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Thoracentesis In Cardiac Surgery Patients With Non-Specific Pleural Effusion: A Case-Control Study

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THORACENTESIS IN CARDIAC SURGERY PATIENTS WITH NON-SPECIFIC PLEURAL EFFUSION: A CASE-CONTROL STUDY

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1 Abstract

THORACENTESIS IN CARDIAC SURGERY PATIENTS WITH NON-SPECIFIC PLEURAL EFFUSION: A CASE-CONTROL STUDY

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Non-specific pleural effusion is common in patients after cardiac surgery. Thoracentesis for non-specific pleural effusion is being used more frequently with informal observations of improved dyspnea, shorter length of inpatient stay (LOS), reduced need for escalation of care, and less postoperative atrial fibrillation (AF). Our hypothesis is that the majority of cardiac surgery patients who undergo thoracentesis for non-specific pleural effusion have improvements in dyspnea, reduced days in AF, and reduced escalation of care compared to similar patients who do not have procedural intervention.

Our study population includes patients with evidence of pleural effusion on chest x-ray during a period postoperative day (POD) 3 – 7, after cardiac surgery performed by a single surgeon at Yale - New Haven Hospital, between Jan. 2013 and Dec. 2014. We have conducted a retrospective Case – Control Study (n = 30, 15/15). Cases are defined as having thoracentesis POD3 – POD7 and are matched by age and cardiac operation to Controls. We have recorded the frequency of improved dyspnea, as defined by ≥2 LPM reduction of daily peak O2 supplementation, after thoracentesis for Cases and compared this to the same period for matched Controls. Postoperative LOS, incidence of AF, and requirement for escalation of care are recorded and compared between Cases and Controls.

Dyspnea improved for 73% of Cases but this was not significantly different compared to Controls during matched periods (11 vs. 7 patients, OR = 3.1, p = 0.14). Length of stay was not different between Cases and Controls (6.7 vs. 5.8 days, p = 0.84) and there was no escalation of care required in either group (95% CI, 0.00 – 0.14). There was no difference in the odds of postoperative AF between Cases and Controls (OR = 0.22, p = 0.13). Patients who had thoracentesis performed before POD5 significantly lower incidence of postoperative AF (0 vs. 6 patients, p = 0.01).

We have concluded that the majority of patients have improvement in dyspnea after thoracentesis for non-specific pleural effusion after cardiac surgery. We observed that this improvement is not significantly different than that experienced by similar control patients. Thoracentesis did not decrease length of stay. Patients might experience fewer days in AF with thoracentesis when performed before POD5. Preoperative risk factors for postoperative AF were not evaluated, could have introduced selection bias for Cases, and therefore, limits this result.

2 Acknowledgements

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3 Introduction

3.1 Non-Specific Pleural Effusion in Cardiac Surgery Patients

Indications for Cardiac Surgery include some of the most common diseases in the United States: including coronary artery disease, valvular heart disease, and other structural heart disease. Coronary Artery Bypass Graft (CABG) for patients with coronary artery disease is one of the most common cardiac surgical procedures and accounts for approximately 400,000 hospital discharges per year in the United States[1]. Aortic Valve Repair (AVR) accounts for an additional 200,000 discharges in the United States annually[2]. Limiting postoperative conditions that can prolong recovery after cardiac surgery has importance in patient health and resource utilization.

Pleural effusions are often observed after uncomplicated cardiac surgery[3, 4]. It is estimated that about half of patients undergoing cardiac surgery will have a postoperative pleural effusion about a week after surgery[5]. The majority of these are small; characterized as blunting of the costophrenic angles with less than 25% of the hemithorax occupied by pleural fluid[5]. The general course of a postoperative pleural effusion has been described as bilateral initial appearance, unilateral (usually left-sided) maintenance at one-week, with spontaneous resolution over time[3, 5, 6]. Such pleural effusions are generally considered "*non-specific*" and thought not to require procedural intervention[7]. More recently, we have seen a limited management paradigm shift toward procedural intervention [e.g. thoracentesis] for non-specific pleural effusion at our institution.

3.2 Clinical Experience with Thoracentesis for Non-Specific Pleural Effusion

Non-specific pleural effusions are a frequent and clinically acceptable observation in patients following cardiac surgery at Yale - New Haven Hospital. Approximately 2-years-ago, our Cardiac Surgery service began to pursue thoracentesis for an escalating number of patients with non-specific pleural effusion. This change in practice stemmed from the clinical observation that a subset of patients with limited pulmonary reserve benefitted from removal of even small volumes of pleural fluid. The utility of thoracentesis has never been formally studied in this population despite its increasing use at Yale – New Haven Hospital.

Mid-level providers from our Cardiac Surgery service have made informal observations of several benefits with use of thoracentesis for non-specific pleural effusion. First, it is thought that patients with limited pulmonary reserve and non-specific pleural effusion have improved dyspnea after thoracentesis versus those who do not have procedural intervention. An interrelated observation is shorter hospital length of stay. This has been attributed to improved dyspnea leading to better participation in inpatient cardiac rehabilitation. Second, it has been informally noted that patients have fewer days of postoperative AF after thoracentesis versus those with effusions who do not have procedural intervention. This observation is said to occur in the setting of similar anti-arrhythmic dosing for all patients with postoperative AF. It is thought that decreased frequency of AF also shortens patient length of stay. Lastly, our mid-level providers have reported that the requirement for escalation of care [e.g. transfer to a unit providing a higher intensity of care] is less frequent in patients who have thoracentesis for pleural effusion versus those who have not.

In order to better understand and characterize these observations, there are three questions that might be addressed. First, how do non-specific pleural effusions develop after cardiac surgery? Second, how might thoracentesis improve pulmonary dysfunction in these patients? Third, is there formal retrospective evidence to support the claims of benefit at our institution? To address these, a comprehensive review of the clinical literature is performed and summarized. The basic science literature is also reviewed and a model for the pathogenesis of non-specific pleural effusion is proposed. Lastly, we will perform a retrospective clinical study comparing outcomes of patients who had thoracentesis and patients who did not have procedural intervention for non-specific pleural effusion after cardiac surgery.

3.3 Pulmonary Dysfunction and Recovery from Cardiac Surgery

Pleural effusion is one of several pulmonary complications with a potential to prolong recovery after cardiac surgery[8]. In general, patients tend to have decreased respiratory function due to restrictive lung changes following cardiac surgery[9]. Impaired chest wall mechanics seem to play a significant role in restriction[9]. In a study of 18 cardiac surgery patients with normal preoperative pulmonary function

testing (PFT) by Van Belle, *et al*; total lung capacity (TLC), 1-second forced expiratory volume (FEV1), and functional residual capacity (FRC) were significantly impaired a week after surgery [(6.2 vs. 4.6L; $p < 0.0001$), (3.4 vs. 2.4L; $p < 0.0001$), (3.2 vs. 2.6L; $p < 0.001$) respectively][10]. The same study reported significantly negative frequency dependent resistance by body-plethysmography, indicating an additional component of airway obstruction[10]. The authors suggested that, in addition to impaired chest wall mechanics, extravascular lung fluid and atelectasis likely play roles in decreased respiratory function[10].

The restrictive changes in ventilation associated with pleural effusion are generally proportional to the size of the effusion[11, 12]. Perhaps the reason why *non-specific* pleural effusions are thought not to require intervention is that they are characterized as small and have a tendency to spontaneously resolve. But this generalization may be misleading in terms of predicting postoperative course after cardiac surgery. In a large study of 2,892 patients by Labidi, *et al*, 192 patients (7%) were found to have "significant" pleural effusions after cardiac surgery[4]. The term "significant" was not well defined and although the majority had symptoms, not all patients were described as symptomatic[4]. Of the symptoms reported, 70% had shortness of breath, 56% had cough, 48% had bronchial secretions, 34% were tachypneic, and 23% had chest pain[4]. In this series, more than half of patients had small effusions occupying less than 25% of the hemithorax and 21% required multiple interventions[4]. The symptomology of small pleural effusions tends to be similar to larger effusions. In a 29-case series of effusion occupying more than 25% of the hemithorax by Rodriguez and Light, *et al*, 76% of patients with a large effusion complained of shortness of breath, 10% complained of chest pain, and 3% complained of fever at 30-days[5, 13]. These studies suggest that size is not proportional to symptoms.

Symptoms of pulmonary dysfunction after cardiac surgery are known to prolong hospital stay and increase costs of care[8]. Pleural effusion has been shown as an independent risk factor for prolonged recovery after cardiac surgery[3-6, 13, 14]. Labidi, *et al*, reported both longer ICU stay (142 ± 643 hrs versus 35 ± 565 hrs; $p < 0.05$) and longer hospital stay (16.2 ± 20.9 versus 7.5 ± 8.6 days; $p < 0.001$) for 192 patients with pleural effusion requiring thoracentesis after cardiac surgery[4]. This same study reported that the majority of patients had small pleural effusions occupying less than 25% of the

hemithorax[4]. These data suggest that non-specific [e.g. small] pleural effusions may also be associated with longer periods of stay and a higher intensity of care in the postoperative period.

3.4 Preoperative Risk Factors for Pleural Effusion

There is limited data on preoperative risk factors associated with pleural effusion after cardiac surgery[4, 15]. In a study of 2,892 cardiac surgery patients by Labidi, *et al*, postoperative pleural effusion was more prevalent in patients with comorbid diagnoses of congestive heart failure (9% vs. 4%), peripheral vascular disease (22% vs. 11%) and atrial fibrillation (10% vs. 5%) versus those without effusion[4]. In terms of heart failure, the preoperative ejection fractions (EF) for patients in the effusion group were clinically similar (56% vs. 59%)[4]. The number of patients with an EF less than 40% was also slightly higher in the effusion group (14% vs. 8%)[4]. Diuretics, anticoagulants, anti-platelet agents, and anti-arrhythmic agents were also associated with pleural effusion in the Labidi study[4]. Whether preoperative conditions or their management is more associated with developing postoperative pleural effusion remains unclear.

