Renal ablation for treatment of hypertension without Symplicity catheter: The first human experience

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Original Article

Abstract

BACKGROUND: Hypertension (HTN) treatment has remained insufficient. New modalities such as "Symplicity method" for the treatment of HTN are a priority, especially in patients with resistant hypertension. In this study, we describe our first experience with a novel percutaneous treatment modality, without using Symplicity catheter.

METHODS: 30 Patients who were resistant to at least three types of antihypertensive medical therapy were selected. Patients received percutaneous renal artery denervation, without Symplicity catheter method, and were followed up for 1 week, 1, 3, and 6 months later after treatment. Ambulatory 24-hour blood pressure (BP) Holter was performed 1 week before intervention and after 1 month. The primary outcome was change in 24-hour ambulatory BP and change in office and home-based BP measurements.

RESULTS: The mean age of the studied patients was 52 ± 15.4 years and 43.3% (n = 13) were female. Systolic and diastolic BP at baseline was 163 ± 17.2 and 95 ± 8.2 mmHg, respectively. Patients took 3.6 ± 1.3 hypertensive medications. Systolic and diastolic BP at 1-week, 1-month, 3-month and 6-month after renal denervation significantly decreased compared to the baseline ($P < 0.0001$). Average BP derived from 24-hour ambulatory BP monitoring changed in parallel with office-based BP measurements. Most of patients (50%) who underwent renal denervation had reductions of 10 mmHg or greater in systolic BP and 56.7% of them had reductions of 5 mmHg or greater in diastolic BP. 33.3% of patients also achieved the target of systolic BP less than 140 mmHg and 60% achieved the target of diastolic BP less than 90 mmHg. No patients showed vascular damage at final angiography.

CONCLUSION: Catheter based renal ablation was associated with a significant reduction in both systolic and diastolic BP, on top of maximal medical therapy, which persisted throughout 6 months follow-up in the first-in-man study without the Symplicity catheter.

Keywords: Renal Denervation, Resistant Hypertension, Catheter

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Introduction

About 30% of populations in the world have hypertension (HTN). Furthermore, its prevalence is increasing in developing countries. HTN is known as "silent killer" and often is asymptomatic. It is a major risk factor for death worldwide. HTN is also a financial problem for governments and their population.[1] HTN treatment has remained insufficient. About 30% of patients with HTN were aware of their disease. Of those aware patients, about 60% were treated. Of those patients treated, about 40% had blood pressure at optimal level.[2] Therefore, new modalities for the treatment of HTN are a priority, especially in patients with resistant HTN. Only 10-15% of patients with resistant HTN are optimally treated.[3]

Sympathetic nerves of renal arteries are essential for occurrence of systemic HTN. Old methods for denervation such as radical surgery for sympathetic nerves were associated with high morbidity/mortality and many complications.[4] Nowadays, catheter-based approach for disruption of renal sympathetic nerves is done[5-9] without long term complications. Percutaneous renal denervation resulted in meaningful reduction in systolic and diastolic blood pressure during medical therapy,

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which persisted for 12 months follow-up in the first human study. The recently published trial "Symplicity 2", which was the first randomized controlled study in this field, confirmed the findings of the first human study. In this study, we wanted to do the first Iranian experience regarding this novel treatment modality and the first human experience of renal ablation without Symplicity catheter.

Materials and Methods

This study was approved by the ethical committee at Vice Chancellor of Research in Isfahan University of Medical Sciences and all patients provided written informed consent. This trial was registered with IUMS.ac.ir number 391001.

Screening was done at HTN clinic in Chamran Heart Hospital, a large teaching, referral heart hospital. Patients were asked to record triple daily automated home blood pressure measurements and to document drug compliance for 10 days before ambulatory 24-hour blood pressure Holter monitoring. Patients were treated with the renal denervation procedure between September 2011 and January 2012, with subsequent 6 months follow-up.

Outpatient (OPD) assessment included patient's characteristics, vital sign, past medical history, physical examination, number and type of medications, blood chemistries (like creatinine and potassium) and ambulatory 24-hour blood pressure Holter. We did follow-up assessments at 1 week and 1, 3, and 6 months, consisted of office blood pressure measurements, surveillance for adverse events, 24-hours blood pressure Holter, serum creatinine and HTN drugs. Office blood pressure measurements were performed in a seated position in at least two visits (1st visit and 2 weeks later) in both arms. Ambulatory 24-hour blood pressure Holter was performed 1 week before intervention and at 1 month follow-up.

