Sex differences in cardiac recovery of ventricular, vascular and metabolic function in a rat model of donation after circulatory death

Joyce Wüthrich, BMA 21-24

Biomedizinische Analytik HF; Inselspital, Department of Cardiac Surgery; University of Bern, Department for BioMedical Research

1. Abstract

Heart transplantation is the top treatment for advanced heart failure, but donor hearts are scarce. Donation after circulatory death (DCD) could expand the donor pool, but warm ischemia limits its use. Current studies on DCD provide limited data on sex differences and their effects on ventricular, vascular and metabolic recovery. This study aimed to investigate sex differences in cardiac recovery in rats using an experimental DCD model with male, female, and ovariectomized (OVX) rats. Males had higher body and heart weights. Hemodynamic and biochemical changes during DCD simulation were similar across groups. Post-ischemic cardiac function and metabolic status were also similar. Non-ischemic groups had better cardiac function, with females showing higher coronary flow. The rat model allowed the investigation of sex differences in cardiac function and vascular and metabolic recovery during a DCD protocol. Overall male, female, and OVX rats exhibit similar tolerance to warm ischemia. Further experiments are needed to confirm these findings.

2. Introduction

Advanced heart diseases, such as heart failure, cause many deaths worldwide[1]. For patients with poor prognoses, heart transplants are the gold standard treatment. Traditionally, heart transplants have relied on donation after brain death (DBD) donors, but the supply is insufficient to meet the rising demand. Using hearts from DCD donors can help increase the availability of donor hearts[2]. Heart donation after circulatory death involves retrieving organs after the heart has stopped beating. After a DCD protocol, hearts subjected to warm ischemia display various damages impacting cardiac, vascular, and metabolic functions. Despite concerns about graft quality, studies show that DCD heart transplants are as safe and effective as DBD transplants, with similar survival rates[3]. Figure 1 below show the DBD and DCD steps for heart harvesting.

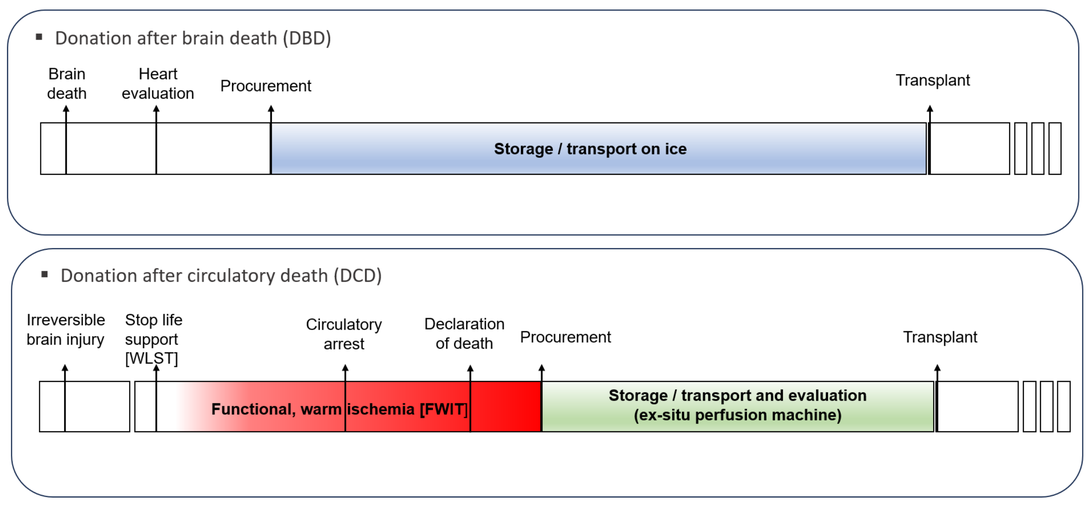


Figure 1: DBD and DCD heart transplantation protocols. While DBD hearts are stored and transported on ice after procurement, DCD hearts, after beeing subjected to warm ischemia, are storaged and transported in an ex-situ perfusion machine. FWIT= functional warm ischemia time, WLST= withdrawal of life-sustaining therapy, (Wüthrich, 2024a).

