Efficacy and Safety of Catheter-Based Radiofrequency Renal Denervation in Stented Renal Arteries

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Background—In selected patients with hypertension, renal artery (RA) stenting is used to treat significant atherosclerotic stenoses. However, blood pressure often remains uncontrolled after the procedure. Although catheter-based renal denervation (RDN) can reduce blood pressure in certain patients with resistant hypertension, there are no data on the feasibility and safety of RDN in stented RA.

Methods and Results—We report marked blood pressure reduction after RDN in a patient with resistant hypertension who underwent previous stenting. Subsequently, radiofrequency ablation was investigated within the stented segment of porcine RA, distal to the stented segment, and in nonstented RA and compared with stent only and untreated controls. There were neither observations of thrombus nor gross or histological changes in the kidneys. After radiofrequency ablation of the nonstented RA, sympathetic nerves innervating the kidney were significantly reduced, as indicated by significant decreases in sympathetic terminal axons and reduction of norepinephrine in renal tissue. Similar denervation efficacy was found when RDN was performed distal to a renal stent. In contrast, when radiofrequency ablation was performed within the stented segment of the RA, significant sympathetic nerve ablation was not seen. Histological observation showed favorable healing in all arteries.

Conclusions—Radiofrequency ablation of previously stented RA demonstrated that RDN provides equally safe experimental procedural outcomes in a porcine model whether the radiofrequency treatment is delivered within, adjacent, or without the stent struts being present in the RA. However, efficacious RDN is only achieved when radiofrequency ablation is delivered to the nonstented RA segment distal to the stent. (Circ Cardiovasc Interv. 2014;7:813-820.)

Key Words: hypertension resistant to conventional therapy ■ renal artery obstruction ■ renovascular hypertension

The efficacy of contemporary revascularization therapies in the treatment of renal artery stenosis (RAS) to treat hypertension is still under debate, as a relevant proportion of patients remain uncontrolled after the procedure.1–4 Nevertheless, RA stenting is still used in selected patients, and the currently accepted indications for revascularization are significant RAS with progressive or acute deterioration of renal function and uncontrollable hypertension, and recurrent flash pulmonary edema.5,6 For patients in whom optimal medical management fails to control hypertension, percutaneous catheter-based renal denervation (RDN) has shown to reduce both office and 24-hour blood pressure (BP) in certain patients.7–12 Because patients with previous RA revascularization have been excluded from published studies,8,10 current guidelines do not recommend RDN in such patients.13,14 To date there are only limited data on the efficacy and safety of RDN by delivery of radiofrequency energy in stented vessels,15–17 and the parameters involved in successful RDN in an artery confined within a stent are unknown. Herein, we report on a patient with resistant hypertension and previous RA revascularization who underwent RDN and showed a marked reduction in BP. Subsequently, we conducted a preclinical study aimed to evaluate the safety and efficacy of RDN using a radiofrequency catheter system (Symplicity Flex; Medtronic Inc, Santa Rosa, CA) in previously stented porcine RA.

Methods

Catheter-Based RDN in a Patient With Previous RA Stenting

The patient was informed of the experimental approach and gave written informed consent. Catheter-based RDN was performed at the Saarland University Hospital as described previously.15 Renal angiography was performed via femoral access and RA denovo or in-stent stenosis (left side) was excluded. The treatment catheter (Symplicity

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WHAT IS KNOWN

- Catheter-based renal denervation (RDN) has been developed as a new treatment modality for patients with resistant hypertension.
- Patients with previous renal artery stenting have been excluded from published RDN trials and the use of radiofrequency (RF)-based RDN in previously stented renal arteries is not known.

WHAT THE STUDY ADDS

- Using a swine model, RF ablation of previously stented porcine renal arteries demonstrated that RF-based RDN provides equally safe experimental procedural outcomes whether the RF treatment is delivered adjacent to or without stent struts being present in the renal artery.
- RDN in a stented segment did not achieve functional reduction in sympathetic nerve activity, suggesting that RF ablation must be delivered distally (>5 mm) in a nonstented segment of the stented artery.