Patients aged at least 15 years were eligible for inclusion, with a systolic blood pressure of 160 mmHg or more (≥ 150 in patients with type-2 diabetes) and/or diastolic blood pressure of 90 mmHg or more, despite at least three antihypertensive drugs or confirmed intolerance to medication. The renal artery anatomy was considered suitable in case of a vessel diameter of ≥4 mm and ≥20 mm length, no significant stenosis, no previous renal artery intervention and no more than one main renal artery.

Exclusion criteria included patients with any known secondary hypertension and a glomerular filtration rate estimated at ≤ 45 ml/min/1.73m² and patients with a history of unstable angina or cerebrovascular accident in the previous 6 months or pregnancy. We did not exclude patients with type 1 diabetes, implantable cardioverter defibrillations and advanced congestive heart failure. Patients whose all blood pressure measurements were below the enrolment criteria for blood pressure in 24-hour BP Holter monitoring were excluded.

Patients were pretreated with 2 mg midazolam and 25 mg pethidine. Using local anesthetics, cannulation of the femoral artery was performed by the standard Seldinger technique. Firstly, a 7 Fr sheath was introduced and heparin was given using an intravenous bolus of 10 IE/Kg with a target activated clotting time (ACT) ≥ 250 S. Then, using an 8 Fr coronary sinus (CS) sheath and a 6 Fr soft tip Rt Judkins catheter, a steerable catheter with radiofrequency energy electrode tip was delivered into the renal artery. Before starting the denervation, 50 μg fentanyl and at least 1 cc ketamine were given to patient by anesthesiologist. We applied discrete, radiofrequency ablations lasting 2 minutes each and of 15 watts or less to obtain six ablations separated both longitudinally and rotationally with a minimum of 5 mm distance in between and with a pullback from distal to proximal within each renal artery. During ablation, the catheter system monitored tip temperature and impedance, altering radiofrequency energy delivery in response to a predetermined algorithm. A non-selective renal angiography was performed before and after the procedure. Intraprocedural diffuse visceral pain restricted to the duration of energy delivery was managed with intravenous narcotics.

After procedure till one month, changes to baseline doses of all antihypertensive drugs were not allowed, unless medically judged necessary. At 1 month after the procedure, we repeated ambulatory 24-hour blood pressure monitoring with readings taken every 30 minutes in day time and every 60 minutes at night time. We calculated average values obtained during the day and night for every patient. Patients were instructed to remain adherent to their prescribed antihypertensive drugs.

The primary outcome was change in 24-hour ambulatory blood pressure and change in office and home-based blood pressure measurements. Secondary end points were procedural safety and composite cardiovascular end points such as myocardial infarction, cerebrovascular accidents, and congestive heart failure.

Statistical analysis

Continuous variables were described with mean ±

standard deviation. Other variables were reported as numbers (percentage). For comparison within different time points, a paired t-test was used.

Role of the funding source

The study was designed by Chairperson of Hospital and Cardiology Department of Isfahan University of Medical Sciences and the sponsor (Chamran Hospital). Procedure was done and data were monitored, collected and managed by an interventional fellow. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between September 2011 and January 2012, of 45 patients with resistant hypertension who assessed for eligibility, 12 (27%) patients did not meet the inclusion criteria and were not entered the study (7 subjects because of blood pressure < 160 mmHg at baseline visit when it was confirmed that patients took drugs for two weeks, and 5 ineligible anatomy). Three (6%) patients also did not enter the study because of not consenting to participate in the trial. Finally 30 (67%) patients underwent renal denervation and were followed up for 6 months (Figure 1).

Table 1 shows baseline characteristics of the patients. The mean age of the studied patients was 52 ± 15.4 years and 43.3% (n=13) were female. Systolic and diastolic blood pressure at baseline was 163 ± 17.2 mmHg and 95 ± 8.2 mmHg, respectively. Patients took, on average, 3.6 ± 1.3 hypertensive medications. Most of them [43 (96%)] received angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

All patients had 24-hour ambulatory blood pressure monitoring at baseline and at follow-up. The mean of systolic and diastolic blood pressure were decreased after renal denervation compared with mean of blood pressure at baseline (Figure 2). Table 2 shows the mean of blood pressure during 6 months of followed-up. Systolic and diastolic blood pressure at 1-week, 1-month, 3-month and 6-month after renal denervation significantly decreased compared to the baseline ($P < 0.0001$).

