Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence of over 50 million cases currently and ≥ 25% lifetime risk across races.1 Although atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a 25% lifetime risk across races,1 the disease is only classified by by broad strokes into paroxysmal, persistent, or permanent. Treatment strategies are limited to antiarrhythmic drugs or catheter ablation and are applied without regard to the stage of the disease or the underlying mechanism.2–4 For example, vagal nerve stimulation and cardioneural ablations have shown promise in AF, but are underutilized and not individually tailored.2,5 Moreover, current attempts at reclassifying AF have been limited to cross-sectional, comorbidity-based heuristics, which considered AF to be a consequence instead of a precursor of other conditions.6,7 To overcome this lack of specificity in the diagnosis of paroxysmal AF, we need to identify specific mechanisms in AF pathognesis, before prescribing therapies. In the earlier stages of AF, triggered activity from atrial tissue, such as ectopic beats, are the underlying *first-mover* in the onset of an episode of AF. Longer, sustained episodes of AF are accompanied by increased atrial scarring and fibrosis, as part of the disease progression. This supports the understanding that earlier phases of paroxysmal AF are driven by electrical triggers, which is ultimately mediated by a maladaptive response of the autonomic nervous system (ANS), such as increased sympathetic activity and acute parasympathetic withdrawal.8,9 Our overarching hypothesis is that sympathetically-triggered atrial activity leads to differential effects on structurally normal and abnormal atria.

To test this, we will leverage several pre-existing, well-established cohorts that has extensive follow-up data, genetic sequencing, EP signal data, and are led by members of the mentorship committee. During my TL1, T32, and F32 scholarship, I worked extensively to collect clinical and electrical signal data in multiple ongoing NIH-sponsored investigations involving my mentorship and advisory team,10,11 developing critical skills in signal processing, biostatistics, and computational genetics. In support of current literature,2 I found supporting evidence that vagolysis lead to abnormal cardiac perfusion and increased cardiovascular mortality.12–15 These abnormalities were identified through electrocardiography-based (ECG) markers, including heart rate variability (HRV), and associated with ANS function and cardiac physiology.16 As a fellow in clinical cardiac electrophysiology (EP), I am positioned to also obtain highly-granular data from EP studies performed during AF ablation, including cardiac-specific blood samples, intracardiac electrograms, and electroanatomical mapping. This mentored research with the appropriate, rigorous training will extend my background in signal processing and biostatistics to computational approaches in epidemiology and genomics. To this end, I have the following aims:

**Aim 1: Identify electrocardiographic phenotypes of paroxysmal AF.** We will generate electrocardiographic parameters in sinus rhythm (atrial and ventricular activation and repolarization indices) and in atrial fibrillation (amplitude of fibrillatory waves, atrial frequency). We will assess the relationship of these parameters to groups of paroxysmal AF with normal left atrial volume. *Hypothesis*: Increased amplitude of fibrillatory waves during atrial fibrillation and increased variability in P wave indices will identify paroxysmal AF with structurally normal atria.

**Aim 2: Determine the electrophysiological characteristics of sympathetically-triggered paroxysmal AF.** In prospectively enrolled individuals with new-onset paroxysmal AF, we will perform electrophysiology studies to measure atrial parameters, including scar burden, conduction abnormalities, and changes in repolarization. We will assess the effect of autonomic modulation on atrial tissue with normal and abnormal structural properties, confirming autonomic effects through assessment of cardiac-specific neurohormones. *Hypothesis*: During increased sympathetic activity and decreased vagal activity, action potential duration alternans will occur predominantly at borders of scar tissue as compared to scar or healthy tissue.

**Aim 3: Evaluate the role of genetic variants in neural and cardiac tissue in the incidence and progression of AF.** We will identify novel and known variants in whole exome sequencing data that may be related to AF risk, including genes present in the neurocardiac axis. Using a Mendelian randomization approach, we will assess the relationship of rare and novel variants with paroxysmal AF. *Hypothesis*: Variants in genes that regulate the neurocardiac axis will be associated with increased risk of paroxysmal AF in structurally normal atria.

The current paradigm in the management of AF is superficial, focusing on therapies that are aimed at pharmacological and ablative modification of cardiac conductive tissue, instead of specific mechanisms, such as the underlying maladaptive autonomic response and interaction between scar and health atrial tissue under stress. Identifying upstream mechanistic, autonomic pathways could lead to targeted therapies that not only decrease the risk of AF, but may also provide benefit in a number of other triggered atrial arrhythmias.5

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