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: Measure the differential electrophysiologic effects of the ANS on the atrial substrate and risk for atrial arrhythmias.** *Hypothesis: EP characteristics with ANS modulation will show regional differences across the atria.* *Secondary hypothesis: Scar tissue will have increased heterogeneity of refractoriness in response to ANS modulation, with an exaggerated shortening of APD, relative to baseline.* During clinically-indicated EP studies for atrial arrhythmias, we will measure EP characteristics under ANS modulation through both pacing (e.g. vagal stimulation) and pharmacological maneuvers (e.g. isoproterenol infusion).

**Aim 2: Compare the efficacy of computational scar-based models of atrial arrhythmias with predictive models accounting for ANS.** We have designed predictive models of atrial arrhythmias based off of scar patterns identified by clinical imaging. This aim will augment the models by incorporating ANS parameters. Hypothesis: Atrial-specific ANS parameters will improve prediction of clinically-relevant arrhythmias. Secondary hypothesis: ANS parameters obtained from **Aim 1** will validate parameters utilized in computational models.

**Aim 3: Explore the contribution of ANS genetic variants to the polygenic risk of atrial arrhythmias.** Using a two-sample Mendelian randomization study design, we will identify SNPs that contribute to stress-related disorders, including potentially novel loci, and assess their impact on the polygenic risk of AF in a validation cohort. Hypothesis: Genetic variants associated with abnormalities in the ANS, including stress-related disorders, will overlap with and partially explain both risk and resilience to future development of 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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