Design of a Prospective Clinical Study on the Quantification of Lipid and Leucocyte Filtration and the Effects on Cerebral and Renal Injury Markers and Pulmonary Function during Cardiopulmonary Bypass

Richard Issitt, Stuart Sheppard, David Voegeli and Bronagh Walsh

Abstract

Background

Neurological complications are common following cardiothoracic surgery using cardiopulmonary bypass; these can range from episodes of temporary delirium to severely debilitating strokes. Despite strong evidence showing the involvement of lipid microemboli, there is currently no established method for the effective removal of these particles. We conceived the study described here to evaluate the clinical use of a new integral lipid filter in reducing lipid microemboli and to determine the impact on markers of cerebral and renal injury and pulmonary dysfunction during the cardiopulmonary bypass period.

Methods/Design

Fifty patients undergoing routine coronary artery bypass grafting using cardiopulmonary bypass will be randomised to either the intervention group, receiving the integral lipid filter during surgery, or a control group which does not. All clinicians and patients will be blinded as to their method of treatment. Measurements of lipid emboli will be taken throughout the surgical period with biochemical markers measured throughout the surgical and postoperative period.

Discussion

Limited success has been found in removing lipid microemboli using currently available methods. An integral lipid filter may well fulfill this role and help reduce the associated morbidity. This paper reports the design and methods for a randomized controlled trial comparing the outcomes of the RemoweLL lipid and leucocyte removing filter with standard equipment for patients undergoing coronary artery bypass grafting using cardiopulmonary bypass.

Trial registration

International Standard Randomised Controlled Trial Number Register: ISRCTN56462370
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BACKGROUND

The Role of Cardiopulmonary Bypass
Cardiopulmonary bypass (CPB) using an Extracorporeal Circuit (ECC) facilitates surgical intervention of the heart. CPB carries out the functions of the heart and the lungs during surgery allowing the surgeon to operate on a flaccid, bloodless environment. It requires the removal and subsequent return of the patient's entire circulating blood volume An ECC circuit consists of 4 major components; a venous reservoir, an arterial pump, an oxygenator and an arterial line filter (Figure 1). The deoxygenated blood enters the venous reservoir from a cannula in the right atrial appendage. The venous reservoir (1a) serves two purposes; acting as a capacitance chamber and a filter. As a capacitance chamber, the venous reservoir can cope with acute volume shifts that occur as a result of surgical manipulation of the heart. The reservoir contains a central column of porous plastic foam and a polypropylene woven screen providing filtration to at least 40µm. This filter removes any particulate matter or gaseous emboli that should enter the circuit via the venous cannula. From the venous reservoir, blood passes into the arterial pump which functions as the ventricles of the heart, pumping blood around the body. There are two types of arterial pump; centrifugal (2a) and roller (2b). When the blood leaves the arterial pump it enters the oxygenator (3); this is made of porous polypropylene membrane arranged into hollow fibres. Integral to the oxygenator is a plastic coated aluminium heat exchanger that enables control of the blood (and therefore the patient's) temperature during the operation. The oxygenator works on a similar concept to the lungs; it has a large surface area but with tiny holes in the hollow fibres creating a virtual blood-gas interface allowing the addition and removal of oxygen and carbon dioxide respectively. The final component is the arterial line filter (4), which removes any further microparticles before return to patient and is a gaseous bubble trap.

