Cardioprotection Following Long-term Cold Ischemic Preservation In Hearts Overexpressing A_1 Adenosine Receptors

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Background: Approximately 1000 children with heart disease await cardiac transplant but the donor pool is small and limited by transport times from wide geographic areas. Currently, heart preservation is limited to 4-6 hours of cold ischemia, yet other solid organs can be preserved for 24-36 hours. By extending preservation time, the donor pool of hearts could be increased and allow time for better tissue matching, resulting in less immunosuppressive therapy. Previous studies show that overexpression of A_1 adenosine receptors in mouse hearts is protective during acute ischemia, but protection during long-term cold ischemia has not been investigated.
Objective: This study was designed to test the hypothesis that hearts overexpressing A_1 adenosine receptors will tolerate longer periods of cold ischemic preservation.
Design/Methods: Hearts from wild type (n=9) and transgenic (n=7) mice that overexpress myocardial A_1 adenosine receptors were perfused on a Langendorff isolated heart apparatus. Following 30min of stabilization, each heart was infused with 2ml of 5°C University of Wisconsin (UW) preservation solution. After 18hrs of cold ischemic storage at 5°C in UW solution, hearts were reperfused for 2hrs at 37°C. Left ventricular end diastolic pressure (EDP) was measured as an index of diastolic function. Left ventricular developed pressure (LVDP) was measured as an index of systolic function. Cell viability was assessed by determination of infarct size with TTC staining.
Results: Transgenic hearts showed greater preservation of function following 18hrs of cold ischemia and reperfusion, as shown by lower EDP (12 ± 3 vs. 25 ± 3 mmHg, $P<0.05$) and higher recovery of LVDP (66 ± 7 vs. 43 ± 7% of the baseline, $P<0.05$). Transgenic hearts also had markedly reduced infarct size when compared with wild-type hearts (30 ± 4 vs. 46 ± 4% $P<0.05$).
Conclusions: Overexpression of A_1 adenosine receptors imparts cardioprotection during long-term cold ischemic preservation. Further study of the mechanism of this protection may lead to improved and prolonged cardiac preservation.

Summary:

- **Objective:** This study examined whether hearts, from genetically altered mice with increased ADENOSINE receptors, can tolerate prolonged periods of ischemia (poor blood supply) that can damage hearts prior to transplantation. Adenosine is a chemical produced by the heart which can protect the heart during periods of poor perfusion.
- **Conclusion:** Hearts with increased numbers of Adenosine receptors can tolerate prolonged periods of cold ischemic.
- **Implications for Children:** Results from this study may enhance the success of heart transplantations for children (and adults) by defining mechanisms which can improve heart preservation prior to transplantation surgery.

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