However, Jensen and Yang found no association between preoperative heart failure and postoperative pleural effusion in a retrospective study of 315 CABG patients[15]. Atrial fibrillation and peripheral vascular disease were not among diagnoses investigated in this study[15]. From a more practical standpoint, the attributable risks for postoperative pleural effusion in terms of the comorbidities studied are low in both studies[4, 15]. The number of patients included in the Labidi study was an order of magnitude larger than the Jensen study, which may have been why they had more statistically significant differences[4, 15]. One criticism that we find with the Labidi study is the number of comparisons made without correction for the family-wise error rate. Perhaps using a Bonferroni or other corrective method would have reduced the number of significant differences. If there were a causal relationship between preoperative comorbidities and postoperative pleural effusion, the attributable risks are small in the best studies available.

3.5 Intraoperative Risk Factors for Pleural Effusion

3.5.1 Topical Hypothermia

Topical hypothermia is thought to provide a cardio-protective benefit during surgery but it is now used less frequently due to concern over pulmonary complications[16-19]. Myocardial hypothermia decreases cellular metabolism, prevents cellular damage from anoxia, and reduces the rigidity of contraction[16]. A study by Allen, *et al*, of 150 nonrandomized consecutive patients showed that topical hypothermia with ice-slush versus no cooling was associated with an increase in postoperative pleural effusion prior to discharge (RR = 2.8, $p < 0.05$)[17]. The ice-slush technique also was associated with increased length of stay (11.2 vs. 8.5 days; $p < 0.05$)[17]. Intraoperative ice-slush was also associated with postoperative pleural effusion in a study of 505 nonrandomized consecutive patients by Nikas, *et al* (RR = 2.4, $p < 0.0001$)[18]. These patients also received concurrent systemic hypothermia and cold cardioplegia[18]. Authors in both studies concluded that phrenic nerve dysfunction results in atelectasis which then leads to pleural effusion[17, 18]. Intraoperative stretch injury was also proposed as a mechanism for phrenic nerve dysfunction by these authors as a similar cause of atelectasis and subsequent pleural effusion[19, 20].

Pleural effusion in patients with true diaphragm paralysis (e.g. myasthenia gravis) has been demonstrated in ICU patients[21]. How this exactly occurs has also not been fully described. One explanation is that elevation of the hemi-diaphragm by elastic recoil of local lung segments attached to the visceral pleura may increase negative pressure in the adjacent pleural space[22]. Mechanically increasing negative pressure in the pleural space would potentiate the hydrostatic driving force for fluid filtration[23]. If filtration exceeds drainage, pleural effusion results. An alternative explanation might be ventilation/perfusion changes in collapsed lung segments leading to localized hypoxemia and lung edema. The ensuing inflammatory response may increase the permeability of the visceral pleura[23, 24]. This would lead to a functional connection between lung and pleural compartments not present in the normal physiologic state[23]. Rising interstitial fluid pressure in the lung would first cause alveolar collapse (e.g. atelectasis). At a certain threshold based on the relative permeability of the visceral pleura, fluid will

overflow causing increased fluid filtration into the pleural space[23]. If fluid filtration overwhelms lymphatic drainage of the pleural space, effusion will develop.

One point of contention for the topical hypothermia data is whether or not phrenic nerve dysfunction is present at all[25]. In a study by Wilcox, *et al*, 93% of 52 postoperative patients receiving topical hypothermia developed left lung atelectasis but less than 10% were found to have unequivocal phrenic nerve dysfunction in the early postoperative period[25]. Multivariate analysis of intraoperative factors showed that number of grafts, operative time, bypass time, opening of the pleura, non-use of a right atrial drain, non-use of a polystyrene shield, and body temperature were predictive for the degree of left lower lobe atelectasis[25]. If there is no disruption of phrenic nerve function but atelectasis and pleural effusion still occurs, then another mechanism is implicated.

Inflammation might better explain both the development of atelectasis and it's relationship with pleural effusion. Although the association between topical hypothermia, atelectasis, and pleural effusion is strong, its interdependence on diaphragm paralysis is less convincing. Cardiopulmonary bypass, aortic cross-clamp time, and positive end expiratory pressure during postoperative mechanical ventilation are also associated with lung injury and inflammatory changes[26, 27]. Similarly, these risk factors are associated with atelectasis and pleural effusion[26, 27]. Exactly how lung injury would be potentiated by topical hypothermia is unclear. It is possible that the use of topical hypothermia might be a confounder for factors that are also strongly associated with pleural effusion. In fact, the Nikas study found that cross-clamp time was elevated (49 vs. 43 min) for those receiving topic hypothermia[18]. The routine use of topical hypothermia is no longer standard of care due, in part, to its relationship with pulmonary complications. However, reexamining these data has been valuable in understanding the plausibility of lung inflammation as part of the pathogenesis of pleural effusion.

3.5.2 Cardiopulmonary Bypass

Another intraoperative risk factor associated with pleural effusion is cardiopulmonary bypass (CPB)[8]. Volume overload in the setting of CPB has been thought an obvious iatrogenic insult because: a)

patients receive an average of 3-4L of crystalloid and colloid fluids during cardiac surgery; b) patients can present with some degree of preoperative fluid overload in the setting of heart failure; c) comorbid renal disease is a common presentation for these patients; and d) pleural effusion is common after cardiac surgery[4, 9, 28, 29]. Pulmonary edema is also associated with CPB[8, 30-33]. It has been suggested that the pathogenesis of pulmonary edema and pleural effusion may be interrelated.[8].

Intravascular hydrostatic forces associated with volume overload may cause both pulmonary edema and pleural effusion[34]. The lung and pleural spaces are separate compartments in the normal physiologic state[23]. In volume overload, elevated pulmonary capillary pressure can exceed osmotic counter pressure in the lung interstitium[34]. This drives fluid into the lung interstitium. Under normal circumstances, lymphatic drainage functions as a recruitable homeostatic mechanism for recovery[23]. Fluid accumulates when the lymphatic reserve capacity to clear fluid from the lung interstitium is overwhelmed[23, 34]. Pulmonary edema can occur rapidly because the lung compartment is relatively non-compliant[23]. The pleural space accumulates fluid by a similar mechanism[34]. Pulmonary and central venous pressures are elevated in the setting of volume overload and this increases the filtration rate of pleural fluid[23]. When the osmotic counter pressure and lymphatic clearance reserves are overwhelmed, pleural effusion results[34].

Volume overload may only be part of a more complete explanation for pleural effusion after cardiac surgery. In a study of 10 patients by Hachenberg, *et al*, intra-thoracic thoracic blood volume (ITBV), pulmonary blood volume (PBV), and extravascular lung water (EVLW) were found to be elevated immediately following separation from CPB[29]. However, at 4-hrs and 24-hours after separation, ITBV and PBV remained elevated while EVLW decreased to preoperative levels[29]. The authors concluded that postoperative hypoxemia resulting from fluid overload was not due to pulmonary edema and that homeostatic mechanisms were maintained after CPB[29]. Both the lung and pleural compartments restore homeostatic fluid balance through recruitment of the lymphatic system[23]. If the homeostatic mechanism for recovery from pulmonary edema is maintained, it is reasonable to assume that this is also maintained in the pleural space [e.g. the lymphatics are not interrupted].

How pleural effusion still develops if there is relative capacity for fluid clearance requires further consideration. The observation that EVLW is reduced within 4-hours of separation from CPB (detailed above) might represent evidence for a non-physiologic lung compartment drainage mechanism that is not recruitable by the pleural compartment[29]. One explanation proposed in chronic heart failure models is that there is a pathophysiologic connection developing between the lung and pleural compartments [e.g. the relative permeability of the visceral pleura increases][23]. By this mechanism, EVLW would be reduced as pleural fluid filtration increases. Wiener-Kronish, *et al*, demonstrated that lung edema induced by inflammatory lung injury resolves by drainage into the pleural space through the visceral pleura in sheep[35, 36]. Another explanation may be that the lymphatics of the pleural space are selectively interrupted by an IMA takedown. However, there is no evidence to suggest that pleural effusion lateralizes to the side of IMA takedown[37].

Inflammatory changes in the lung have been proposed to increase the permeability of the visceral pleura[23, 35, 36]. Acute systemic inflammation and lung inflammation have been shown a consequence of CPB[30-33]. Intubation with positive pressure ventilation is another source of inflammation and pulmonary dysfunction[38]. The Alveolar-arterial (A-a) gradient is more severe after CPB than general surgical procedures, which suggests a higher degree of lung injury and shunt fraction after CPB[39]. The presence of inflammatory mediators in bronchoalveolar lavage (BAL) fluids after separation from CPB also supports local lung inflammation[26]. Markers of systemic inflammation including compliment activation and leukocyte activation have been shown in patients during and immediately after separation from CPB[40, 41]. The compelling evidence for the association between CPB, lung, and systemic inflammatory changes makes it a more reasonable explanation for the contribution of volume overload to pleural effusion.

3.5.3 Surgical Trauma and Pleurotomy

Direct surgical trauma to the pleura has also been identified as a risk factor for postoperative pleural effusion. Patients who undergo CABG using left internal mammary artery (LIMA) grafting versus

saphenous vein grafting (SVG) techniques have been shown to be at greater risk for pleural injury[42-44]. The risk of opening the pleura is higher during IMA takedowns and therefore, it has been identified as an iatrogenic source of pleurotomy[42].

In a study comparing 200 patients by Hurlbut, *et al*, a significantly larger proportion of patients having undergone LIMA takedown manifested pleural effusion on POD6 versus those who had a saphenous vein graft (84% vs. 47%, $p < 0.05$)[42]. Among symptomatic patients, the amount of fluid removed was also larger (1,413 vs. 1,028 mL; $p < 0.01$) and this group had a significantly higher requirement for re-intervention with thoracentesis (4% vs. 0%, p = NR)[42]. There was no difference in atelectasis between the two groups at various perioperative time intervals[42]. Shielding of the myocardium with a cooling jacket and use of a phrenic nerve shield was employed to avoid myocardial damage and avoid postoperative phrenic nerve associated atelectasis[42]. Another study by Jain, *et al*, of 152 patients showed similar results for development of postoperative pleural effusion in LIMA versus SVG techniques (55% vs. 35%, $p < 0.05$)[44]. A third prospective study by Ali, *et al*, of 280 nonrandomized patients showed a significantly higher number of POD3 pleural effusions for LIMA takedown patients where the pleura were surgically violated, versus those in whom the pleura was left intact (5% vs. 20%, $p < 0.05$)[43]. However, in another study of 30 patients, Vargas, *et al*, found no association between surgical violation of the pleura and the development of pleural effusion[14]. One consideration for this finding might be the relatively few patients studied.

