Resistant Hypertension and Renal Denervation. Considerations on the Results of the Symplicity HTN-3 Trial

Hipertensión arterial resistente y denervación renal. Reflexiones tras el estudio Symplicity HTN-3

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Resistant hypertension is undoubtedly a real clinical challenge, given that it increases cardiovascular events and has no effective treatment. Thus, it is easy to see why renal sympathetic denervation (RDN) has raised expectations among physicians treating patients with this serious disease. The SYMPPLICITY HTN-1 trial was a proof-of-principle trial followed by the SYMPPLICITY HTN-2 trial, which was a randomized unmasked trial that compared control patients and patients undergoing RDN therapy. Follow-up indicated significant and lasting reductions in blood pressure in the experimental group, thus raising expectations among physicians and patients. In fact, the European Society of Hypertension, the European Society of Cardiology, and an international panel of experts published position papers on RDN. In the same period, an RDN registry was set up in Europe with the participation of accredited centers. The registry has already collected data on more than 1500 patients. The recent publication of the SYMPPLICITY HTN-3 trial, a single-blind, randomized, sham-controlled trial, confirmed that RDN is safe, but apparently lacks efficacy. Studies on RDN take the SYMPPLICITY HTN-3 trial as the reference study and for this reason critics of the technique have suggested that the antihypertensive efficacy of RDN should be reconsidered in the light of its results. We consider that this viewpoint is questionable and analyze the reasons for our position.

The SYMPPLICITY HTN-3 trial followed an excellent design that randomized patients to RDN or a sham procedure. Analyses were based on the intention-to-treat principle. Thus, the trial included a control group to assess the possibility of a placebo effect. In fact, the SYMPPLICITY HTN-1 and HTN-2 trials were accused of simply showing the placebo effect of the treatment on blood pressure. However, the conclusion that RDN lacks efficacy when compared with a sham procedure has been challenged.

Firstly, there is insufficient evidence that blood pressure was stable during the RDN procedure in the SYMPPLICITY HTN-3 trial in contrast to the SYMPPLICITY HTN-1 and HTN-2 trials. The latter trials included long-term patients with high stable blood pressures in the months and even years prior to the trials. The SYMPPLICITY HTN-3 trial included patients who switched medication in the weeks prior to RDN which, together with better adherence due to participation in the trial, may explain the gradual decrease in blood pressure in both patient groups. This decrease may also have been due to the high percentage of medication changes (40%) during follow-up, which had not been considered in the protocol. This possibility is supported by the finding that blood pressure decreased equally in both groups during ambulatory monitoring. It is known that ambulatory blood pressure monitoring does not demonstrate a placebo effect, which would explain the decrease in blood pressure in both groups of patients receiving drug treatment. However, the absence of significant differences between groups as a result of the RDN awaits explanation.

In this regard, certain aspects have hindered the correct interpretation of the data. Firstly, an analysis of the experimental subgroups suggests a possible lack of a positive effect of RDN in the African-American population compared with the positive effect found in the Caucasian population vs the control group. The editorial comments accompanying the article are also of relevance. The authors suggested that the results may be partly explained by the use of spironolactone, which was used in different percentages in the 2 groups (22.5% vs 28.7%). This suggestion seems unlikely since the percentages of use were low and the patients were spironolactone nonresponders, as indicated by the persistence of very high blood pressures. In fact, the results of our study show that RDN is effective in spironolactone nonresponders. It is also difficult to explain the finding that vasodilator use (minoxidil and hydralazine) was associated with the worst results in the experimental group.

Finally, the most relevant question is whether the treatment assessed was correctly administered. The lack of indicators to verify that RDN was correctly performed highlights the need for proficiency when performing the technique. The RDN technique discussed in the SYMPPLICITY HTN-3 trial is based on a deflectable catheter with a single distal monopolar electrode that has to be guided to apply monopolar radiofrequency energy to the 4 quadrants of the circumference of the endothelial artery and withdrawn over a helical path. In summary, this procedure is far more similar...
to the ablation procedures carried out in electrophysiology laboratories than to the vast majority of procedures performed in radiology or interventional cardiac catheterization laboratories. Although the system that controls energy delivery automatically ensures good contact, this in no way guarantees the correct spatial distribution of lesions. In the study, a total of 364 active interventions were performed in 88 centers, with an average of 3 to 4 patients per operator. In total, 31% of the operators carried out 1 intervention; this percentage rose to just over 50% when those performing more than 2 interventions were included.7 Although an RDN expert assessed the operators, they had performed 1 or, at most, 2 interventions; thus a learning curve issue may have penalized the active treatment group.

We also draw attention to the analysis of the number of radiofrequency applications per patient and the effect achieved in reducing blood pressure. Blood pressure gradually decreased when more than 8 ablations were carried out, although this number of ablations was only performed in 163 patients, i.e., less than half of the patients who underwent RDN (Kandzari D, SYMPLECTITY HTN-3 trial: Predictors of BP response subgroup analysis. Paris: PCR; 2014). This trend in blood pressure reduction with an increasing number of applications was statistically significant when blood pressure was measured in the office setting and was clearly maintained during ambulatory blood pressure monitoring, although without reaching statistical significance.12 In fact, the average number of ablations per patient in the European Registry was higher than in the SYMPLECTITY HTN-3 trial.12 Of interest, post-RDN follow-up angiography showed that just over 60% of patients had 0 or 1 notches.7 This figure indicates that the RDN technique was incorrectly performed in a high percentage of patients.

Finally, we still have to explain why the European Registry12 data suggest that RDN is effective in daily practice. We suggest that these data are mainly accounted for by 2 factors: firstly, the selection of centers with a proven good learning curve in managing the SYMPLECTITY catheter technique; and secondly, good patient selection, as demonstrated by our group performing RDN in just 12% of the potential candidates for the procedure.11

In summary, more and better studies are clearly needed to clarify the role of RDN, but the SYMPLECTITY HTN-3 trial is not, as many have asserted, the end of the road for RDN.

**CONFLICTS OF INTEREST**

L.M. Ruijlohe has been a conference speaker and consultant for Medtronic and St Jude. F. Arribas received a grant from the Instituto de Investigacion i + 12, made presentations on "Atrial Fibrillation Ablation: Atrial Phased Array PVAC", received remuneration for developing a presentation on "Workshops on multisite pulmonary vein ablation technology" and was paid travel expenses for the European Congress of Arrhythmias.

**REFERENCES**