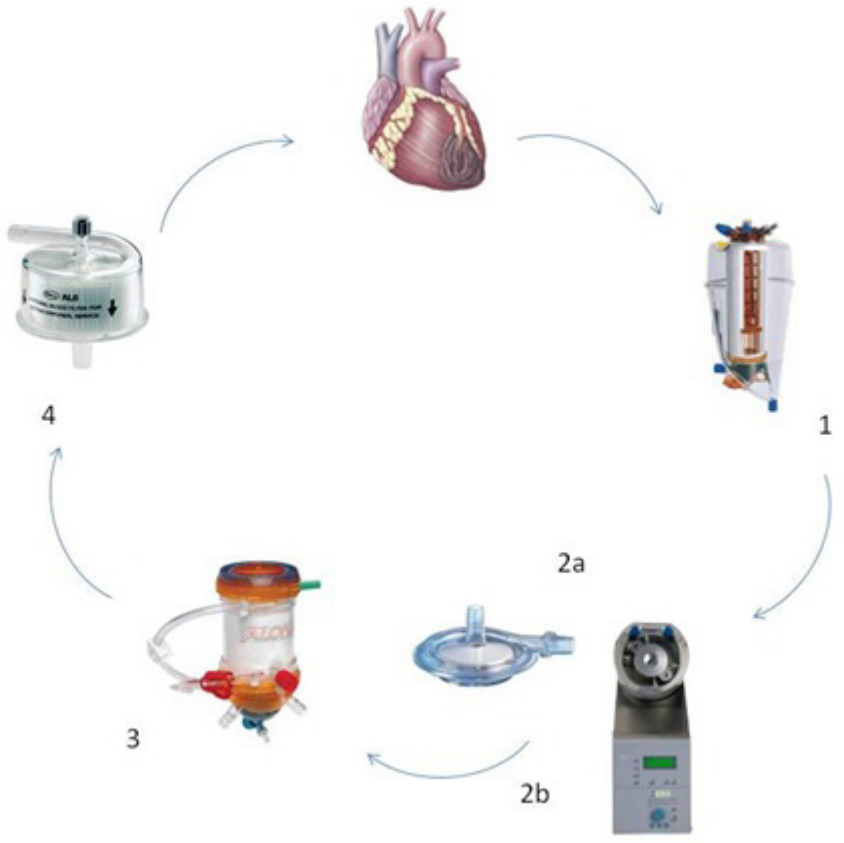

Figure 1. Componenets of the CPB circuit.
1, Venous Reservoir. 2a, Centrifugal Arterial Pump. 2b Roller Arterial Pump. 3, Oxygenator. 4, Arterial Line Filter. See text for details.

Whilst the CPB circuit is made of non-toxic, non-immunogenic materials such as polycarbonate and polyvinyl chloride, blood contact with the artificial surfaces of the circuit causes activation of the clotting cascade. To enable CPB to take place full anticoagulation is required. This is attained using Heparin, which has the added advantage of being able to be reversed using protamine once the operation is completed.

There are various components that can be added to the CPB circuit depending on the diagnosis and treatment of the patient. A separate cardiotomy suction reservoir can be added to manage low pressure suction of blood from the open chest cavity. This blood contains the major source of microemboli and activated inflammatory markers (discussed in more detail later).

Despite the extremely low mortality and morbidity rates of CABG surgery involving Cardiopulmonary Bypass (CPB), there are a number of pathological injuries associated with the CPB circuit. Lipid Microemboli (LME) (produced when performing a sternotomy) mix with blood in the Pericardial Suction Blood (PSB) during surgery. This blood is passed into the CPB circuit and reintroduced into the systemic circulation, promoting an increased inflammatory response and impairing blood flow in capillaries. At the same time, the action of blood coming into contact with the non-physiological surfaces of the CPB circuit causes a significant up-regulation of the patient's inflammatory system leading, in extreme cases, to a Systemic Inflammatory Response Syndrome (SIRS). One of the main components of this unregulated inflammatory response is activated leucocytes, which attack sensitive organs such as the lungs.
The RemoweLL (Eurosets, Mirandola, Italy) oxygenator contains a lipid and leucocyte filter. By filtering lipids and

removing activated leucocytes the severity of injury in sensitive organs such as the brain, kidneys and lungs should be reduced.

This paper reports the design and methods of a study comparing the ability of the RemoweLL to filter lipids and activated leucocytes out of the PSB with standard equipment and will assess the possible effects this has on cerebral and renal injury markers and pulmonary function during and following CPB.

