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Invited review

The future of renal denervation

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ABSTRACT

The rationale for the renal denervation treatment of severe, drug-resistant essential hypertension remains valid, but the field is now at a procedural watershed. With the commonly flawed procedures of the past, most notably in the Symplicity HTN-3 trial, which typically directed ablating energy into the proximal renal arteries, coupled with the absence of testing for achieved denervation, who could guess which of the past negative renal denervation trials, if any, are valid? But renal denervation procedures will now be different in two important ways. First, energy will be directed into the distal renal arteries and renal artery branches, where the renal nerves lie closest to the artery lumen. The need for this change is emphatic and unequivocal. Second, the number of energy point applications will be increased to 12–16 bilaterally. This is required because local perivascular anatomy distorts energy flow, making it unpredictable, so that multiple overlapping energy doses are needed. Applying these principles in experimental animals achieves near-total renal sympathetic nerve ablation, and lowers blood pressure. The "smart" renal denervation trials of the future will include a sham procedure and 24-h ambulatory blood pressure endpoints, but more important than these, which in comparison is clinical trialist "tinkering", will be the procedural revolution in ablative energy delivery.

Contents

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1. Introduction

Eight years after the first patient with resistant hypertension was treated with the Symplicity radiofrequency catheter system, many believe that these initial trials, their continuation to later specified endpoints, accompanying resistant hypertension renal denervation registry files, and trials with other, more recently engineered renal denervation devices have established important therapeutic principles (Esler, 2014c):

1. Efferent sympathetic renal denervation can be achieved with luminal delivery of radiofrequency and ultrasonic energy.
2. Blood pressure reduction can be achieved in a majority of patients, office BP falling materially, with ambulant BP falling less. Renal function is preserved. The BP reduction is durable, demonstrably persisting for 3 years and beyond.
3. New renal artery stenoses in the field of radiofrequency energy delivery are very uncommon.

Many, however, might dismiss this preamble as the misplaced view of renal denervation devotees.

2. Symplicity HTN-3 illusory truths

A body blow to the renal denervation treatment of resistant hypertension came with the Simplicity HTN-3 trial in drug-resistant hypertension, the pivotal study for US FDA licensure (Bhatt et al., 2014), in which the primary efficacy endpoint was not reached. Much was expected of the Symplicity HTN-3 study. Incorporating a blinded sham design, this trial was expected to provide the definitive statement on the value of renal denervation in the treatment of patients with severe hypertension. To many it did–"renal denervation does not work". The sham design was lauded (Shun-Shun et al., 2014). This trial exemplar had comprehensively exposed the fallacy of imagined renal denervation benefits. How was it possible to argue against the findings of the Symplicity HTN-3 trial? But it was possible.

2.1. Praise of the sham design but neglect of Symplicity HTN-3 neuroscience failings

The hyperbole surrounding Symplicity HTN-3 was reminiscent of "knowledge-free management" theory and practice, where the proscribed process, in this case the sham procedure, outranks and overrides the specific and essential knowledge base, in this case neuroscience knowledge of the anatomy of the renal sympathetic nerves, and bioengineering knowledge of their sensitivity to ablation by radiofrequency energy. The power of FDA branding in a pivotal trial added to the allure.

But much was amiss with Symplicity HTN-3. At eighty-eight too many centers were recruited for the trial, and at 111 too many proceduralists (Bhatt et al., 2014; Esler, 2014a). No hands-on experience in renal denervation prior to the trial was possible in US (unlike in the earlier Symplicity trials, where it was mandatory). Although experts in their field of interventional cardiology, all participants were novices in the renal denervation procedure. Proctoring (on-site mentoring) was by company non-medical staffers, unlike in the earlier Symplicity trials, where all proctors were MDs who had performed many experimental denervations in pigs.

It is now a matter of record that the denervation procedure fared badly in Symplicity HTN-3 (Kandzari et al., 2014). Retrospective analysis of stored angiographic records of all RF energy applications demonstrated that in 74% of patients not even one fully circumferential renal artery application of energy was achieved, when it was a *mandatory protocol requirement* that this be achieved bilaterally, making effective nerve ablation impossible (Kandzari et al., 2014). The Symplicity HTN-3 trial is now commonly believed to be seriously flawed in its execution (Esler, 2014a). In the words of the trial co-chief investigator, George Bakris: "it is highly likely that RDN as it was performed in the HTN-3 was technically inconsistent at best, but technically inadequate at worst" (Nathan and Bakris, 2014). So rational enthusiasm can remain for renal denervation as a future treatment of human hypertension. The continuing successes with experimental renal denervation validate this optimism (Henegar et al., 2014).

3. The rationale for renal denervation treatment of hypertension remains valid

Central to the development of radiofrequency renal denervation was knowledge of the physiology of the renal sympathetic nerves, and their pathophysiology in experimental and human hypertension. In untreated essential hypertensive patients, the application of regional noradrenaline isotope dilution methodology (Esler et al., 1984), to measure the outward flux of the transmitter from renal sympathetic nerves to plasma (renal noradrenaline spillover), demonstrates that activation of the renal sympathetic outflow is present (Esler et al., 1988), and known now to be most extreme in resistant hypertension (Fig.1)(Esler, 2015a). This is central to hypertension pathogenesis (DiBona and Esler, 2010). The renal tubules receive a dense sympathetic innervation, at all tubular levels. In experimental studies the renal nerves have been demonstrated to stimulate secretion of renin from

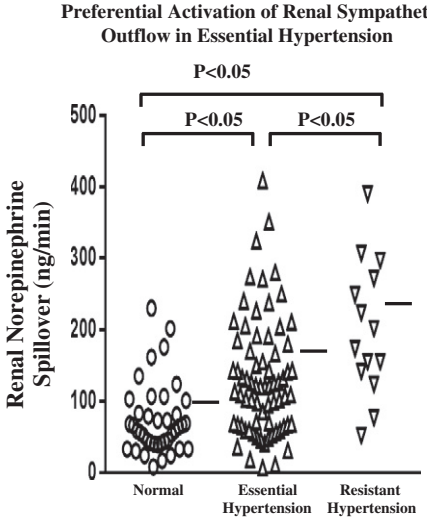

Fig. 1. Sympathetic activity in the kidneys, assessed using isotope dilution measurements of the outward flux of the sympathetic neurotransmitter to plasma (renal norepinephrine spillover) in healthy volunteers and patients with arterial hypertension, in whom renal sympathetic activation was evident in many. In untreated patients with mild-moderately severe essential hypertension (middle column), renal norepinephrine spillover was increased overall, and elevated in approximately 50%. In drug-resistant hypertension renal norepinephrine spillover was higher again. Reproduced from (Esler, 2015a), with permission.