Editorial

Renal Denervation in Treating Resistant Hypertension: Does It Have a Future?

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Renal denervation (RD) has been a "medical research rocket" with almost 400 PubMed papers in the last 12 months. Indeed, the idea that, in a patient with difficult hypertension, a 30-60 min procedure, which is safe and causes little and temporary discomfort to the patient, can induce considerable blood pressure decline is very alluring.[1] Thus, the observed surge in relevant research and the enthusiasm from scientists and industry is to some extent understandable and justified. Moreover, blocking the sympathetic system has always been a central and effective approach in the management of hypertension and cardiovascular disease.

The first evidence of the effectiveness of RD in resistant hypertension, derived from unblinded and relatively small studies, has been very encouraging, with impressive blood pressure reductions, and has raised high expectations.[1-3] The SYMPLICITY HTN-1 open-label, proof-of-concept study in 153 patients showed an impressive 25/11 mmHg decline in systolic/diastolic office blood pressure at 6 months, with a progressive further decline that reached 32/14 mmHg at 3 years.[4] However, there was no control group and 40% of the subjects did not have complete follow up. The SYMPLICITY HTN-2 randomized controlled study in 106 subjects was rather confirmatory, with a 32/12 mmHg blood pressure decline at 6 months and 28/10 mmHg at 12 months in 47 subjects.[5]

Unfortunately, the recently published SYMPLICITY HTN-3 study, which used the same catheter and is undoubtedly the most important trial of the efficacy of RD, not only did not confirm the abovementioned preliminary findings, but has been very disappointing.[6] This single-blind controlled study randomized 535 patients with resistant hypertension to RD or sham procedure in a 2:1 ratio. After 6 months there was a trend towards a greater decline in the RD compared to the sham group, but by only 2.4 mmHg in office systolic blood pressure (primary efficacy endpoint) and 2 mmHg in 24-hour ambulatory systolic blood pressure, neither of which reached statistical significance.[6] More importantly, the 95% confidence intervals excluded any clinically important difference between RD and sham, being 7 mmHg for office and 5 mmHg for 24-hour ambulatory systolic blood pressure.

It is well known that, in clinical trials, the lack or inadequacy of a control group is the most "efficient" approach to enhancing the effect of a medical intervention. The SYMPLICITY HTN-3 study solved major methodological issues that were present in previous RD studies. Key methodological features in the study design were: (i) the sham control group (first ever study in RD); (ii) the use of ambula-

tory blood pressure monitoring for inclusion and efficacy assessment, which is considered as indispensable for the evaluation of resistant hypertension;[7] and (iii) an adequate sample size to provide a study power of 80%. These methodological features become more important when dealing with such an unstable variable as blood pressure. Most of the obstacles in clinical trials, including regression to the mean, the placebo effect, and observer prejudice and bias, are much more prominent in blood pressure rather than lipid trials, and were effectively prevented in SYMPLICITY HTN-3.[6]

There is also some good news. First, no difference was identified in the safety of RD versus sham, assessed using a composite endpoint that included death, renal and vascular complications.[6] Second, the study showed that interventionalists can easily master the technique of RD, as there was no difference in outcomes between operators performing five or more versus fewer procedures, or in earlier versus later procedures in the case of high-volume operators.[6]

With regard to the study population, subjects with severe resistant hypertension were indeed included (baseline average 24-hour ambulatory systolic blood pressure 160 mmHg on an average of 5 drugs, including a high-dose diuretic). It is surprising, however, that only 25% of the subjects were on aldosterone antagonists,[6] which have an important role in the management of resistant hypertension and should probably be a prerequisite before RD. On the other hand, it should be mentioned that severe resistance to treatment might not be the appropriate setting for testing RD, because of advanced arterial stiffness that might lead to irresponsiveness to intervention.

The question whether RD is effective in reducing blood pressure in resistant hypertension might be rather simplistic. The right questions are, first, in which patients will RD probably work and, second, what "dosing" of RD should be applied to achieve effective blood pressure decline in each individual and how can it be quantified?

With all drug classes used for treating hypertension, there are patients who show a considerable response and others with a negligible or no response, in terms of blood pressure decline, reflecting different pressor mechanisms driving the blood pressure rise in different individuals. There is no reason to believe that RD, which targets a single system, will not exhibit the same phenomenon.[8] Because RD, although relatively safe, is an interventional and costly procedure with uncertain and potentially irreversible consequences, it does not make sense to apply it in all subjects with resistant hypertension, as physicians empirically do with antihypertensive drugs, switching regimens if necessary. There should definitely be responders and non-responders to RD,[8] and it is essential that tools are developed for their identification before RD is performed.

The results of the SYMPLICITY HTN-3 should not halt the research into RD for resistant hypertension. However, it is clear, first, that the well-known methodological issues of blood pressure-lowering research should be carefully taken into account in designing future studies. Second, like any other intervention that targets pressor mechanisms, RD will not work for everybody with elevated blood pressure, and research should focus on identifying more reliable markers of sympathetic system overactivity and predictors of the response to RD. Third, more reliable tools should be tested to ensure that efficient RD has been achieved in each individual, given that the optimal "dosing" of all interventions for blood pressure reduction requires individualisation.

In other words, those patients who would benefit from RD need to be identified and effective RD should be applied. Then, the method will definitely work!

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