Cardiovascular Revascularization Medicine 20 (2019) 2–3

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Continued Momentum in Catheter-Based Renal Denervation: The More the Merrier—Better Denervation Wins Again☆

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In this issue of CRM, Petrov et al. have provided further evidence of the safety and efficacy of catheter-based renal denervation (RDN) for the treatment of poorly-controlled hypertension [1]. These results support the concept that the completeness of the renal denervation plays an important role in achieving meaningful blood pressure (BP) lowering. Indeed, the results from their study suggest that with a monopolar catheter, with 20.4±3.9 ablations in the main and branch vessels in humans ("Y" technique), one can achieve substantial, and clinically meaningful, reductions in office and ambulatory systolic BP.

The concept of main renal artery plus distal branch denervation using radiofrequency (RF) ablation is not new. This was inspired by limited human data and porcine data that was highlighted after the failure of the SYMPLICITY HTN 3 trial [2]. These data, describing the spatial distribution of renal sympathetic nerves, demonstrated that a significant number of renal sympathetic nerve fibers were out of range for RF ablation in the main renal artery [3–9]. As many as 50% of the sympathetic nerve fibers may reside at depths of greater than 3 mm from the intimal surface, particularly in the more proximal segments of the renal artery [3–7]. A single RF ablation may also only ablate an arc of only ~30-40^0 in humans, further limiting the completeness of denervation when using less than 6-8 ablations per side, and requiring precise "spiral" electrode placement in all quadrants [7]. These are limitations for RF technologies, whether they are spiral multi-electrode arrays, image guided, or even sensing and image guided, "smart" systems, etc. These observations suggested that successful, and more complete, denervation with RF catheters would likely require additional ablations in the branch vessels where the nerve fibers come closer to the intimal surface [3–9].

This concept has helped to build momentum in the space with the Medtronic SPYRAL program, using a four-electrode catheter that may be better suited for branch vessel denervation. This device has been used successfully in patients, both off medication and on medications, in two randomized, sham controlled trials, with ~44-46 RF ablations per patient, and with ablation in both the main vessel and branch vessels, compared to the ~8 ablations in the main vessel only in the original SYMPLICITY HTN 3 trial [2,10,11]. The current study once again demonstrates that with RF as the treatment modality, denervation in the branch vessels enhances the BP lowering effect [1].

There are several other important observations from this current study, and from other recent published studies, that also support the notion that the completeness of the denervation is an important predictor of efficacy [12–15].

First, there are the observations from the Kandzari's post hoc analysis of the SYMPLICITY HTN 3 trial [15]. This report suggests that there was inadequate denervation, with only 4.2 ablations/artery, and <5% of the patients receiving at least four ablations, and ablations in each of the four anatomic quadrants. With both a lack of depth and a lack of circumferential ablation, it is likely that there was as little as 10-25% denervation in many subjects. Importantly, there was evidence of a "dose-response," with substantial BP lowering among the relatively few patients in the study who received more aggressive denervation, by virtue of numerous (>14-16) RF ablations. [15].

In the current study [1] the ambulatory systolic BP lowering effect was profound, and greater than the BP lowering effects seen in a similar "on-med" population in the SPYRAL "On-Med" study. If this difference is real, and not related to bias or poor control of medications, there may be an explanation.

Although rarely discussed, the depth and arc of ablation with RF is related to the pressure or force and surface area of the electrode against the intimal surface, electrode irrigation or lack thereof (Spyral is non-irrigated), as well as the duration of the ablation [16–18]. That is, not all ablations are created equal. With the original Medtronic monopolar "flex" catheter that was used in the current study, one can push and flex the catheter to get better electrode-to-intima contact and, potentially, a greater depth and/or arc of ablation. In contrast, the Spyral catheter has a passive self-expansion method of engaging the electrode (s) against the intima, which may be more (time) efficient but may reduce electrode contact and potentially lessen the depth of ablation. Although provocative, this effect, combined with a shorter ablation time, may explain the difference between the current results of -22 mmHg systolic ambulatory systolic BP drop ("Y" treatment) in the current study [1] versus the -9 mmHg seen in a similar cohort in the SPYRAL "On-Med" study [10], despite more than twice the number of ablations in the SPYRAL "On-Med" study (n = 46 vs. 20 ablations).

