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Renal Denervation And Pulmonary Vein Isolation In Patients With Drug Resistant Hypertension And Symptomatic Atrial Fibrillation

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Abstract

Systemic hypertension is the most consistent modifiable risk factor for atrial fibrillation (AF) in adults with consistent data from both animal models and human studies suggesting a consistent pattern of autonomic imbalance underlying both conditions. Relative sympathetic nervous system activation is a demonstrably common attendant to the local mechanisms in pulmonary veins that sustain persistent or recurrent AF and may represent a new objective for adjunctive treatment. Established management of AF aims to achieve durable control through either pharmacologic or catheter-based interventions. The introduction of catheter-based renal denervation as a safe, alternate approach to target the sympathetic nervous system therapeutically represents a potential opportunity to treat the shared pathophysiological mechanisms with minimal additional treatment burden when added in this context. Preliminary investigations have demonstrated both proof-of-concept and the technical feasibility of combined renal denervation and AF ablation procedures with the suggestion of benefit in terms of freedom from AF recurrence. The available data is promising but absolute confirmation of efficacy remains unconfirmed in the absence of more definitive evidence. This paper reviews the role of autonomic imbalance in the initiation and maintenance of AF by summarizing the observations from both experimental models and clinical studies from the perspective of potential therapeutic overlap between catheter-based treatments.

Introduction

The relationship between atrial fibrillation (AF) and hypertension is both epidemiologically strong and physiologically complex. AF is the most common sustained cardiac arrhythmia in humans[1] with significant morbidity and mortality associations[1-3] whilst hypertension independently represents a major health burden at a population level as a potentially modifiable risk factor across the spectrum of cardiovascular disease.[4-6] Avenues of potential therapeutic overlap have been increasingly explored in the context of associations between hyperactivity of the sympathetic nervous system, hypertension and both the prevalence and post-treatment recurrence of AF. Pharmacotherapy represents the primary strategy applied to effectively manage both conditions to date though this paradigm has been increasingly challenged by the arrival of catheter-based procedural treatments for each disease.[7,8] As AF and resistant hypertension are frequently coexistent disease states with shared pathophysiological mechanisms underpinning each condition, procedural similarity in terms of an endovascular catheter-based approach easily lends itself to investigation for potential synergy between the two treatments.

Pulmonary Vein Isolation AF Ablation

Predominantly explored in the context of symptomatic drug-refractory AF, pulmonary vein isolation (PVI) by atrial endocardial catheter ablation has emerged into widespread clinical use, obtaining consensus recommendation for this indication.[7] Targeting the primary initiating source of AF,[9] real-world experience has seen a sustained antiarrhythmic response in around 65-75% of cases outside the clinical trial environment.[10] In unsuccessful cases, advanced structural and electrical remodelling as a consequence of hypertension, chronic AF and the influence of angiotensin 2 and aldosterone have been proposed to undermine a lack of durable treatment effect.[11-15] Underlying these influences, a persistent autonomic trigger via either sympathetic nervous overactivity or vagal imbalance remains a demonstrable conspirator to AF vulnerability in both the primary and recurrent settings.[16-21]

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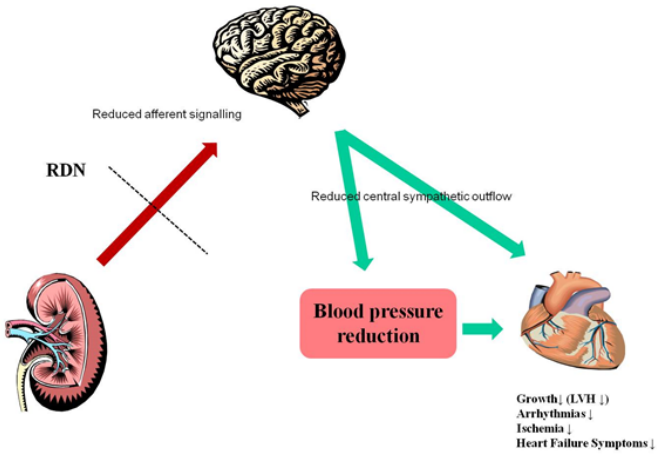

