Negative venous line pressure in a miniaturised cardiopulmonary bypass circuit – the influence of a fenestrated venous cannula and its effect on pump flow.

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# Proposal

We propose to measure the ability of a ‘fenestrated’ venous line cannula to reduce the negative line pressure seen with kinetic-assist active venous drainage (KAVD) in a standard miniaturised cardiopulmonary bypass circuit and thereby increase the flow characteristics of the bypass pump.

# Lay Summary

During the majority of heart surgery a ‘heart-lung machine’ or cardiopulmonary bypass circuit is used to supply blood, carrying oxygen, to the body while the surgeon is operating on the heart. Traditionally the ‘heart-lung’ machine contains a 2-litre reservoir from which blood is supplied with oxygen and delivered back to the body. To avoid the dilution of the blood and to reduce the chance of needing a blood transfusion we have been using a miniaturised heart-lung machine (Mini-CPB), without a venous reservoir, for many of our heart operations in Plymouth for the past 8 years.

Because the pump that pumps the blood back to the patient, in this type of circuit, also pulls the blood from the patient, rather than draining by gravity into a venous reservoir, a negative pressure can be generated in the drainage (venous) pipe. The negative pressure has three potential consequences: a high negative pressure may cause damage to the blood in the pump resulting in fracturing of the blood cells; the negative pressure may cause effervescence (microbubbles) in the blood producing miniaturised air bubbles in the blood and; the flow of blood from the patient can be temporarily and repeatedly interrupted thus reducing the flow back to the patient.

We want to investigate whether a new venous drainage pipe (cannula) which has three sets of drainage holes (three-stage) compared with the standard two-stage cannula, or a three-stage which also has additional windows (fenestrations), can improve the drainage of blood into the circuit, reducing the negative pressure produced and increase the blood flow delivered to the patient. Patients who consent to participate will be randomly assigned to one of three types of venous cannula:

1. Standard venous cannulation with a two-stage venous cannula
2. The three-stage cannula (91437C, Medtronic)
3. The fenestrated three-stage cannula (MC2X, Medtronic)

Apart from measuring the pressures in the pipes and the flow back to the patient we will record any evidence of red cell damage and the number and size of any microbubbles produced in the circuit.

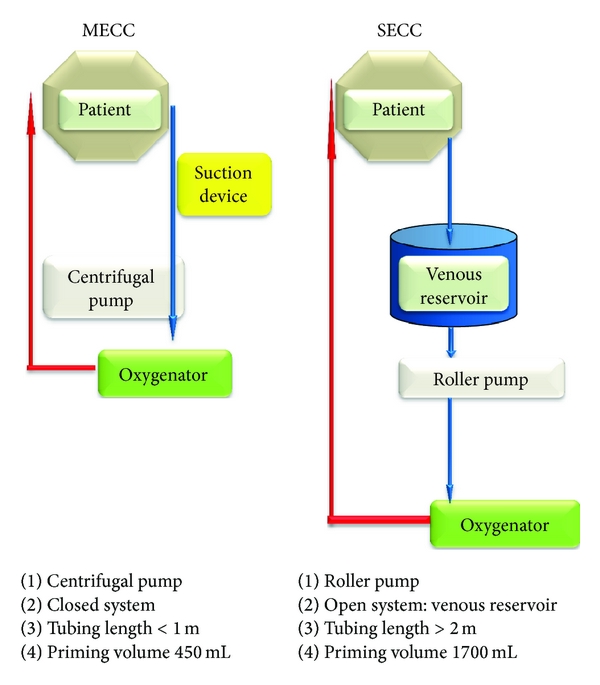
# Background

Generation of marked negative pressures in venous drainage lines is associated with extracorporeal circuits that employ active venous drainage. This is usually associated with attempts to minimise the size of the extracorporeal circuits with smaller diameter tubing or smaller cannulae. Applying a vacuum to the venous reservoir, in vacuum-assisted venous drainage, may generate significant negative pressure in the venous line. Alternatively the centrifugal pump, used to generate forward arterial flow in miniaturised cardiopulmonary bypass circuits (Mini-CPB), without venous reservoirs, results in KAVD, generating negative pressure in the venous line.