3. Aim

The aim of this work was to assess whether there are differences in heart recovery and metabolic status among female, male, and ovariectomized rats following warm ischemia and reperfusion in a donation after circulatory death model. Focusing on:

- Cardiac function
- Vascular function
- Metabolic function

4. Methods

Using a parallel-arm design, three groups of rats: males, females, and OVX females were subjected to either no warm ischemia or 22 minutes of warm ischemia. The following groups were used: End-Reperfusion: Rats underwent carotid artery cannulation, followed by 0 or 22 minutes of warm ischemia and ex-situ reperfusion(see Figure 2). Ex-situ reperfusion time of the heart of 60 minutes with 10 minutes unloaded and 50 minutes loaded mode. End-Ischemia: Hearts experienced 0 or 22 minutes of warm ischemia without ex-situ reperfusion. Control: Hearts were harvested post-anesthesia without carotid cannulation and ischemia. Blood samples were collected during and after ischemia, buffer samples were collected during reperfusion.

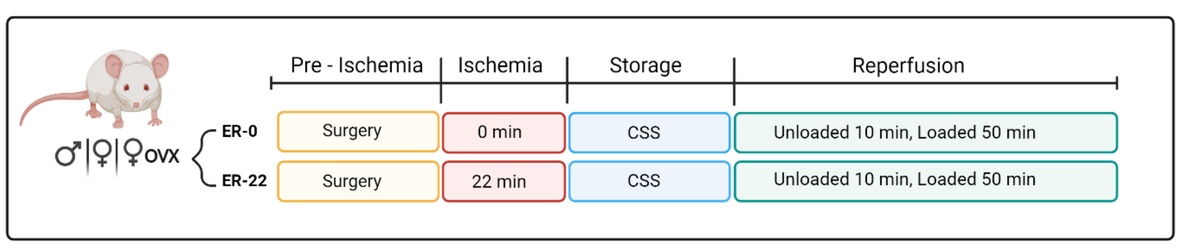


Figure 2: Study design, groups: ER-0 and ER-22 (0 or 22 minutes of ischemia, followed by reperfusion), ER= End-reperfusion, CSS= cold static storage, (Wüthrich, 2024b).