In the current study, 12.0±3.0 ablations were performed per patient for the main vessel cohort, and 20.5±3.9 ablations for the "Y" treatment

☆ **Conflict of interest**: TAF is a co-founder, shareholder and officer of Ablative Solutions, Inc., Kalamazoo, MI and San Jose, CA.

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https://doi.org/10.1016/j.carrev.2018.12.009

(main + distal braches) cohort. It may also be relevant that these "ablations" were only counted as ablations if there was an angiographically apparent "notching" at the site of ablation. Although this may be tedious, with a 56-minute (mean) procedure time for the main vessel only and an 85-minute (mean) procedure for "Y" technique [1], this focus on placement, electrode pressure, and notching may have paid off with a better denervation, resulting in an impressive BP lowering effect. These criteria ("notching") were not applied in the HTN 3 trial, nor in the Spyral trials, and "notching" appears to be less apparent with the Spyral. Thus, in summary, there may be procedural and/or catheter related parameters that would suggest better denervation in the current study than in recent Spyral studies. Alternatively, this could be better operator technique, patient selection, or other biases favoring the outcome in the current study.

One other recent study may also suggest limitations of ablation using the Spyral catheter, even when used with the "Y-pattern" of ablation in the main and branch vessels [12]. In the RADIOSOUND trial, patients were randomized to Spyral RF ablation in the main vessel (17.2 (mean) ablations per patient) versus Spyral RF ablation in the "Y-pattern" in main and branch vessels (35.1 (mean) ablations/patient), versus circumferential and deep ablation using the Recor ultrasound thermal ablation catheter (6.4 (mean) ablations/patient; main vessel only). At three-month follow-up, the average daytime ambulatory systolic BP drop was statistically significant in all three groups compared to the baseline (-6.5, mmHg -8.3 mmHg and -13.2 mmHg, respectively). Despite the small sample size and despite using more than two times the number of main vessel RF ablations that were used in the original SYMPLICITY HTN 3 study (17 vs. 8 ablations), the ultrasound, deep and circumferential ablation in the main vessel only was statistically superior to Spyral RF in the main vessel (-13.2 mmHg vs. -6.1 mmHg, $p = 0.042$), and numerically superior to the ~35 ablations in the main + branch vessels using Spyral RF (-13.2 mmHg vs. – 8.3 mmHg). These data suggest a potential limitation of depth and arc of nerve ablation with passive outward expansion with the Spyral catheter, using a relatively short (30 second) ablation time.

Nonetheless, the positive message for the space is that more denervation, whether using 25-50 RF ablations in main plus branch vessels or using ultrasound thermal ablation in the main vessel, renal denervation does result in clinically meaningful reduction of systolic blood pressure (see Table 1).

It is possible that technologies that can achieve deep and circumferential ablation in the main vessel, such as ultrasound with medial cooling (Paradise™ System, Recor) or possibly, chemical denervation using alcohol (Peregrine™, Ablative Solutions) [19,20], may achieve more complete and predictable denervation than RF. Alternatively, performing at least 20-40 RF ablations in the main renal artery and the branch arteries coming off the main renal artery using the Spyral catheter may also achieve clinically meaningful BP lowering effects.

Finally, this paper also suggests the promise and advantages of a radial or brachial approach to RDN. With age, the effects of gravity gradually "pull down" the renal arteries such that the angulation of the takeoff from the renal artery from the aorta can be unfavorable when approaching from below (femoral approach). The advantage of the brachial and, eventually, radial approach, with longer RDN catheters, will be the ease of access to these downward takeoff renal arteries, which should make RDN easier, more efficient, and an outpatient procedure, looking to the future.

In summary, the current study, combined with the recent series of positive randomized controlled studies over the last 2 years, should encourage physicians and patients that RDN is safe and effective when it is performed carefully and completely, and studied rigorously [1,9,10,12–14,17]. We can look forward to the results from ongoing, upcoming, larger randomized trials that are underway to evaluate RF, ultrasound, and chemical denervation. Based upon the most recent feasibility studies, we should be optimistic that efficacy will improve as we get better at performing complete sympathetic denervation, in appropriately selected patients.

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