Pharmacological Monotherapy Versus Renal Artery Denervation in Controlled Hypertensive Patients

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Abstract

Aim
The aim of this prospective observational non-inferiority study was to compare the capacity for control of essential hypertension between renal sympathetic denervation (RSD) and either angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB).

Methods and Results
Seventy-four previously controlled essential hypertensive patients on ACEI/ARB monotherapy were evaluated; eleven patients agreed to proceed with RSD and had their antihypertensive agent withdrawn on the day of the procedure. During the six months of follow-up, there was no significant change in mean 24-hour ambulatory blood pressure measurements (ABPM) from baseline to three and six months in the ACEI/ARB group (118±8/80±3 vs. 116±8/79±3 and 115±8/79±4 mmHg, respectively). No change was also observed in the RSD group (117±8/81±2 vs. 115±6/80±2 and 114±7/79±3 mmHg, respectively). There were no differences between groups at interval time points. There were also no changes in renal function or echocardiographic parameters, during follow-up.

Conclusion
For the first time, this study reports possible non-inferiority of RSD when compared to ACEI or ARB monotherapy in the control of essential hypertension. A randomized trial with appropriate concealment of treatment, more patients and an extended follow-up period is needed to evaluate the potential benefits of RSD in comparison to ACEI/ARB use in patients with controlled hypertension.

Keywords: essential hypertension; renal sympathetic denervation; controlled blood pressure; sympathetic hyperactivity; antihypertensive drug.


Introduction
Hypertension remains a major global public health burden, and the leading attributable cause of mortality worldwide.⁰ Every 20/10-mmHg increase in blood pressure (BP) is associated with a doubling of cardiovascular mortality.⁴⁴ Epidemiological studies have shown that awareness of this disease is low, with only half of hypertensives adequately treated to target BP levels.⁴⁵⁴⁶ Nowadays, out-of-office BP is an important supplementary method to be evaluated along with conventional office BP measurement, which remains the most important tool.* Corresponding author. E-mail:marciokiuchi@gmail.com
for hypertension screening, diagnosis, and treatment. Office BP use is enshrined over time. However, this method has important limitations that have led to the increasingly frequent suggestion that 24-hour ambulatory blood pressure measurements (ABPM) play an important role in hypertension management. [7] Hypertension is defined as mean systolic BP levels ≥130 mmHg and/or diastolic BP ≥80 mmHg in 24-hour ABPM. [7]

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are among the most widely used drug classes in antihypertensive monotherapy. [7] Chronic activation of the sympathetic nervous system is involved in the development and maintenance of arterial hypertension [8,9] and can be controlled by these antihypertensive drugs. Recently, percutaneous renal sympathetic denervation has emerged as a useful tool to control resistant hypertension. [10] The aim of this prospective, observational non-inferiority study was to compare the capacity for control of hypertension between ACEI/ARB and RSD in patients with essential hypertension previously controlled by one agent.

Methods
We conducted a prospective, longitudinal study of 74 controlled hypertensive patients, on ACEI or ARB monotherapy with normal renal function and normal heart structure and function. The study was conducted in accordance with the Helsinki Declaration and approved by the local ethics committee. All patients gave written informed consent before inclusion.

Study subjects
This study was conducted in the state of Rio de Janeiro, Brazil in the Hospital e Clínica São Gonçalo. Patients were recruited from June 2014 to June 2015 and were derived from the hospital and the health public network of the state county. Patients who had the combination of the following criteria were consecutively enrolled: (i) mean 24-hour ABPM ≥100/≥70 mmHg and <130/<80 mmHg; (ii) controlled essential hypertension for over one year; (iii) healthy heart (ejection fraction > 50%, measured by Simpson’s method on echocardiography); (iv) taking only one antihypertensive agent (i.e. ACEI or ARB monotherapy); (v) age between 18 and 80 years; (vi) glomerular filtration rate estimated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, eGFR,11 >60 mL/min/1.73m2 (without microalbuminuria); and (vii) able to read, understand and sign the informed consent form, and attend clinic visits and exams.

