Comparison of two different radiofrequency ablation systems for renal artery denervation: Evaluation of short-term and long-term follow up

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Abstract
Objectives: To assess the clinical efficacy of renal artery denervation (RAD) in our center and to compare the efficacy of two different radiofrequency (RF) systems.

Background: Several systems are available for RF renal denervation. Whether there is a difference in clinical efficacy among various systems remains unknown.

Methods: Renal artery denervation was performed on 43 patients with resistant hypertension using either the single electrode Symplicity Flex (n = 20) or the multi-electrode EnligHTN system (n = 23). Median post-procedural follow-up was 32.93 months. The primary outcome was post-procedural change in office blood pressure (BP) within 1 year (short-term follow-up). Secondary outcomes were change in office BP between 1 and 4 years (long-term follow-up) and the difference in office BP reduction between the two systems at each follow-up period.

Results: For the total cohort, mean baseline office BP (systolic/diastolic) was 174/94 mmHg. At follow-up, mean changes in office BP from baseline were $-19.70/-11.86$ mmHg ($P < 0.001$) and $-21.90/-13.94$ mmHg ($P < 0.001$) for short-term and long-term follow-up, respectively. The differences in office BP reduction between Symplicity and EnligHTN groups were $8.96/1.23$ mmHg ($P = 0.42$ for systolic BP, $P = 0.83$ for diastolic BP) and $9.56/7.68$ mmHg ($P = 0.14$ for systolic BP, $P = 0.07$ for diastolic BP) for short-term and long-term follow-up, respectively.

Conclusions: In our cohort, there was a clinically significant office BP reduction after RAD, which persisted up to 4 years. No significant difference in office BP reduction between the two systems was found.

KEYWORDS
catheter ablation, hypertension, renal artery intervention

1 | INTRODUCTION

The initial renal artery denervation (RAD) trials demonstrated significant blood pressure (BP) reduction, which persisted up to 3 years.1–3 However, the randomized sham-controlled trial (Symplicity HTN-3) showed no significant difference in BP reduction between the RAD and the sham control arm.4 Inexperienced operators in RAD and lack of bilateral circumferential denervation in most cases were possible reasons for insufficient denervation in Symplicity HTN-3.5,6 Since its first clinical application, RAD technology has evolved rapidly in consideration to different ablation modalities and energy delivery methods.7 Systems that utilize radiofrequency (RF) energy remain the most commonly used. Positive results were reported using both single electrode Symplicity Flex (Medtronic, Minneapolis, MN, USA) and
multi-electrode EnligHTN (Abbott, Chicago, IL, USA) RF systems. Nonetheless, studies on the clinical efficacy of single electrode versus multi-electrode systems have not been published. We previously compared the single electrode Symplicity Flex versus the multi-electrode EnligHTN in a gel based phantom renal artery model that allowed the spatiotemporal assessment of thermodynamics and lesion dimensions produced by each system. In the gel model, Symplicity Flex produced larger lesions compared to EnligHTN. While the difference in lesion size was statistically significant, it was unclear if that difference would be clinically relevant. Moreover, it has been suggested that functional and anatomical reinnervation after RF renal denervation can occur and is likely to be complete by 11 months post procedure. Therefore, we aimed to assess the efficacy of RAD in reducing office BP for a cohort of patients with refractory hypertension who underwent RAD using two RF systems (single electrode Symplicity Flex or multi-electrode EnligHTN system) within 1 year (short-term follow up), and to determine if BP reduction is persistent in the longer-term (between 1 and 4 years; long-term follow up) beyond the suggested time for reinnervation. We also aimed to compare office BP reduction between those two systems at each follow-up period.

2 | METHODS

We prospectively collected data for a total of 43 patients in whom RAD procedure was performed at our center between 2012 and 2015. Symplicity Flex was used in the first 20 consecutive patients, while EnligHTN was used in the subsequent 23 cases. Human Ethics Research Committee at Westmead Hospital approved the study and a written informed consent was obtained from all patients.