Mean of reduction of office blood pressure at 1 week, 1, 3, and 6 months after renal denervation is shown in figure 3. As shown, systolic blood pressure, 1 week after procedure was further reduced at 1, 3, and 6 months. Similarly 1 month after renal denervation diastolic blood pressure was further reduced through subsequent assessments up to 6 months. Thus, average blood pressure derived from 24-hour ambulatory blood pressure monitoring changed in parallel with office-based blood pressure measurements.

Figure 4 shows the proportions of patients achieving defined thresholds of systolic and diastolic blood pressure reduction at 6 months. Most of patients (50%) who underwent renal denervation had reductions of 10 mmHg or greater in systolic blood pressure and 56.7% of them had reductions of 5 mmHg or greater in diastolic blood pressure. 33.3% of patients also achieved the target of systolic blood pressure less than 140 mmHg and 60% achieved the target of diastolic blood pressure less than 90 mmHg.

No patients showed vascular damage at final angiography; however, renal angiographic studies identified focal renal artery irregularities immediately after radiofrequency (RF) energy delivery, none of which was flow limiting at the end of procedure.

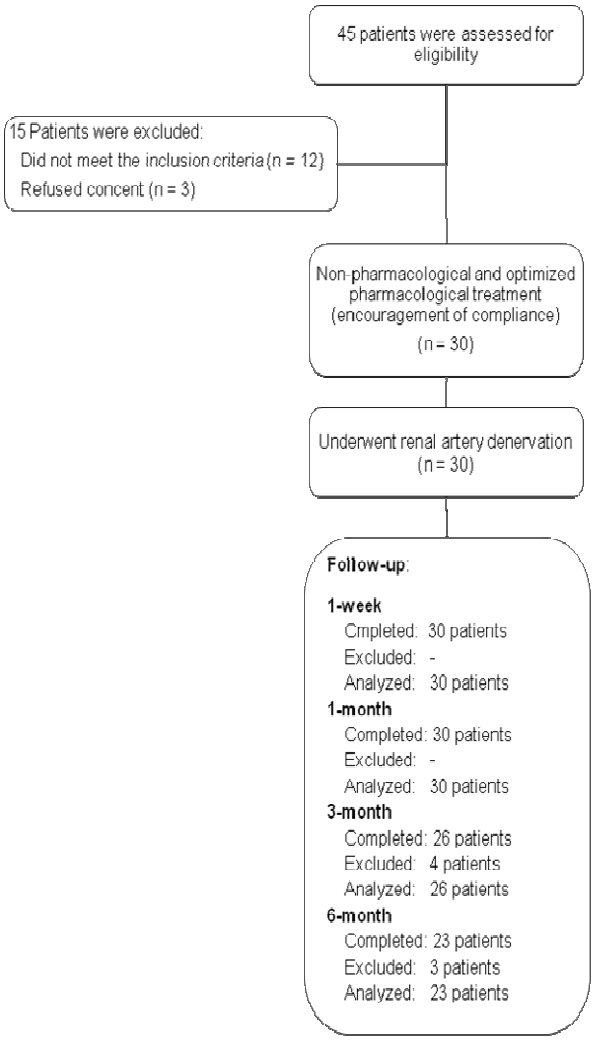

Figure 1. Study profile

Table 1. Baseline characteristics of 30 patients with resistant hypertension who underwent renal denervation

Age (years)	52 ± 15.4
Sex	
Male	17 (56.7)
Female	13 (43.3)
Body mass index	30.6 ± 4.7
Medical history	
Coronary artery disease	16 (54.3)
Type 2 diabetes	5 (17.7)
Hyperlipidemia	8 (26.7)
Cerebrovascular accident	2 (6.7)
Smoking	8 (26.7)
Alcohol use	0
Congestive heart failure	4 (13.3)
Baseline systolic blood pressure (mmHg)	163 ± 17.2
Baseline diastolic blood pressure (mmHg)	95 ± 8.1
K	4.2 ± 0.56
Number of antihypertensive medications	3.6 ± 1.3
Drug history	
Beta blockers	3 (10)
Alpha blockers	8 (26.7)
Vasodilators	2 (6.7)
Diuretics	19 (63.3)
Calcium channel blockers	19 (63.3)
ACE inhibitors/ARBs	27 (81.8)
Serum creatinine (µmol/L)	1 ± 0.12

