13 Perivascular Renal Denervation (PVRD™): Chemical Renal Denervation with Micro-Doses of Ethanol Using the Peregrine™ Renal Denervation Device

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Introduction

In the 1930s–1950s surgical renal sympathectomy was used to treat severe hypertension [1–3]. Despite a successful lowering of blood pressure (BP) observed with surgical denervation, this technique was abandoned due to a relatively high morbidity and mortality, and as a result of the development of more effective oral antihypertensive medications.

Recently, catheter-based renal sympathetic denervation has been performed using a point-by-point, mono-polar radiofrequency (RF) ablation catheter from within the renal artery [4–11]. This technique has been shown to disrupt renal sympathetic nerve activity [4–7], resulting in substantial and sustained blood pressure lowering in patients with severe and medically resistant hypertension [4–11].

The ability to lower blood pressure using a catheter-based ablative technique from within the renal artery has led to a proliferation of new technologies intended to expand and validate this observation, and to improve the ease-of-use, safety, and predictability of catheter-based renal sympathetic denervation [12–14].

Virtually all of these new denervation devices have focused upon "energy-based" denervation, utilizing predominantly RF or ultrasound catheters. These catheters are designed to deliver ablative thermal injury through the intima and medial layers of the renal artery, in order to target and destroy the sympathetic nerve fibers that traverse from the aorta, to the kidney within the adventitial and peri-adventitial space surrounding the renal arteries [4–12].

A number of these "next generation" RF and ultrasound transmural thermal- ablation catheters have been tested in patients and have validated the results from the original Simplicity Trials, with significant BP lowering seen after renal sympathetic (thermal) denervation [11–14].

Despite the moderate efficacy of both the first and next generation RF and ultrasound catheters, there are limitations, and potential safety concerns associated with the use of transmural thermal injury traversing the intimal and medial layers of the renal artery in order to create thermal injury to the sympathetic nerves that may run from 2 to 10 mm deep to the intimal surface [15–18]. In addition, the early generation RF devices appear to have a relatively modest effect upon BP when measured with ambulatory BP monitoring, as well as a relatively high "non-responder" rate.

Rationale for Chemical Renal Denervation with Ethanol

Given the potential limitations of RF and ultrasound, we have developed a novel micro-needle based drug delivery catheter (Peregrine™, Ablative Solutions, Inc. Menlo Park, CA). This device was developed in order to study the feasibility, safety and efficacy of chemical denervation using very small volumes of ethanol (EtOH), a known potent neurolytic agent. With this device (see Fig. 13.1) one can deliver micro-doses (150–600 μL) of EtOH precisely and locally to the adventitial and peri-adventitial space of the renal artery (termed PeriVascular Renal Denervation; PVRD™), with three simultaneously deployed micro-needles. This system has now been evaluated in pre-clinical testing and most recently, in an early human safety and feasibility clinical study, as a means to perform renal sympathetic denervation.

The key concepts and rationale for this methodology to create renal denervation are: (1) to deliver a very small volume of a highly potent neurolytic agent (EtOH) precisely

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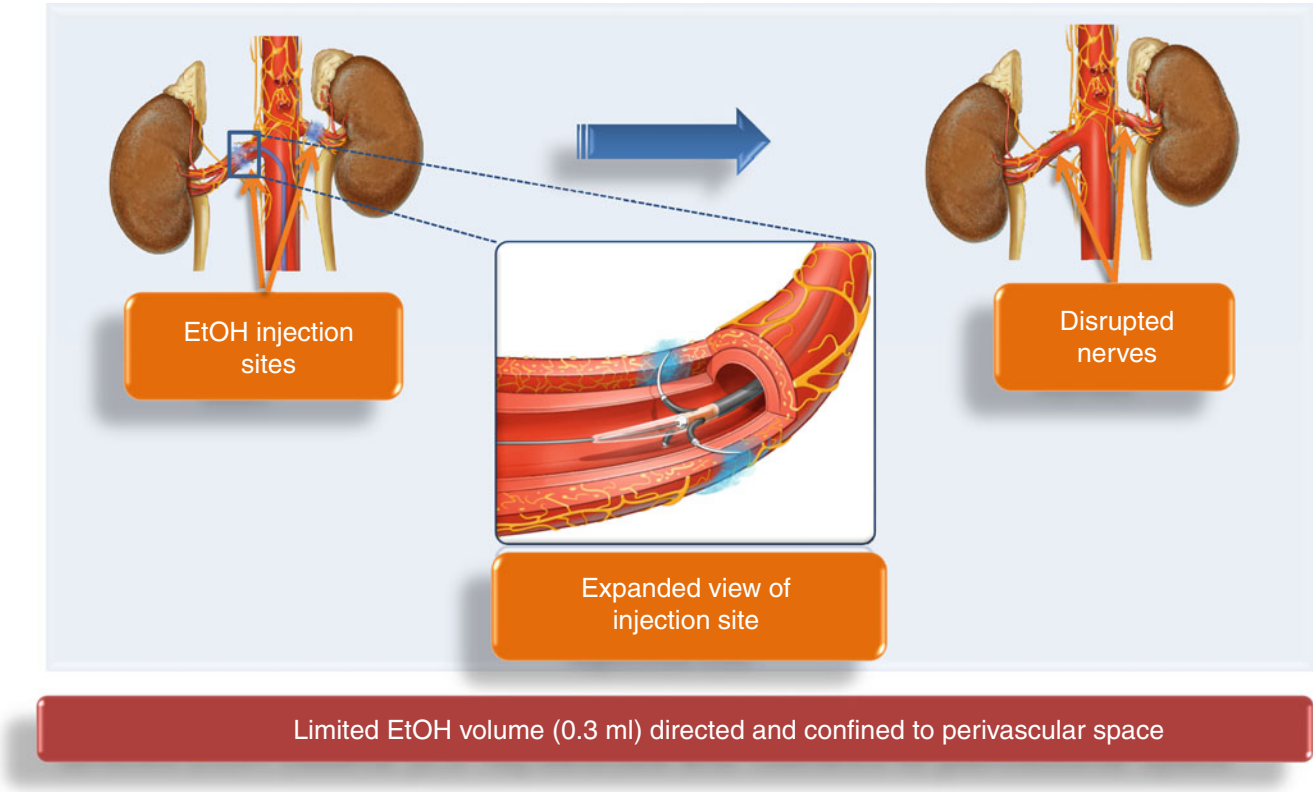