Incidence of Mortality and Morbidity

Whilst there has been a 21% decrease in mortality figures for patients undergoing CABG operations since 2001(Bridgewater 2009), it is estimated that 2-5% of patients undergoing CABG suffer from stroke, with a further 20% experiencing delirium-like symptoms. It has also been suggested that a further 50% of CABG patients exhibit Diffuse Brain Damage (DBD), although higher and lower frequencies are reported by different groups (Engström 2004). The reason behind these varying types of morbidity characteristics is not entirely known (Ali, Harmer et al. 2000). Furthermore, it is not only the brain that suffers injury following CABG surgery; a recent review by Mehta has shown that up to 10% of patients experience Acute Renal Failure (ARF) which, in the most extreme examples, leads to dialysis treatment, renal transplant and even death (Mehta 2005) whilst the inflammatory reaction caused by CPB leads to 20% of patients requiring ventilation times of more than 48 hours due to pulmonary dysfunction. In the most serious cases an Acute Respiratory Distress Syndrome (ARDS) develops which has a 50% mortality rate (Schlensak and Beyersdorf 2005). Therefore, although overall mortality rates are decreasing, the morbidity associated with CPB remains high.

The Pathological Effects of CPB

Inflammatory Response

The CPB circuit is made of large non-physiological surfaces which, when in contact with blood, invoke a complex inflammatory response. It is widely accepted that a systemic inflammatory response, is present in all patients following CPB (Sablotzki, Muhling et al. 2001) although the incidence and severity is variable, ranging from mildly detectable to the severe Multi Organ Dysfunction Syndrome (MODS) (Asimakopoulos 1999).

The inflammatory response to CPB is initiated by numerous injuries to both the cellular and humoral elements of blood. The repeated passage of blood through the CPB circuit leads to contact activation of coagulation factors XII, XI, prekallikrein and high molecular-weight kininogen. This leads to an activation cascade triggering the classical complement cascade (Wan, LeClerc et al. 1997) disrupting haemostasis which generates a whole-body inflammatory response.

Of particular interest is the activation of leucocytes and neutrophils following CPB, mediated by a number factors such as C3a, C5a and platelet activating factor (PAF) and associated with an increase in surface adhesion molecules CD11b/CD18 (Dreyer, Michael et al. 1995; Dreyer, Michael et al. 1995). The non-specific activity induced in leucocytes by CPB leads to assaults on native endothelial cells resulting in cell destruction and SIRS (Matheis, Scholz et al. 2001). In particular, activated neutrophils are associated with postoperative pulmonary dysfunction (Clark 2006), with high levels of neutrophil elastase, a measure of neutrophil activation, at the end of CPB. Although during CPB there is a fall in neutrophil count due to haemodilution and surface adhesion, CPB-induced cytokines facilitate the release of neutrophils from the bone marrow and from vascular walls resulting in a net increase following CPB. Animal studies also suggest that activated neutrophils may contribute to myocardial ischaemia – reperfusion injury (Youker, Hawkins et al. 1994). Rinder and colleagues (Rinder, Bonan et al. 1992) determined that a leucocyte-platelet adhesion was formed in response to CPB resulting in increased activation of phagocytic cells. The use of leucocyte depleting filters has been the subject of much debate with a recent systematic review (Warren, Alexiou et al. 2007) concluding that whilst there were many randomised controlled trials investigating leucocyte filtration, most were small and had limitations, i.e., were not able to detect clinically relevant endpoints, although some benefit was seen in a subsection of patients with certain co-morbidities. A beneficial effect of leucocyte depletion has been seen in patients with preoperative renal impairment (Tang, Alexiou et al. 2002). Mastrangelo et al., (Mastrangelo, Jeitner et al. 1998) have shown that oleic acid (in the form of fat emboli), released following traumatic bone injury, induces increased expression of CD11b on neutrophil surfaces. It has yet to be determined whether this activation of neutrophils may also cause cerebral and renal impairment, and more importantly, whether the filtration of lipids would cause less activation and therefore less ischaemic injury.