5. Results

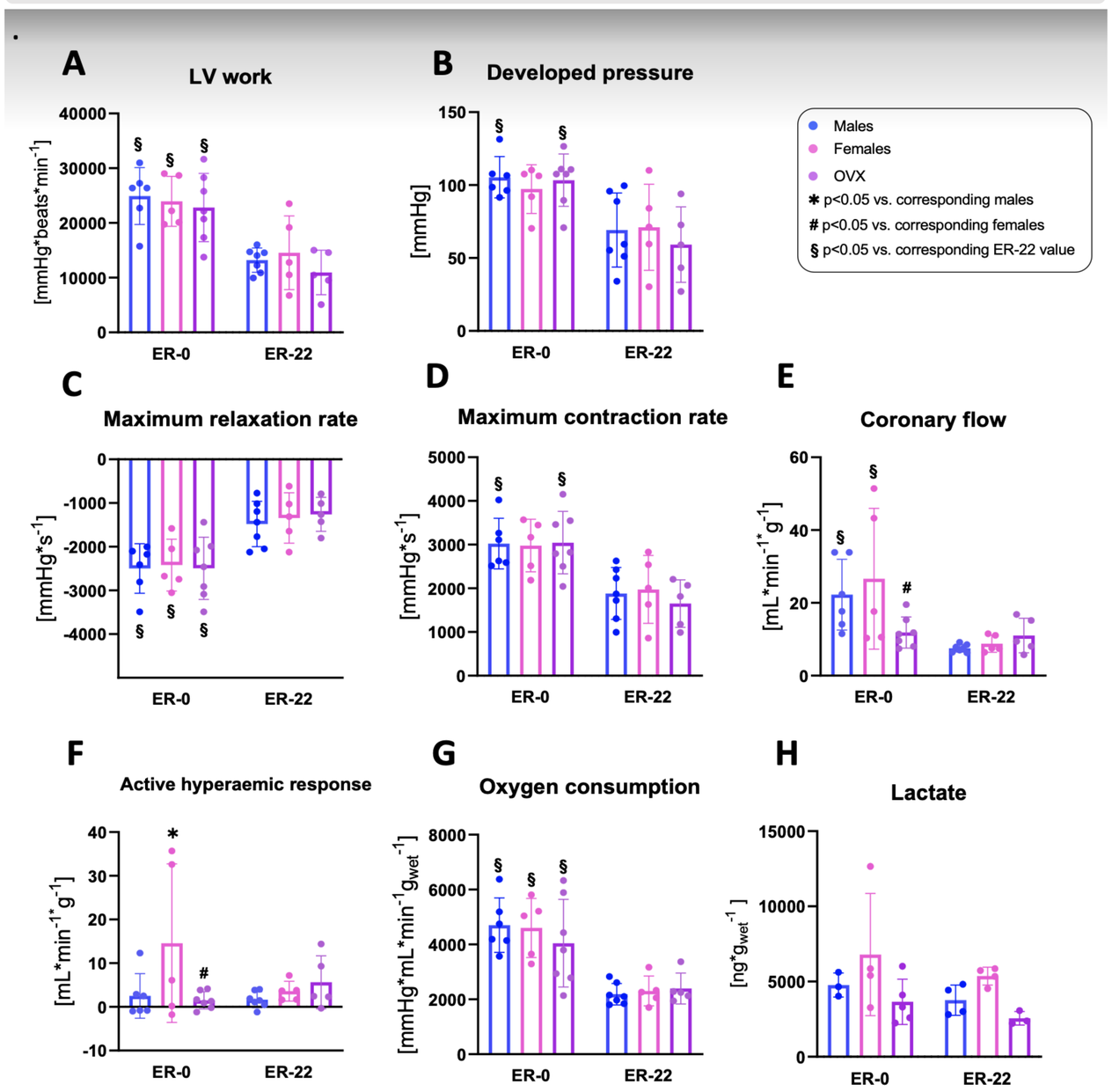


Figure 3: Cardiac function results: (A) Left ventricular (LV) work, (B) Developed pressure,(C) Maximum relaxation rate (D) Maximum contraction rate; Vascular function results: (E) Coronary flow,(F) Active hyperaemic response; Metabolic function results: (G) Oxygen consumption, (H) Lactate. ER-0 = End reperfusion 0 minutes; ER-22 = End reperfusion 22 minutes, (Wuthrich,2024c).

6. Discussion and conclusion

As expected, cardiac recovery was better for the non-ischemic group compared to the ischemic group reaching significance for left ventricular work, developed pressure, as well as maximal contraction rate ($p<0.05$ for all). These findings reflect tissue damage and reduced cardiac function that are associated with ischemia. Analysis of vascular function also revealed higher values for non-ischemic groups, with females showing higher coronary flow than males and OVX. Females in the non-ischemic group showed high variability for coronary flow and active hyperaemic response. Higher values for coronary flow could indicate a leak in the heart during the perfusion phase, emphasizing the importance of thorough heart preparation before perfusion. Oxygen consumption was lower in the ischemic groups than the non-ischemic groups. This makes sense, as the tissue is damaged after a period of warm ischemia. Therefore, it is to be expected that metabolic function is affected after a period of warm ischemia but no differences between the sexes were found. Based on these results, it can be assumed that males, females, and OVX show similar tolerance to warm ischemia following a DCD protocol. Additional experiments are required to confirm these findings.

List of references

[1] (Tomasoni et al., 2019, p. 1)
[2] (Schroder et al., 2023, p. 2)
[3] (Messer et al., 2020, p. 1)

Figures

Figure 1 Wüthrich, J. (2024a) *DBD and DCD description*. medi.
Figure 2 Wüthrich, J. (2024b) *Study design*. medi.
Figure 3 Wüthrich, J. (2024c) *Cardiac recovery results*. medi.