Patients with any of the following criteria were excluded: (i) pregnancy; (ii) valvular heart disease with significant adverse sequelae; (iii) myocardial infarction, unstable angina, stroke or transient ischemic attack within the previous six months; (iv) renovascular abnormalities; (v) psychiatric disease; (vi) allergy to contrast; (vii) inability to be followed clinically after the procedure; (viii) serious disease, which in the opinion of the investigator may adversely affect the safety and/or efficacy of the participant or the study.

From the 74 patients evaluated, eleven patients consented to RSD and had their antihypertensive agent withdrawn on the day of the procedure. All patients were followed for six months. This study aimed to evaluate if RSD was non-inferior to ACEI/ARB in controlling BP, evaluated by the 24-hour ABPM, besides to evaluate renal function and echocardiographic parameters at baseline, three and six months of follow-up. Safety was assessed by Duplex scan of renal arteries at baseline and 6 months post RSD.

Transthoracic echocardiogram
Transthoracic echocardiography was performed at baseline and the sixth-month post RSD using a GE ultrasound system (Vivid i, General Electric, Frankfurt, Germany) equipped with a multifrequency transducer and tissue Doppler imaging software according to the Guidelines of the American Society of Echocardiography. Data were analyzed and interpreted by an experienced echocardiographer blinded to treatment status and sequence of the images. The LV mass was calculated from LV linear dimensions using the Devereux formula.[12,13] LV mass was indexed to the body surface area.[12,14] LVH was considered present when the LV mass exceeded 115 g/m2 for men and 95 g/m2 for women.[12] The LA diameter was measured in the parasternal long axis, perpendicularly to the LA walls. The LA diameter was measured in end-systole, from leading edge of the posterior aortic wall to the leading edge of the posterior LA wall.[15]

24-hour ABPM
The BP monitoring was performed for 24 hours with a clinically validated device (CardioMapa, Cardios, Brazil) before the procedure. The devices were programmed to measure every 15 minutes for 06:00 to 22:00 hours, and every 30 minutes from 22:00 to 06:00 hours. Patients were instructed to continue their regular activities during the recording and go to bed no later than 23:00. The waking period was defined as the range of 08:00 to 22:00 hours, and the sleep period as midnight to 06:00 hours. [7,15] All patients were instructed to record in a diary the hours of sleep and wakefulness, meals, intake of medications in addition to the symptoms and events that could influence BP during this period. Measurements were transferred to a computer so that a series of analyses could be performed.[15] At least 70% of the measured values in the daytime and night-time should be satisfactory or monitoring should be repeated,[15,16]

Renal sympathetic denervation
All procedures were performed in the cath lab (catheterization laboratory) under direct visualization using fluoroscopy and radiopaque contrast. The patients remained under conscious sedation and catheterization of the right femoral artery by the standard Seldinger technic was performed using an 8-Fr valved short sheath, after sub-cutaneous injection of local anesthetic. Subsequently, a renal double curve (RDC) catheter was introduced into this sheath by the standard “over the wire” technique. Unfractionated heparin was administered intravenously, targeting an activated coagulation time (ACT) between 250 and 350 seconds. This sheath was advanced to the level of the renal arteries, and the Ostia were located with nonselective aortography.[17] The introducer was then positioned to anchor at the ostium of each renal artery. Patients underwent RSD using the EnligHTN™ system (St. Jude Medical, St. Paul, Minnesota, USA) inserted through the RDC catheter. At the end of the procedure, the anatomy of the renal arteries was checked by angiography to assess whether there were any complications during the procedure.[18] The procedure was performed without any complications, and the patients remained clinically stable.
and awoke fully from sedation. Intravenous protamine was infused at the end of the procedure, and manual compression of the femoral artery was performed with a mean time of 15 min, followed by the compressive dressing.[17] After the procedure, patients remained hospitalized for 24 hours inside the ward.