There is further cytological evidence for pleural violation as a risk factor for the development of postoperative effusion in CABG patients. In a study of pleural fluid from symptomatic patients post-CABG with IMA takedowns, Sadikot, *et al,* observed a mean red blood cell count of 706 X 10^{12}/L, corresponding to a hematocrit of approximately 5%[37]. Further support for the finding of bloody effusion was described in Labidi's study for symptomatic effusion patients prior to POD15[4]. The type of surgical procedure was not reported for those patients in whom pleural fluid was analyzed and no reference is made as to what proportion had violation of their pleura[4]. A hemothorax is defined as a pleural effusion with a hematocrit of >50% of the blood hematocrit[45, 46]. If the approximate observed hematocrit in these

patients is around 5%, we can assume that there is an additional source of fluid effusion. Sadikot observed early pleural effusions as exudative by Light's Criteria with an approximate hematocrit of 5%[37]. Therefore, it would be reasonable to think that there is another process causing dilution. It is yet unknown exactly how this occurs, whether at the site of pleurotomy or by another mechanism such as increased pleural fluid filtration.

From the current clinical literature, we can speculate that the major contributing etiologies for pleural effusion after cardiac surgery are intraoperative in nature. These etiologies are CPB and pleurotomy. Preoperative risk factors, if contributory, seem to have a small attributable risk. The broader mechanism for the contribution of CPB to pleural effusion is volume overload in the setting of an inflammatory response to lung injury. Pleurotomy is also a potential modifying effect for developing pleural effusion whereby pleural injury and bleeding result in increased fluid filtration into the pleural space. The common pathogenesis for pleural effusion from these risk factors suggests interrelated lung and pleural inflammation. A review of the current basic science research hereafter details evidence that elaborates this further. This evidence is summarized into a more comprehensive model for the inflammatory pathogenesis of pleural effusion after cardiac surgery. A comprehensive understanding of the pathogenesis for pleural effusion after cardiac surgery would be useful in evaluating therapies to address this condition, including thoracentesis.

3.6 Pathogenesis for Non-Specific Pleural Effusion after Cardiac Surgery

Inflammatory processes are the underlying basis for many physiologic and pathologic processes[47]. Given the proximity of the serous pleural layers to local the microcirculation, experts speculate that the number of immune cells normally present in the pleural space represent an ongoing physiologic inflammatory process[24]. There is general agreement that the pathologic processes that underpin most etiologies of pleural effusion [e.g. parapneumonic, asbestosis, etc.] are inflammatory in nature[24]. Cytologic characterizations of inflammation have already been described for several conditions[24]. These include complicated parapneumonic effusion/empyema, tuberculosis, asbestosis, pleurisy, malignant mesothelioma, metastatic carcinomatosis, and pleurodesis[24]. The inflammatory

processes associated with *non-specific* pleural effusion after cardiac surgery has not yet been fully described. Based on the current literature, we can build a broad framework of pleural inflammation for effusion in this clinical setting.

3.6.1 Inflammation: Physiologic Response and Pathologic Consequences

Medzhitov's 2008 Nature Review Article frames inflammation in terms of inflammatory triggers that lead to a purposeful physiologic response[47]. These physiologic responses are generalized. In some circumstances they can have consequences that result in pathology[47]. One example is tissue injury leading to inflammation as a tissue repair response[47]. The consequences of this response that are occasionally observed are fibrosis, metaplasia, or sometimes neoplasia[47]. Another example is physiologic tissue stress or malfunction that leads to inflammation as an adaptation to stress and restoration of a homeostatic state[47]. Occasionally, clinicians observe shifts in the original homeostatic set points, diseases of homeostasis [e.g. insulin insensitivity/DM2], or autoimmune diseases[47].

According to Medzhitov's framework, large ranges of mediators that form complex regulatory networks would coordinate inflammatory responses[47]. One approach to understanding these complex networks is to break them down into individual processes characterized by inducers, sensors, mediators, and effectors[47]. As an inciting signal, endogenous inducers [e.g. surgically altered tissues, edema] would require a sensing mechanism to propagate a response[47]. Modulation of sensors can lead to expression and/or de-sequestration of mediators that ultimately act on effectors[47]. Mediators can be cell derived, tissue derived, plasma derived or derived from the extracellular matrix (ECM) [47]. Effectors can also be cells, tissues, plasma, or the ECM[47]. A process associated with an inflammatory response can simultaneously interact with other sub-routines as a network[47]. Further, processes can interact in series as part of an ongoing response[47]. These interactions are thought to be governed by the balance between pro- and anti-inflammatory signals[47]. In so much as pro-inflammatory signals can lead to physiologic responses such as tissue repair and alterations in homeostasis, anti-inflammatory signals have the potential to lead to resolution of inflammation or return to physiologic homeostatic set points[47].

3.6.2 Lung Injury, Inflammation and Non-Specific Pleural Effusion

Pleurotomy is a traumatic inflammatory trigger for pleural repair. The most obvious inducer to be considered is the surgically induced epithelial-mesenchymal interaction[47]. Epithelial cells are physiologically separated from mesenchymal cells by a basement membrane[47]. The sensors associated with connecting these two tissue layers are poorly characterized. However, some evidence supports pleural tissue macrophages (pMϕ) as having a large role in coordinating the inflammatory response[48]. pMϕ have been shown to produce significant quantities of the chemokine mediators interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) in murine pleurisy models[49]. IL-1β and TNF-α were further shown to induce mesothelial cells to produce the mediators macrophage chemo-attractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), MIP-2, KC and IL-8[48]. These chemokine mediators are known to recruit effector polymorphonuclear neutrophils (PMNs) to damaged tissues from the plasma pool[48].

Volume overload in the setting of CPB may cause increased fluid filtration into the pleural space[28]. Increased visceral pleura permeability in the setting of lung injury may potentiate this effect. Massoudy, *et al*, demonstrated the lung as an ongoing site of platelet sequestration, retention of activated PMNs, and production of cytokines (IL-6, IL-8)[30]. They were able to assess this through right atrial (RA) and pulmonary vein (PV) sampling before and after pulmonary passage [e.g. removal of cross clamp during CPB[30]. Sampling of BAL fluid after separation from CPB also supports the presence of these cytokines in increased concentration compared to plasma[26]. Retention of leukocytes in the pulmonary vasculature following pulmonary passage, combined with elevated cytokines, indicates that exposure of the sub-endothelial ECM is one potential inducer. Factor XII senses vascular endothelial damage through activation; this occurs through contact with collagen and the ECM[47]. Activated factor XII initiates the four proteolytic cascades known to generate the acute phase response[47]. The tunica media of blood vessels secretes IL-6 as a pro-inflammatory cytokine in response to endothelial damage[50].

The increased levels of IL-6 shown in the Massoudy study are of some interest[30]. Endothelial cells are important effectors for IL-6/sIL-6α (soluble IL-6) in that they increase expression of intracellular adhesion molecule 1 (ICAM-1)[51]. ICAM-1 expression enables endothelial cell regulation of leukocyte

recruitment[51]. Additionally, IL-6 promotes the redistribution of VE-cadherin on endothelial cells[51]. This redistribution increases vascular permeability[51]. Moreover, the role of IL-6 is actively being studied for its contribution to the progression of malignant ascites in ovarian cancer and its effect on peritoneal permeability[51]. This interaction may be an important promoter of capillary leakage, pulmonary edema, and permeability of the visceral pleura. The net result would be pleural effusion with extravasation of PMNs into the pleural space.

The recruitment of PMNs to the pleural space after trauma is an evolutionary response with pathologic consequences in the perioperative setting. In contrast to surgical intervention, penetrating trauma to the pleura (or lung) outside of a hospital is usually accompanied by inoculation with bacteria[50]. The normal physiologic immune response is to control infection after trauma[50]. PMNs function as effectors by de-granulation; specifically, they release cytotoxic and histotoxic substances as a means of bactericide[50]. This endogenous insult propagates serosal inflammation and a high degree of metabolic activity by mesothelial cells[52, 53]. Loosening of tight and gap junctions along the vascular endothelium potentiates the migration of circulating Mϕ cells into the pleural space. This increased permeability also increases filtration of fluid into the pleural space. Once in the pleural space, PMNs do not return to the blood stream[49]. These cells will undergo apoptosis and their remnants removed by Mϕ phagocytosis over time[49]. In this framing, PMN degranulation and apoptosis become mediators for mesothelial effector cells. Continuous stimulation of mesothelial cells and leukocyte migration likely potentiates the maintenance of pleural effusion.

Cytological profiles for pleural fluid that are consistent with our inflammatory model have been described for patients after cardiac surgery[37]. Sadikot, *et al,* have shown significant differences to exist between pleural fluids evacuated from patients during early and late periods post CABG[37]. Early effusions (<30 days) have greater levels of neutrophils versus late effusions (0.242 vs. 0.8 X 10^9/L), which supports an early PMN response[37]. Late effusions have lymphocyte predominance (0.68 vs. 0.125 X 10^9/L, $p<0.001$). The later finding supports a humeral response[37, 49]. These clinical observations suggest that there are both acute phase and humeral responses that involve the pleural space.

The complete mechanism of *resolution* of pleural effusion after cardiac surgery is currently unknown. The metabolic profiles of mesothelial cells during effusion suggest these cells play a role in recruitment of circulating Mϕ cells[52, 53]. Recruited circulating Mϕ cells are typically responsible for phagocytic removal for apoptotic PMNs (so called, efferocytosis); but this has not been fully elucidated for the pleural space. Study of rat pleurisy models by Muria, *et al*, has suggested that PMNs have an extended life in the pleural space and apoptotic activity begins very shortly after recruitment to the pleural space[49]. In small animal models of pleural injury, it has also been demonstrated that activated *tissue* Mϕ cells migrate from the pleural space to regional lymph nodes to potentiate a humeral immune response[49]. Therefore, reducing stimulation of tissue Mϕ by leukocytes in the pleural space *may* reduce the persistence of effusion and blunt the development of a humeral response.

