Effect of AATB Standard D5.400 on Donor Cell Viability of Partial Heart Transplant Grafts

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Background: Partial heart transplantation (PHT) is the first clinically successful strategy to deliver growing heart valve implants for children [1,2]. So far, PHTs are procured according to heart transplant donor protocols. To increase the available donor pool, we hypothesized that tissue donor protocols are sufficient to maintain viability of PHT grafts. AATB Standard D5.400 permits up to 15 cumulative unrefrigerated hours during recovery [3].
Methods: In a time-course experiment, donor piglets (n=16) were prepared for unrefrigerated PHT graft recovery from 0 to 15 hours following circulatory death. Following recovery, each tissue component of the PHT grafts (valve leaflet, vessel root suspending the leaflet, and the ventricular sewing ring) were examined using assays for cell viability, mitochondrial respiration, histology, and multi-omics profiling.
Results: Warm ischemia provoked a progressive decay in viability over time (Fig. 1, $p<0.05$). Aortic leaflets reached 50% viability loss at 5.4 h (95%CI:5.2-5.7), failing significantly faster than pulmonary leaflets (8.9 h; 95%CI:8.7-9.0). Respirometry localized a metabolic "tipping point" at 8 hours: grafts recovered >8 hours exhibited Complex I collapse ($p<0.01$) and a pathological succinate surge ($p<0.001$). Multi-omics confirmed oxidative stress markers diverged significantly from baseline after 8-hours ($p<0.05$).
Conclusion: PHT grafts tolerate unrefrigerated recovery but not as long as AATB Standard D5.400 allows. We propose a maximum unrefrigerated recovery time of 5 hours for aortic valves and 8 hours for pulmonary valves. These data form the rational basis for a new AATB tissue procurement standard specifically for PHTs.

Keywords: Congenital heart disease; partial heart transplantation; tissue procurement; translational research; pre-clinical

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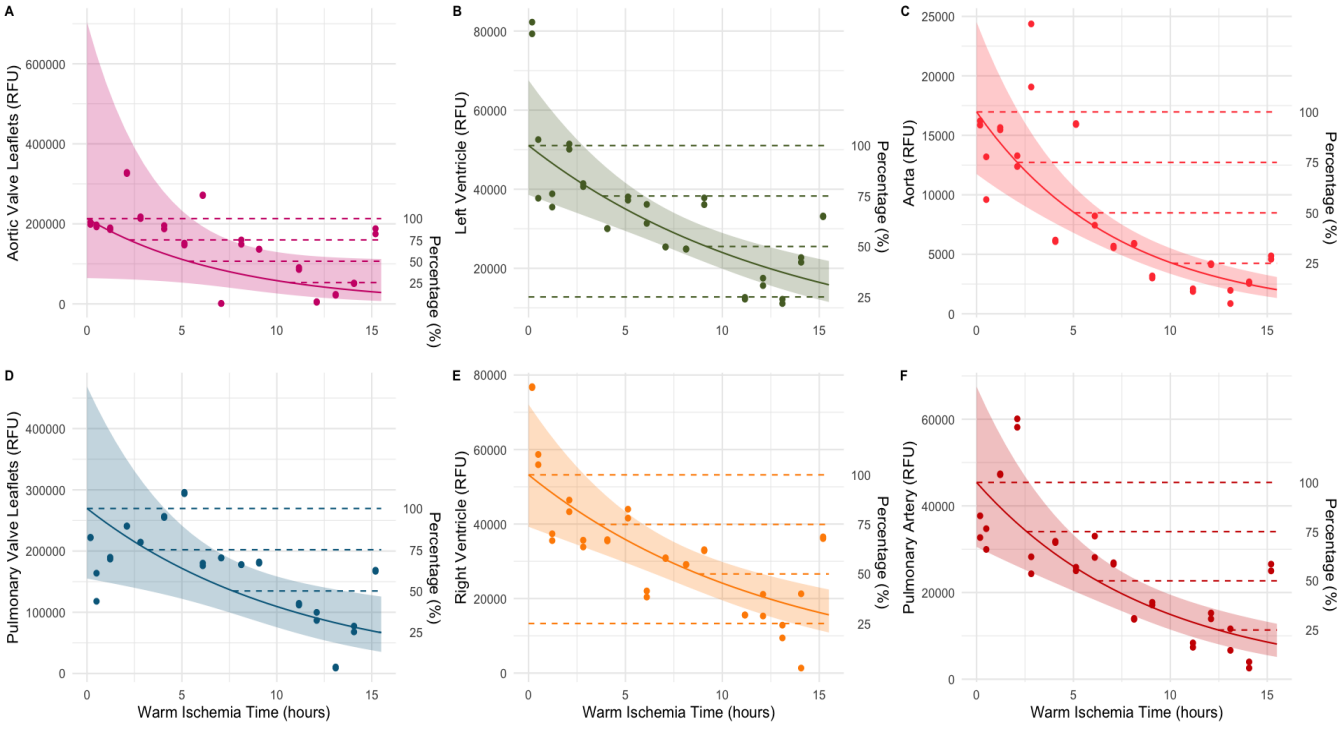


