The efficacy of pecto-intercostal fascial plane catheters for reduction of sternal pain in cardiac surgery patients with complete median sternotomy: A randomized, placebo-controlled trial

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1. Background and Significance

Post-sternotomy pain after cardiac surgery can be debilitating, with associated risks of decreased respiratory function and chronic pain. (1–5) Severe acute sternal pain after cardiac surgery occurs in 49% of patients at rest and 78% of patients during coughing. (6) Post-sternotomy pain is worst during the first two days and improves thereafter. (7,8)

The sternum is innervated by the medial division of the anterior cutaneous branches of the T2-6 intercostal nerves (Figure 1) (1), which may be targeted by several regional anesthetic techniques. (9) Concerns of rare epidural hematoma and possible case cancellations with a bloody tap, in the context of systemic heparinization for cardiac surgery, deters many from utilizing neuraxial analgesia for post-sternotomy pain. (10) Contrarily, parasternal regional blocks such as pecto-intercostal fascial plane block (PIFB) provide a low-risk alternative that targets the anterior cutaneous branches of intercostal nerves, and PIFB has been shown to be effective in improving acute post-sternotomy pain. (1,11)

Nevertheless, single-shot PIFB is limited by its short duration of action, whereas sternotomy pain can remain severe for two postoperative days. (7,8,11) Hence, continuous local anesthetic infusion via bilateral PIFB catheters for 48 hours may improve patient pain experience and related outcomes over single shot PIFB.

This study aims to evaluate whether, in addition to single shot PIFB, continuous local anesthetic infusion (compared with placebo infusion) through bilateral PIFB catheters reduces acute sternal pain at 24 hours after cardiac surgery with complete median sternotomy. The 24-hour time point was chosen as it represents a time where both the post-sternotomy pain is rated as severe, especially with movement and coughing, and the patient is required to start actively participating in the postoperative rehabilitative process. (8,12,13)

2. Study hypothesis

We hypothesize that, in addition to single shot PIFB, continuous ropivacaine infusion through bilateral PIFB catheters will be more effective than placebo infusion in reducing sternal pain score on standardized coughing at 24 hours after cardiac surgery with complete median sternotomy.

3. Methods

3.1 Design:

This will be a prospective, randomized, triple-blinded, placebo-controlled trial in which patients will be randomly allocated to two study groups in a 1:1 ratio:

1) Intervention Group:
   20 mL of ropivacaine 0.2% will be bolused through PIFB catheters on each side, followed by 3 mL/hour infusion of ropivacaine 0.2% for 48 hours each side.

2) Control Group:
   20 mL of ropivacaine 0.2% will be bolused through PIFB catheters on each side, followed by 3 mL/hour infusion of normal saline for 48 hours each side.

3.2 Study population

The target population is adult patients undergoing scheduled cardiac surgery with complete median sternotomy. Patients who are likely to require prolonged postoperative intubation and sedation (See Section 3.2.2 *Postoperative Exclusion Criteria*) are excluded as they are unlikely to benefit from PIFB catheters.

3.2.1 Inclusion criteria

- Scheduled cardiac surgery patients
- Complete median sternotomy
- Adult (19 years old or older)
- English-speaking

3.2.2. Exclusion Criteria

Preoperative Exclusion Criteria:

- Patient refusal
- Emergent surgery
- Inability to provide consent
- Inability to follow up via telephone
- Known preoperative coagulopathy
  - i) Congenital coagulopathy
  - ii) Congenital platelet disorders
  - iii) Platelet count < 50 x 10^9
  - iv) INR or aPTT exceeding the upper range of normal in the absence of anticoagulant use
  - v) Does not include active anticoagulant or antiplatelet use
- Predicted post-operative therapeutic anticoagulation within 48 hours.
- Skin disease over block insertion site that would prevent catheter securement
- Immunodeficiency including uncontrolled diabetes, as defined by HbA1C 7.8% or more (14,15)
- Preoperative advanced liver failure (as defined by Child-Pugh B or C) (16)
- Preoperative advanced renal failure (as defined by eGFR < 30 mL/min/1.73 m^2)

- Opioid tolerance (as defined by morphine oral equivalent >60mg for a period of 7 days or longer pre-operatively) (17)
- Allergy to local anesthetic, acetaminophen, or hydromorphone
- Weight less than 60 kg (18)

Postoperative Exclusion Criteria:

- Postoperative bleeding before randomization as defined by initial chest tube loss of >350 mL, >200 mL per hour loss, > 2 mL/kg/hour loss for 2 consecutive hours, or requiring return to the operating room for surgical management (19)
- Hemodynamic instability, as determined by CSICU attending anesthesiologist
- Anticipated mechanical ventilation of more than 24 hours
- Regional anesthesiologist unavailable to insert PIFB catheter within 4 hours of CSICU arrival

Postoperative exclusion criteria to be checked just prior to randomization.

