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EDITORIAL

The interplay between autonomic tone and atrial arrhythmias

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Increased sympathetic tone is a contributor to certain types of atrial fibrillation (AF) and near universal in heart failure. What is unknown is whether the increased sympathetic tone is a driver of AF or a consequence of the arrhythmia. In this prospective, observational study, Mukai and colleagues discuss how catheter ablation for AF may disrupt the muscle sympathetic nerve activity (MSNA) in the left atrium and how this could result in a reduction in left atrium reverse remodeling (LARR) [1]. While pulmonary vein isolation (PVI) is currently the standard for invasive ablation of AF, the high recurrence rate has led to an increased interest in targeting associated triggers in addition to isolation of the pulmonary veins. The subsequent reconnections between the pulmonary veins and the left atrium in patients undergoing repeat pulmonary vein isolation raises the question as to whether there are alternate triggers that could be targeted to maintain a more durable first procedural response. Unfortunately to this point studies attempting to use adjunctive ablation techniques have had mixed results. STAR AF II assessed whether additional linear ablation and complex fractional electrogram ablation could be used as adjunctive therapy to traditional PVI and found no reduction in the recurrence rate of AF in patients with persistent AF [2]. GANGLIA-AF did not show ablation of gangliated plexuses as superior to PVI in paroxysmal AF patients but did reveal it was effective in hypertensive patients, which is a marker for PVI failure [3]. A sustained reduction in heart rate variability following PVI correlates with a reduction in long-term recurrence of AF which is thought to be secondary to autonomic ganglion injury [4]. Renal innervation has also been a target for autonomic modulation for AF reduction along with cardiac ganglion plexus ablation.

Renal denervation (RDN) was initially trialed as a treatment for resistant hypertension with mixed study results, however, it has shown promise in reducing AF recurrence in patients with AF and concomitant hypertension [5–7]. MSNA and sympathetic nerve activity was significantly reduced in patients with hypertension who underwent bilateral sympathetic RDN [8]. ERADICATE-AF found that patients with hypertension and paroxysmal AF had a significant reduction in AF recurrence with the addition of RDN during the catheter ablation procedure [5]. This subgroup of AF patients is more difficult to maintain in sinus rhythm and has a higher early recurrence rate. In the group with both catheter ablation and RDN compared to catheter ablation alone there was a reduction in AF recurrence [5].

To assess the effects of sympathetic nerve activity, Mukai and colleagues directly recorded MSNA prior to catheter ablation and 12 weeks post procedure in patients with preserved ejection fraction [1]. Heart rate variability and blood pressure were also measured along with left atrial volume indexes. The study showed a significant reduction in MSNA following catheter ablation at the 12 week follow-up interval and an association with a reduction in left atrial volume index. There have been prior studies that evaluate both systolic and diastolic dysfunction as a symptom of AF instead of a primary cause leading to AF development and recurrence [9]. Patients with paroxysmal or persistent AF had diastolic dysfunction that improved following catheter ablation despite having lone AF without traditional risk factors for impaired diastolic function [9]. Parasympathetic left atrial ganglia denervation secondary to pulmonary vein isolation has resulted in a decrease in heart rate variability that correlates with a reduction in late recurrence of AF when evaluated at both 3 and 6 months [4]. A reduction in heart rate variability following ablation may be viewed as a surrogate marker for a reduction in parasympathetic

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activity. This is the first study to directly assess MSNA as an index of sympathetic activity in longer-term follow-up at 3 months post catheter ablation. Prior studies have assessed both parasympathetic and sympathetic responses during catheter ablation and in short-term follow-up post procedure. During catheter ablation, there is an increase in parasympathetic tone and concomitant decrease in sympathetic tone reflected as a decrease in MSNA [10]. There is a reversal of this balance the day following the procedure with sympathetic tone dominating [10]. This was attributed to ablation around the parasympathetic ganglia for pulmonary vein isolation which stimulates the parasympathetic response [10]. Another consideration is that anesthesia would also decrease the sympathetic tone and lead to a further reversal of autonomic balance. This study assessed MSNA directly via a direct recording of sympathetic activity in the peroneal nerve. It appears that although there is an increase in sympathetic tone immediately following ablation, patients have a decrease in sympathetic nerve activity at 12 weeks. Patients with a reduced MSNA and left atrial volume index may be at a lower risk for late recurrence of AF. The differential responses of the sympathetic and parasympathetic tone during catheter ablation and immediately post-procedure versus longer term follow-up could indicate procedural success at targeting gangliated plexuses. The autonomic ganglia of the left atria are predominately epicardial structures so a reduction in sympathetic outflow which is sustained at 12 weeks may represent the degree of success from an endocardial procedure in damaging the ganglia. Although ganglionated plexus ablation is inferior to PVI alone, combining the two procedures results in a lower AF recurrence rate [11, 12]. Although 27% of patients were in AF during the initial MSNA recording pre-ablation, there were no differences in baseline burst frequency or burst incidence compared to those in sinus rhythm. At the 12-week follow-up all patients remained in normal sinus rhythm, so AF recurrence was not a factor in influencing autonomic tone post ablation.

There are several limitations that must be considered when evaluating the impact of this study. These include the small patient size as well as the lack of blinding of the reviewers to MSNA interpretation. The data acquisition both pre and post ablation was only for 10 min which is a very limited data sample along with the absence of a control group.

This study highlights several opportunities for advancement in the clinical care of patients with persistent AF. There is an evolving paradigm shift following both the CASTLE-AF and EAST-AFNET 4 trials in AF management in which patient populations benefit from early aggressive management with upfront catheter ablation [13–15]. Although the initial CABANA trial did not show catheter ablation to be associated with significant reductions in outcomes as compared to medical therapy at 12 months follow-up, subgroup analysis by age have recently shown age-based variations with younger patients benefiting more from aggressive upfront management of AF [13, 16]. Sympathetic tone in these younger patients may be further attenuated by catheter ablation as opposed to older patient populations. Modulation of sympathetic tone with ganglionated plexus ablation in addition to pulmonary vein isolation could prove to be more important in younger patients. This study highlights the multifactorial nature of AF and the opportunities that exist for further optimization for procedural success in the management of this heterogenous arrhythmia.

Mukai and colleagues were able to show that sympathetic tone was attenuated 12 weeks post ablation and that baseline sympathetic outflow was similar among patients both in AF and sinus rhythm prior to the procedure. We are not able to differentiate whether the reduction in MSNA is related to modifying the atrial substrate or whether it is from patients maintaining sinus rhythm for three months. There is a definite need to study larger populations of AF patients to assess the impact of a reduction in autonomic tone with the hopes that this will further reduce AF recurrence.

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Declarations

Conflict of interests None.

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