Fig. 13.1 Schematic drawings showing sequence of chemical denervation with EtOH. The *upper left panel* shows the anatomy of the mid-portion of the renal artery and shows no significant organs in the vicinity of the very localized EtOH delivery. The *middle panel* shows the device deployed with micro-dosing of EtOH targeted to the adventitial space (*blue halos* in *right panel*)

to the target area in the adventitia and the peri-adventitia; (2) to deliver the agent with such tiny (micro) needles such that even with full systemic heparin treatment there would be essentially no peri-arterial bleeding risk after the needle entry through the intima and media and into the adventitia, (3) to use an agent such as EtOH that is lipophilic and agrascopic, such that simultaneous injection from three needles placed in one step, at 120° needle separation radially around the renal artery would reproducibly create circumferential spread of the neurolytic agent, and confined to the adventitial space, and allow circumferential sympathetic nerve kill with minimal effects upon the intima and media of the renal artery (nerve kill without renal artery vessel wall injury); (4) to determine the needle depth and doses required to get "deep" sympathetic nerve kill (nerve injury out to 10–12 mm deep to intimal surface), which may be crucial in achieving reproducible and efficient sympathetic denervation; (5) to determine whether or not there is predictable and dose-dependent sympathetic denervation, as judged by the drop in renal parenchymal norepinephrine levels in a porcine model; (6) to determine the safety as judged by short-term (2 weeks) and longer term (3 month) histopathological and angiographic studies in a porcine model; (7) to determine whether or not this technology could be safely applied in clinical cases and finally; (8) to determine whether or not this procedure could have the potential to create renal denervation in humans without the pain that is associated with "thermal" renal denervation using either RF or ultrasound techniques.

Pre-clinical Testing

Extensive pre-clinical testing has now been completed in order to evaluate the safety and efficacy of chemical neurolysis, via adventitial injection of very small doses of dehydrated EtOH to as a means to perform sympathetic denervation, in a porcine model [19].

A novel, three needle-based delivery device, (Peregrine System™, Ablative Solutions, Inc., Menlo Park, CA) was introduced via the femoral artery into renal arteries of adult swine using fluoroscopic guidance. The drug injection catheter is an endovascular delivery catheter that contains three distal needles housed inside of individual guide tubes, which are contained within the catheter. The catheter has a steerable, radio-opaque 2 cm fixed, floppy guide-wire at its distal end to minimize renal artery trauma and allow steerability, when needed, into appropriate branch vessels (Figs. 13.1 and 13.2a–c).

The animal studies were conducted under the general principles of Good Laboratory Practice (GLP) regulations as set forth in 21 CFR 58. Animals were pre-medicated with 325 mg

