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Comparison of standard renal denervation procedure versus novel distal and branch vessel procedure with brachial arterial access

Ivo Petrov *, Iveta Tasheva, Iskren Garvanski, Zoran Stankov, Iana Simova

Departments of Cardiology and Angiology, City Clinic, Sofia, Bulgaria

ABSTRACT

Objectives: We assessed a novel approach to percutaneous renal denervation for uncontrolled hypertension consisting of ablation beyond the proximal main renal artery (Y-pattern), including the primary branches, and compared it to the standard procedure applied only within the main vessel. We also assessed the safety and practicality of a brachial access approach.

Methods and results: Renal denervation was performed on 119 consecutive patients (60 ± 13 years). In 68 of the patients, femoral arterial vascular approach was used and in 51 brachial. In 80 patients treated with the standard ablation, 12.0 ± 3.0 total ablations (both sides) were applied while 20.4 ± 3.9 total ablations were delivered for the group of 39 patients with Y-pattern denervation ($P < 0.001$). Technically successful renal denervation was achieved in all patients. Office blood-pressure levels at baseline were $170 \pm 17/93 \pm 10$ mm Hg for the standard group and $169 \pm 13/96 \pm 9$ mm Hg for the Y-pattern group. No major adverse events occurred during the procedure or in the postprocedural in-hospital period. Renal denervation was associated with significant decreases in both office and ambulatory systolic and diastolic blood pressure in both groups. The reduction in 24-hour mean ambulatory systolic blood pressure at 6 months was significantly greater ($P = 0.002$) for the Y-Pattern group (-22.1 ± 15.4 mm Hg) compared to the Standard group (-11.8 ± 16.2 mm Hg). Changes in diastolic office and ambulatory pressure were also significantly greater at 6 months in the Y-pattern ablation group. Indices of blood pressure variability improved in both groups.

Conclusion: Renal denervation using a Y-pattern ablation strategy combined with a greater number of lesions is safe and resulted in significant greater decreases in mean 24-hour ambulatory systolic and diastolic blood pressure compared to the conventional approach in this single-centre matched cohort study. Brachial artery access was shown to be feasible and safe for renal denervation.

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1. Introduction

Hypertension affects >25% of the worldwide adult population [1]. Identification of patients with resistant hypertension, defined as failure to achieve control of blood pressure (BP) despite treatment with optimal doses of >3 antihypertensive medications, is critical because of its direct influence on prognosis [2]. In the past, surgical sympathetic denervation was demonstrated to be a highly effective treatment for resistant hypertension, but with an unacceptably high complication rate [3]. Later, percutaneous renal denervation has shown promise as a safe and effective alternative for the treatment of resistant hypertension [4,5]. However, the randomized, blinded and sham controlled SYMPLICITY HTN 3 study failed to demonstrate a significant benefit, despite showing excellent procedural safety [6]. One key limitation of this trial was the possibility that the denervation procedure itself was not adequately performed perhaps resulting in insufficient destruction of the renal nerves [7]. This explanation is supported by anatomical evidence of variable distribution of the peri-arterial renal nerves from the proximal to the distal portion of the artery. More nerve fibres are present in the proximal regions, while the renal nerves are closer to the renal artery lumen in its distal regions [5]. The recently reported results of the SPYRAL HTN-OFF MED trial support this hypothesis. In this prospective, international randomized sham controlled trial of moderately hypertensive patients, renal denervation was performed in both the main and branch arteries and resulted in clinically and statistically significant reductions in both office and ambulatory blood pressure at 3 months [8].

Previous reports of the safety and efficacy of the percutaneous RDN procedure have almost exclusively involved femoral arterial access. Only a few reported cases have described renal denervation using radial or brachial access, despite potential advantages that include reduced risk of bleeding and easier renal arterial access, due to the acute take-off angles of the renal artery from the abdominal aorta [9]. Therefore, the purpose of the present analysis was two-fold. First, we

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* Corresponding author at: 127 Okolovrasten pat, 1407 Sofia, Bulgaria.
E-mail address: petrovheart@gmail.com (I. Petrov).

compared the safety and efficacy of a novel "Y-pattern" of ablation that included treatment in both the main renal arteries and primary branches with the standard main artery ablation-only procedure. Second, we assessed the safety and practicality of a brachial arterial access for renal denervation in comparison to standard femoral arterial access.