Lipid Embolic Events

Since the advent of centrifugal pumps and membrane oxygenators, major neurological complications resulting from emboli occurring from spallation of silicone tubing (the shedding of silicone microparticles due to compression and relaxation associated with roller pumps) within the CPB circuit and air have significantly reduced (Parolari, Alamanni et al. 2000). Recently there has been interest in biological emboli such as aggregates of cells and/or lipid materials. Engström (Engström 2003) and Brooker et al., (Brooker, Brown et al. 1998) have reported diffuse brain damage following the recycling of PSB due to the microembolisation of liquid fat. It is reported that two thirds of the fat emboli developed within a CPB circuit enter through the cardiotomy suction (Jönsson, Eyjolfsson et al. 2009). The fat collects with PSB that when re-introduced into the circulating volume is expelled via the aortic cannula into

the cerebral vessels leading to small capillary arterial dilations (SCADs). Fat emboli typically consist of denatured plasma lipoproteins and lipids whilst the fat recovered in plasma consists of chylomicron aggregates or triglyceride and cholesterol-containing fat particles (de Vries, Gu et al. 2002). It is not only the cerebral vessels that are affected by LME; Brondén et al., (Brondén, Dencker et al. 2006) have shown LME uptake in all organs, especially the kidneys. Appelblad (Appelblad and Engström 2002) has also shown that liquid fat contained within the PSB highly impairs capillary flow function. The treatment of choice for fat containing PSB is of current discussion. The rationale for fat filtration proposed by de Vries et al., (de Vries, Gu et al. 2002) is sound in theory but practically difficult. Kincaid et al., attempted to determine whether various leucocyte filtration methods in conjunction with cell salvage would prevent LME with little success (Kincaid, Jones et al. 2000).

The treatment of PSB has been intensively discussed and debated with some authors advocating the complete disposal of PSB to reduce the associated pathologies (Appelblad and Engström 2002), whilst others propose the Cell Salvage (CS) of PSB to remove harmful inflammatory factors, LME and toxic plasma Free Haemoglobin (FHb) (Jewell, Akowuah et al. 2003; Svenmarker and Engström 2003; Skrabal, Khosravi et al. 2006). Cell salvage involves the collection of shed blood from the operating field which is then centrifuged and washed with saline before returning to the patient; centrifugation removes plasma, platelets and coagulation factors with the result that only RBCs are re-infused after processing. It should be noted however that the majority of these studies had small population sizes and therefore lacked the power to see clinically relevant outcomes such as ventilation times, postoperative bleeding and long term neurocognitive outcome. More recently the Cardiotomy Trial (Rubens, Boodhwani et al. 2007) carried out in Canada, a double-blinded Randomised Controlled Trial (RCT) of 266 patients, comparing CS and rein fusion of PSB and its influence on transfusion and Postoperative Cognitive Dysfunction (POCD) concluded:

1. Whilst no significant differences were seen between groups in terms of neurocognitive outcome, POCD was higher in the treatment group than the control group (45.3% vs. 39%).
2. The CS group had a higher (although not significant) Red Blood Cell (RBC) transfusion rate (42% vs. 36%) as well as higher overall non-RBC transfusion rate (2.06±7.70 vs. 1.12±4.74 units/patient).
3. Postoperative chest drainage was significantly higher in the CS group (p=0.04).
4. CS resulted in a significant reduction in postoperative platelet count (p=0.05) and caused significant coagulation abnormalities with the Partial Thromboplastin Time (PTT) and International Normalised Ratio (INR) significantly increased (p<0.01).