4. Study Centre

All study procedures will take place at St. Paul's Hospital, Vancouver. There are approximately 1000 annual scheduled cardiac surgeries involving median sternotomies at St. Paul's Hospital, of which approximately 850 involve complete sternotomies, providing sufficient patient population size to conduct this study.

5. Recruitment and Informed Consent

Patients will be identified in the Pre-Assessment Clinic by an anesthesiologist or nurse, who is part of the patient's circle of care. Patients will be asked for permission to be approached by a research assistant regarding the study. If permission is granted, a research assistant will explain the purpose of the study, confirm eligibility and propose enrolment. Some patients may be admitted to St. Paul's Hospital prior to their scheduled cardiac surgery and will not be seen at the Pre-Assessment Clinic. In such cases, an anesthesiologist or ward nurse, who is part of their circle of care, will ask for the patients' permission to be approached by a research assistant instead. During current times, telephone consultation with patients may be utilized. In such cases, patient consents forms will be exchanged securely via approved email accounts (BC Health Authority and affiliated BC University email accounts).

Recruited patients will be informed of the study interventions, the chances of being assigned to one of the two groups, the risks and benefits of participating, and their right to withdraw from the study at any time without adversely affecting their clinical care. If the patient decides that they would like to participate, they will be asked to sign the consent form. The investigators will provide the patient with a copy and will retain the original consent form. It will be emphasized that the patients may not eventually receive PIFB catheters if they meet aforementioned exclusion criteria postoperatively.

Consent will be verified on the day of surgery in surgical day care prior to the operation.

6. Group Allocation and Randomization

Randomization:
Participating patients will be randomly allocated 1:1 to one of two study groups (See Section 3.1 Design). Randomization will be stratified by sex, using permuted block randomization with variable block sizes of 4 or 6. A pharmacist of St. Paul's Hospital, Providence Health Care, who is independent of study patient clinical care, study research team, data collection, or data analysis, will generate a computer-generated sequence using Sealed Envelope Ltd. (20) and integrate the sequence into the centralized, secure, web-based randomization system of Sealed Envelope Ltd. (20) The independent pharmacist will store the computer-generated sequence securely using a password-protected file on hospital network.

Within 4 hours of CSICU admission, or in the cardiac surgery operating room (OR) after skin closure, patients will be checked for postoperative exclusion criteria (See Section 3.2.2 Exclusion Criteria). Eligible patients will be randomized into the study: a study team member will alert the pharmacist, who will assign the patient to the next sequential participant number and corresponding study arm. Pharmacy will send the randomized de-labeled study solution of either ropivacaine 0.2% or normal saline to CSICU or OR.

In case of urgent need for unblinding secondary to suspected local anesthetic systemic toxicity or other concerning symptoms, a hospital pharmacist may be called by cardiac surgeon, anesthesiologist, CSICU physician, acute pain service physician, or cardiac surgery ward nurse practitioner (See Appendix). In such cases, patient will be excluded from main analysis (Population I) but will be analyzed as part of sensitivity analysis (Population II; See Section 12.1 Populations for Analysis).

7 Blinding

This study observes blinding of the patients, anesthesiologists, surgeons, nurses, outcome collectors, and data analysts.

7.1 Patient Blinding

Patients will be informed that they will receive one of two solutions (ropivacaine or saline) for infusion, without disclosing which group they are allocated to.

7.2 Anesthesiologists, Cardiac Surgeon, Nurses, Nurse Practitioners, Acute Pain Service Team

Anesthesiologists, cardiac surgeons, CSICU nurses, ward nurses, nurse practitioners, and acute pain service team will be blinded to assignments.

7.3 Blinding of Assessors

Assessment of patients, data collection, and follow-up will be conducted by team members (i.e. research assistant, anesthesiologist, CSICU nurses, and ward nurses, acute pain service team) who are blinded to group allocation.

7.4 Blinding of Data Analyst

The data analysts will be provided a table with two groups of the unique numbers, but which group corresponds with ropivacaine and which corresponds with normal saline will not be revealed until the data analysis has been fully completed.