### Miniaturised Cardiopulmonary Bypass (Mini-CPB)

This closed circuit has eliminated the venous reservoir (see Figure 1 for a comparison of a conventional versus a miniaturised circuit). Compared with a conventional cardiopulmonary bypass circuit (C-CPB) it has a considerably lower priming volume of 800ml and this can be reduced to 300ml after the circuit is retrogradedly primed, causing minimal haemodilution. Because of the change in air-handling capability, standard safety features are employed in different positions and there are now many reports that this is an acceptable solution with a strong safety record. In clinical trials the Mini-CPB system has resulted in a decrease in the inﬂammatory response [[1](#_ENREF_1)], a higher haematocrit during CPB [[1-4](#_ENREF_1)], decreased blood and blood product transfusion [[1-4](#_ENREF_1)], and decreased postoperative blood loss [[4](#_ENREF_4), [5](#_ENREF_5)].

#### Figure 1 – Miniaturised versus Conventional Cardiopulmonary Bypass Circuit



### Venous line negative pressure effects

The two main deleterious effects thought to be associated with excessive negative pressures are generation of gaseous micro emboli and haemolysis [[6](#_ENREF_6), [7](#_ENREF_7)] but it is also recognised that the negative pressure may intermittently and repeatedly occlude blood flow into the pump and in doing so reduce the blood flow to the patient.

#### Gaseous microbubbles

Gaseous micro-emboli (GME) are produced through two mechanisms. Firstly a process termed ‘cavitation’, a transient hydrodynamic phenomena that consists of bubble nucleation, growth, and collapse. It results from extreme (positive and negative) pressure changes within blood. This phenomenon is well described in the context of extracorporeal circuits where excessive negative pressure is generated [[6](#_ENREF_6)].

Secondly negative pressures in the venous line may be transmitted to the right atrium, where air is entrained into the circulation past the cannulation site.

Vacuum-assisted active venous drainage is associated with an increase in microbubble generation with the number of bubbles in the arterial line increasing in proportion to the degree of negative pressure applied to the circuit [[8](#_ENREF_8)]. In an experimental model of Mini-CPB versus Conventional CPB (C-CPB) 20% of all pressure readings in the venous line were less than -150 mmHg. This was associated with a higher number and larger size of gaseous micro emboli detected in the arterial line [[6](#_ENREF_6)], distal to the arterial line filter. Different circuits may vary in their capacity to generate GME [[9](#_ENREF_9)], although it is unclear from these preliminary reports what physical factors result in these differences. The addition of a venous bubble trap does not appear to alter microbubble activity, but circuits with an arterial filter may have the lowest microbubble count [[10](#_ENREF_10)].

The clinical effect of generating microbubbles depends on their size. Bubbles larger than 200μm are of clinical importance with respect to embolic complications. By occluding capillary beds distal ischaemia of the organ supplied by this blood supply results. Many papers studying the incidence of microbubbles concentrate on bubbles of this size only, believing that only occlusive effects are clinically important.

The effect of microbubbles with diameters 50-200μm has been studied in animal models [[11](#_ENREF_11)]. Microbubbles of this size are initially trapped in arterioles, but are eventually displaced by blood. Transit times are in the order of 60 to 360 seconds under normal haemodynamic conditions. In the brain arterioles initially dilate, returning to normal after about 30 minutes, but this recovery is associated with a progressive fall in cerebral blood flow, reaching 50% of baseline measurements 60 minutes after exposure to air [[11](#_ENREF_11)]. Cortical somatosensory evoked response fall to 25% of baseline levels by the time of bubble transit, and this depression continues for several hours after exposure to air. The effect on other organs is not well described, but similar haemodynamic and inflammatory processes can be anticipated.

Smaller microbubbles, less than 50μm in diameter, despite being able to cross capillary beds easily, may also produce deleterious effects. These include cellular and protein activation with the bubble–blood interface acting as a foreign surface. Bubble contact with vascular walls alters the endothelial cells that further promote release of vasoactive mediators and platelet and neutrophil adhesion. These effects have been studied in lungs exposed to gaseous microemboli. The bubble is compressed against the endothelial capillary wall, causing functional stripping of endothelial cells and an increase of large pore radii. In addition gaps between endothelial cells are created both in pulmonary and bronchial microvessels following air embolism. Normally, endothelial cells are tightly joined, preventing intravascular fluids from pouring out into the surrounding tissue. Gap formation allows leakage and resultant interstitial edema [[12](#_ENREF_12)].

