Debate: Renal denervation. The interventional cardiologist perspective

A debate: Denervación renal. Perspectiva del intervencionista

Oriol Rodríguez-Leor[a,b,c,*]

[a] *Institut del Cor, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain*
[b] *Institut per la Recerca Germans Trias i Pujol, Badalona, Barcelona, Spain*
[c] *Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain*

SEE RELATED CONTENT:
https://doi.org/10.24875/RECICE.M19000034

Question: After the negative results of the SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) study, what new studies are dealing with renal denervation (RD) as a possible therapeutic option?

Answer: The results of the SYMPLICITY HTN-3 study[1] were totally unexpected, particularly because those of us who had some sort of experience with this technique had lived a completely different reality. The limitations of the study have to do with the arguable selection of patients (with non-optimized pharmacological treatment that was adjusted during follow-up and generated an unexpectedly positive response in the control group), the operators' lack of experience (most of them conducted their first procedures within the study), and the lack of knowledge on how to conduct this procedure in order to optimize the results.

After the detailed analysis of the SYMPLICITY HTN-3 study,[1] two different studies were designed with an improved device to conduct the procedure and their results have recently been made public.

The first study, the SPYRAL HTN-OFF MED[2] was a randomized sham-controlled clinical trial (with a sham control group) as the proof-of-concept on the efficacy of RD to reduce arterial blood pressure (BP) in patients without concomitant pharmacological treatment. Patients with mild-to-moderate arterial hypertension (HT) (office systolic BP 150 mmHg to 180 mmHg and diastolic BP > 90 mmHg, and 24-hour ambulatory systolic BP 140 mmHg to 170 mmHg) were included in the study. Patients did not receive any prior treatment or had been without any pharmacological treatment for 3 to 4 weeks. The protocol included a drug screening of serum and plasma to confirm the absence of drugs. Patients were randomized on a 1:1 basis to RD using the multielectrode radiofrequency catheter designed by Symplicity Spyral (Medtronic Inc., Minneapolis, United States) (n = 38) or to sham control (n = 42). The primary endpoint included changes in the 24-hour ambulatory BP, much more sensitive and specific to detect changes in the BP that measuring BP at the doctor's office. The analysis of the first 80 patients showed a significant reduction of the 24-hour ambulatory systolic BP and office systolic BP at 3 months in favor of RD. We should mention here that during follow-up no relevant adverse events were reported in any of the two treatment arms and, as former studies had already shown, the procedure turned out to be safe and had an extremely low rate of complications.[1]

The endpoint of the second study, the SPYRAL HTN-ON MED,[3] was to assess the efficacy of RD in a different context. The study population were not patients with resistant HT or HT naïve to drug therapy but non-severe hypertensive patients on drug therapy. Same as it happened with the SPYRAL HTN-OFF MED[2] study, the primary endpoint included changes in the 24-hour BP instead of office-recorded BP changes. The patients included in the study had mild-to-moderate HT (office systolic BP between ≥ 150 mmHg and < 180 mmHg, office diastolic BP ≥ 90 mmHg, and 24-hour ambulatory systolic BP between 140 mmHg and 170 mmHg). RD reduced the 24-hour ambulatory systolic BP and the office systolic BP at 6-month follow up compared to the control arm.[2]

Also, a third study with a totally different device based on ultrasounds and not radiofrequency, the RADIANCE-HTN SOLO,[4] confirmed the good results shown by the SPYRAL HTN-OFF MED[2] in patients with moderate untreated HT with similar results in the monitoring of BP figures at follow-up, which reinforces the idea of RD for the management of HT.

Q.: What kind of technical advances have led to these positive results and what are the limitations of this kind of therapy?

* **Corresponding author:** Unitat de Cardiologia Intervencionista, Institut del Cor Germans Trias i Pujol, Hospital Universitari Germans Trias i Pujol, Ctra. de Canyet s/n, 08916 Badalona, Barcelona, Spain.
E-mail address: oriolrodriguez@gmail.com (O. Rodríguez-Leor).

Online: 22-07-2019.
https://doi.org/10.24875/RECICE.M19000033

A.: The critical analysis of the results shown by the SYMPLICITY HTN-3[1] taught us how to improve the results obtained with this procedure. It confirmed that the patients' response was significantly better when the four quadrants of the renal artery were treated. Also, further studies showed that RD was more effective not only when the main stem of the renal artery was treated but also when the secondary branches were treated as well. A look at the anatomy of the sympathetic innervation revealed that although there were more nervous fibers at a proximal level (where treatment was formerly recommended), these fibers were at a distance from the vascular lumen that made it difficult for the radiofrequency energy released inside the blood vessel to actually reach them. On the contrary, at the most distal portion, nervous fibers are closer to the lumen and they are affected by the radiofrequency lesion. Finally, the number of radiofrequency applications somehow had something to do with efficacy in such a way that today it is adviseable to perform the maximum number of applications.

In order to simplify the procedure and taking all these premises into consideration, a new RD catheter was developed, the Symplicity Spyral, whose main characteristics with respect to the Symplicity Flex catheter (Medtronic Inc., Minneapolis, United States) with which the SYMPLICITY HTN-3[1] study was conducted were that it was a tetrapolar catheter (compared to the former one that was monopolar) meaning that up to 4 simultaneous radiofrequency applications could be performed; also, it cut down the duration of the application from 120 to 60 seconds. Also, the spiral-shaped catheter allowed the radiofrequency application to cover the 4 quadrants of the renal artery. Finally, the optimized caliber of the new device facilitated treating arteries of up to 3 mm in diameter vs 4 mm with the former device.