Data are presented as mean ± SD or number (percent)

In total, an average of 5.2 ± 1 RF ablations was performed in the left renal artery, and 5.8 ± 1 RF ablations in the right renal artery. The mean use of contrast was 80 ± 20 ml. Mean fluoroscopy time was 11 ± 2 minutes. The mean time of the procedure (i.e. from puncture of the femoral artery to closure) was 38 ± 8 minutes. After the procedure, there was no change in serum creatinine (1 ± 0.12 µml/L compared with 1 ± 0.11 µml/L; P = 0.93). No changes in medication was noted at 1-month follow-up; however; 18 (60%) of patients who underwent renal ablation had drug reductions prior to 6-month follow-up and none of them had drug increases prior to 6-month. In general, there was no a per-procedural complication or complications during follow-up.

Table 2. Comparison of 24-hour baseline ambulatory blood pressure monitoring with follow-up period in 30 patients with resistant hypertension who underwent renal denervation

	SBP (mmHg)	DBP (mmHg)
Baseline (n=30)	163 ± 17.2	95 ± 8.1
1-week (n=30)	136.2 ± 13.1	85.3 ± 8.9
P	< 0.0001	< 0.0001
1-month (n=30)	137.8 ± 8.5	80.7 ± 8.2
P	< 0.0001	< 0.0001
3-month (n=26)	136.4 ± 9	81.8 ± 6
P	< 0.0001	< 0.0001
6-month (n=23)	145.7 ± 10.1	86.3 ± 5.6
P	< 0.0001	< 0.0001

Data are presented as mean ± SD; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

P-values calculated by paired samples t-test compared to the baseline

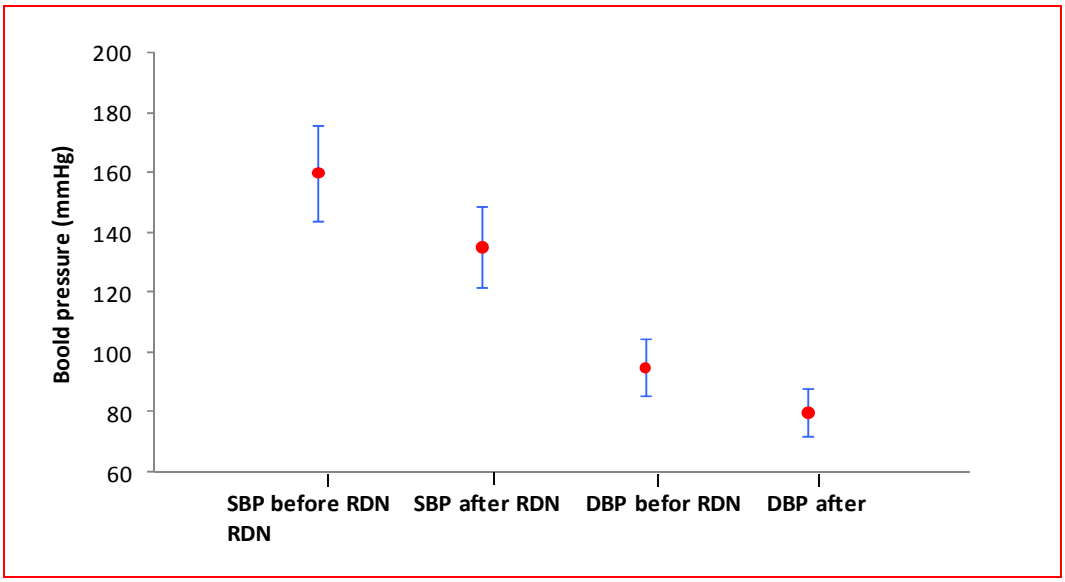

Figure2. Mean of 24-hour ambulatory blood pressuremonitoring for systolic and diastolic blood pressure before and after renaldenervation in 30 patients with resistant hypertension

