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Calcium Activation of Mitochondrial Oxidative Phosphorylation is Maintained in Heart Failure Levels of Extramitochondrial Sodium

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Extramitochondrial [Na^+] and [Ca^{2+}] are characteristics of heart failure. It is suggested that high cytosolic [Na^+] inhibits respiration by decreasing mitochondrial matrix [Ca^{2+}] through the Na^+-Ca^{2+} exchanger. However, it is unknown how this elevated [Na^+] affects Ca^{2+} activation of mitochondrial respiration, due to the interplay between the Na^+-Ca^{2+} exchanger and the Ca^{2+} uniporter. **PURPOSE:** First, we determined if the Ca^{2+} concentration needed to induce maximal mitochondrial respiration differed between healthy (5 mM) or failing (15 mM) Na^+ concentrations. Second, we examined mitochondrial O_2 consumption rate (J_O), NADH, and mitochondrial membrane potential ($\Delta\Psi$) at intermediate respiration rates to determine the effects of elevated [Na^+] on the oxidative phosphorylation pathway. **METHODS:** Mitochondria were isolated from adult male rat hearts and J_O was monitored using a Clark-type O^2 electrode at 37°C. Isolated mitochondria were incubated with 5 or 15 mM NaCl and maximal (State 3) J_O was determined with varying [Ca^{2+}] (100-1500 nM). Intermediate respiration rates were examined with 5 and 15 mM NaCl with and without Ca^{2+}. **RESULTS:** Mitochondrial respiration increased with increasing [Ca^{2+}] up to 1000 nM; maximal J_O occurred at the same Ca^{2+} concentration between 5 and 15 mM NaCl incubations. Without additional Ca^{2+}, intermediate J_O was no different between 5 or 15mM NaCl incubations: 162±20 vs. 167±14 nmol O_2/mg/min at ΔG_{ATP}=$^-$13.1 kcal/mol and 75±5 vs. 74±4 nmol O_2/mg/min at ΔG_{ATP}=$^-$14.4 kcal/mol. The addition of Ca^{2+} activated intermediate respiration rates, but there was no difference in intermediate J_O between 5 or 15mM NaCl incubations: 319±20 vs. 388±32 nmol O_2/mg/min at ΔG_{ATP}=$^-$13.1 kcal/mol and 103±6 vs. 105±8 nmol O_2/mg/min at ΔG_{ATP}=$^-$14.4 kcal/mol. **CONCLUSION:** In conclusion, health and failing extramitochondrial [Na+] do not alter the necessary Ca^{2+} for optimal respiration. Moreover, the importance of extramitochondrial [Na^+] appear to be diminished with Ca^{2+} activated respiration, thereby alluding to the greater role of Ca^{2+} import though the mitochondrial Ca^{2+} uniporter.

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