Our interpretation of the literature is that the pathogenesis of non-specific pleural effusion after cardiac surgery is interrelated lung and pleural acute phase inflammation that can evolve into a humeral response. The presence of apoptotic neutrophils in the pleural space could be a propagating mechanism for pleural inflammation and effusion. Prolonged pleural inflammation may also increase the likelihood a late humeral response by an unknown mechanism. If this is the case, reducing PMN recruitment into the pleural space, or removing apoptotic PMNs from the pleural space might shorten the duration of pleural inflammation and effusion. Further, it might also blunt the development of a humeral response. Heidecker and Sahn suggested that early [e.g. non-specific] and late pleural effusions were based on different etiologies with different pathogenesis[54]. We speculate that an evolving inflammatory response might be a better explanation.

3.6.3 Post-pericardiotomy Syndrome, Atrial Fibrillation and Pleural Effusion

Post-pericardiotomy syndrome (PPS) is a condition that affects 10-40% of patients after cardiac surgery[55]. PPS is cited to be the result of a humeral inflammatory response with a poorly understood pathogenesis[55, 56]. The syndrome is characterized by a specific constellation of symptoms at approximately 1-6 weeks after any type of pleuro-pericardial trauma[55]. The generally accepted

diagnostic criteria includes presentation with 2 of the following: 1) fever; 2) pleuritic chest pain; 3) rubs (pericardial or pleural); 4) pericardial effusion; or 5) pleural effusion (with or without elevated CRP)[55, 57]. The progression of the syndrome is thought to start with an iatrogenic trigger (cardiac surgery) and has a "sub-clinical" latency period until symptoms appear approximately 2-3 weeks later[55]. The "sub-clinical" latency period is often characterized by maintenance or development of a late pleural effusion[5]. Symptoms of PPS can be important because approximately 2-3% of symptomatic patients go on to develop constrictive pericarditis[55, 56]. As such, these patients may require more vigilant follow up after surgery[55, 56].

We are interested in the PPS for several reasons that are based on our understanding of pleural effusion after cardiac surgery. First, it is estimated that up to 85% of patients with a diagnosis of PPS present with a pericardial effusion but up to 90% will present with a pleural effusion[56]. Second, on-treatment analysis in the COPPS-2 randomized controlled trial showed that perioperative colchicine reduces pericardial effusion and pleural effusion after cardiac surgery (relative risk reductions 44%, 52% respectively)[57]. The mechanism of action for colchicine includes inhibition of TNF-α synthesis by macrophages and down regulation of TNF-α-receptor expression on both macrophages and endothelial cells[58]. Additionally, colchicine inhibits microtubule assembly in PMNs, which blunts mobilization[58]. Therefore, the expected effect would be reduction of tissue macrophage activation and PMN recruitment to the pleural space. Considering our current model, we might have expected a reduction in pleural effusion from this therapy. Unfortunately during the COPPS-2 trial, colchicine had to be discontinued in 22% of patients due to gastrointestinal side effects[58].

Third, we are interested in the 45% reduction in postoperative atrial fibrillation (NNT=11) found on on-treatment analysis from the COPPS-2 trial[57]. The authors did not comment on the covariance of reduction in pleural effusion and atrial fibrillation. However, our Cardiac Surgery service has anecdotally noted reductions in maintenance of atrial fibrillation with early thoracentesis on patients with postoperative pleural effusions. The authors of the COPPS-2 trial indicated that there were two possible mechanisms for reduction in postoperative AF in patients receiving colchicine[57]. These included reduction of calcium-

induced ectopy by inhibition of microtubule assembly and by reduction of PMN recruitment to damaged cardiac tissue[57].

Further, a retrospective multivariate analysis of 969 patients by Stamou, *et al*, found that postoperative pleural effusion was an independent risk factor for atrial fibrillation (RR = 3.2, 95% CI 1.0-9.4, p=0.03)[59]. Pericardial effusion is also a known risk factor for AF and up to 63% of patients maintain a sub-clinical pericardial effusion 1-week after surgery[60]. Vargas, *et al*, have previously demonstrated that the persistence of pericardial effusion is dependent on the persistence of pleural effusion after myocardial revascularization[61]. Perhaps this is explained by relationship between the lymphatic systems for both the pericardium and pleurae[62]. The majority of the pericardium and left chest is drained through the upper thoracic duct. This route has a high recruitable capacity for pleural drainage but recruitment may impact the system's capacity for pericardial drainage[23]. Mechanical compression activates pericardial mesothelial cells (by effusion) and promotes pericardial inflammation[52]. If pericardial effusion is a risk factor for AF and resolution of pericardial effusion is dependent on resolution of pleural effusion, it would be reasonable to think that treating pleural effusion may have a downstream effect on resolution of AF. Whether or not draining the pleural space has an impact on prevalence of postoperative AF is unknown.

3.7 Thoracentesis: A Role in Non-Specific Pleural Effusion?

The clinical considerations for use of thoracentesis in non-specific pleural effusion after cardiac surgery should weigh risk of injury against the potential for benefit. Up until the past 10-15 years, the historical safety profile of thoracentesis had been poor. In 1993, a review by Bartter, *et al* of 337 thoracenteses performed without imaging guidance cited a major complication rate of 4-30%[63]. These complications consisted primarily of pneumothorax but also included hemothorax, splenic laceration, and even a retained surgical instrument[63]. The overall percentage of patients requiring intervention for complications was 6%; and these included tube thoracostomy, blood transfusion, and thoracotomy[63]. There were also several deaths in critically ill patients requiring thoracentesis[63].

However, the sensitivity and increasing adoption of thoracic ultrasound has dramatically changed the safety profile of thoracentesis over the last decade. For cardiac surgery patients, this has been realized in terms of both improved "real-time" detection of pleural effusions and reduced complications[64, 65]. In a recent study by Usta, *et al*, 135 patients requiring thoracentesis had their procedures performed under ultrasound guidance[65]. The resulting therapeutic yield was 100% [e.g. fluid was obtained from patients] with a 0% complication rate[65]. The overall reduction in complications with thoracic ultrasound has led our Cardiac Surgery service to reexamine the utility of thoracentesis in patients with non-specific pleural effusion.

The *generally* accepted therapeutic mechanism for thoracentesis is the reduction of restricted ventilation[11, 12]. Symptoms of restricted breathing tend to increase with the size of pleural effusion[11, 12]. However, symptoms of respiratory dysfunction are independent of size in *non-specific* pleural effusion[3-6, 13]. These symptoms are clinically significant and negatively correlate with outcomes. In the previously cited study by Usta, *et al*, thoracentesis was reserved for patients with a pre-procedure pleural fluid volume estimate of >480mL[65]. Patients undergoing thoracentesis were discharged on POD 9–10, whereas patients with smaller effusions that were managed with diuretics stayed 3 ± 1.5 days longer[65]. This suggests that patients with smaller pleural effusions might have had clinically significant symptoms that led to longer hospital stay.

Clinical benefits for thoracentesis in patients with non-specific pleural effusion after cardiac surgery have not been described. Based on the current literature, we can only speculate that patients with non-specific pleural effusion *might* benefit from thoracentesis. Symptomatic improvement after thoracentesis is generally correlated with increasing volume of pleural fluid removed[11, 12]. However, benefit in *non-specific* pleural effusion would have to be realized from a different mechanism because the effusions are small. Our interpretation of the current literature is that the pathogenesis of non-specific pleural effusion after cardiac surgery is interrelated lung and pleural inflammation. The presence of apoptotic neutrophils in the pleural space is a propagating mechanism for lung and pleural inflammation. Symptoms of respiratory dysfunction, including dyspnea, are a known consequence of lung and pleural

inflammation[32]. Therefore, we can speculate that early reduction of PMN burden in the pleural space with thoracentesis *might* shorten the duration of lung and pleural inflammation, as well as pleural effusion. Thoracentesis might also result in fewer days in atrial fibrillation if treating a non-specific pleural effusion is associated with resolution of sub-clinical pericardial effusion.

4 Study Design, Specific Aims, and Hypothesis

4.1 Statement of Purpose and Specific Aims

This study retrospectively compares clinical outcome measures for cardiac surgery patients with non-specific postoperative pleural effusions, some of whom had procedural intervention with thoracentesis and others that did not. The use thoracentesis in this setting is currently based on clinical judgment that weighs established risk against poorly described benefit. Complications from thoracentesis performed by our Thoracic Interventional Program Service (TIPS) under transthoracic ultrasound guidance are generally regarded as infrequent and are beyond the scope of this study. Some cardiac surgeons assert that there is benefit to early thoracentesis for non-specific pleural effusion in specific cases. However, the current literature neither provides sufficient data on the frequency of improved dyspnea [e.g. clinical benefit] after thoracentesis, nor formal comparisons of clinical outcomes to fully support expanded use in this population. Better understanding of these outcomes to inform clinical judgment is emerging as a clinical imperative at our institution.

The purpose of this study is to 1) measure the frequency of improved dyspnea after thoracentesis on cardiac surgery patients with non-specific pleural effusion; and 2) compare clinical outcomes between patients who had thoracentesis versus those who did not. The scope of clinical outcomes studied is informed by the current literature but limited to the anecdotal clinical observations reported by mid-level providers at Yale - New Haven Hospital. To our knowledge, this is the first comparative evaluation of outcomes for “therapeutic” thoracentesis in cardiac surgery patients with non-specific pleural effusion.

4.2 Study Design

A Case – Control design is chosen for this study. Cardiac surgery patients with postoperative pleural effusion who had thoracentesis in the early postoperative period (Cases) are matched by age and operation with patients who did not undergo thoracentesis (Controls).

