RENAL NERVE ABLATION REDUCES AUGMENTATION INDEX IN PATIENTS WITH RESISTANT HYPERTENSION

Running title: Renal denervation and augmentation index

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ABSTRACT

Objective: Renal denervation (RDN) has been demonstrated to reduce muscle sympathetic nerve activity (MSNA) and blood pressure (BP) in patients with resistant hypertension (RH). Whether alterations of arterial stiffness may contribute to BP lowering effects of RDN is unknown.

Methods: We measured office BP and arterial stiffness using fingertip tonometry derived augmentation index (AI) (EndoPAT2000) at baseline and at 3 month follow-up in 50 consecutive patients with RH. Fourty patients received RDN and 10 patients served as controls. MSNA was obtained in 20 RDN and 10 non-RDN patients.

Results: Baseline BP averaged 170/92±19/15 mmHg (RDN) and 171/93±14/8 mmHg (non-RDN) despite the use of 4.9±1.9 and 4.4±2.0 antihypertensive drugs, respectively. RDN significantly reduced systolic (170±19 vs. 154±25 mmHg; $p<0.001$) and diastolic BP (92±15 vs. 84±16 mmHg; $p<0.001$), AI (30.6±23.8 vs. 22.7±22.4%; $p=0.002$), AI@75 corrected for heart rate (22.4±21.6 vs. 14.4±20.7; $p=0.002$) and MSNA (80±15 vs. 71±18 bursts/100 heartbeats; $p<0.01$). Changes in AI@75 with RDN were unrelated to systolic ($r=0.043$; $p=0.79$), and diastolic BP ($r=0.092$; $p=0.57$) and MSNA changes ($r=-0.17$; $p=0.49$). No changes in BP, AI, AI@75 or MSNA were observed in the non-RDN group.

Conclusions**:** RDN results in a substantial and rapid reduction in AI which appears to be independent of BP and MSNA changes. These findings are indicative of a beneficial effect of RDN on arterial stiffness in patients with RH and may contribute to the sustained BP lowering effect of RDN.

Key words: resistant hypertension, augmentation index, renal denervation, sympathetic nerve activity

INTRODUCTION

Arterial stiffness is a hallmark of hypertension and increasingly recognized as an independent predictor of total and cardiovascular (CV) morbidity and mortality [1-6]. Loss of aortic distensibility has been directly associated with the composite outcome of cardiovascular events in the general population and is particularly evident in patients with hypertension [7]. Augmentation index (AI) is an established marker of arterial stiffness and a major determinant of central blood pressure (BP). Carotid or radial AI is linearly associated with increased cardiovascular risk [8], coronary artery disease [9], hypertension-related target organ damage [10, 11] and all cause and cardiovascular mortality [12, 13]. AI derived from fingertip tonometry correlates with cardiovascular risk [14], abnormal ventricular-vascular coupling [15] and has been found to be elevated in polycystic kidney disease [16] and sclerodermia [17].

Several factors including extracellular matrix composition [18], metabolic abnormalities [19], inflammatory biomarkers, high-salt intake [20], genetic factors [21, 22], age and gender [23] have been proposed to play a role in structural vascular remodelling associated with increased CV complications. However, altered sympathetic activation, consistently evident in arterial hypertension as demonstrated by increased rates of efferent sympathetic-nerve firing and total body noradrenaline spillover [24] may also play a causal role in the development and progression of artery stiffening in refractory hypertension. While sympathetic denervation increases arterial distensibility in experimental models [25, 26], studies evaluating the relationship between direct measures of sympathetic nervous system activation and arterial stiffness in humans are limited to healthy subjects [27-30].

Despite broad availability of effective non-pharmacological and pharmacological interventions that modulate vascular stiffening, the poor cardiovascular outcomes suggest failure of present strategies [31].

