Justin Davies

Stanislav Pekarskiy

Promising studies on renal denervation in the entire length of the main artery, as well as treatable branches, including accessories

Renal denervation (RDN) is a procedure that ablates sympathetic nerves as a means of lowering blood pressure in patients with uncontrolled hypertension. Optimising the target site of RDN is a potential means of achieving greater reduction in blood pressure. *Confluence* spoke with Dr Justin Davies, Senior Research Fellow and Consultant Cardiologist at the Hammersmith Hospital, Imperial College London, UK, and Dr Stanislav Pekarskiy, Researcher at the Tomsk National Medical Research Centre, Tomsk, Russia, about advances in RDN and the results of their safety and efficacy studies on RDN in the main trunk and distal segmental branches of the renal artery.

What is renal denervation?

Justin Davies (JD): Renal denervation (RDN) is a medical procedure that aims to improve control of blood pressure and other diseases associated with overactivation of the sympathetic nervous system. The procedure uses devices that are designed to reduce sympathetic nerve activity by ablation of nerves running close to the lumen of the renal artery.

Stanislav Pekarskiy (SP): We use RDN to target patients with high blood pressure who have been treated with at least three antihypertensive drugs, including a diuretic, for 3 months. The time taken to perform the procedure varies depending on the device used.

JD: The extent of ablation also impacts the time taken to perform the study. It is always important to do as complete an ablation as possible. Using the Medtronic Symplicity Spyral™ catheter, the procedure can take anywhere from 40 to 90 minutes, including branch and main trunk denervation.

Can RDN only be performed by experts?

SP: It is not true that this procedure is exceptionally complicated – it could theoretically be done by any interventional physician. The main difficulty is accessing the artery with a very narrow angle of take-off from the aorta.

JD: I think anyone who is skilled in the use of catheters, 0.014" guide wires and X-ray imaging would potentially be a suitable operator for RDN. There are more challenges of performing denervation at the site of the distal branches than at the main trunk due to increased anatomical variability, but overall it's a procedure that most interventional cardiologists or radiologists could routinely perform.

How important is total nerve ablation for lowering blood pressure?

JD: This question currently remains unanswered. Previous studies achieved denervation with a surgical approach and transection of the sympathetic chain,[1,2] but it's challenging to achieve that level of transection using a percutaneous intra-arterial denervation catheter. With RDN, you can be certain about the actual number of ablations that have been performed, but what that translates into, in terms of nerve injury and efficacy of nerve traffic reduction, is very difficult to say. At the moment, the focus is on performing more ablations and extending the total amount of vessel length treated. It's essentially a probability game; the more ablations you perform, in both the main segment and the branches, the greater the likelihood of performing successful RDN.

Can RDN be applied to unusual anatomy, such as tortuous or diseased vessels?

SP: It's really important to apply RDN to a non-diseased vessel wherever possible, because the impact of RDN on a diseased segment remains unknown at this time. So in our experience we try to apply the treatment to a part of the vessel that is free of any disease manifestation.

JD: There is an opinion that RDN should also target accessory arteries when they supply a significant portion of the renal blood flow. Typically, this is when accessory arteries are over 3 mm in diameter, which is the minimum requirement for most catheter systems. I completely agree that you always have to be careful and take into account any underlying disease when performing RDN. The presence of pre-existing stenosis or conditions such as fibromuscular dysplasia make us wary with regard to the denervation site. Some therapy candidates may even be excluded if the stenosis or dysplasia are particularly extensive within the vessel.

Is there an upper or lower limit to the number of ablations that should be applied?

SP: In our experience, we started observing some results, in terms of lowering blood pressure, with at least six ablations per artery, or per kidney.

JD: All data published, including our recent safety study, have shown the safety of RDN. So, in my current practice using the next-generation multi-electrode system, the minimum number of ablations that we perform is eight – at least four in each renal artery. In reality, the mean number is somewhere between 20 and 35; it's a much bigger number than the minimum because the potential for RDN is much larger when you also start treating the branches of the renal artery. Ablation of the segmental branches is what a lot of studies using the Medtronic devices are now focusing on, such as SPYRAL HTN-ON and SPYRAL HTN-OFF. This is a new philosophy that's based on the findings from animal data a couple of years ago, as well as more recent studies.

Dr Pekarskiy, why did you believe that RDN in the distal branches might yield better results in terms of lowering blood pressure?

