Succinate accumulation during warm and cold ischaemia in mouse, pig and man:

Mechanistic and therapeutic implications for transplant ischaemia-reperfusion injury

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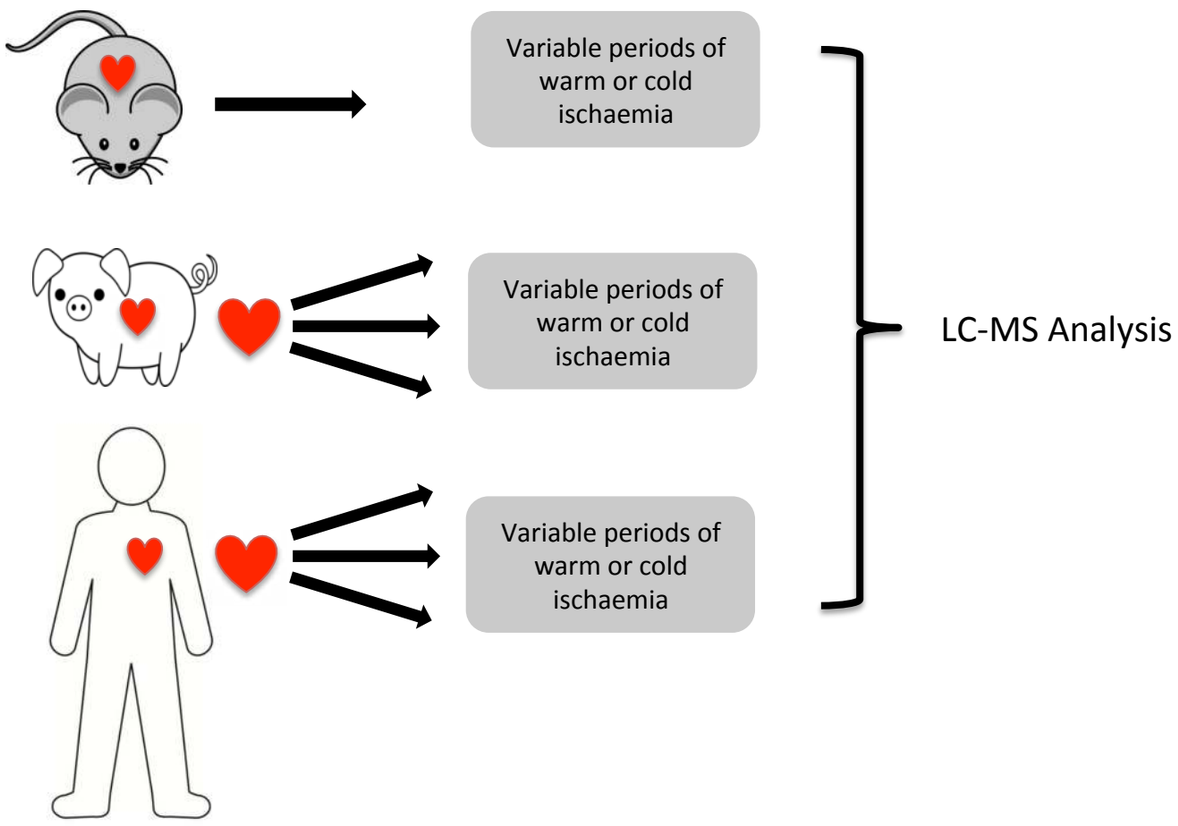
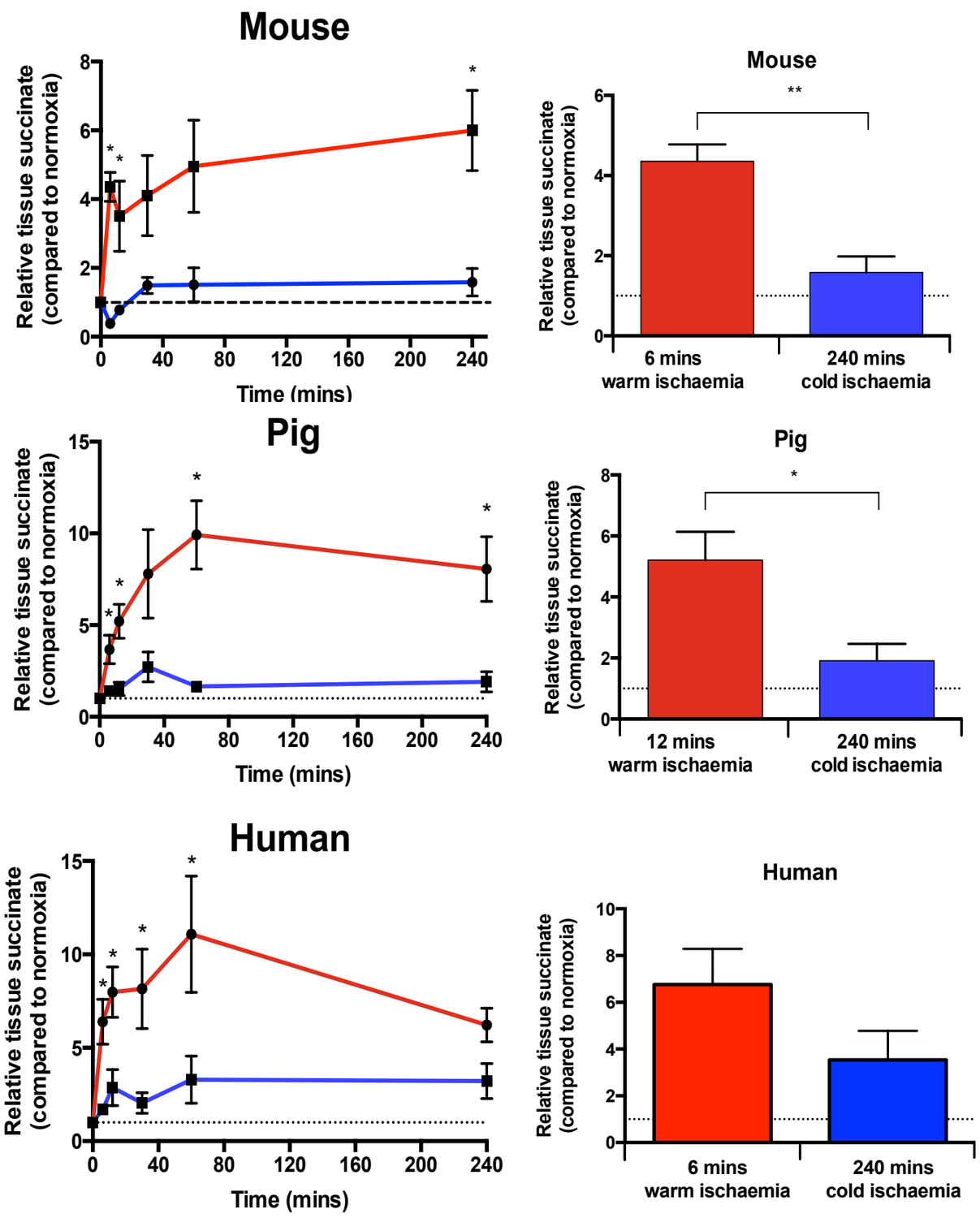
Introduction: Recent evidence from rodents suggests that the burst of reactive oxygen species associated with ischaemia-reperfusion (IR) injury is mediated through a specific metabolic pathway involving mitochondrial accumulation of the metabolite succinate.

