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| protocol  |
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|  **Effect of warm humidified carbon dioxide insufflation on pericardial tissue viability during open-chamber cardiac surgery. A randomized controlled trial.**  |

 |
| Protocol Number: 2018.008Version: 2.0Date: 21/02/2018 |
|  |
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| **CONFIDENTIAL**This document is confidential and the property of Royal Melbourne Hospital. No part of it may be transmitted, reproduced, published, or used without prior written authorization from the institution.**Statement of Compliance**This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95). |

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| **STUDY SYNOPSIS (please provide brief information)** |  |

|  |  |  |
| --- | --- | --- |
| Title: |

|  |
| --- |
| Effect of warm humidified carbon dioxide insufflation on pericardial tissue viability during open-chamber cardiac surgery. A randomized controlled trial.  |

 |
| Short Title: | MATCH – Myocardial de-Airing and Tissue preservation using CO2 with Humidification. |
| Design: | Randomised controlled trial |
| Study Centres: | Royal Melbourne Hospital – city campus |
| Hospital: | Royal Melbourne Hospital |
| Study Question: | In adults undergoing open-chamber cardiac surgery, does the use of humidified warm CO2 insufflation reduce pericardial tissue damage and the incidence of micro-emboli when compared to traditional dry CO2 insufflation? |
| Study Objectives: | To assess the impact of humidified warm CO2 insufflation into cardiac cavity:on cellular viability of the pericardium.on intra-cardiac emboli using trans-oesophageal echocardiogramon regional cerebral oxygen saturation. |
| Primary Objectives: | * Cellular viability of pericardial tissue
 |
| Secondary Objectives | * Number of microemboli according to transoesophageal echocardiogram evaluation.
* Change of cerebral oxygenation using near infrared spectroscopy (NIRS).
* De-airing time before cardiac ejection, starting at removal of aortic cross-clamp and ending at beginning of cardiac ejection.
* Cardiopulmonary bypass sweep speed in order to maintain the PaCO2 between 35-45 mmHg.
* Presence of in-hospital complications, specifically, death, cardio-respiratory arrest, cardiac events (infarction or ischaemia) and wound dehiscence.
* Length of hospital stay.
 |
| Inclusion Criteria: | * Adult patients aged ≥18 years
* Able to give informed consent
* Scheduled for open-chamber cardiac surgery
 |
| Exclusion Criteria:  | * Non-English speaking
* Contraindications to transoesophageal probe insertion, including severe oesophageal disease
* Emergency surgery
 |
| Number of Planned Subjects: | 40 |
| Investigational product: | Fisher and Paykel HumiGard™ Surgical Humidification System |
| Safety considerations: | This trial will involve the additional risk of two pericardial biopsies. The first pericardial biopsy will be taken intra-operatively when the pericardium is opened. The second pericardial biopsy will be taken intra-operatively when the pericardium is closed, or 2hrs after opening the pericardium (whichever time point is earlier) There is a small risk of bleeding from the tissue biopsy, however this can be easily identified by the surgeon at the time of biopsy and treated with cautery.  |
| Statistical Methods: | Fisher-exact test or х2 test will be used for non-parametric data. Unpaired two-tailed t-test or Mann Whitney U-test will be used for parametric data. A P value < 0.05 is considered statistically significant.  |
| Subgroups: | None |

## **Glossary of Abbreviations & Terms**

|  |  |
| --- | --- |
| **Abbreviation** | **Description (using lay language)** |
| CPB | Cardio-pulmonary bypass |
| CO2 | Carbon Dioxide  |
| TEE | Transoesophageal echocardiogram |

## **Study Sites**

### Study Location/s

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Site** | **Address** | **Contact Person** | **Phone** | **Email** |
| Royal Melbourne Hospital | Grattan St, Parkville | Dr Irene Ng | 03-93427540 | Irene.Ng@mh.org.au |

## **Introduction/Background Information**

### Lay Summary

During open-heart surgery, gaseous micro-emboli (small gas bubbles) are commonly seen in the heart and bloodstream. This is thought to be associated with post-operative cognitive decline. To minimize this, it is common practice to insufflate the heart cavity with dry carbon dioxide (CO2) via a small tube. It is believed that CO2 causes less gaseous micro-emboli because it is denser and more soluble than air. However, dry and cold CO2 insufflation can cause tissue damage. A more sophisticated device, called the HumiGardTM system, is currently available in the market. It allows a continuous flow of warm and humidified CO2 to be insufflated via a gas diffuser into the heart cavity. In this study, we would like to test if warm and humidified CO2 will reduce the amount of tissue damage and also the number of micro-emboli travelling within the heart and to the brain, when compared to dry and cold CO2 insufflation.