2. Methods

Renal denervation using a mono electrode radiofrequency catheter ablation system (Symplicity Flex, Medtronic) was performed in our hospital on 119 consecutively presenting patients with resistant hypertension between January 2013 and June 2016. Patient selection was based on a history of therapeutically resistant hypertension, ongoing therapy with >3 antihypertensive drug classes (at least one of which was diuretic) and 24-hour mean ambulatory BP > 160/90 mm Hg. Procedural groups were not randomized, and the earliest presenting patients received the standard ablation procedure while the later presenting group received the Y-Pattern. All patients provided written informed consent.

2.1. Procedural details

1. For Femoral Approach:

Under fluoroscopic control and local anaesthesia, a 7 Fr Radifocus® Introducer (Terumo) 10 cm femoral sheath was inserted within the segment of the common femoral artery lying above the femoral head. An initial digital subtracted angiogram of the abdominal aorta with the pigtail catheter positioned on the level of the first lumbar vertebra was performed to reveal aortic and iliac vessel tortuosity, atherosclerotic changes and calcium containing lesions, the number and size of the renal arteries. Using "road map", a supra-selective cannulation of the renal artery was performed using a 55 cm long Launcher RDC 7 Fr (Medtronic) guiding catheter. Cannulation was performed with initial supra-selective engagement with a 0.035" Storq wire (Cordis) with a floppy steerable tip in the case of a horizontal renal artery take off. In the case of a very sharp angle between the aortic axis and the renal arterial axis leading to difficult direct supra-selective cannulation, a telescopic technique was applied. Over the Storq wire, additional support was provided with a diagnostic Glidecath catheter 0.038" (Terumo). The latter device was inserted in the Y connector of the guiding catheter and, after deep supra-selective cannulation of the target renal artery and using "push-pull" manoeuvre, the guiding catheter was selectively inserted over the set of "Storq wire-diagnostic catheter". Once a supra-selective insertion was achieved, renal denervation energy application was initiated from distal to proximal applying in helicoidal pattern at least 3 points of ablation per segment. In the cohort of patients receiving the "Y-pattern" ablation strategy, the monopolar Symplicity "Flex" catheter (Medtronic) itself, slightly curved with the lever was used for supra-selective cannulation of the renal artery branches and 3 to 5 ablations were performed in these segments in a helicoidal fashion. In the case of unsuccessful femoral approach for supra-selective renal artery cannulation, a switch to the brachial approach was undertaken. A final subtraction angiogram was performed to evaluate number of ablation notches and potential damage to the renal artery (Fig. 1).