2.1 Study population

Patients were referred for the procedure after an initial assessment by their treating cardiologist or nephrologist. Referral criteria included average baseline office systolic blood pressure (SBP) of ≥150 mmHg while on a minimum of three antihypertensive medications, or those with office SBP > 140 mmHg and intolerant to antihypertensive medications or had recurrent admissions with malignant hypertension. All patients reported compliance to their antihypertensive medications. They all had a CT renal angiogram prior to the procedure for anatomical assessment of their renal arteries and to exclude adrenal adenomas. Patients were excluded if they had significant bilateral renal artery stenosis, bilateral renal artery stenting or a small renal artery diameter (<4 mm) bilaterally. Also, those with a secondary cause of hypertension were excluded.

Renal artery tortuosity index was calculated for each patient using the arc: chord ratio method, as described previously.

2.2 Renal artery denervation procedure

Renal artery denervation procedures were performed by an interventional cardiologist and a vascular surgeon, under conscious intravenous sedation using midazolam and fentanyl. Intra-arterial Heparin was administered in all cases at a dose of 50 units/kg. A 6 Fr (Symplicity) or 8 Fr (EnligHTN) sheaths were introduced into the right femoral artery for access. Selective right and left renal arteriograms using a 6 Fr LIMA guiding catheter (Symplicity) or an 8 Fr EnligHTN guiding catheter (EnligHTN) were performed to assess vessel anatomy for denervation suitability. Prior to RF application, a 200 mcg bolus of glyceryl trinitrate was administered into each renal artery to prevent arterial spasm. Radiofrequency ablations in a spiral fashion were delivered into each renal artery wall starting distally and using the clinically recommended settings for both systems (Table 1). A final arteriogram was performed at the end of ablation to exclude complications including severe spasms, perforation, or dissection. The femoral arterial access site was closed with a ProGlide closure device if suitable. The following day, patients were reviewed for any adverse events or complications and discharged home if well. All patients were advised to continue the same antihypertensive medications, unless advised otherwise by their treating cardiologist or nephrologist.

2.3 Follow-up

Data including office BP, antihypertensive medications, and adverse events including dizziness or postural hypotension, readmission with malignant hypertension, stroke or transient ischemic attack (TIA), cardiac events and all-cause mortality were collected through phone communication with patients or from clinic and medical record review. Each patient had multiple follow-ups to record BP measurements at different time-points. Office BP measurements were recorded by the treating doctors on follow-up. Mean office BP was determined during the short-term and long-term follow-up periods for each patient.

2.4 Outcomes

The primary endpoint was overall change in office BP from baseline in the short-term follow-up. Secondary outcomes included; change in office BP in the long-term follow-up and the difference in office BP reduction between the Symplicity and the EnligHTN groups during the two follow-up periods. Secondary outcomes relating to safety included peri-procedural complications and long-term adverse events (cardiac events, stroke or TIA, and death from any cause).

2.5 Statistical analysis

Statistical analyses were performed in SPSS 24 (IBM Corp., Armonk, NY, USA) and S-PLUS 8.2 (TIBCO software Inc., Palo Alto, CA, USA)

**TABLE 1** Summary of the clinical parameters for the Symplicity and EnligHTN renal denervation systems

| System parameters | Symplicity | EnligHTN |
|-------------------|------------|---------|
| Monitoring        | Temperature and impedance based algorithm | Temperature controlled algorithm |
| Number of electrodes | 1 | 4 |
| Maximal power delivered (W) | 8 | 6 |
| Maximal temperature at electrode tip (°C) | 70 | 75 |
| Duration of each ablation (sec) | 120 | 90 |
statistical software. Baseline characteristic for the two groups were compared using independent sample t-tests for continuous variables and Chi Square tests for categorical variables. Two-tailed tests with a significance level of 5% were used throughout. Data for baseline characteristics were expressed as the mean ± standard deviation.

Linear mixed effect models were used to investigate the changes in SBP and diastolic blood pressure (DBP) post procedure during short-term and long-term follow-up periods, and to test for association (interaction) between the effect of time (three-level factor, pre-op baseline, short-term follow-up and long-term follow-up) and system (two-level factor). Linear mixed effect models were also used to test for association between the effect of time and each of the baseline or procedural covariates including baseline SBP, heart rate, body mass index (BMI), ablation time, ablation number, and tortuosity index. Patient identifier was considered as a random effect and the time factor as both a fixed effect and as a random effect with a general positive definite covariance structure. The procedural or baseline covariates and their two-way interactions with the time factor were considered as fixed effects. Parameter estimates (estimated mean) and their 95% confidence intervals (95% CI) were used to quantify the changes observed in both follow-up periods.