Recent data indicated that renal denervation (RDN) results in substantial and sustained BP control and reduced noadrenaline spillover and central sympathetic outflow in patients with resistant hypertension (RH) [32-35]. Moreover, we recently demonstrated that renal denervation (RDN) effectively and rapidly attenuated peripheral AI in a small series of patients with RH and moderate to severe chronic kidney disease [36]. Whether alterations of arterial stiffness may contribute to BP control following RDN is unknown. We therefore examined whether sympathetic nerve ablation affects peripheral arterial stiffness assessed as AI derived from finger arterial tonometry in high risk patients with RH.

Methods

Subjects

A total of 50 patients (39 males/11 females) with RH were enrolled in this prospective clinical study aimed at assessing the effects of RDN on AI, fourty of whom (31 males/9 females) underwent the procedure. Ten patients (8 males/2 females) who were eligible for the procedure but did not to undergo RDN at the time served as controls (non-RDN). The procedure is approved in Australia by the Therapeutic Goods and Drug Administration (TGA) and the study was approved by the Institutional Ethics Committee. Written, informed consent was obtained from all patients.

All participants had been evaluated previously by local specialists before being referred to our hypertension clinic for further assessment and management. Patients underwent a complete medical history and physical examination and comprehensive evaluation of cardiovascular risk factors. Hypertension was diagnosed based on the current European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines for the management of arterial hypertension [37]. Patients had previously been screened for secondary forms of hypertension as listed in the current guidelines [37] and were excluded if present, with the exception of obstructive sleep apnea, diagnosed in 7 patients, 4 of whom were treated with continuous positive airway pressure (CPAP) therapy and n=3 who were not treated due to intolerance of CPAP. RH was defined according to the current statement of the American Heart Association [38]. Only patients with true resistant hypertension with daytime SBP >135mmHg were included in this study. All patients had renal artery imaging (Doppler ultrasound, CT or MR-angiography) prior to enrolment to exclude severe renal artery stenosis or other abnormalities such as fibromuscular dysplasia, which was confirmed by renal angiogram just prior to the RDN procedure.

Serum and urine biochemistry

To exclude major health issues aside from hypertension routine blood tests (hemoglobin, glucose level, HbA_1c, lipid profile, kidney and liver function, electrolytes), urinary albumin-to-creatinine ratio (UACR, morning spot urine), estimated glomerular filtration rate (eGFR) calculated using the MDRD (Modified Diet in Renal Disease) [39] formula were performed in all participants prior to study enrollment. To assess safety of the procedure kidney function tests were repeated at 3 month follow-up.

Office-seated and ambulatory blood pressure

Average sitting office BP was measured after at least 5minutes of rest on both arms and was calculated as the average of three consecutive measurements within a 1-minute interval at baseline and during each visit at follow-up with a validated device (Omron HEM-907, Omron Healthcare Singapore PTE Ltd). The arm with higher BP readings was used for subsequent measures.

To exclude pseudo-resistant hypertension all participants underwent 24-hour blood pressure and heart rate monitoring (ABPM) using a validated device (Spacelabs 90207 or 90217 recorder; Spacelabs Healtcare, Washington, USA) at baseline as described previously [36]. However, a few patients (n=3) in the RDN group were unable to tolerate ABPM due to sleep disturbances and local arm discomfort during night-time measurements at baseline. As recommended in the current guidelines, only ABPM data fulfilling the described standards in regards to the proportions of valid values for the day and night periods recordings were used for analysis [37]. At 3 month follow-up analysable ABPM were available from 23 patients out of these 37 patients as the remaining 14 patients were participants of the Symplicity HTN-2 trial, the protocol of which required ABPM to be performed at 6, but not at 3 month follow up.

Muscle sympathetic nerve activity (MSNA)

Sympathetic nerve activity to the muscle vascular bed was recorded continuously by obtaining multi-unit recordings of postganglionic sympathetic nerve activity (662C-3 Nerve Traffic Analysis System, Bioengineering of Iowa University, USA). A tungsten microelectode (UNA40F2S; FHC, Bowdoinham, ME, USA) was inserted directly into the peroneal nerve posterior to the fibular head. The neural signals were amplified, filtered, rectified, and integrated to obtain a voltage display of sympathetic nerve activity. MSNA was identified through careful inspection of the voltage neurogram. The amplitude of each burst was determined and sympathetic activity was calculated as bursts/min and as burst incidence (bursts/100 heart beats) as described previously [24, 40].

