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PERIPHERAL VASCULAR DISEASE

Original Studies

Blood pressure lowering with alcohol-mediated renal denervation using the Peregrine infusion Catheter is independent of injection site location

Felix Mahfoud MD[1] | Stefan Bertog MD[2] | Lucas Lauder MD[1] | Michael Böhm MD[3] | Axel Schmid MD[4] | Wojciech Wojakowski MD[5] | Helen Parise ScD[6] | Tim A. Fischell MD[7] | David E. Kandzari MD[8] | Atul Pathak MD[9] | Alexandre Persu MD[10] | Horst Sievert MD[2,11,12,13]

[1]Department of Internal Medicine III, Cardiology, Angiology, Intensive Care Medicine, Saarland University Medical Center, Homburg, Germany

[2]Department of Medicine, CardioVascular Center Frankfurt, Frankfurt, Germany

[3]Klinik für Innere Medizin III, Saarland University Hospital, Homburg, Germany

[4]Institute of Radiology, Universitätsklinikum Erlangen, Erlangen, Germany

[5]Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland

[6]Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, Connecticut, USA

[7]Ablative Solutions, Inc., Wakefield, Massachusetts, USA

[8]Interventional Cardiology, Piedmont Heart Institute, Atlanta, Georgia, USA

[9]Department of Cardiovascular Medicine, Princess Grace Hospital, Monaco, Monaco

[10]Division of Cardiology, Cliniques Universitaires Saint-Luc and Pole of Cardiovascular Research, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium

[11]Faculty of Medical Science, Anglia Ruskin University, Chelmsford, UK

[12]University of California San Francisco UCSF, San Francisco, California, USA

[13]Yunnan Hospital Fuwai, Kunming, China

Correspondence
Felix Mahfoud, Department of Internal Medicine III, Saarland University Hospital, IMED, Geb. 41, Kirrberger Strasse 1, 66421 Homburg/Saar, Germany.
Email: felix.mahfoud@uks.eu

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Abstract

Objectives: The current analysis utilized core laboratory angiographic data from a prospective, single-arm, open-label, multi-center feasibility study to ascertain whether the location of alcohol infusion within main renal arteries during renal denervation (RDN) had an impact on the BP-lowering effect at 6 months.

Background: The influence of the location of alcohol infusion during RDN, within the main renal artery (proximal, middle, or distal), on the magnitude of the blood pressure (BP) lowering is unstudied.

Methods: The Peregrine Catheter was used to perform alcohol-mediated RDN with an infusion of 0.6 mL of alcohol per artery as the neurolytic agent in 90 main arteries and four accessory arteries of 45 patients with hypertension.

Abbreviations: ABP, Ambulatory blood pressure; BP, Blood pressure; CTA, Computed tomography angiography; HTN, Hypertension; LS, Least squares; MRA, Magnetic resonance angiography; RDN, Renal denervation; RF, Radiofrequency; SEM, Standard error of the mean.

Results: No relationship between the site of alcohol infusion and change from baseline in both office systolic and 24-hour systolic ambulatory BP (ABP) at 6 months was observed. When analyzed at the artery level, the least squares (LS) mean changes ± SEM from baseline to 6 months post-procedure in 24-hour systolic ABP when analyzed by renal arterial location were −11.9 ± 2.4 mmHg (distal), −10 ± 1.6 mmHg (middle), and −10.6 ± 1.3 mmHg (proximal) (all $p < 0.0001$ for change from baseline within groups). The results were similar for office systolic BP. There was no difference between treated locations (proximal is reference).

Conclusion: In this post-hoc analysis, the location of alcohol infusion within the main renal artery using the Peregrine system, with alcohol as the neurolytic agent for chemical RDN, did not affect the magnitude of BP changes at 6 months.