RDN: Renaldenervation; SBP: Systolic blood pressure; DBP: Diastolicblood pressure

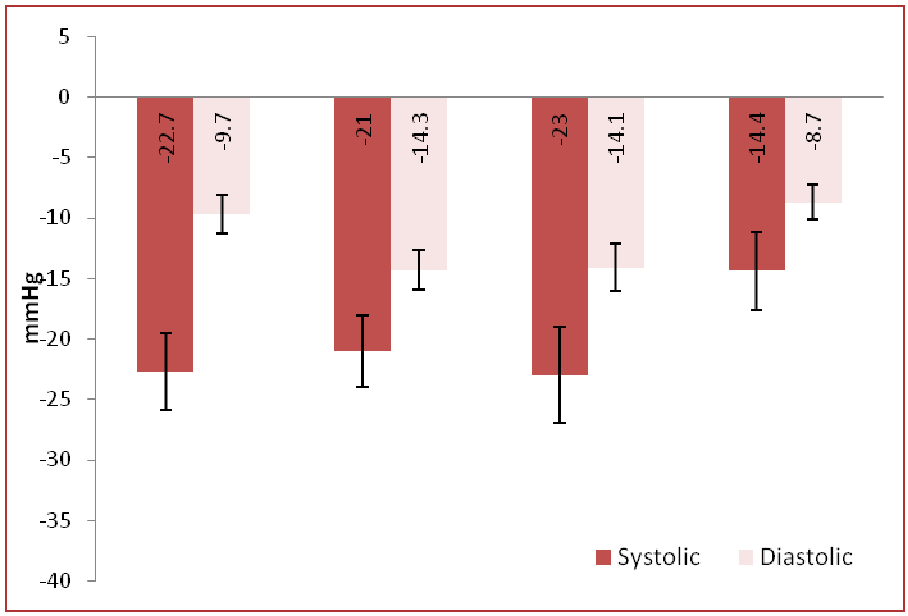

Figure 3. Change in office-based measurements of systolic and diastolic blood pressures at 1 week, 1 month, 3 months, and 6 months for renal denervation. Error bars are Standard Error

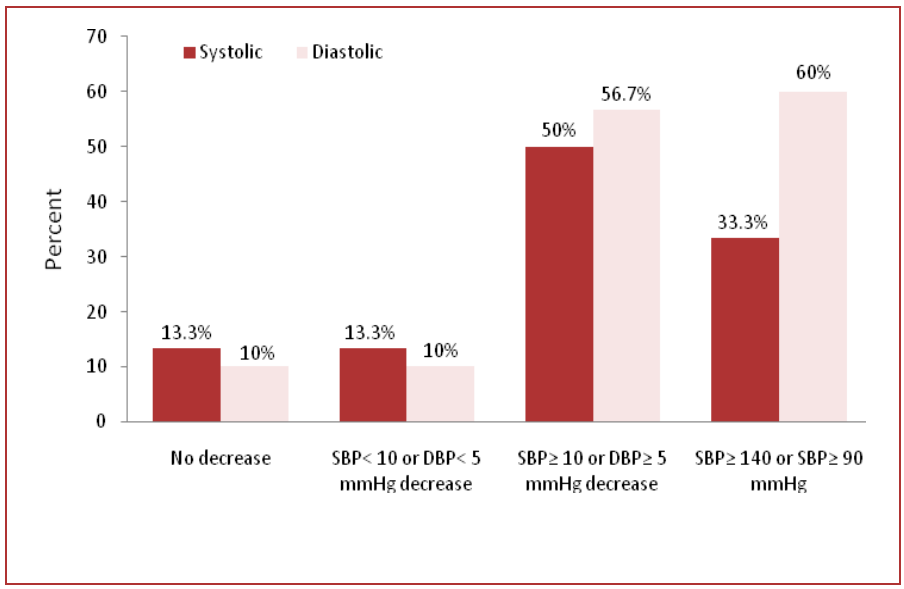

Figure 4. Proportion of blood pressure status after renal denervation after 6 months based on 24-hour ambulatory blood pressure monitoring (n = 30)
SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Discussion