Hypothesis: We hypothesized that succinate accumulation during ischaemia is a fundamental process that is shared by mouse, pig and man and may underlie the greater detrimental impact of warm ischaemia compared to cold ischaemia.

Methods: Hearts from anaesthetised mice were exposed to varying periods of warm or cold ischaemia (n=5-8 per group). Porcine (n=5) or human (n=4) apical heart tissue was procured immediately after exsanguination (porcine) or following cross-clamp during donation after brainstem death (DBD) with appropriate ethical approval and informed consent. The apical tissue was rapidly divided into full-thickness myocardial sections and stored for variable periods of warm and cold ischaemia. Metabolite concentrations were determined using mass spectrometry and compared to background levels in fully oxygenated tissue snap-frozen immediately upon removal.



Results: Similar metabolic changes were observed in mice, pigs and humans. Succinate accumulation was at least 2 fold higher after 12 mins of warm ischaemia than 240 mins of cold ischaemia (human; 8.0±1.4 vs 3.2±0.9 [n=4] p=0.03, pig; 5.2±0.9 vs 1.9±0.6 [n=5] p=0.02 (mean±SEM change compared to normoxic control). Thus compared to cold ischaemia, warm ischaemia resulted in a much greater and more rapid increase in succinate levels.



Discussion: Greater succinate accumulation during warm ischaemia may underlie increased IR injury and organ dysfunction following donation after circulatory death (DCD). Prevention of succinate accumulation using inhibitors of the enzyme succinate dehydrogenase is therefore a promising therapeutic strategy to ameliorate IR injury in organ transplantation.

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