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The scientific power of a "sham" arm?

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We recently received the disappointing news that SYMPLICITY HTN-3 failed to meet its primary efficacy endpoint defined as a difference of 10 mmHg office systolic blood pressure between the sham and active renal denervation groups while it met the primary safety endpoint[1]. In response to this, the Chairmen of the Resistant Hypertension Course issued a statement urging caution that we need to wait "until the peer-reviewed publication of clinical data, most likely around the end of March 2014, to have further information rather than speculating[2]." Whilst sharing the disappointment of those involved, our thoughts turn to a reminiscence of previous experiences with the use of "sham" technology at the beginning of this current century.

In 2000, the group of Peter Fitzgerald, Renu Virmani, Frank Kodologie and Paul Yock presented data regarding the application of intravascular sonotherapy. They showed, in a swine model, that sonotherapy decelerated cellular proliferation and decreased the growth of neointimal hyperplasia after stenting. Naturally, these results were considered as an effective form of non-ionising energy to reduce in-stent restenosis. The data, and in particular I would refer here to figure 2 of their paper (which was ultimately published in Circulation), led to the birth of a new hype[3]. Very soon, leading interventionists such as Jeffery Moses and Antonio Colombo demonstrated – with live cases at TCT – the Pharmasonics (Sunnyvale, CA, USA) technology for antirestenotic therapy in humans.

In the same way, our group in Rotterdam was very much attracted by the potential of this treatment for in-stent restenosis. We performed a pilot study with 37 patients but, unfortunately, we came to the conclusion that a late lumen loss of 1.05 mm and a restenosis rate of 25% was in keeping with conventional treatments[4].

Nevertheless, the great captain of industry, Menahem Massi, wanted to demonstrate with certainty the antirestenotic aspects of this technique. It was the first time in our career, both in the EU and the US, that a trial was designed using a "sham". This "sham" meant that the catheter had to dwell for 10 minutes in the stented lesion, which in itself could generate an adverse event. We convinced the hospital ethics board that for a sham treatment arm we would need to cannulate the artery with the catheter without actually activating the sonotherapy. The beauty of the trial was that it was truly blind as both treatment arms were cannulated, and when the operator "pressed the button of the device" he was unable to know whether activation of the sonotherapy was actually performed. When the study was completed, no difference between the two groups could be demonstrated. We were unable to publish this trial in a major journal, with only the now obsolete International Journal of Cardiovascular Interventions willing to publish the data[5]. This is a lesson I never forgot.

When you have a mechanical device that is supposed to make a physiological or biological change, and when the assessment of the result is based on indirect measurements of bioclinical effects such as blood pressure, it is essential to show that the placebo effect of the device is fully masked with a sham treatment. With the sham treatment, you can fully isolate the safety of the therapy and, likewise, the catheter itself and the intubation of the vessel, as it is in this case concerning the renal artery. The ablation could generate side-effects: in the case discussed here, the simple introduction of the catheter into the renal artery without doing anything else could do this, and the sham by itself allows you to observe whether there are any detrimental effects.

By performing a sham, on one hand, you isolate the positive from the negative aspects of the catheter and, on the other hand, you judge the bioclinical effect in a very objective manner, similar to using a placebo medication in randomised pharmacological studies. Another classic example of "sham" is the treatment of refractory angina pectoris by transmyocardial revascularisation through the creation of a reptilian heart by means of endocardial perfusion.

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The hype was spectacular until the group of Martin Leon randomised this therapy with sham therapy. As the laser treatment was noisy, both patient groups had headphones with classical music to protect the blinding[6].

With respect to the use of sham in the Symplicity HTN-3 trial – and awaiting the publication of the results – to correlate sham with the study's failure, is at this moment, pure speculation. One could postulate that other factors may have influenced the results.

For example, on a technical level, the cannulation of the catheter is relatively straightforward, however, the renal nerves are widely distributed and perhaps catheter orientation issues appeared. As in all new therapies, a learning curve exists, perhaps this was a contributing factor. The majority of the first studies, and the Symplicity HTN-1 and 2, were performed at selected sites in Europe and Australia, whereas the Symplicity HTN-3 trial was performed at selected sites in the United States and Australia. Despite the strict inclusion/exclusion criteria in HTN-3, did the patients truly have resistant hypertension? How did the investigators confirm medication adherence when a recent publication recently reported that 43 to 65.5% of patients with presumed resistant hypertension are non-adherent[7]? What about changes in antihypertensive drug treatment close to randomisation or within the study? Was the HTN-3 primary efficacy endpoint of a 10 mmHg systolic pressure difference between the two groups overly ambitious? Some experts explain that a long-term sustainable 5 mmHg decrease in systolic pressure is still beneficial for the patient group, suggesting that this decrease is the equivalent of adding one additional tablet.

Is renal denervation a hype that is now over? Only with a robust analysis of the HTN-3 results will we know, and it is at that time that we will have to ask ourselves – will we ever really know? Is the outcome of Symplicity HTN-3 related to the first generation device that has been used? What about the other investigational devices with different design and energy sources? Perhaps the focus will be redirected to the early work on various secondary indications, such as the role of renal denervation in the treatment of cardiac arrhythmias, chronic heart failure, chronic kidney disease and diabetes[8].

Ultimately, the evolution of these treatment options for resistant hypertension, be it through pharmacological and/or non-pharmacological pathways, will always have a prominent place in cardiovascular research. The need for progress and further development is clearly justified by the immense patient group involved, and their significant risk for stroke, myocardial infarction and kidney failure.

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