However, the authors also found in a subset of patients (n=154) that PSB processing with CS improved the cardiovascular and haemodynamic performance but did not significantly improve the mechanical pulmonary function or gas exchange (Boodhwani, Nathan et al. 2008). Therefore the question over how best to remove the pathological effects of PSB remains unsolved, especially as these studies clearly demonstrate current methods cannot remove LME, and are furthermore associated with adverse outcomes (increased bleeding and POCD). To this end, the study aims to determine if the RemoweLL lipid and leucocyte removing filter can provide an alternative, method of PSB processing which includes LME removal.

As yet no research has been published investigating a dedicated lipid filtration device on cerebral and renal injury markers and pulmonary function, despite strong supporting evidence.

The RemoweLL oxygenator is the first and only CPB circuit that incorporates a lipid and leucocyte depleting filter within the cardiotomy reservoir. The main aims of this research will be to;

1. Quantify the reduction of lipid microemboli, in the pericardial suction blood, and activated leucocytes, returning into circulation.
2. Determine the effect of lipid and leucocyte filtration on renal injury markers.
3. Determine the effect of lipid and leucocyte filtration on cerebral injury markers.
4. Determine the effect of lipid and leucocyte filtration on pulmonary function.

METHODS/DESIGN

Study Design

The study will be a blinded, randomised control trial of the RemoweLL oxygenator, compared to a current standard oxygenator, the Admiral. The two circuits are identical and therefore indistinguishable to the Surgeon and Anaesthetist, so allowing the study to be double-blinded. The laboratory staff undertaking the test procedures will also be blinded to the treatment allocation. The subjects, patients undergoing CABG surgery, will be involved in the study that will last 5 days from the day of surgery. The study is expected to take two (2) years.

Participants

The study will include participants with ischaemic heart disease requiring coronary artery bypass grafting between the ages 18 and 90. Whilst the number of blood samples required is high (11 in total), due to the haemodilutive nature of CPB, the effects on the patients' blood volume is negligible. A more details list of eligibility criteria is given in table 1.

Study Settings

The Perfusion department of University Hospitals Southampton NHS Foundation Trust will be responsible for recruiting and treating all patients in this study. The Research and Development department will be respon-

sible for medical device safely, and University of Southampton will be responsible for the data management and statistical analyses.

Objectives

The primary objective is to determine the efficacy of the RemoweLL lipid and leucocyte depleting filter on reducing the numbers of activated leucocytes and removing the LME load of patients undergoing CABG surgery with CPB.

The secondary objectives are to determine the effects, if any, of LME and leucocyte filtration on cerebral and renal injury as measured by biochemical and immunological markers, and pulmonary function as measured by calculation of the respiratory index and ITU ventilator settings. Using ITU stay, blood product and fluid usage, the cost implications for this new treatment will be evaluated and compared to the control group; our current standard care.

Outcome Measures and Endpoints

The primary outcome measures are quantifying LME removal and activated leucocyte filtration. Lipid microemboli will be counted and sized using light microscopy as previously described (Kaza, Cope et al. 2003) and activated leucocytes will be analysed with Fluorescence-Activated Cell Sorting (FACS) of the leucocyte activation maker CD11b during the immediate surgical procedure and for 24 hours following surgery, with reference values taken pre-surgery, in a certified laboratory.

The secondary outcome measures, markers of cerebral and renal injury (including Neurone-Specific Enolase (NSE), and Cystatin C) will be determined by biochemical/haematological analysis. Markers of injury will be measured before during and for 3 days following surgery. Determination of pulmonary dysfunction will be calculated from ITU observation charts and calculation of the respiratory index.

Due to the variability of patients, in terms of biochemical marker values, subtraction analysis shall be employed on all data collected (i.e. all values subtracted from baseline measurements).

The study will end once 50 patients have completed the study assessments and the data has been analysed.