**Statistical analysis**

The results were expressed as the mean and standard deviation (mean ± SD) of the mean in the case of normal distribution and as the median with inter-quartile range otherwise. Statistical tests were all two-sided. Comparisons between two paired values were performed by the paired t-test in case of Gaussian distribution or, alternatively, by the Wilcoxon test. Comparisons between more than two paired values were performed by ANOVA for repeated measures or with Kruskal-Wallis ANOVA as appropriate complemented by a post hoc test. Frequencies were compared with Fisher’s Exact Test. P-values <0.05 were considered significant. Correlations between two variables were performed by Pearson in the case of Gaussian distribution or, alternatively, with the Spearman correlation test. All statistical analysis was performed using the program GraphPad Prism v.7.0 (GraphPad Software, La Jolla, CA, USA).[18]

**Results**

**Baseline characteristics of patients**

General features of the patients are listed in Table 1, overall (n=74), for the ACEI/ARB continuation group (n=63) and for the RSD group (n=11).

**Safety evaluation of RSD**

No patient had or presented with procedural complications. Real-time renal artery imaging was performed to assess eventual structural changes related to the procedure. Some small focal irregularities of the renal arteries that were present during the procedure (possibly due to minor spasm or oedema) were no longer seen postoperatively.[18] At the sixth month after the procedure all the patients from RSD group underwent a Doppler scan of renal arteries without any evidence of stenosis or flow limitation.[18]

**Effects on blood pressure**

During the six months of follow-up, there was no significant change in mean 24-hour ABPM from baseline to three and six months in the ACEI/ARB group (118±8/80±3 vs. 116±8/79±3 and 115±8/79±4 mmHg, respectively). No change was observed from baseline to three and six months in the RSD group (117±8/81±2 vs. 115±6/80±2 and 114±7/79±3 mmHg, respectively). There was also no difference in the comparison between groups at the same time points as shown in Figure 1.

**Effects on renal function**

During the six months of follow-up, there was no significant change in mean creatinine values from baseline to three and six months in the ACEI/ARB group (0.77±0.11 vs. 0.75±0.10 and 0.75±0.11 mg/dL, respectively), and no change was also observed from baseline to three and six months in the RSD group (0.75±0.14 vs. 0.75±0.12 and 0.74±0.11 mg/dL, respectively). There was no difference in the comparison between groups at the same time points. Consequently, there was no significant change in mean eGFR from baseline to three and six months in the ACEI/ARB group (97.3±19.2 vs. 98.6±18.5 and 99.0±18.5 mL/min/1.73m2, respectively). Also, no change was observed in eGFR from baseline to three and six months in the RSD group (94.1±24.5 vs. 95.3±24.1 and 100.2±19.0 mL/min/1.73m2, respectively). There was no difference in the comparison between groups at the same time points either, as shown in Figure 2.

Table 1. General features of patients at baseline

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Overall</th>
<th>ACEI/ARB</th>
<th>RSD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>74</td>
<td>63</td>
<td>11</td>
<td>---</td>
</tr>
<tr>
<td>Age, years</td>
<td>55±12 a</td>
<td>55±12</td>
<td>54±11</td>
<td>0.8625</td>
</tr>
<tr>
<td>Body mass index, kg/m2</td>
<td>26±2a</td>
<td>25±2</td>
<td>26±1</td>
<td>0.5347</td>
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<tr>
<td>Male sex (%)</td>
<td>47 (64%)</td>
<td>40 (63%)</td>
<td>7 (64%)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>White ethnicity (%)</td>
<td>74 (100%)</td>
<td>63 (100%)</td>
<td>11 (100%)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>74 (100%)</td>
<td>63 (100%)</td>
<td>11 (100%)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Type 2 Diabetes Mellitus (%)</td>
<td>26 (35%)</td>
<td>24 (38%)</td>
<td>2 (19%)</td>
<td>0.3088</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>18 (24%)</td>
<td>16 (25%)</td>
<td>2 (18%)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m2</td>
<td>96.8±19.9a</td>
<td>97.3±19.2</td>
<td>94.1±24.5</td>
<td>0.6287</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>63.1±5.6a</td>
<td>63.1±5.5</td>
<td>63.2±6.2</td>
<td>0.9697</td>
</tr>
</tbody>
</table>