Figure 1: **Possible mechanisms contributing to the potential beneficial effects of renal denervation (RDN) on atrial fibrillation burden. RDN may reduce afferent signalling via renal sensory nerves which can result in reduced central sympathetic outflow to various organs including the heart. Reduced sympathetic cardiac nerve activity, either alone or in combination with RDN induced BP lowering may have several beneficial effects on the heart as illustrated.**

Renal Sympathetic Denervation

Renal sympathetic denervation is an intra-arterial catheter-based intervention primarily applied for the treatment of drug-resistant hypertension. Radiofrequency ablation pulses are delivered endoluminally in a distal-to-proximal fashion along each renal artery with longitudinal and radial separation to target the sympathetic nerves located in the adventitia of the vessel wall. Though the majority of studies have been performed to safety and blood pressure endpoints in patients with severe and treatment resistant hypertension, assessment of norepinephrine spillover has demonstrated that treatment with a single electrode device on average results in a 47% reduction of renal sympathetic nerve activity[8] with corresponding reductions whole-body sympathetic nervous activity.[22] The potential implications of these effects range across a wider spectrum of disease states associated with sympathetic up-regulation other than simply hypertension alone.

Promising results from the first in-human clinical trials Symplicity HTN-1[23, 24] and Symplicity HTN-2[25, 26] demonstrated substantial and durable reductions in average office and home blood pressure measurements of the order of 32/14 mmHg and 20/12 + 13/7 mmHg respectively in denervated patients. The rate of procedural complications was < 3% in both trials. The release of Symplicity HTN-3[27] in early 2014, the first and largest randomised trial incorporating a double-blind sham-controlled design across 535 patients, has cast doubt on the superiority of antihypertensive effect compared to medical therapy through failure to reach the primary efficacy endpoint at 6 months follow up. Whilst this was the most rigorous trial performed thus far, shortcomings in execution relating particularly to medication changes during the 6 month follow up phase and inexperience of operators, with only a small number of patients actually receiving adequate treatment where bilateral circumferential ablation was achieved, put these results into perspective. Irrespective of these issues but very relevant to the potential use of this approach in other indications, the primary study safety endpoint was met with a <2% adverse event rate and reinforced prior experience that renal denervation is a relatively safe intervention with minimal expectation of clinical harm. This observation remains consistent with an approach to potentially expand treatment horizons under formalised research conditions exploring safety and efficacy across broader indications where sympathetic overactivity is a feature such as impaired glycemic control,[28] sleep apnea,[29, 30] and cardiac arrhythmias such as AF.

Evidence of Autonomic Dysfunction in AF

Observations in both animal models of provoked AF and in humans have suggested that the autonomic nervous system is an important factor in the precipitation and maintenance of AF. Modulation of β-adrenergic and cholinergic stimulation in the intact canine heart has demonstrated a gate-keeper role for autonomic tone fluctuations in arrhythmogenesis. Excess sympathetic stimulation appears to act as a potential AF trigger whilst background adrenergic (vagal) tone may modulate the relative threshold at which AF can be initiated and maintained under cholinergic drive.[31] Further work monitoring stellate ganglion and vagus nerve activity in ambulatory canines with pacing induced AF demonstrates more easily inducible and sustained patterns of arrhythmia with progressive sympathetic activation in the setting of higher baseline vagal tone.[32] Spectral analysis of heart rate variability data from ambulatory Holter monitoring in humans with paroxysmal AF has reinforced dynamic autonomic imbalance with sympathetic excess (via acute disruption in vagal tone or cumulative sympathetic excitation) as a closely time-associated factor in acute AF episodes.[17, 33, 34] Either pathway to autonomic imbalance may contribute to dysrhythmia by variation in action potential lengths and refractory duration of the atria.[35]

Generalised pharmacological inhibition of the sympathetic nervous system by moxonidine has been trialled in humans as both an adjunct to PVI in patients with symptomatic AF[36] and as add-on antihypertensive therapy alone in hypertensive patients with paroxysmal AF.[37] Addition of the centrally acting sympathoinhibitory agent appears to alleviate AF morbidity and significantly prolong time to recurrence independent of any systolic antihypertensive effect.

