A Simplified Rodent Model for Heterotopic Heart Valve Transplantation

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Background

Congenital heart disease affects 7 in 1000 children in North America and causes over 180,000 infant deaths per year worldwide[1]. Often the treatment involves surgical heart valve replacement with a mechanical or chemically fixed implant. However, conventional valve implants do not grow with the recipient children. As a result, morbid re-operations to exchange the heart valve implants for successively larger versions are required as the children grow[2]. We propose heart valve transplantation as a new operation designed to deliver growing heart valve replacements for neonates and infants.

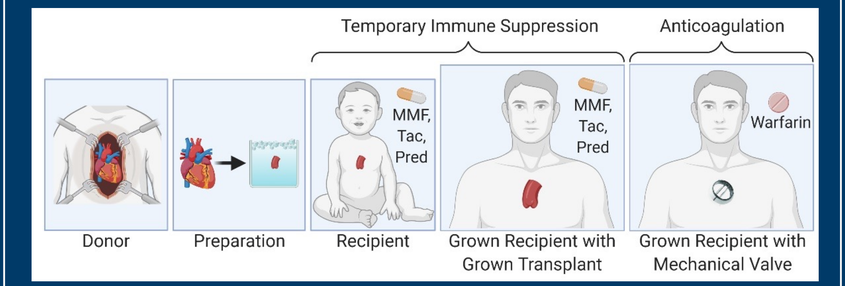

Fig. 1. Partial heart transplant involves transplantation of a heart valve and temporary immune suppression until the transplanted valve can be exchanged for an adult-sized prosthetic valve in the grown child.

However, the immunobiology of heart valve transplants remains unexplored. Therefore, there is a need for models to study this new type of transplant. Rat models for heterotopic aortic valve transplantation into the abdominal aorta have previously been described, though they are technically difficult and costly. To address this barrier to progress, we developed a renal subcapsular heterotopic transplant model in rats as a practical and simpler method for studying heart valve transplant immunobiology. Here we compare our simplified model with the conventional rodent model for heterotopic heart valve transplantation.

Methods

For group 1, donor aortic valves were heterotopically transplanted into the abdominal aorta as an interposition graft (n = 30). For group 2, a single leaflet of the donor aortic valve was implanted below the renal capsule (n = 33). Statistical analysis was performed using the Chi Square test (Prism Software).

Results

Operative survival was 17% (5 / 30) in group 1 and 97% (32 / 33) in group 2. This difference was statistically significant ($p < 0.001$). Survival beyond the peri-operative period was 0% (0 / 30) in group 1 and 97% (32 / 33) in group 2. Again, the difference was statistically significant ($p < 0.001$).

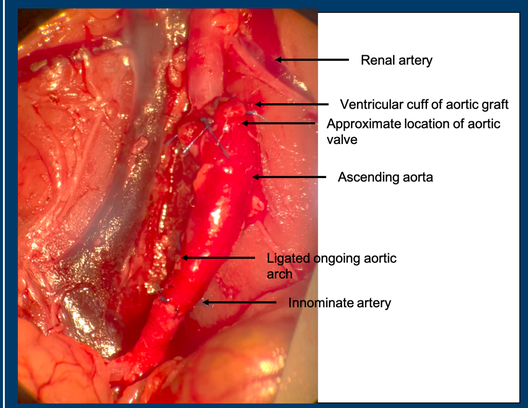

Fig 2. Aortic valve heterotopically transplanted into the abdominal aorta as an interposition graft.

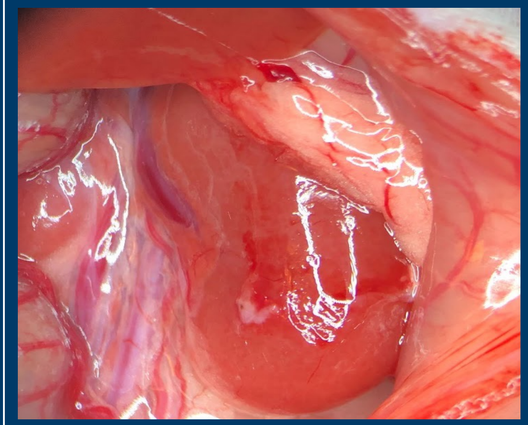

Fig 3. Aortic valve leaflet transplanted below the renal capsule.

Group 1
Advantages:
Maintains physiologic flow

Disadvantages:
Size mismatch
Technically challenging
Prone to thrombosis
No long-term survival

Group 2
Advantages:
Simpler Technically
Well-vascularized space
Tissue is easily recovered

Disadvantages:
No physiologic valvular flow

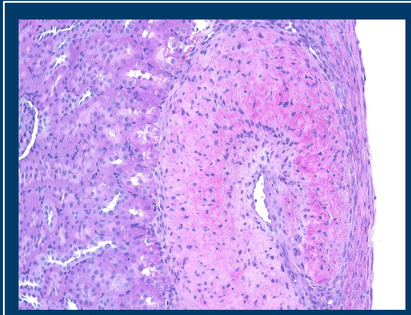

Fig 4. Histologic analysis of a syngeneic aortic valve leaflet transplanted under the renal capsule for 7 days.

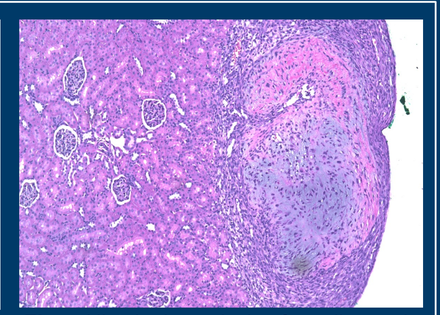

Fig 5. Histologic analysis of an allogeneic aortic valve leaflet transplanted under the renal capsule for 7 days.

Summary

Conventional rodent models for heterotopic heart valve transplantation have a steep technical learning curve for microsurgeons and require considerable investments of effort and resources. In contrast, our newly developed subcapsular implant model is simplified and has excellent survival rates. The kidney is easily accessible and transplanted tissue is securely contained in a subcapsular space that is well vascularized and that can accommodate a variety of tissue sizes. Furthermore, because a single rat can provide three donor aortic leaflets and a single kidney can provide multiple sites for transplanted tissue, fewer rats are required for a given study.

Finally, our model is suitable to obtain valve histology and immunohistochemistry to study the transplant immunobiology and ischemia-reperfusion injury of heart valve transplants.

References

1. *Global, regional, and national burden of congenital heart disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017.* Lancet Child Adolesc Health, 2020. **4**(3): p. 185-200.
2. Husain, S.A. and J.W. Brown, *When reconstruction fails or is not feasible: valve replacement options in the pediatric population.* Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu, 2007: p. 117-24.