2. For Brachial Approach:

Under similar anaesthetic conditions as for the femoral approach, a 5 Fr Terumo 10 cm sheath was inserted in the right brachial artery. An oblique LAO projection was employed to present the aortic arch. A floppy Storq wire and diagnostic pigtail or JR catheter were used to engage the descending aorta. An initial digital subtracted angiogram of the
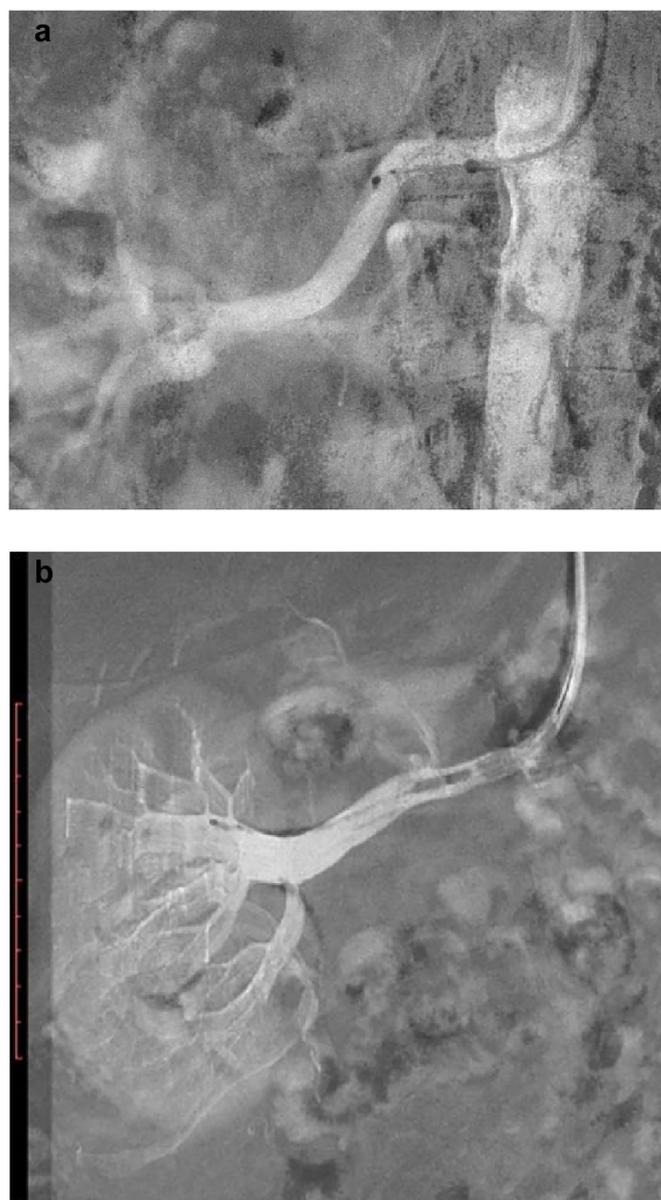
Fig. 1. Case example of subtraction fluoroscopic angiograms used for procedural guidance using the brachial approach: a) Standard ablation: Once a supraselective insertion was achieved, the renal denervation itself is started from distal to proximal applying on helicoidal pattern 3–5 points of ablation per segment. b) "Y" pattern ablation: The Simplicity catheter itself was used to selectively cannulate the major renal artery branches and 3 to 5 ablations were performed in these segments on a helicoidal fashion.

abdominal aorta, with the pigtail catheter positioned on the level of the first lumbar vertebra, was then performed to reveal aortic tortuosity or atherosclerotic changes as well as the number and size of the renal arteries A 5 Fr, 90 cm CheckFlo hydrophilic sheath (Cook Medical) was inserted over the Storq wire into the distal thoracic aorta. Over a "road map" masque, a supra-selective cannulation of the renal artery was performed using a simple diagnostic 5 Fr JR 100 cm catheter. The 90 cm sheath was engaged supra-selectively in the main renal artery over the selectively inserted set "Storq wire-diagnostic catheter". The renal denervation procedure was then performed in an identical manner as for the femoral approach (Fig. 1).

After achieving initial vascular access, an i.v. bolus of Heparin (70 IU per body weight in kg) was applied. In addition to the conscious sedation, additional local anaesthesia was performed with direct infusion of 10 ml 1% Lidocaine in the ablated renal artery. Only ablations producing a visible "notch" in the vessel wall on the fluoroscopic image, decrease

in impedance >10% and a temperature > 60 °C were counted as "ablated points". All periprocedural, in-hospital and late complications were registered. Both pre-and post-procedural values of creatinine were measured to assess possible effect of the greater number of lesions on renal function. Limited double antiplatelet prophilaxis (ASA 100 mg/daily plus Clopidogrel 75 mg daily) was maintained for 1 month.

Office blood pressure readings were performed at baseline, 1st, 3d and 6th month post procedure. During the follow-up visits, routine renal artery Duplex investigation was performed in order to check patency of the main and branch vessels. Ambulatory 24-hour blood pressure recordings were performed at baseline and 6th months post procedure. Antihypertensive medications remained unchanged for both groups for the duration of the follow-up unless medically necessary because of significant changes in blood pressure. However, objective testing of antihypertensive drug adherence was not performed.

Statistical comparisons for continuous baseline variable and changes in continuous variables between baseline and follow-up were performed via two-tailed paired t-test for within group comparisons and unpaired t-test for between group comparisons. Categorical baseline variables were compared via chi squared analysis. One-way Analysis of Variance (ANOVA) with Tukey adjustment was applied to compare systolic and diastolic office blood pressure drops within groups between baseline and 1, 3 and 6-month visits. A probability (P) value <0.05 was considered significant.

