Renal Sympathetic Denervation in Patients with Resistant Hypertension: A Feasibility Study

Kazuomi Kario\textsuperscript{a} Jose Ramon Rumoroso\textsuperscript{b} Yukie Okawara\textsuperscript{a} Armando Pérez de Prado\textsuperscript{c} Eulogio García Fernandez\textsuperscript{d} Hideaki Kagitani\textsuperscript{e} Francisco Javier Goicolea Gómez\textsuperscript{f} Oriol Rodríguez Leor\textsuperscript{g} Goran Stankovic\textsuperscript{h}

\textsuperscript{a}Department of Cardiovascular Medicine, Jichi Medical University School of Medicine, Tochigi, Japan; \textsuperscript{b}Interventional Cardiology Department, Hospital Galdakao, Bilbao, Spain; \textsuperscript{c}Department of Cardiology, Hospital de Léon, Léon, Spain; \textsuperscript{d}Department Interventional Cardiology, Hospital Montepríncipe, Madrid, Spain; \textsuperscript{e}Terumo Corporation, Tokyo, Japan; \textsuperscript{f}Interventional Cardiology Unit, Hospital Puerta de Hierro/Majadahonda, Madrid, Spain; \textsuperscript{g}Interventional Cardiology Unit, Hospital Germans Trias i Pujol, Barcelona, Spain; \textsuperscript{h}Department of Cardiology, Clinical Center of Serbia, Belgrade, Serbia

Keywords
Resistant hypertension · Renal sympathetic denervation · Ambulatory blood pressure measurement · Responder · First-generation radiofrequency catheter

Abstract
\textbf{Background/Aims:} We assessed the feasibility of renal sympathetic denervation (RDN) treatment in patients with resistant hypertension using the Iberis\textsuperscript{®} RDN system. This study was a prospective, multicenter, single-arm feasibility registry. \textbf{Methods:} We collected data from patients who underwent RDN treatment using the Iberis system. From November 2014 to February 2016, 16 patients from 6 centers in Europe were enrolled in this registry. \textbf{Results:} Consistent reductions in the 24-h systolic blood pressure (SBP) and diastolic blood pressure were obtained. At any follow-up point, more than 70\% of the patients were responders. The change in the 24-h SBP at 1 month was strongly correlated with that at 12 months. \textbf{Conclusion:} The Iberis system is safe and effective in patients for the treatment of resistant hypertension. Furthermore, our results suggest that we can estimate the effect of RDN in the long term at the 1-month follow-up point using the 24-h SBP.
Introduction

Resistant hypertension is defined as high blood pressure (BP) despite appropriate lifestyle interventions and administration of 3 different antihypertensive drugs at optimal dose amounts, which should include a diuretic agent [1, 2]. Treatment of resistant hypertension is complex and multidisciplinary, consisting of nonpharmacological and pharmacological measures. Nonpharmacological measures include reversal of lifestyle factors contributing to treatment resistance, and discontinuation or minimization of interfering substances. There is usually a beneficial result with a lower-salt diet (<100 mEq of sodium/24 h), ingestion of a low-fat and a high-fiber diet, weight loss in obese or overweight patients, moderation of alcohol intake of no more than 2 drinks per day for most males and 1 drink for women or lighter-weight people, advising smoking cessation, and regular physical activity. Pharmacological treatment of resistant hypertension involves, by definition, combinations of 3 or more drugs of different classes at maximum tolerated doses, including at least one diuretic. However, these lifestyle and pharmacological interventions are often insufficient to control BP, and treatment-resistant hypertension is recognized as a serious clinical challenge associated with increased cardiovascular risk [3]. Renal sympathetic denervation (RDN) with a catheter has shown highly promising results in the Symplicity-HTN 1 trial, the Symplicity-HTN 2 trial, and the Global Symplicity registry, which confirmed the safety and effectiveness of RDN [4–9]. However, recent results of the Symplicity-HTN 3 trial have provided an opportunity to consider the optimal conditions [10].

In this study, we assessed the safety and efficacy of RDN treatment in patients with resistant hypertension using the Iberis® RDN system. The Iberis system delivered low-level radiofrequency energy through the wall of the renal artery to achieve RDN, and a catheter provided either of radial access to minimize vascular complications or femoral access.