8 Patient Management

8.1 Preoperative and Intraoperative Phases:

After the patients have been recruited, the research assistant will educate recruited patients on the use of IV Patient-Controlled Analgesia (IV PCA) and NRS pain scores. Otherwise, preoperative and intraoperative management, including the use of sedatives and analgesics, will be up to the discretion of the anesthesiologist in accordance with standard practice.

8.2 Postoperative Phase and Study Intervention

See usual patient care protocol in CSICU and 5B ward in Appendix.

Block performance:

Within 4 hours of CSICU admission, or in the cardiac surgery OR after skin closure, the patient will be checked for postoperative exclusion criteria. If no exclusion criteria are present, the patient will be randomized as previously described. A member of the regional anesthetic team will be contacted. Each regional anesthetic team member is a staff anesthesiologist or anesthesiology fellow with previous experience performing the PIFB. Randomized solutions (ropivacaine 0.2% or saline) for infusion will be sent to CSICU or OR from pharmacy accordingly.

While the patient remains sedated and intubated, bilateral PIFB catheters will be inserted under ultrasound-guidance. The InfiltraLong 600T (Pajunk, Geizingen, Germany), a 19-gauge, 600 mm multi-orifice catheter (45 orifices in the first 100 mm) will be inserted parasternally using a 17-gauge, 6-inch Tuohy needle. The needle approach will be caudal-to-cranial, 2 centimeters away from the sternal border, extending from T6 to T2.

Up to 5 mL of D5W per side may be given via the Tuohy needle for catheter placement. Time zero is at the single bolus of 20 mL of ropivacaine 0.2% through each catheter. In other words, 20 mL of ropivacaine 0.2% per side will be given through each catheter at time zero. Each catheter will then be connected to a CADD Solis Pump, set at a continuous infusion rate of 3 mL per hour of the study solution. The catheters will be removed after 48 hours.

Multimodal Analgesic Protocol:

All patients will be provided standard post-operative pain control regimen:

1) Acetaminophen 1300 mg PR within 2 hours of admission to CSICU
2) Acetaminophen 650 to 975 mg PO QID regular

3) NSAIDs will not be used in the first 48 hours
4) Prior to extubation or IV PCA initiation (Discontinued with initiation of IV PCA):
   a) Hydromorphone IV 0.2-0.4 mg q5min PRN for pain
5) After extubation with resumption of cognition to utilize IV PCA:

a) Hydromorphone (0.6 mg/mL) IV PCA, set at 0.2 mg bolus (Range: 0.1-0.3 mg, titrated as clinically indicated), 6-minute lockout, and no continuous infusion. 0.3 mg clinician bolus q10min PRN, with maximum 3 clinician boluses per hour.

Patients will be assessed daily by the Acute Pain Service team for PCA management.

9. Outcomes

9.1 Primary Outcome Assessed

The primary outcome is NRS sternal pain score on coughing at 24 hours. Coughing will be elicited with a standardized script for a sitting patient:

"Please use both hands to hold on to the pillow in front of you to hold your chest in. Take a deep breath in, and give me three coughs in a row"

Patient will be considered a reliable reporter if they are able to follow the directions as above and then report an NRS pain score.

9.2 Secondary Outcomes Assessed

1) Cumulative opioid consumption (in IV morphine equivalents) at 24 and 48 hours
2) NRS sternal pain scores from 8th to 48th hour, at rest and with coughing, analyzed using:
   a) Multivariate analysis using mixed models with random subject intercept
   b) Area under the curve (AUC)

3) Nausea or vomiting within 48 hours (Yes/No)
4) Quality of Recovery-15 score at 48 hours
5) Chronic sternal pain (Yes/No) at 3 months postoperatively

10. Assessment

10.1 Outcome Assessment

CSICU nurses will be responsible to assess and record NRS sternal pain scores at rest and on coughing every 8 hours until the 48th hour after time zero. Once the patient has been transferred to the 5B ward from CSICU, the nurses from 5B will record this data until the 48th hour.

At 48 hours, the research assistant will administer patient questionnaire of QoR-15 and ask whether patient experienced nausea or vomiting over the past 48 hours. The research assistant will review the medical record for narcotic usage within 48 hours.

Patients will be followed up by the research assistant via telephone at 3 and 6 months to determine the presence or absence of chronic sternal pain.