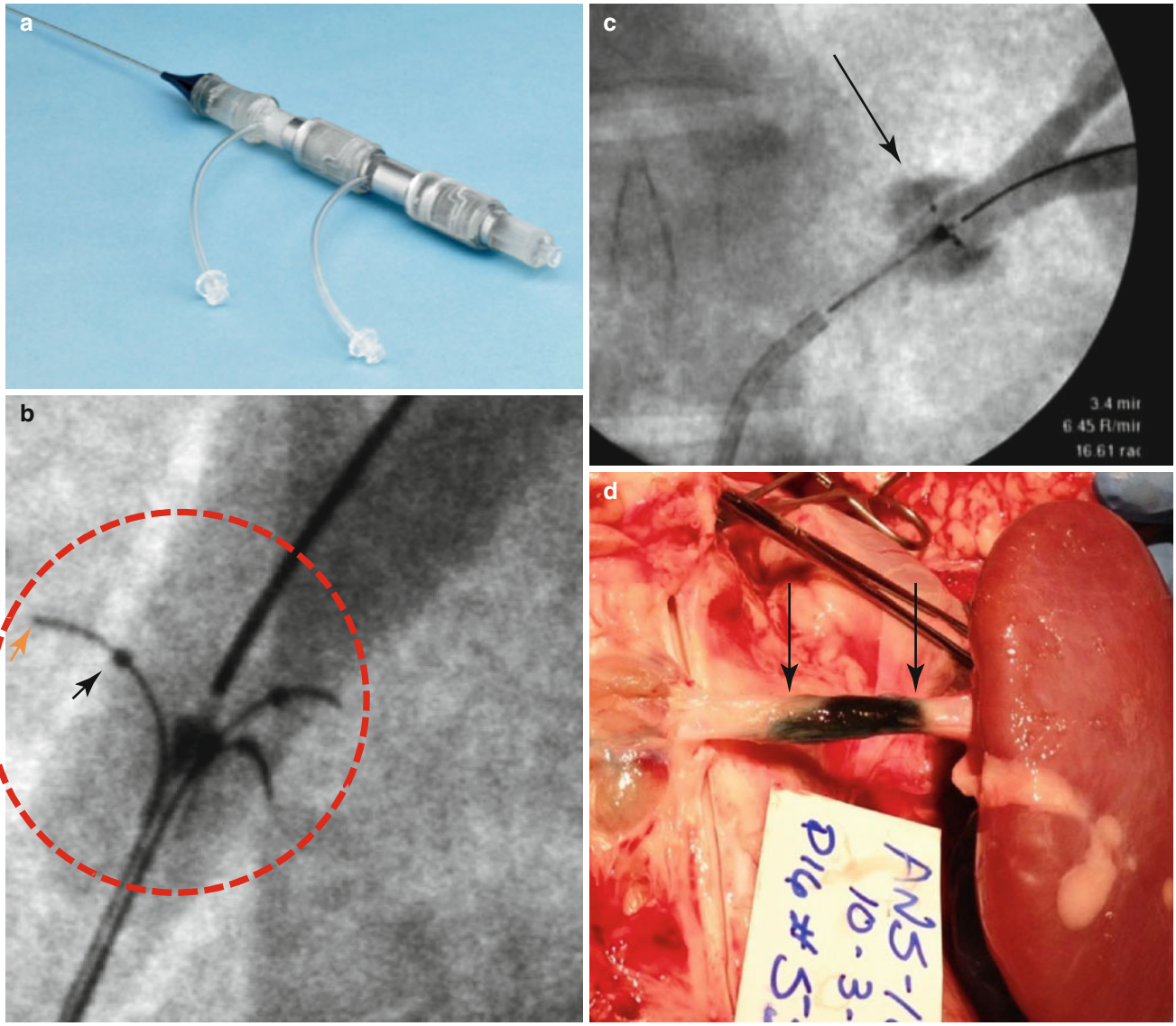

Fig. 13.2 Panel (**a**) shows the device handle that controls the tubes, needles and injection port. In (**b**), the device is deployed and centered in a porcine renal artery during contrast injection from the guiding catheter. *Black arrow* shows tip of guide tube against the intima and *orange arrow* shows tip of radio-opaque 0.008″ injection needle. Panel (**c**) show injection of ~0.2 ml of dilute contrast demonstrating injection 100 % limited to the adventitial space. The *black arrow* shows the appearance of a small volume of dilute contrast that is angiographically apparent in the adventitial and peri-adventitial layer of the renal artery after the purposeful injection of 0.30 ml of dilute contrast through the deployed Peregrine needles. In Panel (**d**) immediate necropsy is shown after injecting 0.15 ml EtOH combined with methylene blue to define the circumferential and very defined longitudinal (*black arrows*) spread of EtOH in the tunica adventitia

of aspirin and 75 mg of clopidogrel by mouth once daily for 2 days before the procedure. The animals were assigned to study groups at random, before the procedure began.

The animals were pre-medicated with intramuscular injection of telazol combined with atropine. When recumbent, animals were anesthetized with a mixture of isoflurane and oxygen delivered via facemask. When sufficiently anesthetized the animals were intubated and connected to a closed-circuit anesthesia system and maintained on isoflurane combined with oxygen. Blood was collected for evaluation of hematology (CBC) and serum chemistry. Urine was obtained via cystocentesis.

After the animals were prepared for sterile surgery, one femoral artery was accessed using the Seldinger technique, and a seven French introducer was placed. Intravenous heparin was given in all animals to achieve an ACT of >250 s. In all cases the right and left renal arteries of the pig were engaged using a seven French RDC guiding catheter. Prior to ethanol or saline injections, angiography of each renal artery was performed using iodixanol contrast diluted by 25 % with normal saline.

The Peregrine™ device was advanced into the left or right renal artery via the guiding catheter. Once the operational section of the device was positioned within the target site in

the mid-portion of the renal artery, the three guide tubes are deployed spatially at 120°, one to another (see Figs. 13.1 and 13.2b). The tubes were simultaneously deployed up against the intimal surface (Figs. 13.1 and 13.2b), using the advancement mechanism in the control handle (Fig. 13.2a). These atraumatic tubes have radiopaque distal tip markers such that one can clearly define the position of the tubes, particularly when contrast is injected via the guiding catheter (Fig. 13.2b).

Once deployed, the three tubes serve to reproducibly "center" the device within the renal artery. The 0.008″ needles that reside within the distal tip of the tubes are advanced to a depth of 3.5 ± 0.25 mm deep to the intima (i.e., beyond the tip of the guide tube). This function is also performed via the specialized handle, which allows simultaneous advancement of the three injection needles. These tiny needles are made radiopaque, so that they can be easily seen under fluoroscopy. Although not part of the clinical protocol, in animals dilute contrast can be injected once the needles are positioned to confirm placement relatively deep in the adventitial space (Fig. 13.2c).

It should be noted that these needles are the equivalent of a ~30 gauge needle so that they can be safely advanced through the renal arterial wall without causing bleeding. Prior to conducting this study we confirmed that needles of this size could be repeatedly advanced through the wall of the renal artery of pigs that had been pre-treated with high doses of heparin (ACTs 300–600), with no detectable bleeding at the needle puncture sites. This is a key observation relevant to the safety of this approach.

Once the tubes and needles are deployed it is easy to confirm, fluoroscopically, that the needle tips are well outside the luminal space and ~2.5–3.0 mm deep to the media and the external elastic lamina in a normal porcine renal artery (Fig. 13.2b). This corresponds to an injection depth that approximates the border between the renal artery adventitia and peri-adventitia, and which corresponds to a depth to the middle of the renal sympathetic nerve field, as defined in pressure-fixed human histopathological studies by Virmani et al. [18].

The successful deployment of the tubes and needles was confirmed by angiography. EtOH or saline (sham) fluid was then administered, using a 1.0 ml luer-lock syringe attached to the proximal injection lumen at the handle of the catheter. This injection lumen is in fluid continuity with the distal end of all three needles. The injection is performed over 15–20 s.

Three volumes of EtOH were used in this study: 0.15 ml/artery (n = 3 pigs/6 arteries), 0.30 ml/artery (n = 3 pigs/6 arteries) and 0.60 ml/artery (n = 3 pigs/6 arteries). A procedural control group was also studied using the injection of 0.4 ml of saline/artery (n = 3). This was a "sham" arm to control for nonspecific effects that might be caused by mechanical injury from either the guide tubes or the needles, and/or any non-specific effects of fluid delivery. Once the treatment agent was injected, the dead-space of the catheter was flushed with a very small volume of normal saline. After treatment of the first renal artery the device was removed from the animal, inspected and flushed. The contra-lateral renal artery was then engaged and the same fluid injection sequence was performed in the contralateral renal artery. After the treatment of the second renal artery, the animals were recovered and housed for restudy and sacrifice at 2 weeks post-intervention. The animals were treated with aspirin 162 mg/day for 7 days after intervention.