Methods

This study was a prospective, multicenter, single-arm, open-label registry in Spain and Serbia. We collected descriptive data from patients who received RDN treatment in accordance with routine hospital practice using the Iberis system (Clinical Trials.gov; identifier NCT02295683).

Patients aged >18 years were eligible if they were diagnosed with true resistant hypertension. Resistant hypertension was defined as an office systolic BP (SBP) >160 or >150 mm Hg in case of type 2 diabetes and 24-h ambulatory blood pressure measurement (ABPM) with an average SBP >130 mm Hg or a mean daytime SBP >135 mm Hg in more than 70% of the measurements. Patients were on stable hypertension therapy for at least 8 weeks before the procedure, including spironolactone, if they were respondent as indicated by the specialized center or excellence unit on hypertension.

All patients provided written informed consent. Major exclusion criteria were primary hyperaldosteronism, evidence of renal artery atherosclerosis (defined as renal artery stenosis >50%), main renal arteries of <4 mm in diameter or <20 mm in length, presence of multiple main renal arteries in either kidney, an estimated glomerular filtration rate <45 mL/min per 1.73 m², and a known lack of adherence to medical treatment.

The 24-h ABPM was assessed using standard devices of each hospital, e.g., Meditech, UK; and Space-Labs, USA. The interval of 24-h ABPM was decided at the physician discretion, e.g., every 15 min during the day and every 30 min at night.

The device under investigation was the Iberis RDN system (AngioCare, Shangai, China; Terumo Corporation, Tokyo, Japan), which was designed to deliver low-level radiofrequency energy with a single electrode through the wall of the renal artery to achieve RDN. A catheter provided radial access to minimize vascular complications as well as femoral access. The safety and efficacy of the system were validated by the preclinical animal studies [11–13]. This system obtained CE approval in March 2013. The Iberis system consists of a disposable catheter and a console-generator. In addition to the femoral access as a conventional method, the
catheter can be inserted into the radial artery to minimize vascular complications. The system images are presented in online supplementary Figure 1 (see www.karger.com/doi/10.1159/000490620 for all online suppl. material).

**Procedure**

The standard procedure was based on the instructions for use. The Iberis system was placed into the target artery, and radiofrequency ablation was performed for 120 s under the appropriate temperature. Some biophysical parameters including temperature, impedance, radiofrequency power, producer countdown, and warning/instructional message in real time during delivery of radiofrequency are displayed on the generator. The generator automatically stops delivering radiofrequency energy if a temperature exceeds to 85 °C. Once the treatment was completed, the catheter was repositioned to locate the next target treatment site, with spacing of at least 5 mm between treatment sites.

**Statistical Analysis**

Continuous variables are presented as values and the mean and standard deviation. Specific descriptions of the statistical method are shown in each figure and table legend. All statistical analyses were performed using SAS software version 9.4 (SAS institute Inc., Cary, NC, USA).

**Results**

From November 2014 to February 2016, 16 RDN treatment patients from 6 centers in Europe were enrolled in this registry. All patients were Caucasians, with a mean age of 59.81 ± 11.19 years, and 62.50% were males. The average body mass index was 29.92 kg/m². Seven (43.75%) patients had sleep apnea, and 6 (37.50%) were diagnosed with type 2 diabetes (Table 1). Patients were taking a mean number of 5.6 ± 0.83 antihypertensive medications at baseline, 4.73 ± 1.58 at 1 month, 4.73 ± 1.58 at 3 months, 4.71 ± 1.73 at 6 months, and 4.18 ± 1.60 at 12 months (Table 1). RDN procedure in our study has been described in Procedure section. The mean number of complete 120-s ablation was 16.50 ± 6.92. The mean 24-h SBP and diastolic BP (DBP) at baseline was 163 mm Hg and 97 mm Hg, respectively. Consistent reductions in 24-h SBP and DBP were obtained. SBP and DBP were significantly decreased 3 months after the procedure compared with baseline (p < 0.05, Fig. 1a) in the patients who had the 24-h ABPM measured more than once. According to the definition of response by a mean reduction in 24-h SBP of >5 mm Hg in ABPM, we found that the proportions of patients who were responders were 80.0% at 1 month, 70.0% at 3 months, 75.0% at 6 months, and 85.7% at 12 months (Fig. 1b). At any follow-up point, more than 70% of the patients were responders.

