Peregrine System™ Infusion Catheter for Perivascular Renal Denervation[1]

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1 Background

Since the 1930s, it has been known that injury or ablation of the sympathetic nerves in or near the outer layers of the renal arteries can dramatically reduce high blood pressure. As far back as 1952, the use of alcohol (ethanol) has been reported for tissue ablation in animal experiments. Specifically, Berne [1] describes the use of "painting" alcohol on the outside of a dog's renal artery to produce nerve damage, leading to denervation.

Current technology to achieve renal denervation includes local heat-delivery using endovascular ablation catheters based on RF or ultrasound energy These devices include Symplicity™ (Medtronic, Dublin), EnligHTN™ (St. Jude Medical, St. Paul, MN), and Vessix™ system developed by Boston Scientific, Marlborough, MA. These devices are delivered into the renal artery in a procedure similar to an angioplasty or stent deployment in which a guiding catheter will facilitate the advancement of the ablation device into the renal arteries. A randomized, placebo-controlled clinical trial of Symplicity™ showed that this technique may not be consistently effective, as the depth of penetration of the RF-generated heat does not reach the deeper nerves, nor provide "circumferential" ablation, thus resulting in inadequate denervation [2].

The objective for the research that follows is to demonstrate that needle based ethanol injection into the perivascular space from a percutaneously inserted catheter can be safe and potentially effective in human use.

2 Methods

An innovative intravascular fluid delivery catheter, the Peregrine System™ Infusion Catheter developed by Ablative Solutions, Inc. has the potential to be more effective in denervating the renal sympathetic nerves via the placement of three injection needles through and beyond the medial layer of the renal artery. The infusion of a microvolume of alcohol (ethanol) (<1 ml) forms a "doughnut-like" envelope outside of the artery and, therefore, effectively inactivates the sympathetic nerves without causing significant damage to the intima or medial layers of the arterial wall. While RF ablation is extremely painful to the patient, the Peregrine causes no pain or minimal discomfort. This is a major advantage over thermal "burning" catheters. The lack of pain is likely due to the fact that the pain receptors reside in the medial layer of the artery itself. Furthermore, alcohol is known to be a local anesthetic.

The design, development, and testing of an intravascular fluid delivery catheter that can reliably enable three 0.008 in. diameter microneedles to penetrate through the wall of the renal artery without causing bleeding or arterial damage was a major technical challenge. In addition, the needles also needed to have a precise penetration depth of several millimeters outside of the medial layer of the artery in order to ensure that the ethanol penetrates far enough to inactivate the deep-seated sympathetic nerves. The critical components of the design to meet the above criteria are the three guide tubes, which house the needles. These have sufficient structural rigidity to reliably and atraumatically expand outwardly against the intima of the renal artery. Once placed against the wall of the artery, the guide tubes enter the catheter and provide support for the thin microneedles, which can then be advanced through the wall of the artery into the perivascular (adventitial) space.

Figure 1 shows the sequence of use of the Peregrine Catheter with side views on the left and cross sections on the right. Figure 1(*a*) shows the guide tubes and needles deployed through the wall of the renal artery with the functioning nerves shown. Figure 1(*b*) indicates the start of infusion of ethanol into the perivascular space. Figure 1(*c*) indicates the needles and guide tubes retracted back into the Peregrine catheter with the ethanol now forming a doughnut-like spread in the perivascular space surrounding the artery. Finally, Fig. 1(*d*) indicates the nerves now inactivated by the neurolytic action of ethanol. Note that the alcohol does not penetrate into the (media) wall of the artery itself, enhancing safety.

Figure 2 shows a fluoroscopic image of the fully deployed Peregrine. Markers at the end of the guide tubes provide proper visualization of tubes locations against the wall of the renal artery (dashed line).

The microneedles themselves have been constructed to be radio-opaque so they too can be clearly seen here penetrating through the arterial wall into the perivascular space.

3 Results

Upon the completion of extensive preclinical studies [3], a first-human-use evaluation was conducted. The results were very encouraging: Eighteen patients and 37 vessels (one had a accessory renal artery) were treated with 0.3 ml of ethanol in each renal artery using only modest, standard diagnostic cath lab sedation (Versed and Fentanyl at low doses).

