

Renal Artery Denervation:

A Brave New Frontier

Emerging therapies for treating patients with severe, treatment-resistant hypertension.

COMPILED BY KRISHNA J. ROCHA-SINGH, MD, FACC, FAHA, FSCAI, FSVM

Suboptimal blood pressure control is a leading cause of death globally and is responsible for 7 million deaths annually.¹ It is estimated that one in four adults worldwide are hypertensive, equating to nearly 1 billion people—a number that is expected to grow to nearly 1.5 billion by 2025.¹ Current therapeutic strategies center on lifestyle changes and pharmacologic interventions; however, the rates of blood pressure control and therapeutic efforts to reduce the rate of progression of hypertensive end-organ damage (resulting in myocardial infarction, stroke, and renal dysfunction) remain a neglected priority.²

Preclinical and human experiments have convincingly established the role of increased renal sympathetic nerve activity in the pathogenesis of hypertension.³ As such, renal denervation has been used successfully in a variety of experimental models.^{4,5} In humans, surgical denervation via splanchnicectomy in severely hypertensive patients was performed in the 1920s to 1930s.⁶ This radical approach to blood pressure control, which did not specifically target renal nerves, was ultimately abandoned due to associated perioperative complications. However, experience in renal transplantation, a procedure in which the renal nerves are selectively severed, suggests that the denervated kidney can maintain volume and electrolyte homeostasis.⁷ Based on these observations, the specific targeting of renal nerves as a major operative in the pathophysiology of hyperten-

The iterations of next-generation catheter designs, various energy and pharmacologic ablation sources, and the potential for a noninvasive approach are truly intriguing.

sion and other conditions associated with increased sympathetic activity (renal dysfunction and heart failure) appears to be an attractive therapeutic approach.

A new therapeutic paradigm of percutaneous renal artery denervation using the application of radiofrequency (RF) energy (Symplicity renal denervation system [Ardian, acquired by Medtronic, Inc., Minneapolis, MN]) has recently been demonstrated to be safe, effective, and durable in significantly reducing systolic blood pressure in patients with resistant hypertension. This initial success, coupled with the substantial unmet global need for successful resistant hypertension therapies, has led to the rapid emergence of several different modalities for renal artery denervation. In the following sections, several new and promising concepts for renal denervation are explained by company representatives.

EXTERNALLY APPLIED FOCUSED ULTRASOUND

Kona Medical

Michael Gertner, MD

Chief Executive Officer

Adjunct Associate Professor of Surgery, Stanford University

Renal nerve ablation, and by extension, regional and system-wide suppression of the sympathetic nervous system, has the potential to radically alter the treatment of hypertension and prevent associated mortality. In today's medical world, a procedural solution for hypertension, which would decrease costs, pharmaceutical burden for patients, and essentially enforce compliance, would be of enormous worldwide benefit.

Almost all current renal denervation devices require the intravascular manipulation of catheters to deliver energy, pharmaceuticals, etc. Specific therapies deliver pharmaceuticals through the arterial wall via micropuncture to reach the adventitia (eg, Mercator Bullfrog catheter [Mercator MedSystems, Inc., San Leandro, CA]). There are several limitations to these invasive approaches: (1) the expense and logistics of using a cath lab; (2) the requirement that all treatments be completed during a single procedure because multiple invasive procedures are not practical; (3) current devices only allow fluoroscopic visualization, not visualization of the target area, and therefore, the extent and thoroughness of the procedure cannot be fully assessed; and (4) only patients with highly resistant hypertension are considered for these invasive procedures.

KONA TECHNOLOGY OVERVIEW

Kona Medical (Campbell, CA) is attempting to address these limitations. The system delivers energy from outside the



Figure 1. Kona Medical noninvasive treatment system based on Doppler signals from the renal artery.

patient to the renal nerves. Ultimately, the procedure will be a “no puncture,” noninvasive technique, compatible with technologies that will allow for temperature and lesion mapping. A noninvasive procedure will allow titration of the therapy—that is, the application of patient-specific dose fractions while monitoring therapeutic effect in between fractions.

