PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	**Anesthetics to Prevent Lung Injury in Cardiac Surgery**
Principal Investigator	**Brian O'Gara MD**

B1. PURPOSE OF PROTOCOL

Hypothesis:

Volatile anesthetics provide anti-inflammatory protection against pulmonary ischemia-reperfusion injury observed during cardiopulmonary bypass

Specific Aims:

1) To determine the feasibility and protocol adherence of a prospective trial investigating the potential lung protective effects of volatile anesthetics
2) To investigate whether the use of volatile anesthetics during cardiac surgery can result in a reduction in inflammatory lung injury as defined by key biomarkers found in bronchoalveolar lavage fluid and serum
3) To investigate whether the use of volatile anesthetics during cardiac surgery can result in a reduction in the composite outcome of perioperative pulmonary complications

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

***Background*:**

Of the more than 400,000 patients undergoing cardiac surgery with cardiopulmonary bypass per year in the United States, an estimated 25% of them will experience respiratory dysfunction for up to one week (Taggart). Furthermore, respiratory failure requiring prolonged endotracheal intubation and mechanical ventilation occurs in nearly 10% of patients, who then suffer over a 6 times higher in-hospital mortality rate than patients without respiratory failure (Filsoufi). The acute respiratory distress syndrome (ARDS), a severe form of inflammatory lung injury, has been found to occur in only as many as 3% of such patients, but the mortality rate for those with this condition is between 40-50%, a figure in stark contrast to a 1-1.5% overall mortality rate for the cardiac surgical population (Milot, Kogan). Although the etiology of postoperative pulmonary complications amongst cardiac surgical patients is multifactorial, a substantial body of evidence exists suggesting that the pulmonary ischemia-reperfusion injury known to occur during CPB is a major contributor.

During cardiopulmonary bypass, the lungs are dependent on a very limited blood supply, receiving less than 1% of the blood flow observed under normal conditions (Apostolakis 2010). When CPB is weaned, fully oxygenated blood flow is restored to the lung tissue resulting in a massive inflammatory response with release of inflammatory mediators and complement activation. This ultimately leads to diffuse pulmonary capillary leak and accumulation of fluid, protein, and cellular debris within the alveolar space, ultimately resulting in impaired oxygenation and ventilation (Hall 1997). Evidence is available that suggests that patients who experience an exaggerated release of pro-inflammatory cytokines during CPB have increased rates of postoperative hypoxia and prolonged dependence on mechanical ventilation (Tomasdottir 2003, Grunenfelder 2004). Thus it seems logical that interventions to reduce the amount of lung inflammation known to occur during CPB may potentially lead to improved outcomes for many thousands of cardiac surgical patients.

The volatile anesthetic sevoflurane has been shown to both prevent and minimize the extent of inflammatory lung injury in multiple preclinical models of ARDS, ventilator induced lung injury (VILI),

endotoxin exposure, and pulmonary ischemia-reperfusion injury (Ferrando, Strosing, Fortis, Casanova). Proposed mechanisms for this observed effect include a reduction in the release of inflammatory mediators from pulmonary neutrophils and macrophages and preservation of alveolar/endothelial integrity. The result of these effects is reduced migration of pulmonary neutrophils, fluid, and protein into the alveolar space in the injured state. Data supporting the anti-inflammatory effect of sevoflurane on human lungs comes from the thoracic anesthesia field, where reductions in inflammatory markers have been shown when sevoflurane use is compared to propofol (Sugasawa 2011/2012, Potocnik 2014, Schilling 2011, Ertuk 2014). Furthermore, sevoflurane use as compared to propofol in such patients has been found to be associated with a reduction in postoperative pulmonary complications including pneumonia, reintubation, and ARDS (DeConno). Surprisingly, despite the knowledge of the high risk of inflammatory lung injury for patients undergoing CPB and the evidence suggesting the potential for sevoflurane to mitigate this risk, this concept has not been formally investigated.