3 | RESULTS

3.1 | Study population

The study population baseline characteristics are summarized in Table 2. A total of 43 patients were followed up for a median of 32.93 months (IQR 29.43–42.87). For the total cohort, mean baseline office SBP was 174 ± 20 mmHg and mean baseline office DBP was 94 ± 16 mmHg. There was no significant difference in baseline office BP between the Symplicity and EnligHTN groups (Table 1). In both groups, patient enrolment rates were greater for males than females but not significantly different between groups (P = 0.4). Overall, there was no significant difference in baseline characteristics including risk factors between the two groups.

3.2 | Procedural parameters

Based on anatomical variation including vessel length and diameter, 4–12 RF ablations were delivered into each renal artery. Total ablation duration was similar between the two groups despite the longer duration per ablation with Symplicity system. This was due to the overall greater number of ablations in the EnligHTN group compared to Symplicity (Table 3). Four patients in total had unilateral denervation (one from the Symplicity group and three from the EnligHTN group). Reasons for unilateral denervation included difficult anatomy with failure to engage the vessel (n = 1), presence of previous renal artery stent unilaterally (n = 1), and a small renal artery diameter (≤3.5 mm) on one side (n = 2). Accessory renal arteries were present in five patients (one from the Symplicity group and four from the EnligHTN group). No ablation was performed in accessory renal arteries. Table 3 summarizes the procedural parameters for both groups.
In total, 33 patients (76.7%) had changes to their antihypertensive medications by their final follow-up. Half of the patients (53.6%) had a total decrease in medications number or dose, with or without class change, five patients (11.6%) had an increase in the number of antihypertensive medications, and five patients (11.6%) had a class change only.

### 3.4 | Outcomes

#### 3.4.1 | Overall blood pressure reduction from baseline

For the entire study population, there was a significant reduction in both systolic and diastolic office BP within all follow-up periods (Figure 1B,C).

Mean change in office BP from baseline was $-19.70/ -11.86$ mmHg (95% CI (SBP/DBP): $[-30.08, -9.34]/[-17.14, -6.58]$, $P < 0.001$ for SBP and DBP) and $-21.90/ -13.94$ mmHg (95% CI: $[-28.38, -15.43]/[-17.14, -6.58]$, $P < 0.001$ for SBP and DBP) for short-term and long-term follow-up, respectively.

No association between the change in office SBP and baseline or procedural characteristics including heart rate, BMI, ablation duration, ablation number, and tortuosity index was found ($P = 0.33, 0.06, 0.17, 0.68,$ and $0.24$ for association with each covariate, respectively). The only significant association was seen between baseline office SBP and the change in office SBP at 1 year ($P < 0.001$).

![FIGURE 1](image-url)  
**Figure 1**  
Number of antihypertensive medications per system at baseline and at each follow-up period (A). Scatter plot of office BP at baseline and both follow-up time points for the total cohort of patients. (B) SBP and (C) DBP. Change in BP from baseline for Symplicity and EnligHTN groups at each follow-up time point, (D) SBP, (E) DBP.
3.4.2 | Blood pressure reduction per system

There was no significant difference in post-procedural BP change between Symplicity and EnligHTN groups during any follow-up period (difference of −8.96/−1.23 mmHg, 95% CI (SBP/DBP): [−30.86, 12.93]/[−12.61, 10.16], P = 0.42 for SBP, P = 0.83 for DBP, and −9.56/−7.68 mmHg, 95% CI: [−22.39, 3.27]/[−15.89, 0.52], P = 0.14 for SBP, P = 0.07 for DBP), for short-term and long-term follow-up, respectively. With respect to the EnligHTN group, mean change in office BP was not statistically significant during the short-term follow-up (−15.51 mmHg, 95% CI: [−32.53, 1.50], P = 0.07). However, the change in office SBP became significant at the long-term follow-up (−17.34 mmHg, 95% CI: [−26.23, −8.45], P < 0.001). Mean change in office DBP was −12.23 mmHg (95% CI: [−15.90, −4.56], P < 0.001) and −10.23 mmHg (95% CI: [−21.34, −3.12], P = 0.01) for short-term and long-term follow-up, respectively.