Q.: What would the actual indications of this technique be, if any?

A.: The clinical practice guidelines established by the European Society of Cardiology and the European Society of Hypertension that have been published recently[5] are older compared to the knowledge acquired from the last studies we mentioned before. In these clinical guidelines, recommendations were based on the SYMPLICITY HTN-3[1] and its use was recommended in the setting of clinical trials only and outside the routine clinical practice.

The results of the new studies consistently show that RD is effective when it comes to improving the monitoring of the BP. Similarly, different observational registries have shown significant improvements in a large number of patients with resistant HT. In Spain we conducted a registry[6] that included 125 of these patients and saw a good response in over 80% of these patients, not only when it comes to the office BP but also, and most important, when it comes to monitoring ambulatory BP. Also, RD significantly reduced pharmacological treatment, a finding that opens the door to future studies. With the evidence available today, in my opinion, patients with maintained non-monitored HT on multi-drug therapy, including aldosterone antagonists, can benefit from this procedure. We know that a reduction of 20 mmHg in systolic BP or 10 mmHg in diastolic BP cuts in half mortality risk due to cardiovascular causes. This improvement is not difficult to achieve in many of these patients after RD.

On the other hand, there are many gaps of knowledge still to be filled in in the field of RD. It is essential to identify those patients who may respond better to this procedure since the pathophysiology of HT is complex and is not always due to alterations in the regulation of the sympathetic nervous system. With regard to the procedure itself, the lack of markers to determine whether RD has been successful or not puts us on a holding pattern to see how the BP figures have evolved before determining its efficacy. The development of a non-invasive test to obtain this information should be the goal of future research. Also, the arrival of new technologies to perform RD procedures requires assessing its safety and efficacy profile in the long run.

Q.: What studies do we need so that clinical practice guidelines can recommend RD as a therapeutic alternative for the management of HT?

A.: Yet despite the raising awareness on the risks of HT and the development of new and better drugs over the last 70 years, data from 2010 in developed countries showed that one third of those who had the disease did not know about it, a little over half of them received pharmacological treatment, and less than a third had an adequate blood pressure monitoring. In this sense, the road ahead of us is a long one.

With the new Symplicity Spyral catheter the long-term safety profile is an issue we should take into consideration to give more robust guarantees that the treatment algorithm—substantially more aggressive than the algorithm used in the SIMPLICITY studies—does not cause complications.

The number of patients included in the studies is not large enough to give us evidence that the reduced BP levels observed after RD actually reduce the rate of cardiovascular events at follow-up. Improving BP is but a surrogate primary endpoint, although it is accepted that there is a correlation between lower BP levels and less cardiovascular events. Also, similar BP reductions to the ones obtained in these studies led to less events in pharmacological studies. A study that showed clinical benefits beyond the monitoring of BP would actually be conclusive in this context. Unfortunately, the high number of patients who should be included in this study probably makes such a study unfeasible. However, we should not forget that damage caused by sympathetic hyperactivity goes beyond hypertension itself and is cause for the worse glucose metabolism seen in diabetic patients, the arterial stiffness of atherosclerosis, the poor prognosis of heart failure and the impaired renal function seen in renal failure, to mention but a few.

The SPYRAL HTN-OFF MED[2] and RADIANCE SOLO[4] clinical trials have given us the first evidence, in a consistent way, on the possible clinical utility of RD for the management of hypertensive patients who may wish, or not, to use antihypertensive drugs. These preliminary results should be confirmed by the ongoing fundamental studies that intend to include a much larger number of patients. The pharmacological treatment of HT is a long-term option and, in most cases, for life. Even though drugs are usually well-tolerated, the noncompliance to pharmacological treatment is a common problem to the extent that almost one third of all hypertensive patients do not start a new prescription of antihypertensive medication and 50% of them become noncompliant during the first year after starting their antihypertensive medication.

In my opinion, should these results be confirmed, there will be a change of paradigm in the management of hypertension. Also, we will have to take every patient's individual preference (shared decision-making process) into consideration on whether to follow pharmacological treatment for life or undergo a more individualized therapeutic approach through a catheter-based invasive procedure that has proven safe and with an active effect at all time.

Finally, in light of the preliminary results seen in other conditions, it will be essential to see if there is an added benefit to regulating the activity of the sympathetic nervous system beyond reducing the BP in other diseases where there is an increased sympathetic nervous system activation such as within cardiology, atrial fibrillation, and heart failure.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Bhatt DL, Kandzari DE, O'Neill WW, et al. A Controlled Trial of Renal Denervation for Resistant Hypertension. *N Engl J Med.* 2014;370:1393-1401.
2. Townsend RR, Mahfoud F, Kandzari DE, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. *Lancet.* 2017;390:2160-2170.
3. Kandzari DE, Böhm M, Mahfoud F, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet.* 2018;391:2346-2355.
4. Azizi M, Schmieder RE, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet.* 2018;391:2335-2345.
5. Williams B, Mancia G, Spiering W, et al. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens.* 2018;36:2284-2309.
6. Rodríguez-Leor O, Segura J, García Donaire JA, et al. Renal denervation for resistant hypertension treatment in Spain. Flex-Spyral registry. Rev Esp Cardiol. 2019. https://doi.org/10.1016/j.recesp.2019.05.013.