3. Results

A total of 80 (67%) patients received the standard ablation whereas the modified Y-pattern ablation was applied in 39 (33%) patients. The traditional femoral arterial approach was used in 68 (57%) patients while the brachial in 51 (43%) subjects. Denervation was performed via brachial access in 20 (25%) of the Standard ablation group and in 31 (79%) of the Y-Pattern group (Table 1). Despite the lack of randomization, the two groups were well matched demographically (Table 2). "Technically successful" renal denervation, defined as at least three lesions (positive for notch-impedance-temperature criteria) in both renal arteries, was achieved in all patients. The Y-Pattern group received significantly more lesions than the Standard group (Table 3). Procedural time was 56 ± 15 min for the Standard group and 85 ± 27 min for Y-pattern group (P < 0.001). The mean X-ray time for the Standard group was 29 ± 16 min, and 23 ± 15 min for the Y-pattern group (P = 0.054). The volume of contrast medium was significantly higher for the Standard group (155 ± 53 ml) compared to the Y-pattern group (124 ± 48 ml; P = 0.003).

No major adverse events occurred during the procedure or in the postprocedural in-hospital period. Three minor access site-bleeding complications and seven hematomas occurred in the brachial subgroup, as compared to four and five, respectively in the femoral group. All events were considered minor and resolved after manual compression. Four pseudo-aneurysms were also observed, including three which resolved after manual compression and one which required suture repair (brachial group subject). A limited dissection of the renal artery without flow compromise occurred in one patient of the brachial group and resolved spontaneously during the follow-up period without sequelae. The procedural approach was switched from femoral to brachial in 4 patients due to inability to achieve supraselective guiding catheter insertion to the renal artery. No one subject was converted from brachial to femoral approach.

Table 1
Patient procedural assignment.

	Femoral access	Brachial access	Total
Standard denervation	60	20	**80**
"Y-Pattern" denervation	8	31	**39**
Total	**68**	**51**	**119**

Table 2
Baseline population demographics.

	All N = 119	Standard ablation N = 80	Y-Pattern ablation N = 39
Age (years)	60 ± 13	60 ± 14	60 ± 14
Gender (male)	61 (51.3%)	37 (46.3%)	20 (51.3%)
Gender (female)	58 (48.7%)	43 (53.7%)	19 (48.7%)
BMI (kg/m^2)	28 ± 4	28 ± 4	27 ± 5
Antihypertensive medication classes	5.6 ± 0.9	5.7 ± 0.9	5.6 ± 1.0
Serum creatinine (μmol/L)	158 ± 173	167 ± 193	140 ± 121
Blood pressure (mm Hg)			
Office systolic	170 ± 16	170 ± 17	169 ± 13
Office diastolic	94 ± 10	93 ± 10	96 ± 9
24-Hour systolic	163 ± 18	162 ± 19	168 ± 18
24-Hour diastolic	88 ± 8	88 ± 8	88 ± 8
Daytime systolic	167 ± 18	166 ± 18	168 ± 18
Daytime diastolic	92 ± 8	92 ± 8	92 ± 9
Night time systolic	160 ± 19	159 ± 21	161 ± 13
Night time diastolic	84 ± 11	84 ± 11	83 ± 10
Cardiovascular disease history [N (%)]			
Coronary artery disease	54 (45)	34 (43)	51
Stroke/TIA	9 (8)	7 (9)	5
Hypocholesteraemia	66 (55)	47 (59)	49
Current smoking	17 (14)	9 (11)	21
CKD	24 (20)	18 (23)	15

Renal denervation resulted in significant reductions in office systolic and diastolic blood pressure at 1, 3 and 6th month of follow up in both groups (Table 3; Fig. 2). The decrease in office blood pressure was significantly greater at 1 month in the Y-Pattern group as compared to the Standard group and numerically greater at 3 and 6 months (Fig. 2). Likewise, the decrease in diastolic pressure tended to be larger in the Y-Pattern group, although the difference reached significance only at the 6-month follow up (Table 3).