The basis of the technology is focused ultrasound, not high intensity (HIFU) as one might see and expect in the treatment of tumors, but low-intensity focused ultrasound (LIFU). The biologic underpinnings of this treatment are described in past literature for treating nerves using ultrasound.⁸ Nerves are particularly sensitive to mechanical vibration and heat. They are more sensitive to these energy modalities than the surrounding structures such as the artery; it is this differential effect that allows treatment of the nerves without damage to the blood vessel. The heat effect on nerves is well known, and the safety and efficacy of this approach is the likely basis of the Symplicity radiofrequency treatment.

ANIMAL AND HUMAN STUDIES

The effect of vibratory mechanical energy on nerves is less widely appreciated but adequately described in early literature in which focused and unfocused ultrasound was shown to permanently disable nerves without heating. An additional differential effect exists among the different types of nerves such as between myelinated and nonmyelinated, or efferent and afferent renal nerves, respectively. These differential effects are possibly due to the insulating ability of the myelin sheath and/or the interfacial effects of the ultrasound at various frequencies. Our preclinical studies are beginning to verify some of these underpinnings with respect to the renal nerves.

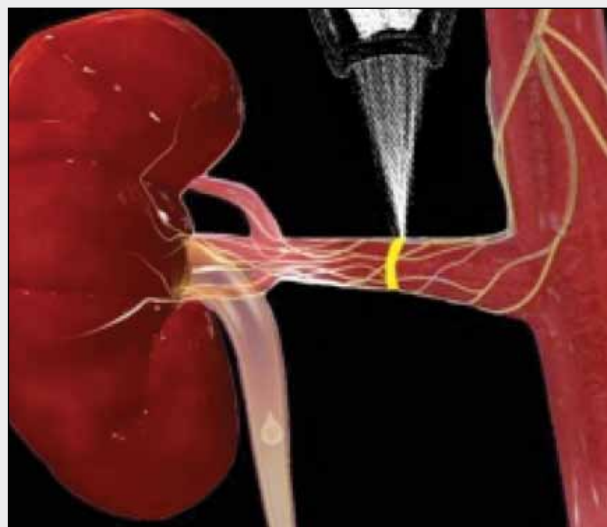


Figure 2. The concept of “outside-in” energy delivery to the renal nerves without instrumentation of the vessel.

To allow safe treatments, Kona is starting human studies with a targeting catheter, a sub-mm beacon that signals the exact spot of the artery for the ultrasound array to create a pattern around. The catheter allows characterization of the tissue paths and adds a “belt and suspenders” approach for the development of this fully noninvasive system.

Figure 1 shows the Kona noninvasive system. The system is depicted in a custom chair; another version of the system is compatible with a standard fluoroscopy or MRI table.

Both ultrasound (through elastography and the evolution of temperature mapping and MRI) allow further imaging and analysis of the treatment area. Figure 2 shows that the dose distribution surrounding the artery is that of an annular ring around the wall of the artery. Kona has shown in animal studies that a heat/vibratory cloud at one plane along the artery is highly effective at long-term inhibition of renal nerves with no visible effect on any portion of the artery at any time point.

THE TIVUS SYSTEM CardioSonic Ltd.

Ariel Svertdlik

Chief Technology Officer and Cofounder

CardioSonic's (Tel Aviv, Israel) solution for renal denervation is a high-intensity, nonfocused ultrasonic (US) catheter system named TIVUS (Therapeutic IntraVascular UltraSound) (Figure 3). By applying ultrasonic energy, the TIVUS technology enables remote, localized, controlled, and repeatable thermal modulation of the renal vessel wall tissue, resulting in safe renal nerve ablation. The remote thermal effect is located in the adventitia and perivascular region, with no thermal damage to the endothelium and media, therefore, preventing the development of vessel injury processes.

Use of the TIVUS catheter requires standard catheter-based interventional skills. The procedure requires no direct mechanical contact with the arterial wall, thereby minimizing potential damage to the vessel

intima. In preclinical studies, the TIVUS system has demonstrated a significant reduction of 50% in kidney tissue norepinephrine (NE) concentration, indicating effective renal nerve ablation. Histopathology of treated vessels shows no damage to the endothelium or media and no new hyperplastic lesions noted through 90-day follow-up.