Hypothesising that lowering sympathetic burden through renal denervation could reduce the occurrence of AF (Figure 1), the first proof-of-principle intervention studies investigated the impact of the procedure on AF inducibility during rapid atrial pacing in the canine model.[38] Despite an immediate and sustained fall in atrial refractory time in response to rapid pacing in control animals, those undergoing renal denervation had no suppressive effect on atrial effective refractory period. Frequency and duration of inducible AF episodes were significantly lower in denervated animals compared to non-denervated controls (1.0 + 1.26 vs 3.14 + 2.54 observed episodes, P=0.03 and 16.5 + 25.1 vs 86.6 + 116.4 seconds per episode, P=0.02 respectively).[38] A further denervation case-control study in the pacing-stimulated hyper-sympathetic canine model had consistent findings. AF induction rates were strongly associated with shorter atrial effective refractory times and higher plasma norepinephrine levels under stimulated conditions. Both parameters returned to baseline levels in the renal nerve ablated animals with a substantial reduction in AF inducibility whilst remaining unaltered in the non-denervated controls.[39] A significant post-intervention blood pressure reduction was also noted in the treated study arm.

Proof of Concept in Humans

To translate proof of this concept into humans with AF, Pokushalov and colleagues[40] prospectively trialled the use of adjunctive renal denervation in combination with pulmonary vein isolation in

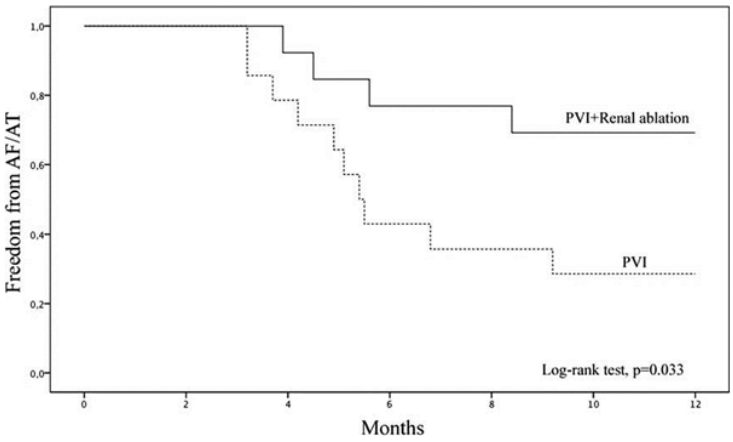

Figure 2: **Incidence of AF recurrence in patient with PVI alone compared to those with PVI and renal ablation (from 40).**

hypertensive subjects (systolic blood pressure >160mmHg despite triple drug therapy) and symptomatic or persistent atrial fibrillation refractory to 2 or more dysrhythmic agents. Concentrating on patients without significant chronic kidney disease (eGFR by MDRD >45ml/min/1.73m2), the 27-patient study population was predominantly non-diabetic (89%) middle-aged males (77%) all prescribed at least 3 drugs for blood-pressure lowering in addition to 3 agents for AF control. 13 patients were randomised to the combined PVI plus renal denervation procedure against 14 patients receiving catheter based PVI alone to the endpoints of antiarrhythmic drug free rhythm maintenance and office blood-pressure measurements at 3 monthly intervals to 12 months follow up.

Though catecholamine spillover measurements were not reported, in contrast to more recent trials in resistant hypertension, successful renal sympathetic denervation was confirmed by observation of attenuated systolic pressure surge to intra-arterial high frequency nerve stimulation in all patients. In terms of primary outcome, nine of the 13 patients (69%) undergoing dual intervention had maintained anti-arrhythmic drug free sinus rhythm at the 12-month visit compared to 4 of 14 patients (29%) in the PVI only arm (P = 0.033) (Figure 2).