3.4.3 | Safety outcomes

All RAD procedures were performed safely with no major procedural complications. Minor complications included femoral hematoma managed conservatively in three patients (7%) and transient contrast nephropathy in a single patient who had mild renal impairment at baseline. Eight patients reported symptoms of postural hypotension on follow-up, and four patients had readmissions with hypertensive episodes. There was one case of recurrent stroke at 9 months and 45 months. Three patients had hospital admission for myocardial infarction and there were two mortalities of unknown cause. Table 4 summarizes procedural complications and adverse events for both groups.

4 | DISCUSSION

In this study, RAD resulted in a significant BP reduction within the first year, which persisted up to 4 years post procedure in our total cohort of patients who underwent the procedure using two different RF systems. When assessing each treatment group independently, mean reduction in office SBP from baseline was significant at all follow-up periods for the Symplicity group. While mean reduction in office SBP for the EnligHTN group did not achieve significance within the short-term follow-up. A delayed effect on SBP occurred over the long-term follow-up. This could be due to increased lesion depth achieved with Symplicity Flex (3.8 mm) compared to EnligHTN (3.4 mm) as demonstrated in our previous work using the phantom model, given that both systems were tested under identical conditions including vessel diameter, flow rate and with optimal electrode contact.11 Nonetheless, there was no significant difference in office systolic or diastolic BP reduction between the Symplicity and the EnligHTN group at any follow-up period. The lack of significant between-group differences in BP reduction may suggest a class effect of various RAD devices, whereby adequate injury to efferent and afferent nerve fibers was attained by both systems. Alternatively, it could be explained by the small number of patients in this study. Therefore, a larger study may be required in order to detect significant differences between the two systems.

Notably, the reduction in BP was not associated with an increase in the number of antihypertensive medications (Figure 1A). In fact, half of the total cohort had a reduction to the number or the dose of their antihypertensive medications. Thus, the BP reduction is unlikely to be related to medications.

The Symplicity HTN-3 trial also used Symplicity Flex; however, inadequate operator training and lack of experience in performing RAD had resulted in a high failure rate for achieving bilateral circumferential ablation (74% of cases).6 Therefore, it is likely that denervation in these cases was unsuccessful. While the Symplicity Flex may deliver greater heat energy penetration, catheter manipulation to achieve adequate contact and a circumferential ablation pattern is technically challenging, and thus requires rigorous training and greater operator experience compared to multi-electrode based systems. The primary proceduralist in our study had extensive experience in RF ablation and catheter manipulation.

Furthermore, it is still unclear what extent of denervation is required to result in a desired clinical response. In a subset of patients (n = 10) who underwent assessment of noradrenaline spillover (marker for efferent sympathetic nerve activity) in the Symplicity HTN-1 trial, there was a 47% reduction in noradrenaline spillover at 15–30 days post RAD, confirming the mechanistic effect of ablation on suppression of sympathetic activity. Mean reduction in office BP at 6 months in this subgroup was 22/12 mmHg,1 suggesting that ablation to achieve a target noradrenaline spillover of about 50% could be

| Complications and adverse events | Symplicity | EnligHTN | Total | p-value |
|----------------------------------|------------|----------|-------|---------|
| Femoral hematoma                 | 1 (5%)     | 2 (8.70%)| 3 (7%)| 0.64    |
| Contrast nephropathy             | 0          | 1 (4.35)| 1 (2.33)| 0.35    |
| Length of stay (days)            | 1.05 ± 0.22| 1.74 ± 1.68| 1.40 ± 1.26| 0.08    |
| Postural hypotension             | 3 (15%)    | 5 (21.74%)| 8 (18.60%)| 0.57    |
| Readmission with hypertension    | 2 (10%)    | 2 (8.70%)| 4 (9.30%)| 0.88    |
| Cardiac events                   | 3 (15%)    | 0        | 3 (7%)| 0.05    |
| Stroke or TIA                    | 1 (5%)     | 0        | 1 (2.33%)| 0.28    |
| Mortality                        | 0          | 2 (8.70%)| 2 (4.65%)| 0.17    |