SP: Our study evaluated the efficacy of RDN in the distal segmental branches of the renal artery versus conventional application of the procedure at the main trunk. Surgical and anatomical studies have shown that the renal plexus has a triangular form with a wide base directed towards the aorta and converging towards the kidney (Figure 1). This form means that the majority of the nerves in the proximal artery are simply unavailable for endovascular treatment. Therefore, we believed that this type of plexus would best be targeted at the segmental branches of the distal renal artery where the nerves are concentrated around the artery and are very close to the lumen.

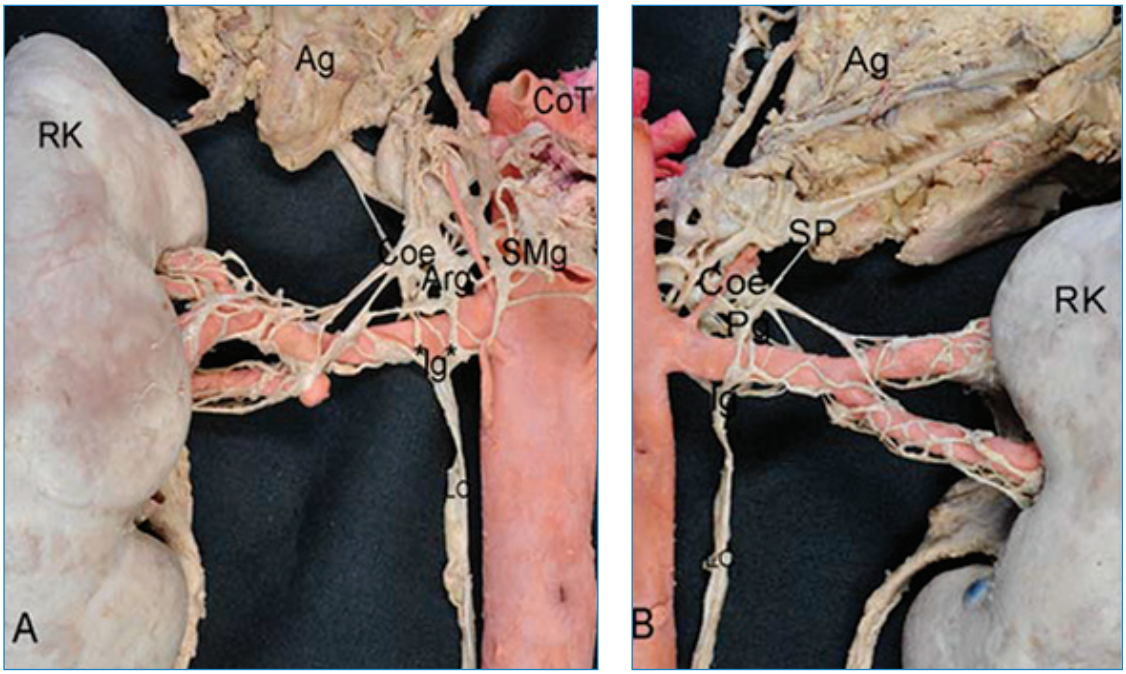

fig. 1

A) Anterior and B) posterior view of the renal sympathetic renal plexus of a right kidney.

Ag: adrenal gland

Arg: aorticorenal ganglion

Coe: coeliac ganglion

CoT: coeliac trunk

Ig: renal inferior ganglion

LC: contribution of the lumbar chain to the renal plexus

Pg: renal posterior ganglion

RK: right kidney

SMg: superior mesenteric ganglion

SP: Thoracic splanchnic nerves.

Please describe the trial design and methodology.

SP: We performed a single-centre, double-blind, randomised controlled trial, which used similar criteria to the SYMPLICITY™ trials and included 55 patients with resistant hypertension. Twenty-eight patients received distal treatment, mainly in the segmental branches of the renal artery and 27 patients were treated conventionally, with denervation only at the main trunk. Fifty-one patients completed 6 months' follow-up – 27 from the distal group and 24 from the conventional model of RDN. We expect further results of 12 months' follow-up shortly. An important point to highlight is that the study was performed with the earlier generation Symplicity Flex™ catheter, which is a different design from the latest generation Symplicity Spyral™ catheter currently being investigated in Medtronic's clinical studies. Unfortunately, this newer technology was not available in Russia at the time we conducted our studies.