TIVUS PRODUCT AND PROCEDURE OVERVIEW

The TIVUS system uses high-intensity, nonfocused ultrasound to facilitate percutaneous transluminal renal artery denervation. The system components are as follows: the 0.014-inch guidewire-based TIVUS catheter equipped with the CardioSonic proprietary ultrasound transducer, the TIVUS control console, and the 6-F flexible introducer sheath.

The single-use TIVUS catheter, which is highly flexible and torqueable, is advanced into the renal artery under fluoroscopic guidance and positioned within the vessel lumen. Real-time US feedback is provided to the operator, allowing for accurate positioning of the TIVUS device



Figure 3. The 0.014-inch guidewire-based TIVUS catheter positioned within the renal artery lumen through a 6-F flexible sheath. Note that the ultrasound-emitting element (positioned superiorly) does not make direct contact with the vessel wall (inset).

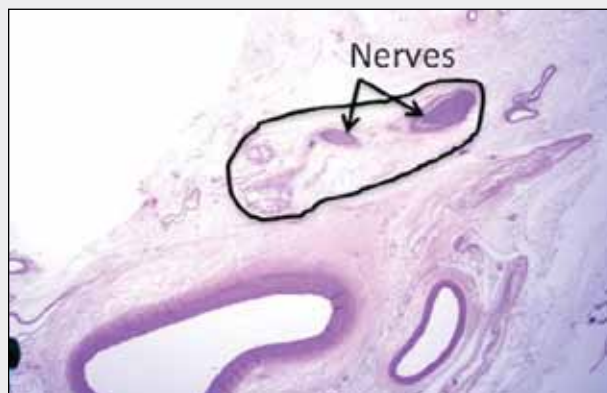


Figure 4. Hematoxylin and eosin histological section through the renal artery and surrounding adventitia 30 days post-treatment with the TIVUS catheter. Note that the renal intimal and medial layers are free of damage, whereas renal nerves in the adventitia (circled in black with arrows) show evidence of vacuolar degeneration consistent with nerve cell death.

to avoid contact with the arterial wall. At the desired longitudinal position within the renal artery, ultrasonic ablation is performed at specific circumferential locations. The TIVUS catheter is then removed and positioned in the contralateral renal artery, and the procedure is repeated. The total treatment time is anticipated to be < 10 minutes, and recovery time should be rapid. The anticipated outcome is a significant and sustained reduction in blood pressure.

PRECLINICAL RESULTS

A total of 80 acute and 20 follow-up studies on pigs have been performed to date, aimed at determining the optimal treatment parameters of energy delivery duration and intensity. Studies of kidney tissue NE concentrations at 30- and 90-day follow-up have demonstrated successful renal denervation as witnessed by a 50% or more decline in tissue NE.

Several TIVUS ablation points were performed along the same longitudinal arterial location; at 30- (Figure 4) and 90-day follow-up, no stenotic intimal lesions were evident on angiography or histopathology and demonstrated ablation of renal nerves.

POTENTIAL CLINICAL ADVANTAGES

TIVUS is a percutaneous catheter-based technology, which may offer substantial ease of use and shortened procedure times compared to the currently available modality, with a total treatment duration estimated to be 5 minutes per renal artery. Other potential clinical advantages include easy catheter positioning and navigation, which provides immediate online safety feedback (eg, ultrasonic energy is not applied if vessel wall contact is present); precise control on the thermal effect location and application of variable levels of thermal modulation of the target tissues; real-time information on the direction and location of the applied energy and spatial orientation of the therapeutic catheter tip; treatment of early bifurcating renal arteries with short treatment segments; and real-time blood temperature feedback (energy application is terminated if blood temperature is unsafely elevated). The localized damage to the nervous tissue at the treatment site suggests that minimal pain may be caused by this treatment. Additionally, TIVUS is a potential platform technology that could be applied to other clinical applications requiring directional and localized tissue thermal modulation/ablation, without damage to the blood vessel wall.

PARADISE TECHNOLOGY

ReCor Medical, Inc.

