Cardioprotective therapy in a rat model of donation after circulatory death (DCD)

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1. Abstract

Heart transplantation remains the gold standard treatment for end-stage heart failure. Due to the shortage of donor hearts, donation after circulatory death (DCD) has become an important solution. However DCD hearts are exposed to a harmful period of functional warm ischemic time (FWIT), followed by ischemic- reperfusion injury (IRI), which remains a major challenge affecting graft recovery. In this thesis, a rat DCD model was used to investigate whether the cardioprotective drug malonate can improve post- ischemic cardiac recovery. Furthermore, sex- dependent differences were assessed, to better understand potential differences in response to cardioprotective treatment. 20 Wistar rats were included in this study. Following simulated DCD and 22 minutes of FWIT, hearts were explanted and connected to an ex- situ heart perfusion system. During the first 15 minutes of perfusion, hearts received either malonate treatment or dimethylsulfoxide (DMSO) as control. Cardiac recovery was assessed by evaluating functional, metabolic and vascular parameters throughout reperfusion.

2. Introduction

During reperfusion after IRI, the sudden increase of oxygen in the ischemic myocardium can lead to the formation of reactive oxygen species (ROS), leading to cellular and myocardial injury. Malonate is a drug which inhibits succinate dehydrogenase (SDH) and may reduce ROS formation by limiting succinate oxidation during reperfusion [1].

Sex- dependent differences in cardiac recovery after IRI have been reported. In DCD rat models, female hearts showed better post-ischemic recovery than males [2]. Female hearts may have better tolerance to ischemic injury, due to the cardioprotective effects of female sex hormones, especially estrogen [3].

3. Aim and Leading Questions

Aim: Determine if malonate has cardioprotective effects on rat DCD hearts and whether female and male rats show different responses to malonate treatment during ex- situ perfusion after simulated DCD.

- Does malonate improve left ventricular, metabolic and vascular recovery compared to the control groups?
- Does the response to malonate differ between the sexes?

4. Methods and Material

20 Wistar rats (11 female, 9 male) were used in a simulated DCD protocol. After withdrawal of life- sustaining therapy, a FWIT of 22 minutes was simulated before the heart was procured. The hearts were then connected to an ex- situ heart perfusion system. During the Langendorff, hearts received either malonate as treatment or DMSO as control for 15 minutes. This was followed by 5 minutes of unloaded perfusion and 50 minutes of working- mode perfusion, resulting in a total ex- situ perfusion time of 70 minutes. Cardiac recovery was assessed by measuring left ventricular (LV) function including LV work, developed pressure, maximum contraction and relaxation rates and cardiac output. Metabolic recovery was evaluated by oxygen consumption and efficiency, while vascular recovery was assessed by coronary flow. Perfusate samples were collected during the experiment for analysis of myocardial cell injury markers, including myoglobin and heart type fatty acid binding protein (H- FABP). Perfusion data were recorded using LabChart which was assessed using a Millar pressure catheter inside the heart. The data was then processed in Excel. Statistical analysis was performed using GraphPad Prism. Cardiac recovery data were analysed by linear regression.

5. Results

Left ventricular recovery

Female hearts treated with malonate showed significantly improved LV work, developed pressure and maximum contraction rate compared with male malonate treated hearts and female DMSO hearts.

Metabolic recovery

Malonate increased oxygen consumption in male hearts and improved oxygen efficiency in female hearts compared with DMSO.

Coronary flow

Malonate increased coronary flow in both male and female hearts, with the highest flow observed in female malonate- treated hearts

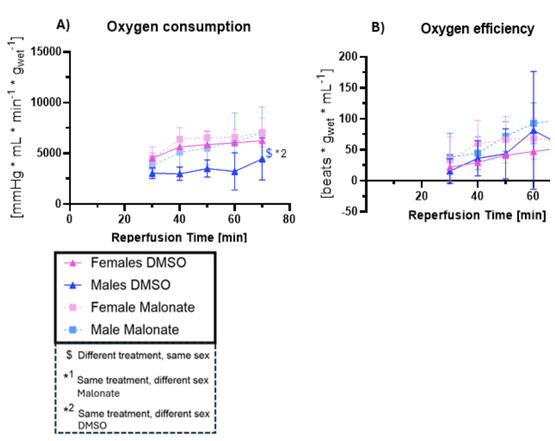

Figure 2: Metabolic recovery. A) Oxygen consumption, B) Oxygen efficiency (left ventricular work*cardiac output/oxy consumption); statistical significance was performed by lir regression analysis and adjusted for multiple comparison modified, sequential,rejective Bonferroni procedure; n = 4 group