Neutrophils play a central role in mediating air embolism-induced lung injury [[13](#_ENREF_13)]. They aggregate around the bubble to produce clumps. A local destructive process takes place, probably by superoxide and hydroxyl radical production and proteolytic enzyme release. These molecules increase membrane permeability to fluids and proteins and facilitate interstitial pulmonary edema [[14](#_ENREF_14)]. Activation of complement by circulating microbubbles commences at the air-liquid interface that surrounds gas-filled particles [[15](#_ENREF_15)].

Therefore the generation of microemboli of any size may result in neurological deficits secondary to ischaemia or necrosis, neurocognitive dysfunction with a decrease in cerebral blood flow or effects due to the inflammatory response. A similar pattern of injury or dysfunction may occur in the kidneys, liver, gut or heart.

#### Haemolysis

Secondly, negative pressure is thought to induce haemolysis. Under experimental conditions applying a range of positive and negative pressures, 1000mmHg to -710mmHg, to static blood [[16](#_ENREF_16)] and a similar range of pressures (720mmHg to -720mmHg) to flowing blood, did not result in significant haemolysis in the absence of a blood-air interface and bubble formation [[17](#_ENREF_17)]. In all experiments the maximum wall stress was less than 480 dynes.cm2 and a maximum Reynolds number of 750, so that all flows were laminar. In the presence of a blood-air interface, cavitation, resulting in blood haemolysis did not occur until a negative pressure greater than -680mmHg was reached [[16](#_ENREF_16)]. The degree of haemolysis increased in proportion to both the increase in negative pressure applied, and with the degree of exposure to air [[18](#_ENREF_18)]. One of the putative advantages of the miniaturised CPB circuit is the absence of a blood-air interface. Whether this is absolute enough to prevent cavitation, even with negative venous pressures, remains to be determined.

Microbubble formation has long been recognized in the presence of local high-pressure gradients generated by regions of turbulent flow. This has most often been noted in the region distal to mechanical heart valves [[19](#_ENREF_19), [20](#_ENREF_20)]. This suggests that microbubble generation may not require large negative pressure gradients, but that more moderate negative pressure, in the presence of areas of turbulent flow, may generate microbubbles. Recent advances in CPB circuit design, especially of the oxygenator, may limit areas of turbulence.

Increased levels of free RBC constituents together with an exhaust of their scavengers result in a variety of serious clinical sequelae, such as increased systemic and pulmonary vascular resistance, altered coagulation profile, platelet dysfunction, renal tubular damage, and increased mortality [[21](#_ENREF_21)]. Sub-lethal RBC damage is characterized by decreased microperfusion and hypoxic RBCs, leading to end organ dysfunction caused by cellular ischemia.

Negative pressure applied to hard-shell reservoirs to facilitate vacuum-assisted venous drainage is associated with haemolysis at negative pressures of -40 to -80mmHg compared to the haemolysis with gravity siphon [[7](#_ENREF_7)]. Although other authors have failed to demonstrate significant levels of haemolysis associated with active venous drainage compared with gravitational drainage [[22](#_ENREF_22)].

Despite the negative pressures generated by the Mini-CPB system some authors report less haemolysis with Mini-CPB [[23](#_ENREF_23)]. Under experimental conditions there was no difference in haemolysis or in sub-lethal red cell membrane damage between gravity drainage, vacuum-assisted or kinetic-assisted venous drainage [[24](#_ENREF_24)]. In a similar pattern to the detection of gaseous microbubbles different Mini-CPB circuits appear to have different capacities to induce haemolysis [[25](#_ENREF_25)].

