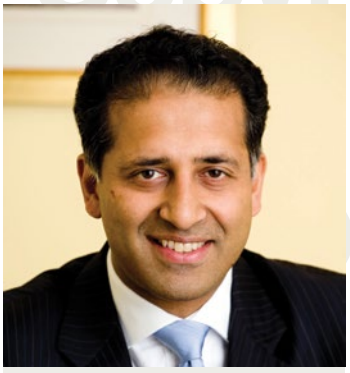
EDITORIAL

Renal sympathetic denervation: cautious optimism and careful next steps

Melvin D Lobo



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Despite the high and growing prevalence of hypertension worldwide, and the increasing attention focused on the challenge of resistant hypertension (RHTN), it is somewhat extraordinary to note the lack of data attesting to the epidemiology and management of RHTN at the present time. Few studies have described the incidence and prevalence of this condition, yet, it is very clear that, once diagnosed with RHTN, patients are at strikingly elevated risk of cardiovascular events, and thus clearly defined treatment strategies are urgently required.[1] Quite remarkably, when reviewing the evidence base in RHTN for the recent National Institute for Health and Care Excellence (NICE) hypertension guidelines, the authors could find just one head-to-head randomised-controlled trial in this patient cohort, and only six retrospective cohort studies, with the largest being a *post hoc* analysis of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study, where the use of spironolactone as a fourth-line agent was associated with blood pressure (BP) reductions of ~20/10 mmHg.[2] Currently, we are hopeful that trials, such as the British Hypertension Society (BHS)-led Pathway 2 study (UKCRN.org.uk ID 4500) and the Resistant Hypertension Optimal Treatment (ReHOT) study (Clinicaltrials.gov ID NCT01643434), will help improve our drug therapy of RHTN. Nonetheless, it should be recognised that, while pharmacotherapy of hypertension is proven (at least up until the point of RHTN), issues with physician inertia, poor concordance and drug intolerance continue to undermine our efforts to get patients to target BP.

The past three years has serendipitously seen the emergence of a novel class of device therapies for hypertension with renal sympathetic denervation (RSD) and baroreflex activation therapy currently leading the way. The intense interest in RSD is reflected in the fact that there are now more than 60 device manufacturers competing in this environment to produce technologies that cause renal nerve destruction through a variety of energy modalities based upon the fact that renal nerves are exquisitely sensitive to thermal and vibrational energy. Thus RSD is now feasible, not only with radiofrequency energy, but also low-intensity and high-intensity ultrasound energy, cryoablation techniques and microwave energy. Importantly, all of these therapies are delivered via an endoluminal approach and, to a variable extent, result in endothelial injury, which may have ramifications for renal artery health in the long term, although no data exist to support or challenge this notion at present. However, opportunities to achieve RSD through direct neurolysis with alcohol or guanethidine microinjection into the adventitia without intimal damage look promising, and, certainly, are worthy of further study.

Issues

A major issue with RSD at present is the fact that the treatment is predicated on the crucial role of renal sympathetic nerve signalling in hypertension perpetuation, and, while impressive data have accrued indicating an important role for these nerves in hypertension in both animal and human models, it is by no means clear that the renal sympathetic nervous system (SNS) is a critical component of all forms of RHTN.[3] Furthermore, a major disadvantage of current RSD technologies is the inability to determine whether or not ablation has been delivered successfully to result in renal nerve destruction. While the limited clinical trials dataset to date has indicated encouraging responses to RSD, a number of criticisms have been voiced and there is a paucity of well-constructed, randomised-controlled studies in rigorously screened RHTN patients.[4] In the published clinical trials, encompassing only very small numbers of patients, the non-responder rate of 10–15% seems overly optimistic and the lack of ambulatory blood pressure monitoring (ABPM) data is a concern. Even smaller datasets pertaining

to Hypertension Centres of Excellence indicate, worryingly, that success rates of the therapy are much lower and, thus, the hypertension community eagerly awaits the 2014 publication of the Symplicity HTN-3 study, which is a prospective, single-blind, masked procedure trial with ABPM mandated at entry.[5-7]

RSD has been taken up with unbridled enthusiasm globally and, in Germany alone, more than 100 centres are offering the procedure with several thousand patients denervated to date. The UK uptake, however, remains restricted, given that presently the treatment is not commissioned and, thus, centres wishing to treat patients with RSD have had to do this within the framework of sponsored clinical trials or using their own funds. In recognition of both the unmet need in RHTN for better therapies, and also the need for the UK to develop experience in the procedure and remain competitive in the areas of therapeutic innovation and research, the Joint UK Societies' Consensus Statement on Renal Denervation has outlined a clear framework for the screening of patients and the place of RSD in the hypertension treatment algorithm as a final last step when conventional measures to treat RHTN have failed.[8] Furthermore, NICE has now produced interim guidance to assist clinicians with patient selection for RSD.[9]

Progress in the UK

Recently, National Health Service (NHS) England has announced the intention to progress adoption of renal denervation for hypertension as a specialised service within the 'Commissioning through Evaluation' programme.[10] This will allow 10–15 centres throughout the UK the opportunity to undertake RSD in several hundred patients per annum over the next three years, permitting centres to develop and maintain proficiency by undertaking reasonable numbers of the procedure. It is expected that centres selected will be able to demonstrate expertise in the investigation and management of secondary and resistant hypertension and have relevant multi-disciplinary assessment to safely plan and carry out RSD. Reimbursement for the procedure will be contingent upon operators submitting full datasets for collection into the National Registry for renal denervation – currently in the final stages of development – to be hosted at the National Institute for Cardiovascular Outcomes Research (NICOR). While there may be disappointment at restriction of RSD to such small numbers of procedures/centres, this seems an eminently practical and sensible approach to introducing the therapy in the absence of data supporting its use as a standard of care within the NHS.

There is a real danger that RSD is perceived by clinicians and patients alike as a panacea for RHTN, and possibly even milder forms of hypertension, yet, there is still much to learn about the technology and many questions remain to be answered. These include defining precisely the mechanisms of action and time to full effect of the therapy, durability, safety and who may benefit most. As such, it is encouraging to consider that, apart from potential value to the hypertensive population, RSD has already been of proven benefit in two vitally important areas. First by bringing together clinicians from disparate specialties (including interventional cardiologists/radiologists, nephrologists, endocrinologists, general physicians and hypertension specialists) to work in teams in a way that no other organ-based specialty has previously established. Second, it has refocused our attention on the role of renal sympathetic nerves in hypertension and illustrated how much there is still for us to learn about nervous system regulation of BP. Further progress in this arena must inevitably lead to the involvement of yet another specialty – the autonomic physiologist ●

Conflict of interest

Dr Lobo is a co-author of the Joint UK Societies' Consensus statement on renal denervation and a Specialist Adviser to NICE on interventional therapy of hypertension. He is on the medical advisory board of St. Jude Medical.

Editors' note

See also the article by Patel and Di Mario entitled 'Renal denervation for hypertension: where are we now?' on pages 142–7 of this issue.

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