At 6 months follow-up mean ambulatory 24-hour, daytime and night time systolic and diastolic blood pressure decreased significantly from baseline in both groups (Table 3; Fig. 3). The reduction in **24-hour mean ambulatory systolic** blood pressure was significantly greater (P = 0.002) for the Y-Pattern group (−22.1 ± 15.4 mm Hg) compared to the Standard group (−11.8 ± 16.2 mm Hg). This was associated with significantly greater decreases in daytime (−18.8 ± 16.9 vs −8.7 ± 15.6 mm Hg, P = 0.03), but only numerical, statistically not significant difference in night-time (−22.5 ± 14.3 vs −16.0 ± 7.7 mm Hg, P = 0.06), systolic pressure. The magnitude of night-time systolic blood pressure dipping increased in both the Standard group (4.2 ± 7.3 vs 9.5 ± 6.0 mm Hg; P < 0.001) and in the Y-Pattern group (2.2 ± 8.7 vs 8.1 ± 5.4 mm Hg; P < 0.001). Daily systolic blood pressure variability also decreased in both the Standard group (19.0 ± 4.2 vs 16.6 ± 4.3 mm Hg; P < 0.001) and the Y-pattern (19.5 ± 6.2 vs 18.2 ± 6.3 mm Hg; P = 0.01) group, respectively. The number of prescribed antihypertensive medications remained without significant change during the follow-up (Tables 2 and 3) and the medication compliance was strictly controlled by the investigational team. Serum creatinine levels increased in the Standard treatment group from baseline by 14.6 ± 25.3 μmol/l (P = 0.003) and by 12.7 ± 29.3 μmol/l in the Y-pattern group (P = 0.03; P = 0.75 between groups).

4. Discussion

The strategy to apply renal denervation therapy beyond the proximal main artery originated from human histological [10], anatomical [11] and animal pre-clinical [12,13] reports indicating that the distance between the vessel lumen and the renal nerve fibres is lower in the distal regions suggesting that the distal nerves may be more vulnerable to RF energy. Recently Pekarskiy and colleagues compared renal denervation therapy in the distal main vessel and the arterial branches to ablation in the proximal main artery in 51 randomized hypertensive

Table 3
Between Group comparison of blood pressure and other parameters at follow up.

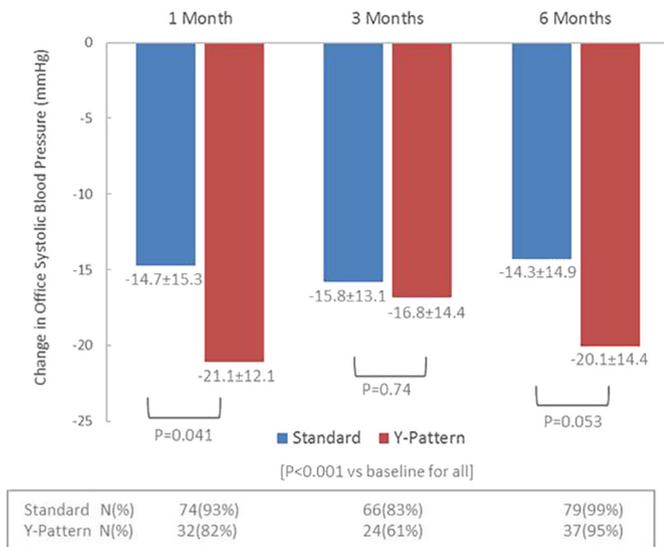| Change in office diastolic blood pressure (mm Hg)	Standard	Y-Pattern	P (Standard vs Y)
1 Month	−8.0 ± 13.2[*]	−9.8 ± 8.5[*]	0.49
3 Months	−6.3 ± 6.9[*]	−6.4 ± 9.0[*]	0.96
6 Months	−5.0 ± 9.0[*]	−9.9 ± 10.8[*]	0.01
Change in ambulatory diastolic pressure (mm Hg)			
24-Hour	−5.2 ± 8.4[*]	−6.2 ± 10.0[*]	0.61
Daytime	−3.2 ± 9.4[*]	−5.6 ± 10.0[*]	0.24
Night time	−7.6 ± 8.4[*]	−6.5 ± 11.5[*]	0.56
Antihypertensive medication classes	4.9 ± 1.1[*]	5.3 ± 0.8[*]	0.07
Total number of lesions[a]	12.0 ± 3.0	20.4 ± 3.9	<0.001

[*] P < 0.05 vs. Baseline.