KEYWORDS
angiography, hypertension, renal artery

1 | INTRODUCTION

Catheter-based renal denervation (RDN) has been studied using radiofrequency (RF),[1] ultrasound ablation,[2] and perivascular alcohol injection (chemical denervation),[3] respectively. Anatomical studies of kidney sympathetic nerve innervation have shown that the nerve fiber localization vary along the length of the renal artery with nerves located closer to the intimal surface distally, and with a deeper more distant distribution of nerves proximally.[4–7] This has posed challenges for RDN utilizing RF, as RF ablation has a usual penetration depth of approximately 4–7 mm from the electrode contact on the intimal surface of the renal artery, suggesting that a relevant portion or number of the nerve fibers in the proximal and middle renal artery may be missed.[8–11] As a result, recent RF RDN techniques have focused on distal renal artery and branch treatment, which reduces variability and improves response rates.[10–12]

Chemical RDN uses alcohol to target the renal nerves located in the adventitial space and results in a circumferential ablation, with approximately 8–10 mm depth with a single infusion.[13,14] Based upon pre-clinical data, we hypothesized that the features of chemical-RDN would be adequate to perform sufficient ablation to result in blood pressure (BP) lowering, even when the treatment was performed in the more proximal locations of the main renal artery, independent of the site ablation infusion location (proximal, middle, or distal).[13] The current analysis utilized core laboratory angiographic data from the prospective, single-arm, open-label, multi-center feasibility study[3] to ascertain whether the location of alcohol infusion had an impact on the BP-lowering effect at 6 months.

2 | METHODS

Data were analyzed from the previously published, prospective, single arm, open label, multicenter trial ($N = 45$) intended to collect early feasibility, safety, and efficacy data of the Peregrine Catheter (Ablative Solutions, Inc., San Jose, CA), to perform alcohol-mediated (bilateral) RDN with an infusion of 0.6 mL of alcohol/artery.[3] Written informed consent was obtained from patients before any study-related procedures were conducted.

2.1 | Procedure

Renal duplex ultrasound was performed in all patients at baseline and at 6-months post-procedure to evaluate renal vascular safety by looking for potential flow-limiting stenosis (core laboratory: VasCore, MA). Imaging by magnetic resonance angiography (MRA) or computed tomography angiography (CTA) was performed for baseline assessment of existing anatomical abnormalities of the renal arteries. Images were assessed by an independent core laboratory (Cardiovascular Core Analysis Laboratory, Stanford University, Stanford, CA).

The RDN procedure was performed without administration of general anesthesia, and with minimal conscious sedation using a seven French guiding catheter introduced to both renal arteries via the femoral artery using fluoroscopic guidance. Interventionalists were generally advised to perform the ablation in the middle segment of the main renal artery. The neurolytic agent (0.6 mL of undiluted alcohol) was infused over 1–2 min through the infusion lumen of the catheter to enhance the uniform diffusion of the alcohol. After treatment of the first renal artery, the device was removed, inspected for patency and flushed with heparinized saline. The contralateral renal artery was then engaged, and the same procedure was performed.

2.2 | Anatomical parameters

Renal artery anatomical parameters were assessed from the baseline CTA/MRA and from the procedural fluoroscopic angiogram, which included renal artery length, mean distance from ostium to infusion site, mean diameter at the infusion site, and diameter stenosis.

2.3 | Statistical methods

The 6-month office systolic BP and 24-hour ambulatory systolic blood pressure (ABP) change (vs. baseline) were analyzed in relation to the location of alcohol infusion, evaluated by the core lab data (the core lab was blinded to the BP results). Segments of the renal arteries in terms of distance from the ostium to the bifurcation (assessed during the angiographic procedure) were designated as proximal (first third of the distance), middle (second third of the distance), and distal (final third of the distance). Categorization of proximal, middle, and distal segments of main renal artery were then scored on a per patient level as follows:

- −1: if all arteries (including accessory arteries) were treated proximally
- −0.5: if at least one was proximal and the remaining were middle or proximal
- 0: if all were middle or one was distal and one was proximal
- 0.5: if at least one was distal and the remaining were middle or distal
- 1: if all arteries were treated distally