**Antihypertensive**

<table>
<thead>
<tr>
<th></th>
<th>ACEI (%)</th>
<th>ARB (%)</th>
<th>24-hour ABPM, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35 (47%)</td>
<td>39 (53%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 (48%)</td>
<td>33 (52%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (45%)</td>
<td>6 (55%)</td>
<td></td>
</tr>
</tbody>
</table>

Mean±SD; ABPM, ambulatory blood pressure measurements; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; N, number of patients; RSD, renal sympathetic denervation.

**Figure 1.** Mean systolic (black and green bars, for ACEI/ARB and RSD group, respectively) and diastolic (white and blues bars, for ACEI/ARB and RSD group, respectively) 24-hour ABPM at baseline, at 3 and 6 months of follow-up. ABPM, ambulatory blood pressure measurements; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; DBP, diastolic blood pressure; RSD, renal sympathetic denervation; SBP, systolic blood pressure. ACEI/ARB group (n=63) and RSD group (n=11).
Effects on echocardiographic parameters

No significant changes occurred in left ventricular ejection fraction (LVEF), left atrial diameter (LAD), end diastolic left ventricular internal dimension (LVIDd), and LV mass index[15] at six months of follow-up in ACEI/ARB or RSD groups vs. respective baseline values. Furthermore, comparisons at the same time point between groups did not show differences (Table 2).

Discussion

For the first time, a study reports that an antihypertensive drug was withdrawn in a monotherapy regimen, and RSD was performed successfully in controlled hypertensive patients taking ACEI or ARB monotherapy. The RSD effect on mean 24-hour systolic and diastolic ABPM did not differ during follow-up or in comparison to ACEI/ARB effects on hypertensive control at any time point. We calculated eGFR using the CKD-EPI equation, which is known to perform better for a larger range of GFR values.[11] As we know, sympathetic activation is a hallmark of the essential hypertensive state occurring early in the clinical course of the disease.[19-21] In hypertension, the mechanisms of the hyperadrenergic state are manifold and include reflex and neurohumoral pathways. [19,21,22] We believe that, in part, this overactivity from the essential hypertensive state has been controlled by ACEI/ARB or RSD, since patients remain normotensive. The interruption of this axis, reducing the sympathetic overactivity and of the feedback loop of the renin-angiotensin-aldosterone[23] system may, at least in part, account for our findings explaining that nerve blockade is as efficient as chemical suppression.

ACEI and ARB are among those most widely used in antihypertensive therapy. Some meta-analyses have suggested that ACEI may be somewhat inferior to other classes in preventing stroke[24-26] and that ARB may be inferior to ACEI in preventing myocardial infarction[27] or all-cause mortality. [28] The hypothesis raised by these meta-analyses has been undermined by the results of the large ONTARGET, directly comparing outcomes under treatment with the ACEI ramipril and the ARB telmisartan.[29,30] ONTARGET[7] has shown telmisartan not to be statistically inferior to ramipril as far as the incidence of major cardiac outcomes, stroke, and all-cause death is concerned. ONTARGET has also disproved the hypothesis that the peroxisome proliferator-activated receptor (PPAR) activity of telmisartan may render this compound more effective in preventing or delaying the onset of diabetes: the incidence of new diabetes was non-significantly different between telmisartan and ramipril in ONTARGET. The findings of ONTARGET showed that the combination of an ACEI and an ARB are accompanied by a significant excess of cases of the end-stage renal disease, and have recently been supported by the results of the ALTITUDE trial in diabetic patients.[31] Among the well-known ancillary properties of ACEI and ARB, are their peculiar effectiveness in reducing proteinuria[32,33] and improving outcomes in chronic heart failure.[32]

