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 Surprisingly, the disease is only classified by broad strokes into paroxysmal, persistent, and permanent, which parallels the lack of granularity in antiarrhythmic drugs and catheter ablation strategies, which have not noticeably changed over the past 20 years.2,3 Our overly simplistic model disallows us to understand the disease or match interventions to the specific stage of progression. Current attempts at reclassifying AF have been limited to cross-sectional, comorbidities-based heuristics, which consider AF to be a consequence instead of a precursor of other conditions.4,5 A paradigm shift is needed – differentiation of the underlying spectrum of paroxysmal AF would allow us to identify those at risk for progression, and tailor therapies that target the underlying pathophysiology.

To overcome the lack of specificity in the diagnosis of paroxysmal AF, we intend to focus on the earlier, trigger-predominant stages of AF using both population-level and individual-level methods. Triggered electrical activity, such as ectopic beats, are the underlying *first-mover* in the onset of AF, and ultimately are driven by maladaptive activity of the autonomic nervous system (ANS).6,7 We propose that the acute, inappropriate vagolysis at times of increased adrenergic tone drives triggered events that lead to episodes of AF.8 To test this, we will leverage two pre-existing, well-established cohorts: (A) an atrial arrhythmia registry enriched for paroxysmal AF,9 and (B) a mental stress cohort with a significant burden of inappropriate vagolysis.10 Both cohorts have extensive follow-up data, genetic sequencing, and are led by members of the mentorship committee. Our overarching hypothesis is that there exists a common, vagally-triggered endophenotype of paroxysmal AF that can be defined by its triggered activity and abnormalities in neurocardiac signal and neurohormone receptors.

During his TL1, T32, and F32 scholarship, the applicant has worked extensively to collect clinical data in both ongoing NIH-sponsored investigations involving his mentorship and advisory team.9,10 The applicant has extracted meaningful electrocardiographic-based (ECG) features, which will allow for further analysis of atrial abnormalities using signal-averaged P wave morphology and ANS dysfunction using heart rate variability (HRV). Using these features, along with analysis of large-scale, longitudinal electronic medical record data, the applicant can identify the multitude of trajectories of AF progression. He will integrate existing data from the parent atrial arrhythmia registry (A) to validate these subphenotypes. As a fellow in clinical cardiac electrophysiology, the applicant is positioned to also obtain highly-granular data from electrophysiology studies (EPS) performed during AF, including cardiac blood sampling, intracardiac electrograms, and electroanatomical mapping, allowing him to identify physiological patterns within these subphenotypes. As a secondary component to the this investigation, the applicant has identified subsets of individuals with inappropriate vagolysis and increased rates of CV mortality (B). The applicant will assess for genetic variants on the neurocardiac axis that are associated with this vagolysis Using a two-sample Mendelian randomization approach, the applicant will identify genetic variants in (B) associated with inappropriate vagolysis, and compare these instruments with the trigger-predominant subphenotype of AF in (A). The applicant will extend his previous experience in signal processing to other computational approaches through additional rigorous training in natural language processing and genetic analyses. To this end, the applicant has the following aims:

**Aim 1: Investigate the clinical and electrophysiological determinants that identify trigger-predominant subphenotypes of pAF.** *Trigger-predominant pAF will have shorter, symptomatic episodes of AF with decreased atrial scar burden.* Population level data will be leveraged to identify critical features of arrhythmia burden and recurrence, atrial pathology, and time-varying components of potential risk-factors obtained through clinical, ECG, and echocardiography markers. These features will be validated against findings during EPS of conduction disease and atrial scarring.

**Aim 2: Determine the role of autonomic mechanisms in subphenotypes of pAF.** *Trigger-predominant pAF will be associated with increased electrical and neurohormonal biomarkers of vagolysis* The subphenotype of pAF will be supported by findings from **Aim 1**. Our measure of vagolysis will include increased levels of NPY and Gal (coronary sinus blood), decreased arrhythmia thresholds (intracardiac electrograms), and decreased high frequency HRV (ECG), measured during EPS.

**Aim 3: Evaluate the role of genetic variants in cardiovagal receptors for the risk of trigger-predominant pAF through Mendelian randomization.** Using a two-sample Mendelian randomization study, we will identify patients with genetic variants in a phenotyped cohort with maladaptive autonomic responses. *The identified variants will associate with increased arrhythmia burden of pAF,* as assessed in **Aim 1** and **2**.

The current paradigm in the management of AF focuses on antiarrhythmic modulation of cardiac ion channels and ablative strategies targeting atrial endocardium, which however is only directed at the literal surface of the problem. 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.11

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