Significance:
The finding that sevoflurane use can result in a reduction of inflammatory lung injury and postoperative pulmonary complications in cardiac surgical patients could have a major impact on perioperative anesthetic management. The simple intervention of anesthetic selection represents an attainable practice change for cardiac anesthesiologists looking to provide the ideal anesthetic for the more than 400,000 patients a year under their care. Furthermore, the knowledge gained from this trial could potentially be expanded to potentially reduce morbidity for other patient groups at risk for lung injury in the operating room and beyond.

Rationale:
Clinical equipoise exists as to the superiority of a volatile anesthetic regimen versus an intravenous based regimen for patients undergoing cardiac surgery. Volatile anesthetics may provide protection from pulmonary ischemia-reperfusion injury known to occur during cardiopulmonary bypass. This protection from injury may result in improved pulmonary outcomes for patients anesthetized with the volatile agents.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Research Question:

Does the use of inhaled anesthetics during cardiac surgery with cardiopulmonary bypass reduce inflammatory lung injury and pulmonary complications compared to the use of total intravenous anesthesia (TIVA)?

Study Overview:

Prospective, randomized, feasibility trial at a single institution. Enrolled patients will be randomized into one of two groups: one receiving inhaled anesthetics only for anesthetic maintenance (IA group) or a group receiving total intravenous anesthesia (TIVA group). Subjects will undergo a protocolized anesthetic regimen based on their group assignment. Study investigators will evaluate for any difference between groups in the presence of indicators of inflammatory lung injury in bronchoalveolar lavage fluid (BALF) obtained before and after exposure to cardiopulmonary bypass, a known precipitant of ischemia-reperfusion lung injury. To investigate whether or not a presumed reduction in lung inflammation can lead to differences in clinical outcomes, we will observe patients in the perioperative period for the occurrence of pulmonary adverse events. Additionally, the investigators will assess for any potential differences between groups with respect to evidence of lung and myocardial injury as well as systemic inflammation found in patient serum. Lastly, the investigators will determine the feasibility of performing this study and adherence to protocol so that future studies into this concept can be adequately designed.

Trial Design:

Prospective, randomized, feasibility study at a single institution.

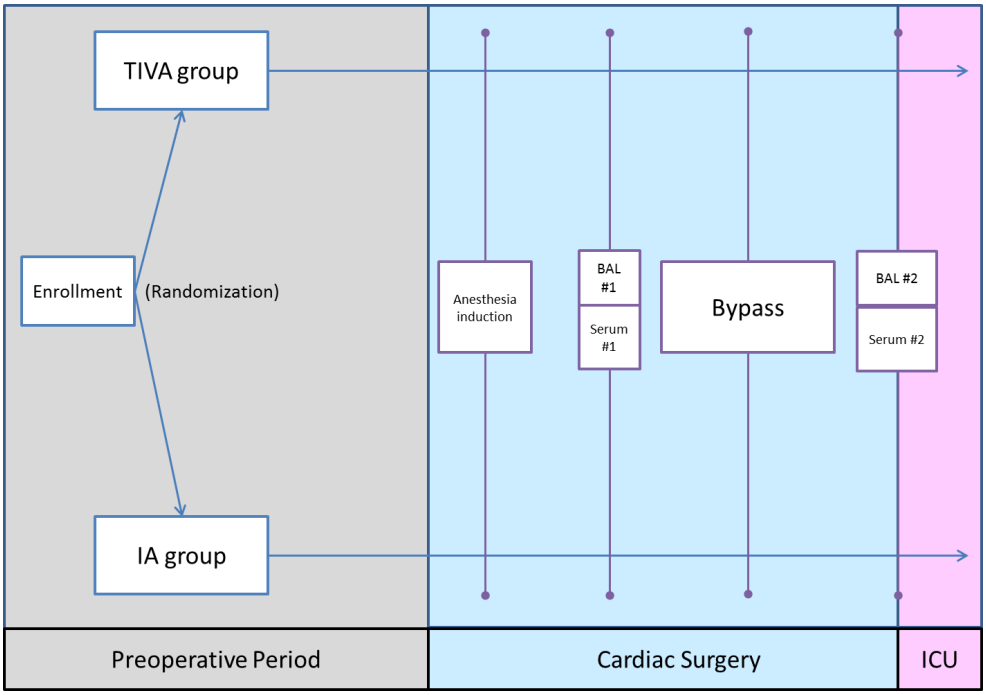
As the feasibility of performing a study investigating the occurrence of inflammatory lung injury in BIDMC cardiac surgical patients is unknown, a study involving a convenience sample of 45 patients (20 in each group, allowing for potential dropout of 5 patients) will be conducted investigating the effect of volatile versus intravenous anesthesia with regards to pulmonary inflammation and injury.