To avoid bias, these definitions and the scoring system for infusion location were defined prior to data analysis. The location was used to evaluate the relationship of infusion location with reductions in office systolic BP (responders with BP change ≥ 10 mmHg) and 24-hour mean systolic ABP (responders with BP change ≥ 5 mmHg) at 6 months. Linear regression of change in systolic BP (office and 24-hour ABP), versus average distance from ostium to site of alcohol infusion, versus the percentage of renal artery length calculated as distance from ostium to treatment site/distance from ostium to bifurcation, and versus location score were conducted. At the patient level, continuous variables are presented as means and standard deviation (SD), while categorical variables are presented as frequency and percentages. Plots of continuous variables were reviewed and did not appear to deviate substantially from normality. As the location of infusion was measured for each artery, and arteries are nested or clustered within each subject, artery-level analyses were also conducted using the generalized estimating equations (GEE) approach to the linear regressions where each artery was included as its own observation and the correlation of arteries within subject were accounted for via compound symmetry. In this model, a score or an average distance was not created as location (proximal/mid/distal) and distance were analyzed per artery. From the GEE model, the least squares (LS) means and standard error of the means (SEM) were provided. Missing data were excluded from the analysis. Patients with one or more missing parameters were included for those parameters that were measured. For patient averaged distances and location, if data were missing for one artery, the remaining artery was used as the "averaged" data. *P*-values are presented as descriptive in nature. A p-value < 0.05 was considered significant without adjustment for multiplicity. Analyses were conducted in SAS Version 9.4.

3 | RESULTS

Baseline and demographic characteristics of subjects who participated in this study and procedural parameters have been described in detail previously.[3]

A total of 90 main renal arteries and four accessory arteries in 45 subjects were treated (5 [6%] proximally, 54 [62%] in the middle location, and 28 [32%] distally; location data were missing for seven renal arteries (Table 1).

As reported previously[3] the mean 24-hour ABP reduction at 6 months post-procedure versus baseline was −11 mmHg [95% CI: −15,-7] for systolic and − 7 mmHg [−9, −4] for diastolic (p < 0.001 for both). Office systolic BP was reduced by −18/10 mmHg [−25,−12/−13,−6] at 6 months.

For all renal arteries, the subject-averaged mean (SD) renal artery length was 33.9 (9.6) mm, the mean distance from the ostium to the infusion site was 20.2 (6.6) mm, the mean (SD) infusion location as a percentage of renal artery length (distance from ostium to infusion site/renal artery length) was 59.6 (12.4)%, the mean (SD) renal artery diameter was 5.3 (0.8) mm, and the mean (SD) location of infusion score was 0.3 (0.4) (Supplementary Table 1). The most proximal infusion location was 5 mm distal to the renal artery ostium, and the most distal infusion 1 mm away from the branching of the distal portion of the main renal artery. Representative angiographic images of the Peregrine catheter deployed in proximal, middle, and distal segments of the renal artery are presented in Figure 1. Procedural fluoroscopic renal vasculature parameters were similar between ABP and office BP responders. The subject-averaged mean (SD) renal artery length for ABP non-responders and responders, respectively was 38.9 (9.8) mm and 32.5 (8.7) mm, the mean distance from the ostium to the infusion site was 22.4 (6.2) mm and 19.6 (6.8) mm, the mean (SD) infusion location as a percentage of renal artery length was 59.0 (11.3)% and 59.1 (12.8)%, the mean (SD) renal artery diameter was 5.1 (0.8) mm and 5.4 (0.8), and the mean (SD) location of infusion score was 0.3 (0.3) and 0.3 (0.5) (Supplementary Table 1). The results were similar when considering office BP responders (Supplementary Table 2).

At 6-months of follow-up, 44 and 43 subjects had valid office, and ABPM data available, respectively. There was no relationship between average distance from the ostium to the site of alcohol infusion and the change from baseline in both office systolic and 24-hour systolic ABP at 6-months. This was also the case for the relationship between the BP change from baseline (office and 24-hour ABP) at 6 months and distance measured as the percentage of renal artery length (Supplementary Figure 1). In addition, there was no relationship between the change from baseline in both office systolic and 24-hour systolic ABP at 6 months when the treatment location score of the alcohol infusion was examined (Figure 2).

