Original Paper

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

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

^aDepartment of Cardiovascular Medicine, Jichi Medical University School of Medicine, Tochigi, Japan; ^bInterventional Cardiology Department, Hospital Galdakao, Bilbao, Spain; ^cDepartment of Cardiology, Hospital de León, León, Spain; ^dDepartment Interventional Cardiology, Hospital Montepíncipe, Madrid, Spain; ^eTerumo Corporation, Tokyo, Japan; ^fInterventional Cardiology Unit, Hospital Puerta de Hierro/Majadahonda, Madrid, Spain; ^gInterventional Cardiology Unit, Hospital Germans Trias I Pujol, Barcelona, Spain; ^hDepartment of Cardiology, Clinical Center of Serbia, Belgrade, Serbia

Keywords

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

Abstract

Background/Aims: We assessed the feasibility of renal sympathetic denervation (RDN) treatment in patients with resistant hypertension using the Iberis® RDN system. This study was a prospective, multicenter, single-arm feasibility registry. **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. **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. **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.

© 2018 S. Karger AG, Basel

Kazuomi Kario, MD, PhD
Department of Cardiovascular Medicine
Jichi Medical University School of Medicine, 3311-1, Yakushiji
Shimotsuke, Tochigi 329-0498 (Japan)
E-Mail kkario@jichi.ac.jp

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 (ClinicalTrials.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 SpaceLabs, 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, Shanghai, 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 artery as a conventional method, the

Table 1. Baseline characteristics of the patients (*N* = 16)

Age, years	59.81±11.19 (16)
Male, %	62.5 (10/16)
Body mass index, kg/m ²	29.92±4.47 (16)
Race, %	100 (16/16)
Sleep apnea syndrome, %	43.75 (7/16)
Diabetes, %	37.5 (6/16)
Total number of antihypertensive drugs used	
Baseline	5.6±0.83 (15)
1 month	4.73±1.58 (15)
3 months	4.73±1.58 (15)
6 months	4.71±1.73 (14)
12 months	4.18±1.6 (11)

Values are presented as mean ± SD unless otherwise indicated.

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.

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.

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

Fig. 2. Pearson correlation between the mean change in the 24-h SBP at 1 and 12 months. Regression analysis with a linear mixed effect model showing the least squares means. We provided Pearson's r to estimate the relationship between the baseline and 12-month values.

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.

Acknowledgements

We thank Ayako Okura from Jichi Medical University School of Medicine for editorial and submission assistance and Ellen Knapp, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of the manuscript. This study was funded by Terumo Corporation, Tokyo, Japan. Editorial assistance was provided by Fumiyo Uosaki, PhD, from Terumo, Tokyo, Japan.

Disclosure Statement

Dr. K. Kario received research funding from Teijin Pharma Limited, Omron Healthcare Co., Ltd., Fukuda Denshi, Bayer Yakuhin Ltd., A and D Co., Ltd., Daiichi Sankyo Company, Limited, Mochida Pharmaceutical Co., Ltd, EA Pharma, Boehringer Ingelheim Japan Inc., Tanabe Mitsubishi Pharma Corporation, Shionogi and Co., Ltd., MSD K.K., Sanwa Kagaku Kenkyusho Co., Ltd., Bristol-Myers Squibb K.K., and honoraria from Takeda Pharmaceutical Company Limited and Omron Healthcare Co., Ltd, outside the submitted work. Dr. A. Pérez de Prado reports grants and personal fees from Terumo during the conduct of the study, and personal fees from Boston Scientific outside the submitted work. The other authors declare that they have no conflicts of interest to disclose.

References

- 1 Mansia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HA, Zanchetti A: European Society of Hypertension; European Society of Cardiology. 2007 ESH-ESC Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Blood Press* 2007;16:135–232.
- 2 Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B, Carey RM: American Heart Association Professional Education Committee. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 2008;117:e510–e526.
- 3 Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, O'Connor PJ, Selby JV, Ho PM: Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation* 2012;125:1635–1642.
- 4 Symplicity HTN-2 Investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M: Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomized controlled trial. *Lancet* 2010;376:1903–1909.
- 5 Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M: Catheter-based renal sympathetic denervation for resistant hypertension: a multi-centre safety and proof-of-principle cohort study. *Lancet* 2009;373:1275–1281.
- 6 Krum H, Schlaich MP, Sobotka PA, Böhm M, Mahfoud F, Rocha-Singh K, Katholi R, Esler MD: Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet* 2014;383:622–629.