10.2 Cohort Characteristic Assessment

Information regarding cohort characteristic will be collected from chart review and questionnaire administration at 48 hours, 3 months, and 6 months.

Baseline information including age, weight, height, BMI, sex, cardiac surgery type, duration of surgery, and ASA classification will be collected. Relevant co-morbidities, including coronary artery disease, valvular disease, congestive heart failure, respiratory conditions such as asthma or COPD, diabetes, and chronic pain presence and score will be recorded. Baseline QoR-15 score, EQ-5D-5L score, and chronic sternal pain presence and score will be collected.

Intraoperative data including duration of surgery, intraoperative analgesic use, and intraoperative nausea and vomiting prophylaxis use will be collected.

Post-operative cohort characteristics and safety data will be collected, including time to extubation, CSICU length of stay, hospital length of stay, delirium within 48 hours, reintubation within 48 hours, emergency re-sternotomy within 48 hours, PIFB catheter removal prior to 48th hour, local anesthetic systemic toxicity, other safety issues with catheter, sternal wound infection, death, chronic sternal pain severity at 3 months and 6 months, and EQ-5D-5L at 48 hours, 3 months, and 6 months.

11 Sample size calculation

The sample size is estimated based on previous finding the mean NRS on coughing at POD1 was 6.45 with a standard deviation (SD) of 2.96 (8). Using 2-sample t-test, a type I error of 0.05 and a type II error of 0.80, and assuming a reduction on NRS at 24 hours of 2.1 to be significant (24) in patients treated with PIFB catheters, 33 patients per group would be required. Preliminary data at our institution demonstrates a 10% risk of severe delirium or altered mental status that preclude primary outcome assessment. Thus, accounting for a 20% attrition rate, 40 per group (n=80 total) would be required. Sample size calculations were conducted using the “pwr” package in R.

12 Analysis plan

12.1 Populations for Analysis

Analysis will be based on the following two populations:

- Population I – All randomized participants under consideration without the following postoperative conditions within 48 hours:
    - Death
    - Emergency re-sternotomy
    - Hemodynamic or respiratory instability necessitating reintubation
    - Suspected or confirmed local anesthetic systemic toxicity leading to interruption of infusion and/or unblinding from randomization
    - PIFB catheter removal
    - Severe delirium, confusion, or altered level of consciousness that precludes patients from utilizing NRS pain scale or follow commands to initiate cough as per standardized script

  This population will serve as the main analysis. Missing data, assumed to be missing at random, will be imputed using multiple imputation technique.

- Population II – All randomized participants under consideration. This population will serve as a sensitivity analysis. Missing data, assumed to be missing at random, will be imputed using multiple imputation technique.

12.2 Primary outcome analysis – NRS pain score on coughing at 24 hours

Descriptive summary will be provided.

Analysis will be performed for the Population I and Population II. Multivariable analysis using *a priori* variables of age (7), sex (21–23), cardiac surgery type (2 categories: harvesting of bilateral internal mammary arteries or not) (24), preoperative chronic pain (25), and postoperative cumulative opioid consumption as covariates will be used to assess the difference in NRS pain score on coughing at 24 hours between the two arms. The choice of the model will be guided by the distribution of the outcome.

12.3 Secondary outcome analyses

Similarly, all analyses of secondary outcomes will be performed for Population I and Population II.

1. Cumulative opioid consumptions at 24 and 48 hours will be compared using t-tests or Mann-Whitney U test, as appropriate, after applying the Shapiro-Wilk test as a confirmation of normality.

2. Quality of Recovery-15 scores at 48 hours will be compared using t-tests or Mann-Whitney U test, as appropriate, after applying the Shapiro-Wilk test as a confirmation of normality.
3. Postoperative nausea or vomiting within 48 hours (Yes/No) will be compared using Chi-squared test or Fisher's Exact Test, as appropriate.
4. Chronic sternal pain at 3 months will be compared using Chi-squared test or Fisher's Exact Test, as appropriate.
5. For NRS pain scores at all time points from 8 to 48 hours:
    a. Multivariate analysis using mixed models with random subject intercept will be performed. *A priori* variables of age (7), sex **(21–23)**, cardiac surgery type (2 categories: harvesting of bilateral internal mammary arteries or not) (24), preoperative chronic pain (25), and postoperative cumulative opioid consumption will be utilized as covariates and the interaction term between the time point and treatment arm will be included in the model to assess the difference in pain score between the two arms at each timepoint and overall. The choice of the model will be guided by the distribution of the outcome.
    b. Mixed model AUC summary statistics will also be computed. (26) The difference in AUC summary statistics between the two arm and its 95% confidence interval estimated via bootstrap method will be derived.

