Interview

Novel insights into renal denervation

Stephen Worthley speaks to Caroline Telfer, Assistant Commissioning Editor

Stephen Worthley

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Professor Stephen Worthley graduated in Medicine at the University of Adelaide (Australia). His training included his cardiology fellowship at the Royal Adelaide Hospital, his PhD at the Mount Sinai Medical Center in New York (USA), and postdoctoral research and interventional fellowship at Monash Medical Centre (Australia). He established the first dedicated Cardiac Computed Tomography and Magnetic Resonance units in the Asia Pacific region, as well as leading the Cardiovascular Research Centre (University of Adelaide) as the Helpman Professor of Cardiovascular Medicine, a position he has held since 2004. He has published over 150 manuscripts and five book chapters, and coedited a cardiovascular textbook. He leads a number of novel international multicenter cardiovascular therapy trials, and his clinical and research expertise spans natriuretic peptide and stem cell therapies though to transcatheter valve implantation and renal artery denervation therapy. He sits on numerous industry advisory boards, journal editorial boards and government advisory groups. In 2002, he initiated a radial artery access program at the Royal Adelaide Hospital, which rapidly evolved to become the largest volume radial access program in Australia. He is on the steering committees of interventional meetings including the ANZET and ANZET Radial meetings in Australia, and is a regular faculty member of the Transcatheter Cardiovascular Therapeutics and EuroPCR meetings. He is internationally renowned for his interventional and imaging academic output, and early development programs for novel therapies in cardiovascular disease.

■ **Can you tell us a little bit about your career background?**

I am from Australia originally. I trained in Adelaide and did my PhD at Mount Sinai Medical Center in New York (USA) on MRI of atherosclerosis during the 1990s. I worked in Melbourne (Australia) at Monash Medical Centre in the field of intravascular ultrasound imaging and then took up the post of Professor of Cardiovascular Medicine at the University of Adelaide (Australia) in 2004, which I currently hold. I worked at the Royal Adelaide Hospital (Australia) for 8 years managing the cardiovascular interventional program there and I currently run the cardiac interventional program at a University hospital called St Andrews Hospital (Australia). I have research interests in novel devices, therapies and imaging so my involvement with renal denervation is a natural extension of these interests.

■ **What would you consider to be your greatest achievement to date?**

I would probably say this project – to have been greatly involved in renal denervation in a very early nascent phase of the development and to have worked with a company like St Jude Medical (MN, USA) to help them develop their multielectrode system, has been as good as any of the other developments I have been involved with.

■ **Can you explain a little bit about the theory behind renal denervation for drug-resistant hypertension?**

We have understood for a long time that sympathetic drive is the key initiator and maintainer of high blood pressure (BP). We know that there is cerebral–neural interplay running through the nerves from the aorta along the outside of the kidney arteries to the kidneys; these nerves, when activated, cause the kidneys to release a number of hormones that are key in high BP. These hormones are called renin, angiotensin

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and aldosterone. When released, these hormones retain salt and water, they increase intravascular volume and cause arteries to constrict; they contribute to the pathophysiological features of hypertension. We also know that those same nerves actually take information back from the kidneys to the brain to modulate central sympathetic activity. The natural adrenaline in your body – the fight or flight system – is mediated by your brain, and is also controlled by the kidneys. We knew from around the 1940s, that when you surgically disrupted the nerves around the kidney artery, two things occur: a reduction in hormones (renin, angiotensin and aldosterone), which cause BP to reduce (the efferent system); but equally we think that by disrupting the afferent system (the system from the nerves in the kidney back to the brain), central sympathetic activity is also reduced. Both of these probably have some role to play in the BP reduction that we have seen with this percutaneous renal denervation. That was all open surgical procedure; the real advancement that we have seen with these catheters is that we can now cause disruption to those nerve fibers by carrying out a minimally invasive or percutaneous technique, by placing a very small fine catheter through the artery in the groin and damaging the nerves from inside the artery.

■ **You have spoken about the EnligHTN I trial, for which you are a primary investigator, which is now 1 year down the line. Can you explain a little about the background of this trial?**

This was a first-in-human study of the EnligHTN catheter. The EnligHTN was the first multi-electrode catheter; it has four electrodes on a nitinol self-expanding basket that allows you to place the lesions in order to damage the nerves that feed the kidney arteries in the ideal position. This is the first time that this has been carried out with multiple different electrodes and we were looking to show the safety of this approach and also the efficacy. A total of 46 patients were treated with this method across three centers in Australia and in one site in Greece. At 1 month, we saw that there was a rapid, significant reduction of systolic BP by 28/10 mmHg; at 3 months, this was sustained, it was 27/10 mmHg; at 6 months, it was statistically no different at 26/10 mmHg; and today we presented the 12-month data, showing a 27/11 mmHg reduction, thus attesting to the fact that a statistically significant, early reduction remains constant over the 12 months since we first started the study.

■ **What were the inclusion criteria for this study?**

A resistant hypertension group of patients. These are patients that are on multiple drug therapies; they had to be on at least three antihypertensives, one of which had to be a diuretic and they needed a BP that was greater than 160 mmHg. There were also some key exclusion criteria, such as atherosclerotic disease in the renal arteries, multiple main renal arteries or Type I diabetes.