### Introduction

The HumiGard™ system is a heat delivery system that allows insufflation of warm humidified CO2 into the open wound cavity. The device has been used for patients of all ages undergoing open or laparoscopic abdominal surgical procedures where CO2 insufflation gas is used. There are only limited research studies on the use of the device in open-chamber cardiac surgery.

This study will randomize participants to either having dry CO2 insufflation via standard technique or having warm and humidified CO2 insufflation via the HumiGardTM system. The research question is: In adults undergoing open-chamber cardiac surgery, does the use of humidified warm CO2 insufflation reduce pericardial tissue damage and the incidence of micro-emboli when compared to traditional dry CO2 insufflation?

### Background information

Cognitive impairment is a common complication following cardiac surgery. The reported incidence ranges from 32% to 83% [1, 2] and longitudinal studies have demonstrated that it may persist for up to 5 years [3]. One of the contributing factors to this clinical outcome is believed to be the presence of gas emboli, which enter the cerebral circulation following weaning from the cardio pulmonary bypass (CPB). In addition to transient neurocognitive effects, system air emboli can also cause permanent neurological defects and life threatening arrhythmias [4-7].

For this reason several de-airing techniques are employed to reduce air emboli and their consequences. Techniques such as the use of the Trendelenburg position, partial side clamping of the ascending aorta and flooding the operative field with Carbon Dioxide (CO2) are frequently used in combination with different vents to evacuate the retained air in the left side of the heart during cardiac surgery [5-7]. Several reports have demonstrated insufflation of dry CO2 into the cardiac cavity significantly reduces system air embolism during open surgery [8-13]. This has become common practice in many institutions.

Insufflation of dry CO2, however, can cause tissue desiccation leading to tissue damage. It is a recognized problem in laparoscopic surgery where the continuous insufflation of dry CO2 has been found to cause evaporation, manifesting itself by a dramatic increase of viscosity of the peritoneal fluid [14] and cellular damage and inflammation [15]. Moreover, in thoracoscopy [16], as well as in off-pump coronary artery bypass surgery [17], the insufflation of dry CO2 has been shown to cause severe cell damage to the pleural and endothelial surfaces, respectively. In both cases, however, the destructive effects could be alleviated by humidification of the gas [14,16]. In addition to cellular protection, humidification may also improve de-airing capability by increasing CO2 absorption [16]. This can potentially reduce the number of micro-emboli in the circulation.

The HumiGard™ system is a heat delivery system that allows insufflation of warm humidified CO2 into open wound cavity. Its use is increasing recently in open and laparoscopic abdominal surgical procedures where CO2 insufflation gas is required. The device delivers CO2 via a gas diffuser (Carbon VITA diffuser®, Cardia Innovation AB, Stockholm, Sweden), which acts to reduce the flow velocity and create laminar CO2 flow. This leads to effective displacement of air and prevention of entrainment of air from the room into the cavity [18]. In open-chamber cardiac surgery, this may potentially reduce micro-emboli in the circulation.

There are currently very limited studies on the use of the HumiGard™ device in open-chamber cardiac surgery. The aim of this study is to investigate whether the use of humidified warm CO2 insufflation into the cardiac cavity via the HumiGard™ device can reduce pericardial tissue damage and the incidence of micro-emboli when compared to traditional dry CO2 insufflation in adult patients undergoing open-chamber cardiac surgery.

## **Study Objectives**

### Hypothesis

In adults undergoing open-chamber cardiac surgery, the use of humidified warm CO2 insufflation reduces pericardial tissue damage and the incidence of microemboli when compared to traditional dry CO2 insufflation.

### Study Aims

#### To assess the impact of humidified warm CO2 insufflation into cardiac cavity:

#### on cellular viability of the pericardium.

#### on intra-cardiac emboli using trans-oesophageal echocardiogram.

#### on regional cerebral oxygen saturation.

### Outcome Measures

**Primary endpoint:**

* Cellular viability of pericardial tissue
	+ Pericardial biopsies (5x5x1mm) will be taken remote from the area of mechanical trauma due to retractors at two separate time points by the operating surgeon. Biopsy # 1: on opening of pericardium. Biopsy # 2: on closure of pericardium or at 2hrs post biopsy # 1 (whichever is earlier). Pericardial samples will be placed into pre prepared fixative Fixed samples will be transported to Peter MacCallum Cancer Institute (Ramsay Laboratory) for Scanning Electron Microscopy (SEM). A blinded assessor will assess the surface morphology. Pericardial damage will be defined as mesothelial cell morphology change with bulging and delamination (early signs of damage), exposed basal lamina (later signs of damage), using an ordinal scale of 0-4 to grade severity of changes (0=0-5%, 1= 6-25%, 2 = 26-50%, 3 =51-75%, 4 = >76%). Microvilli damage (calculated as % of normal remaining microvilli) will also be assessed [19, 20].