Design of the Experimental Study

All animal studies were performed in accordance with the guide for the care and use of laboratory animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). All animal experiments were performed at Synchrotron Laboratories (Durham, NC) and adhered to the Guide for the Care and Use of Laboratory Animals under an approved Institutional Animal Care and Use Committee protocol, in compliance with the Animal Welfare Act and the Food and Drug Administration Regulations and their amendments. The study was designed to compare renal nerve ablation within the stented artery segments and radiofrequency ablation distally to the stented area, as well as comparison with the radiofrequency ablation of nonstented RAs in male (castrated) or female (nulliparous) Yorkshire Domestic Farm swine, weighing between 35 and 50 kg. Specifically, 29 to 30 days before radiofrequency catheter ablation using the Symplicity Flex system (Medtronic) groups 1 to 3 were stented using the Hippocampus Renal Rx Stent System (Medtronic): (1) radiofrequency in-stent group: 6 RAs (3 animals) underwent deployment of the renal stents bilaterally with each RA receiving 2 stents, overlapping or nonoverlapping, depending on vessel length, to allow for a complete coverage of the RA (eg, covered from the ostium to 5 mm from the bifurcation); (2) radiofrequency distal to stent group: 6 RAs (3 animals) underwent deployment of the renal stents with each RA receiving only 1 stent positioned at the RA ostium; (3) stent-only group: 12 RAs (6 animals) were stented for control purposes, with no subsequent radiofrequency ablation; (4) radiofrequency-only group: 12 arteries (6 animals) underwent radiofrequency ablation only; (5) naive group: 12 arteries (6 animals) served as complete naive vessels with no stent or radiofrequency ablation treatments. Although the procedures for the radiofrequency in-stent treatment and distal to stent treatment were performed >2 different weeks, control animals were included at both times to insure matching animals in all groups.

Stenting Before Radiofrequency Ablation

The targeted vessels were evaluated via angiography before renal stent placement, during deployment and poststent deployment. All stented animals were allowed 29 to 30 days for healing and re-endothelialization.

Procedural Description of Radiofrequency Ablation and Follow-Up

The designated ablation groups were treated with the Symplicity Flex Catheter System, which delivered radiofrequency energy to the treated arterial wall. Radiofrequency treatment was performed in 6 RAs that had received 2 stents with complete coverage of the RA (radiofrequency in-stent group) and 6 RAs that had received 1 proximal stent (radiofrequency distal to stent group), as well as 12 nonstented controls (radiofrequency-only group). Once angiography was performed, the RDN catheter was advanced into both RAs and sequential treatment ablations were performed. For arteries with 2 stents encompassing the entire main RA, ablations occurred only within the stented segment of the artery. For arteries stented with 1 proximal stent, ablations were performed starting in the distal artery and moving toward the aorta, to no closer than 5 mm distal to the stent. For the nonstented control arteries, treatment was performed with the first ablation starting 5 mm proximal to the bifurcation, treating distally to proximally until the ostium was reached over the length of the whole artery. A total of 14±1 days after the radiofrequency ablation treatments were performed, all test animals underwent follow-up angiography to check for vessel patency, and tissues were collected from all animals (including the naive animals) after termination of histopathologic and bioanalytical analysis.

Determination of Renal Norepinephrine

The tissue samples were obtained from each kidney adjacent to those taken for axon density and kept frozen at ~80° C. The samples were homogenized in 0.4 mol/L perchloric acid and centrifuged to give a clear supernatant, and the supernatants were analyzed for norepinephrine content by high-performance liquid chromatography. Quantitative determination of norepinephrine was performed using high-performance liquid chromatography as follows; a mobile phase solution was run with the samples using the following parameters: Dionex WPS-3000TBS set at 4°C pump and autosampler, ESA Coullochem III detector, Phenomenex Gemini C18, 5-μm 150x3.0 mm column at a flow rate of 1 mL/min and average run time of 16 minutes.