<table>
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<tr>
<th>Table 1. Baseline characteristics of the patients (N = 16)</th>
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<td>Age, years</td>
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<td>Male, %</td>
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<tr>
<td>Body mass index, kg/m²</td>
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<td>Race, %</td>
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Values are presented as mean ± SD unless otherwise indicated.
The change in 24-h SBP at 1 month was strongly correlated with 24-h SBP at 12 months (Fig. 2). In this analysis, we included 7 patients who had the data at 1 and 12 months of follow-up (Fig. 2). With regard to the safety of the procedure, 1 patient had a renal artery obstructive dissection caused by deep intubation with the guide catheter, then a conventional stent was implanted successfully. The patient recovered with complication and the hospital stay was not prolonged due to this event.

**Discussion**

This study was conducted to assess the safety and efficacy of RDN treatment in patients with uncontrolled hypertension using the Iberis system in Spain and Serbia. In this study, ABPM was measured in patients at baseline, and 1-, 3-, 6-, and 12-month follow-up points. We also measured home and office BP (online suppl. Table 1). In this single-arm, open-label, multicenter registry of 16 patients, the Iberis system showed significant and clinically meaningful improvements in clinical outcomes in 12 months. Similar results were observed in previous feasibility studies [14–16]. During the follow-up period, there was a tendency for doctors to prescribe a tapering of medication (Table 1). This result supported our finding that

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**Fig. 1.** 

a Changes in ABPM measurement and heart rate (HR) from baseline to 12 months. We performed a mixed model to obtain an estimated value and a $p$ value. b Change in the 24-h SBP from baseline to 12 months in each patient.
RDN using the Iberis system led to improvement in patients with treatment-resistant hypertension. Notably, the result of 24-h SBP at the 1-month follow-up were strongly correlated with the results of the 24-h SBP at 12 months. Based on the fact that ABPM provides the best measure of actual BP, our results suggest that we could estimate the effect of RDN at 12 months after the procedure based on the outcome at the 1-month follow-up. It is clinically useful to have reliable information that doctors could use to discuss and decide on treatment principles for reducing BP in the near future in patients who would respond to RDN well. Although the Symplicity-HTN 3 trial demonstrated the safety of RDN, there was no significant difference in office or ambulatory BP 6 months after renal artery denervation compared with sham controls. We initially planned to enroll up to 30 patients, but our study was stopped because of the Symplicity-HTN 3 results. This study was conducted with a first-generation radiofrequency catheter. In recent years, some preclinical studies have shown that sympathetic nerves are closer to the adventitia in more distal portions of the arterial tree and treatment of the main artery plus branches produces the greatest change in renal norepinephrine [17–19]. The unipolar catheter system of RDN is more technically difficult to assure 4-quadrant ablation compared with that of multipolar systems. In the Symplicity-HTN 3 trial, only 19 treated patients received 4-quadrant ablations in both renal arteries using the first-generation Symplicity radiofrequency catheter [20]. Therefore, a second-generation device is being developed in some companies. With regard to the Iberis system, the Multi Electrode Renal Denervation System was investigated in a clinical trial (NCT02901704). The SPYRAL HTN-OFF MED trial, which was conducted with a new second-generation device and novel study design, has been published [21, 22]. This trial showed a marked reduction in BP in the RDN group, indicating biological efficacy of RDN. However, the SPYRAL HTN-OFF MED trial was a proof-of-consent study with a small population and it was not sufficient for establishing treatment of RDN. Further preclinical and clinical research is required to determine the ideal setting for RDN.

A major limitation of this study is the small number of patients who were enrolled and some missing data. Since we did not assess exercise behavior, food intake, and medical...
adherence including objective evaluations in this study, we did not reveal why some patients had BP elevation. We performed a feasibility study to evaluate the Iberis system in the short term. However, a greater follow-up period with a larger patient population is required to assess the long-term durability and safety of RDN.

Conclusion

The Iberis system is safe and effective in patients for treatment of resistant hypertension. Furthermore, our results suggest that we can estimate the long-term effect of RDN at the 1-month follow-up point using the 24-h SBP.

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Disclosure Statement

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References