## Why is this research needed now?

One aspect of Mini-CPB, related to the nature of the blood flow from the patient into the circuit, requires further attention [[26](#_ENREF_26)]. Because of the continuous nature of the circuit, without a venous reservoir, the arterial inflow rate dictates the demand from the venous return. This kinetic-assist venous return generates negative pressure in the venous line. If the patient is relatively hypovolaemic (low blood volume) then venous flow into the circuit may fall, with a corresponding reduction in achieved arterial flow back to the patient. If the venous return to the circuit falls significantly then the negative pressure causes collapse of the right atrial chamber around the venous cannula, completely occluding venous return. The chamber then refills and venous return is re-established. This intermittent opening and collapsing of the right atrium around the walls of the cannula is often referred to as ‘chatter’.

The magnitude of this interupted venous return to the circuit was investigated by our group [[27](#_ENREF_27)]. Average cardiopulmonary bypass pump flow was significantly lower with Mini-CPB (2.37 ± 0.25 l.min-1.m-2) compared with C-CPB (2.71 ± 0.21 l.min-1.m-2 (*p* <0.0005 (95% CI (Mini-CPB – C-CPB) -0.39 to -0.29)).

In a retrospective case-control study [[28](#_ENREF_28)] of 120 patients comparing Mini-CPB with a standard circuit, the Mini-CPB patients had a significantly lower nadir of low flow lasting more than 2 minutes 1.75±0.23 v. 2.20±0.22 l.min-1.m-2, a longer duration of low ﬂow (defined as less than 2l.min-1.m-2) during bypass of 64±41 v. 1±4 min, a lower mean cardiac index during low ﬂow 1.78±0.15 1.98±0.06 l.min-1.m-2 and a lower mixed venous saturation.

### What do we already know about negative pressure in the venous line and the fenestrated cannula?

In a preliminary investigation we have retrospectively measured the degree and duration of negative pressure in the venous line using a conventional 2-stage venous cannula in 74 patients undergoing either CABG, AVR or combined CABG+AVR with a single surgeon and all cases utilizing Mini-CPB. The median (inter-quartile range) negative pressure was -45 (11.2) mmHg. Peak negative pressure was -96 (56) mmHg.

Another group has reported the range of negative pressures associated with Mini-CPB [[6](#_ENREF_6)], with 20% of venous pressure values below -150mmHg. Pressures below -100mmHg were recorded in the right atrium for 10% of the duration of CPB.

There is currently no published data regarding the fenestrated venous cannula. In a preliminary analysis in our group (n=6) we measured similar median negative pressures of -50 (19.5) mmHg but with lower peak negative pressures of -77 (23). We cannot draw any firm conclusions from these results.

Similarly there is no published data on the rates of either microbubble formation or on haemolysis comparing a conventional 2-stage cannula with either a 3-stage or fenestrated 3-stage cannula.

## Importance of this research

Prevention of organ dysfunction that results in short- or long-term morbidity has become the new challenge after cardiac surgery [[29](#_ENREF_29)]. Between 50%and 75% of patients have what is characterised as an “uncomplicated course”, but the others have a prolonged recovery, a residual minor limitation or dissatisfaction with lifestyle or serious organ system dysfunction. 40% of the yearly hospital costs forCABG are consumed by 10 to 15% of the patients who have seriouscomplications after surgery. Many of these unsatisfactory outcomes, with dysfunction of one or more organ systems, can be attributed to either oxygen delivery or to inflammation. The importance of a continuous, uninterrupted delivery of well-oxygenated blood and without generation of microbubbles or haemolysis, addresses both of these important areas.

# Aims and Objectives

## Primary outcome question

Is the three-stage cannula (91437C, Medtronic) or the fenestrated three-stage cannula (MC2X, Medtronic) associated with higher average flow to the patient during bypass compared with the standard two-stage cannula (91251C, Medtronic)?

## Secondary outcome questions

Does a venous line cannula with additional fenestrations reduce the duration and depth of negative pressure readings from the venous line during cardiopulmonary bypass compared with either a standard two-stage or three-stage cannula?

Is there a reduction in the number and size of microbubbles detected in the venous and arterial lines of the bypass machine with the fenestrated cannula?

Are there measurable differences in the rate of haemolysis associated with the fenestrated venous cannula?