Those undergoing the combined intervention protocol experienced a substantial reduction in both systolic and diastolic office blood pressure (25+5mmHg and 10+2mmHg respectively) compared to no significant change seen in the PVI-only group. The trajectory of this blood pressure decline was both rapid and sustained, achieving nadir pressure at 3 months follow-up which was maintained consistently out to 1 year.

From an operational perspective, the addition of renal denervation to PVI added a mean of 38 minutes to the total procedure time off a PVI-only group baseline approaching 2 1/2 hours, remaining well within reported data for treatment time by other investigators.[41] No significant difference was noted in terms of added fluoroscopy time. Clinical safety of the combined procedure was confirmed in-line with experience in the resistant hypertension studies with no procedural complications noted in either study arm and no evidence of renal arterial stenosis detected by magnetic resonance angiography at 6 months post-intervention.

Irrespective of the potential contribution that optimised blood pressure control may make in preventing AF recurrence and accepting no specific markers of a sustained reduction in sympathetic drive or autonomic balance were reported, this study was the first to demonstrate that renal denervation may safely reduce the reduce the risk of AF recurrence in drug-resistant hypertensive patients.

The same group has gone on to detail their cumulative experience of combined procedures across a broader spectrum of hypertension via a summary analysis of two separate studies;[42] the first a continuation of the initial pilot trial with the addition of a further 11 study patients (n=38) and the second in 48 patients with refractory AF and more moderate hypertension (office blood pressure readings >140/90 and <160/100 mmHg). The dual trials ran in parallel across multiple centres with identical active intervention arms randomised on a 1:1 basis to PVI with adjunctive renal denervation against a control group of PVI alone. The aggregated study population was consistent with the initial pilot cohort, being predominantly middle aged (56+6 years) non-diabetic (94%) males (71%), though a substantial proportion of eligible patients (43%) were excluded either due to refusal of consent or 'unsuitable' renal anatomy. The combined procedure added a mean of 34 minutes to overall procedure time (186+32 vs 152+26 minutes), a similar margin to the initial trial and with no statistically significant difference in active fluoroscopy time. No procedural complications were noted in relation to the renal denervation procedure nor were any occurrences of arterial stenosis detected at 6 month magnetic resonance surveillance. Despite showing practical feasibility, the assessment of primary outcome measures demonstrated that the addition of sympathetic denervation did little to alter the pattern of AF recurrence in the moderate hypertension group with 15 of 23 (65%) and 11 of 21 (52%) patients followed up in the active and control arms respectively maintained in drug-free sinus rhythm at 12 months. The group with more severe hypertension at baseline found 11 of 18 (61%) adjunctively denervated patients were free of AF recurrence and anti-arrhythmics compared to 5 of 18 (28%) of the PVI-only arm (P=0.03). Office blood pressures showed a fall consistent with magnitude observed in the pilot study and SYMPLICITY-1 and SYMPTLICITY-2 studies.

Potentially overemphasising the beneficial effect of the combination treatment, the primary success rate of PVI alone in both this extended experience and the initial study are lower than expected given reports from other investigators where primary success rates approach 70%.[10-12, 43] This observation may be a particular function of the truly severe refractory hypertension associated with AF in these trials and, although hypertension is an independent risk factor for AF recurrence, the relationship with degree of blood pressure elevation is somewhat more obscure.

A number of active clinical trials are ongoing presently into the feasibility and efficacy the concomitant addition of renal denervation to PVI in the hypertensive patient (Table 1). The H-FIB study[44] (clinicaltrials.gov NCT01635998) is the largest of these with the hypothesis that adjunctive renal denervation will reduce AF recurrence after PVI ablation. The trial is a multicentre prospective 1:1 randomised double-blind controlled study of 300 patients to the primary efficacy endpoint of drug-free absence of AF recurrence through 12 months of follow up. Whilst catheter treatments are consistent with prior trials, the entry criteria differ slightly in terms of the hypertensive range which, whilst still defined by systolic >160mmHg and/or diastolic >100mmHg, has single antihypertensive agent as the minimum for patient inclusion. Enrolling since late 2012 and estimated for completion in 2017, recruitment is currently suspended per the local data and safety monitoring board (August