The least squares (LS) mean changes ± SEM from baseline to 6 months post-procedure in office systolic BP when analyzed by discrete renal arterial location were −22.2 ± 4.7 mmHg (distal, $n = 27$, $p = 0.82$ vs. proximal), −16.4 ± 2.3 mmHg (middle, $n = 53$, $p = 0.20$ vs. proximal), and −23.7 ± 5.5 mmHg (proximal, $n = 5$, Table 2). The LS mean changes ± SEM for 24-hour systolic ABPM were −11.9

TABLE 1 Summary of procedural fluoroscopic angiogram (Core Lab)

	Total mean ± SD (*N*) or %(*n*/*N*)	Averaged mean ± SD (*N*) or %(*n*/*N*)	Left renal artery mean ± SD (*N*) or %(*n*/*N*)	Right renal artery mean ± SD (*N*) or %(*n*/*N*)
Treated	94	45	45 (Main)/2 (Accessory)	45 (Main)/2 (Accessory)
All renal arteries				
Renal artery length[a]	34.1 ± 12.6 (89)	33.9 ± 9.6 (45)		
Distance from ostium to infusion site	20.3 ± 8.3 (89)	20.2 ± 6.6 (45)		
Diameter at infusion site	5.2 ± 1.0 (90)	5.3 ± 0.8 (45)		
Infusion location as percentage of renal artery length (ostium to infusion/RA length)	60.1 ± 15.8 (87)	60.1 ± 12.3 (45)		
Location of infusion score[b]	0.3 ± 0.6 (87)	0.3 ± 0.4 (45)		
Location of infusion[c]				
Proximal	5.7% (5/87)		2.3% (1/43) / 100% (1/1)	2.3% (1/41) / 50% (1/2)
Middle	62.1% (54/87)		67.4% (29/43) / 0% (0/1)	61.0% (25/41) / 0% (0/2)
Distal	32.2% (28/87)		30.2% (13/43) / 0% (0/1)	34.1% (14/41) / 50% (1/2)
Main renal arteries				
Renal artery length[a]	33.3 ± 11.9 (86)	33.4 ± 9.5 (45)	30.8 ± 10.6 (44)	35.9 ± 12.7 (42)
Distance from ostium to infusion site	20.2 ± 8.3 (86)	20.2 ± 6.5 (45)	18.3 ± 7.3 (44)	22.2 ± 9.0 (42)
Diameter at Infusion Site	5.3 ± 0.9 (87)	5.3 ± 0.8 (45)	5.4 ± 0.8 (44)	5.2 ± 1.0 (43)
Accessory renal arteries				
Mean renal artery length[a]	56.2 ± 12.0 (3)	56.2 ± 12.0 (3)	50.74 ± .(1)	59.0 ± 15.6 (2)
Mean distance from ostium to infusion site	22.6 ± 9.2 (3)	22.6 ± 9.2 (3)	15.74 ± .(1)	26.0 ± 9.9 (2)
Mean diameter at infusion site	3.7 ± 0.5 (3)	3.7 ± 0.5 (3)	3.14 ± .(1)	4.0 ± 0.0 (2)
Renal artery diameter[d]				
Proximal minimum			5.8 ± 1.1 (44)	5.5 ± 1.2 (44)
Proximal maximum			6.1 ± 1.1 (44)	6.0 ± 1.1 (44)
Middle minimum			5.4 ± 0.9 (43)	5.2 ± 0.9 (44)
Middle maximum			5.8 ± 1.0 (43)	5.5 ± 1.0 (44)
Distal minimum			5.4 ± 1.1 (42)	5.1 ± 0.8 (44)
Distal maximum			5.7 ± 1.1 (42)	5.5 ± 1.0 (44)

Abbreviations: *N*, number of subjects with sub-group of responders/non-responders; *n*, number of patients within each infusion site category; RA, renal artery; SD, standard deviation.

