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The Role of Renal Sympathetic Denervation in Atrial Fibrillation

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Abstract

Endocardial catheter ablation is a widely used alternative for the treatment of atrial fibrillation (AF). Despite technical improvements, and increased understanding of mechanism, and acquired technical experience over many years, the results are not yet optimal. This results in an ongoing search for new therapeutic approaches.

Because cardiac sympathetic drive is potentially responsible for triggering and sustaining AF, modulation of sympathetic tone has been proposed as a viable treatment objective. The early attempts to test this concept were limited by nature=highly intrusive techniques but new approaches and targets have been recently introduced. Specifically, renal nerve ablation has been introduced and the first attempts to employ this technique for treatment of cardiac arrhythmias give as a promise of new therapeutic avenues in near future.

This review focuses on the possible role of renal denervation in treatment of atrial fibrillation, the contemporary evidence supporting this approach, and the ongoing trials to establish its therapeutic role.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting millions of people worldwide.[1] Among all supraventricular arrhythmias, it has a special place due to an extremely high prevalence and strong association with morbidity and mortality.[2]

Currently, the catheter-based isolation of pulmonary veins (PVI) is the most widely used interventional approach for treatment of drug-refractory AF. This therapeutic concept, largely based on the landmark work of Hassaguerre et al.,[3] has been introduced over two decades ago. Since then a substantial experience has been accumulated. Although this treatment modality is currently recommended as class I indication for symptomatic AF refractory to at least one antiarrhythmic medication,[4] its efficacy is suboptimal. Various clinical trials reported efficacy of 66-89%[5] but the real-world cohort validation through large surveys disclosed even lower success rates of 55-70%.[6] Given that every third patient requires more than one procedure,[4] these observations need to be carefully interpreted.

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This hard clinical realty results in an ongoing search for a new adjuvant treatment or promising alternative approach. Consequently, in addition to PVI other ablation techniques have been proposed. These techniques include the empiric modification of arrhythmogenic substrate by adding ablation lesions on the left atrial roof and the mitral isthmus,[7] ablation of complex fractionated electrograms (CFAEs)[8] or modulation of autonomic heart innervation by targeting of ganglionated plexi.[9] Recently, this particular additive form of cardiac autonomic manipulation has been proposed as an important element in the therapeutic effect of PVI in patients with AF[10-13] and gained renewed interest. Although plexi modulation alone has produced contradictory results,[14-19] addition of ganglionated plexi ablation to PVI has increased success rate in both catheter-based [20-22] and minimally-invasive surgical ablation.[23-26]

Those encouraging preliminary results, suggesting a positive impact of adjuvant sympathetic modulation on AF, opened the door for another concept. Renal denervation (RND) has now being widely tested for treatment of resistant hypertension[27,28] with excellent results. This approach has revolutionised our perception of sympathetic modulation and suggested to us the possible utility of RND as an antiarrhythmic intervention.

Pathophysiological Insights

In addition to mechanisms such as atrial stretch and atrial remodeling,[29-33] the activity of the autonomic nervous system has been thought to contribute to the development of AF.[34] In experimental

animal models, the ß-adrenergic agonists (i.e. isoproterenol) in conjunction with rapid atrial pacing have been successfully used to induce AF.[35,36] At the cellular level, it has been observed that sympathetic overstimulation may lead to increased calcium levels along with subsequent shortening of the action potential and refractoriness of atrial myocardium.[37] Moreover, increased sympathetic activity is correlated with prolonged episodes of AF and possibly a precondition for sustained AF.[38] Recent series of animal studies have also shown that sympathetic inhibition through RDN may suppress the development of AF induced by rapid atrial pacing[39] and additionally, may inhibit atrial remodeling after prolonged AF.[40] Moreover, in animals subjected to stimulation of left stellate ganglion and rapid atrial pacing for 3 hours, the resulting increased AF induction rate, shortened and dispersed atrial effective refractoriness as well as elevated plasma norepinephrine levels were almost reversed by subsequent RDN as compared with shame procedure group.[41]

Increased sympathetic activity and hypertension interactions also affect AF haemodynamically as both acute and chronic blood pressure elevation can increase atrial stretching and dilation, resulting in the promotion of arrhythmogenic substrate and/or induction of AF. Recently, it has been shown in an animal model that the hypertensive group developed a progressive increase in mean arterial pressure, longer mean effective atrial refractory periods, progressive bi-atrial hypertrophy, atrial inflammation and left atrial dysfunction,[42] all potentiators of AF. The role of hypertension as a risk factor for the development of AF in long term follow-up has been also documented in large epidemiological studies.[43] Furthermore, in an experimental animal models, RDN is associated with a decrease of sympathetic drive, plasma renin activity and aldosterone concentrations.[44,45] Moreover, in model for obstructive sleep apnea and AF provocation, RDN reduced the post apnoeic blood pressure rise, frequency and duration of AF episodes by inhibiting apnea-induced reduction of atrial refractoriness.[46]

Encouraging Preliminary Results

Given the previously discussed pathophysiological considerations, as well as experimental and clinical observations, the concept of RDN in the treatment of AF emerged.