Catheter-based renal denervation (RDN)

Radiofrequency catheter (Symplicity; Medtronic Ardian Inc., Palo Alto, California, USA) was introduced into each renal artery via femoral access. All patients underwent bilateral renal nerve ablation in one session with the catheter positioned in the lumen of the renal artery, as described previously [32-34]. To minimize local visceral pain during the energy delivery anxiolytics and analgesics were administered intravenously.

Peri-and post-procedural medications

To assess the true effects of RDN on BP, AI, and MSNA baseline medication was kept unchanged for at least 6 weeks prior to renal nerve ablation and this treatment was maintained until at least 3 months follow-up. Similarly, baseline medication was not altered in the 10 control subjects throughout the study period. Medication records of each patient were reviewed and documented at each visit. All female subjects (n=11) enrolled in this study were post-menopausal and were not receiving hormone replacement therapy.

Peripheral Arterial Tonometry

Augmentation index (AI) was measured non-invasively from the digital pulse wave volumes by Peripheral Arterial Tone (PAT) signal using the EndoPAT2000 device (Itamar Medical Inc., Caesarea, Israel). PAT measures beat-to-beat plethysmographic recordings of the finger pulse wave amplitude (PWA) with pneumatic probes. These EndoPAT bio-sensors were placed on the index fingers of both arms. Peripheral augmentation Index (AI) and AI corrected for heart rate of 75 (AI@75) were calculated automatically through a computer algorithm provided by Itamar Medical. AI is considered a surrogate marker of peripheral arterial stiffness and its close correlation with multiple devices including the Sphygmocor has recently been demonstrated [41].

Study protocol

At the first visit, all subjects underwent comprehensive clinical investigation. All measurements described above were obtained at baseline (before renal denervation) and at 3 months after the procedure. Hypertensive controls underwent the same measurement at baseline and at 3 month follow-up, without having undergone RDN. BP was measured as described above followed by fasting serum and urine biochemistry assessments. On the second visit patients were studied in a supine position after fasting for at least 12 hours in the morning or early afternoon. After 15 minutes of rest, peripheral augmentation index was measured over 5 minutes of stable wave form recordings. Then sympathetic nervous system measurements using microneurography was obtained from the right peroneal nerve. Resting MSNA was measured over 15 minutes of stable recordings. Subjects were asked to refrain from smoking and from alcoholic beverages for at least 12 and 48 hours, respectively prior to a study protocol.

Data analysis

A random code was attributed to all recordings and all data analyses of AI, AI@75 and MSNA were performed blinded to the identity of the patient and measurement (at baseline and at 3 month follow-up) during which the recording had been performed. MSNA analysis was performed over a 5 minute period of stable recording. Sympathetic bursts were identified by a single experienced investigator (DH) without the knowledge of the patient identity.

Statistical analysis

Data are presented as median ± SD (standard deviation) with interquartile range where indicated. Statistical analysis was performed using SigmaStat Version 3.5 (Systat Software, Point Richmond, CA). All data were normally distributed. Comparisons between changes in

AI, AI@75, BP and MSNA at baseline and at 3 month follow-up were performed using a paired t-test. A p-value of <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Table 1 presents baseline clinical characteristics of the 40 treated patients (RDN) and 10 controls (non-RDN). The RDN cohort had a mean age of 60±11 years and non-RDN 60±6 years, respectively. Body mass index was 32±6 kg/m^2 (RDN) and 30±5 kg/m^2 (non-RDN), waist circumference was 107±17 cm (RDN) and 104±5 cm (non-RDN), and waist-to-hip ratio was 0.95±0.1 (RDN) and 0.93±0.1 (non-RDN). Four patients from each cohort were current smokers. On average, RDN patients were taking 4.9±1.9 antihypertensive drugs, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers or dual blockade (16 patients), β-blockers, calcium-channel blockers, diuretics, α-blockers, vasodilators, and centrally acting sympatholytic agents. Coronary artery disease was diagnosed in 33% of RDN patient cohort, type 2 diabetes mellitus in 31%. Obstructive sleep apnoea was previously diagnosed in 7 out of 50 investigated patients, 4 of whom were on CPAP therapy, which was unaltered during the study. Average creatinine-based eGFR of RDN patients was 74.3±17.6 ml/min./1.73m^2.

