Collaboration with Clinicians Improves Safety and May Improve Translational Outcomes in Large Animal Surgery – Lessons from A Porcine Preclinical Cardiac Filtration Device Model

Imperial College London

Authors & Affiliations: Karl Riley, Noora Naghavi, Gregory Quinlan, Nathan Davies, Alan C.Spivey

1. Initial Development of Protocol

An issue in translational animal research is that good quality science does not always result in patient benefit.

Involving clinicians in protocol development can result in models that more closely represents clinical practice and creates a better testing environment.

With multidisciplinary team (MDT) collaboration, we established a porcine cardiac surgery protocol with cardiopulmonary bypass machine (CPB) and a protocol to test the prototype device; this device was designed to remove toxic iron-based byproducts introduced into patients during cardiac surgery via CPB.

This poster is a summary of how we reviewed and refined the porcine cardiac surgery protocol and illustrates why clinical input and continuous iteration is key to a successful study.

2. Cadaver Study

A cadaveric study was conducted to identify potential gaps in equipment suitability and the surgical protocol.

Problem: Lack of equipment for temperature control. A heater cooler unit costs >£10,000. Fig 1.

Solution: MDT discussion resulted in use of water bath as an alternative temperature control equipment Fig 2.

Problem: The cadaver study was conducted at a surgical temperature of 36.5'C (standard for humans). Standard for porcine is at 38.5'C.

Solution: MDT discussion led to change in surgical temperature to align with clinical setting.

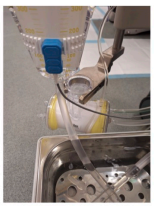

Fig 2. Tubing heated within water bath is less efficient, requires more MDT collaboration.

Fig 1. Heater cooler units utilise cross current water/blood flow for efficient temperature control.

3. Refinement of Protocol

Critical safety issues discussed by MDT throughout study. Protocol was continuously adapted and reviewed to maximise safety. Some early pilot animals were lost and lessons were learned.

In addition the pilot animals were used to power the study appropriately. - An important part of refinement.

Some key problems encountered were:

- Species limitations for equipment. Fig 3.
- Excessive haemodilution occurrence.
- Surgical and anaesthetic bleeding Fig 8, Fig 5.

MDT approaches to safety issues and protocol developments are in Sections 4, 6, 7.

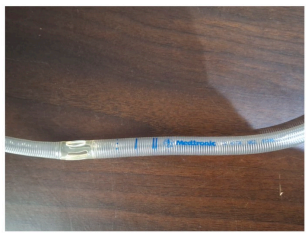

Fig 3. **Example of equipment limitation**: Venous cannula (size 32/40), which sits in the right atrium and inferior venacava, are too large for 38kg porcine but fit similar patients. We **increased minimum sizes of animals to 50kg** to better suit adult CPB disposables.

4. Cardiac Anaesthetic Input

Critical care fluid and drug protocols developed with cardiac anesthetists and the MDT.

Problem: Fluid requirements 1-2 hours post CPB ↑↑. Drug requirements post CPB ↑↑. Heart emptied post op Fig 3.

Solution: Developed fluid and drug protocols to safely 'refill' heart post CPB. Full heart Fig 4.

Intraoperative monitoring options also improved.

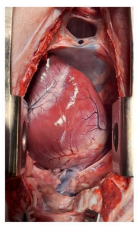

Fig 4. Size of heart is larger pre-CPB. Pre-haemodilution.

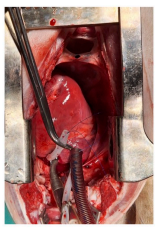

Fig 3. Size of heart smaller post-CPB. Additional fluid required urgently to combat consequence of haemodilution.

5. Start of Study

After cadaver and pilot studies were complete then study commenced, Fig 5 highlights surgical setup.

Fig 5. Surgical setup: Diathermy, instrument table, surgically draped porcine, cardiopulmonary bypass machine, anaesthetic machine.

6. Surgical Input

Critical cannula risks identified and managed with cardiac surgeon and MDT input. Decannulation is a **Single Point Failure Event (SPFE)** and must be risk mitigated to minimise harm.

Problems: 1) Loss of cardiac output (spontaneous removal), 2) Tissue damage (planned removal).

Solution: Kept arterial and venous cannula in situ post CPB – minimise risk of significant surgical bleeding from right atrium or aorta Fig 5.

Solution does impede right ventricle filling post operatively but was an accepted risk.

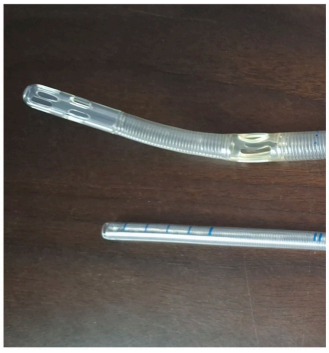

Fig 5 **Bottom**: Arterial cannula; **Top:** Venous cannula; Narrow lumen, high pressures in arterial cannula and critical anatomical location (aorta) are contributing factors to technical difficulties when removing arterial cannula.

7. Perfusionist Input

During CPB, porcine heart and lung function is completely controlled by the CPB machine.

Problem: "Weaning" from CPB (returning control from the CPB machine to the porcine heart and lung) is another **SPFE**; it is a complex operation event in which technical skills, communication skills and clinical awareness are critical to safety.

Solution: "Off Bypass" protocol developed by MDT with Perfusionist input to restore native heart and lung control Fig 6.

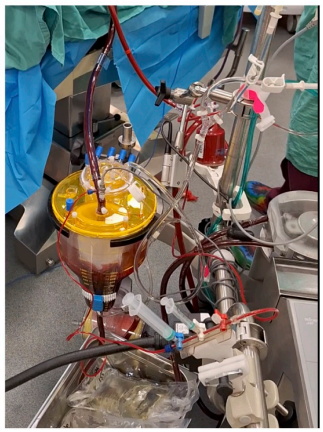

Fig 6. CPB disposables just before "weaning" off bypass commences.

Fig 7 **Haemochron Activated Clotting Time (ACT) machine:** Used as a clinical tool to overcome anaesthetic bleeding post CPB due to excessive anticoagulant heparin. Achieved via titration of anticoagulant, heparin vs pro-coagulant, protamine.

8. Completion of Study

Study was conducted successfully and next steps towards medical device development are underway.

Without heavy clinical input and continuous iteration, important nuanced aspects of surgical methodology may be overlooked.

Involving clinical practitioners at all stages of experimental design leads to improvements in animal surgical safety, contributing to Reduction and Refinement as part of the 3R's.

This may lead to improvements in translational outcomes.