The circumferential spread of EtOH was evaluated in separate experiments by combining 0.125 ml of EtOH with 0.25 ml of methylene blue (stain). The volume of 0.15 ml was then injected under fluoroscopic guidance. Immediate necropsy was performed and demonstrated reproducible and circumferential spread of the 0.15 ml of the EtOH/methylene blue mixture (Fig. 13.2d). Histopathology was also used to evaluate circumferential spread of alcohol by having the pathologist evaluate and document the location (in terms of circumference) of any noted neuritis and neurolysis. The histopathological examination showed extensive and circumferential nerve injury at the 0.15, 0.30 and 0.60 ml EtOH injection volumes.

Safety and effectiveness of the device were evaluated. The efficacy of denervation was determined by measurement of renal parenchymal norepinephrine (NE) levels (analyzed by HPLC, with electrochemical detection), and using histopathologic evaluation of the peri-renal nerves at the end of the 2-week survival period (Fig. 13.3). Safety was evaluated by histopathologic evaluation of the renal artery and kidney as well as evaluation of clinical pathology. Blood and urine were collected in all animals treated with the device for evaluation of systemic and renal health at baseline and at the time of sacrifice.

The animals were survived for 14 ± 3 days after treatment. At the end of the study period the animals were anesthetized and angiography of the treated right and left renal arteries was obtained to evaluate vessel patency and to look for any luminal narrowing compared to baseline angiography. Four additional animals were studied with follow-up with angiography and pathology at 3 months after ethanol denervation using 300 μL of EtOH (Figs. 13.4 and 13.5).

After angiographic follow-up at 14 days and at 3 months, a necropsy was performed. The renal arteries and kidneys were harvested for histopathological evaluation. Gross pathology to examine the status of the renal arteries was performed to look for renal artery abnormalities such as aneurysms, perforations, dissections, hematoma, etc., as well as inspection of the surrounding tissues for any abnormalities. The renal arteries and kidneys were harvested, retaining the peri-adventitial tissue around the artery. The renal artery tissue was embedded in paraffin using standard techniques. Tissue was stained with H&E. Multiple sites

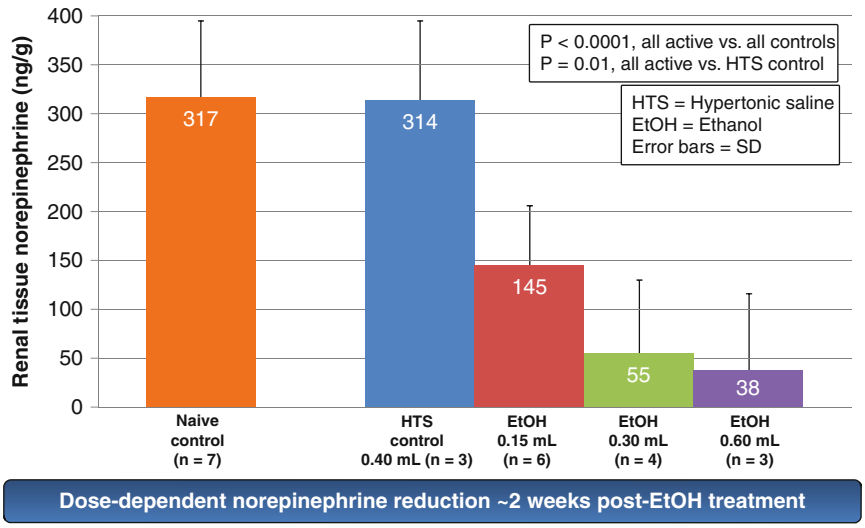

Fig. 13.3 Bar graph showing the dose-response effect of adventitial EtOH delivery upon renal parenchymal norepinephrine level at 14 ± 3 days. There is a marked and dose-dependent reduction of NE levels versus both naive control animals and sham control animals injected with saline. Mean NE reduction was 54 % with 0.15 ml; 78 % with 0.30 ml and 88 % using 0.60 ml/artery. Standard deviation (SD) for each data set as shown. P values as shown