Functional Sympathetic Nerve Quantification

The function of the renal sympathetic nerves was assessed by quantitative immunohistochemistry at 2 levels: (1) viability of renal nerves distal to treatment and (2) density of terminal axons in the renal cortex. Fresh sections from the 2 most distal blocks of each RA and 8 tissue samples from each kidney were cut on a rotary microtome at 5 to 6 μm. All sections were stained immunohistochemically for tyrosine hydroxylase (TH) as an indicator of functional and viable sympathetic nerves. All sections were digitized by scanning on Aperio ScanScope AT and saved as whole slide images. The number of intact (TH positive) and ablated (TH negative) renal nerves were assessed on the whole slide images by Aperio ImageScope software and customized positive pixel count algorithm. The percentage of affected nerves around the distal RAs was expressed as % nonfunctional nerve area (ie, the TH-negative area). The comparative evaluation is presented as percentage of functional area, representing the relationship between structural non-neuronal elements of the nerve (such as Schwann cells...
and stroma), which are typically negatively stained, and the viable sympathetic nerves in the evaluated area are stained positively. In a similar manner, terminal sympathetic axons were quantified in the renal cortex as density of positive staining in the observed sections.

**Statistical Comparisons of Functional End Points**

Differences in renal norepinephrine concentration, the percentage Functional Area and Axonal Density were evaluated by Kruskal–Wallis with Dunn Multiple Comparison test. \( P \) values for all multiple comparisons were 2 sided, and values obtained from different tissues of the same animal were considered independent for statistical purposes. Differences in procedural parameters were calculated with 1-way ANOVA with Tukey multiple comparison test.

**Results**

**Clinical Observations: Effect of RDN in a Patient With Resistant Hypertension and Previous RA Stenting**

The patient was a 61-year-old, severely hypertensive male despite maximally tolerated medical therapy with a history of resistant hypertension with left ventricular hypertrophy and coronary artery disease. Because of hemodynamically significant RAS, he underwent PTA and stenting of the left RA 18 months ago. However, BP remained uncontrolled after the procedure. Despite adherence to full-dose antihypertensive treatment with an angiotensin receptor blocker (candesartan 32 mg once daily), an angiotensin-converting enzyme inhibitor (ramipril 10 mg once daily), a \( \beta \)-blocker (metoprolol 95 mg twice daily), a loop diuretic (torasemide 10 mg once daily), a central sympatholytic (moxonidine 0.3 mg twice daily), and an \( \alpha \)-blocker (doxazosine 2 mg twice daily) office BP at baseline was 215/108 mm Hg with a 24-hour BP of 167/98 mm Hg. Aldosterone antagonists and calcium channel blockers were not tolerated. The patient underwent catheter-based RDN of both RAs with radiofrequency ablations distal to the stented segment (>5 mm). There were no procedural or periprocedural complications. At 6-, 12-, and 24-month follow-up, office BP was 153/91, 139/73, and 141/76 mm Hg, respectively. Ambulatory BP decreased to 157/90 and 145/86 mm Hg at 12- and 24-month follow-up, respectively. Renal duplex ultrasound was performed at each follow-up visit, and significant in-stent or denovo stenosis was excluded. Renal resistive indices in the right and left kidney were 0.67/0.71, 0.70/0.69, 0.69/0.70, and 0.65/0.65 at baseline, 6-, 12-, and 24-month follow-up. Renal function measured by cystatin C glomerular filtration rate remained unchanged during the follow-up (baseline, 68.7 mL/min; 24-month follow-up, 70 mL/min).

**Experimental Observations in Pigs**

The Table summarizes the resulting procedural parameters for the respective treatment groups. No complications occurred after any radiofrequency ablation treatments, and all arteries were observed to have good blood flow without any apparent angiographic abnormalities. The mean duration of radiofrequency ablation in control, nonstented vessels was 118±4 s. When radiofrequency energy was delivered distal to the stent, the recorded duration of radiofrequency ablation was similar and consistent (120 s per ablation point) to the radiofrequency-only group, indicating that the treatment was completed according to the prescribed generator algorithm. In the radiofrequency distal to stent group, the decrease in number of ablations per artery, and therefore total ablation time per procedure, was because of the limited length of the nonstented portion of the artery (Table; 5.2±0.7 versus 7.8±0.8 ablations/artery in radiofrequency-only group; \( P<0.001 \) and 622 versus 931 s total ablation time in the radiofrequency-only group; \( P<0.001 \)). When radiofrequency ablation was performed within the stent struts (radiofrequency in-stent), the conditions for successful radiofrequency energy could not be consistently completed because of the procedure termination by the generator when rapid heating was detected by the safety algorithm. This resulted in a decreased mean duration of ablation time of 48±25 s per single lesion (\( P<0.001 \)) and reduction of the total ablation time to 450 s, when compared with 118 s mean ablation duration and 931 s total ablation time in the radiofrequency-only group (\( P<0.001 \)). The increased number of ablations per artery in the radiofrequency in-stent group (9.3±1.7 versus 7.8±0.8 in radiofrequency-only group; \( P=0.027 \)) represents a compensation attempt to maximize the possible radiofrequency ablation in this treatment group. The number of successful full durations in the radiofrequency in-stent group was significantly less than the mean number for the radiofrequency-only and radiofrequency distal to stent groups (2.2±1.8 versus 7.8±0.9 versus 5.2±0.7; \( P \) for all <0.001).