[a] Lesions were counted only if producing a visible "notch" in the vessel wall on the fluoroscopic image, a decrease in impedance > 10% and a temperature > 60 °C.

subjects [14]. The magnitude of the 24-hour pressure drops at 6 month post procedure for the "distal" vs "traditional" approach achieved using the same (Symplicity Flex) denervation system (22.6 ± 20.0 vs 9.4 ± 18.7 mm Hg; P < 0.05) were very close to those reported in the present analysis (Fig. 3). In a separate investigation, Davies and colleagues also showed good safety and significant decreases in ambulatory blood pressure and improvements in renal artery hemodynamics with branch and main vessel therapy [15]. In another dual-center prospective analysis Fengler reported comparative efficacy and safety between a group of 25 treatment resistant hypertension patients treated with ablation of main renal artery, side branches, and accessory arteries to a matched control group (N = 25) with only main renal artery ablation [16]. Systolic 24-hour mean ABP decreased significantly after 3 months in the combined ablation group (−8.5 ± 9.8/−7.0 ± 10.7 mm Hg, P < 0.001/0.003), but not in patients with main artery treatment (−3.5 ± 11.1/−2.0 ± 7.6 mm Hg, P = 0.19/0.20) and systolic daytime BP was significantly lower in patients with combined ablation compared to main artery ablation (P = 0.033). The intermediate results of the ongoing Global SYMPLICITY Registry have also shown a trend towards greater office blood pressure reduction in 45 patients treated with the Y-pattern with a multi electrode device, as compared to 138 patients treated in the main vessel only (−21.9 ± 22.6 vs. −14.4 ± 27.9 mm Hg, respectively, P = 0.052) [17]. Most recently, the prospective randomized sham controlled SPYRAL HTN-OFF MED trial demonstrated significantly greater reductions in both office and 24-hour blood pressure at 3 months following renal denervation in both

the main artery and the distal branches in 80 moderate hypertensive patients who were not prescribed any hypertensive medications (24-h SBP −5.5 mm Hg (95% CI −9·1 to −2·0; P = 0·0031–0·5 mm Hg (95% CI −3·9 to 2·9; P = 0·7644),) [8]. All these data strongly support both the safety and enhanced blood pressure reductions associated with the more aggressive Y-pattern strategy.

The present analysis is the largest single clinical report to date of the "Y-pattern strategy" of percutaneous renal denervation applied in humans. Our results demonstrate that this strategy is safe and results in greater decreases in systolic office and 24-hour blood pressure as compared to the standard approach (Figs. 2 and 3) together with improvements in indices of blood pressure variability. These results are comparable to previous reports of improved blood pressure variability following renal denervation [18,19]. The Y-pattern approach was associated with lower contrast volume usage despite similar x-ray exposure time and longer procedural times as compared to the Standard group. This apparent discrepancy may have been due to the serial design of the investigation, leading to a "learning curve" effect, and the more extensive use of brachial approach, leading to much easier and lower time-consuming cannulation of the renal arteries. Procedural accessibility of the distal renal artery anatomy should continue to improve as a recently introduced "next generation" multi-electrode catheter system features over-the-wire guidance and the ability to apply 4 geometrically dispersed lesions simultaneously [8].

The radial/brachial approach for percutaneous interventions has several potential advantages over the femoral approach including reduced bleeding risk, increased patient comfort and earlier

Fig. 2. Change in Office Systolic Blood Pressure from baseline at 1, 3 and 6 months post ablation for the Standard denervation sub group and the Y-Pattern denervation group. Inlaid table indicates number of patients available for follow up at the intermediate timepoints.
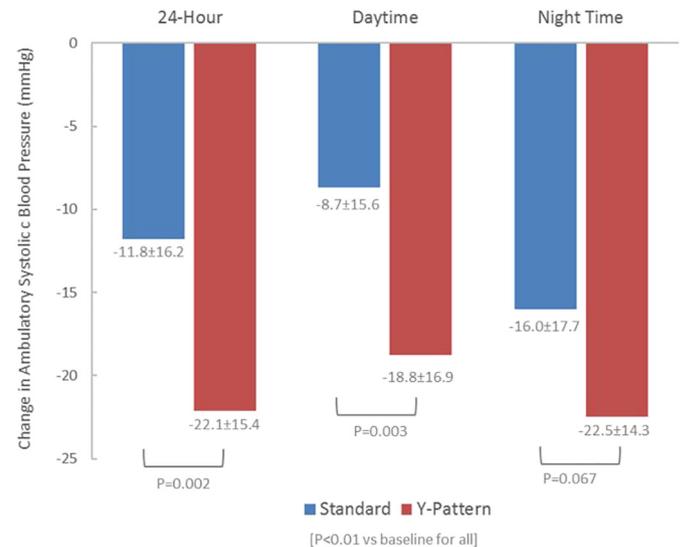
Fig. 3. Change 24 h, daytime and night time mean ambulatory systolic blood pressure at 6 months post ablation. Paired data were available for 80(100%) of the Standard group and for 33 (87%) of the Y-Pattern group.