We have chosen to match patients by age and operation for several reasons. First, surgical trauma and CPB have been identified as risk factors for both developing and maintaining a pleural effusion [Section 3.4]. If an outcomes comparison is to be made regarding postoperative pleural effusion, the extent of surgical trauma and general use of CPB should be comparable. There is inconsistent evidence for *time on CPB* as risk factor for postoperative pleural effusion and for this reason we consider this less contributory[4, 25]. Second, the Cardiac Surgery team at Yale – New Haven Hospital acknowledges differences in length of stay that is operation specific (e.g. CABG patients tend to have shorter lengths of stay than CABG patients with concurrent AVR). Third, there is insufficient data to control for the potential the modifying effects of specific operations on the development or persistence of AF in the postoperative period. Therefore, matching by operations may provide a more meaningful comparison between cases and controls. Fourth, age is a known risk factor for both length of stay and the development of AF[66]. Matching by age would attempt to eliminate this source of selection bias. Outcomes experienced by patients are summarized and where appropriate, compared between Case and Control groups.

For this analysis, 30 patients were selected based on the Statistical Considerations outlined in Section 5.7. Medical chart data is collected from documented outcomes observed, including a surrogate measure of dyspnea, hospital length of stay (LOS), rate of escalation of care, days in atrial fibrillation, markers of systemic inflammatory response, and requirement for further outpatient management of pleural effusion after discharge. Data is collected from a population of patients after cardiac surgery by a single surgeon to limit inter-operator variability and at a single institution to limit variability in postoperative care.

Observational end points are the subject of this study for several reasons: 1) Mid-level providers reported their informal observations for patients that have already received care at our institution, 2) The

clinical outcomes of interest are sufficiently well documented in the electronic medical record, 3) There is currently a lack sufficient clinical data to reasonably justify a prospective study at this point; and 4) Outcomes data can be used in further hypothesis refinement for potential prospective trials if warranted.

4.3 Hypothesis

We believe that the majority (>50%) of patients who undergo thoracentesis for non-specific pleural effusion have improved dyspnea. We will formally measure the frequency of improved dyspnea experienced by these patients to support this assertion. In terms of comparative clinical outcomes, the null hypothesis is that there is no difference between patients having thoracentesis versus no procedural intervention for non-specific pleural effusion after cardiac surgery in terms of: 1) the frequency of improved dyspnea, 2) LOS, 3) requirement for escalation of care, and 4) days of AF. The alternative hypothesis is that thoracentesis improves these clinical outcomes. Our argument for an alternative hypothesis is based on: a) increased length of stay is associated with persistence of dyspnea and AF[65, 67], b) decline in pulmonary status is a common reason for escalation of care at our institution, and c) our current model of inflammation for non-specific pleural effusion after cardiac surgery suggests that persistence of effusion and days in AF might be reduced by removal of PMNs from the pleural space.

4.4 Study Endpoints

Primary Endpoint: What is the frequency of improved dyspnea after thoracentesis for non-specific pleural effusion after cardiac surgery?

Secondary Endpoint: Is there a difference in postoperative length of stay for patients who had thoracentesis versus those who did not?

Tertiary Endpoint: What are the rates of escalation of care for patients who underwent thoracentesis and those who did not?

Additional Endpoints: Is thoracentesis associated with fewer postoperative days in AF in cardiac surgery patients? Was the medical management of AF with amiodarone in Controls and Controls different? Is there a difference in incidence of post-pericardiotomy syndrome? What is the requirement for post-discharge care of pleural effusions in those who had early thoracentesis and those who did not? What was

the average hospital length of stay from intervention (thoracentesis) to discharge? What was the 30-day mortality? What was the absolute mortality? What amount of fluid is removed from patients requiring thoracentesis? Were there markers of systemic inflammation during the postoperative period for Cases or Controls?

4.5 IRB Review and Approval

This medical record review was conducted according to the current revision of the Declaration of Helsinki. The Institutional Review Board at Yale University approved the clinical study protocol prior to study initiation on December 14th, 2014 as HIC #1412015043.

5 Methods

5.1 Roles and Responsibilities

This project is the culmination of efforts by many individuals. A detailed list study contributors is shown below (**Table 1**). The medical student (David R. Kull, MPH) role was limited to the following work: Coordination of Research Team Contributions, Primary Authorship and Revision of Study Protocol, Case-Control Selection, Abstraction of Clinical Outcomes Data (All Records), Statistical Analysis of Outcomes Data, and Primary Authorship of Manuscript. The medical student did not participate in the following activities or responsibilities: Principal Investigator, Expert Review of Study Protocol, Expert Review of Manuscript, Draft or Submission of HIC Documentation (based on Study Protocol).

Table 1: Key Study Personnel

Principal Investigator: Umer M. Darr, MD Department of Surgery, Section of Cardiac Surgery **Role**: Principal Investigator, Protocol Review, Manuscript Review	**Co-Investigator:** David Kull, MPH (Medical Student) Yale University School of Medicine **Role(s)**: Author Protocol, Case/Control Selection, Records Abstraction, Data Analysis, Author Manuscript
Co-Investigator: Gaetane C. Michaud, MD Dept. of Medicine, Section of Pulm. and Crit. Care **Role(s)**: Protocol Review, Manuscript Review	**Co-Investigator:** Jonathan T. Puchalski, MD Dept. of Medicine, Section of Pulm. and Crit. Care **Role(s)**: Clinical Contributor
Co-Investigator: Christina Carbone, CCRP (Research Coordinator) Dept. of Medicine, Section of Pulm. and Crit. Care **Role(s)**: HIC Application Draft and Coordination, Protocol Review	**Co-Investigator:** Barbara Stahl, APRN, DNSc (Acute Care NP) Department of Surgery, Section of Cardiac Surgery **Role(s)**: Protocol Review
Co-Investigator: Vladimir Shumaster, MD (Research Fellow) Department of Surgery, Section of Cardiac Surgery **Role(s)**: Protocol Review	**Co-Investigator:** Kelsey Johnson, MSc, PA-C (Clinical PA) Department Surgery, Thoracic Interventional Program **Role(s)**: Protocol Review
Study Personnel: Rowena Saga-Abrina, APRN (Clinical NP) Department of Surgery, Section of Cardiac Surgery **Role(s)**: Protocol Review	**Study Personnel:** Ann Roselle, MS, PA-C (Clinical PA) Department of Surgery, Section of Cardiac Surgery **Role(s)**: Protocol Review
Study Personnel: Eileen Taylor, RN, MBA Department of Surgery, Section of Cardiac Surgery **Role(s)**: Protocol Review	**Thesis Sponsor:** Frank Detterbeck, MD Department of Surgery, Section of Thoracic Surgery **Role(s)**: Thesis Review

5.2 Study Population

Patients who are status-post cardiac surgery, performed by a single surgeon (Umer M. Darr, MD) at Yale - New Haven Hospital during the two-year period commencing January 1st, 2013 and ending December 30th, 2014, with a radiographically evident pleural effusion were considered. Cases and Controls were selected amongst patients meeting Inclusion and Exclusion Criteria (described in Sections 5.2.1 and 5.2.2 respectively) by the procedure defined in Section 5.3. In brief, the Case group is comprised of patients meeting inclusion and exclusion criteria in which thoracentesis was performed during the early postoperative period. The Control group is selected amongst age and operation matched patients, who did not undergo early thoracentesis during the same period.

5.2.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be entered into the study:

1. Post-primary open cardiac surgery (CABG, valve, CABG + valve, etc.)
2. Age 40-85 years
3. Postoperative pleural effusion in the early postoperative period (POD3 - POD7)

5.2.2 Exclusion Criteria

Any of the following will exclude the subject from study:

1. Prior cardiac surgery
2. History of pleurodesis
3. Patients with pleural effusion known to be associated with non-cardiac related etiology (e.g. pancreatitis, malignancy, etc.)
4. Operative complications (intraoperative bleeding requiring massive transfusion protocol or documented inadvertent intraoperative injury)
5. Maintenance of a chest tube or tunneled pleural catheter during the early postoperative period
6. INR > 2.5 (for Cases, at the POD of thoracentesis; Controls, the matched POD)

Rationale for exclusion criteria: The primary endpoint of the study is to formally measure the frequency of reduced dyspnea after cardiac surgery, whereby an inflammatory response is considered an underlying mechanism. Intra-thoracic fibrosis from prior surgery may complicate the course of non-specific pleural

effusion (e.g. formation of loculations). Pleurodesis causes fibrosis within the thoracic cavity and may change the course of non-specific pleural effusion[53]. Micro-metastatic malignancy is thought to cause pleural effusion by a separate process that may promote persistence of pleural effusion[24]. Major operative complications, defined as intraoperative bleeding requiring massive transfusion protocol and documented injury of intra-thoracic structures, may provoke an immune response beyond that experienced by most cardiac surgery patients. Additionally, we can reasonably assume this would impact length of stay and requirement for escalation of care. Maintenance of an indwelling tunneled pleural catheter has been associated with spontaneous pleurodesis[68]. Intraoperative insertion of a chest tube to drain the left pleural space has also been shown to reduce pleural effusion after cardiac surgery[69]. INR >2.5 is a reference value at the upper standard deviation of increased risk for the development of hemothorax requiring transfusion after thoracentesis[70]. From our current interpretation of the literature subclinical, bleeding might prolong pleural inflammation and effusion.

5.3 Selection of Cases and Controls

Query of electronic medical records resulted in a Primary Search Group (PSG) of 377 records for consideration amongst patients of Umer M. Darr, MD at Yale - New Haven Hospital during the two-year period commencing January 1st, 2013 and ending December 30th, 2014. Within the PSG, 58 patients had undergone thoracentesis. Manual search of these records yielded 34 patients having had thoracentesis during the period of interest (POD3-7). Of these, 21 patients met the remaining inclusion criteria. Of those meeting inclusion criteria, 4 patients met exclusion criteria on further review due to non-cardiac etiology of a chronic pleural effusion (3) or prior sternotomy(1). The 17 remaining patients were assigned to the preliminary Case Group.

Re-generation of the PSG excluding the 58 patients found to have undergone thoracentesis during the perioperative period produced 319 patients. 84 patients were identified as age matched by list sort. Through manual search, 19 procedure matches were identified amongst matched ages. These records were assigned to the preliminary Control Group.