Our first attempts at evaluating RDN for AF treatment were designed to examine the adjunct role of RDN in combination with catheter-based PVI. The breakthrough trial was recently reported as a randomized, prospective study by Pokushalov et al.[47] describing the effect of RDN in patients with a history of refractory paroxysmal or persistent AF who were on at least 2 antiarrhythmic drugs and had resistant hypertension (systolic blood pressure 160 mm Hg despite triple drug therapy). In the study, 27 patients were enrolled and randomized to either PVI only (n=14) or PVI and RDN (n=13). At the scheduled 1-year follow-up visit, significant reductions in systolic (from 181 to 156 mm Hg, $p < 0.001$) and diastolic blood pressure (from 97 to 87mm Hg, $p < 0.001$) were observed in patients treated with PVI and RDN without significant change in the PVI only group. The freedom from AF was also significantly improved in the experimental group when compared with conventional PVI ablation only: 69% vs. 29% ($p = 0.033$). Considering the relatively moderate success of radiofrequency ablation in the treatment of AF in a long

Table 1: Overview of ongoing trials in field of RDN and SVT.

Trial Identifier	Official Title	Sites	Interventions	Status	Expected Completion Date
NCT01952743	Concomitant Renal Denervation Therapy in Hypertensive Patients Undergoing Atrial Fibrillation Ablation - A Feasibility Study	Mayo Clinic, Rochester, Minnesota, US	PVI + RDN vs. PVI only	recruiting	09/2016
NCT01898910	Ganglionated Plexi Ablation vs Renal Denervation in Patients Undergoing Pulmonary Vein Isolation. A Randomized Comparison	Meshalkin Research Institute of Pathology of Circulation, Novosibirsk, Russian Federation	PVI + RDN vs. PVI + Ganglionated Plexi ablation	completed	06/2013
NCT01907828	A Feasibility Study to Evaluate the Effect of Concomitant Renal Denervation and Cardiac Ablation on AF Recurrence	recruiting	PVI + RDN vs. PVI only	not yet open	05/2016
NCT01897545	The Role of Renal Denervation in Improving Outcomes of Catheter Ablation in Patients With Atrial Fibrillation and Arterial Hypertension	The Valley Health System, New York, US; Athens Euroclinic, Athens, Greece; State Research Institute of Circulation Pathology, Novosibirsk, Russian Federation	PVI + RDN vs. PVI only	completed	6/2013
NCT01959997	Randomized Comparison of Redo Pulmonary Vein Isolation With vs. Without Renal Denervation for Recurrent Atrial Fibrillation After Initial Pulmonary Vein Isolation	The Valley Health System, New York, US; State Research Institute of Circulation Pathology, Novosibirsk, Russian Federation	Redo PVI vs. Redo PVI + RDN	recruiting	09/2016
NCT01686542	Circumferential Pulmonary Vein Isolation (CPVI) Plus Renal Sympathetic Modification Versus CPVI Alone for AF Ablation: a Pilot Study	The Second Affiliated Hospital of Chongqing Medical University Chongqing, China	PVI + RDN vs. PVI only	recruiting	12/2016
NCT01635998	Adjunctive Renal Sympathetic Denervation to Modify Hypertension as Upstream Therapy in the Treatment of Atrial Fibrillation (H-FIB)	11 centers from US and Europe	PVI + RDN vs. PVI only	recruiting	07/2017
NCT01713270	Safety and Effectiveness Study of Percutaneous Catheter-based Renal Sympathetic Denervation in Patients With Drug-resistant Hypertension and Symptomatic Atrial Fibrillation	First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China	RDN vs. best medical treatment (hypertension) vs. Direct-Current Cardioversion	recruiting	06/2015
NCT01873352	Evaluate Renal Artery Denervation In Addition to Catheter Ablation To Eliminate Atrial Fibrillation (ERADICATE–AF) Trial	The Valley Health System, New York, US; State Research Institute of Circulation Pathology, Novosibirsk, Russian Federation	PVI + RDN vs. PVI only	recruiting	06/2014
NCT01814111	Safety and Effectiveness Study of Percutaneous Catheter-based Sympathetic Denervation of the Renal Arteries in Patients With Hypertension and Paroxysmal Atrial Fibrillation	The First Hospital of Nanjing Medical University, Nanjing, Jiangsu, China	RDN vs. best medical treatment (AF)	recruiting	06/2015
NCT01952925	Combined Atrial Fibrillation Ablation and Renal Artery Denervation for the Maintenance of Sinus Rhythm and Management of Resistant Hypertension	Oregon Health & Science University, Portland, Oregon, United States	PVI + RDN vs. PVI only	not yet open	01/2019

term follow-up and the highly promising results of the additional RDN, this new approach has a potential to become a clinically important therapeutic option for patients with AF and hypertension.

Initial data in human studies testing the application of RDN as a stand-alone therapy are also encouraging. Recently, a case report of persistent drug-resistant AF successfully being treated with RDN instead of PVI was presented.[48] Shortly after the procedure, spontaneous termination of persistent AF was observed and AF recurrence did not appear during the follow-up of 8 months. Furthermore left atrial size was also significantly reduced from 45mm to 36mm at 6 months of follow-up.

Moreover, a significant improvement of rate control after RND was clinically observed and further successfully tested in an animal model.[49]

Ongoing Trials: Answers are on the Way

Even though these data are encouraging, they are still premature to support the potential anti-arrhythmic role of RDN and its possible role in treatment of supra-ventricular arrhythmias. However, more evidence is expected to come in the near future as a multitude of clinical trials are ongoing. Most of the trials are focusing on the adjuvant role of RDN in combination with PVI vs PVI only but also a role of RND as stand-alone therapy and comparison to antiarrhythmic drugs will be addressed. A comprehensive overview of a design, sites and time schedule of ongoing trials can be found in Table 1.

Conclusions:

RDN is a novel and innovative approach to AF and other difficult to treat arrhythmic conditions. Early clinical results are promising. The mechanism by which RDN may be effective can be mediated by better control of hypertension and/or modulation of sympathetic tone. Ongoing and future studies will determine its ultimate clinical role.

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