Atrial fibrillation (AF) is the most common arrhythmia worldwide, with a prevalence of over 50 million cases currently and ≥ 25% lifetime risk across races.1 Surprisingly, the disease is only classified by its time course – divided by broad strokes into paroxysmal, persistent, and permanent. The management parallels this lack of granularity with homogenous rate and rhythm strategies that have not noticeably changed over the past 20 years.2,3 A paradigm shift is needed. Clinical phenotypes of AF would allow for individualized management and targeted therapy strategies that expand past antiarrhythmi drugs and catheter ablation.

The long-term goal as an electrophysiologist, clinician, and scientist is to personalize the management of paroxysmal AF using earlyy identification and pathophysiologyy driven strategies. AF is often considered to be a consequence instead of precursor of other cardiovascular conditions,4 however the plurality of paroxysmal AF in the other, rare, classification studies are younger individuals with a low burden of other comorbidities.5 This large subgroup have AF that is brought on by triggered activity, which is ultimately driven by autonomic activity.6,7

We propose that the acute, inappropriate vagolysis at times of increased adrenergic tone drives these triggered events in individuals with a susceptible cardiac substrate.8 To test this, we would leverage two pre-existing, well-established cohorts and develop a third smaller and deeply phenotyped cohort with physiological testing: (A) an atrial arrhythmia registry enriched for paroxysaml AF with genetic sequencing,9 (B) a mental stress cohort with a significant burden of inappropriate vagolysis and genetic sequencing,10 and (C) a cohort of paroxysmal AF who will undergo intracardiac electrophysiology studies with neurocardiac biomarker samples and electroanatomical mapping data. 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.

**Aim 1: Identify triggered subphenotypes of pAF.** *Intracardiac and extracardiac electrical features will classify pAF into triggered versus re-entrant subphenotypes.* Population level data will be leveraged to identify clinical subphenotypes of pAF, incorporating ECG and echocardiography markers, arrhythmia burden, recurrence, and time-varying components of potential risk-factors. These subphenotypes will be compared against intracardiac findings to validate triggered arrhythmia phenotypes.

**Aim 2: Determine the role of autonomic mechanisms in triggered pAF.** *Triggered pAF will be associated with increased electrical and neurohormonal biomarkers of vagolysis.* Neuropsychological markers of stress will be obtained through clinical interview prior to PVI, and will be clinically phenotyped (**Aim 1**). Coronary sinus levels of NPY, Gal, S100B and arrhythmia thresholds will be obtained before and after PVI, and at the time of any additional physiological testing (catecholamine infusion, vagal nerve stimulation).

**Aim 3: Evaluate the role of cardiovagal receptor genotypes in the risk of vagally-triggered arrhythmias.** *We hypothesize that novel variants exist that may explain the risk of vagally-triggered arrhythmias.* A subset of patients identified with both decreased rest and reactivity cardiovagal outflow and increased CV mortality have been identified. Genetic analysis will be performed to discover novel mechanisms and biomarkers of arrhythmia risk. Identified variants will be validated in a separate cohort to evaluate the arrhythmia risk and electrical phenotypes identified 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

1. Kornej J, Börschel CS, Benjamin EJ, Schnabel RB. Epidemiology of atrial fibrillation in the 21st century: Novel methods and new insights. Circulation Research 2020;127:4–20. doi:[10.1161/CIRCRESAHA.120.316340](https://doi.org/10.1161/CIRCRESAHA.120.316340).

2. Wyse D, Waldo A, JP D, Domanski M, Schron E, Rosenberg Y, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. New England Journal of Medicine 2002;347:1825–1833. doi:[10.1056/NEJMoa021328](https://doi.org/10.1056/NEJMoa021328).

3. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, et al. Early rhythm-control therapy in patients with atrial fibrillation. The New England Journal of Medicine 2020:1–11. doi:[10.1056/NEJMoa2019422](https://doi.org/10.1056/NEJMoa2019422).

4. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: Relationships among clinical features, epidemiology, and mechanisms. Circulation Research 2014;114:1453–1468. doi:[10.1161/CIRCRESAHA.114.303211](https://doi.org/10.1161/CIRCRESAHA.114.303211).

5. Pastori D, Antonucci E, Milanese A, Violi F, Pignatelli P, Palareti G, et al. Clinical phenotypes of atrial fibrillation and risk of mortality: A cluster analysis. European Heart Journal 2020;41. doi:[10.1093/ehjci/ehaa946.2893](https://doi.org/10.1093/ehjci/ehaa946.2893).

6. Zipes DP, Rubart M. Neural modulation of cardiac arrhythmias and sudden cardiac death. Heart Rhythm 2006;3:108–113. doi:[10.1016/j.hrthm.2005.09.021](https://doi.org/10.1016/j.hrthm.2005.09.021).

7. Taggart P, Boyett MR, Logantha SJRJ, Lambiase PD. Anger, emotion, and arrhythmias: From brain to heart. Frontiers in Physiology 2011;2 OCT. doi:[10.3389/fphys.2011.00067](https://doi.org/10.3389/fphys.2011.00067).

8. Mehra R, Tjurmina OA, Ajijola OA, Arora R, Bolser DC, Chapleau MW, et al. Research opportunities in autonomic neural mechanisms of cardiopulmonary regulation: A report from the national heart, lung, and blood institute and the national institutes of health office of the director workshop. JACC: Basic to Translational Science 2022;7:265–293. doi:[10.1016/j.jacbts.2021.11.003](https://doi.org/10.1016/j.jacbts.2021.11.003).

9. Chalazan B, Mol D, Darbar FA, Ornelas-Loredo A, Al-Azzam B, Chen Y, et al. Association of rare genetic variants and early-onset atrial fibrillation in ethnic minority individuals. JAMA Cardiology 2021;6:811–819. doi:[10.1001/jamacardio.2021.0994](https://doi.org/10.1001/jamacardio.2021.0994).

10. Vaccarino V, Almuwaqqat Z, Kim JH, Hammadah M, Shah AJA, Ko YA, et al. Association of mental stress-induced myocardial ischemia with cardiovascular events in patients with coronary heart disease. JAMA - Journal of the American Medical Association 2021;326:1818–1828. doi:[10.1001/jama.2021.17649](https://doi.org/10.1001/jama.2021.17649).

11. Shivkumar K, Ardell JL. Vagal neuromodulation for atrial arrhythmias. JACC: Clinical Electrophysiology 2017;3:939–941. doi:[10.1016/j.jacep.2017.06.018](https://doi.org/10.1016/j.jacep.2017.06.018).