Renal nerve ablation has experienced ups and downs over recent years and had become side-lined as a potential treatment for hypertension. However, following the publication of new studies in May 2018, it appears to be back on track. European Heart Journal Editor-in-Chief Thomas Lüscher looks at the background to the fall, and subsequent rise of renal nerve ablation.

Hypertension has long been recognized as a major and often ‘silent’ risk factor for cardiovascular diseases as many people do not realize they have the condition. Patients with high blood pressure (BP) will usually be treated with between two or three, or possibly more anti-hypertensive drugs to control BP. Renal nerve ablation is indicated for those patients who are experiencing problems despite using three anti-hypertensive drugs, including a diuretic.

Lüscher says: ‘The role of the sympathetic nervous system is recognized as being very important for BP regulation in the short term, through the baroreceptors in the cerebrovascular arteries, but in the long term it’s the kidney that regulate BP via hormones or through water and sodium in haemostasis. We know that when you activate the sympathetic nervous system the kidney starts to retain water and salt and starts to produce renin and in turn angiotensin, and BP increases. It has been shown that some patients, particularly young patients with high BP have an overactive sympathetic nervous system and this gave rise to the concept that these over-reactive nerves could be destroyed by radiofrequency energies.

This is similar to the way electrophysiologists treat atrial fibrillation. This was shown to work by surgeons in the 1950s who surgically denervated the kidneys and showed not only a fall in BP, but also a fall in mortality. With the advent of commonly available drugs to lower BP, this sort of surgical procedure effectively vanished, although the notion of renal ablation remained.

Murray Esler of the Baker Institute in Melbourne, Australia, an expert on the sympathetic nervous system in relation to hypertension, came up with the idea of using renal radiofrequency via a catheter to destroy the sympathetic nerves as a treatment for high BP. He initially published a series of registry studies showing a fall in BP following this procedure, followed by a randomized, controlled trial which recorded similar results and suggested good potential for the procedure. However, in 2014, the Symplicity HTN-3 trial—a sham control trial—where randomized patients were told they were going to get a renal angiogram only or a renal nerve ablation, and followed-up 6 months later, changed the landscape. The study which was published in the New England Journal of Medicine showed no real effect of renal nerve ablation.

Lüscher takes up the story: ‘This was a catastrophe for the whole field and most people abandoned this method. However, a few, those that were really interested, were more critical of Symplicity HTN-3 and what it really means. Indeed, it was noted that an insufficient number of renal nerve ablations had been performed in many patients. In fact, even the investigators of Symplicity HTN-3 did a sub-analysis where they looked at patients who had received up to 16 ablations in renal arteries when compared with those who got less’. Importantly, those who had been given a larger number of ablations in both kidneys also experienced a marked decrease in BP. This stimulated further debate and more trials including some influential studies that were recently published in the Lancet appear to indicate a turnaround in the effectiveness of renal nerve ablation in lowering BP but were not sham controlled.

The narrative changed in May 2018 with the publication three studies: Spyral off-med to assess the effect of renal denervation on BP in the absence of anti-hypertensive medications, and Spyral on-med to obtain an assessment of the efficacy and safety of renal denervation in the presence of three standard anti-hypertensive medications. Moreover, a similar trial was testing an ultrasound balloon catheter for renal nerve ablation. These three new trials that were published in the Lancet showed that off-med patients who were not using anti-hypertensive drugs and who underwent this procedure experienced a BP drop; it also showed that on-med patients who weren’t well-controlled also experienced a significant reduction in BP. There was also a third study done with ultrasound energy and a balloon catheter which also showed a reduction in BP.

Lüscher suggests that further trials could focus on whether the procedure is lowering BP and contributing to a subsequent reduction in cardiovascular events. The difficulty with renal nerve ablation in comparison to other interventional procedures is, he says, a difficulty in gauging effectiveness. ‘When you do something like stenting, you can see the effect immediately and measure the blood flow and so on, but in the case of renal nerve ablation procedures you don’t see the nerves. The patient experiences pain so you are aware that the procedure has had an effect, but it’s difficult to measure the depth and effectiveness of nerve destruction’.
Currently, the procedure is mostly being performed within trials, but Lüscher suggests that following the slowdown in progress that followed in the wake of Symplicity HTN-3, we are likely to see it recover sufficiently to be used as a clinical tool in the not too distant future. Ongoing trials into renal denervation using alcohol also show potential for this to be used as well as ultrasound and radiofrequency energy in the procedure, pending further investigation.