**Comparative Arterial Histopathology**

Histopathologic characteristics of the stented RAs and the healing attributes related to the radiofrequency treatment within or distally to the stent struts were observed. At 44±2 days after stenting (and at 14 days postradiofrequency treatment, in respective radiofrequency-treated groups), all stented arteries had patent lumens and all stents were fully incorporated with neointimal growth (see representative images in Figure 1A and 1B). The neointimal growth was generally well organized and composed of dense circumferentially layered smooth muscle cells. The luminal surfaces were all covered with endothelium. The radiofrequency-exposed wall of the treated arteries showed no dissections or thrombosis associated with radiofrequency treatment.

<table>
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<th>Table. Procedural Details Between the Groups</th>
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<td>Treatment</td>
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<tr>
<td>Naive (no treatment, n=12)</td>
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<tr>
<td>Stent only (no ablation, n=12)</td>
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<tr>
<td>RF only (n=12)</td>
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<tr>
<td>RF distal to stent (n=6)</td>
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<td>RF in-stent (n=6)</td>
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*Significantly different from RF only (\( P<0.001 \)).
†Significantly different from RF only (\( P=0.027 \)) and RF distal to stent (\( P<0.001 \)).
‡Significantly different (\( P<0.001 \)) from RF-only and RF distal to stent groups.
Histopathology: Radiofrequency Treatment Effects

Figure 1C and 1D shows representative images depicting radiofrequency-affected areas in the perivascular space of the RAs from radiofrequency-only, radiofrequency in-stent, and radiofrequency distal to stent treatment groups. The radiofrequency-damaged nerves manifested variably degrees of inflammatory response, fibrosis, and atrophy depending on level of section and arm. Although the radiofrequency-affected nerves in the radiofrequency-only and radiofrequency distal to stent groups encompass multiple bundles spanning around the lesion, the radiofrequency-affected nerves within the ablated stented area in the radiofrequency in-stent group were shallow and were adjacent to the vessel wall (Figure 1C and 1D).

Figure 2 shows quantitative summary of comparative histological evaluation of vascular and perivascular tissues and the nerves in the RAs from the radiofrequency-only, radiofrequency distal to stent, and radiofrequency in-stent groups. The artery was divided and evaluated in 9 to 15 consistent segments depending on artery length, oriented from the proximal end of the RA toward the distal end (Figure 2A). Optically scanned and digitized histological sections were digitally annotated and mapped to outline the thermally affected areas and the affected nerves within the histological sections (lesion maps). The thermal ablation zones (Figure 2B) shown in the highlighted areas around RAs remain in close proximity of the artery when radiofrequency is applied to a stented artery segment without expanding deeper into the perivascular space, whereas the ablation zone propagates outward into the adventitia/perivascular space and around a nonstented segment of artery, involving nerves within the resulting thermal ablation field (Figure 1C and D).

Comparative Nerve Pathology

Figure 2C further outlines the longitudinal artery histopathology from serial artery sections after radiofrequency ablation in the radiofrequency-only, radiofrequency in-stent, and radiofrequency distal to stent groups. The depth of the radiofrequency treatment effect is denoted by the linear graph in Figure 2C, and it correlates spatially and functionally with the subsequent nerve pathology that is manifested across the corresponding segments of the RA. The nerve pathology at the radiofrequency ablation site is denoted by the fibrosis score (scale of 0–4), whereas the distal effects of the radiofrequency ablation are denoted by the nerve atrophy score (scale of 0–4; Figure 2C). In the radiofrequency-only group, the nerve fibrosis associated with direct thermal injury is manifested largely in sections with the greatest depth of thermal injury, eg, in segments (levels) 1 to 9 and is consistent with the systematic electrode advancement through the length of the RA during treatment. In the radiofrequency distal to stent group, the nerve fibrosis is clustered in the distal segments (levels 6–11), consistent with the distal thermal electrode positioning. In contrast, the terminal nerve atrophy resulting from the radiofrequency ablations is observed in segments distal to the zones of direct thermal injury (levels 6–11) with the radiofrequency-only group and in segments 8 to 15 in RAs from radiofrequency distal to stent group (Figure 2C). Radiofrequency ablations performed within the stented artery segments resulted in a relatively limited degree of direct thermal injury and fibrosis, and subsequently little resulting nerve atrophy (Figure 2C).