# Plan of Investigation

## Summary of Design

The study proposed is a single centre, prospective, randomised, double-blind (responsible perfusionist and anaesthetist and patient) trial in which patients undergoing cardiac surgery will be recruited and randomised either to either a conventional 2- or 3-stage venous cannula or to a fenestrated 3-stage venous cannula. Because the conventional venous cannula is a 2-stage cannula (drainage holes at the tip and more proximally), and because the fenestrated cannula shares many properties with a 3-stage cannula we will have 3 groups.

### Groups

1. Standard venous cannulation will be with a two-stage venous cannula 36Fr and 51Fr for each of the two stages (91251C, Medtronic) inserted through the right atrial appendage.
2. The fenestrated three-stage cannula (MC2X, Medtronic) is 29Fr, 29Fr and 29Fr for each of the three stages.
3. The standard three-stage cannula (91437C, Medtronic) is 29Fr, 46Fr and 37Fr for each of the three stages.

### Duration of trial involvement

Trial involvement will be for the duration of the patient’s hospital stay up to the point where the patient is considered to be ‘fit for discharge’.

## Trial participants

48 patients, scheduled for heart surgery where the use of a miniaturised cardiopulmonary bypass (‘bypass’) is indicated (coronary artery bypass grafting and aortic valve surgery), will be randomised to either a conventional venous cannula (either C-2VC or C-3VC) or to the fenestrated venous cannula (F-VC).

### Inclusion criteria

All patients over the age of 18 years of age scheduled to undergo isolated CABG or isolated AVR, who are able and willing to consent.

Consultant surgeon willing to operate using either Mini-CPB for CABG or AVR surgery.

### Exclusion criteria

Re-operation and emergency surgery

Patients refusing or unable to provide informed consent

### Recruitment and consent

We will invite all eligible patients undergoing first time CABG or AVR surgery at Derriford Hospital to participate in this study. Prior to the clinic the patient’s notes will be screened to identify any exclusion criteria. Patients will be given a verbal introduction to the study and handed an information sheet at their first outpatient appointment with the cardiac surgical team. This will detail the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Once the patient is admitted for surgery they will be visited in person by a member of the research team and any issues arising from the project will be discussed. If they are willing to participate then he or she will be asked to consent to inclusion. The participant will personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

The person who obtains the consent will be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the study site.

### Randomisation

The patient will be randomised to one of the 3 groups by an independent perfusionist at the start of the surgical procedure, using a sealed envelope method. In order to have equal groups we will have 24 envelopes for CABG and 24 envelopes for AVR. Without informing the operating perfusionist and the anaesthetist the cannula will be given to the scrub team.

The surgeons and theatre nursing staff will all be aware of which system is being used for practical and safety reasons. Apart from these staff, the patient and other clinicians involved in caring for the patient will be blinded to the allocation.

## Sample size

Sample size is based on the primary outcome question that either a three-stage or a fenestrated three-stage cannula might increase the average CPB flow (index), and our previous data [[27](#_ENREF_27)] demonstrated a mean (SD) CPB flow index of 2.44 (0.21) l.min-1.m-2 with a 2-stage cannula. To formally detect an increase in CPB flow of 10%, assuming a common standard deviation, requires 16 patients in each of 3 groups, giving a total of 48 patients, to give 80% power, using a two-tailed t-test with Bonferroni correction, comparing each new procedure to the existing standard procedure at the (0.05/2) 0.025 significance level.

# Study procedures and interventions

Apart from the different venous cannula all other interventions will be the same between the three groups.

## Venous cannulation

1. (C-2VC) Standard venous cannulation will be with a two-stage venous cannula 36Fr and 51Fr for each of the two stages (91251C, Medtronic) inserted through the right atrial appendage.
2. (F-VC) The fenestrated three-stage cannula (MC2X, Medtronic) is 29Fr, 29Fr and 29Fr for each of the three stages.
3. (C-3VC) The standard three-stage cannula (91437C, Medtronic) is 29Fr, 46Fr and 37Fr for each of the three stages.

## Trial measurements

## Perfusion variables

1. Average flow, oxygen delivery and perfusion pressure recorded throughout the duration of CPB
2. Depth and duration of negative venous line pressure recorded throughout the duration of CPB
3. Microbubble count and microbubble volume in the venous and arterial lines.

