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

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Extramitochondrial [Na⁺] and [Ca²⁺] are characteristics of heart failure. It is suggested that high cytosolic [Na⁺] inhibits respiration by decreasing mitochondrial matrix [Ca²⁺] through the Na⁺-Ca²⁺ exchanger. However, it is unknown how this elevated [Na⁺] affects Ca²⁺ activation of mitochondrial respiration, due to the interplay between the Na⁺-Ca²⁺ exchanger and the Ca²⁺ uniporter. **PURPOSE:** First, we determined if the Ca²⁺ concentration needed to induce maximal mitochondrial respiration differed between healthy (5 mM) or failing (15 mM) Na⁺ concentrations. Second, we examined mitochondrial O₂ consumption rate (J₀), NADH, and mitochondrial membrane potential (∆Ψ) 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 J₀ was monitored using a Clark-type O₂ electrode at 37°C. Isolated mitochondria were incubated with 5 or 15 mM NaCl and maximal (State 3) J₀ was determined with varying [Ca²⁺] (100-1500 nM). Intermediate respiration rates were examined with 5 and 15 mM NaCl with and without Ca²⁺. **RESULTS:** Mitochanndrial respiration increased with increasing [Ca²⁺] up to 1000 nM; maximal J₀ occurred at the same Ca²⁺ concentration between 5 and 15 mM NaCl incubations. Without additional Ca²⁺, intermediate J₀ was no different between 5 or 15 mM NaCl incubations: 162±20 vs. 167±14 nmol O₂/mg/min at ∆G_ATP=13.1 kcal/mol and 75±5 vs. 74±4 nmol O₂/mg/min at ∆G_ATP=14.4 kcal/mol. The addition of Ca²⁺ activated intermediate respiration rates, but there was no difference in intermediate J₀ between 5 or 15 mM NaCl incubations: 319±20 vs. 388±32 nmol O₂/mg/min at ∆G_ATP=13.1 kcal/mol and 103±6 vs. 105±8 nmol O₂/mg/min at ∆G_ATP=14.4 kcal/mol. **CONCLUSION:** In conclusion, health and failing extramitochondrial [Na+] do not alter the necessary Ca²⁺ for optimal respiration. Moreover, the importance of extramitochondrial [Na⁺] appear to be diminished with Ca²⁺ activated respiration, thereby alluding to the greater role of Ca²⁺ import through the mitochondrial Ca²⁺ uniporter.

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