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## Characterization of Respiratory Phenotype in Very Long-chain Acyl-CoA Dehydrogenase Deficient Mice.

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**Rationale:** Very Long-chain Acyl-CoA dehydrogenase (VLCAD) deficiency is the most common inherited long-chain fatty acid disorder. The VLCAD enzyme catalyzes the first step of mitochondrial fatty acid oxidation and loss of the enzyme results in energy deficiency as well as accumulation of long chain fatty acids. Recently, a related enzyme, Long-chain Acyl-CoA dehydrogenase (LCAD), which unlike VLCAD is not highly expressed in metabolic tissues like liver, heart and skeletal muscle, was found to be expressed in the lung and surfactant and lung dysfunction was observed in LCAD deficient mice. Respiratory distress syndrome has been described in other fatty acid oxidation disorders. VLCAD is expressed in lung, and likely plays an important role in lung compliance.

**Methods:** VLCAD deficient mice and litter-mate controls were fasted for 18 hours, then exercised on a treadmill for 2 hours. Breathing was immediately assessed using whole body plethysmography in unanaesthetized spontaneously breathing mice. After a stable baseline was achieved, mice were given a “respiratory” challenge with 7% hypercapnia. In a subgroup of animals, pulmonary mechanics were assessed using Flexivent (Scireq).

**Results:** Following exercise, VLCAD deficient mice had a decreased tidal volume and minute ventilation compared to their wild type controls. However, post-exercise VLCAD deficient mice were able to stabilize to similar levels as wild-type during baseline. The VLCAD deficient mice had a decreased response to a respiratory challenge with 7% hypercapnia. Early preliminary results suggest that VLCAD deficient animals have lower airway resistance.

**Conclusions:** Respiratory insufficiency was demonstrated in a fasted and exercise challenged VLCAD deficient mice.

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