Figure 1. **Marginal prediction of the log-linked Gaussian mixed-effects model for each tissue** (A. Aortic valve leaflets, B. Pulmonary valve leaflet, C. Aortic valve muscle, D. Pulmonary valve muscle, E. Aortic valve vessel, F. Pulmonary valve vessel). Solid lines and the shaded area represent the marginal prediction and its corresponding 95% confidence interval. Dotted

lines represent 100%, 75%, 50% and 25% of the cell viability compared to baseline value (0 hour). Colored points represent measurements for each tissue.

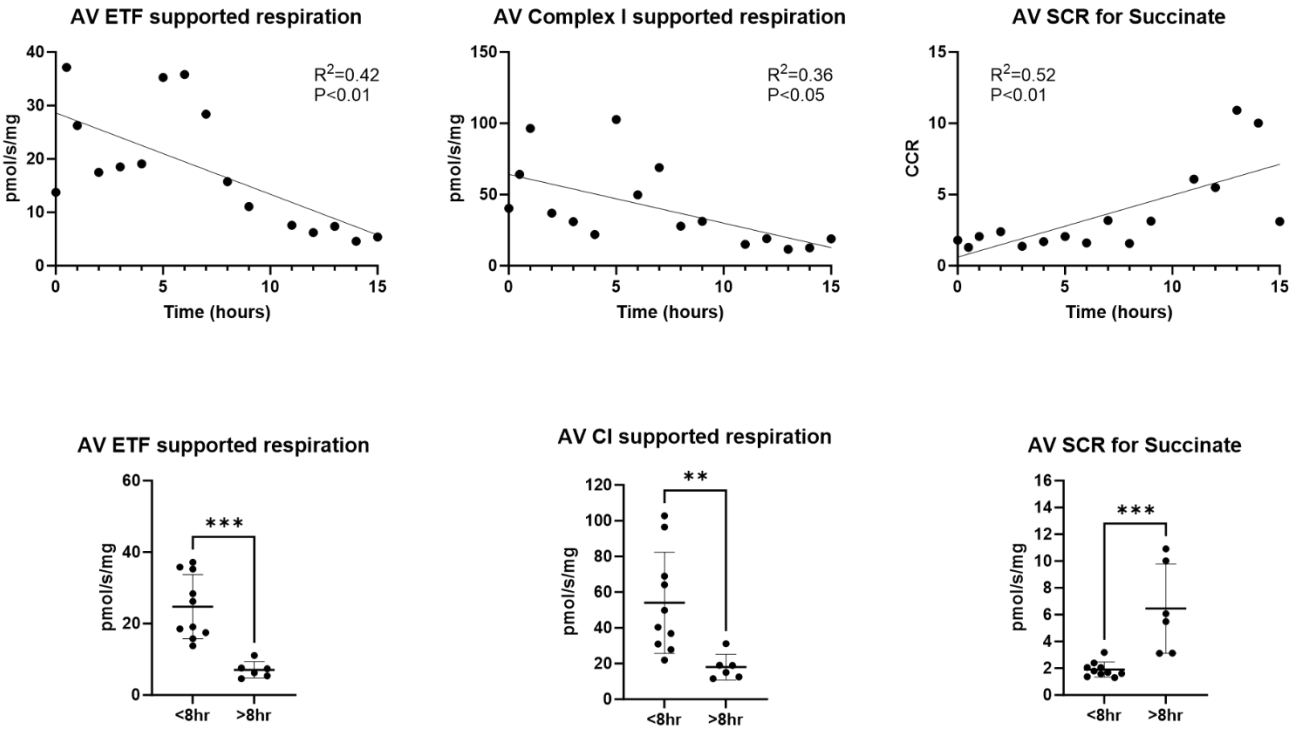


Figure 2. Unrefrigerated recovery more than 8 hours after circulatory death, resulted in significantly lower cellular respiration supported by fatty acid oxidation and complex one, and significantly higher cellular respiratory control for succinate.

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ABSTRACT

Background. Partial heart transplantation (PHT) delivers growing heart valve implants for children, but grafts are currently procured under heart transplant donor protocols. AATB Standard D5.400 permits up to 15 cumulative unrefrigerated hours during recovery. We tested whether tissue donor protocols preserve PHT graft viability.