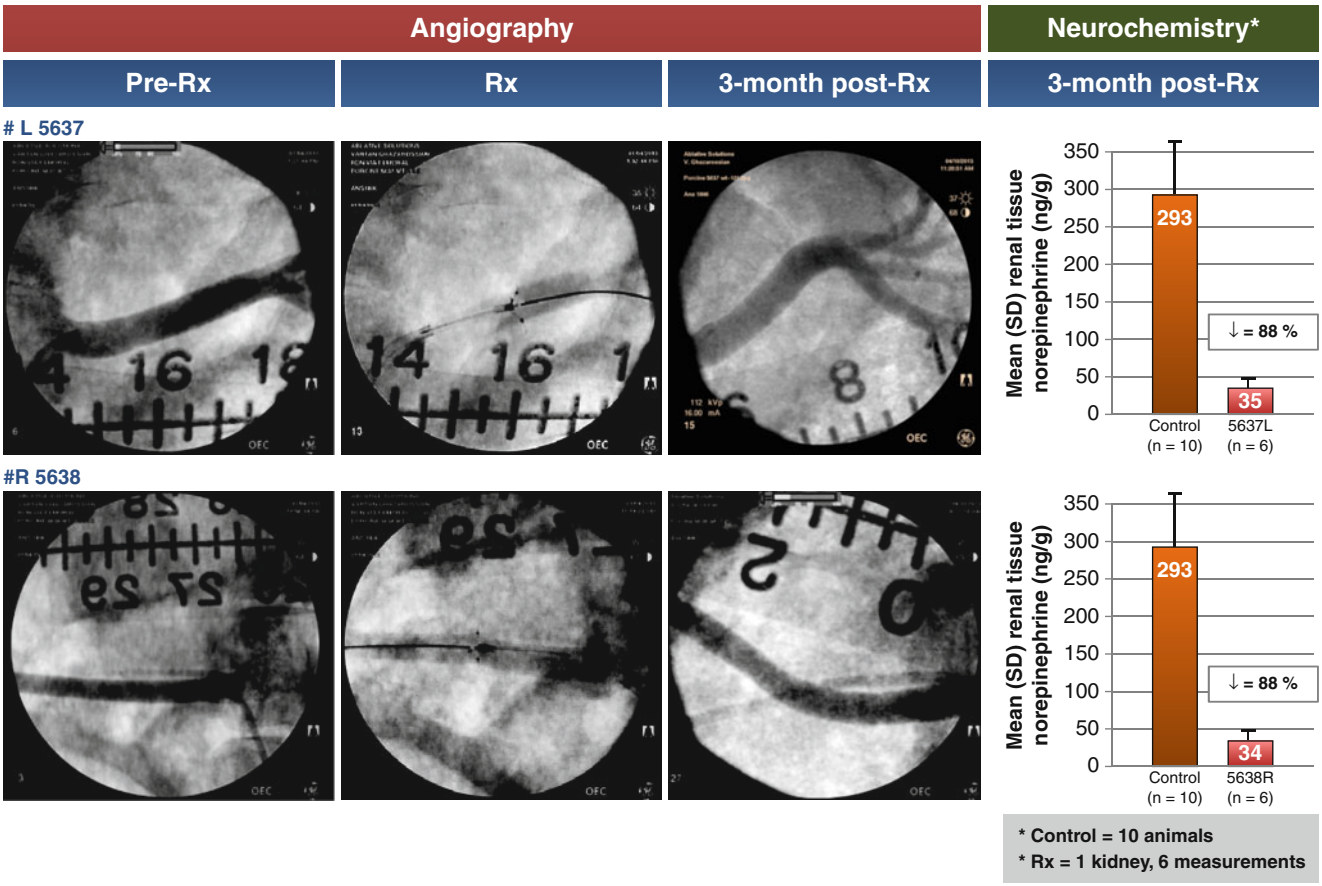

Fig. 13.4 Angiographic pictures and norepinephrine data from two pigs (*upper* and *lower panel* sets) at 3 month follow-up after 0.30 ml injection of EtOH in adventitial space by Peregrine™ device. *Left panels* show renal angiogram prior to treatment. Middle angiogram shows Peregrine™ device deployed during EtOH delivery and right angiographic panels show 3-month results with no evidence of any stenosis. In both of these kidneys there was an 88 % drop in renal parenchymal norepinephrine relative to untreated control kidneys (*far right panels*)

from each renal artery segment were labeled and sent for (blinded) microscopic evaluation by a board certified veterinary pathologist.

In all kidneys, four samples were obtained from random locations at each of the proximal, mid and distal regions of each kidney for a total of 12 samples/kidney. The tissue

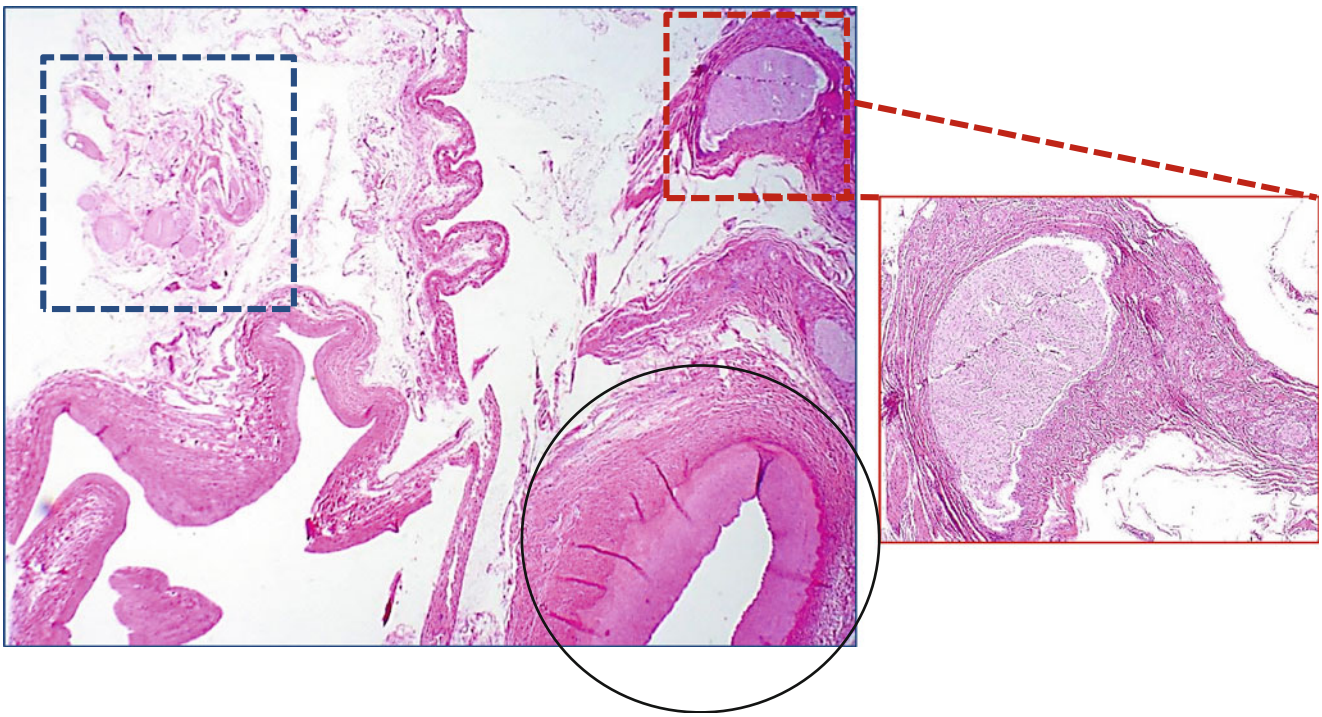

Fig. 13.5 Histopathology (H & E) of renal denervation at 30 days with 0.30 ml EtOH injection. The renal artery (intima and media) appears intact without evidence of injury or inflammation (*black circle*). The reaction to the EtOH appears quite limited to the adventitial layers. There is severe damage to the deep renal nerve bundles with vacuolization, nerve fiber disruption, and fibrosis of the perineural structures at a depth of 4–14 mm deep to the intima (*blue hatched and red hatched boxes* and magnified view from *red* box)

samples were weighed, placed in cryovials and flash frozen by immersion into dry ice. The frozen samples were then stored at −70 °C. They were sent in dry ice to an independent laboratory for (blinded) measurement of renal parenchymal norepinephrine levels.