12.4 Plan for Missing data

For all outcome analyses for both Population I and Population II, multiple imputation procedure (MI and MIANALYZE in SAS or MICE package in R) will be used to impute missing data, which are assumed to be missing at random. Depending on the distribution of the final data, the outcomes will be multiply imputed using the MCMC or fully conditional specification method as appropriate. *A priori* variables to be included in the imputation model are age (7), sex (21–23), cardiac surgery type (2 categories: harvesting of bilateral internal mammary arteries or not) (24), preoperative chronic pain (25), postoperative cumulative opioid consumption, postoperative nausea or vomiting (Yes/No), chronic sternal pain incidence at 3 months postoperatively (25), pain scores from 8 to 48 hours, and QoR-15 scores at 48 hours.

There are no plans for an interim analysis due to the relatively small sample size. Data will be analyzed using SAS 9.4 and/or RStudio (ver. 1.3.1093).

13 Feasibility

The study centers perform an average of 1000 annual scheduled cardiac surgeries involving midline sternotomy, of which 850 involve complete median sternotomies. Assuming 75% of those are eligible for the study, 20% approve the study, and assuming 50% of approved patients get randomized due to logistical issues, 64 patients can theoretically be recruited annually. As such, the entire study can be completed within 1.5 years.

14 Confidentiality

All printed study data will be kept in a locked file cabinet in the St. Paul's anesthesia office, accessible only to research personnel; all digital study data will be kept on encrypted USB key or Research Electronic Data Capture (REDCap; REDCap Consortium, Vanderbilt University, Nashville, TN, USA) REDCap. Patients will be assigned study ID numbers to maintain confidentiality during data entry and analysis. Any presentation or publication of research results will be done using aggregate data with no identifiable patient information.

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Figure 1. Innervation to the Sternum (Reprinted with permission from Liu et al.)

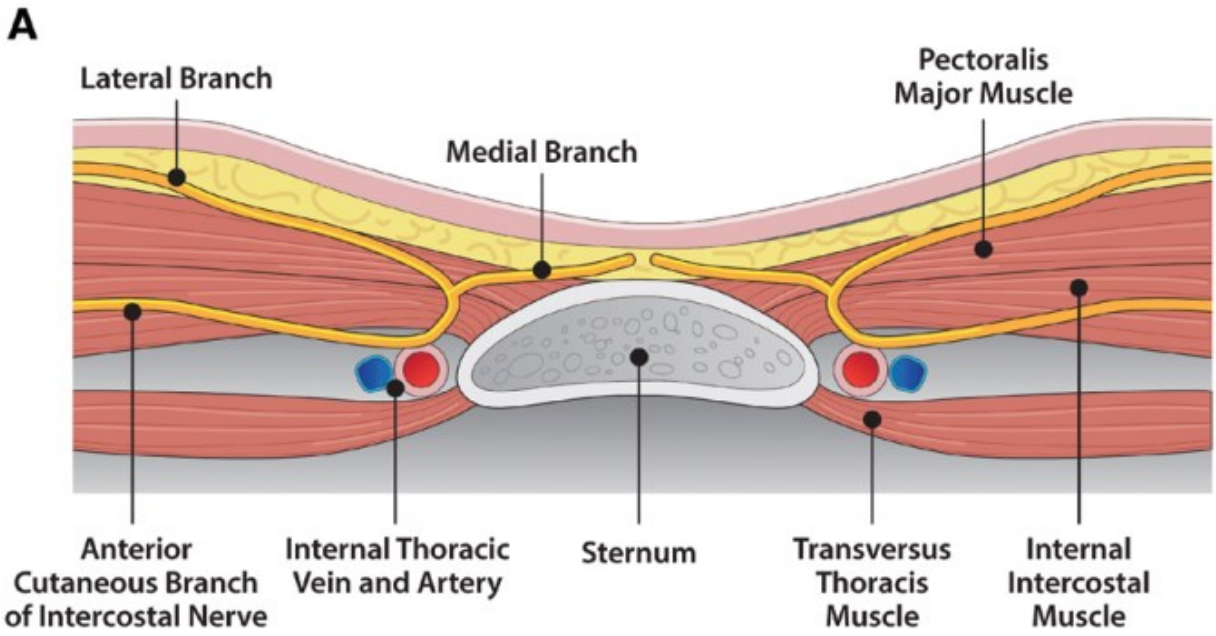
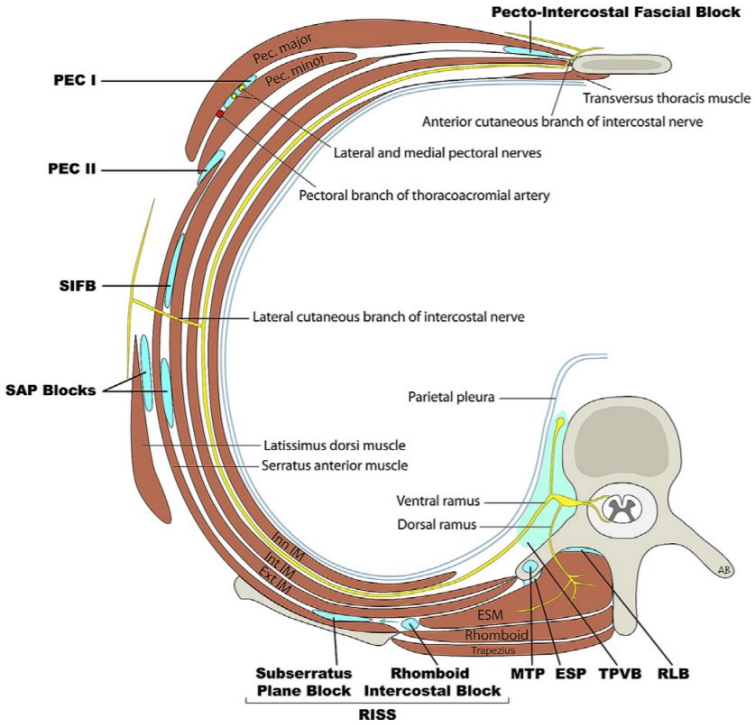