The 1st report of the Global SYMPLICITY Registry on the effect of RSD in patients with uncontrolled hypertension reported that in clinical practice, renal denervation resulted in significant reductions in office and 24-hour ABPM with a favorable safety profile. Greater BP-lowering effects occurred in patients with higher baseline pressures.[34] The recent results of the SYMPLICITY HTN-3 trial have challenged preclinical science, clinical anecdote, and the consistency observed across early phase trials. Although the trial demonstrated the safety of RSD, among 535 patients identified with treatment-resistant hypertension the difference in 6-month BP decline between RSD and sham-treatment groups was not significantly different for office or ambulatory measures.[35] Based on the results of multivariable analysis to identify predictors pursued[36] of systolic blood pressure change, and analysis of pre-specified and post hoc subgroups to identify potential confounding factors that may have affected the trial results, three areas of investigation were pursued[36]: changes in antihypertensive medications, outcomes in selected subgroups, and detailed assessment of procedural data that may have impacted the delivery of effective RSD. Nevertheless, the Enlighten I study provides evidence that the multi-electrode ablation system constitutes a safe method of RSD in patients with drug resistant hypertension and is accompanied by an early and sustained reduction of office, ambulatory and home blood pressure at 24 months after the procedure. However, none of the potential predictive demographic variables assessed were associated with response to RSD at long term follow-up.[37]

We believe that from the results obtained in our study, RSD offers potential value in the area of hypertension therapy[38] and seems to be equivalent to the monotherapy with ACEI/ARB. It may become a therapeutic option for patients who respond to these classes of medications regarding BP control, but do not want to make use of any antihypertensive agent.

Study Limitations

Our data report a similar contribution of RSD in patients with controlled hypertension in comparison to ACEI/ARB use, but in a small patient cohort. This relatively small sample of the study can be seen as a limitation. However, as far as we know, the present series is unique in the literature comparing RSD to ACEI/ARB use.

Table 2. Echocardiographic parameters during the follow-up period

<table>
<thead>
<tr>
<th>Echocardiographic parameters</th>
<th>ACEI/ARB (n=63)</th>
<th>RSD (n=11)</th>
<th>P value at 6th month</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (Simpson %)</td>
<td>63.1±5.6</td>
<td>62.8±5.6</td>
<td>63.2±6.2</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>34.9±3.2</td>
<td>34.5±2.9</td>
<td>34.8±3.2</td>
</tr>
<tr>
<td>LVIDd (mm)</td>
<td>51.0±3.4</td>
<td>49.9±3.4</td>
<td>49.3±3.7</td>
</tr>
<tr>
<td>LV mass index (g/m2)</td>
<td>92.2±9.3</td>
<td>91.3±8.9</td>
<td>95.1±9.0</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LV, left ventricular; LVIDd, end-diastolic left ventricular internal dimension; RSD, renal sympathetic denervation.
in patients with controlled hypertension. These findings should be interpreted with caution given the unblinded non-randomised nature of the study. A randomised trial[15] with appropriate concealment of treatment, more patients and a longer follow-up period is required to address the potential benefits of RSD in comparison to ACEI/ARB use in patients with controlled hypertension.

The use of echo-Doppler[18] to assess damage in the renal arteries is in some way a limitation. However, early complications caused by the RF applications were excluded by angiography performed at the end of the procedure.

In future studies the sympathetic neuromuscular activity (MSNA) can be measured, which can contribute greatly to assess the degree of sympathetic blockade.

Conclusion
For the first time, a study reports that an antihypertensive drug was withdrawn in a monotherapy regimen, and RSD was performed successfully in patients with controlled essential hypertension using only ACEI or ARB. The RSD effect on mean 24-hour systolic and diastolic ABPM did not differ during follow-up or in comparison to ACEI/ARB effects on hypertensive control at any time point. A randomised trial with appropriate concealment of treatment, more patients and for a long follow-up period is required to address the potential benefits of RSD in comparison to ACEI/ARB use in patients with controlled essential hypertension.

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Conflict Of Interest
None declared.

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References