**Secondary endpoints:**

* Number of micro-emboli according to transoesophageal echocardiogram (TOE) evaluation
	+ The left atrium and ventricle and the proximal part of the ascending aorta will be assessed, during the following time periods; from the release of the aortic cross-clamp to start of cardiac ejection, from cardiac ejection to finished de-airing.
	+ A scale of 0-3 is used to grade the bubbles present in the heart: [21]
		- 0 – no bubbles detected
		- 1 – few bubbles
		- 2 – moderate number of bubbles
		- 3 – large number of bubbles
* Baseline and lowest cerebral oxygenation using near infrared spectroscopy (NIRS).
* De-airing time before cardiac ejection, starting at removal of aortic cross-clamp and ending at beginning of cardiac ejection.
* Cardiopulmonary bypass highest sweep speed in order to maintain the PaCO2 between 35-45 mmHg.
* In-hospital complications, specifically death, cardio-respiratory arrest, cardiac events – infarction or ischaemia and wound dehiscence and device malfunction will be noted. The presence of these specific complications will be collected from the discharge summary of the same admission and reported as per reporting guidelines for approving Human Research Ethics Committee.
* Length of hospital stay – from date of surgery to date of discharge.

**Other measures:**

* Patient baseline characteristics

Age

Sex

Height

Weight

ASA physical status

* Type of cardiac operation
	+ Valve replacement – type of valve
	+ Aortic root repair
	+ Ascending aorta repair
* Operation data
	+ Cardiopulmonary bypass time
	+ Cross-clamp time
	+ Operating time
* Anaesthetic drugs used

# **Study Design**

### Study Type & Design & Schedule

This is a blinded randomised controlled, prospective trial in patients undergoing open-chamber cardiac surgery. Subjects will be randomly allocated to one of two groups. Participants will be blinded to their allocation.

**Group 1: Conventional group - dry CO2 insufflation into cardiac cavity via standard Oxygen Catheter/Distal Eye (Unomedical, Conva Tec Limited, UK)**

**Group 2: Warm humidified CO2 insufflation into cardiac cavity via HumiGard™ Humidification System (Fisher & Paykel Healthcare, NZ)**

The study is a single-centred study conducted at the Royal Melbourne Hospital.

Baseline demographic and procedural information as listed above will be recorded. Primary and secondary outcomes will be recorded as per case report form.

The data will be collected by an independent observer.

Study visits will be simply the time for the planned operation. There are no extra visits after the operation. Recruitment will be open for 12-24 months until the total recruitment number is completed. Data entry and analysis may take up to two months.

This study will include the participation of a Doctor of Medicine student (Scholarly selective student from University of Melbourne), who will be using the study as his scholarly selective project submission.

|  |  |
| --- | --- |
| **Assessment/Procedure** | **Day of operation** |
| **Informed Consent** | **x** |
| **Demographic Information** | **x** |
| **Procedure and data collection** | **x** |

### Standard Care and Additional to Standard Care Procedures

|  |  |  |
| --- | --- | --- |
| **Standard Care Procedures** |  | **Intervention Procedures/Additions To Standard Care** |
| **Procedure** | **Time/Visit** | **Dosage/Volume** |  | **Procedure** | **Time/Visit** | **Dosage/Volume** |
| Open-chamber cardiac surgery. Routine dry CO2 de-airing of cardiac cavity via small plastic tubing | Day of operation | As per routine care. Dry CO2 insufflation into cardiac cavity via standard Oxygen Catheter/Distal Eye (Unomedical, Conva Tec Limited, UK) |  | Open chamber cardiac surgery. Warm, humidified CO2 de-airing of cardiac cavity via HumiGardTM system | Day of operation | Warm humidified CO2 insufflation into cardiac cavity via HumiGard™ Humidification System (Fisher & Paykel Healthcare, NZ) |
|  |  |  |  | Tissue biopsy x 2 of pericardium | Day of operation  | 5x5x1mm |

### Randomisation

Randomisation will occur after consent is obtained and after the patient’s eligibility is confirmed based on the inclusion and exclusion criteria. Randomization will be conducted using random numbers obtained by a computer-based random number generator in blocks of ten. Concealment will be achieved by the use of opaque envelopes opened at surgery by the un-blinded perfusionist.