Uncontrolled hypertension is a common clinical condition and causes significant morbidity and mortality such as cardiovascular and cerebral events. Thus, appropriate control of HTN result in prevention of cardiovascular morbidity and even mortality. A new catheter system has been developed, making the endovascular approach to renal denervation an attractive therapeutic option in patients with resistant hypertension. The "Symplicity Catheter System" (Medtronic-Ardian) was the first and only system available.[3] Previous studies about radiofrequency renal-nerve ablation in patients with resistant hypertension showed the feasibility and safety of it and reported encouraging blood pressure reductions, with no major complications due to the technique.[4-7] In our study, novel catheter-based treatment of resistant hypertension without using of "Symplicity" catheter was assessed and to the best of our knowledge this

is the first human experience. Our results showed that after renal denervation, systolic and diastolic blood pressure decreased compared with blood pressure at baseline. Moreover, systolic and diastolic blood pressure at 1-week and 1, 3 and 6 months after renal denervation significantly decreased compared to baseline. Reductions of 10 mmHg or greater in systolic blood pressure and 5 mmHg or greater in diastolic blood pressure occurred in 50% and 56.7% of patients, respectively.

The Symplicity Catheter System as a new approach to renal denervation was studied in several trial, the first study, a cohort study, was done on 50 patients with resistant hypertension, renal sympathetic ablation was achieved using a radiofrequency ablation catheter inserted through the femoral artery and selectively engaging the renal artery bilaterally (Symplicity, Ardian Inc., Palo Alto, Calif, USA). This study showed safety of denervation of renal sympathetic nerve endings. However, two complications were occurred but not related to ablation itself (complication of site of puncture). Then authors carried out a randomized controlled trial, the Symplicity HTN 2 study, on 106 patients with resistant hypertension, to compare the antihypertensive efficacy of this procedure plus drug treatment with that of drug treatment alone. They reported that catheter-based renal denervation can safely be used to substantially reduce blood pressure in treatment resistant hypertensive patients with a low incidence of immediate per-procedural complications and short- and medium-term renal and vascular complications.[5] In another study in 2010, a total of 11 patients who were resistant to at least three types of antihypertensive medical therapy, underwent treatment by renal artery radiofrequency ablation using Symplicity catheter and concluded that catheter-based renal denervation seems an attractive novel minimally invasive treatment option in these patients, with no serious adverse events per-procedurally or at follow-up.[7]

Our findings showed that a significant reduction in blood pressure, based on 24-hour blood pressure monitoring, can be achieved with catheter-based renal denervation in patients with resistant hypertension which was uncontrolled despite treatment with three or more antihypertensive drugs. Also no vascular damage at angiography or per-procedural complications was observed. This finding supports the results of previous investigations[4-7] even though, the procedure was different in present study, which was catheter-based treatment of resistant hypertension without using of Symplicity catheter, compared to other studies that used Symplicity catheter.

The main limitation of present study is that this was not a randomized controlled trial and factors such as regression to the mean and Hawthorne effect need to be considered in the interpretation of these results, because there is no control group with which to make evaluations about blood pressure responses over time. On the other hand, patients in our study were followed for 6-month whereas the efficacy of this new treatment should be investigated in long-term follow-up not only in the short-term. It seems randomized controlled clinical trials are required to confirm this primary experience in long-term follow-up. Accordingly, renal artery denervation without using of Symplicity catheter, which is not ready in any cathlab and is an expensive catheter, opens new opportunities for the treatment of patients with resistant hypertension and further researches are needed to identify groups of patients who might benefit from this intervention such as patients with milder forms of hypertension, patients intolerant to medication and in several other conditions.

In conclusion, previous studies in catheter-based renal denervation represented an advanced new technique to effectively reduce blood pressure in patients with resistant hypertension. Similarly, findings of this study indicated that renal nerve ablation achieved by a catheter-based approach without using of Symplicity catheter has the potential to improve blood pressure control in these patients, simpler and less expensive. For example, in our country, each Symplicity catheter is about $300 while the catheters for our technique are less than $30. The Symplicity system is about $30000 but we did renal nerve ablation by radiofrequency ablation system of our electrophysiology (EP) cathlab. However, randomized controlled clinical trials are needed to compare these two techniques.

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Conflict of Interests

Authors have no conflict of interests.

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