Table 1: Active trials of Pulmonary Vein Isolation and Renal Sympathetic Denervation versus Pulmonary Vein Isolation alone in the treatment of drug resistant atrial fibrillation

Trial Identifier	Trial Title	Country	Recruitment Target	Status	Expected Completion
NCT01635998	Adjunctive renal sympathetic denervation to modify hypertension as upstream therapy in the treatment of atrial fibrillation (H-FIB)	USA, Europe	300	Halted	2017
NCT01686542	Circumferential pulmonary vein isolation (CPVI) plus renal sympathetic modification versus CPVI alone for AF ablation: a pilot study	China	100	Recruiting	2016
NCT01873352	Evaluate renal artery denervation in addition to catheter ablation to eliminate atrial fibrillation (ERADICATE-AF)	USA, Russia	300	Recruiting	2014
NCT01897545	The role of renal denervation in improving outcomes of catheter ablation in patients with atrial fibrillation and arterial hypertension	USA, Greece, Russia	60	Completed *	2013
NCT01907828	A feasibility study to evaluate the effects of concomitant renal denervation and cardiac ablation on AF recurrence	Germany	100	Recruiting	2016
NCT01952743	Concomitant renal denervation therapy in hypertensive patients undergoing atrial fibrillation ablation: A Feasibility Study	USA	40	Recruiting	2016
NCT01952925	Combined atrial fibrillation ablation and renal artery denervation for the maintenance of sinus rhythm and management of resistant hypertension	USA	40	Not yet open	

* no reported data

2014).

Perspectives

Expanding the clinical indications of renal sympathetic denervation remains an exciting frontier across the spectrum of diseases with sympathetic overactivity as a common feature. The overlap in contributing physiology between AF and hypertension represents an opportunity to explore modulation of the common autonomic pathway as therapy in both conditions given the relative lack of sustained efficacy of pharmacotherapy alone and the morbidity associated with chronic drug treatment. Current therapeutic observations are limited to relatively small numbers with coexistent severe refractory hypertension and AF whereas most potential candidate patients have much more moderate degrees of blood pressure. Though there is the suggestion of benefit in small prospective studies, the collective experience is insufficient to support the routine application of combined intervention outside the formalised trial setting. The issue of demonstrable benefits for incremental cost will require close attention however performing both interventions concomitantly appears not to detract from the known safety profile of both procedures independently, with little added in terms of procedural time or infrastructure requirements.

In the broader context, it is interesting to observe a parallel evolution in the role of autonomic modulation via renal denervation in the management of ventricular tachyarrhythmias, where sympathetic over-activation is a similarly key contributant[45-47] and the porcine model of ischaemia-induced ventricular arrhythmia[48] has provided proof of concept. Following the first-in-man report where renal denervation restored ventricular electrical stability after failure of conventional strategies,[49] further small case-series have reported substantial reductions in the acute burden of electrical storm when used as a salvage procedure.[50-53] Whilst encouraging and potentially signifying a universal application for renal denervation in the treatment of arrhythmias per se, these results await confirmation under trial conditions before more widespread adoption could be supported.

Given the relatively early stage of this translational science, many unanswered questions remain with even more forthcoming as clinical outcome data is reported regarding the durability of treatment effect and the potential for extrapolation into patients with modest hypertension, or even normal blood pressure. Ultimately a mechanistic understanding will be important in evaluating if the apparent benefits of combined treatment are independent of blood pressure lowering and if reduction of sympathetic tone is the key mediator. A challenge will be to identify the most appropriate candidates for this approach. Learning about the outcomes of active randomised controlled trials will help to address these important clinical questions.

Conclusion

Whilst catheter based PVI is well established in the management of drug refractory AF, the role of adjunctive renal sympathetic denervation is encouraging but unconfirmed. Theoretically enticing from the perspective of the physiologic and therapeutic overlap, appropriate trials are in progress to evaluate the extent of any durable benefits that may be seen in the management of AF and hypertension.

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