[a]Measured as distance from ostium to bifurcation.

[b]Infusion Score ranges from −1 (all arteries treated proximally) to +1 (all arteries treated distally).

[c]Segment of main renal artery (distance from ostium to bifurcation); distal: first third, middle: sending third, and proximal: final third.

[d]Parameters measured during the screening CTA/MRA.

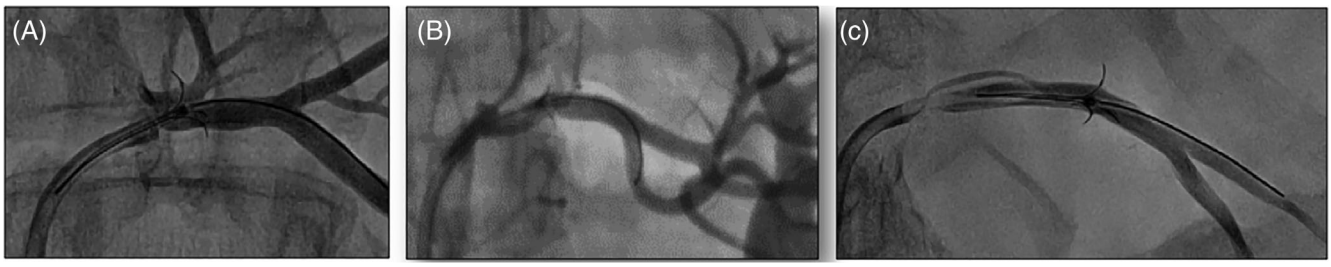

FIGURE 1 The Peregrine Catheter inserted and needles deployed at proximal, middle, and distal segments of the renal artery. Needle deployment in the proximal (panel A), middle (panel B), and distal (panel C) segments of the renal artery