Sample Size

In vitro studies have shown that the RemoweLL oxygenator removes 40–50% of leucocytes and 55–70% of lipid microparticles. Recent *in vivo* data (unpublished) show that the numbers of LME in the RemoweLL system compared to a standard circuit is 1095±579 vs. 2970±1405.29 particles /mL giving an average percentage removal of 63±8.4%. The number of patients in each study group (25) was determined by an a *priori* power calculation using G*Power Version 3.1.0 (Universität Kiel, Germany) to achieve a power (1-β) of 0.95 with α=0.001 for an effect size index of 1.745 that may be expected in clinical practice based on the i*n vivo* data. These power calculations allow for a 15% drop out rate or loss to follow up. No data is available to indicate the direct relationship that LME and leucocyte filtration will have on biochemical markers of organ injury; for this reason a *post hoc* power analysis will be undertaken to determine the actual achieved power of this study. Previous studies have shown that the lower the serum concentrations of NSE, the better the outcome of patients after CPB (Ali, Harmer et al. 2000). For this reason a tentative a *priori* power calculation has been undertaken based on Bonacchi's work (Bonacchi, Prifti et al. 2006) where the average postoperative peak serum NSE concentration was 17.7±6.5µg/L. An assumption was made that for a significant, clinically relevant, difference in peak circulating NSE, a minimum reduction of 33% (i.e. a one-third reduction) should be seen in the study group compared to control group assuming equal standard deviations in

Table 1. Inclusion and Exclusion criteria

Inclusion Criteria
• Male or Female, aged 18 years or above
• Patients undergoing elective CABG surgery
• Angiographically proven coronary artery stenosis

Exclusion Criteria The participant may not enter the study if ANY of the following apply
• Age less than 18 or more than 90 years old
• Emergency CABG surgery
• Previous CABG surgery
• Gross haemodynamic instability: hypertension (systolic blood pressure >160mmHg), hypotension (systolic blood pressure <90mmHg), or bradycardia (heart rate <60 beats/min)
• Obesity (BMI >35)
• Pre-operative heparin regime.
• Abnormal preoperative white cell count (<4 or >10x10^9 cells/L).
• Renal failure (serum creatinine >150µmol/L)
• Pulmonary dysfunction (e.g. COPD)
• Participant is unwilling or unable to give informed consent for participation in the study (any documented history of cognitive impairment will exclude the patient as this may have an effect on biochemical markers of cerebral injury)

both groups. Based upon these assumptions an effect size of 0.923 can be calculated. Therefore, a sample size of 50 (twenty-five subjects per group) is sufficient, with power (1-β) of 80% and α=0.05, to show a 33% reduction in NSE allowing for a drop out or loss to follow up rate of 15%.

Feasibility

At the study site, approximately 1800 cardiothoracic procedures are undertaken every year, of which at least 500 are routine CABGs. Based upon data from previous years of patients with similar eligibility criteria, it is confirmed that 10 patients could be enrolled every month. Therefore the target sample size is achievable and, assuming a slow starting period, recruitment should take about 6-8 months.

Sampling Method

All blood samples will be collected from the central venous catheter and placed into EDTA, lithium heparin, serum and full blood count tubes (depending upon the tests required) and processed as soon as possible following the end of bypass, or upon collection. Samples for CD11b analysis will be kept in ice until processed.

Measurement Process

All patients will be screened for eligibility and, if appropriate enrolled into the study which will have a measurement of 4 days. During this period blood and urine samples will be taken at 11 time points.

Screening

When attending the preoperative surgical assessment, a patient meeting the inclusion criteria will be verbally informed of the research and given a written Patient Information Sheet (PIS) in the presence of the Consultant Surgeon. Verbal confirmation that the patient has read the PIS will be gained, and informed consent taken in the presence of an investigator or Consultant Surgeon on the evening before surgery. If the patient gives written informed consent then the patient's GP will be informed of their participation in the trial and sent a copy of the PIS. The patient may withdraw their consent at any time during the study. Once the patient is consented they are given a Study-Specific Identifier (SSI) which is used for data analysis throughout the study. Patient identifiers are removed from any study data and details linking patient number and SSI will be kept separately to study data in a locked filling cabinet in the office of SS. If a patient withdraws consent during the study, their data will be removed from the study analysis. Where English is not the patient's first language an interpreter will be sought. The Patients will not undergo any screening process outside of the normal remit for CABG surgery.