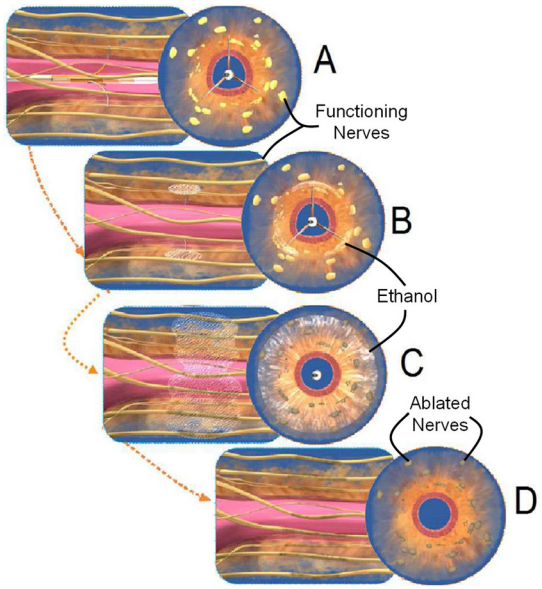

Fig. 1 Sequence of use for the Peregrine™ to perform perivascular renal denervation

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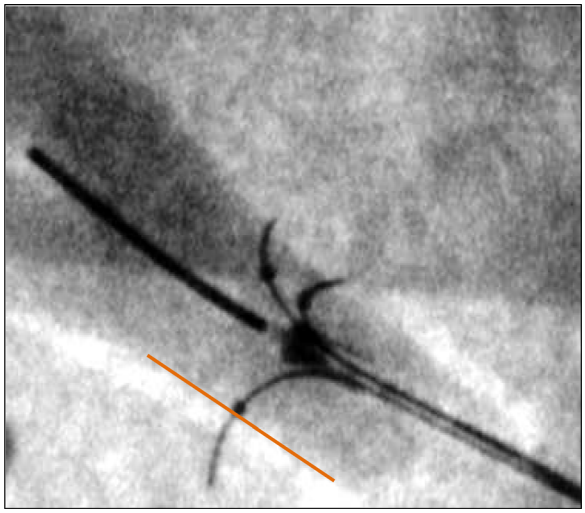

Fig. 2 Angiographic visualization of the distal portion of the Peregrine™ renal denervation catheter during the first in man clinical study

The overall results from the study showed:

- no acute complications: no clots, spasm, perforation, or dissections
- no long term effects on renal function
- arteries appeared unchanged 6 months post-treatment (evaluated by angiography)
- excellent device performance: 100% device success (37/37 vessels)
- brief treatment time: avg. 7 min/artery (range 3–8 min)
- successful navigation to the target site in all renal arteries, including challenging anatomies—short segments and tortuous segments
- a reduction of office-based blood pressure, despite a decrease in antihypertensive medications in the majority of patients
- no/minimal procedural pain, under modest sedation
- when noted, mild, transient discomfort (<1 min)

Baseline and follow-up blood pressures are presented in Fig. 3 for 17 of the 18 patient cohort (one patient passed away from unrelated causes ~2 months after treatment). The results showed a (mean) 23 mm Hg drop in systolic blood pressure in spite of reduction of an average of 1 blood pressure drug.

Furthermore, none of the patients experienced the intensive pain that occurs during RF ablation against the wall of the renal artery. A majority of patients had no pain, those that had pain it was transient (i.e., <1 min).

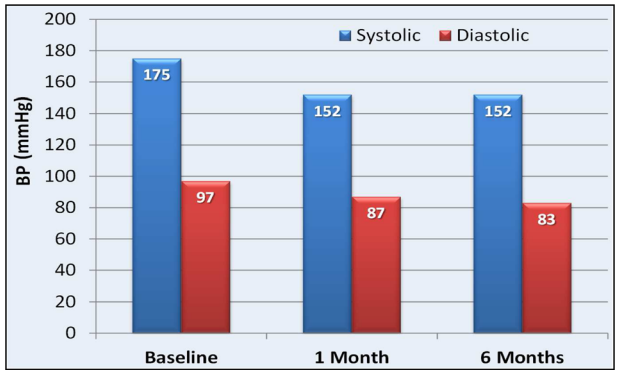

Fig. 3 First in man results. Mean blood pressure before and after perivascular renal denervation ($N = 17$).

4 Interpretation

Three factors stand out from the results of the first clinical evaluation of the Peregrine system. First, because there is no capital equipment such as an RF generator and only a single 0.3 ml injection per renal artery, the time and cost for the procedure are projected to be significantly lower than that of RF ablation-based renal denervation procedures.

Second, the pain receptors are located within the inner wall of the artery (the media), and the injected alcohol does not penetrate back, as seen in animal studies, hence resulting in minimal or no pain, and dramatically less than RF procedures.

Finally, because the infusion requires less than 10 mm of vessel length, the Peregrine enables the treatment of shorter length arties; a critical limitation for RF based devices that require at least a 20–30 mm length renal artery to achieve modest nerve ablation.

In summary, the early results with the Peregrine System are encouraging and now await prospective, sham controlled studies to fully assess the safety and efficacy of the system.

The Peregrine System received a 510(k) clearance by the U.S. FDA for intravascular delivery of diagnostics and therapeutic agents in April 2014. Clinical trials for the European CE Mark have begun, with approval expected in 2015. U.S. clinical studies are slated to begin in 2015.

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