■ **You have been speaking today at EuroPCR on the results after 1 year. Are these results as expected?**

Although they were expected, there are always potential reasons why they could have been different, for example, could the BP reduction have been greater? There has been a concept that the afferent system can sometimes mature over 6–12 months and that you could have a greater BP reduction. There was also the risk that the BP reduction was less at 12 months, than was seen earlier. This could occur owing to a number of reasons. It could be less since the patients are potentially coming off medications between 6 and 12 months because as part of the study design, we mandate that you have to stay on medication for 6 months but it is then decided clinically thereafter. Some of the reasons that we may have seen a smaller blood reduction at 12 months, versus the earlier time points, is that patients may have started reducing the number of antihypertensive medications they were on, thus attenuating any BP reductions seen. Theoretically, we could start to see a smaller BP reduction if there was any renal artery renervation. If this occurred, then we could expect to see the office BP rising again. So showing that the BP reductions seen at earlier time points were maintained at 12 months is a very important finding.

■ **St Jude Medical has just announced the enrollment of the first patient in the EnligHTN III trial.**

Can you explain a little about this trial?

One of the things about this multielectrode system is that you still have to deliver the therapies sequentially. Each one is given one at a time so, although it is simple to do, it means that the procedure can be lengthy. Our normal procedure time is approximately 45 min. What they have done is made a number of different algorithm changes so that they are now able to deliver therapy simultaneously to all four electrodes at the same time. That may sound simple to do but it is technically very challenging as the impedances of all of the electrodes will be different, the contact will be slightly different and the power output to each electrode needs to be different. A lot of preclinical testing has gone on, to find the right length, temperature and power, and now they have been able to reduce the time taken to deliver these therapies by sixfold. The time to deliver the treatment used to be 24 min, it is now 4 min. Given that it was an algorithm change, it was important to do a first-in-human study with this new generator to ensure that the same results are obtained. In Australia and New Zealand, we have treated ten patients in total now and, pleasingly, there have been no safety concerns at this early stage.

■ **What are the enrollment criteria for this trial? Are they the same as the first?**

They are essentially identical. This gives us the ability to review the magnitude of benefit seen with the first dataset and therefore allows for some comparability between the two.

■ **What will be the end points for this trial and how long will it be monitored for?**

Safety is the primary end point, which is all adverse events reported, both serious or standard adverse events, and the primary efficacy end point is the change in systolic BP at 6 months. These patients will be followed-up for 2 years.

■ **How do you predict the results from EnligHTN III will build upon the results from EnligHTN I?**

I would like to think that we will see a very similar reduction in BP to that in the EnligHTN I study. There is no reason for me to think that it will be much different but this is why we perform the study; to ensure that indeed what we think we will be able to achieve preclinically is what is delivered to our patients. Already we have seen in the EnligHTN I study that, at 24 h, there was a 23/8 mmHg reduction. I have seen the 24-h data in our patients and I can give you some context in that it seems to be very similar to this.

■ **What do you predict will be the progress in the use of renal denervation for the treatment of resistant hypertension in the next 5 years?**

I think it will be very significant in the next 5 years, and even in the next 1–2 years. However, I think that we are still in an early stage of clinical research with regards to renal denervation due to the lack of large data sets with hard clinical outcomes. We have seen a significant investment from both St Jude Medical and Medtronic (MN, USA) in patient outcomes and as we get larger numbers of patients, greater patient years and hard outcomes, such as death, myocardial infarction and stroke reduction, we will see that this becomes a standard clinical therapy.

■ **What are the next steps for the EnligHTN system?**

The EnligHTN program has a number of arms to it that are continuing at the moment. There is the EnligHTN IV trial, which is not yet initiated but a lot of work is going into it. This is the investigational device exemption, randomized, controlled trial in the USA; approximately 590 patients are randomized 2:1 to renal denervation versus standard of care. Then there is the EnligHTNment trial, which is a very ambitious 4000–5000-patient outcome-driven study that will enrol across Europe and the Asia–Pacific regions. This is a very exciting program that will hopefully be underway sometime in the next 2–6 months. So there are a number of investigator-led studies that have been supported to look at some of the surrogate outcomes: looking, for example, at MRI indices of cardiac and vascular function; obstructive sleep apnea-induced hypertension; and renal function. We should

start to see a lot of evidence emerge in the next 6–12 months.

■ It is day 3 of EuroPCR. What have the highlights been for you?

I think the structural program, with renal denervation and transcatheter aortic valve implantation lead the way. There have been presentations from the REPRISE trials (Boston Scientific, MA, USA) with their transcatheter valve, the Sadra Lotus™ valve. Professor Ian Meredith presented the REPRISE I and II data, showing excellent clinical results with minimal aortic regurgiation with the Lotus transcatheter aortic valve. We have seen some data emerge around the second-generation aortic valve devices. In the renal denervation field, this morning at the first-in-human study session, we saw Covidien (MA, USA) present their data from New Zealand with John Ormiston. We saw Medtronic present their second-generation device, with Rob Whitbourn showing a 16/7 mmHg reduction at 1 month. Of course, we have also had the 12-month data from EnligHTN I and also procedural data from the second-generation EnligHTN III system.

Disclaimer

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