There were 2 additional patients meeting criteria for Cases and 4 additional patients meeting criteria to match as Controls to 4 of the first 15 Cases selected. The 2 additional preliminary Cases were not assigned because there was no ability to appropriately age and/or procedure match amongst the available Controls. There were 4 additional Controls that could have been matched to Cases. We selected those that were closest in age as this would be the most reliable comparison. The Case and Control groups were then finalized with the best matches available. A schematic for Case and Control Selection by numbered step is shown in Figure 1.

5.4 Data Abstraction

Data abstraction was performed by manual search by a medical student and is documented using the Data Abstraction Form attached as Appendix A. Data abstracted was handled per the Data Management procedure listed in Section 5.5.

Figure 1: Case and Control Selection

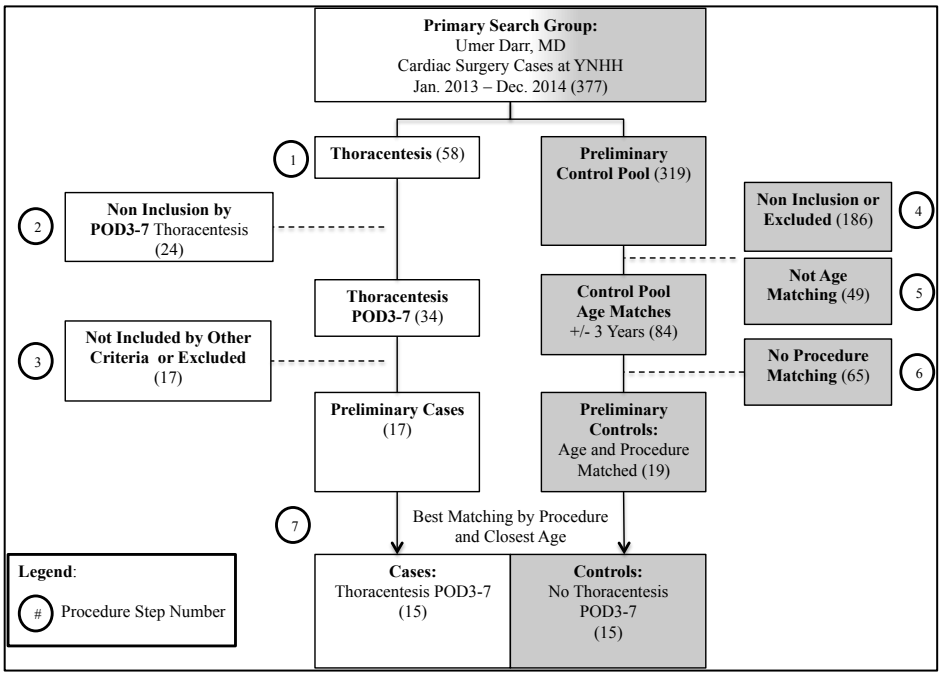

Figure 1: Cases and Control selection; 377 patients considered; 58 patients were to found to have undergone thoracentesis for non-specific pleural effusion; 41 preliminary Cases were removed by inclusion/exclusion criteria. 2 preliminary cases were unmatched. Of 319 potential controls, 84 were age matched and 19 were procedure matched. Matching by closest age yielded 15 Cases and 15 Controls

5.4.1 Specific Data Elements

Data elements are retrospectively abstracted from patient charts for the following:

- Baseline Data
    - Age
    - Cardiac surgical procedure
- Cardiopulmonary Recovery
    - Daily Peak Supplemental O2 Requirement (LPM), POD3 to discharge (or POD7)
    - Daily Occurrence of AF POD3 to discharge (or POD7)
    - Cumulative dose requirement for amiodarone POD3 to discharge (or POD7)
    - Number of days with fever (e.g. T > 38.3° C) POD3 to discharge (or POD7)
    - Labs: Daily WBC and Platelets (POD3 - POD7, or last lab draw)
    - POD of thoracentesis (Cases)

- Pleural fluid volume removed (Cases)

- Postoperative Course
  - Length of post-operative inpatient stay (LOS)
  - Requirement for escalation of care (e.g. Step-down or CTICU re-admission)

- Post-discharge Course
  - Diagnosis of post-pericardiotomy syndrome
  - Death (< 30-days)
  - Requirement for hospital re-admission
  - Requirement for outpatient management of pleural effusion

5.5 Data Management

The study is exclusively conducted at Yale University School of Medicine through Yale - New Haven Hospital. Hard copy, de-identified Case Report Forms are used to collect data are secured under lock-and-key in a binder within the Section of Cardiac Surgery on completion of Data Abstraction. All electronic media is held in accordance with IRB policies and procedures. Additionally, de-identified data is periodically loaded into Microsoft Excel® and STATA (STATA LP, College Station, TX, USA) for analysis and safeguarded on an encrypted hard drive per IRB policies and procedures. All data records used for the study, paper and electronic, will be destroyed on or before a period of 5 years (12/31/2019).

5.6 Data Analysis

The primary endpoint of this study is frequency of improved dyspnea as measured by daily peak supplemental O2 requirement before and after thoracentesis. The generally accepted criteria for therapeutic thoracentesis in our patient population includes symptoms[5]. We have chosen peak supplemental O2 requirement as a measure of dyspnea for several reasons. At Yale – New Haven Hospital, the order for titration of oxygen supplementation is nursing-driven and is given as:

Nasal Oxygen Titration (Adult)

- [Timing], [Duration], [Start Date, Time], [End Date, Time]
- Starting Liter Flow (LPM): 2.0 LPM

- SpO2 Goal: > or = 92%
- Indications: Treat/Prevent Hypoxemia
- Flow Range: [Flow Range]
- Titrate Flow: [Titration Flow]
- Notify MD/LIP: [Any Specific Notification Instructions]

The translated action by nursing staff is most often to supplement oxygen to "prevent hypoxemia." Further, an acceptable interpretation of these orders often results in nurses adding 2L of oxygen for what they deem as, "patient comfort." This commonly occurs when SpO2 is above 92% to prevent hypoxemia in the setting of early increased work of breathing. The initial flow typically given is also in accordance with physician orders, which is 2 LPM. Oxygen is titrated up based on a combination of increased work of breathing and trending of hypoxia by SpO2. The peak oxygen supplementation that is the end result of titration is probably a good measure of exactly how much dyspnea someone is experiencing prior to changes in supplementation.

Does everyone get 2 LPM of oxygen when they're experiencing some increased work of breathing? This is also probably not the case. The subjectivity of a nurses' assessment of increased work of breathing may be influenced by, among factors, recent thoracentesis. If a thoracentesis has been performed, there might be an expectation that someone will get better. This could be an influence for a nurse to titrate less aggressively if there is a subjective expectation. The measure of SpO2 has been used in prior studies to measure hypoxia in patients before and after thoracentesis[65]. We considered using this measure, however, many patients requiring cardiac surgery have chronic obstructive pulmonary disease. It is common for these patients to have a low baseline SpO2 without significant changes in baseline work of breathing. If a patient's work of breathing isn't dramatically changed, this may result in less aggressive initiation of oxygen supplementation by nurses if the SpO2 is > 92%. Lastly, it is rare at our institution for someone to have an SpO2 < 92% at the time of surgeon orders for thoracentesis. This result is primarily a function of the physician order set for oxygen titration. For these considerations, we are choosing to use daily peak O2 supplementation as a measure of dyspnea. Further, we think that a relevant measurable

difference is 2 LPM because the oxygen titration starts at a 2 LPM by our order set. Although this has never been measured and is not dictated by the order set, our practitioners report that most patients are titrated off oxygen from 2 LPM. We would therefore consider "improved dyspnea" by a reduction of 2 LPM.

We feel POD3 - POD7 is a reasonable inpatient study period for several reasons. Patients at our institution are admitted to the CT-ICU following open cardiac surgery. On approximately POD 1-3, patients' chest tubes are typically removed and they are transferred to the CT-SDU. Following 24-48 hours in CT-SDU, patients are transferred to the Cardiovascular Medical Floor (CMF) where they typically remain until discharge. Thoracentesis for non-specific pleural effusion occurs after chest tubes are removed (usually POD2). The literature suggests that non-specific pleural effusions resolve within 1 week of surgery (POD7)[5]. Therefore, we choose these as the limits of data to examine.

The secondary endpoint is hospital length of stay (LOS); which is defined as period of time commencing with the day of the primary operation and ending the day of discharge. A mean difference in hospital stay for patients of at least 1 day is considered meaningful because inpatient hospital stay is recorded by the day in our EMR. Patients are recorded as discharged based on the date of the hospital discharge summary. Therefore, there is no difference recorded if a patient is discharged before or after 11:00 AM (the official time of discharge set by hospital administration for billing purposes). Mid-level practitioners estimate that the average hospital LOS for patient at our institution is typically 5-6 days, although this has not been formally measured. The literature suggests that patients with symptomatic pleural effusion after cardiac surgery stay 9-10 days after thoracentesis, and 12-13 days if diuretics are used as an intervention[65].

The tertiary endpoint is requirement for escalation of care. This is defined as the physical relocation of a patient to another Unit where the intensity of care is higher due to clinical need. Our Cardiac Surgery service accepts a rate of escalation of care of ≤10%. In the rare case that a patient is not transferred from the CT-SDU to the CMF due to bed management issues, and documentation of an adverse change in

clinical course is present in the patient Discharge Summary, the patient were recorded a having had an escalation of care.

Additional outcome endpoints include days of documented atrial fibrillation; a requirement for outpatient thoracentesis for pleural effusion after discharge; evidence of systemic inflammation [e.g. WBC, Fever, platelets]; incidence of post-pericardiotomy syndrome; average hospital length of stay from intervention to discharge; amount of pleural fluid removed during thoracentesis; 30-day and absolute mortality.

Statistical analysis of study data is accomplished in STATA/IC 10.1 (Stata Corporation, 4905 Lakeway Dr., College Station, TX 77845 USA) using the Do-Command Program, written by the medical student (David R. Kull, MPH) and attached hereto as Appendix B.