## Laboratory analysis

In addition to routine monitoring the following laboratory tests will be conducted for the purposes of the study:

1. Rate of haemolysis. LDH, ALT and AST measured after induction of anaesthesia (baseline t0), 10 minutes after initiation of CPB (t1), 40 minutes after initiation of CPB (t2), 30 minutes after the end of CPB (t3).
2. Markers of inflammation – CRP, leucocyte count, Troponin-I measured at baseline and 30 minutes after the end of CPB.

## Data collection and analysis

Data will be collated in the CRF and then uploaded into an excel spreadsheet and database.

## Follow-up

Patients will be followed-up during their hospital stay until they are deemed ‘fit for discharge’. They will be reviewed for any AEs or SAEs until this time.

## Standard care

### Anaesthesia and Surgical Management

All patients will be anaesthetised with a low-dose opioid technique, using 10 µg.kg-1 of fentanyl. Maintenance of anaesthesia will be with a combination of Isoflurane and Propofol. Surgical technique will not differ between groups. Arterial access is the same in all patients and is achieved through an ascending aorta cannulation (24fr angled (72524, Medtronic)). Venous cannulation will vary depending on group (as above).

The Mini-CPB circuit is a preconnected closed-loop circuit incorporating a RotaFlow centrifugal pump (Maquet, Germany), an Affinity Fusion oxygenator (Medtronic, USA). There is a venous bubble detector and a venous bubble trap (Maquet Cardiopulmonary). Pericardial blood is aspirated into an Autolog cell-saver device (Medtronic, USA). If sufficient volume is aspirated it will be processed and re-transfused at the end of the operation. In cases where large volumes are returned to the cell-saver the processed blood will be returned to the circuit via a drip-chamber to the venous bubble-trap. The tubing circuit, drip-chamber and venous bubble trap is heparin-coated (Bioline Coating, Maquet Cardiopulmonary). The oxygenator is not coated. The extracorporeal circuit is primed with 800ml Gelofusine that is reduced to between 300ml by retrograde autologous priming following aortic cannulation.

### Management of Cardiopulmonary bypass

All CPB will be identical apart from the venous cannula. The circuit is primed by the clinical perfusionist ready for its use during the surgical procedure. Moderate hypothermia to 34ºC, alpha-stat pH management, and target flow rates of 2.5 l.min-1.m-2 will be used for all 3 groups. Mean arterial pressure target is 50-60mmHg. Anticoagulation to achieve an activated clotting time > 400s will be achieved with heparin 300IU.kg-1. Final cardioplegia concentrations will be the same (K+ 20mmol.l-1 induction and 10mmol.l-1 maintenance). Retrograde autologous priming of the circuit will be undertaken over ≤1 minute prior to the commencement of bypass. Target haematocrit (Hct) during bypass will be maintained at 21% or higher, with red blood cell transfusion given as necessary. The circuit will incorporate an arterial and venous line oxygen electrode to permit continuous calculations of oxygen delivery and consumption throughout the duration of cardiopulmonary bypass (see diagram).

# Outcome measures

Actual pump flow achieved (RotaFlow, Maquet) will be automatically collected by the JocapXL data acquisition system on the bypass machine. Arterial PaO2, and arterial oxygen saturation (SaO2) (M4: Spectrum Medical, Medtronic and CDi500, Terumo) will be recorded by their respective devices. The JocapXL has a sample frequency every 15s. Average pump flow over the whole period of bypass will be recorded by the JocapXL system. Arterial blood gas measurements will be taken every 30 min during bypass, measured with the ABL815 blood gas analyser (Radiometer) and entered onto the electronic database management system. Venous line pressures will be measured and stored by the Jocap XL system. Simultaneous right atrial pressures, to estimate closing pressure, will be stored by the JocapXL system.

Microbubble number and size will be detected and measured with the BCC200 system (GAMPT GmbH, Zapfendorf, Germany). This system detects and counts microbubbles. It can detect microbubbles as small as 20 μm. Microbubble count will be additionally verified using the M4:Spectrum (Spectrum Medical, Medtronic).