Findings. Warm ischemia caused progressive, tissue-specific viability loss. Aortic leaflets lost 50% viability at 5.4h, significantly faster than pulmonary leaflets at 8.9h. Respirometry localized a metabolic tipping point at 8 h, beyond which respiration at Complex I declined and succinate rose.

Implication. PHT grafts tolerate unrefrigerated recovery, but for less time than D5.400 allows. We propose 5h for aortic and 8h for pulmonary valves.

BACKGROUND

- PHT is the first clinically successful strategy to deliver growing heart valve implants for children [1,2].
- PHT grafts are procured under heart transplant donor protocols, which sharply limits the available donor pool.
- Tissue donor protocols draw on a far larger pool. AATB Standard D5.400 permits up to 15 cumulative unrefrigerated hours during recovery [3].
- The viability window is unknown for PHT grafts, which depend on living donor cells for growth.

METHODS

Time-course design

- Donor piglets (n=16); unrefrigerated PHT graft recovery at 0-15 h following circulatory death.

Tissue components assayed separately for both aortic and pulmonary grafts

- Valve leaflet
- Vessel root suspending the leaflet
- Ventricular sewing ring

Endpoints

- Cell viability
- High-resolution mitochondrial respirometry
- Histology
- Multi-omics profiling
- Viability modeled with a log-linked Gaussian mixed-effects model; 50% viability-loss times estimated per tissue with 95% CI.