- 7 Symplicity HTN-1 Investigators: Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* 2011;57:911–917.
- 8 Gomez SI, Urbandt P, Beohar N, Santana O: Renal denervation: current status and future applications. *Rev Cardiovasc Med* 2014;15:351–357.
- 9 Böhm M, Mahfoud F, Ukena C, Hoppe UC, Narkiewicz K, Negoita M, Ruilope L, Schlaich MP, Schmieder RE, Whitbourn R, Williams B, Zeymer U, Zirlik A, Mancía G; GSR Investigators: First report of the Global SYMPPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled hypertension. *Hypertension* 2015;65:766–774.
- 10 Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL; SYMPPLICITY HTN-3 Investigators: A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014;370:1393–1401.
- 11 Rousselle SD, Brants IK, Sakaoka A, Hubbard B, Jackson ND, Wicks JR, Dillon KN, Naiche LA, Hart R, Garza JA, Tellez A: Neuromatous regeneration as a nerve response after catheter-based renal denervation therapy in a large animal model: immunohistochemical study. *Circ Cardiovasc Interv* 2015;8:e002293.
- 12 Hubbard B, Sakaoka A, Brants IK, Dillon KN, Brady DA, Rousselle SD, Devireddy CM, Mahfoud F, Tellez A: Subacute safety and efficacy evaluation of a single versus double treatment cycles of a monopolar radiofrequency catheter-based renal nerve ablation and its chronic evolution in a large animal model. *J ATAMIS* 2016;1:30–38.
- 13 Sakaoka A, Takami A, Onimura Y, Hagiwara H, Terao H, Kumagai F, Matsumura K: Acute changes in histopathology and intravascular imaging after catheter-based renal denervation in a porcine model. *Catheter Cardiovasc Interv* 2017;90:631–638.
- 14 Jiang XJ, Dong H, Liang T, Zou YB, Xu B, Gao RL: First-in-man report of a novel dedicated radiofrequency catheter for renal denervation via the transulnar approach. *EuroIntervention* 2013;9:684–686.
- 15 Honton B, Pathak A, Sauguet A, Fajadet J: First report of transradial renal denervation with the dedicated radiofrequency Iberis™ catheter. *EuroIntervention* 2014;9:1385–1388.
- 16 Dong H, Jiang X, Liang T, Zou Y, Guan T, Peng M, Song L, Zhang H, Wu H, Xu B, Yang Y, Gao R: Transradial renal denervation for the treatment of resistant hypertension. *J Invasive Cardiol* 2014;26:322–327.
- 17 Sakakura K, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR, Kolodgie FD, Virmani R, Joner M: Anatomic assessment of sympathetic peri-arterial renal nerves in man. *J Am Coll Cardiol* 2014;64:635–643.
- 18 Mahfoud F, Tunev S, Ewen S, Cremers B, Ruwart J, Schulz-Jander D, Linz D, Davies J, Kandzari DE, Whitbourn R, Böhm M, Melder RJ: Impact of lesion placement on efficacy and safety of catheter-based radiofrequency renal denervation. *J Am Coll Cardiol* 2015;66:1766–1775.
- 19 Mahfoud F, Edelman ER, Böhm M: Catheter-based renal denervation is no simple matter: lessons to be learned from our anatomy? *J Am Coll Cardiol* 2014;64:644–646.
- 20 Kandzari DE, Bhatt DL, Brar S, Devireddy CM, Esler M, Fahy M, Flack JM, Katzen BT, Lea J, Lee DP, Leon MB, Ma A, Massaro J, Mauri L, Oparil S, O'Neill WW, Patel MR, Rocha-Singh K, Sobotka PA, Svetkey L, Townsend RR, Bakris GL: Predictors of blood pressure response in the SYMPPLICITY HTN-3 trial. *Eur Heart J* 2015;36:219–227.
- 21 Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, Ewen S, Tsioufis K, Tousoulis D, Sharp ASP, Watkinson AF, Schmieder RE, Schmid A, Choi JW, East C, Walton A, Hopper I, Cohen DL, Wilensky R, Lee DP, Ma A, Devireddy CM, Lea JP, Lurz PC, Fengler K, Davies J, Chapman N, Cohen SA, DeBruin V, Fahy M, Jones DE, Rothman M, Böhm M; SPYRAL HTN-OFF MED trial investigators: Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. *Lancet* 2017;390: 2160–2170.
- 22 Kandzari DE, Kario K, Mahfoud F, Cohen SA, Pilcher G, Pocock S, Townsend R, Weber MA, Böhm M: The SPYRAL HTN Global Clinical Trial Program: rationale and design for studies of renal denervation in the absence (SPYRAL HTN OFF-MED) and presence (SPYRAL HTN ON-MED) of antihypertensive medications. *Am Heart J* 2016;171:82–91.