on several other risk factors such as glucose metabolism [43,44] remains unclear. Secondly, even if it is discovered that RDN impacts further risk factors, the benefit for cardiovascular risk can only be mathematically determined if said risk factors are incorporated into risk stratification models.

Lastly, in order to verify the calculated risk reductions and prove a significant clinical benefit, patients must be followed up in regard to incidence of and death by cardiovascular diseases.

Limitations

Two of the most central limitations of this study are the small sample size and the lack of randomization. The majority of patients listed in both single-centre registries had to be disqualified due to missing variables for risk score calculation. This might have contributed to selection bias. Furthermore, the fact that the single-centre registries were not based on the same study design may be criticised. However, both studies were similar in design and shared an almost identical set of inclusion and exclusion criteria meaning patient collectives were near to uniform. Moreover, seeing as this study was non-randomized non-responders had to be used for comparison instead of an untreated control group or sham group leaving a possible placebo effect undetected. The use of three different denervation catheters may be a further concern, although all procedures have proven to be equally effective and showed equal rates of response in this study.

In order to generate statistically sound results, it is essential that comparison groups are similar in regard to their characteristics. In this study however, responders and non-responders differed significantly in group size, mean age, mean OSBP and in number of subjects with diabetes and renal insufficiency. Furthermore, both groups were predominantly male. In sum, larger cohorts, better matching and a balanced gender ratio would have been preferable. Considering the small sample size further subgroup analyses were not undertaken.

Patients and physicians were instructed not to change antihypertensive medication during the study unless medically required. Nonetheless, only 55% of all patients showed consistent medication regimes during follow-up while roughly 42% of responders and non-responders underwent drug reduction and 17% to 19% had their medication increased. Amongst responders it is plausible that medication was reduced due to symptomatic hypotension. Likewise, increases in the non-responder group are most likely to have occurred due to persistent hypertension. However, due to lack of documentation reasons for increases in medication amongst responders and reductions amongst non-responders remain unclear. Additionally, even though patients were interviewed about drug compliance no toxicological analyses were conducted to verify statements meaning non-adherence cannot be completely factored out. These changes in medication make it difficult to determine the independent blood pressure lowering effect of RDN.

Conclusion

Renal denervation significantly reduces office blood pressure, but has no impact on cholesterol or C-reactive protein. Once again, office systolic blood pressure proved to be a positive predictor for RDN response, but further predictors must be identified in order to discern which patients are most likely to benefit from RDN. Furthermore, the extent of systolic blood pressure reduction achieved by RDN realizes a significant improvement in individual estimated 10-year cardiovascular risk.

Ultimately, further research regarding the effect of RDN on other risk factors and on short- and long-term risk as well as the development of more accurate risk prediction tools are required in order to fully uncover the true potential of RDN in regard to the primary prevention of cardiovascular diseases.

Acknowledgements

We would like to thank the study nurses, study coordinators and research assistants at both sites for their outstanding help with patient management and data acquisition**.**

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