Joachim Weil

Renal denervation: can it reduce ambulatory blood pressure in patients with true resistant hypertension and why are referral networks important?

Renal denervation is a technique that has been shown to reduce blood pressure in most patients with multiple drug-resistant hypertension. *Confluence* spoke to Dr Joachim Weil, Professor of Medicine, Lübeck Medical School and Sana CardioMed Heart Center, to investigate this treatment option and to better understand why referral networks are vital for this technique's success.

How is true resistant hypertension defined?

By guideline definitions, patients with true treatment resistant hypertension have systolic blood pressure (BP) above 140 mm Hg, in spite of three different anti-hypertensive medications (including a diuretic) and normal renal function (in current renal denervation trials, the lower threshold is 160 mm Hg or greater, or 150 mm Hg or greater if the patient is diabetic). This means we need to exclude all secondary causes of hypertension. One problematic secondary cause we need to exclude is poor compliance to medication in our patients. This can sometimes be difficult and we might see patients who are perhaps truly resistant, but still have poor compliance.

Can you explain what renal denervation is, how it works and the history of this therapy?

It is well understood that the kidney plays an important role in the development of hypertension. One of the roles of the sympathetic nervous system is innervation of the kidney. This means that efferent and afferent nerves travelling to and from the kidney to the central nervous system, play a role in regulating the BP. By modifying these nervous signals, it was observed that hypertension could be managed. Indeed, over 50 years ago, surgeons performed sympathectomies in patients with malignant hypertension. At that time they just cut away the sympathetic chain which is in the abdomen. This was shown to be very effective and led to a reduction in mortality. However, as it was a big operation there were often a lot of complications – for example, orthostatic syncope, since you destroyed the whole sympathetic innervation of the lower part of the body. With the development of new drugs, this method stopped being widely used.

Renal denervation is a new technique to treat treatment resistant hypertension by modifying the sympathetic nervous system. As the nerves lie around the renal artery in the adventitia, three to four millimetres from the lumen, the idea was to use different energy sources, normally radiofrequency energy, to heat the tissue at the site of the lumen and intentionally modify the nervous tissue. During the procedure, a catheter is brought in over the femoral artery and into the renal artery and then the ablation catheter is inserted and the energy is supplied to the luminal tissue, thereby affecting the sympathetic nerve system.

What data are available to support the use of renal denervation?

The proof-of-concept trial of the original Ardian device (Symplicity™ renal denervation system), the so-called Symplicity HTN-1 trial, was initiated in Australia in 2008. The initial trial with 45 patients expanded to sites in Europe and the US and included a total of 153 patients. Although it did not have a control group, results showed that systolic blood pressure (SBP) was reduced by 25–30 mm Hg and diastolic blood pressure (DBP) by approximately 15 mm Hg for three years following treatment with renal denervation –

though it is important to note that we are speaking about office BP. These patients all had true resistant hypertension, meaning secondary causes of hypertension were excluded.

Whilst this trial demonstrated the efficacy of this treatment, it was a non-randomized trial and so two years later a small randomized trial, Symplicity HTN-2, which used the same device, was initiated. In this trial, 106 patients were randomized 1:1 to treatment with renal denervation vs. a control group. The control group remained on their antihypertensive medication, while the renal denervation group also remained on medication, but had renal denervation performed in addition. The primary endpoint was reduction in office BP after six months, while the secondary endpoint was safety of the procedure. It was again demonstrated that office BP was reduced in the patients with truly resistant hypertension. The control group was then crossed over to the renal denervation group after six months and patients were followed for another six months. Basically, the same effect of renal denervation was observed again. We now have approximately 30 months of follow-up in this second trial and it looks like the reductions in BP are still present after two years. It should be noted that approximately 10% of patients were found to be non-responders (defined as a reduction in BP of less than 10 mm Hg) in this trial.

While there is a growing body of evidence to support renal denervation for the treatment of resistant hypertension, when compared with studies looking at pharmacological treatment it is still a relatively new therapy with a small but quickly growing evidence base.

Do these studies provide any data on ambulatory BP?

There were only a few patients in the HTN-2 trial that had appropriate 24-hour ambulatory BP monitoring (ABPM) values. However, in a recent paper by Felix Mahfoud and our group at Lübeck,[1] data were pooled from different centres that had performed renal denervation therapy in patients – we all now use 24-hour ABMP to monitor our patients – and this showed a reduction of BP, but only in patients with truly resistant hypertension. If patients had white coat hypertension then the effect was not as pronounced. However, reduction in 24-hour ABPM was lower on average than that seen in office BP. This is a common occurrence even in drug trials where the 24-hour ABPM takes into account the lower reading during night time.

What are the aims of treatment with renal denervation and what influences its outcomes?

The goal of this procedure is to reduce blood pressure in patients whose blood pressure is otherwise uncontrollable, as stated by the guidelines, so bringing them close to 140/90 mm Hg or below. It is not, however, meant to be a method that allows you to reduce medication afterwards. While we do see some patients who have a really dramatic drop in BP in whom you might have to reduce the medication, this is not the goal of treatment at this stage. We always have to tell our patients that they should stay on their medication, and we don't change their medication, except if they have very low BP.

There is evidence that shows that the effect of renal denervation therapy on BP depends on baseline BP.[2] This means that the higher the BP is prior to treatment, the more effect treatment is likely to have, and *vice versa*, the lower your BP, the lower the effect.

What complications are associated with this procedure?