Functional Effect on the Sympathetic Nerves

The quantitative summary for the percentage of functional area of the renal nerves in radiofrequency in-stent and radiofrequency distal to stent treatment groups when compared with radiofrequency-only, stent-only, and naive controls is shown in Figure 3. The greatest reduction in the viable sympathetic nerves along the RAs was observed in the radiofrequency-only and radiofrequency distal to stent groups relative to naive controls (67% and 53% relative reduction, P <0.001) but not when the treatment was applied within the stented segment. Quantification of norepinephrine revealed a significant decrease in concentration relative to naive tissues when radiofrequency ablation was applied with the radiofrequency-only and radiofrequency distal to stent groups (−93% and −87% when compared with naive, P <0.001 and P=0.021, respectively) but not when the treatment was applied within the stented segment. Quantification of norepinephrine revealed a significant decrease in concentration relative to naive tissues when radiofrequency ablation was applied distal to the implanted renal stent or to the nonstented vessel (radiofrequency distal to stent, 91% decrease when compared with naive; P<0.001 and radiofrequency-only, 90% decrease when compared with naive; P<0.001; Figure 3C). A small, nonsignificant decrease in renal norepinephrine was seen when radiofrequency ablation was applied within the stented segment (P=0.40 versus naive).
Discussion

RA stenting in patients with RAS often fails to control BP to target values. Catheter-based RDN has been developed as a new treatment modality for patients with resistant hypertension. For potential efficacy and safety concerns, patients with previous RA stenting have been excluded from published RDN trials. However, it is essential to determine the feasibility of RDN for patients with previously stented RAs, who are scheduled to undergo a RDN procedure for the treatment of uncontrolled hypertension as data on the use of radiofrequency-based RDN in previously stented RAs were limited. Herein, we were able to demonstrate that RDN with radiofrequency ablations performed distal to stented segments is safe and effective in both, a clinical observation in a patient with resistant hypertension despite stenting of RAS and a preclinical investigation in pigs.

Whenever radiofrequency ablation was performed within the stented vessel portion, the parameters for continuous successful radiofrequency energy delivery from the generator could not be achieved because of premature termination from high impedance and temperature readings during treatments by the safety algorithm. Thus, the duration of ablation time per individual radiofrequency application in the radiofrequency in-stent group was substantially decreased by 60% because of the early termination (48 s per radiofrequency application when compared with 118 s/radiofrequency application in nonstented, treated controls) and only an average of 2.2 from an average of 9.3 radiofrequency ablations were delivered completely (Table). In an attempt to compensate and achieve utmost possible radiofrequency ablations in the radiofrequency in-stent group, an increased number of ablations per artery group (9.3 versus 7.8 in the radiofrequency-only group; \( P=0.027 \); Table) were performed. Given that the temperature readings at the distal tip of the catheter are integral algorithm components within the generator system to insure that the RA is not exposed to unsafe treatment parameters, these findings emphasize that areas covered by stent struts should not be treated with radiofrequency energy. However, when radiofrequency treatment was delivered >5 mm distally to stent struts, there was no interference with radiofrequency treatment, which was successfully completed without triggering any system alerts. In agreement, the recorded duration of radiofrequency ablations was similar to those of nonstented arteries (120 s/lesion when compared with 118 s/lesion in nonstented treated controls; Table).