Control patients were on an average of 4.4±2.0 antihypertensive drugs. Detailed BP lowering drugs and medical history of the non-RDN patient cohort are depicted in Table 1. Average creatinine-based eGFR of non-RDN patients was 84.4±9.1 ml/min./1.73m^2.

At baseline, average office-seated systolic blood pressure (SBP) was 170±19 mmHg and diastolic blood pressure (DBP) was 92±15mmHg, with a heart rate (HR) of 65±15 beats per min (bpm) in RDN patients, and SBP 171±14 mmHg, DBP 93±8 mmHg, and HR 65±17 bpm in non-RDN controls, respectively (Table 1).

Procedural aspects

Renal angiograms were performed prior to the introduction of the RF treatment catheter via femoral access and anatomic eligibility and absence of significant vascular pathology was confirmed in all patients. An average of 9.0±1.8 ablations treatments using a predetermined treatment protocol and algorithm [32, 34] were delivered in each patient without any peri-or post-procedural complications. Angiographic evaluation before and directly after the procedure did not reveal any compromise of the treated arteries. There were no intra- or periprocedural complications. No short-term (at 3 month follow-up) adverse events related to the procedure were noted in any of the treated patients.

Effects of renal denervation

Average office SBP and DBP at baseline and at 3 month follow-up for both groups are depicted in Table 2. RDN significantly reduced office SBP ($P<0.001$) and DBP ($P<0.001$) at 3 month follow-up (Table 2). Mean decrease in sitting office SBP and DBP following the procedure was -16/-8 mmHg (SD 21/11), respectively. RDN resulted in a significant reduction in daytime SBP (151+19 vs. 144±18 mmHg; $P<0.05$) and DBP (87±15 vs. 83±12 mmHg; $P<0.05$). RDN tended to reduce night-time SBP (138±25 vs. 130±23 mmHg; $P=0.07$), but not night-time DBP (77±14 vs. 73±14 mmHg; $P=0.15$).

There were no changes in office SBP and DBP at 3 month follow-up in hypertensive controls (Table 2). Daytime SBP (156±19 vs. 155±15 mmHg; $P=0.85$) and DBP (94±14 vs. 92±9 mmHg; $P=0.7$) as well as night-time SBP (143±28 vs. 142±22 mmHg; $P=0.78$) and DBP (81±12 vs. 82±11 mmHg; $P=0.62$) remained unchanged at 3 month follow-up in non-RDN group.

Resting office HR remained unaltered at follow-up in RDN patients and non-RDN controls (Table 2).

AI was significantly reduced 3 months after the procedure in RDN patients (30.6±23.8 vs. 22.7±22.4 %; P=0.002), but not in non-RDN controls (30.2±27.4 vs. 32.0±20.7 %; P=0.80) (Figure 1a and Table 2). Independent analysis of AI corrected for heart rate (AI@75) confirmed a significant reduction at follow-up in RDN patients (22.4±21.6 vs. 14.4±20.7 %; P=0.002), but not in non-RDN controls (21.2±21.4 vs. 21.2±19.7 %; P=0.99) (Figure 1b and Table 2).

Individual changes in AI@75 corrected for heart rate in RDN group are shown in Figure 2.

MSNA significantly decreased 3 months following RDN (49±9 vs. 44±13 bursts/min.; P<0.05) (Table 2). The reduction in MSNA after the procedure was also evident when sympathetic activation was expressed as bursts/100 heart beats (80±15 vs. 71±18; P<0.01) (Table 2). In contrast, there were no changes in MSNA in non-RDN controls at 3 month follow-up (Table 2).

