

## The Effects of Daily Dose of Intense Exercise on Cardiac Responses and Atrial Fibrillation Lay Summary

The study was motivated by recent publications concluding that there is a U-shaped (or J-shaped) response of cardiovascular health outcomes to exercise. In this regard, while moderate exercise is shown to reduce susceptibility to many cardiovascular disease conditions (such as hypertension, coronary artery disease, obesity and diabetes), high levels of endurance exercise and sport have been linked to adverse changes in atrial tissue along with increased risk of an arrhythmia known as atrial fibrillation (AF). Our study is the first to directly quantify and assess the impact of “exercise dose” on cardiac responses and AF vulnerability in a mouse swim model. For technical reasons (outlined in the paper), the exercise dose was varied by altering the total daily swimming durations (120, 180 or 240 minutes/day). Assessments were then made after all mice performed the same total work during swimming (estimated by measuring oxygen consumption while exercising). Although ventricular adaptations and aerobic conditioning improved equally between the exercise groups, we found atrial fibrosis, inflammation and hypertrophy, alongside AF vulnerability, all increased as daily swim durations were prolonged. By comparing oxygen consumption measurements in our mice during exercise to measures reported in humans (in terms of MET-hours/week), we argue that our studies shed light on the exercise dose-dependency of AF vulnerability in athletes. We also propose a potential mechanism to explain our observation involving the effects of varied exercise on venous filling pressures. Since elevated atrial pressures are common in AF patients with cardiovascular and (or) metabolic diseases as well as aging, we believe our findings may also have broader implications for the AF population.