Renal norepinephrine concentrations in the treated animals from this study were also compared to values from naïve control animals of the same age and species (n = 7) with renal tissue sampling performed in an identical fashion to the treated animals.

The safety of ethanol injection was also assessed in a separate nephrotoxicology study (n = 4). After deep engagement of the renal arteries 0.6 ml of EtOH was injected directly in both the right and left renal arteries (1.2 ml total EtOH/animal), over 20–30 s to replicate the timing of injection into the adventitial space when therapeutic EtOH neurolysis was performed. These animals had serial measurement of serum BUN, creatinine, electrolytes and body weight at days 1, 7 and at 30 days after the injection. Histopathological evaluation of the renal parenchyma was performed in all such treated kidneys at 30 days to look for any evidence of renal injury.

Additional, longer-term safety evaluation was obtained with angiographic follow-up at 90 days, in four additional animals (n = 8 arteries) treated with 300 μl (0.30 ml) EtOH. These studies were performed to look for any evidence of late renal artery stenosis (Fig. 13.4).

For statistical analysis, between-group comparisons were made using a Wilcoxon rank-sum test, performed in R (Version 2.14.1, Vienna, Austria). Data are shown in graphs as mean ± SD. A p value of <0.05 was considered significant.

Device success was defined as successful injection of the designated fluid without serious adverse events. The device was used successfully in all 16 animals and 32 renal arteries. Procedure time, measured from the advancement of the device into the renal artery, followed by deployment of needles, injection, and withdrawal back into the guiding catheter averaged approximately 90 s for each renal artery (range – 55–140 s). A small hematoma at the femoral access site was recorded in one animal. There was no other study-related morbidity or mortality.

At 2-weeks after ethanol-mediated renal denervation measurements of renal tissue NE showed an essentially linear dose response ($R^2 = 0.95$) between the EtOH volume delivered and the reduction of the renal parenchymal NE level (Fig. 13.3). The mean renal NE reductions were 54, 78 and 88 % at doses of 0.15 ml/artery, 0.30 ml/artery and 0.60 ml/artery, respectively ($p < 0.0001$ vs. combined controls; Fig. 13.3). The other statistical comparisons are shown in Fig. 13.3 and demonstrate a statistically significant reduction ($p < 0.05$) in renal parenchymal NE at all three doses, vs. sham controls.

Angiographic follow-up of all 24 treated vessels at 14 ± 3 days showed no evidence of renal artery narrowing at

EtOH doses of 0.15, 0.30 or 0.60 ml/artery. There were no other abnormalities noted, including no aneurysmal changes or thrombus. Angiography at the 90-day time point in four additional animals (eight arteries) treated with 0.3 ml EtOH, demonstrated no detectable renal artery narrowing (Fig. 13.4).

Histological examination revealed marked, and deep, circumferential renal nerve injury at depths of 1.5–12 mm from the intimal surface (Fig. 13.5). There was no discernible nerve injury in the saline, sham control injected animals. Nerve injury in the EtOH treated vessels was characterized by vacuolization, loss of internal architecture, and the development peri-neural fibrosis (Fig. 13.5). There was no evidence of device-related or EtOH-induced injury to the intimal layer of treated vessels. There were no thrombi. There was no evidence of any significant EtOH-induced injury to the intimal or medial layers of the renal arteries at the 0.30 ml dose at 3 month follow-up (Fig. 13.5). There was no discernible injury to tissue deep to the peri-adventitial plane.

There were no adverse nephrotoxic or systemic effects seen. The pigs' serum creatinine, BUN and electrolytes remained unchanged over the study period. Finally, direct injection of EtOH into the renal artery, at 200 % the likely therapeutic dose (i.e., 0.6 ml vs. 0.30 ml), resulted in no detectable renal toxicity as measured by creatinine, BUN, or electrolytes measured at 1, 3, 7 and 30 days after EtOH injection (all p's = NS). There were no discernible renal pathological effects seen on sectioning of the renal parenchyma at the 30-day follow-up.

First in Man Feasibility

The first in man early safety and feasibility study was started in September 2013. Bilateral renal angiography was performed in nine patients with severe refractory hypertension. Heparin was administered to achieve an ACT of >250 in all patients. Following anticoagulation unilateral denervation using 300 μL of EtOH was performed successfully in the first five patients. Unilateral intervention was done in these first five patients, as per protocol, to make certain that this technique was safe, prior to attempting bilateral denervation in one setting.

These patients were re-studied at 1 month after their first intervention. Angiography demonstrated no injury, stenosis or thrombus in any of the five treated vessels. After re-study of the initial target vessel, bilateral denervation was completed by denervation, as per protocol with 300 μL (0.3 ml) in the contralateral renal artery. Four additional patients were treated with bilateral denervation following this first "staged" cohort.

The procedure is very simple technically and also much faster than first or even second generation energy-based "burning" catheters. The mean time from device advancement into the target renal artery, to device withdrawal and final angiography was ~3 min (range 1.5–4 min). There were no complications, and device success was achieved in 9/9 cases and in 19/19 vessels (one patient treated who had dual renal/accessory renal arteries). There were no observations of vasospasm, thrombus, dissection or perforation in any of the 19 renal arteries treated. Interestingly, in two of the nine patients radiofrequency renal denervation would have been contraindicated (one patient with a short (12 mm) main renal artery length; one patient with dual renal arteries to the left kidney).