In RDN patients, the reduction in MSNA corrected for heart rate (bursts/100 heart beats) was related to SBP (r=0.45; P=0.04) and DBP (r=0.59; P=0.005) decreases 3 months after the procedure.

Changes in AI corrected for heart rate (AI@75) were unrelated to SBP (r=0.043; P=0.79) and DBP (r=0.092; P=0.57). The reduction in AI@75 was also unrelated to MSNA decrease (r=-0.17; P=0.49) at follow-up. Similarly, no significant relationship were found between changes in AI and SBP (P=0.98), AI and DBP (P=0.88); and AI and MSNA (P=0.14), respectively, after the procedure.

There were no significant alterations in kidney function assessed by estimation of GFR based on serum creatinine (74.3±17.6 vs. 71.9±18.0 mL/min/1.73m^2; P=0.31), plasma potassium (4.0±0.4 vs. 4.1±0.5 mmol/L; P=0.93) and sodium (139.2±2.4 vs. 139.0±2.1 mmol/L; P=0.50) levels after RDN.

DISCUSSION

The present findings provide the first evidence that catheter-based renal sympathetic nerve ablation reduces peripheral augmentation index in high risk patients with RH. The main results of this study are that selective bilateral sympathetic RDN (1) decreases peripheral AI, (2) reduces efferent MSNA, and (3) results in rapid BP lowering in cohort of patients with RH. The improvement of peripheral AI in RH appears to be independent of the changes in BP and sympathetic nerve firing. The BP reduction associated with RDN in patients with RH was significantly related to a decrease in efferent sympathetic outflow.

Our findings indicate that high risk patients with RH and several co-morbidities including diabetes, coronary heart disease, and obstructive sleep apnea may obtain specific clinical benefit from bilateral RDN that is not restricted to improvements of BP and MSNA, but also extend to peripheral AI, which is independent of brachial BP decrease and sympathetic inhibition.

The contribution of enhanced sympathetic drive to the development and progression of arterial hypertension and cardiovascular-related disease is well recognized. Increased sympathetic activation to the heart and the kidneys is a key modulator in the early phase of essential hypertension [42, 43] and is potentiated with disease development [44]. Particularly, renal sympathetic nerves participate predominantly in the pathology of human hypertension [45]. Amongst the multiple pathophysiological factors contributing to arterial stiffening, the sympathetic nervous system appears to be a major contributor as evidenced by the reduction in arterial distensibility in response to sympathetic activation [46-48]. Moreover, loss of sympathetic innervation following hand transplantation has been shown to increase arterial distensibility indicating that sympathetic tone influences arterial wall properties [49].

While RDN significantly reduced systolic and diastolic BP in our study, the improvement in peripheral AI was not related to changes in BP. These findings indicate that RDN may have more direct effects on arterial stiffening, such as modification of the complex interactions between changes in distending pressure, smooth muscle tone and arterial wall composition [47]. Indeed, recent antihypertensive strategies to improve arterial stiffness primarily targeting the renin angiotensin system [50, 51] have demonstrated that both ACE-inhibitors and angiotensin receptor blockers can improve arterial stiffness independent of BP lowering [50, 51], suggesting that increased arterial stiffness may be attributable to structural change in the arterial wall rather than BP elevation alone [52]. While currently used approaches to reduce arterial stiffening are primarily directed at hemodynamic vasoconstrictor components [18], novel approaches such as the use of advanced glycation end-products (AGEs) cross-link breakers have shown promising results by targeting structural components of arterial wall composition rather than hemodynamic factors [53, 54].

In analogy, modification of sympathetic tone by renal denervation may attenuate alterations of arterial wall matrix, possibly by its recently demonstrated impact on stress-induced release of tissue plasminogen activator from sympathetic nerves in the arterial wall as the primary source [55]. In this context, it is noteworthy that thoracic sympathetic denervation improved structural and functional remodeling of the aortic wall in experimental models [56].