Overall, complications are rare in renal denervation. Most complications are associated with puncturing the arteria femoralis. However, there are two case reports in the literature that show that even using the radiofrequency energy with a single electrode device may cause renal artery stenosis. Therefore, if you have an artery with heavy atherosclerotic disease, you should not treat this, although if it is very localized you can treat the healthy part of the vessel and stay away from the atherosclerotic part of the vessel.

Another very rare complication is severe spasm of the artery, though this usually resolves after time. You can also see local oedema, after the procedure, but this has usually gone if you check after a month. In smaller vessels, the risk of causing spasm or local oedema is far larger, so people should only operate in vessels larger than 4 mm in diameter.

Furthermore, approximately 20% of patients don't respond to treatment even if you treat according to indication. One possible explanation for this is that sympathetic tone does not play a role in these patients. Since we do not have an easy test to see beforehand if somebody has a high sympathetic

tone or not, we never know. The second possible reason is that while carrying out this procedure, we do not have an immediate read-out, unlike doing ablation in atrial fibrillation for example. We have to wait for up to six months and look for the effect on BP. Until then we can't really say whether the procedure has been successful or not. While there have been some proposed indicators for non-response, there is nothing conclusive. However, it looks as if patients take centrally acting hypertensives like clonidine, this seems to be a group which responds very well.

What are the challenges with this technique at present?

As there is only one randomized trial and the number of patients studied is rather small, further data will be needed to convince people of the value of this technique. There is a second small non-randomized trial from another company (St. Jude) that has a renal denervation system on the market which shows the same data. In my eyes it is a relatively safe procedure; I have performed 140 procedures so far, but the important part is to identify the right patients. This is the major challenge. Data presented by Prof. Böhm, at a recent ESC meeting, on the renal denervation registry (GREAT Registry) shows that about 35% of the patients who were treated were treated outside the indication.[3] In our clinic, we have screened close to 1,000 patients to find the 100 who are eligible for this procedure and this appears to be representative; if you look for the prevalence of these patients it is round about one in ten.

What data are still required to increase the uptake of this technique?

Based on the current data, renal denervation has been given a IIb rating in ESC guidelines, however, the next big step will be the Symplicity HTN-3 trial data, which will be very important.

This trial has a number of aspects that are important: firstly, it includes the same patients as previously studied – truly resistant patients – but in addition they also monitor 24-hour ABPM to clearly show the effect on overall BP profile during the course of the day. Secondly, this will be the biggest trial to date, comprising approximately 530 patients. Finally, these patients will be blinded to treatment and will get a sham operation, an angiography, to better exclude any placebo effect associated with the procedure. The results are still pending and are likely to be published next year. A criticism of renal denervation is that it has been difficult to show that a reduction in BP translates into a reduction in mortality and morbidity. Unfortunately, studies to demonstrate such an effect may not be easy; the relatively low risk or event rate of these patients is likely to mean a lot of patients and a long follow-up period are required and I don't know if such trials will be carried out. However, existing data from meta-analyses show that lower BP usually translates into reduced mortality or morbidity. For example, our group has shown that in responders and the older patients, renal denervation therapy can also result in a reduction of pulse wave velocity, an important risk factor for cardiovascular events. This is still an open question, but I believe that if we officially get BP down then that will also have an effect on mortality and morbidity.

Why are referral networks important?

They are very important because you have to screen a relatively high number of patients to find those with truly resistant hypertension. Patients are often excluded from treatment as they have not had three or more medications, or they have normal BP. Even if patients meet these criteria, you have to do some work-up for secondary causes of hypertension. About 90% of the patients have essential hypertension, but you still have to find those 10% who might have a tumour, for example. The treatment only produces optimal results in patients with truly resistant hypertension, so referral networks help us to direct our efforts toward these patients.

We have developed a set of questions for our referring physicians that tells us how many medications patients take, what the 24-hour ABPM looks like and their office BP. Those are the three most important things. If the patient fits the correct profile, we see the patient and do further work-up if necessary.

How long has it taken you to set up this thorough network and do you have any tips for those looking to build up a similar programme?

Two years. We feel it is better to have specialized centres with an extensive referring network and a high number of cases performed, than to have many sites with a small number of procedures. While the procedure is relatively easy to handle –

that is not the issue – the challenge is in correctly identifying and working up the patients and this is better achieved by a specialist centre.

The first thing you have to do is to create awareness of this method. A lot of colleagues have never heard about this technique. I started out in my own hospital, creating awareness amongst my colleagues, who then passed on this information to their friends and colleagues. I then tried to inform our local physicians, so going into doctors' networks, for example, giving presentations and workshops, inviting nephrologists – a very important group of referring physicians – who may require persuasion. You have to really convince them using your own data and by the quality of the work that you deliver.

How important is the multidisciplinary team?

In my eyes it is also very important to have an interdisciplinary team where you have an endocrinologist, nephrologist and cardiologist; these are the key people. That is what we have in our centre. This helps us to ensure that patients are referred efficiently and then receive the correct work-up for hypertension.

What does the future hold for renal denervation?

People are now also looking for pleiotropic effects; the sympathetic tone plays a role in other diseases as well, for example in heart failure. Dr Justin Davies from London published a pilot trial in heart failure patients, just modulating the sympathetic tone.[4] There are also some preliminary data on diabetes, sleep apnoea and patients with end-stage renal failure. There are a lot of new questions in this area.

One session on the recent ESC meeting in Amsterdam was entitled: "Hypertension comes back to cardiology". This is very true. People are now paying more attention to hypertension and it is coming back into focus again. Hypertension is a very important disease, which is in the beginning of the cardiovascular continuum, so it is critical to treat these patients to prevent many other diseases, such as coronary artery disease and heart failure.

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