## Study methodology

*Anaesthetic procedure:*

Patients are induced with a combination of opioid, propofol and sevoflurane as per individual anaesthetic practice. Anaesthesia is maintained with sevoflurane, propofol or combination. Bispectral index depth of anesthesia monitoring (Covidien plc, Dublin, Ireland) is used to maintain a bispectral index of 40 to 60. Patients are monitored as per routine with Transoesophageal echocardiography (TOE), cerebral oxygen saturation using near infrared spectroscopy (NIRS) and invasive arterial, central venous and pulmonary artery pressures.

*Operative procedure:*

Surgery is performed using standard surgical technique. Cardiopulmonary bypass (CPB) is performed using a HLP (LivaNova, Dandenong South, Australia) or XCOATED Combined Perfusion Pack (LOVELL Surgical Supplies international, Melbourne, Australia) circuit and either CAPIOX® FX25 (Terumo Corporation, Tokyo, Japan) or INSPIRETM (Sorin Group, MO, Italy) oxygenator with continuous flow of 2 – 2.4 L/min/m2.

Arrest of the heart is achieved with anterograde and retrograde tepid (20-22°C) blood cardioplegia. Perfusion is non-pulsatile with mean arterial pressure maintained in the range of 60 – 80 mmHg. CPB fresh gas flows are altered to maintain arterial carbon dioxide tension between 35 – 45 mmHg on bypass. During CPB, core temperature is allowed to drift to 34°C. Rewarming is initiated prior to aortic cross-clamp removal with a target above 36.0°C to separate from CPB.

*Carbon dioxide (CO2) de-airing technique:*

Before the cannulation for CPB, the CO2 insufflation will be accomplished as follows: CO2 is delivered via the Oxygen Catheter/Distal Eye (Unomedical, Conva Tec Limited, UK) in the conventional group or via the HumiGard™ Humidification System (Fisher & Paykel Healthcare, NZ) in the intervention group. CO2 flooding is commenced at least 5min prior to opening of intra-cardiac chambers or the aorta. The CO2 delivery cannula will be placed in the sternotomy wound at a depth of 5 cm below the skin in either the aortic clamp area or near the inferior vena cava as per surgeon preference. Use of coronary and vent suction will be restricted to a minimum to maintain adequate CO2 concentration in the cardiothoracic cavity.

After completion of the surgical procedure and closure of the heart, the heart and lungs will be passively filled with blood from the CPB circuit. The heart will be massaged gently, and the left side will be de-aired continuously through the left ventricle (LV) apical vent. Full ventilation will be resumed, the LV vent is clamped, and the aortic root de-aired by active suctioning until it collapses completely. The aortic cross-clamp will then be released, and the LV vent opened. The heart will be defibrillated to sinus- or pacemaker-induced rhythm. After good cardiac contraction and normal central haemodynamics are achieved, the LV preload will be gradually and successively increased by reducing the venous return to the CPB circuit, and de-airing continued through the vent in the LV apex under transoesophageal (TOE) monitoring. When no gas emboli are observed in the left side of the heart, the LV vent will be reduced and the heart allowed to eject; the time will be noted (de-airing time before cardiac ejection). De-airing will be continued, and when no further gas emboli are observed in the left side of the heart, the patient will be weaned from CPB and the LV vent clamped in situ. The time will be noted again (de-airing time after cardiac ejection).

## **Study Population**

### Recruitment Procedure

The study population will be adults requiring open-chamber cardiac surgery. Patients will be identified and approached in the pre-admission clinic by the investigator if they have a date scheduled for surgery. A pre-admission clinic visit for patients will occur between one to four weeks prior to their procedure. Patients will only be approached on the day of surgery if the previous method of recruitment is not successful. Investigators will provide information about the study to eligible patients that are contacted at the pre-admission clinic or on the day of surgery. When approached, the patients will be provided the Participant Information Sheet and Informed Consent form (PIS/ICF). Sufficient time will be given to patients to decide in favour of or against the study participation. Patients will have the opportunity to ask any questions concerning the study participation.

We perform on average about 4 open-chamber cardiac operations per week. We estimate that we can recruit about 1-2 patients per week, then we will need at least 40 weeks to complete recruitment for this study.

