Mitochondrial integrity at early reperfusion predicts post-ischemic cardiac graft recovery

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Background and Aims

Identifying strategies for cardioprotection, as well as finding reliable means for graft evaluation, are essential for facilitating donation after circulatory death (DCD). Given that mitochondrial preservation during early reperfusion is critical for recovery after warm, global ischemia, we aimed to

- ➡ investigate the effects of ischemic duration on cardiac mitochondrial integrity during early reperfusion.
- ➡ determine the value of early reperfusion mitochondrial and hemodynamic parameters in the prediction of cardiac recovery.

Methods

Experiments were performed in an isolated working rat heart model of DCD. Hearts of adult Wistar rats (♂) underwent 0 (no ischemia), 21, 24, 27, 30, or 33 min warm, global ischemia (Fig. 1).

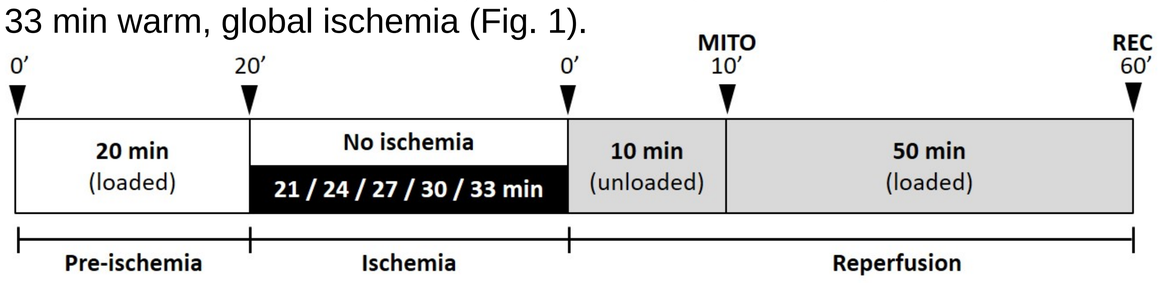

Fig. 1: Perfusion protocols for assessment of post-ischemic cardiac functional recovery (REC) **and mitochondrial integrity** (MITO).

After 60 min reperfusion, cardiac functional recovery (left ventricular work) was determined. After 10 min reperfusion, mitochondrial ROS emission, mitochondrial Ca^{2+} content and retention capacity, cardiac O_2 efficiency, mitochondrial coupling, net ATP, and cytochrome c release were measured.

Results

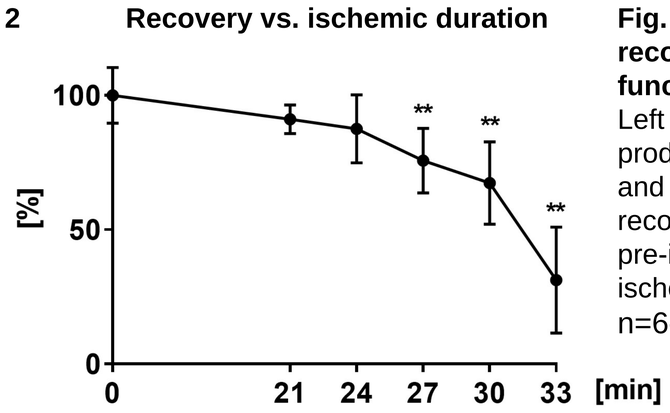

Fig. 2: Post-ischemic cardiac functional recovery at 60 min reperfusion as a function of ischemic duration.
Left ventricular work is calculated as the product of ventricular developed pressure and heart rate. Left ventricular work recovery is expressed as percentage of pre-ischemic value, normalized to non-ischemic controls.
n=6-8 / group; **:p<0.01 vs.no ischemia