During bypass the following measures, used to calculate oxygen delivery, will be measured continuously with the Sorin Spectrum M4 and used to calculate oxygen delivery and consumption:

Pump flow l.min-1

PaO2

SpO2

Haemoglobin concentration g.dl-1

Arterial and venous line oxygen electrode measurements

Mean and range of oxygen delivery and consumption measured throughout 3 phases of CPB:

During the initial cooling phase

During the stable period of hypothermia

During the period of re-warming

Measures of adequacy of end organ oxygen delivery will be derived from:

Urine output during cardiopulmonary bypass

Measures of cerebral oxygenation (mean, lowest, highest, duration of CMvO2 < 25% from baseline).

Evidence of hyperlactaemia

Average and range of mixed venous saturation during all phases of CPB

In addition to the range of routine blood samples outlined above the following blood samples will be taken to measure rates of haemolysis and inflammation:

Lactate dehydrogenase, ALT, AST, CRP, troponin I

Blood samples will be collected before CPB (t0), 10min (t1) and 40min (t2) after commencing CPB, and 30min after CPB termination (t3).

## Data acquisition and statistical analysis

Continuous variables will be compared using a Student t-test to test for a difference in means between the two patient groups. Two-sample tests of proportions will be used to test for differences in proportions of patients with given characteristics or outcomes in the two groups. Comparisons of dichotomous data will be made using Fisher’s exact test. A Bonferroni adjustment will be applied to allow for multiple testing.

For all the tests, a *p* value of 0.05 or less will be deemed statistically significant. Statistical analysis will be performed using the software package R (R Development Core Team, Vienna, Austria).

Summary statistics for patient demographics, co-morbidities, intra-operative and ICU variables and clinical outcomes will be reported as Bonferroni adjusted mean +/- standard deviation or n (%), (95% Confidence interval (Fenestrated cannula – Conventional cannula)).

# Study forms

## Patient information sheet

See Appx 1

## Patient consent form

See Appx 2

# End of trial

The trial will be ended when we have recruited, consented, randomised, surgery has been performed on and all data collected for the intended number of included patients.

# Discontinuation or withdrawal of trial participants

Given the short time scale from inclusion and consent to the end of a participant’s involvement in the trial we only anticipate withdrawal for:

Ineligibility – planned operation unable to be performed with Mini-CPB (addition of mitral valve surgery)

Consent withdrawn

Technical problem with venous cannulation – requiring the use of a Ross basket rather than a venous cannula

The reason for withdrawal will be recorded in the CRF.

# Source data

Hospital notes, Innovian electronic operative and critical care record, JocapXL electronic perfusion data record, laboratory records.

Completed CRFs will be retained in a locked office until publication and then transferred for storage for the 5 years.

# Safety reporting

## Adverse Events (AE)

### Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

• Results in death

• Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

• Requires hospitalisation, or prolongation of existing inpatients’ hospitalisation

• Results in persistent or significant disability or incapacity

• Is a congenital anomaly or birth defect

The relationship of AEs to the trial intervention will be assessed by a medically qualified investigator. Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

### Reporting Procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

#### Non serious AEs

All such events, whether expected or not, should be recorded.

#### Serious AEs

A SAE form should be completed and faxed to the Chief / Principal Investigator within 24 hours. However, relapse and death due to conditions specifically listed on the patient’s operation consent form, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the Research Ethics Committee and copied to the R&D Office where in the opinion of the Chief / Principal Investigator, the event was:

• ‘related’, i.e. resulted from the administration of any of the research procedures; and

• ‘unexpected’, i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief / Principal Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies.

Serious AEs will include any of the list below if it is judged that the adverse event either results in death or is considered ‘life threatening’.

Myocardial infarction defined as electrocardiographic evidence (new ST elevation, new LBBB) and biochemical evidence of a fresh myocardial infarction.

Cardiac failure (a low cardiac index (1.8 l.min-1.m-2) despite adequate ﬂuid replacement and high dose inotropic agents (the use of dopamine at a dose greater than 5µg.kg-1.min-1 or any other inotropic agent for more than 1 hour postoperatively), or the requirement for at least one of the following: an intra-aortic balloon pump, intraoperative placement of a temporary or permanent right or left ventricular assist device or extracorporeal membrane oxygenator, or preoperative placement of intra-aortic balloon pump).