The improvement in peripheral AI demonstrated in our study may prove to be of wider clinical significance, given that RDN seems to attenuate peripheral arterial stiffness in patients with RH even in the presence of several co-morbidities such as sleep apnea, diabetes and chronic kidney disease [36] with the effect being independent of the BP reduction achieved.

The strengths of our study include precise evaluations of therapeutic effects of RDN on peripheral AI, MSNA and BP responses in a reasonably large and homogenous sample of

patients with RH associated with several co-morbidities who failed pharmacological treatment. Secondly, we included data for a matched control group of patients with RH who underwent comparable assessment without having RDN. Third, antihypertensive medication was unchanged and maintained following the procedure as well as remained unaltered in controls thereby eliminating potential confounding effects of antihypertensive treatment *per se* on AI, BP and MSNA in this patient cohort.

Study limitations

The potential limitation of our study include a relatively a small number of patients with a large variability of AI. However, our results are in line with findings showing a wide range of intra-individual coefficient of variation in AI [57]. Secondly, the use of peripheral fingertip tonometry as the sole measure of arterial tone in our patients may be questionable. Although, carotid-femoral PWV is considered as the measurement of choice for arterial stiffness [32], there is a clear evidence indicating that EndoPAT-derived AI index is reproducible [58] and correlates closely with aortic AI (r=0.79) or radial AI (r=0.88) measured by the sphygmocor device [41, 59]. Thirdly, we included relatively few post-menopausal females and have not performed gender-dependent analysis. While menopause status influences arterial stiffening [60], the improvement in peripheral AI in our post-menopausal women may indicate an important clinical benefit from renal nerve ablation also in this population. Finally, available ABPM data following the procedure were obtained in a limited number of patients.

Conclusion

RDN results in a substantial and rapid reduction in AI which appears to be independent of BP and MSNA changes. These findings indicate that RDN may exert a beneficial effect on arterial stiffness in patients with RH, thereby contributing to potentially improved outcomes in this high risk patient cohort with RH.

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STATEMENT OF COMPETING FINANCIAL INTERESTS

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F**igure Legends**

Figure 1a. Changes in augmentation index (AI) at baseline and at 3 month (M) follow-up (FU) in renal denervation (RDN) patients and in controls (non-RDN). Data are expressed as mean±SD.

Figure 1b. Changes in augmentation index corrected for heart rate (AI@75) at baseline and at 3 month (M) follow-up (FU) in renal denervation (RDN) patients and in controls (non-RDN). Data are expressed as mean±SD.

Figure 2. Individual changes in augmentation index corrected for heart rate (AI@75) at baseline and at 3 month (M) follow-up (FU) in renal denervation (RDN) patients.

Table 1. Baseline characteristics and blood pressure levels of the treated patient cohort (RDN) and the hypertensive control group (non-RDN).

Parameter	**RDN (n=40)**	**non-RDN (n=10)**
Age (years)	60±11	60 ± 6
Gender (Males/Females)	31/9	8/2
CAD	13 (33%)	2 (20%)
T2DM	12 (31%)	2 (20%)
OSA	6 (13%)	1 (10%)
Number of antihypertensive drugs	4.9±1.9	4.4±2.0
ACEI	22 (54%)	7 (70%)
ARB	31 (79%)	8 (80%)
ACEI + ARB	16 (41 %)	5 (50%)
β-blocker	24 (62%)	6 (60%)
Calcium-channel blocker	28 (72%)	6 (60%)
α-blockers	10 (25%)	2 (13%)
Diuretics (thiazide type or loop)	100%	100%
Aldosterone antagonists (spironolactone)	16 (41%)	2 (20%)
Central acting sympatholytics	25 (64%)	3 (30%)
Office SBP (mmHg)	170 ± 19	171 ± 14
Office DBP (mmHg)	92 ± 15	93 ± 8
HR (bpm)	65 ± 15	65 ± 17

Data are presented as mea ±SD and/or percentage (%). CAD indicates coronary heart disease; T2DM, type 2 diabetes mellitus; OSA: obstructive sleep apnea; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beat per minute.

There were no significant changes between RDN group and control group.