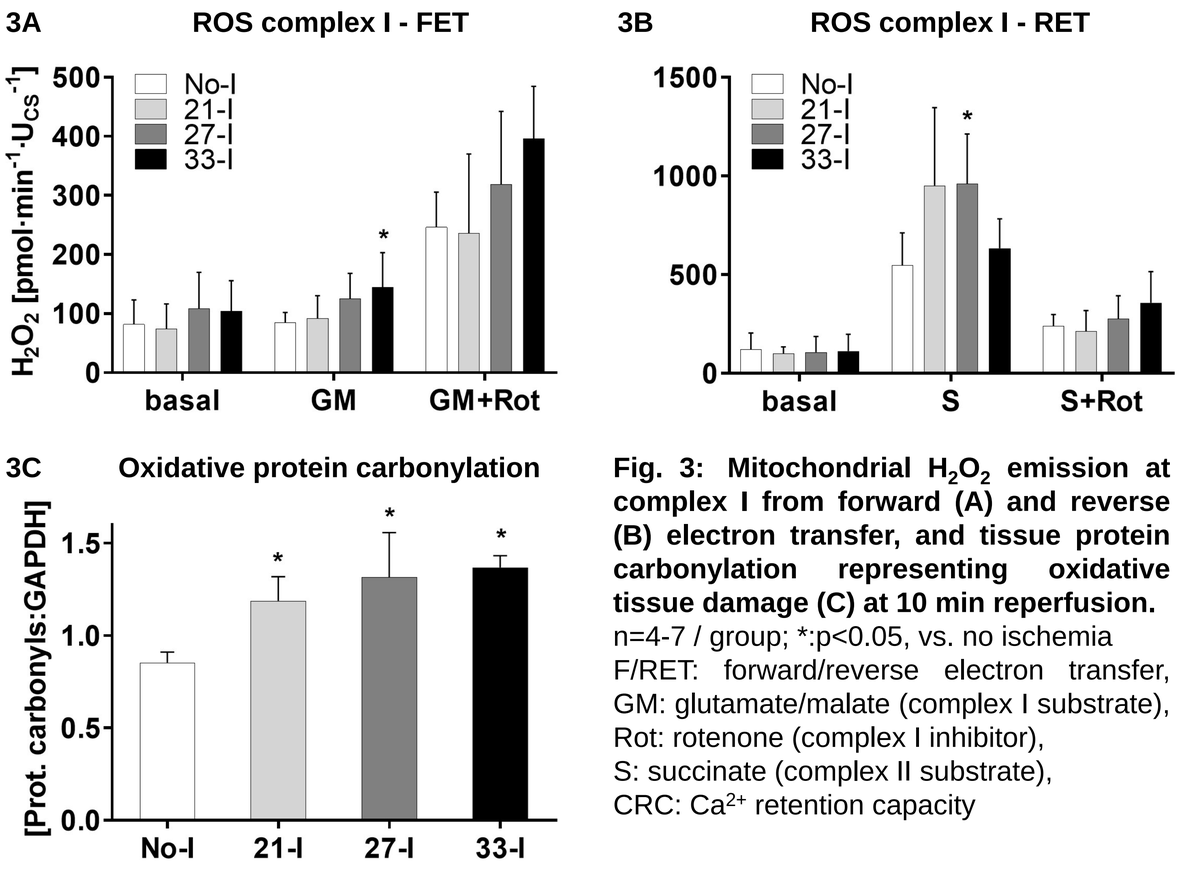

Fig. 3: Mitochondrial H_2O_2 emission at complex I from forward (A) and reverse (B) electron transfer, and tissue protein carbonylation representing oxidative tissue damage (C) at 10 min reperfusion.
n=4-7 / group; *:p<0.05, vs. no ischemia
F/RET: forward/reverse electron transfer, GM: glutamate/malate (complex I substrate), Rot: rotenone (complex I inhibitor), S: succinate (complex II substrate), CRC: Ca^{2+} retention capacity

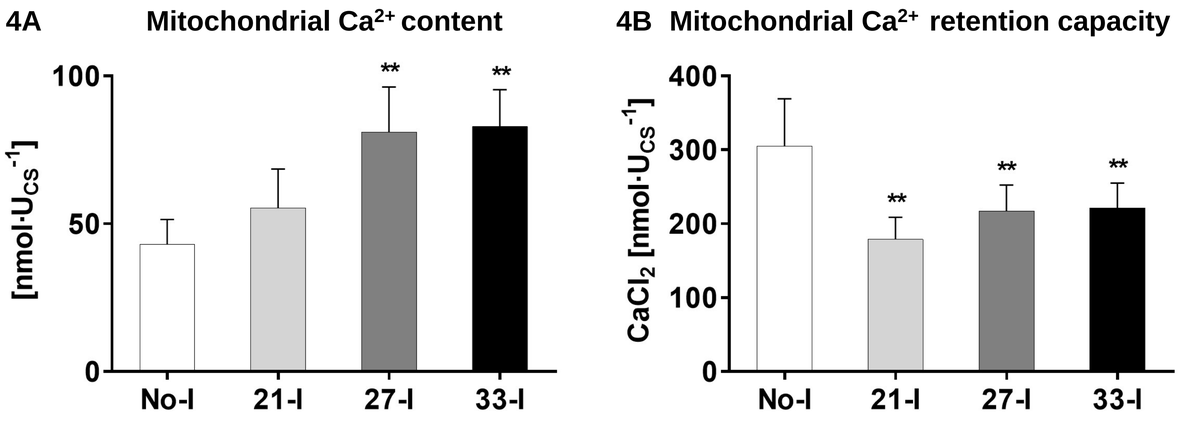

Fig. 4: Mitochondrial Ca^{2+} content (A) and mitochondrial Ca^{2+} retention capacity (B) at 10 min reperfusion. n=5-7 / group; **:p<0.01, vs. no ischemia