What did the results of this study show?

SP: The primary outcome of the study was the change in 24-hour mean systolic blood pressure between patient groups. Six months after the procedure, we found a nearly two times greater reduction in blood pressure for patients treated at the distal segmental branches compared with intervention at the main trunk alone, with a decrease in 24-hour mean systolic blood pressure of –21.1 mmHg and –10.3 mmHg, respectively. There was also a significant difference in the decrease of daytime systolic blood pressure between patient groups. Therefore, we came to the conclusion that conventional treatment of the main trunk of the renal artery is significantly less effective than treatment focusing on the distal parts of the artery.

With regards to the device, we found that the Symplicity Flex™ catheter, with a single steerable tip electrode, was well suited to performing RDN in the narrow, curved anatomy of the distal vessels. In terms of safety, the procedure was well tolerated, especially with regard to distal treatment of the segmental branches. There was only one procedure-related event that was not related to the treatment of the renal artery. Additionally, we found no significant change in blood flow in the segmental branches after distal denervation when using an ultrasound Doppler examination.

Dr Davies, how did you assess the safety of ablation in both the main trunk and arterial branches in your study?

JD: We performed an invasive safety assessment to compare whether denervation at both the main trunk and distal segmental branches had a similar safety profile to denervation performed in the main trunk alone. This was part of a broader study that looked at basic physiological changes that occur as a result of RDN with the Symplicity Spyral™ catheter, with assessment from baseline immediately after denervation to invasive 6-month follow-up.

Patients underwent bilateral RDN in the segmental branches and the main trunk, and were brought back in at 6 months for repeat angiography imaging and physiology measurements in the arteries. The angiography images were then blinded and anonymised, and the characteristics of the renal artery were then assessed by three independent, international reviewers. The results were tabulated and un-blinded to observe if there had been any pathological changes, such as formation of *de novo* stenosis and further narrowings or expansions of the vessel. In this study, we did not find any safety issues.

How did you overcome bias?

JD: One of the huge degrees of variability that we see in a lot of the RDN studies is due to patients not following the pharmacological regimen that is prescribed by the physician. With our patients, we were very careful to ensure that they were taking the medications as prescribed by using observed tablet feeding for 2 days prior to catheter lab visits. We also used a standardised regimen in the catheter lab, so every patient had the same amount of sedation and the same amount of pain killers when seen both at baseline and at the 6-month follow up. Of course, nothing is perfect; our study didn't have a sham control arm, but we used a very rigorous study design to try and eliminate as much bias from the study as possible.

What were your key findings?

JD: One of the main conclusions of our study was that 6 months after extensive RDN was performed there were no abnormal features or abnormal changes observed in the artery. We saw no cases of dissection, thrombus or significant spasms for arteries ablated at either the main trunk or distal branches. From a safety perspective, the study

showed a similarly strong safety profile when compared with studies such as HTN-3, despite far more extensive denervation with an average of 23–24 ablations.

Perhaps our most interesting observation was that the tone or stiffness of the renal artery decreased following RDN, and that this decrease persisted at 6 months. Tone was calculated by measuring pressure and flow simultaneously inside the proximal portion of the renal artery. The reason for this change in tone was likely due to the sympathetic denervation of arteries. We found that patients who have a high sympathetic tone, as measured by the stiffness of the artery, were the people who exhibit the largest reductions in blood pressure. Rather than being just an efficacy observation, this result highlighted a potential method of predicting the patient groups that are most likely to benefit from the procedure.

With regards to safety, is there a way to measure nerve damage during the procedure?

JD: I don't think that a convincing method of measuring nerve damage has yet been shown. Measuring the stiffness of the vessel and the renal artery tone provides a surrogate measurement, which is really a measure of how the sympathetic tone in the vessel is decreased by denervation. We found the same result 6 months later: the tone had decreased from baseline and persisted to the same value as after denervations. So I think that renal sympathetic tone could potentially be used to measure nerve damage, but the direct measurement of nerve activity is really quite tricky, as there are so many potential variables and the signal being measured is so small.

Are there any challenges regarding ablating in the distal segmental branches?