Figure 2. Possible areas of nerve blockade for post-sternotomy pain



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Appendix. Postoperative Management at CSICU and 5B

Standard post-operative management on CSICU:
- Continuous monitoring of invasive blood pressure, central venous pressure, heart rate, ECG, ETCO2, SpO2 and respiratory rate
- Regular monitoring of temperature, Richmond Agitation Sedation Scale (RASS), Behavioural Pain Scale (BPS), peripheral pulses, and pupillary status
- Hourly fluid input and output (urine and chest tube losses)
- Ventilatory support with appropriate tidal volumes and SpO2 target >92%
- Inotropic/vasopressor support at the discretion of the attending Anesthesiologist
- Maintenance of sedation with propofol or dexmedetomidine
- Correction of anemia, coagulopathy and electrolyte abnormalities at discretion of attending Anesthesiologist
- Management of nausea with antiemetics as per existing protocol

Extubation criteria:
- Stable respiratory and hemodynamic status
- Intact airway reflexes and effective cough
- Richmond Agitation-Sedation Scale (RASS) score ≤ +1 and Behavioural Pain Scale (BPS) score ≤ 6
- Absence of pulmonary pathology on Chest X-ray (CXR)
- Normothermia

Chest tube removal criteria:
- Chest tubes in-situ for 6-8 hours and drainage less than 100ml in past 4 hours
- No evidence of air leak
- Stable respiratory and hemodynamic status
- Weaned from mechanical ventilation
- Coagulation studies within normal limits

Criteria to transfer to 5B ward from CSICU:
- Stable, unsupported hemodynamic status
- Stable respiratory status on no/minimal oxygen therapy
- At least 4 hours after extubation, 1 hour after CVC/arterial line removal, 1 hour after first beta blocker dose
- Protected airway
- Incision intact and sternum stable
- Adequate urine output
- Pain controlled

Postoperative management will otherwise be at the discretion of attending CSICU intensivist or cardiac surgeon without influence from this study.

Nursing staff will be directed by a detailed protocol to identify any symptoms of local anesthetic systemic toxicity (ie. perioral numbness, tinnitus, visual and auditory disturbance, twitching/tremors, seizures, apnea, arrhythmia, cardiovascular collapse). If

such symptoms were noted, the CSICU intensivist will be alerted. If blinding needs to be broken in case of suspected local anesthetic systemic toxicity or other concerning symptoms, pharmacy will be called for unblinding.