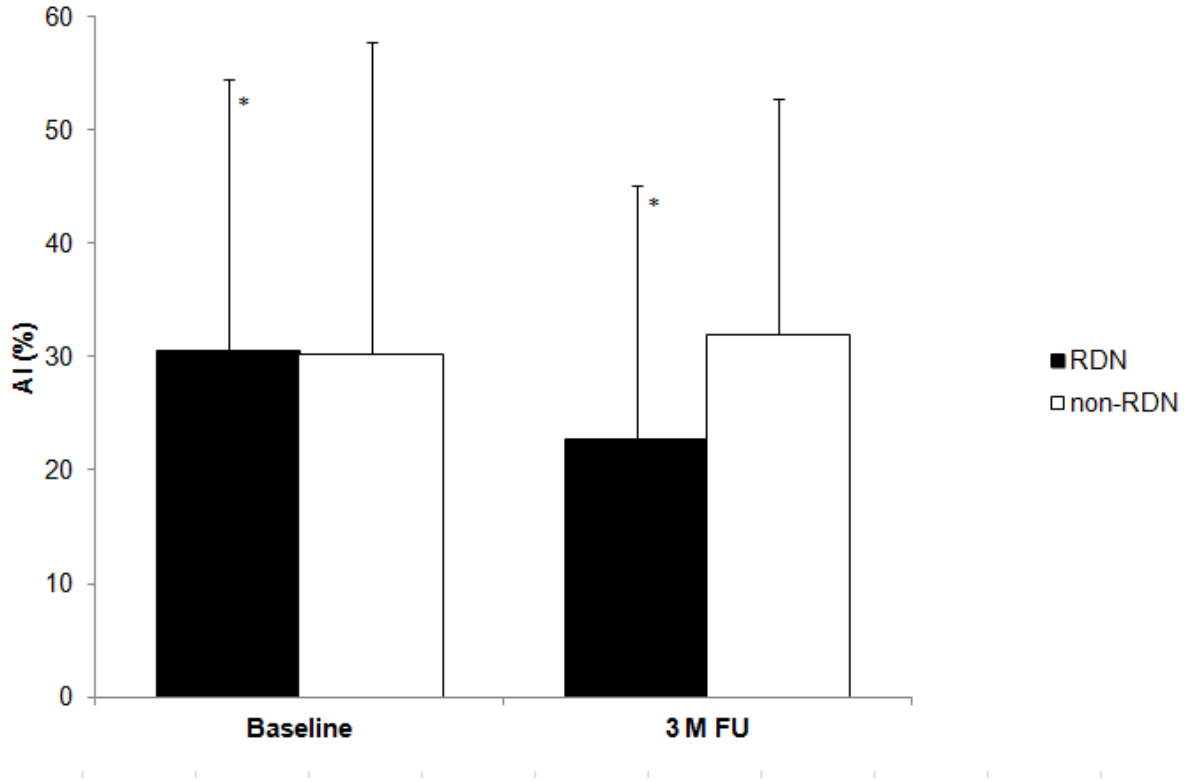
Table 2. Peripheral augmentation index (AI), office-seated blood pressure, heart rate, and muscle sympathetic nerve activity (MSNA) in patients who underwent renal denervation (RDN) and in controls (non-RDN) at baseline and at 3 month follow-up.

Parameter	RDN (n=40)			non-RDN (n=10)		
	BSL	**3 M FU**	***P-value***	**BSL**	**3 M FU**	***P-value***
AI (%)	30.6 ± 23.8	22.7 ± 22.4	*P=0.002*	30.2 ± 27.4	32.0 ± 20.7	*P=0.80*
AI@75 (%)	22.4 ±21.6	14.4 ± 20.7	*P=0.002*	21.2 ± 21.4	21.2 ± 19.7	*P=0.99*
SBP (mmHg)	170 ± 19	154 ± 25	*P<0.001*	171 ± 14	169 ± 11	*P=0.63*
DBP (mmHg)	92 ± 15	84 ± 16	*P<0.001*	93 ± 8	92 ± 11	*P=0.69*
HR (bpm)	65 ± 15	66 ± 14	*P=0.57*	65 ± 17	63 ± 13	*P=0.43*
*MSNA (bursts/min)	49 ± 9	44 ± 13	*P=0.02*	46 ± 4	47 ± 8	*P=0.76*
*MSNA (bursts/100 hb)	80 ± 15	71 ± 18	*P=0.009*	80 ± 17	83 ± 13	*P=0.46*

