HIRAD A. FERIDOONI
BSc (Honours in Biochemistry and Molecular Biology), Dalhousie University, 2013

DEPARTMENT OF PHARMACOLOGY

TITLE OF THESIS: THE IMPACT OF AGE AND FRAILTY ON CARDIAC FUNCTION IN HEALTH AND DISEASE CONDITIONS IN NATURALLY AGEING MICE

TIME/DATE: 9:30 am, Monday, September 17, 2018

PLACE: Room 3107, The Mona Campbell Building, 1459 LeMarchant Street

EXAMINING COMMITTEE:

Dr. Michael Czubryt, Department of Physiology & Pathophysiology, University of Manitoba (External Examiner)

Dr. Scott Grandy, School of Health and Human Performance (Kinesiology), Dalhousie University (Reader)

Dr. Kishore Pasumarthi, Department of Pharmacology, Dalhousie University (Reader)

Dr. Susan Howlett, Department of Pharmacology, Dalhousie University (Supervisor)

DEPARTMENTAL REPRESENTATIVE: Dr. Morgan Langille, Department of Pharmacology, Dalhousie University

CHAIR: Dr. Jure Gantar, PhD Defence Panel, Faculty of Graduate Studies

ABSTRACT

Frail people with cardiovascular disease experience worse outcomes and higher mortality than non-frail patients, but the links between frailty and myocardial function are unclear. Assessing frailty in mice is now possible with the recent development of a mouse clinical FI tool. The present study investigated the links between age, frailty, and cardiac contractile function before and after exposure to ischemia and reperfusion. Frailty was quantified as deficit accumulation in adult (≈8 mos) and aged (≈27 mos) C57BL/6 male mice using the mouse clinical FI tool. Contractile function was evaluated in Langendorff-perfused hearts before and after exposure to ischemia and reperfusion (IR). Contraction and underlying Ca^{2+} homeostasis was measured in individual ventricular myocytes in voltage clamp experiments. Mean cardiac hypertrophy increased with age. Furthermore, under basal conditions, left ventricular developed pressure plus rates of pressure development and decay declined with age. Interestingly, ventricular myocytes from aged mice had smaller and slower contractions. These smaller contractions were due to smaller Ca^{2+} transients and Ca^{2+} currents. Smaller Ca^{2+} currents were attributable to a decrease in CaV1.2 expression in aged hearts in comparison to adult hearts. Interestingly this age-dependent remodelling in the intact hearts and individual myocytes was graded by frailty. By contrast, hearts from aged mice had better recovery of function and less cell death in comparison to adult hearts following exposure to IR. However, functional recovery and myocardial injury were not correlated with FI scores. These results show that age-dependent cardiac remodelling at the level of the intact heart and at the cellular and subcellular levels are graded by the overall health of the mouse and that there may be underlying mechanisms that protect against IR in ageing.