Mano Iyer

President and Chief Executive Officer

ReCor Medical, Inc. (Ronkonkoma, NY) has developed a unique, therapeutic, nonfocused ultrasound system for performing renal denervation in patients with resistant hypertension. The PARADISE technology (Percutaneous Renal Denervation System) includes a 6-F compatible catheter with a cylindrical transducer that emits ultrasound energy circumferentially, allowing for a more efficient renal denervation procedure.

Ultrasound energy consists of high-frequency sound waves (ie, rapid mechanical oscillations), which are emitted circumferentially by the cylindrical transducer. These sound waves pass through the surrounding fluids and generate frictional heating of soft tissues, resulting in a temperature increase and nerve damage at depth. Pathologist Renu Virmani, MD, confirmed that based on assessment of the ReCor preclinical data, this approach “did not affect the arterial wall.”

The ultrasound transducer lies within a low-pressure balloon that allows for self-centering of the transducer and gentle contact with the artery wall for uniform circumferential denervation. This means that nerves below

the surface of the artery wall are damaged in 360° with a single emission. The balloon also enables cooled fluid to circulate during the energy delivery process, thereby cooling the endothelial wall and protecting it from any excessive heating that could be caused by other energy sources or designs (Figures 5 and 6).

The advantage of PARADISE over other technologies is its ability to uniformly, circumferentially denervate while simultaneously cooling the endothelial wall to help enable a safe, consistent, and fast renal denervation procedure. The use of an energy source that does not require direct tissue contact allows for a balloon to be inflated around the transducer and has the following clinical benefits:

- PARADISE’s balloon enables cooled fluid to circulate during the energy delivery process and keeps the artery wall cool, minimizing damage to nontarget tissues.
- PARADISE’s balloon centers the ultrasound transducer in the artery and enables controlled, uniform, and circumferential energy delivery.
- PARADISE’s controlled, uniform, and circumferential heating is independent of catheter positioning or tissue characteristics and reduces the number of treatment sites required to achieve renal denervation.
- PARADISE’s reduced number of treatment sites diminishes the overall procedure times and minimizes pain and discomfort for the patient.

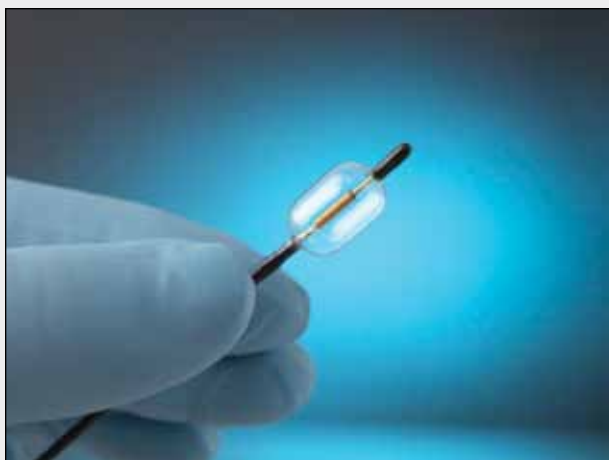


Figure 5. The PARADISE catheter. The ultrasound transducer is centered within a fluid-filled balloon.

ReCor has conducted significant preclinical work in the swine model. Renal denervation performed using the PARADISE system in 43 animals showed the following:

- Consistent energy delivery within the renal artery and proven impact of denervation
- Minimal endothelial damage (5%) due to cooling with a low-pressure balloon
- Safety out to 6 months (n = 10)
- Statistically significant norepinephrine reduction of 72% ($P = .006$).



Figure 6. The PARADISE catheter deployed within a renal artery.

ReCor Medical is currently completing the REDUCE first-in-man study, which has shown clinically relevant blood pressure reductions in patients with resistant hypertension out to 3 months. These results are to be confirmed by the REALISE study, which is starting in the first quarter of 2012 at a renowned European site.

PARADISE received CE Mark in the fourth quarter of 2011, and a postmarket study (ACHIEVE) will be initiated across multiple countries in Europe in the second quarter of 2012.