RESULTS

Warm ischemia drives progressive, tissue-specific viability loss

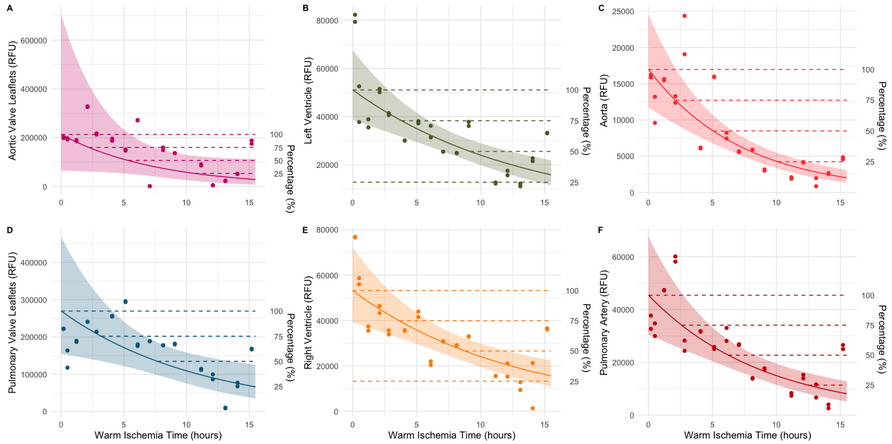


Figure 1. Marginal predictions of the log-linked Gaussian mixed-effects model by tissue: aortic leaflet (A), left ventricle (B), aorta (C), pulmonary leaflet (D), right ventricle (E), pulmonary artery (F). Solid lines and shaded bands are the marginal prediction and 95% CI; dotted lines mark 100%, 75%, 50% and 25% of baseline (0 h) viability. Points are individual measurements.

Respirometry localizes a metabolic tipping point at 8 hours

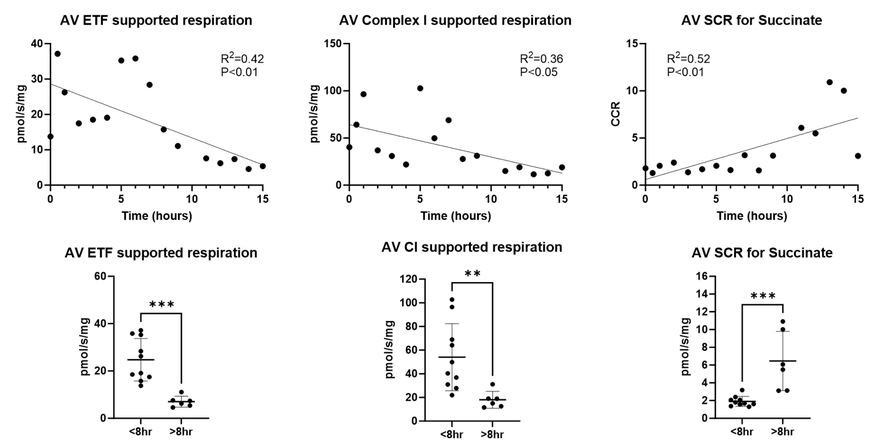


Figure 2. Aortic valve grafts recovered >8 h after circulatory death showed significantly lower respiration supported by fatty acid oxidation (ETF) and Complex I, and significantly higher respiratory control for succinate. **p<0.01, ***p<0.001.

KEY FINDINGS

Viability decays progressively. Every tissue component lost viability with increasing warm ischemia ($p<0.05$).

Aortic grafts fail first. Aortic leaflets reached 50% viability loss at 5.4 h (95% CI 5.2–5.7), significantly faster than pulmonary leaflets at 8.9 h (95% CI 8.7–9.0).

A metabolic tipping point at 8 h. Grafts recovered beyond 8 h showed Complex I collapse ($p<0.01$) and a pathological succinate surge ($p<0.001$).

Multi-omics concordant. Oxidative stress markers diverged from baseline after 8 h ($p<0.05$).

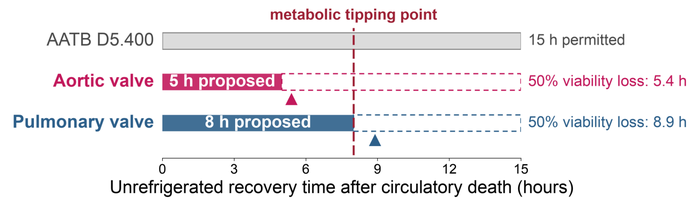


Figure 3. Proposed unrefrigerated recovery limits against the 15 h currently permitted by AATB Standard D5.400. Triangles mark the measured 50% viability-loss times.

CONCLUSIONS

- PHT grafts tolerate unrefrigerated recovery, but not for as long as AATB Standard D5.400 allows.
- We propose a maximum unrefrigerated recovery time of 5 hours for aortic valves and 8 hours for pulmonary valves.
- These data form the rational basis for a new AATB tissue procurement standard specific to PHT grafts.

REFERENCES

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