Atrial fibrillation (**AF**) is the most common sustained cardiac arrhythmia, with a prevalence of over 50 million cases currently and ≥ 33% lifetime risk across races.1 Although there is emphasis on re-classifying the stages of AF,2 the current phenotypes are time-course based and described broadly as paroxysmal (self-terminating), persistent (requiring intervention to terminate), or permanent (sustained, without further rhythm-focused interventions).3 Catheter ablation, along with antiarrhythmic drugs (**AAD**), are the mainstay of treatment for AF, with increasing emphasis on rhythm-control strategies.2 However, even ablation has an efficacy between 50-80% for AF recurrence within 12 months after initial procedure, which has not significantly changed over recent years.2,4 Ther treatment approaches do not necessarily consider the underlying mechanism of AF in individuals, which remains a crucial gap in our understanding of the disease.4

Alternative attempts at classifying AF have been based on clinical comorbidities,5,6 which consider AF as the downstream sequelae of other conditions but do not account for atrial-specific factors, although we know that up to 20% of AF cases have an underlying genetic basis.7 We need to identify specific mechanisms in AF pathogenesis to help tailor interventions. An important mechanistic step in AF pathogenesis may be the role of the autonomic nervous system (**ANS**) in the initiation and maintenance of AF.8–10 ANS interaction with atrial tissue can lead to an increase in afterdepolarizations and ectopic beats, as well as facilitate re-entrant rhythms by shortening action potential durations (**APD**), which are two of the most common pathways in AF pathogenesis.11 For example, vagal nerve stimulation and cardioneural ablations have shown promise in AF, but are not standard of practice nor individually tailored.4,10 Our overarching hypothesis is that by understanding the ANS contributions to atrial arrhythmias, we can identify earlier stages and phenotypes of AF pathogenesis to prevent, individualize, and optimize treatment strategies.

To test our hypothesis, we will leverage the strength of pre-existing, well-established cohorts and analytical pipelines, including electrophysiology (**EP**) signals, genetic sequencing, and cardiac imaging data. During both clinical training (internal medicine, cardiology, and electrophysiology) and research fellowships (TL1, T32, F32), I worked extensively to collect electrical, clinical, and genetic data in multiple ongoing NIH-sponsored investigations involving my mentorship and advisory team,12,13 developing critical skills in signal processing, biostatistics, and computational genetics. The mentored training allowed for better understanding in the role of the ANS and stress psychophysiology in cardiovascular disease, from abnormal cardiac perfusion, increased cardiovascular mortality, to arrhythmia susceptibility.14–19 It also allowed for the opportunity to extend my background in signal processing and biostatistics by developing computational approaches with open-source software.20–22 As an EP fellow, I am positioned to obtain highly-granular data from EP studies performed during AF ablation, and with the expertise of the mentoring committee, I can expand my training in computational modeling of arrhythmias and genetics, allowing for a multifaceted understanding of the ANS in AF pathogenesis. Our main objective is to elucidate the contribution of the ANS on atrial arrhythmogenesis to determine the **autonomic phenotype** of AF, which we will accomplish through the following aims:

**Aim 1: Profile the autonomic phenotypes of paroxysmal AF who may benefit from combined cardioneuroablation and PVI ablation approaches.** *Hypothesis: Heightened sympathetic activity and impaired vagal activity will associate with an adrergic phenotype of AF, which will have increased rates of AF recurrence.* Sympathetic outflow, measured through stellate ganglia activity surrogates (skin sympathetic nerve activity, cardiac biomarkers of NPY and Gal1) and parasympathetic outflow (baroreceptor reflex, heart rate variability) are somewhat antagonistic, with exaggerated antagonism being predictive of those at risk of future AF despite PVI. The identification of an adrenergic phenotype of AF can help identify autonomic-targeted therapies in AF.

**Aim 2: Characterize the dynamic atrial substrate and fibrillatory area using MRI-based computational modeling to identify potential ablation targets.** *Hypothesis: Sympathovagal imbalance amplifies conduction heterogeneity in fibrotic tissue, augmenting the dynamic fibrillatory and re-entry area, increasing propensity for AF initiation under stress.*  
Cardiac MRI before and after PVI can assess scar and fibrosis burden of the atria in static manner. By including the dynamic information of autonomic tone, the true potential fibrillatory thresholds can be determined, which can be obtained and verified during EP study. Moreso, ablation approaches for specific atrial substrates can be tailored to increase efficacy.

**Aim 3: Explore the genetic and epigenetic determinants of autonomic dysfunction that predispose to AF.** *Hypothesis: Genetic variants associated with neurocardiac regulation, and epigenetic changes on similar trait loci, increases the risk of future AF occurrence.* By creating a polygenic risk for abnormal neurocardiac responses to mental stress (the Emory Myocardial Ischemia and Mental Stress study), key neurocardiac genes can be identified. By evaluating those genes, and their epigenetic modifications, in large biobank databases (Million Veterans Project, UK Biobank), we can quantifiy part of the polygenic and allostatic contribution to AF.

Our work will allow us to customize therapies, including AAD choice and ablation strategies, to target the underlying mechanism of behind AF, and will lead to future trials that can target the prevention and progression of AF at earlier stages.

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