In conclusion, Lüscher says: ‘Renal nerve ablation intervention is clearly back. As is often the case in medicine, there is a big initial hype and a feeling that we have found the cure for everything. This sense of

dot:10.1093/eurheartj/ehy717
Renal nerve ablation for hypertension: Update from an insider

The recent publication of three positive, sham-controlled renal denervation studies has turned this field on its head, dispelling any lingering doubts as to efficacy which might still linger from the flawed Symplicity HTN-3 trial.1 Ambulatory blood pressure was similarly and materially lowered in the SPYRAL HTN-OFF MED trial,2 the SPYRAL HTN-ON Med trial,3 and RADIANCE-HTN SOLO trial.4 Not surprisingly, the ups and downs in the fortunes of renal denervation has been unsettling for patients, one of my own patient pioneers saying ironically: ‘So the special blood pressure treatment which fixed me up ten years ago does work after all’. What made the difference?

The procedural revolution in renal denervation

Renal denervation trials now include a sham procedure and 24-h ambulatory blood pressure endpoints, but more important than these in underwriting the recent positive trials was a procedural revolution in ablative energy delivery. By comparison, inclusion of the sham and 24-h BP trial elements amounts to clinical trialist ‘tinkering’. Recently implemented RDN procedural changes are based on the new neuroanatomical knowledge that renal sympathetic nerves, as they course towards the kidneys, are closest to the artery lumen in the distal renal arteries and renal artery divisions,5 and on the fact that after release in the artery lumen, radiofrequency energy is very materially diverted by tendons and lymph nodes and absorbed in veins.6 To best achieve nerve ablation, radiofrequency energy is best administered into the distal renal artery and the renal artery branches; the safety of doing this seems to be established. Further, the energy should be administered at multiple application points,2,3 many more than in customary past practice,1 to maximize the chance of energy finding a path through to the ablation target.

Is there a class effect for renal denervation?

It is probable that there is a class effect for blood pressure (BP) lowering with renal denervation, where the blood pressure fall is independent of how the denervation is achieved. Surgical denervation lowered pressure in the era of surgical thoracolumbar sympathectomy for severe and malignant hypertension, where renal sympathetic denervation was performed inadvertently, and in experimental models of hypertension. Radiofrequency renal nerve ablation also lowers BP in essential hypertension,7 although it has taken 10 years to reach the point where this can be said unequivocally.7 And now the RADIANCE-HTN SOLO study documents the antihypertensive effect of renal denervation achieved with administered intravascular ultrasound energy.8 So, there is likely a generic antihypertensive benefit of renal denervation. This is not to deny that one mechanism of denervation might eventually clinically outrank others.

Issues old, and issues new: selecting patients, confirming denervation

At the inception of catheter-based renal denervation two central questions were, ‘which hypertensive patients would benefit most from renal denervation?’, and ‘how can achieved renal denervation be documented?’ These two questions are still key today and remain unanswered.

Ideal patient selection, it is thought, would follow from identifying those with the phenotype of neurogenic hypertension.8 The difficulty here is that there is no simple, available and valid test for this phenotype. Valid tests, such as the measurement of renal noradrenaline spill over,8 are too complex. Some progress does appear to have been made in this regard, almost by default, with recognition that patients with isolated systolic hypertension have reduced BP responsiveness to renal denervation.9 Their hypertension is probably primarily biomechanical rather than neurogenic. In the absence of valid clinically available tests for neurogenic hypertension, perhaps selection might skip the sympathetic testing, and identify and select for RDN patients with ‘de-facto neurogenic hypertension’,10 which includes those with obesity-hypertension, or early, mild essential hypertension, in whom sympathetic nervous activation is common.8,10,11 This idea is plausible but has never been tested.

Conflict of interest: none declared.