Patients will be screened for recruitment according to inclusion/exclusion criteria utilizing hospital scheduling systems and medical record review. Informed consent will be obtained in all subjects. Once enrolled, patients will be randomly assigned 1:1 prior to surgery into one of two groups: maintenance of anesthesia with volatile anesthesia or maintenance of anesthesia with intravenous anesthesia.

Collection of serum and bronchoalveolar lavage fluid (BALF) will occur at 2 time points. The first set of samples will be obtained after induction of general anesthesia and before surgical stimulus begins. The second set will be obtained approximately 2-4 hours after the removal of the aortic cross clamp. Depending on the completion time of the operation, the second collection of serum and BALF samples may take place in the OR or the ICU. We will collect 10cc of serum and approximately 10-20cc lavage specimen at each of the 2 time points. In addition, clinical data such as vital signs, lab results, radiology results, ventilator settings, medications administered, and incidence of postoperative pulmonary complications will be collected before, during, and after surgery.

Conduct of the assigned anesthetic will take place according to a pre-defined protocols constructed in collaboration with the cardiac anesthesia service. These protocols are provided below. Cardiac surgery will take place according to current hospital standards.

Please refer to the following figure for a flow diagram of patient group assignment and timing of patient laboratory samples:



Intervention:

Inhaled anesthetic with sevoflurane versus total intravenous anesthesia (TIVA) for maintenance of anesthesia throughout the operative course including cardiopulmonary bypass.

Inhaled anesthetic protocol:

Induction of anesthesia will take place according to the discretion of the anesthesiologist. Inhaled anesthetic maintenance will be accomplished thereafter using a range of 0.7-1.5 MAC Sevoflurane. This dosing range was selected based on doses previously described as effective in preventing lung injury in animal and human studies (Sugasawa 2011/2012, Potocnik 2014, Schilling 2011). To allow for changes in this dose to be made by the anesthesiologist who may need to respond to a rapid change in clinical status, we ask that this range be accomplished as an average MAC dose per hour of anesthetic. Sevoflurane was chosen as the anesthetic to be used in this study based on background evidence of its efficacy and its prevalent use by our anesthesia team.

To reduce the potential confounding influence of known inflammatory or anti-inflammatory exposures, the anesthesia team will be asked to refrain from the use of systemic steroids, nitrous oxide, or cisatracurium throughout the course of anesthesia in the OR. Use of alternative, similar acting medications is permissible.

Intravenous anesthetic protocol:

Maintenance of intravenous anesthesia will be accomplished with the use of a continuous infusion of propofol (50 – 200mcg/kg/min). Dosing of these infusions will be within these prescribed ranges but will ultimately be at the discretion of the anesthesiologist and will be selected based on achievement of adequate plane of anesthesia, satisfactory surgical conditions and safe hemodynamic profile. Although most clinicians will use a BIS monitor to monitor the depth of anesthesia for such patients it is not a requirement for this study. As with patients in the inhaled anesthesia group, we will ask the anesthesiologist to refrain from administering systemic steroids, nitrous oxide, or cisatracurium throughout the course of anesthesia in the OR. Use of alternative, similar acting medications is permissible.