It is apparent from the histology that radiofrequency treatment in a native RA or distal to a renal stent results in direct thermal injury to multiple nerves extending deep into and

Figure 2. Pathology of renal nerves. A, Schematic representation of the segmentation system used for the histological evaluation. B, Representative lesion maps indicating nerve inclusion and orientation, size, and shape of the radiofrequency (RF) induced; green areas indicate renal artery cross section, yellow areas thermally ablated tissue, red areas renal nerves. C, Longitudinal pathology of renal nerves; groups include ablation only, ablation distal to stent, and ablation within renal stent.
around the electrode contact point into the perivascular space, with subsequent atrophy and functional reduction of renal sympathetic nerves. In contrast, treatment within the stented area results in a shallow radiofrequency effect range adjacent to the vessel wall with significantly fewer nerves affected. Longitudinal assessment of radiofrequency ablation affected sections across multiple segments of treated RAs shows that radiofrequency ablation performed distal to the stent and performed to nonstented arteries had comparable effect on the perivascular nerve viability (Figure 3). These data reveal that RAs ablated distal to a stent had axonal damage consistent with the application of radiofrequency treatment and that the scale and extent of the downstream nerve atrophy in this group were comparable with nonstented arteries treated with radiofrequency energy.

The functional assessment of sympathetic denervation in the kidney, using TH efferent sympathetic nerves staining and a bioanalytic evaluation of norepinephrine generation (Figure 3) reveals comparable outcomes for radiofrequency ablation without stenting and with radiofrequency treatment applied distally to the stent when compared with naive or stent-only groups. It is particularly remarkable that an average of only 5.2 ablations per artery in the radiofrequency distal to stent group and an average of 7.8 ablations in the radiofrequency-only group produced a comparable degree of sympathetic nerve ablation, suggesting an ablative saturation effect at ≈5 circumferential ablative lesions per artery in this model system. Because the ablations performed distal to stent were confined to the distal portion of the RA, it is possible that the distal treatment optimized access to the renal nerves as their close proximity to the RA increases in frequency at the distal end of the main RA. Potentially, this phenomenon may, in part, explain why the Symplicity HTN-3 trial did not find a significant reduction in BP because an adequate number of distal ablations may not have been performed.19 The histological presence of atrophied nerves distal to already radiofrequency-treated segments of arteries suggests that further radiofrequency treatment performed in artery segments with largely atrophied nerves may yield little therapeutic gain although additional studies are required to clarify this observation quantitatively. Radiofrequency treatment in stented segments did not result in effective nerve damage, indicated by no significant changes in renal nerve viability and axonal density. In line, norepinephrine content in the kidneys was
not significantly reduced after in-stent radiofrequency ablation and the reduction was far less pronounced when compared with radiofrequency-only (−90%) or radiofrequency distal to stent (−91%). The concept of temperature input to the operational algorithm of the system was intended to prevent potentially harmful thermal damage to the RA specifically. Although such heating could also ablate nerves in the proximity of the stent, such measures are clearly not warranted because treatment in a position distal to the stent is highly effective in safely ablating renal nerves, as demonstrated by the reduction in norepinephrine. The reduction in kidney norepinephrine after radiofrequency treatments confirms renal sympathetic nerve impairment and substantiates the functional connection between sympathetic nerve injury and distal atrophy, cortical sympathetic axon depletion, and subsequent reduction in renal norepinephrine production.

Limitations
RDN studies conducted in porcine models assume that similar renal nerve anatomy and function provide a reasonable simulation to the intended patients. Although this seems reasonable, some debate remains about the precise location and depth of renal sympathetic nerves in humans, consequently this question remains unresolved and deserves further investigations. The RAs in young, healthy swine may be different from the RAs of the likely human recipient of RDN treatment with regard to atheroma, calcification, mechanical compliance, length, and tortuosity. In addition, these parameters may also differ in hypertensive swine or humans. As a result of this difference, absolute effectiveness of radiofrequency-mediated ablation should be viewed as optimal in the porcine model and may be affected by disease and anatomic limitations in the human setting.

Conclusions
A clinical observation in a resistant hypertensive patient with previous RA stenting and a detailed analysis evaluating radiofrequency ablation of previously stented porcine RAs demonstrated that radiofrequency-based RDN provides equally safe experimental procedural outcomes in a porcine model whether the radiofrequency treatment is delivered adjacent to or without stent struts being present in the RA. To achieve an efficacious RDN procedure in a stented artery and functional reduction in sympathetic nerve activity, these data suggest that radiofrequency ablation must be delivered distally (>5 mm) in a nonstenosed segment of the stented artery.

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