



**LATE-IN-LIFE TREADMILL-TRAINING AMELIORATES THE DECLINE IN  
CARDIAC AUTOPHAGY ASSOCIATED WITH AGING IN MICE**

**Kellsey Ly (J. David Symons, Caroline Ramous, JaeMin Cho, Lauren Thompson, Kiana Luu, Alex Margretts, Skye Buzianis, Michele Hansen, Karla Maria Pires, Kevin Whitehead, Kandis Carter, Marcio Buffolo, Seul-Ki Park, Sihem Boudina)  
Department of Nutrition and Integrative Physiology**

Protein aggregates accumulate and organelles become damaged and / or dysfunctional during the process of healthy aging. A progressive loss of the cellular quality control mechanism autophagy (i.e., “self-eating”) contributes to this age-associated decline in cellular function in many organs. Evidence for an age-associated repression in cardiac autophagy is not consistent. We hypothesized that 24-month old (old) male C57Bl6/J mice exhibit repressed autophagosome formation in the heart, an accumulation of cardiac protein aggregates, myocardial dysfunction, and reduced exercise capacity vs. 6-month old (adult) mice. First, cardiac lysates from old mice displayed reduced ( $p < 0.05$ ) accumulation of LC3II / GAPDH and degradation of p62 vs. adult animals (assessed via immunoblotting;  $n = 12$  per group). Second, the lysosomal acidification inhibitor chloroquine (CQ) induced accrual ( $p < 0.05$ ) of LC3II / GAPDH and p62 in hearts from adult but not old mice (quantified by immunoblotting;  $n = 7$  per group). Third, the number and size of protein aggregates was higher ( $p < 0.05$ ) in hearts from old vs. adult mice (measured via scanning electron microscopy;  $n = 5$  per group). Fourth, left ventricular mass / tibial length was greater ( $p < 0.05$ ), and indices of systolic, diastolic, and global left ventricular function (measured via transthoracic echocardiography) were impaired ( $p < 0.05$ ), in old vs. adult animals ( $n = 12$  per group). Finally, maximal workload performed during a treadmill-test, and soleus muscle oxidative enzyme capacity (citrate synthase activity assessed via ELISA), were less ( $p < 0.05$ ) in aged ( $n = 11$ ) vs. adult ( $n = 12$ ) mice. To determine whether late-in-life exercise training improves cardiac autophagy to an extent that demonstrates functional relevance, separate cohorts of older male mice completed a progressive-resistance treadmill-running program (old-ETR) or remained sedentary (old-SED) from 21-24 months. Body composition (estimated via nuclear magnetic resonance), exercise performance during a maximal workload test, soleus muscle citrate synthase activity, indices of cardiac antioxidant enzyme activity (quantified via immunoblotting), markers of cardiac autophagy, accumulation of cardiac protein aggregates, and indices of myocardial function, all improved ( $p < 0.05$ ) in old-ETR ( $n = 11$ ) vs. old-SED ( $n = 12$ ) mice. These data are the first to demonstrate that markers of cardiac autophagy are elevated, and indicators of protein aggregate removal and myocardial function are improved, in older mice that complete a treadmill-training regimen that is sufficient to increase skeletal muscle CS activity and maximal exercise capacity. Our results provide strong proof of concept to evaluate cause and effect relationships among exercise-training, myocardial autophagy, and cardiac function using genetic approaches in pre-clinical models and these studies are ongoing in our laboratory.