Paediatric Heart Surgery

**Principal Investigators:** Mr. Massimo Caputo  
Dr. Mohamed Ghorbel

**Collaborators:** Prof Saadeh Suleiman  
Prof Andrew Wolf  
Mr Ash Pawade  
Mr Andrew Perry  
Dr Barnaby Reeves  
Dr Chris Rogers

In the last five years we have established a core group of researchers and clinicians whose primary aim has been to improve myocardial protection and cardiopulmonary bypass strategies in paediatric heart surgery. More recently this scope has been widened to a genomic approach to the molecular mechanisms underlying reperfusion injury.

**Myocardial protection strategies**

We have studied the impact of age and cyanosis on myocardial protection, and the pathology related differences that exist in congenital heart surgery. This work has demonstrated that in paediatric patients undergoing open-heart surgery i) cold blood and cold crystalloid cardioplegia provided similar myocardial protection in normoxic hearts, ii) cyanotic hearts are more dependent on the type of cardioplegic protection, iii) crystalloid cardioplegia was associated with significant ischaemic stress and myocardial cellular injury in cyanotic hearts, iv) blood cardioplegia provided better protection than crystalloid in cyanotic hearts and v) evidence of ischaemic stress were almost totally abolished if blood cardioplegia was supplemented with a terminal dose of warm cardioplegia immediately prior to unclamping the aorta in hypoxic hearts (1-9).

**Normothermic vs hypothermic cardiopulmonary bypass (CPB)**

A RCT (total 160 patients) of cold (28°C) vs warm (37°C) CPB in paediatric heart surgery is in progress. The aim of the first part of this trial was to investigate the effect of CPB temperature on biochemical markers of myocardial reperfusion injury, oxidative stress, and inflammatory response. Normothermic CPB was associated with reduced oxidative stress compared with hypothermic CPB, and similar myocardial reperfusion injury and whole body inflammatory response (10). The recruitment to the study has been very slow because of new ethics regulations.
Nevertheless, we are hoping to complete the study in the next eight months, to investigate primary clinical end points.

**Reoxygenation injury in cyanotic patients**

Children with cyanotic congenital heart disease undergoing corrective cardiac surgery have poorer clinical outcome than acyanotic patients and suffer worse myocardial reoxygenation/reperfusion injury following similar periods of ischaemic cardioplegic arrest to that of acyanotic patients. It is thought that hypoxia in these children reduces the antioxidant reserve capacity, leading to a greater susceptibility to the oxidative stress of ischaemia. In a recent study we have shown that reintroduction of high oxygen levels to cyanotic patients on CPB leads to myocardial damage prior to ischaemic cardioplegic arrest [11, see Figure].

We are now conducting a RCT (total 150 patients) to compare normoxic (70-100 mmHg) versus hyperoxic (200-300 mmHg) CPB prior to the ischaemic cardioplegic arrest in cyanotic children undergoing cardiac surgery. Primary endpoint is in-hospital morbidity, secondary endpoint is sub-system (ie. neurological, renal, myocardial) organ dysfunction.

**Reducing stress and inflammation with epidural anaesthesia**

We have recently evaluated the use of spinal anaesthesia as a strategy to reduce stress and inflammatory responses to surgery (12). A RCT was conducted in 60 children aged up to 24 months undergoing open heart surgery. Patients were randomly assigned to receive either high-dose intravenous opioid or high-dose intravenous opioid plus spinal anaesthesia. Continuous spinal anaesthesia reduces stress responses in infants and young children undergoing cardiac surgery with CPB more effectively than high-dose intravenous opioids alone. Spinal anaesthesia is now routinely used in the majority of children undergoing cardiac surgery at our institution.

**A genomic approach to the molecular mechanisms underlying reperfusion injury**

The recent appointment of Dr Ghorbel (BHF Intermediate Research Fellowship) has given us the unique opportunity to bring together the most advanced skills in pediatric cardiac surgery and molecular genomics and proteomics. The scientific thrust of the research is directed towards using microarray and proteomics techniques to delineate the molecular mechanisms underlying reoxygenation/reperfusion injury in order to improve myocardial protection.

We hypothesise that during cyanotic heart surgery, transcriptomic alterations take place resulting in heart susceptibility to reoxygenation/reperfusion injury. We are delineating the gene networks and the molecular mechanisms involved in these alterations and the possible beneficial effects of controlling the reoxygenation in cyanotic hearts during surgery.

We are using the Affymetrix GeneChip Human Genome U133 Plus 2.0 Array
which provides comprehensive coverage of the transcribed human genome with variants from over 47,000 well-substantiated human genes. Our preliminary results indicate that the ischemia, following the cardioplegic arrest, alters the heart gene expression profile in cyanotic children undergoing surgery. Of the 47,000 interrogated genes and transcribed sequences, 216 were up or down-regulated by more than 2-folds. Of these, 153 were up-regulated and 63 down-regulated. We are currently extending our study to acyanotic patients to uncover the genes implicated in chronic hypoxia. Additionally we’re investigating the gene expression profile in cyanotic hearts following re-perfusion and test whether any genetic expression changes associated with the ischemia/re-perfusion injury can be prevented by the use of controlled reoxygenation.

**Future Strategy:**

To complete the RCTs on:

- Normothermic vs hypothermic CPB
- Normoxic vs hyperoxic CPB in cyanotic patients
- Further elucidating the molecular mechanisms underlying reperfusion injury and provide clues to the next generation of therapeutic treatments aimed at myocardial protection
- Development of a cardiopulmonary bypass piglet model to study ischaemia/reperfusion injury.

**MOVE REFS**
Relevant references