Mechanical ventilation protocol (intra-op):

As mechanical ventilation can potentially induce confounding inflammatory lung injury through barotrauma and volutrauma and high fraction of inspired oxygen (FiO_2) concentrations can potentially contribute to worse outcomes from reperfusion injury, we will restrict the mechanical ventilation and oxygenation of the study patients according to the following guidelines:

Tidal volume – 6-8cc/kg of ideal body weight

PEEP – 2-12 cm H_2O

FiO_2 equal to or less than 50%

- Titrate to target SpO_2 > 92%
- Brief exposure (<20 min) to 100% FiO_2 for hypoxia or immediate post CPB allowed

Peak airway pressure < 40 cm H_2O

Plateau pressure < 35 cm H_2O

$PaCO_2$ > 20, <60 mmHg

PaO2 > 60, < 200 mmHg

Protocol adherence will be monitored by a member of the study team in real time by direct conversation with the anesthesiologist and review of the anesthetic record. If a deviation from protocol is found, a conversation with the anesthesia team will take place so that corrective measures can be taken.

Bronchoalveolar Lavage Protocol:

All bronchoalveolar lavage samples will be obtained by a member of the study team with the appropriate training in the performance of bronchoalveolar lavage according to current BIDMC policy and procedure for BAL collection #RC-4.08.16. Direct vision bronchoscopy will be utilized for this purpose to minimize the risk of trauma from unintentional misplacement of a catheter. A flexible bronchoscope will be passed through the endotracheal tube and gently wedged into the right lower lobe bronchus. 60cc of a sterile saline solution will then be used to lavage the cavity. Gentle continuous suction will then be used to obtain the residual lavage specimen (usually 10-20cc) for laboratory analysis of the markers indicated below.

Blood and lung fluid specimens:

Blood and BAL specimens will be centrifuged. The plasma and buffy coat will be separated from red blood cells, aliquoted into small samples, labeled and frozen at -80ºC for future use. The BAL specimen will also be aliquoted into small samples, labeled and frozen at -80ºC for future use. All samples will be stored in a freezer in a locked laboratory at BIDMC. They will be labeled with a unique coded ID and will not contain any patient identifiers. These specimens may be sent to an outside lab for analysis of markers of inflammation and injury or they may be analyzed in a lab at BIDMC. No specimens will be sent outside BIDMC without a fully executed DTA from OSP. No PHI will be sent to the lab.

The study investigators will be establishing a specimen repository under a separate IRB protocol number. Any specimens left after testing from this protocol will be saved to the repository for future investigations.

Subjects may be co-enrolled in this study and 2016-P-000144 and/or 2008-P-000151. Since specimens are collected in the OR for all 3 studies, if a subject is co-enrolled, specimens may be collected in tandem to increase the risk-benefit ratio. For all 3 studies, informed consent will be obtained only by co-investigators who are listed on the Research Staffing Form for each individual study.

Primary Outcome:

Measures of trial feasibility including recruitment, enrollment, and adherence to protocol in order to form the basis for a potential larger clinical trial.

Secondary Outcomes:

1) Incidence of inflammatory lung injury

Incidence of inflammatory lung injury will be defined as an increase in key lung specific markers of inflammation and injury, identified in bronchoalveolar lavage (BAL) and serum.

2) Incidence of postoperative pulmonary complications

Incidence of postoperative pulmonary complications will be defined according to a composite outcome of clinically relevant adverse pulmonary complications including:

- prolonged intubation (greater than 48 hours)
- failed extubation (reintubation within 24 hours of extubation)
- reintubation (any time after 24 hours post extubation)
- hypoxia (defined as PaO_2:FiO_2 ratio of less than 300)
- respiratory acidosis (defined as serum PCO2 > 45)
- ARDS according to the Berlin criteria:
    - acute onset
    - bilateral infiltrates on CXR
    - p:f ratio less than 300
    - not explained solely by cardiac failure

- chest x-ray findings of pulmonary edema, pleural effusion, atelectasis or infiltrate
- pneumonia
- pneumothorax
- bronchospasm
- exacerbation of chronic lung disease

Collection of complications data will occur throughout the hospital stay, until time of discharge.