Abbreviation: TIA, transient ischemic attack.
an adequate endpoint of long-term functional denervation. A post-mortem study demonstrated that for nerve fibers found within 10 mm depth from the renal artery intima, between 50% and 75% of fibers occurred at a depth between 2.44 and 4.28 mm in the main vessel. Therefore, both systems could cause injury to >50% but ≤75% of nerves providing that ablation is performed optimally by ensuring consistent electrode contact and energy delivery in a circumferential pattern along the artery wall.

The newer multi-electrode Symplicity Spyral is likely to offer a greater ablation consistency. However, it was found to have less heating depth than Symplicity Flex. Therefore, injury to 50% of nerve fibers may not be achievable when ablation is performed in the main vessel using Symplicity Spyral. Hence, RF ablation distal to the bifurcation in addition to the main vessel is now recommended when utilizing Symplicity Spyral, as nerve fibers are located closer to the intima in the branches compared to the main vessel.

Patient selection is another important factor that influences the clinical efficacy of RAD. In our study, the only factor that was associated with BP response within 1 year was office SBP at baseline. Nonetheless, it has become evident that patients with combined systolic and diastolic hypertension (SBP > 140 mmHg and DBP > 90 mmHg) respond better to RAD compared to those with isolated systolic hypertension (ISH). This is likely owing to the coexistence of arterial stiffness in patients with ISH. Increased arterial stiffness as measured by invasive pulse wave velocity was found to be a negative predictor of denervation response. Nonetheless, when stratifying patients with ISH according to their pulse wave velocity tertiles, those in the low tertile were found to have significant BP reduction after RAD, which was comparable to those with combined systolic and diastolic hypertension. Therefore, arterial stiffness is likely to play a significant role in confounding the outcomes of RAD in this subgroup of patients, because the mechanism of hypertension may be complicated by the influence of structurally mediated vascular dysfunction, rather than, or in combination with vascular dysfunction mediated by sympathetic overstimulation. Therefore, not all those with ISH should be excluded from RAD.

Finally, as reported in major clinical trials our study illustrates that RAD remains a safe procedure with low periprocedural complication rates.

5 | LIMITATION

There are several limitations to our study. First, this was a non-randomized comparison of a small patient cohort from a single center without a sham control arm. However, the two groups were matched in all baseline characteristics. In addition, the sham effect was absent in recently published sham-controlled trials including the SPIRAL HTN and RADIANCE-HTN SOLO. Second, no assessment of ambulatory BP at baseline and at follow-ups was carried out, which could lead to inclusion of patients with pseudoresistance and white-coat syndrome. Furthermore, all Symplicity procedures were performed first, followed by EnlighTHN procedures consecutively. This could lead to bias, favoring the EnlighTHN system, as the proceduralist was more experienced by that stage. Nonetheless, the primary operator is an experienced interventionalist and electrophysiologist who is very familiar with RF ablation.

Moreover, longer follow-up period was available for Symplicity patients compared to EnlighTHN. However, no difference in BP reduction was found between the two systems even when analysis was limited to 1 year. Finally, medication reduction during the study period could potentially mask treatment effect. Therefore, it is difficult to demonstrate superiority of one system over the other; however, this study demonstrates non-inferiority.

6 | CONCLUSION

Although the two RAD systems did not differ significantly, they have shown an overall reduction in office BP between selected timelines compared to baseline measurements. Our study further supports the role of RAD in treating appropriate patients with resistant hypertension.

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CONFLICT OF INTEREST

P. Qian and M Barry are inventors of a microwave catheter for renal artery denervation. The intellectual property is owned by the University of Sydney and Westmead Hospital. Australian Patent AU2015902225 issued December 6, 2015. J Swinnen received an unconditional grant from Medtronic for a drug eluting balloon study in restenosis of the native hemodialysis access fistula (2014–2017). The other authors have no conflict of interests.

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