Mid Atlantic Regional Chapter
of the
American College of Sports Medicine

Annual Scientific Meeting, November 1st – 2nd, 2019
Conference Proceedings
International Journal of Exercise Science, Volume 9, Issue 8

Calcium Activation of Mitochondrial Respiration is Maintained in Heart Failure Despite Altered Mitochondrial Membrane Potential

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Heart failure is a complex condition in which the heart is unable to meet the body's demand for fuel and oxygen, and patients often suffer from exercise intolerance. One theorized mechanism of this dysfunction is a reduction in mitochondrial ATP production, but it has been reported that maximal respiration rate (J_O) is unaltered in mitochondria (mito) from failing human hearts. Ca^{2+} entry into the mito is critical for the activation ATP production; however, elevated cellular Na^+, which have been reported in failing hearts, may reduce matrix Ca^{2+} activation by activating the Na^+/Ca^+ exchanger. **PURPOSE:** The goal was to examine how high and low extramitochondrial Na^+ affected oxygen consumption, membrane potential (Ψ_m), and redox potential in mito from healthy and failing hearts. **METHODS:** Heart failure was induced in male rats via transverse aortic constriction. J_O, Ψ_m, and NADH fluorescence were measured in isolated mito from control and failing rat hearts. The effect of Ca^{2+} on maximal and intermediate J_O, Ψ_m, and redox potential in mito incubated with healthy (5mM) or failing (15mM) [Na^+] were determined. Force-flow analysis was used to estimate the effective activity of the electron transport chain (ETC) and of the ATP synthase and the adenine nucleotide translocase (ANT). **RESULTS:** Maximal J_O was similar between failing and control hearts when incubated with healthy (498.2 ± 35.8 vs. 426.9 ± 40.1 nmol/mg/min) or failing Na^+ (520.9 ± 50.5 vs. 448.5 ± 46.0 nmol/mg/min). Maximal J_O occurred at the same [Ca^{2+}] between failing and control hearts. Intermediate J_O was similar between failing (199.7 ± 62.1 to 539.9 ± 143.1 nmol/mg/min) and control mito (126.8 ± 19.3 to 398.7 ± 23.4 nmol/mg/min), but failing mito respired across a smaller range of membrane potential (3.3 vs. 7.2 mV). The activity of the ATP synthase and ANT was similar between failing and control mito, but ETC activity in failing mito was about 2 to 5 fold greater than control. **CONCLUSION:** Elevated [Na^+] does not result in altered Ca^{2+} activation in mito from failing or control hearts. Failing mito had similar maximal and intermediate J_O compared to control, yet failing mito respired with smaller changes in Ψ_m suggesting control of mitochondrial respiration is altered in heart failure.

Supported by The American Heart Association Scientific Development Grant (**16SDG30770015)**