Data are presented as mean±SD. AI@75 indicates augmentation index corrected for heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beat per minute; M, month; FU, follow-up; hb, heartbeats.

*Of note, MSNA was only obtained in n=20 patients (RDN) and in n=10 controls (non-RDN). AI, BP and HR were obtained in n=40 patients (RDN) and in n=10 controls (non-RDN).

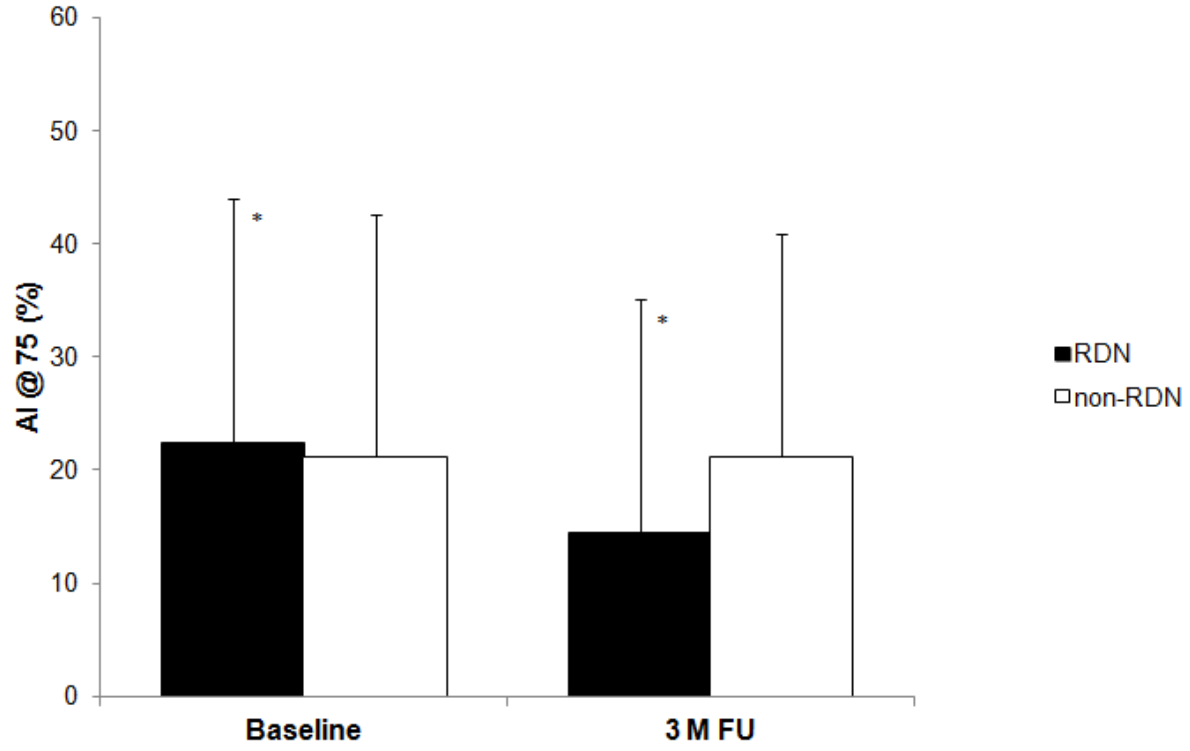
Figure 1 a.



Renal denervation (RDN) significantly reduces augmentation index at 3 month follow-up.

*P=0.002

Figure 1 b.



Renal denervation (RDN) significantly reduces augmentation index corrected for heart rate at 3 month follow-up. *P=0.002

Figure 2.