Study Period

All subjects will be treated according to the local standards at Southampton General Hospital. Following induction of anaesthesia and placement of central venous and urinary catheters, blood and urine samples shall be collected for the pre-operative, baseline characteristics. The subjects will then undergo routine CABG surgery using CPB. During this period blood samples will be collected from the CPB circuit as described in Table 2. For the following 3 postoperative mornings, blood and urine samples will be collected from the subject by nursing staff and sent for analysis.

Statistical Methods

The patients will be randomised to either the control or study group on the morning of surgery using a previously compiled randomisation table system (QuickCalcs Randomise1, GraphPad Software Inc, USA), which will be held in the locked office at Southampton General Hospital. On the morning of surgery the investigating Perfusionist will telephone the office and be given the study specific number and be told whether the patient is to be put into group A or B; with only the investigating Perfusionist knowing what groups A and B relate to (i.e. study or control). Fifty (50) patients given a unique study code will be randomised into the study group, (RemoweLL, twenty-five patients (25)) or control group (Admiral, twenty-five patients (25)). Primary and secondary endpoints will be analysed using the SPSS statistical package by the Principle Investigator and independently reviewed by a statistician from the University of Southampton. As many of the parameters will be measured at various time points, e.g. C – Reactive Protein, Repeated Measures ANOVA will be undertaken to explore differences between groups. Parameters will also undergo Analysis of Covariance to examine possible correlation. Any parameters showing skewed as opposed to normal distribution shall be log transformed if possible. If log transformation is not appropriate for the skewed parameters then the equivalent non-parametric test shall be performed.

DISCUSSION

Evidence suggests that lipid microemboli are a major cause of multi-organ dysfunction although the area requires further investigation. Current strategies for the removal of lipid microemboli lack efficacy and in some situations are associated with increased loss of haemostatic integrity (Issitt and Sheppard 2011). This study will examine the efficacy of lipid and leucocyte filtration in patients requiring cardiopulmonary bypass for cardiothoracic surgery. It is hoped that the results generated by this study will advance cardiopulmonary bypass practice and provide further areas for research.

Study Status

This trial is funded by Eurosets Medical Devices, Italy, and approval was provided from the Oxford Research Committee C, Ethics Ref: 10/H0606/30 on the 24th June 2009 and registered on EudraCT, Number: 2009-011503-23 on the 9th March 2009 and on the International Standard Randomised Controlled Trial Number Register: ISRCTN56462370 on the 20th September 2010. The study formally began on the 26th March 2013 and is intended to be open for about 10 months.

Table 2. Study Assessment Overview.

Timepoint	Tests Required
1 Pre-Op	Renal Profile CRP and Lipid Profile Urine Osmolality Urine Electrolytes Urine Microalbumin NSE Cystatin C Full Blood Count CD11b
2 5 Min on CPB	CRP and Lipid Profile
3 30 min on CPB	CRP and Lipid Profile
4 5 Min before X-Clamp Release	CRP and Lipid Profile
5 5 Min Before End CPB	CRP and Lipid Profile NSE CD11b
6 1 Hour Post CPB	CRP and Lipid Profile Full Blood Count CD11b
7 6 Hours Post CPB	NSE
8 24 Hours Post CPB	CRP and Lipid Profile NSE Full Blood Count CD11b
9 1ST Post-op Morning	Renal Profile Urine Osmolality Urine Electrolytes Urine Microalbumin Cystatin C
10 2nd Post-op Morning	Renal Profile Urine Osmolality Urine Electrolytes Urine Microalbumin Cystatin C
11 3rd Post-op Morning	Renal Profile Urine Osmolality Urine Electrolytes Urine Microalbumin Cystatin C

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