5.7 Statistical Considerations

The primary endpoint of this study is frequency of improved dyspnea as measured by daily peak supplemental O2 requirement before and after thoracentesis. Our study objectives are to review enough patient records sufficient to provide for both the statistical power required to be reasonably confident in the measurement of our primary and tertiary endpoints. Additionally, we would like to detect meaningful differences between Case and Control groups for the secondary endpoints. We will not purposefully power the study to detect differences in other endpoints.

A sample size of 30 (n) is chosen (Cases=15, Controls=15) based on the following considerations:

Primary Endpoint: The primary endpoint of this study is frequency of improved dyspnea. This is defined by a reduction in daily peak O2 supplementation of 2 LPM after thoracentesis. We conservatively estimate that the majority of patients (>50%) have improved dyspnea after thoracentesis. In order to be reasonably confident in our actual rate being above 50%, we would need to observe rates that differ by the number of patients:

Observed Rate (%)	Actual Rate (%)	Confidence (%)	Patients (n)
60	50	95	152
70	50	95	36
80	50	95	15
90	50	95	7
70	50	90	26
80	50	90	11

Statistical estimates can be made for the magnitude of difference in means for daily peak O2 supplementation before and after thoracentesis. We estimate that the average thoracentesis patient in our population requires daily peak O2 supplementation of about 4 LPM (+/- 2 LPM) to maintain SpO2 above 92%, although this has not been formally measured. A minimum post-thoracentesis value would be 2 LPM (+/-2) based on our definition of "improved dyspnea." To detect this difference where $\alpha = 0.05$ and $\beta = 0.20$, a minimum of 12 patient records must be analyzed (n=12).

We expect that patients who do not have thoracentesis will also have improved dyspnea, as non-specific pleural effusion is known to resolve spontaneously[5]. The perioperative day-to-day course of spontaneous dyspnea improvement [e.g. when and how much] in this population has not been described. We believe that the majority of patients will have improved dyspnea after thoracentesis *independent* of the POD of intervention. However, the proportion of patients with spontaneous improvement is presumed to be higher in the early versus later perioperative course [e.g. POD dependent]. Therefore, we will measure and compare differences in improvement of dyspnea for Cases and Controls but we do not yet have enough information to formally power the study to detect these differences.

Secondary Endpoint: Our secondary endpoint is hospital length of stay measured in days. The average hospital stay for patients following cardiac surgery is approximately 5 days (+/- 1-day). A mean difference in hospital stay for patients of at least 1 day is considered meaningful because inpatient hospital stay is typically recorded and billed by the day. The mean hospital length of stay will be calculated based on collected data and a paired t-test will be performed. Assuming that the average length of stay is 5 days with a standard deviation of 1 day, and an average mean difference

in length of stay is 4 days with a standard deviation of 1 day where $\alpha = 0.05$ and $\beta = 0.20$, a minimum of 12 patient records per group must be analyzed (n=24).

Tertiary Endpoint: The tertiary endpoint of our study is requirement for escalation of care as measured by physical transfer to a unit where the intensity of care is higher. We have units for three levels of care at Yale New Haven Hospital [e.g. Cardiovascular Medical Floor, Cardiothoracic Step Down, and CTICU] and therefore our definitions and thresholds for transfer may be specific to our institution. Estimates of escalation of care available in the current literature are therefore difficult to generalize for our institution. However, the rate of escalation of care for postoperative cardiac surgery patients ranges from approximately 4-13% based on hemodynamic instability and the rate of iatrogenic injury from thoracentesis requiring intervention is between 0-6%[63, 67]. At our institution, a clinically acceptable rate of escalation of care will be defined as ≤10%. The rate of escalation of care in our population has not yet been defined. No comparison will be made for escalation of care between Cases and Controls. However, the rates of escalation of care will be calculated for each group and confidence intervals will be calculated using Newcombe's interval (with continuity correction). The Probability (P) of observing the rates of complications for our analysis based on an acceptable comparison rate of ≤10% (p) will be calculated by binomial expansion. We accept that at one patient in ten will have required an escalation of care. To be 80% confident (P) that our rate is ≤10%, the observed rate in our study must be 7% per group. A sample size of 15 per group (n=30) will allow us to detect an observed rate of 7% [e.g. 1 event amongst 15 patients] with 80% confidence that our actual rate is ≤10%.

The minimum sample size for our study is n=30 (15 Cases, 15 Controls), which is driven by two requirements. First, we would like higher confidence in our primary endpoint because the estimation of our actual rate is conservatively low (>50%). Our mid-level providers assert that our recent rate of improved dyspnea is 90-100%. We think that a 15-patient Case group provides us with sufficient patients for 95% confidence if our observed rate is 80%. The second requirement is reasonable confidence (80%) in our rate of escalation of care being ≤10%. We think that 80% confidence is reasonable given that this is a pilot

study and this rate has never been measured. The sample sizes required for the primary and secondary endpoints are lower based on the best available estimates of absolute differences expected between Cases and Controls.

6 Results

6.1 Baseline Patient Characteristics

Of patients studied, 20 underwent CABG, 6 underwent aortic valve repair (AVR), and 4 underwent CABG with AVR as shown in Table 2. The mean age of the Case group was 75.3 years (SD = 8.2) versus 74.9 years (SD = 8.1); (p = 0.89).

6.2 Primary Endpoint: Frequency of Improved Dyspnea

The primary endpoint of this study is frequency of improved dyspnea as measured by daily peak supplemental O2 requirement before and after thoracentesis. All patients maintained a pleural effusion on POD3 during the study period irrespective of Case or Control status. Of 15 Cases, 11 had decreased peak supplemental oxygen requirement ≥2 LPM the day after thoracentesis (RR=0.73, 95% CI 0.45 – 0.92). Of the remaining Case patients, 2 patients had no change in dyspnea and 2 had worsening of dyspnea (≥2 LPM increase). Additionally, 7 of 15 matched Control patients *also* experienced improved dyspnea over the equivalent postoperative period. We did not detect a significant difference in the odds of *improved* dyspnea between Cases and matched Controls (OR = 3.1, p = 0.14, 95% CI 0.7 – 14.5) or any other change in dyspnea (p = 0.79). These results are shown in Table 2.

The day of thoracentesis ranged from POD3-POD5. The frequency of thoracentesis on POD3, 4, and 5 was respectively 5, 6, and 4. Mean daily peak supplemental O2 requirement the day following thoracentesis for Cases was significantly lower than the day before thoracentesis (1.7 versus 3.3 LPM, p = 0.01). The mean daily peak O2 requirement during the equivalent period for matched Controls was *also* significantly lower over the same period (0.4 versus 1.7 LPM, p = 0.01). There was no relationship between the volumes of pleural fluid removed and improved dyspnea by logistic regression analysis (p = 0.59).

Figure 2: Postoperative Changes in Dyspnea Amongst Cases and Controls

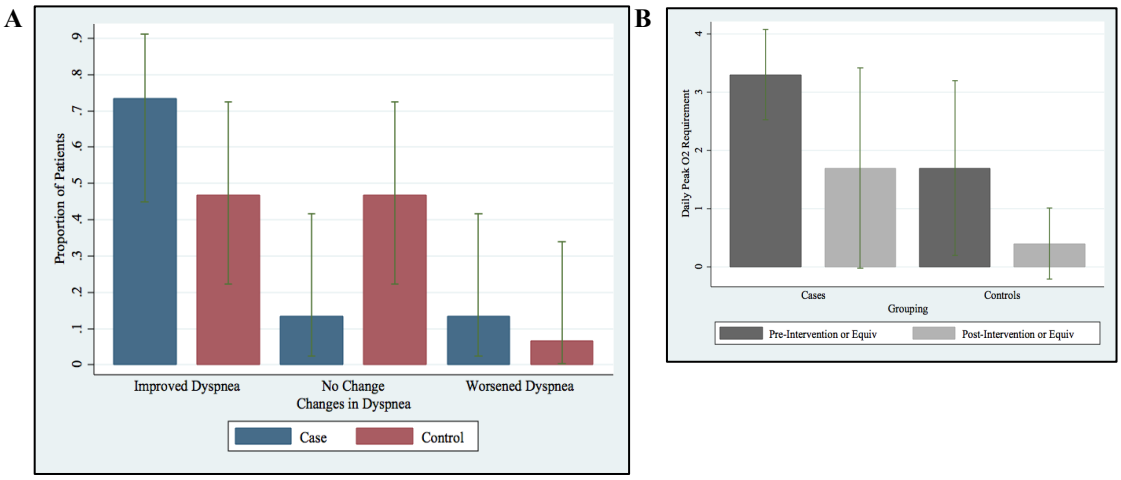

Figure 2: A. *Primary Endpoint:* Frequency of improved dyspnea in cardiac surgery patients with non-specific pleural effusion after thoracentesis (Cases) or a matched period (Controls), as measured by ≥2 LPM reduction in daily peak O2 supplementation. Of 15 Cases, 11 patients had improvement in dyspnea, and of 15 Controls, 7 patients had improvement. There was no significant difference in the odds of improved dyspnea between Cases and matched Controls (OR = 3.1, p = 0.14). **B.** Daily peak O2 requirement was significantly lower for Cases after thoracentesis (1.7 versus 3.3 LPM, p = 0.01). The difference was also significantly lower over the same period for Controls (0.4 versus 3.7 LPM, p = 0.01).**

** Significance determined by paired t-test; which is independent of 95% confidence interval overlap in Figure 2B.

6.3 Secondary Endpoint: Postoperative Length of Stay

Study patients accounted for 188 days of postoperative hospital stay. The total postoperative days experienced by cardiac surgery patients who had thoracentesis for non-specific pleural effusion were 101 days versus 87 days by those who did not have procedural intervention. The mean postoperative LOS for Cases was 6.7 ± 3.2 days (median = 6) versus 5.8 days ± 1.6 days (median = 5) for Controls (p=0.84). The mean length of stay from intervention to discharge for Cases was 2.8 ± 2.7 days and was not significantly different versus the equivalent Control day to discharge, 1.9 ± 1.8 days (p = 0.84). Regression analysis revealed a significant relationship between the volumes of pleural fluid removed during thoracentesis and length of stay (Coef = 90 mL/day, p = 0.03).