Additionally, to track other important intraoperative and postoperative factors related to overall patient outcome and protocol adherence we will record other clinical data including:

- Vital Signs
- Medications administered
- Ventilator settings
- Urine output
- End tidal carbon dioxide concentration
- Dead space ventilation
- Alveolar-Arterial oxygen gradient
- Pre/post ejection fraction from transesophageal echocardiography
- Blood transfusion history
- Length of operation
- Length of aortic cross clamp time
- Type of operation

Adverse Event Reporting:

This patient population is undergoing high risk surgery and it is expected that they may have a number of unrelated adverse health events during their hospital course. Patients in this study are being randomized to anesthetic protocols that are both considered within the standard of care. Therefore, we will limit the scope of AE monitoring and reporting to the following:

- All Serious Adverse Events, including unexpected death, believed to be related to the study
- All non-serious Adverse Events believed to be related to the study procedures or unexpected based on the patient's clinical condition

We will assess for adverse events during the intraoperative period, as well as for the first 48 hours post-surgery.

B. Statistical Considerations

a. Sample Size Justification:

The ability to perform a study investigating the occurrence of lung injury on cardiac surgical patients is unknown. Because of this we plan to conduct a feasibility study of 45 patients (20 in each group) investigating the effect of inhaled versus intravenous anesthesia with regards to pulmonary inflammation. A sample size of 20 patients per group will allow us to assess our feasibility, adherence/compliance and recruitment aims. Encouragingly, previous data has suggested that only 16 subjects per group are necessary to detect a difference of more than 40% in alveolar cytokine concentrations with an alpha level of 0.05 and 80% power (Schilling 2011). This suggests that even in a small feasibility study, and allowing for some potential dropout, we may be able to identify significant differences in our secondary outcomes, namely changes in alveolar TNF alpha and IL-8 concentrations.
We estimate that 65 patients will be enrolled (consented) in order to achieve this sample size.

This increase in sample size is required because it is possible that patients can be withdrawn before randomization (i.e. cancelled surgery) as well as after randomization, but before receiving either of the pre- and post-bypass bronchoscopies. Enrollment will be stopped once we have complete data for 45 patients. However, patients who were enrolled prior to the completion of 45th subject will be followed and go through the study procedures.

b. ***Data Analysis:***

The primary outcome of this feasibility trial will be recruitment, enrollment, and adherence to protocol in order to form the basis for a potential larger clinical trial. We will calculate recruitment by considering all those cardiac patients who meet the inclusion and exclusion criteria and are asked to be part of the study. The total number of eligible participants who agree to take part in the study will be divided by the total number of individuals who meet eligibility criteria without any exclusions, regardless of participation. The proportion of patients in each group who receive their assigned study intervention will also be reported.

Because this trial will serve as a feasibility trial for a larger prospective randomized trial, this trial will not be powered to assess for differences in secondary outcomes, however analyses will give insight into effect estimates for the larger trial. We plan to assess the following clinical and biomarker outcomes, as well as safety parameters:

- Difference in markers of inflammation and lung injury found in BALF: IL1B, IL6, IL8, TNFa, MCP1, protein, neutrophil count, sRAGE, angiopoietin 1 and 2, surfactant protein D, sICAM1
- Difference in serum markers of lung injury: sRAGE, surfactant protein D, sICAM1, e selectin, VWF
- Incidence of perioperative hypoxia (defined as PaO2:FiO2 ratio of less than 300)
- Incidence of perioperative respiratory acidosis (defined as serum PCO2 > 45)
- Time to extubation
- Incidence of failed extubation/need for reintubation
- Incidence of pulmonary edema, effusion, atelectasis or infiltrate on postoperative CXR
- Incidence of pneumothorax seen on post op CXR
- Blood transfusion data

Descriptive statistics of the data will be performed and presented, including baseline demographics, intraoperative data and inflammatory markers. Categorical data will be reported as frequencies or proportions and assessed with chi-square (or Fisher's Exact test as appropriate). Continuous data will be represented using mean (± SD) or median (IQR) for variables not normally distributed and compared using parametric or non-parametric tests as appropriate. Both linear and logistic regression will be used in order to test our secondary hypotheses. Changes in inflammatory markers over time will also be assessed. All p-values < 0.05 will be considered statistically significant. SAS 9.3 or later (SAS Institute, Cary, NC) will be used for all analyses.