ambulation. We have also observed that hypertensive subjects often present with very tortuous infrarenal aortas, and the angle of origin of the renal arteries is often too acute for a selective catheter positioning from femoral approach. Based on this experience, we switched to a primarily upper (brachial) approach for renal denervation procedures. The main reason to use brachial and not radial approach was that the ablation (Symplicity Flex) catheter usable length (90 cm) was not compatible with standard length (100 cm) Judkins Right guiding catheters, otherwise used routinely for renal interventions with radial access in our practice. The alternative brachial access and the low profile 5 Fr telescoping protocol elaborated by our group was associated to high rate of successful renal artery (100%) cannulation with no significant periprocedural complications in this pilot investigation. Previously, Heradien and colleagues reported on two cases of renal denervation with the same system using a radial and a brachial approach, respectively, with good safety results [8].

No major safety concerns regarding the effect of renal denervation on renal arterial wall integrity were observed, thereby confirming a recent report that renal denervation does not increase the risk of long-term renal artery narrowing [20]. Studies have shown that ablation notches, visible immediately after the procedure, do not harm the arterial wall and do not affect the long term patency of the renal arteries [21,22] confirmed in our series as well.

Post-hoc analysis of the randomized and sham-controlled SYMPLICITY HTN-3 trial indicated that the blood pressure response to renal denervation may depend on the number of lesions applied [6]. In this analysis as much as 63% of the patients in the treatment arm received only 0–1 ablations resulting in fluoroscopically visible notch and only 19 patients out of 394 received "full" ablation in four quadrants in both renal arteries [7]. On contrary in our study the mean number of denervation lesions applied in both groups applied on helicoidally pattern was relatively high (Table 3) and accordingly the decrease in blood pressure was significant. The present data support that achievement of complete denervation may be a key to a successful procedure even independent from the actual ablation pattern.

More recent prospective controlled trials (SPYRAL HTN OFF MED [8], DENER HTN [23], INSPiRED [24]) have all shown significant improvements in 24-hour blood pressure in denervated patients compared to standard of care. Ongoing randomized sham controlled trials featuring various device technologies should provide important insight into the proper procedure and most appropriate populations to best demonstrate significant blood pressure reductions [25].

Several important limitations of the present trial should be considered. Treatment group assignment was sequential and not randomized. Hence, Y-pattern procedures and brachial approach generally occurred later than standard and femoral procedures, respectively. Thus, it is possible that the single center operators' "learning curve" may have impacted the results, although demographics were well matched. We applied brachial, rather than radial, approach because the length of the Symplicity Flex catheter did not allow use of a standard length (100 cm) guiding catheter. Although both the office and ambulatory blood pressure results (Figs. 2 and 3) support the hypothesis that Y-pattern denervation is associated with greater blood pressure reductions, the results of the ABPM analysis appeared to be more robust than the office blood pressure results. Indeed, ambulatory blood pressure may be a superior endpoint in studies of resistant hypertension due to its relative immunity from measurement bias and "white coat" effects [26].

Conclusion: Renal denervation using a "Y-Pattern" of ablation including the major branches executed from either a femoral or brachial approach is a feasible, safe and effective method in selected patients with resistant hypertension. The Y-pattern for denervation and the greater number of ablations did not carry greater risk for renal function or for vascular complications and was associated with greater drops in 24-hour and daytime ambulatory systolic blood pressure. Further refinement of denervation systems and tools should make the less invasive and more efficient approaches to renal denervation more efficient and attractive.

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