Renal denervation on life support?

¿Denervación renal en soporte vital?

In January 2014, the Medtronic corporation`s press release that the SYMPLICITY HTN-3 clinical trial had not met its primary efficacy endpoint left many in the medical community perplexed. In multiple previous studies of a similar patient population to SYMPLICITY HTN-3, catheter-based radiofrequency denervation of the renal arteries had emerged as a promising therapy for resistant hypertension based on experimental and clinical data and it was already being used clinically throughout Europe, South America, Australia and Canada. For example, in SYMPLICITY HTN-2, the drop in office systolic blood pressure at 6 months averaged –32±23 mmHg on follow up with no change in blood pressure in a control population not undergoing any procedure but maintained on their current antihypertensive medications.[1]

The recent publication in the *New England Journal of Medicine* of the results of SYMPLICITY HTN-3 indicated that at 6 months, there was indeed a drop in office systolic blood pressure in the group undergoing denervation (–14,1±23,9 mmHg) but this was not statistically different from the control population (–11,7±25,9 mmHg) in whom a sham procedure (renal angiography without denervation) was performed.[2] Furthermore, this drop in office systolic blood pressure with renal denervation was very similar to the average drop in systolic blood pressure recently reported in the Global SYMPLICITY Registry of 1000 "real world" patients presented at the American College of Cardiology meeting in Washington DC in March of 2014.[3] What then might be responsible for the failure of SYMPLICITY HTN-3 to meet its primary efficacy endpoint (a paltry drop in office systolic blood pressure of ≥5 mmHg at 6 month in comparison to control)?

The first question that should be addressed is whether or not the catheter system was at fault and thus the patients treated did not experience renal sympathetic denervation. While there is no test to confirm successful denervation, preclinical data, the radiofrequency catheter system used that can monitor arterial wall contact and the deliverance of energy to the arterial wall make this possibility less likely.[4] It will be interesting to see how the other 4 catheter systems already in use in Europe for renal denervation might alter their approach to treatment of resistant hypertension based on the results of SYMPLICITY HTN-3.

The other possible explanation relates to the concept of renal denervation as a treatment for resistant hypertension. Does it actually work and are all patients with resistant hypertension appropriate candidates? While there is ample experimental data that radiofrequency ablation of the renal arteries can lead to a reduction in sympathetic tone,[4-8] the data on blood pressure reduction in clinical trials were not always consistent (a wide standard deviation) and were never adequately controlled. It has also been argued that some forms of secondary hypertension such as that associated with obesity and sleep apnea may not be mediated by heightened sympathetic tone.[9]

The major difference between SYMPLICITY HTN-3 and the other denervation trials was the drop in systolic blood pressure in the control population that underwent a sham procedure. No other study of renal denervation utilized such a control population. Prior studies either compared the treated group to the baseline blood pressure or to an unblinded control population. Some might argue that the blood pressure reduction in the control population represented regression to the mean. Blood pressure was elevated at baseline and just became lower subsequently. However, given the rigorous blood pressure criteria utilized to enter this trial and the fact that only about 1/3 of eligible patients were randomized, I believe this possibility is less likely. Of course, it is possible that medication adherence was different between the treated and control populations or that given the large standard deviation of the change in blood pressure on follow up, a subpopulation of hypertensive patients might ultimately be found to benefit from renal denervation.

However, the most likely explanation for these unanticipated results was that there was a significant placebo effect in both groups which accounted for the findings unrelated to denervation. The placebo effect in medicine is well known and it is substantial in many cardiac conditions contributing to a majority of the clinical response. In systemic hypertension, the contribution has been variable and mostly noted on office measured blood pressures but not on 24 hour non–invasive ambulatory blood pressure monitoring.[10] In SYMPLICITY HTN-3, the control population underwent a sham procedure and was blinded to the treatment strategy. The difference of only –2.4 mmHg in systolic office-measured blood pressure between denervation and sham patients at 6 month follow up could be construed as a costly manifestation of a patien-

t`s presumed treatment strategy. Of interest and as yet unreported, all patients in this trial were questioned as to whether or not they thought they had undergone denervation. It would support the placebo hypothesis if the drop in blood pressure was significantly greater in those who believed they underwent renal denervation (that is, they thought they were in the treated group) compared to those who thought otherwise. Thus, the exuberance for renal denervation as a viable option for resistant hypertension must be significantly lessened by the results of this trial. There will likely be additional analyses of this and other ongoing registries and trials. I suspect that there will be an attempt in the future to identify subgroups of patients with resistant hypertension who might either benefit or in whom denervation should not be attempted. But for now, unless new positive data become available, renal denervation might be hovering on terminal life support with little hope of long term survival.

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