###  Inclusion Criteria

Patient inclusion criteria will be all of:

* + Adult patients aged ≥18 years
	+ Able to give informed consent
	+ Scheduled for open-chamber cardiac surgery

### Exclusion Criteria

Exclusion criteria

* + Non-English speaking
	+ Contraindications to transoesophageal probe insertion, including severe oesophageal disease
	+ Emergency surgery

### Consent

Individual written informed consent will be obtained from each participant, using the PICF explained by the investigator. The PICF shall be completed and signed by the patients personally and on their own free will, and will be provided with a copy of the signed document. The subjects are entitled to terminate their participation in the study and withdraw their consent at any time without statement of any reasons. The withdrawal of consent will not entail any disadvantages for the patients’ further medical treatment.

1. **Participant Safety and Withdrawal**

### Risk Management and Safety

The study-related risk is considered to be extremely low, since the application of CO2 insufflation in open surgery is CE-certified, TGA approved and Medsafe WAND notified, and is used in routine clinical use outside the study. The risk of localised bleeding associated with biopsy of the pericardium is minimal considering the surgeon will have direct visualisation of the area and will be able to cauterise any ongoing bleeding from biopsy site.

The HumiGard™ Humidification System (Fisher & Paykel Healthcare, NZ) is approved for use in laparoscopic surgery in Australia and the risks of use are considered low. The following intraoperative complications and postoperative\* complications will be collected for the purpose of this trial and reported as per the approving Human Research Ethics Committee reporting guidelines:

* Death
* Cardio-respiratory arrest
* Myocardial infarction
* Myocardial ischaemia evident on electrocardiograph
* Postoperative surgical wound dehiscence

\* Postoperative period will start at the time of admission to Post Anaesthetic Care Unit (PACU) and will conclude at day 3 (time of admission to PACU + 72hrs) or time of discharge from hospital if this occurs earlier than day 3.

### Handling of Withdrawals

All participants who are randomized and undergo general anaesthesia for surgery must be followed for the duration of the study (unless they withdraw consent) even if they are withdrawn from the active phase of the trial. If a participant withdraws from the trial, data collected to the point of withdrawal will be included in data analysis.

### Replacements

If required, replacement participants will be recruited within the study timeframe. If the withdrawal occurs after the closure of the study period, replacement participants will not be recruited, and the data will be analyzed using an intention to treat analysis. A withdrawal rate less than 5% will not meaningfully impact the statistical significance of the study.

# **Statistical Methods**

### Sample Size Estimation & Justification

Based on previous laboratory mice study [20], minimal mesothelial damage (defined as ≤25% morphology change with bulging and delamination or grade 0 and 1 on the damage severity scale) occurs in 100% of the tissues that were exposed to warm and humidified CO2 insufflation, as opposed to 66% in the control group. A sample size estimation shows that with 80% power at the 0.05 level of significance, 20 patients are required in each group.

*Power Calculations*; Please see above.

### Statistical Methods To Be Undertaken

Data will be analyzed using Fisher-exact test or х2 test, depending on the size of data set, for categorical data. Unpaired two-tailed t-test or Mann Whitney U-test will be used to examine parametric data, depending on the normality of the data. A P value < 0.05 is considered statistically significant.

**Storage of Blood and Tissue Samples**

## Details of where samples will be stored, and the type of consent for future use of samples

The Ramsay Laboratory at Peter MacCallum Cancer Institute is set up to perform all the biopsy assessment described and is familiar with the processing and storage of clinical material associated with trials. Biopsy samples will be discarded at the conclusion of the study.

**Data Security & Handling**

### Details of where records will be kept & How long will they be stored

Data will be recorded on a standardised case report form and transferred to a Microsoft Excel spreadsheet. The data collected and all the research-related documents (both hard copies and electronic copies) will be stored securely in a locked office in the Department of Anaesthesia and Pain Management at the Royal Melbourne Hospital. Only the principal investigator and the co-investigators are allowed to have access to the documents. The records will be kept for 5 years following study closure.

### Confidentiality and Security

All the data and biopsy samples collected will remain anonymous and confidential. A unique subject number, not used for any other purpose, will be used. The front page of the case report form (CRF) which contains both the randomisation number and patient information will be stored separately to the remainder of the CRF containing data about the patient to ensure data is re-identifiable. No person outside the investigators will have access to the data. Investigators involved with biopsy processing will not have access to participant details or allocation group.

### Ancillary data

The raw data generated by scanning electron microscopy of the biopsy sample will be in the form of images, which will be stored to complement the grading of the pericardial tissue damage. The images will be kept for 5 years following study closure.

# **Appendix**

**List of Attachments included:**

|  |  |  |
| --- | --- | --- |
| **Document Name** | **Version Number** | **Date**  |
| Case report form | 2 | 21 February 2018 |
| Patient information and consent form | 2 | 21 February 2018 |

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