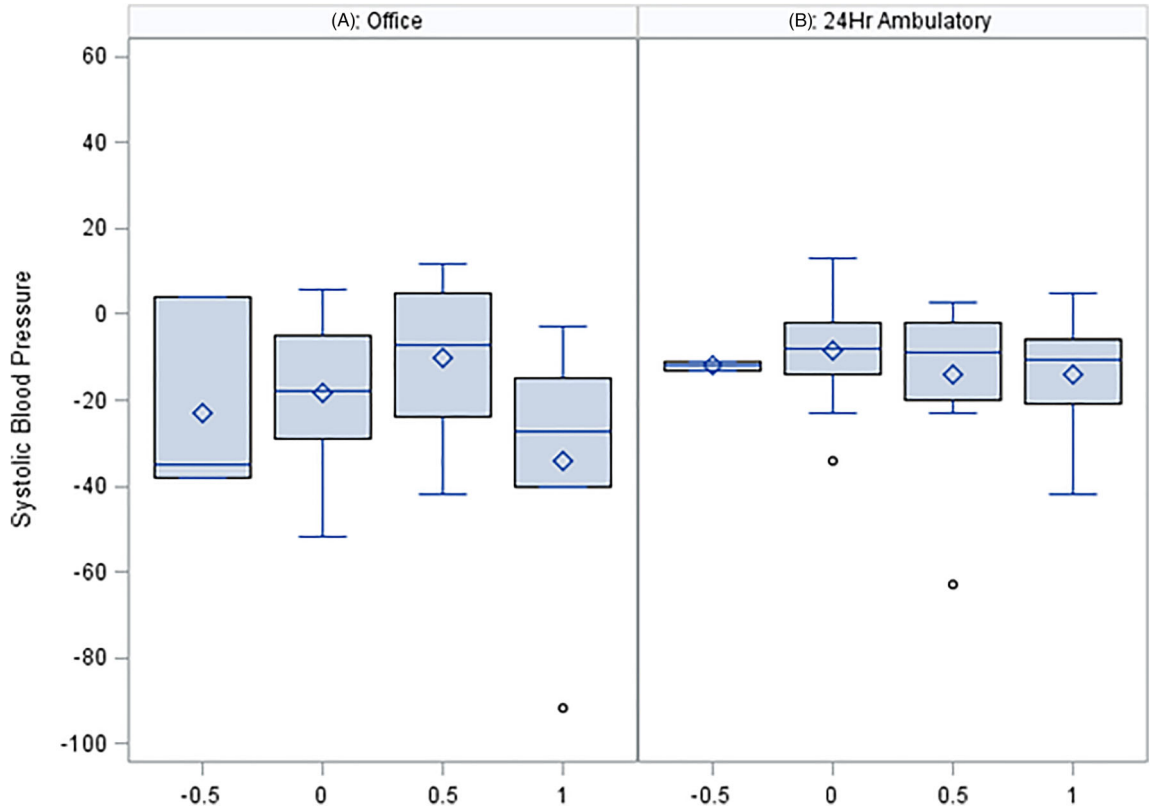

FIGURE 2 Linear regression of change in BP (as a continuous variable) versus location score (patient averaged). Main renal artery location of infusion score −1: if both arteries were treated proximally; −0.5: if one was proximal and one was middle; 0: if both were middle or one was distal and one was proximal; 0.5: if one was distal and one was middle; 1: if both arteries were treated distally

TABLE 2 Generalized estimating approach to the analysis of blood pressure (office and 24-hour ambulatory) versus renal artery location of renal denervation

	Change in office systolic blood pressure (mmHg) from baseline to 6-months[a]				Change in 24-hour systolic ambulatory blood pressure from baseline to 6-months (mmHg)			
Location[b]	Least squares mean	Standard error	p^c	p^d	Least squares mean	Standard error	p^c	p^d
Distal	−22.2	4.7	<0.0001	0.82	−11.9	2.4	<0.0001	0.4
Middle	−16.4	2.3	<0.0001	0.20	−10.2	1.6	<0.0001	0.77
Proximal	−23.7	5.5	<0.0001	-	−10.6	1.3	<0.0001	-

Note: Each main artery is treated separately and the correlation of arteries within a subject is properly accounted for.
[a]Post-procedure.
[b]Segment of main renal artery (distance from ostium to bifurcation); distal: first third, middle: second third, and proximal: final third.
[c]*i*-value for testing of the hypothesis that the change from baseline to 6-months within each location is different from zero.
[d]*i*-value for testing the difference in the change from baseline between locations (distal vs. proximal and middle vs. proximal, proximal is reference).

± 2.4 mmHg (distal, $n = 26$, p = 0.40 vs. proximal), −10 ± 1.6 mmHg (middle, $n = 51$, p = 0.77 vs. proximal), and − 10.6 ± 1.3 mmHg (proximal, Table 2). The diameter of the renal artery at the alcohol infusion site was similar among office BP and ABP non-responders and responders.

The analyses of the baseline and procedural predictors versus office BP and ABP response at the subject level revealed that only type II diabetes mellitus and baseline 24-hour systolic ABP were predictors of office systolic BP response (type II diabetes mellitus: odds ratio [OR] (95% confidence interval [CI]) 0.25 (0.07 to 0.95); $p = 0.041$; baseline 24-hour systolic ABP 0.95 (0.903–0.996); $p = 0.035$) (Supplementary Table 2). Only baseline body mass index (BMI) was a predictor of 24-hour systolic ABP change (OR 0.88 [0.77–1.0]; $p = 0.047$). Also, the presence of an untreated accessory artery was not a predictor of either office or 24-hour systolic ABP ($n = 7$; OR [95% CI]) 3.64 [0.39–34.21], $p = 0.26$; 2.2 [0.23–21.11]; $p = 0.49$) (Supplementary Table 1). There was no evidence of a difference by site conducting the procedure.