Perhaps most importantly, the ethanol denervation procedure was essentially painless. In 6/9 patients there was 0/10 pain throughout the procedure. In three patients there was a very transient (~60 s of discomfort, rated as 3–4/10). Only modest conscious sedation was used. In all cases the patients were essentially awake and actively conversant during the EtOH injection. In the three patients who had any discomfort, the pain was rated as 0/10 at 1–2 min after the EtOH injection. Lab tests, including BUN and CR were unchanged at 24 h after the procedure. Further follow-up is pending. Early data suggests a significant drop in both systolic and diastolic BP at 4 weeks after unilateral denervation (n = 5). These data need to be confirmed in a larger cohort.

Discussion

In these studies we have demonstrated the apparent safety, and predictability, as well as a dose-dependent efficacy of low dose ethanol injection via micro-needles into the perivascular space to achieve circumferential sympathetic nerve ablation (PeriVascular Renal Denervation, or PVRD™), with minimal injury to the normal renal artery intimal and medial layers, in a porcine model. The ability to target and deliver a neurolytic agent to a deep peri-adventitial space may allow more complete renal denervation than might be easily, or safely obtained using energy-based systems from within the renal artery.

Renal denervation may prove to be a valuable intervention to treat severe hypertension as well as a number of other conditions that may be driven by sympathetic imbalance, or "overdrive." Denervation of the renal artery has been shown to be effective in the treatment of refractory and drug-resistant hypertension [4–7], and possibly in the treatment of congestive heart failure [20], central obstructive sleep apnea [21, 22], left ventricular hypertrophy [23], metabolic syndrome [24, 25], chronic kidney disease [26, 27] and in patients with atrial and/or ventricular arrhythmias [28, 29]. There is a need to develop and evaluate the safest and most effective methods to perform renal denervation.

The drug-delivery catheter used in this study is a novel endovascular delivery device that contains three distal needles housed inside of individual guide tubes, which are contained within the catheter. The catheter is used under

fluoroscopic guidance by a single-operator using standard endovascular techniques to access the vessel of choice and perform injection into the adventitial and peri-adventitial space of that vessel. The radio-opaque micro-needles are deployed with minimal trauma to the normal renal arterial wall and to target delivery in the adventitial and peri-adventitial space. There is no obstruction of renal blood flow during the deployment of this device. The device was very simple to use, with catheter positioning and denervation being performed in less than 2 min from the time that the catheter entered the renal artery via the guiding catheter in virtually all cases. There were no device-related complications.

The known neurolytic agent, Dehydrated Alcohol Injection, USP (ethanol – EtOH, 98 %), was chosen for the evaluation of the drug-delivery catheter used in this study [30–34]. Ethanol is indicated and FDA approved for therapeutic neurolysis, and produces injury to tissue cells by dehydration and by precipitation of protoplasm. At very low doses, ethanol is known to produce neuritis and nerve degeneration (neurolysis). Deliberate injury to nerves by the targeted injection of ethanol results in more or less enduring block of sensory, motor and autonomic function [29–33].

As seen in this study, the dose of ethanol that is effective to create nearly complete renal sympathetic neurolysis involves a dose that is so small that it will produce no apparent systemic effects. Even when double the expected therapeutic dose of 0.3 ml EtOH was purposefully injected directly into the renal artery, we could not detect any signs of renal toxicity. Even at the highest dose used in this study (0.60 ml), contains less alcohol than a single alcoholic drink.

The porcine renal denervation model has been well characterized, and does appear to predict the efficacy in the treatment of refractory hypertension in human subjects. In this study it was possible to verify, and quantify denervation of the kidneys by measurement of the renal parenchymal levels of the neurohormone, norepinephrine (NE). We further validated the neurohormonal effects of ethanol-mediated denervation by using careful, and blinded histological examination of both treated and sham controlled arteries.

The histopathology demonstrated profound and circumferential renal sympathetic nerve damage, with nearly complete sparing of the normal intimal and medial architecture of the renal artery, using doses of 0.15–0.60 ml of EtOH/artery. Evaluation at this time point indicates normal arterial healing, although evaluation at longer time points is needed to more fully evaluate safety.

At ethanol doses of 0.30 and 0.60 ml there was essentially complete denervation, as judged by the 78 % and 88 % reduction in renal parenchymal norepinephrine levels, respectively. These reductions observed with 0.30 and 0.60 ml EtOH are substantially equivalent to the reduction seen with surgical denervation in a porcine model.

Despite the reasonable efficacy of both the first and next generation RF and ultrasound catheters [3–7], there are a number of potential limitations, and safety concerns associated with the use of transmural thermal injury using either RF or ultrasound, traversing the intimal and medial layers of the renal artery. In order to create thermal injury to the sympathetic nerves that may run from 2 to 10 mm deep to the intimal surface [15–18], there will be collateral damage to the intimal and medial layers of the renal artery wall. The ability to predictably damage the renal sympathetic nerves in a dose-dependent fashion, using very low volumes of EtOH delivered in the adventitial space may have a number of potential advantages over energy-based systems.

The concerns and limitations of transmural, thermal-injury catheters, that could potentially be overcome with chemical neurolysis, include: (1) potential failure to adequately denervate deeper nerve fibers due to the heat sink as the thermal injury traverses the renal artery wall, resulting in "non-responders" and/or an inadequate BP lowering response (See Fig. 13.6) [4, 6, 7, 9], (2) failure to create circumferential nerve ablation such that many nerves pass uninjured to the kidney, resulting in suboptimal efficacy [4, 6, 7, 34], (3) intense pain related to thermal ablation requiring high doses of benzodiazepines in combination with very high doses of narcotic analgesia, with attendant respiratory depressive effects and the risk of prolonging hospitalization [4–10], (4) the risk of luminal thrombus formation on the endoluminal surface at sites of thermal "burn" injury, with the subsequent risk of downstream thrombo-embolization and potential for renal injury [15], (5) large volumes of contrast use injected directly into the renal arteries bilaterally during repeated positioning of a unipolar electrode RF system, with the potential risk of contrast induced renal injury, (6) long case duration with high levels of radiation exposure to the patient and the operator [4–11], (7) the expense of purchasing and maintaining complex capital equipment required to perform RF and/or ultrasonic ablation, and finally, (8) the risk of provoking neointimal hyperplasia and/or negative remodeling from transmural thermal arterial injury, which may result in subsequent renal artery stenosis and recurrent hypertension [16, 17].