BULLFROG MICROINFUSION CATHETER **Mercator MedSystems, Inc.**

Kirk Seward, PhD

President and Chief Technology Officer

Renal efferent sympathetic nerve activity is contributory to hypertension.⁹ Renal denervation has been shown to be safe and effective for relieving uncontrolled hypertension in preclinical models,¹⁰ historically in human surgical models¹¹ and recently in human clinical trials.^{12,13} Mercator MedSystems, Inc. proposes to reduce resistant hyperten-

sion by producing a partial denervation of the kidneys with localized administration of guanethidine monosulfate to the adventitia and perivascular tissue of the renal arteries.

BULLFROG SYSTEM DESIGN AND STUDIES

The Mercator Bullfrog microinfusion catheter (Figures 7 and 8) is a catheter-guided system designed to inject therapeutic agents directly, nonsystemically, and safely through blood vessel walls into adventitial tissues and has received US Food and Drug Administration 510(k) clearance.

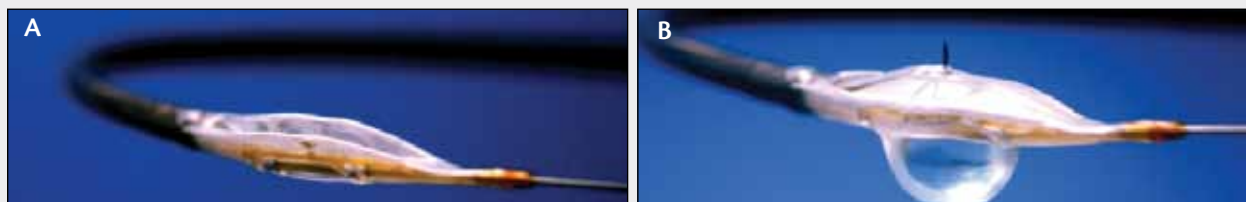


Figure 7. The deflated (A) and inflated (B) Bullfrog microinfusion catheter. Balloon walls sheath the needle (0.9 mm in length and 130 μ m in diameter) and protect the vessel during catheter placement. When the balloon is inflated, the needle slides through the vessel wall, allowing drug delivery to the adventitia and perivascular tissue. The balloon is then deflated, and the catheter is moved to another target site or removed from the body.

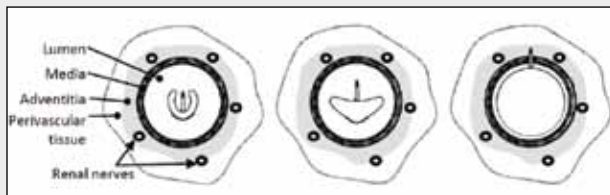


Figure 8. As the Bullfrog balloon inflates, the microneedle slides through the media and into the adventitia and perivascular tissue.

The Bullfrog catheter is tipped with a balloon-sheathed microneedle and is guided and inflated in a manner similar to an angioplasty catheter but with far lower expansion pressures (2 atm vs 6–20 atm) in vessels of 3 to 6 mm in diameter. It is compatible with 0.014-inch guidewires and 6-F introducer sheaths. The closed balloon provides a protective covering for a tiny injection needle as it is safely guided through the vasculature. When the desired injection site is reached, the balloon is inflated with saline and radiopaque contrast, securing the system for injection and sliding the microneedle through the vessel wall. Nonclinical studies have shown that the Bullfrog catheter is able to deliver up to 5 mL per injection into the renal artery adventitia with no apparent safety concerns.

Guanethidine is delivered to the renal artery adventitia to accomplish sympathetic denervation. Guanethidine was approved by the US Food and Drug Administration in

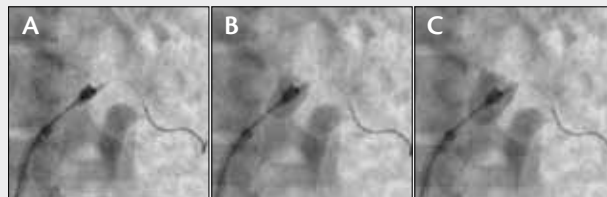


Figure 9. Renal artery drug delivery with Bullfrog catheter. Bullfrog catheter inflated in a porcine left renal artery (A). After a 0.5-mL adventitial infusion (B). After a 1-mL adventitial infusion (C). Note that the contrast mixed with drug provides an immediate visual feedback to confirm adventitial delivery.