C. Subject Selection

Inclusion Criteria:

- Adult patients (age 18+)
- Undergoing cardiac surgery with cardiopulmonary bypass

Exclusion Criteria:

- Emergency surgery
- History of severe COPD, emphysema, or ILD
- Recent (<2wk) or current use of systemic glucocorticoids
- Prior history of pneumothorax
- Allergy/contraindication to intravenous anesthetics (egg white or soybean allergy)
- Personal or family history of malignant hyperthermia or high risk for malignant hyperthermia

Drop Out Criteria:

- Inability to safely provide adequate anesthetic maintenance with prescribed regimen for the duration of the case (at the discretion of the cardiac anesthesiologist).

- Inability to safely perform a bronchoscopy secondary to:
  - severe hypoxia defined as a p:f ratio of less than 100 or SpO_2 < 90%
  - > 15 cm H_2O PEEP or > 80% FiO_2 requirement to maintain SpO_2 > 90%

Women of childbearing potential:

Women of childbearing potential will be eligible for enrollment in this study. Preoperative pregnancy testing will take place according to the current BIDMC cardiac surgery and anesthesia guidelines.

Gender and Racial Distribution of Subjects:

We anticipate that our study population will reflect the normal distribution of race and gender currently seen in the BIDMC cardiac surgical population.

B4. POSSIBLE BENEFITS

As this is a feasibility study, it is not possible to predict whether there will be direct benefit to the individual subject. However, based on the data we have reviewed regarding this topic, it is possible that the use of volatile anesthetics in our subjects will result in a lower incidence or severity of inflammatory lung injury. It is also possible that potential differences in the levels of biomarkers could translate to a benefit to the patient in the form of a reduction in pulmonary complications. We hope to use the information we learn from this study to design a larger randomized, controlled trial that would be more adequately powered to detect a potential difference in patient-specific outcomes.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

The following includes descriptions of reasonably foreseeable risks or discomforts associated with participation in this study:

<u>Risks associated with serum collection</u>

It is anticipated that serum collection will be done using existing indwelling catheters, thereby reducing the risks and discomforts to the patient. It is possible that, in some circumstances, venipuncture could be required to collect the specimen. The primary risks of phlebotomy include local discomfort, occasional bleeding or bruising of the skin at the site of needle puncture, and rarely hematoma, infection, or fainting.

<u>Risks associated with bronchoalveolar lavage</u>

Bronchoalveolar lavage (BAL) is a safe, easily performed, and well-tolerated procedure. This will be performed on patients who are already intubated and sedated, and done by experienced clinicians following standard clinical operating procedures to obtain BAL fluids with minimal risk and discomfort to patients. We will not perform the BAL procedure on patients who are suffering from hypoxia (defined in the drop out criteria above) to minimize the risk of even transiently worsening this condition secondary to the study procedure.

The most commonly reported complication of the procedure is transient hypoxia, with a rate reported of around 5% (Hertz 1991, Prebil 2014). Other rare (<1% incidence) complications such as bleeding and pneumothorax are made even more rare when BAL is performed without an accompanying biopsy, as it will be in this study. We will utilize trained personnel to perform specimen collection in a manner consistent with local clinical practice, observing all standard safety measures including hemodynamic monitoring, patient positioning and suction pressure.

In the event a subject experiences any of the risks above, or any unanticipated problems, the Principal Investigator will be available to coordinate care and counsel, as necessary.

Risks attributable to the anesthetic agents:
The two agents being used in this study, Propofol and Sevoflurane, have a long track record of widespread use worldwide and an excellent safety record. They are both considered standard of care anesthetics. Therefore we do not anticipate any additional risk to the study population given either of these anesthetic agents.

Both agents come with the principal risk of hypotension through vasodilation, common to any of the inhaled or intravenous anesthetic maintenance agents.

Sevoflurane, along with all other halogenated inhaled anesthetics, is associated with an incredibly rare risk of Malignant Hyperthermia (MH). MH is a condition characterized by accelerated muscle metabolism in patients with a mutation in the ryanodine muscle receptor (www.mhaus.org). Due to its rarity (less than 1/200,000 anesthetics) and the presence of the antidote Dantrolene, the inhaled anesthetics including Sevoflurane are the most widely used anesthetic agents despite this risk. Patients at risk for MH or with a personal or family history of MH will be excluded from our study to further reduce this risk. Sevoflurane use has been linked to a concern for nephrotoxicity when used in low flow states in anesthetics given to rats (gas flows less than 4L/min). This concept has not been proven in humans.

