

Renal Denervation – A Flight of Icarus?

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Editorial

Since its introduction in 2008 Renal Denervation (RDN) has garnered enthusiasts among physicians, patients and the medical device industry. In December 2013 a research and consulting firm predicted a growth of the global renal denervation market in the next 6 years from approximately 3,000 procedures in 2012 up to nearly 40,000 by 2019 (representing a value of over \$170 million). Even though the optimism was toned down after 5 years of trial applications of RDN (initial expectations mentioned a market on the order of a billion dollars by 2020), the hype surrounding this invasive therapy method for patients with treatment-resistant hypertension was still on the rise. This all changed in January 2014 when Medtronic announced that its pivotal SYMPPLICITY HTN-3 trial failed to meet its primary efficacy endpoint. After promising data obtained from SYMPPLICITY HTN-2 Medtronic's this next trial, that included a sham-control group, was supposed to strengthen the position of RDN as an emerging leading therapy in patients with treatment resistant hypertension. Putting aside the discussions about the necessity and usefulness of a control sham treatment (according to some experts the pain caused in a number of patients by denervation reduced the validity of blinding) and differences between using ambulatory BP monitoring, home electronic BP monitoring and repeated office electronic measurement as an endpoint, SYMPPLICITY HTN-3's failure has been widely received as a major blow to the potential future worldwide deployment of RDN in the treatment of hypertension. SYMPPLICITY HTN 4, HTN-India und HTN-Japan trials have been consequently called off, while previously, at the end of 2013, the EnligHTN II trial was stopped (apparently due to recruitment difficulties). Many have spelled the demise of RDN at this point even though the actual data from the SYMPPLICITY HTN-3 trial still needs to be fully analysed. Some are trying to look at the bright side of recent developments - now is the time to take a step back and analyse the underlying principle of this treatment method - interruption of signal transmission in the renal sympathetic nervous system. There are still some contradictory views on the longitudinal distribution of renal sympathetic nerves along renal arteries which may affect the currently advised course of RDN procedure (distal to proximal) [1]. Furthermore the radial distribution of nerves in renal artery walls, which seems to be the most important anatomic factor for intravascular RDN, has only been studied in small groups both in animal models and human cadavers [1-3]. It is widely accepted that most (up to 90%) nerves are situated within 2 mm of the lumen-intima interface [2,3].

To obtain a successful result an ablation depth of 4 mm is targeted but it is well known that some ablation related changes might extend to a depth of up to 6 mm [4], thus introducing a potential risk of irreversible injury to the artery itself. Dissections and vasospasm during ablation have been reported and well documented but there are some new reports of delayed renal artery stenosis related to RDN [5,6]. Templin et al used Optical Coherence Tomography (OCT) to document wall oedema after RDN Procedures but they have also admitted to a limitation of their results as a consequence of limited imaging depth of OCT (0.5 to 2.0 mm) [7]. In vivo monitoring of acute RDN related changes in arterial walls remains challenging. In conclusion transcatheter renal radiofrequency ablation is still not yet ready to be widely introduced into clinical practice and must be further investigated. On the other hand different methods of RDN might come into limelight, such as an intravascular ultrasound based technique, chemical transcatheter denervation with ethanol, MR-based or CT-based perirenal denervation with ethanol or an extracorporeal high-intensity focused ultrasound. Despite many concerns, the future of RDN seems to be bright.

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