1960 under the trade name Ismelin. It was provided in an oral dosage averaging 25 to 50 mg/d and is indicated for the treatment of moderate-to-severe hypertension. When taken orally, guanethidine builds up in low concentrations in the sympathetic nerves and reversibly interferes with the transmission of neural hormones, decreasing blood pressure. Given locally, guanethidine is known to induce an autonomic denervation directly and through an immune-mediated pathway.¹⁴ Mercator's preclinical experiments have shown that guanethidine, injected at appropriate concentrations into the adventitial space around renal arteries, selectively ablates the nerves in the adventitia around the renal artery after a single, 20-minute procedure (Figure 9).

THE ONESHOT RENAL DENERVATION SYSTEM

Maya Medical, Inc.

Michel Accad, MD
Chief Medical Officer

Maya Medical, Inc. (Saratoga, CA) is an early-stage company that is rapidly emerging in the expanding renal denervation market for the treatment of resistant hypertension. Founded in 2010, Maya Medical is developing a portfolio of catheter-based systems designed to utilize the clinical benefits of renal denervation while significantly reducing procedural times and minimizing user variability, fundamental limitations that the company believes are inherent in current device-based systems.

Maya Medical's first product offering, the OneShot renal denervation system, was born out of the company's extensive expertise in radiofrequency (RF) ablation and percutaneous coronary interventions (PCI), drawing upon the benefits and best practice standards of each distinct yet complementary clinical discipline. The result is a unique product platform that could further accelerate the paradigm shift in the management of resistant hypertension.

Balloon-Based Platform

Leveraging the procedural benefits of the standard percutaneous transluminal angioplasty (PTA) technique, the

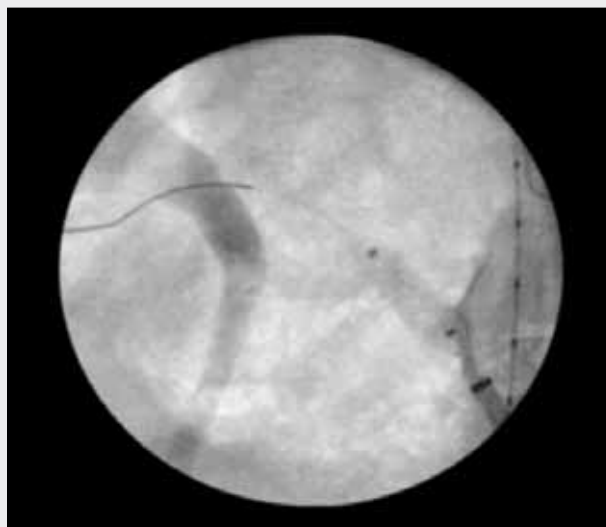


Figure 10. Single treatment per artery using the Maya Medical OneShot renal denervation system.

Maya OneShot renal denervation system features a proprietary balloon-based platform to deliver a single RF treatment per artery (Figure 10), representing a significant reduction in procedural times relative to point-by-point renal denervation systems.

In addition to recognizing the need for reduced procedure times, Maya also saw the need for enhanced consistency of treatment. Current point-by-point systems require a series of pullback and rotation motions after each sequential ablation to create the desired helical ablation pattern along the length of the renal artery. As a result, the approach is highly user- and technique-dependent, the inherent variability of which may become more pronounced as the number of users and diversity of skill level continues to expand.

Utilizing a helical electrode configuration as shown in Figure 11, the Maya OneShot catheter ensures enhanced consistency of the treatment pattern while also avoiding the potential for circumferential injury, attributes that are expected to result in safer and more reproducible outcomes. Also consistent with Maya's balloon-based



Figure 11. Maya Medical OneShot catheter.

approach is the ability to deliver predictable apposition of the RF electrode to the vessel wall for more controlled targeted delivery of the RF energy. By offering a more reliable single-treatment approach coupled with enhanced ease of use and reduced procedure times, Maya Medical believes its OneShot renal denervation system has the potential to significantly expand clinical adoption within this emerging therapeutic field. Strategically focused on markets outside the United States, Maya Medical anticipates initiating a tiered market release by the third or fourth quarter of 2012.



ALLIANCE OF EXCELLENCE

V² RADIOFREQUENCY BALLOON

Vessix Vascular, Inc.