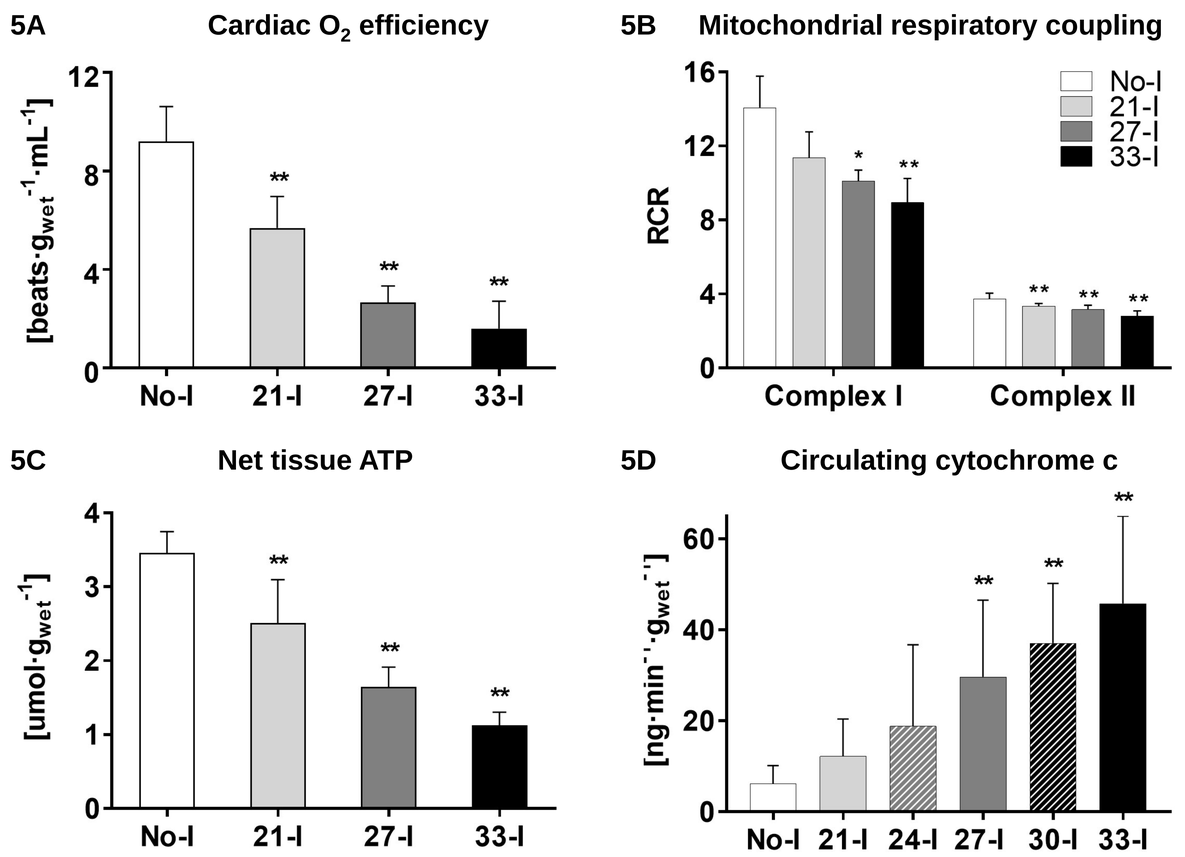

Fig. 5: Cardiac O_2 efficiency (A) calculated as the ratio between left ventricular work and O_2 consumption, **respiratory coupling of mitochondrial complexes I and II (B) and net tissue ATP content (C) at 10 min reperfusion.** (RCR:respiratory control ratio); n=5-7 / group; *:p<0.05, **:p<0.01, vs. no ischemia
And circulating cytochrome c levels (D) at 10 min reperfusion. n=6-8 / group; **:p<0.01 vs. no ischemia