4 | DISCUSSION

A number of technologies, including RF, ultrasound, and chemical ablation, are under investigation for RDN in patients with uncontrolled hypertension. All of these approaches have device-specific features that relate to the distribution of target nerve ablation. In this study, we found that the BP-lowering effects of alcohol-mediated RDN using the Peregrine catheter for drug delivery, appears to be independent of the location of ablation in the renal artery (proximal, middle, and distal) unlike RF RDN.

A recent study comparing RF RDN restricted to the main renal artery with versus treatment applied to the distal branches, beyond the main bifurcation, demonstrated a statistically significant greater decrease in 24-hour mean systolic ABP in the "distal" therapy group compared with main renal artery treatment (-22.6 ± 20.0 vs. -9 ± 18.7 mmHg, $p < 0.05$).[15] Histological analysis of ablated nerves in a porcine model demonstrated that a single electrode RF ablation affects approximately 25% of the circumference of the artery. Furthermore, histomorphometry and computational modeling illustrated that RF treatments directed at large accompanying veins resulted in incomplete ablation and suboptimal efficacy. Accounting for measured nerve distribution patterns and the annular geometry of the artery, revealed that total ablation area and circumferential coverage were the prime determinants of renal denervation efficacy, with increased efficacy at smaller diameters.[16] Therefore, it has been suggested that ablation would be required in four quadrants of the renal artery in order to provide complete, circumferential nerve ablation.[17] With RF RDN, however, nerves in the proximal and even middle portions of the main renal artery are less amenable to ablation due to the limited penetration depth. Preclinical data indicate that the distribution of injury, rather than 'depth', is important for successful RDN, since it is highly dependent upon the microanatomy with heat sinks and tanks.[11,18] This is supported by clinical evidence suggesting that RDN performed in the main renal artery only is associated with limited BP reductions when compared with main and branch treatment.[5]

These findings are further supported by evidence from the RADIOSOUND-HTN study, a 3-arm, single-blind trial conducted in 120 patients with resistant hypertension who were randomized to either (1) RF RDN of the main renal arteries, (2) RF RDN of the main renal arteries, side branches, and accessories, or (3) endovascular ultrasound–based RDN of the main renal artery. Results of the primary endpoint analysis (change in daytime systolic ABP at 3 months post-treatment) demonstrated that ultrasound-based RDN, which has presumably greater depth of ablation than RF, was found to be superior to RF ablation of the main renal arteries only, whereas a combined approach of RF ablation of the main arteries, accessories, and side branches was not.[19]

RDN using alcohol as the neurolytic agent facilitates a deep and circumferential nerve ablation of the main renal artery.[13,14] The current study suggests that alcohol-mediated RDN results in clinically meaningful decreases in office systolic BP and 24-hour systolic ABP irrespective of the treatment location (proximal/middle/distal). Similarly, the responder and non-responder rate, using either office systolic BP or 24-hour systolic ABP, was not influenced by the infusion location. In this post-hoc analysis, few baseline characteristics were found to predict BP response, i.e. absence of type II diabetes mellitus and higher baseline 24-hour systolic ABP were associated with subsequent reductions in office systolic BP and lower baseline BMI was associated with 24-hour systolic ABP reductions. The presence of a small and untreated accessory artery was not predictive for future BP change.

4.1 | Limitations

The present analysis was post-hoc in nature and the study was not initially designed or powered to assess the impact of treatment location on outcomes. The predictors of response analyses were not adjusted for multiplicity and the corresponding p-values for baseline parameters that were predictors of BP response were close to the error probability of 5%. The current study was open label in design and was conducted in a small number of patients, so data should be interpreted with caution and regarded as hypothesis-generating.

5 | CONCLUSION

The relative location of alcohol infusion within the main renal artery using the Peregrine system for chemical RDN, did not affect the magnitude of BP lowering at 6 months. Further study will be required from the larger, randomized, sham-controlled clinical trials to validate the concept that the location of ablation has no impact on BP lowering when using chemical denervation.

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CONFLICT OF INTERESTS

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Felix Mahfoud https://orcid.org/0000-0002-4425-549X
Lucas Lauder https://orcid.org/0000-0003-1434-9556

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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