In addition, a recent study by Meier and colleagues, they have found that ~45–50 % of patients with refractory hypertension have renal anatomy that is not suitable for energy-based "burning" denervation systems. The large majority of these cases could, in theory, be treated with the current Peregrine™ chemical denervation catheter, since this device can treat 3.5–7 mm diameter arteries, only requires a 2–3 mm landing zone for the operational piece of the catheter, and can perform denervation in ~1.5–2.0 min per artery.

Although the limitations of thermal ablation for renal denervation are real, and the very early clinical use of the Peregrine™ device appears promising, it remains to be

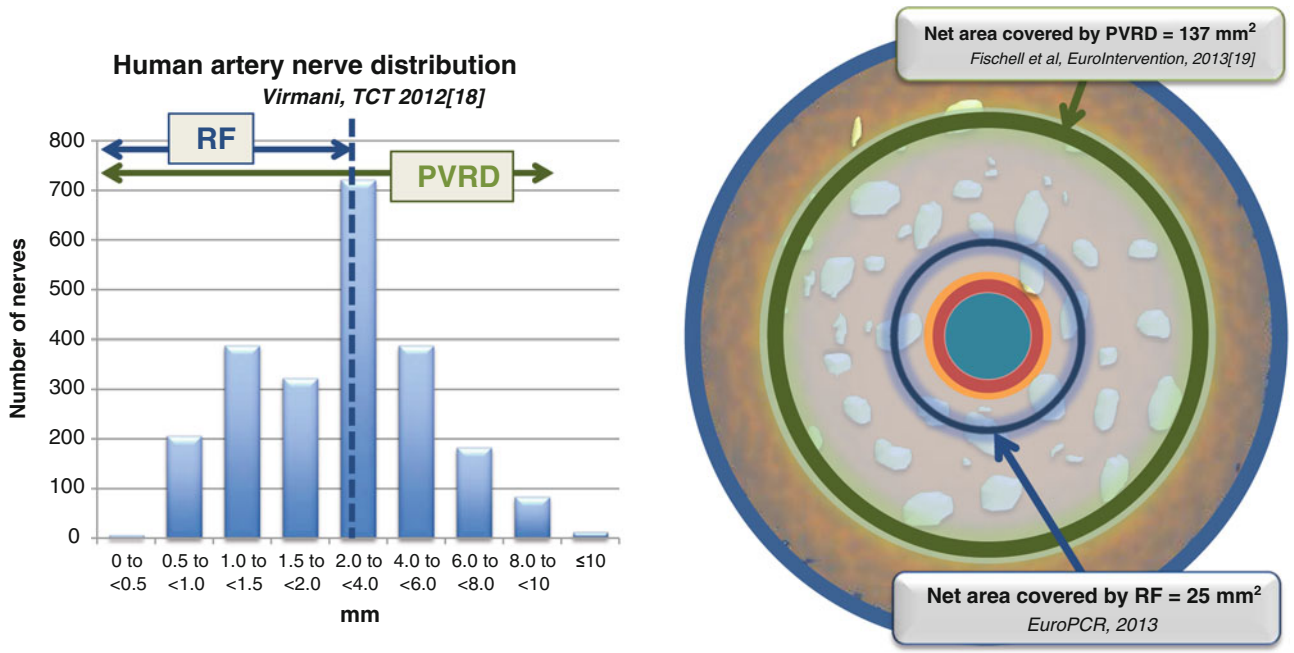

Fig. 13.6 Display of theoretical advantages of chemical EtOH denervation versus RF ablation in depth and extent of sympathetic nerve disruption. *Left panel* depicts sympathetic nerve distribution as function of depth from intimal surface in pressure fixed human renal arteries from presentation from Dr. Renu Virmani. On *right* is cartoon depicting predicted and reported depth of nerve disruption using RF (2.5 mm from intima; *blue circle*) vs. EtOH when delivered as 0.30 ml into adventitia using the Peregrine™ device (*green circle*; 10–14 mm depth from intima). Overall it is estimated that the cross-sectional area of nerve disruption is potentially six to seven times greater with chemical neurolysis using EtOH as compared to RF delivered from the intimal surface

determined how effectively chemical denervation with EtOH, and the use of this novel drug delivery catheter might overcome each of these drawbacks.

Limitations

There, of course, remain a number of unanswered questions regarding the long-term safety and efficacy of ethanol mediated renal denervation. It should be appreciated that renal parenchymal norepinephrine is only a surrogate marker for efficacy in patients. The exact correlation between drops in renal parenchymal norepinephrine levels and antihypertensive efficacy in humans has not been definitively correlated.

Although these data from the porcine model and the first in human experience are encouraging, the true safety and efficacy of ethanol mediated perivascular renal denervation will need to be validated in long-term clinical trials.

Summary

In summary, we report the first use of adventitial and peri-adventitial, local delivery of very low doses of dehydrated EtOH to perform successful renal sympathetic denervation in a porcine model. Circumferential and deep peri-adventitial delivery of very low doses of EtOH has the potential to be a simple, safe, predictable and appealing alternative to energy-based systems to achieve substantial, and dose-dependent renal denervation, with minimal injury to the normal renal arterial wall. Ongoing clinical trials demonstrate that this device and method can be used safely in patients and with essentially no pain during renal denervation. Further clinical evaluation and longer term follow-up will be required to determine the role of alcohol renal denervation using the Peregrine™ system in treating patients with refractory hypertension.

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