Raymond W. Cohen

Chief Executive Officer

Vessix Vascular, Inc. (Laguna Hills, CA) has created a second-generation percutaneous renal denervation system for the treatment of medication-resistant hypertension. The V² renal denervation system (Figure 12) consists of the V² catheter, a patented noncompliant balloon catheter with RF electrodes and thermistors mounted on the exterior of the balloon, and the proprietary V² bipolar RF generator. Once inserted into the renal artery, a 30-second inflation/treatment per renal artery delivers simultaneous RF therapy with independent temperature control to all electrode pairs. Given that deployment via a balloon catheter is quite familiar to interventionists and rapid RF treatment time greatly increases the efficiency of the procedure, significantly reduces discomfort for the patient, and provides the benefits of lower exposure to radiation, lower amount of contrast dye, and therefore lower renal toxicity to the patient, the Vessix V² system promises to be an easier, faster, and less-invasive renal denervation product.

The V² catheter is available in balloon diameters ranging from 4 to 7 mm, with a balloon length of 25 mm. Larger-diameter balloons have eight electrode pairs, and smaller-diameter balloons have four to six electrode pairs made of solid gold, which are biocompatible and facilitate good electrode contact with the renal arterial wall. In addition, the electrodes are radiopaque, allowing the V² catheter to be easily visualized under fluoroscopy.

The V² catheter connects directly to the V² generator or by means of an optional 3-m extension cable. In a clinical setting, the V² balloon catheter is inflated at a very low pressure (3 atm) until the electrodes are properly apposed against the renal artery wall. The V² generator then delivers controlled ultra-low-power bipolar RF energy briefly to the electrodes. This delivery of energy causes thermal heat to perfuse through the



Figure 12. Close up of RF electrodes on balloon catheter.

artery wall into the adventitia layer of the artery and results in denervation of the target renal nerves. The RF generator is a one-button operation device with a high-resolution color graphical user interface that provides visible prompts to guide the operator through setup and treatment steps.

V² STUDIES

In 2011, the V² renal denervation system completed preclinical animal studies to verify that the product meets appropriate standards and that the performance of the device meets the design parameters necessary to achieve the desired therapeutic result. During all RF renal denervation treatments, no complications occurred, and there were no acute dissections, perforations, or thrombi immediately after RF treatment or prior to necropsy at any of the time points. No stenosis developed inside the renal arteries due to the RF treatments at any of the follow-up periods. For efficacy, a decrease in NE kidney tissue concentration was utilized as a surrogate marker of efficacy following renal denervation. The reduction in NE levels after V² RF treatment was similar to the NE reduction observed following surgical denervation, which served as a positive control for renal denervation in animals.

Beginning in the first quarter of 2012, the V² renal denervation system will be utilized in the company's first international, multicenter clinical study: REDUCE-HTN.

CONCLUSION

The results of the Symplicity HTN-1 and Symplicity HTN-2 trials have generated considerable interest among physicians, patients, medical device entrepreneurs, and the investment community. St. Jude Medical's (St. Paul, MN) announcement in late 2011 of the first patient to be enrolled in their first-in-man ARSENAL trial¹⁵ at the University of Adelaide reflects the speed of which new device designs are being iterated. Undoubtedly, this new

procedure will focus attention on the more aggressive identification and treatment of the hypertensive patient. Coupled with the early potential effects of renal denervation on improved glucose control, sleep apnea, and treatment of heart failure syndromes and renal dysfunction (all consequences of sustained hypersympathetic activity), we are truly on the verge of a brave new frontier that holds the promise of substantially improving the lives of our patients. ■

Krishna J. Rocha-Singh, MD, FACC, FAHA, FSCAI, FSVM, is Medical Director, Prairie Research and Education Cooperative, St. John's Hospital in Springfield, Illinois. He has disclosed that he is a consultant to Medtronic, Inc., Vessix Vascular, Inc., ev3 Inc., and CardioSonic Ltd.; however, Dr. Rocha-Singh did not contribute to the writing of any of the individual sections contained in this article. Dr. Rocha-Singh may be reached at ksingh@prairieheart.com.

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