Propofol carries a risk of an allergic reaction in patients with egg or soybean allergies. Patients with such allergies will be excluded from our study to mitigate this risk.

Analysis of Risk/Benefit Ratio:
Although there is substantial evidence supporting the potential lung protective effect of the volatile agents in preclinical trials, the human data is lacking. We believe that further research including the proposed study is necessary in order to provide more meaningful insight into the potential impact the anesthesiologist's choice of anesthetic regimen can have on a safe outcome for the cardiac surgery patient. Detailed knowledge of this impact and the potential mechanisms of effect could guide future study into how volatile anesthetics may benefit patients suffering from or at risk for other types of inflammatory lung injury. We believe that these potential benefits justify the moderate risk associated with limited serum and BAL sample collection.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment
Members of the study team will screen operating room schedules and patient medical records for the presence of inclusion or exclusion criteria to determine eligibility for enrollment. A secure screening and enrollment log will be kept. If a patient is deemed a potential candidate, they will be approached for informed consent.

Consent
Once a patient is found eligible, he or she will be approached by a physician co-investigator for

informed consent. Non-physician study team members may initiate the discussion about potential study participation and answer questions. This may occur in the cath lab holding area, PAT clinic, cardiac surgery clinic, or in the preoperative holding area. All subjects will be consented with curtains drawn or the door closed, assuring patient privacy. The subjects will have the opportunity to ask any and all questions, and are free to decline participation at any time. Written informed consent will be obtained prior to surgery and any research procedures. Copies of the signed consent will be provided to the patient and filed in the medical record.

The study team undergoes standardized, rigorous training regarding the informed consent process for research. Within the Center for Anesthesia Research Excellence (CARE) at BIDMC, this training is personally overseen by the Clinical Research Administrator and includes: didactic sessions, mandated attendance at CCI/HSPO seminars related to the informed consent process, shadowing of informed consent in a variety of contexts, trainee-led informed consent conversations with the aid of consenting checklists and accompanied by senior staff member and/or PI, robust feedback sessions, and clear communication when the team member is skilled enough to engage in informed consent discussions without direct supervision. All CARE members, including non-physicians, undergo this training.

Subject Protection
Although patients of co-investigators may be approached for inclusion in this study, it will be clearly stated that the subjects' decision to participate or refrain from participation in the research study will not affect the performance or outcome of their upcoming surgery.

B7. STUDY LOCATION

Privacy
All study interactions will take place in private settings with curtains/doors closed so as to provide privacy and comfort for the subject. For patients being approached for informed consent, if they are uncomfortable answering questions regarding their medical history with someone other than a medical provider, an approved MD participating in the study will be contacted to conduct that portion.

Physical Setting
Enrollment will take place at BIDMC. Study procedures (blood and BALF specimen collection) will take place in the OR and/or ICU. Data collected will be housed on password-protected BIDMC network servers and/or locked filed cabinets/offices.

B8. DATA SECURITY

All electronic files containing PHI will be stored on a secure research server behind the BIDMC firewall on password protected computers; paper files will be stored in locked cabinets/offices at BIDMC. Limited information will be retained on patients who are prescreened and do not qualify, or who are approached and declined, for the purposes of generating a CONSORT diagram at the conclusion of the trial. Blood and BAL specimens will be stored in a freezer in a locked laboratory at BIDMC. These specimens will be labeled only with a unique coded ID and will not contain any patient identifiers.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☐ No
Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☐ No

B10 Dissemination of Research Results

Patients will be thanked for their time throughout the study. There is no plan to share the data at the conclusion of the trial. Because study results are likely to be published a few years after a given subject's participation, it is not feasible to send subjects follow-up with the published results. The study investigators are concerned that mailing the published manuscript and an additional thank-you note years after participation risks violating subject privacy, as mailing addresses are increasingly likely to change with passing time. It is out of the scope of this study to continue tracking mailing addresses after completion of enrollment since this is not a longitudinal study.