Neurological morbidity (focal or global neurologic deﬁcits or death without awakening). Postoperative delirium requiring sedative agents.

Renal morbidity (new onset renal failure requiring dialysis). Peak rise in postoperative creatinine level before discharge.

Re-exploration (a formal surgical procedure usually required as a consequence of bleeding, involving reopening the chest to investigate a source of bleeding).

Incidence of new atrial fibrillation (as evidenced by an ECG and requiring treatment with electrolytes, DC cardioversion or an antiarrhythmic drug).

# Quality control and Quality assurance procedures

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

# Ethics

There are no ethical considerations that are anticipated relating to the study.

## Declaration of Helsinki

The Investigator will ensure that this study is conducted taking into account the principles of the Declaration of Helsinki.

## ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

## Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and the host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

## Participant Confidentiality

The trial staff will ensure that the participants’ anonymity is maintained. The participants will be identified only by initials and a participant’s ID number on the CRF and any electronic database. All documents will be stored securely on the hospital g: drive and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act (1998) which requires data to be anonymised as soon as it is practical to do so. All participant data will be anonymised before the trial sponsor (Medtronic) can access it.

# Project management

## Personnel and Day-to-day study management

The Chief Investigator (MJB) is responsible for the overall running of the study. The Principle Investigator (CTL) with the Surgical Care Practitioners (Estelle Eaglestone (EE) and Tania Riches (TR)) co-ordinating activities on a day-to-day basis. The local investigator (GW) is responsible for all aspects of Cardiopulmonary Bypass, including data management, reporting of any safety concerns, blood sampling during the intraoperative period, supervision of the clinical perfusionists. The Trial Management Team will comprise MJB, CTL, EE, TR, and R&D staff. This team will meet monthly throughout the duration of the study to: monitor progress; monitor patient recruitment, follow-up and budget; discuss analysis, results, draft reports and dissemination.

The study will be sponsored by Plymouth Hospitals NHS Trust and approved by a research ethics committee and local Trust R&D department. A Clinical Trials Authorisation from the MHRA is not required. The study will be conducted in accordance with the Research Governance Framework for Health and Social Care (2005).

## Time schedule

See Appx 3

The single surgeon involved with this trial operates on 175 patients per year. We estimate that 125 will have either CABG or isolated AVR. From these 60 will be both eligible for inclusion and willing to participate. Therefore we anticipate recruitment of 48 patients in 10 months. Total trail duration, including ethical committee approval, recruitment, analysis and write-up is 15 months.

# Financing and Insurance

## Budget summary and Costings

See Appx 4

Based on 16 patients per group (total 48) and to permit 10% withdrawal for any reason. Final total 54 patients.

### Stationary

Information sheets (2 sheets) 108 @4p/sheet 8.64

Consent form (2 sheets) 54 @4p/sheet 4.32

CRF (20 pages) 54 @4p/sheet 43.20

Miscellaneous stationary 78.84

### Recruitment and Consent

Recruitment SCP Band 7 40.5 @25.59/hour 1036.40

Consent SCP Band 7 40.5 @25.59/hour 1036.40

### Trial related additional laboratory tests

Full Blood Count Baseline and t3 54 407.70

AST/ALT/LDH Baseline and t0 to t3 54 3105.00

CRP Baseline and t3 54 684.45

Troponin I Baseline and t3 54 496.80

### R&D costs

Trust overheads 207.28

R&D overheads 207.28

### Publication

Open access publication fee 1500.00

TOTAL 8,816.30

### Monitoring equipment

We have the use of the bubble counter. No additional peripherals required.

We have the use of a cerebral oximeter. No additional peripherals required.

### Publication

We will reserve monies sufficient to fund open-access publication to maximise the exposure of the results of this study.

Estimated cost 1500.00

# Publication policy

We will aim to publish and present the results of this study both nationally and internationally, including publication in the Cardiothoracic Surgical and Clinical Perfusion literature. We will also make the study details available on a public access database such as ClinicalTrials.gov.

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