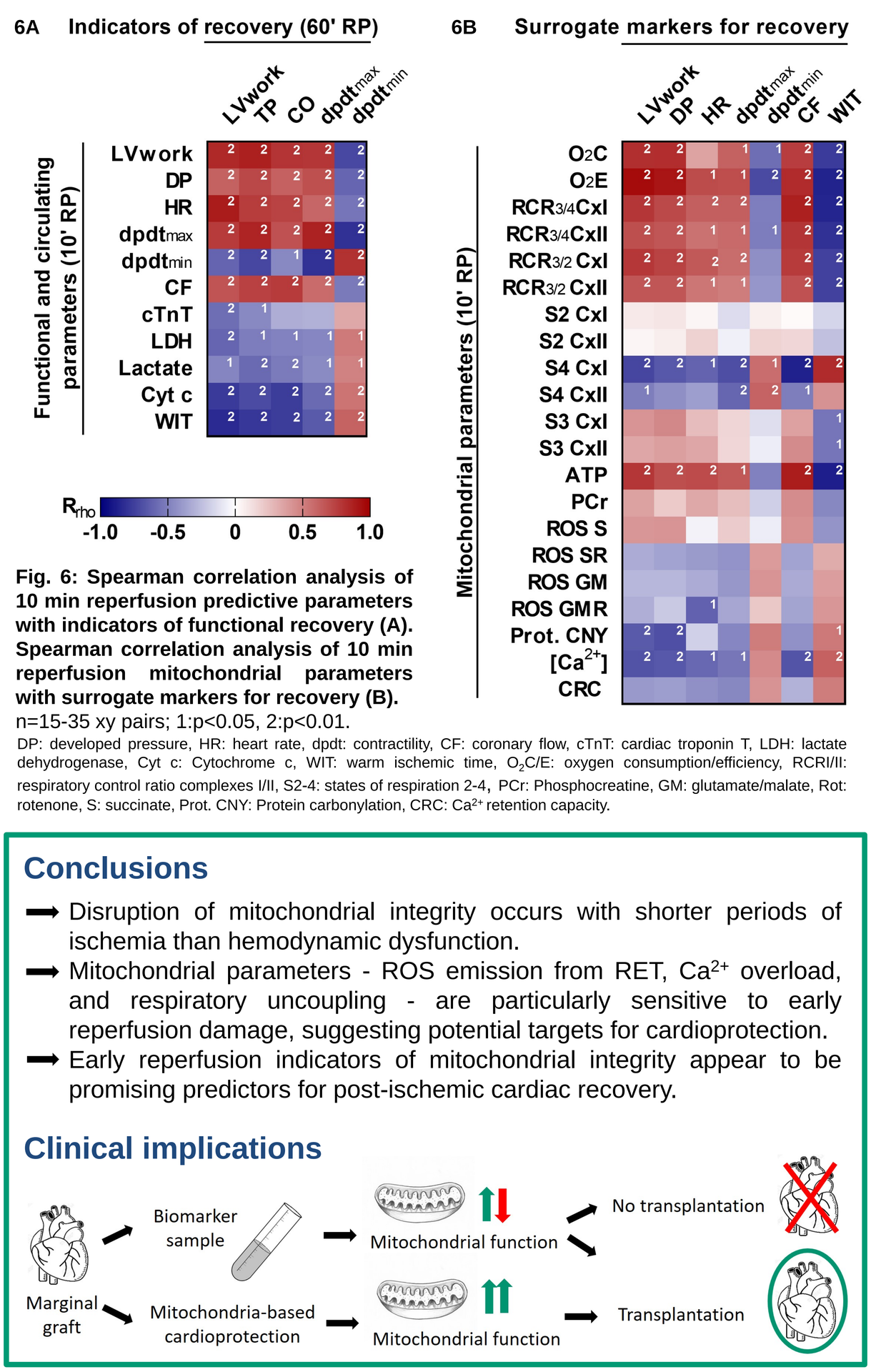

Fig. 6: Spearman correlation analysis of 10 min reperfusion predictive parameters with indicators of functional recovery (A). Spearman correlation analysis of 10 min reperfusion mitochondrial parameters with surrogate markers for recovery (B).
n=15-35 xy pairs; 1:p<0.05, 2:p<0.01.
DP: developed pressure, HR: heart rate, dpdt: contractility, CF: coronary flow, cTnT: cardiac troponin T, LDH: lactate dehydrogenase, Cyt c: Cytochrome c, WIT: warm ischemic time, O_2C/E: oxygen consumption/efficiency, RCRI/II: respiratory control ratio complexes I/II, S2-4: states of respiration 2-4, PCr: Phosphocreatine, GM: glutamate/malate, Rot: rotenone, S: succinate, Prot. CNY: Protein carbonylation, CRC: Ca^{2+} retention capacity.

Conclusions

- ➡ Disruption of mitochondrial integrity occurs with shorter periods of ischemia than hemodynamic dysfunction.
- ➡ Mitochondrial parameters - ROS emission from RET, Ca^{2+} overload, and respiratory uncoupling - are particularly sensitive to early reperfusion damage, suggesting potential targets for cardioprotection.
- ➡ Early reperfusion indicators of mitochondrial integrity appear to be promising predictors for post-ischemic cardiac recovery.

Clinical implications

No financial relationship to disclose.
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