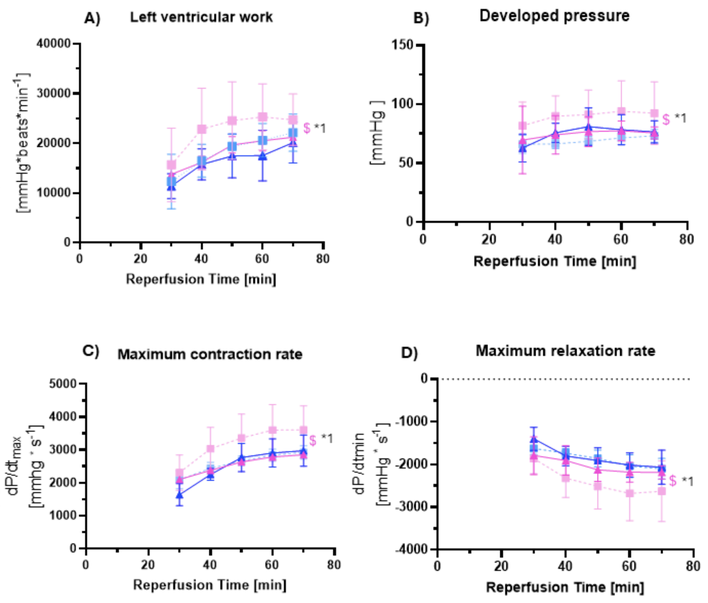

Figure 1: Cardiac recovery measured as left ventricular function. A) left ventricular work (developed pressure*heart rate), B) Developed pressure (dP/dtmax-dP/dtmin), C) Maximum contraction rate, D) Maximum relaxation rate, dP/dtmax,maximum contraction rate; dP/dtmin, maximum relaxation rate; statistical significance was performed by linear regression analysis and adjusted for multiple comparison by the modified, sequential, rejective Bonferroni procedure; n = 4- 6 per group

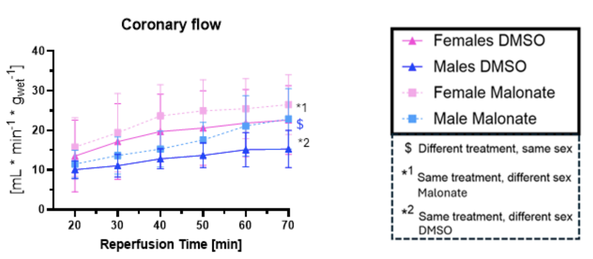

Figure 3: Vascular recovery. Coronary flow during whole reperfusion; statistical significance was performed by linear regression analysis and adjusted for multiple comparison by the modified, sequential, rejective Bonferroni procedure; n = 4- 6 per group

6. Discussion and conclusion

Effect of malonate

Malonate treated hearts showed better cardiac, metabolic and vascular recovery compared with DMSO controls. The better recovery may indicate better preservation of mitochondrial function during reperfusion. The improved coronary flow may suggest less vascular injury after reperfusion. Overall, these findings support a protective effect of malonate during early reperfusion.

Sex differences

Female hearts showed a stronger response to malonate than male hearts, particularly in ventricular function recovery and coronary flow. This may indicate a higher tolerance to IRI in female hearts. Differences in response to malonate and the cardioprotective effects of estrogen may contribute to this sex- dependent response.

Conclusion

Malonate showed a cardioprotective effect during early reperfusion after DCD, and the stronger response in female hearts suggests that sex- specific mechanisms influence the effectiveness of cardioprotective treatments.

List of References:

[1] Chahardehi et al., 2025, p.1547
[2] Clavier et al., 2025; Helmer et al, 2026
[3] Helmer et al., 2026

Figures:

Fig 1. Tinguely G., Left ventricular recovery
Fig 2. Tinguely G., Metabolic recovery
Fig 3. Tinguely G., Vascular recovery