

The Far Eastern View on Renal Denervation – A Trailblazer for the Rest of the World

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Arterial hypertension is the most important preventable cause of cardiovascular morbidity and mortality worldwide.¹ Over the last decades, many epidemiological studies and pharmacological intervention trials have demonstrated the beneficial and clinically meaningful effects of lowering office blood pressure down to the level of 120/80 mmHg. Besides lifestyle modification, pharmacological drug treatment is the main pillar of hypertension therapy. However, lifelong polypharmacy as a strategy to improve hypertension control has failed.² Adherence to medication remains a major problem in hypertension treatment.³

The aforementioned aspects emphasize the need for alternative methods to control blood pressure such as non-pharmacological interventional approaches. One of these could be catheter-based renal denervation (RDN).

In this issue of the *Acta Cardiologica Sinica*,⁴ Wang and colleagues provide an excellent consensus statement taking account the current knowledge of RDN as a treatment option for patients with hypertension.

Renal denervation techniques use radiofrequency energy, ultrasound or chemical denervation, to disconnect renal nerves within the adventitia of the renal arteries, thereby reducing sympathetic afferent and efferent signaling to and from the kidneys.⁵

As many new technical developments in medicine, RDN has gone through Gardner's Hype Cycle: The HTN-1 trial, showing the feasibility of RDN in humans, was the initial technology trigger.⁶ The introduction of minimal-invasive, catheter-based approaches to effect renal

denervation modulating the sympathetic nervous system, a major driver of arterial hypertension, created tremendous enthusiasm among the physicians worldwide. As a logical consequence, randomized clinical studies, the HTN-2 trial and other trials, were initiated, demonstrating a marked and sustained reduction in blood pressure with the use of a broad range of different devices and technologies.⁷ These findings led to a peak of inflated expectations around the world. The promise of catheter-based RDN was one that represented a therapeutic holy grail of treating hypertension. However, due to the neutral result of the first randomized and sham controlled RDN trial ever performed (HTN-3), the expectations ended in a trough of disillusionment. In this trial, over 500 patients with treatment-resistant hypertension were either randomized to a sham procedure or to RDN with a monopolar electrode catheter (SYMPPLICITY Flex). Office as well as 24-h ambulatory blood pressure was reduced in both study arms, however no significant further improvement was observed in the denervation arm compared to control.⁸

It took a long time and much scientific effort to recover from HTN-3. Poor patient selection, non-compliance with antihypertensive medication and inadequate technical performance of the procedure were identified as potential confounders.⁹ This left the scientific and clinical community to question whether RDN is an effective therapeutic tool or not. However, the unmet medical need to treat hypertension effectively kept investigations and clinical trials to continue. Recently, the 3 months results of the SPYRAL HTN OFF-MED trial demonstrated a significant and clinically meaningful reduction in 24-hr ambulatory and office blood pressure in patients with mild to moderate hypertension but without antihypertensive medication receiving ablation by a multielectrode radiofrequency catheter (SPYRAL Medtronic), compared with sham control patients.¹⁰ In addition, the results of the RADIANCE HTN SOLO trial, again in patients

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with mild to moderate hypertension without blood pressure lowering drugs, using an endovascular ultrasound RDN system (Paradise, ReCor) revealed similar results.¹¹ The positive result of both trials provides a biological proof of principle for the efficacy of RDN.

In parallel, the efficacy of RDN for patients with moderate, uncontrolled hypertension despite anti-hypertensive drugs (1-3 medications according to current guidelines) was evaluated in the SPYRAL HTN ON-MED trial with similar study design. Very similar to the OFF-MED trial, office and 24-hr ambulatory blood pressure decreased significantly in the renal denervation group compared to sham control. Over the next 6 months the extent of blood pressure reduction in the RDN group increased.¹² No major adverse events were observed in the above-mentioned trials indicating the safety of RDN. The positive results of these better designed trials breathed new life into the RDN field and brought back the slope of enlightenment.

The statement of the Taiwan Hypertension Society and the Taiwan Society of Cardiology now expands upon the content in the previous statements and guidelines, specifically focusing on the three key concepts. First, consider RDN as a legitimate alternative antihypertensive strategy. Second, potential clinical and behavioral predictors of patients who will benefit most from RDN, are summarized the five subgroups of hypertensive patients (Resistant hypertension, patients with blood pressure-mediated vasculature or organ Damage, Non-adherent to antihypertensive medications, Intolerant to antihypertensive medications, secondary [2ndary] causes treated but hypertension still uncontrolled; dubbed “RDN i2”), as the preferred candidates for RDN. Third, the Task Force recommends evaluation of three features in advance to make certain that RDN could be performed correctly: 1) Renal artery anatomy eligibility assessed by computed tomography or magnetic resonance renal angiography if not contraindicated, 2) Genuine uncontrolled BP confirmed by 24-hour ambulatory BP monitoring, and 3) Secondary hypertension identified and properly treated, labelled “RAS” (R for renal, A for ambulatory, S for secondary). Thereby, this consensus statement suggests very pragmatic recommendations to the readers for identifying eligible patients for RDN.

The authors acknowledge that hypertension management is a shifting landscape and have arrived at this

consensus as of May 2019. They offer it with the understanding that determining the best care for each patient requires careful decision-making – weighing the risks and benefits of various management strategies, including RDN.

In conclusion, the initiative of the Taiwan Hypertension Society and the Taiwan Society of Cardiology on RDN for the management of arterial hypertension is a very welcome and much needed step. The consensus statement should serve as an inspiration to other groups within this field. Increased attention to patient-centric outcomes and core outcome sets are much needed. Overall, the universal target is to find more potent treatment regimens for arterial hypertension – this consensus statement is the first step. To quote the Chinese philosopher Lao Tzu: The journey of a thousand miles begins with one step!

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

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