SP: The main challenge with distal treatment is a technical one; either the procedure cannot easily be performed, or the procedure is stopped by the Symplicity G2™ generator, which has a built-in algorithm that stops the procedure when there are significant deviations in impedance or temperature. This occurs relatively more frequently during the treatment of branches, where smaller vessels have relatively lower blood flow. Therefore, using the prior-generation Symplicity Flex™ catheter we are frequently unable to perform the distal treatment completely when working with very complicated anatomy and cannot always do the treatment as we would like to do. I look forward to having the Symplicity Spyral™ catheter available in my country, as my understanding is that this latest technology facilitates branch treatment much more than prior technology that we used.

JD: The generator used in the Symplicity Spyral™ and Flex™ cases evolves the technology that was developed for the first commercial RDN studies. The most important difference is that the new Symplicity G3™ generator can simultaneously deliver and monitor energy to four electrodes. This can reduce procedural time, improve patient experience and reduce time-related costs.

In both of your opinions, are there different challenges when ablating at the distal rather than proximal vessel?

JD: Yes, definitely. There is a different level of complexity and more challenges with regard to performing RDN in the distal segmental branches, rather than main trunk, as some branches have a 90-degree take-off. In some patients there may be four or five overlapping branches that require denervation, so the operator must have a good idea of the three-dimensional anatomy of the vessels and a carefully individualised treatment plan. They must also have a good educational grounding of how to use the equipment – the catheters, wires and denervation system itself – so that they can manipulate the catheter into the side branches. Although ablation at the distal end is a little bit more challenging, the additional difficulty is worth it if the procedure is more effective with regard to the potential for improved sympathetic nerve reduction, transmission reduction and reduction of blood pressure.

SP: I absolutely agree with Dr Davies that the anatomy of the segmental branches is greatly variable. Distal denervation is technically more complicated to treat, due to not only bifurcation, but also because the branches after bifurcation may deviate from the frontal plane, turning backward or forward. In these cases it can be challenging to visualise the branches from the typical frontal view in anterior–posterior projection.

How do you think that results from the efficacy and safety studies will impact the field?

SP: I believe that our results help to prove that conventional treatment in the main trunk is simply

inadequate and ineffective when compared to RDN in the segmental branches. Branch treatment is so different from treatment in the main trunk because it first requires consideration of complicated anatomy.

JD: The results from the safety study show that with intensive invasive follow-up there is no detectable arterial injury sustained when using the Symplicity Spyral™ device in the distal branch and main trunk. We are now waiting for the results of the SPYRAL HTN-ON and HTN-OFF studies to elucidate more information with regard to efficacy.

Another huge area of interest is the ability to predict the efficacy of the procedure. In this study we found that we could probably have excluded 20% of patients who were unlikely to respond to treatment based on baseline measurements of arterial tone. Our initial encouraging results suggest that we need to further investigate a non-invasive way of measuring renal artery tone to identify the patients who are most likely to benefit from the procedure. Such measurements could be worthwhile if you know that success can be achieved in eight out of ten cases where the tone is appropriate. Our goal is to use these initial results to design new studies that confirm this hypothesis.

What further studies would you like to see to advance the application of RDN?

SP: I would like to see a much larger, multi-centre study focusing on the efficacy of distal treatment. More direct comparisons of RDN in the segmental branches versus treatment of the main trunk alone could help to build on the results of our pilot study.

JD: I agree that the most important area to focus on at the moment is to show the efficacy of the whole therapy using these technologies, and I think there is a whole range of clinical trials that will start reporting data next year and help to show that. One of these studies is the REACH study, which I have been leading at Imperial College London, which will examine the potential of RDN as a treatment for congestive heart failure. However, the most important studies will be the SPYRAL HTN-ON and SPYRAL HTN-OFF studies, which are randomised sham control studies designed to robustly explore the reduction in blood pressure with RDN. I expect these studies to report in the near future, but perhaps with smaller blood reductions than were observed in the SYMPLICITY HTN-1 and -2 studies. Subsequently, other ways to fine tune the procedure or help with identifying patients who are likely to respond will be very exciting topics to explore in larger patient cohorts.

Address for correspondence
Dr Justin Davies
Hammersmith Hospital Campus B
block South, 2nd floor
NHLI – Cardiovascular Science
Du Cane Road
London W12 0NN
UK

justin.davies@imperial.ac.uk

+44 20 7594 1024

Dr Stanislav Pekarskiy
Cardiology Research Institute
Tomsk National Research
Medical Centre
111a Kievskaya Str
Tomsk 634012, Russia

pekarski@cardio-tomsk.ru

+7 382 255 8122

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