Figure 3: Postoperative Length of Stay Amongst Cases and Controls

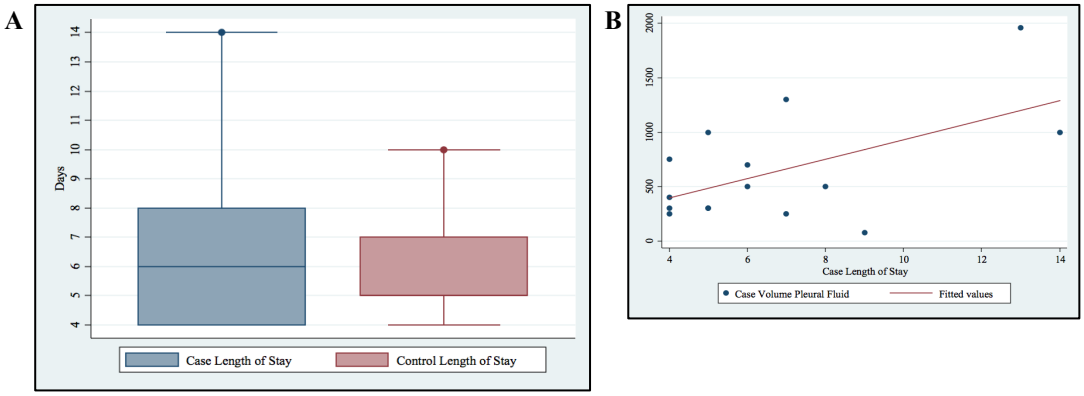

Figure 3: A. *Secondary Endpoint:* The postoperative LOS for cardiac surgery patients who had thoracentesis was 6.7 days ± 3.2 (median = 6) versus 5.8 days ± 1.6 (median = 5) for those with non-specific pleural effusion who did have procedural intervention (p=0.84). **B.** Larger requirement for pleural fluid removal significantly correlated with Case length of stay (Coef = 90 mL/day, p = 0.03).

6.4 Tertiary Endpoint: Requirement for Escalation of Care

During this study, there was no requirement for escalation of care documented amongst cardiac surgery patients with non-specific pleural effusion. The 95% confidence interval for the rate of escalation of care is 0% –14% based on an *observed* rate of 0% in 15 patient groups.

Table 2: Comparison of Cases and Controls: Major Study Endpoints

		Cases	Controls		
		n = 15	n = 15		
		Mean (SD)	**Mean (SD)**	**(p)**	**95% CI**
Baseline Data					
Age	Age	75. 3 (8.2)	74.9 (8.1)	0.89	
Procedure	CABG	10	10		
	Aortic Valve Repair (AVR)	3	3		
	CABG + AVR	2	2		
Dyspnea					
	Improved	11	7	0.14	
	No Change	2	7		
	Worsened	2	1		
	Pre-/Post- Thoracentesis (or matched period) Difference for Daily Peak O2 Requirement (LPM)	-3.2[¥] (4.6)	-2.3[¥] (4.2)	0.36	-3.6 – 2.6
	Median Pleural Fluid Drained	0.5 L			
Postoperative LOS					
	Total Days	101	87		
	Average Days	6.7 (3.2)	5.8 (1.6)	0.84	
	Thoracentesis (or Matched POD) to Discharge	2.8 (2.7)	1.9 (1.8)	0.84	
Requirement for Escalation of Care					
	Req. Esc. Care	0	0		0.00 - 0.14[*]

Table 2: Comparison of Cases who underwent thoracentesis versus age and procedure matched Controls who had no procedural intervention for non-specific pleural effusion after cardiac surgery. Age was not significantly different between Cases and Controls (75.3 vs. 74.9 years, p=0.89). There is no significant difference for improvement of dyspnea between Cases and Controls (11 vs. 7 patients, OR = 3.1, p = 0.14). Length of stay (LOS) was not significantly different between Case and Control Groups (6.7 vs. 3.2 d, p = 0.84). LOS after thoracentesis (or matched POD) was also not significantly different between Cases and Controls. There was no requirement for escalation of care in either group (95% CI 0.00 – 0.14).

[¥] Reported as difference in means, consistent with the appropriate paired t-test. This is not as group mean
[*] Confidence interval is estimated for actual rate of escalation of care, based on an observed rate of 0% in 15 patient groups.

6.5 Other Endpoints

6.5.1 Requirement for Post-Discharge Care of Pleural Effusion

The requirement for post-discharge outpatient management of pleural effusion was equal, 7% for Cases who had thoracentesis and 7% for Controls who did not have procedural intervention (95% CI 0.00-0.34). The requirement for readmission was equal, 13% for both Cases and Controls (95% CI 0.02-0.42).

6.5.2 Incidence of Atrial Fibrillation

A total of 11 patients with pleural effusion experienced at least one postoperative day of AF following cardiac surgery from POD3-POD7 (RR = 0.37, 95% CI 0.21 – 0.56). There was no significant difference between Cases and Controls for the incidence of postoperative AF (3 versus 8 patients, OR = 0.22, p = 0.13). Cases experienced postoperative AF for a mean of 2.3 days (SD = 1.5) and Controls experienced a mean of 1.8 days, (SD = 0.7) (p=0.45) as shown in Table 3. Where thoracentesis was performed before POD5 (n = 11), there was no incidence of AF in Case patients. This was significantly lower compared to 6 of 11 Control patients who experienced AF as shown in Table 4 (p = 0.01).

There was no significant difference in the mean daily dose of amiodarone between Cases and Controls during postoperative stay, 670 ± 1070 mg versus 730 ± 1070 mg, (p = 0.43). Cases required significantly less amiodarone than Controls if thoracentesis was performed before POD5 (n = 10), 220mg ± 520 versus 930mg ± 1190, (p=0.01). Postoperative AF had resolved by discharge for Cases, however, 1 Control patient was in AF on the day of discharge.

6.5.3 Incidence of Post-pericardiotomy Syndrome

During this study, there was no incidence of post-pericardiotomy syndrome documented amongst cardiac surgery patients with non-specific pleural effusion.

6.5.4 Evidence for Systemic Inflammation

During the inpatient study period, there was no significant difference in daily WBC for cardiac surgery patients who had thoracentesis for pleural effusion versus who did not have procedural intervention. Mean WBC during the inpatient study period was 9.8 ± 0.7 for Cases versus 9.9 ± 0.9 for Controls (p = 0.46). Mean WBC the day after thoracenteses was 7.1 ± 5.1 for Cases versus 7.2 ± 5.4 X 10^3 cells/mL for Controls on the equivalent POD (p=0.48). There were no fevers reported for Case or Controls during the study. The mean platelet count the day after thoracentesis was 139 ± 94 for Case and 151 ± 108 X 10^3 cells/mL for Controls on the equivalent POD (p = 0.37).

6.5.5 30-day Mortality

There was neither 30-day mortality nor absolute mortality documented amongst cardiac surgery patients with non-specific pleural effusion during this study.

6.5.6 Pleural Fluid Volumes Evacuated (Cases)

The median volume of pleural fluid removed from Case patients was 0.50 ± 0.50 L (Range 0.08 – 1.96L)

Table 3: Comparison of Cases and Controls: Incidence of Atrial Fibrillation

		Cases	Controls		
		n = 15	n = 15		
		Mean (SD)	**Mean (SD)**	**(p)**	**95% CI**
Atrial Fibrillation (AF)					
	Total Patients with AF	3	8	0.13[#]	
	Mean Days AF	2.3 (1.5)	1.8 (0.7)	0.45	
	Cum. Dose Amiodarone	670 (1070)	730 (1070)	0.43	
	Patients Discharged in AF	0	1	0.32	
Sensitivity Analysis by POD					
	AF in Patients where Thoracentesis < POD5 (n = 11)	0	6	0.01[#]	
	Cum. Dose Amiodarone	220 (520)	930 (1190)	0.01	
Evidence of Systemic Inflammation					
WBC	Mean	9.8 (0.7)	9.9 (0.9)	0.46	
	Day after Thoracentesis (or Matched POD)	7.1 (5.1)	7.2 (5.2)	0.48	
Fever	Days (T > 38.3°C)	0	0	0.5	
Platelets	Mean on Day after Thoracentesis (or Matched POD)	139 (94)	151 (108)	0.37	
Mortality					
	30-day	0	0		0.00 - 0.14[*]
	Absolute	0	0		0.00 - 0.14[*]

Table 3: Comparison of Cases who underwent thoracentesis versus age and procedure matched Controls who had no procedural intervention for non-specific pleural effusion after cardiac surgery. There was no significant difference in the study incidence of AF between Cases and Controls (3 vs. 8 patients, p = 0.13). The mean number of days in AF for individual patients was approximately 2 days and was not significantly different between groups (p = 0.45). Cases who underwent thoracentesis earlier than POD5 (n = 10) had no postoperative atrial fibrillation. This was significantly lower compared to 6 Control patients who had AF (p = 0.01). The cumulative dosing of amiodarone was significantly lower in Case patients when thoracentesis was performed <POD5 (n = 10, 220 vs. 930 mg, p = 0.01). There were no significant differences in markers of systemic inflammation including WBC (p = 0.46), fever (p = 0.5), or platelet counts (p = 0.37). No patients died during the inpatient or outpatient study periods in this study. The estimated 95% CI based on the study observation of death is 0 –14%.

[#] Determined by two – tailed Fisher's Exact Test

[*] Confidence interval is estimated for actual rate of mortality, based on an observed rate of 0% in 15 patient groups.

Table 4: Postoperative AF and Day of Thoracentesis: Comparison of Cases and Controls

	POD of Thoracentesis	Age	Operation	Postoperative Day (POD) POD3	POD4	POD5	POD6	POD7
Cases	3	84	CABG					D
	3	77	CABG					D
	3	85	CABG				D	D
	3	69	CABG			D	D	D
	3	62	CABG			D	D	D
	4	74	AVR					
	4	79	CABG					
	4	83	AVR				D	D
	4	66	CABG			D	D	D
	4	75	CABG			D	D	D
	4	80	CABG+AVR			D	D	D
	5	84	AVR	A	A	A	A	A
	5	60	CABG	A		A		
	5	81	CABG + AVR	A				
	5	71	CABG					
Controls	POD3-4 Match	81	CABG				A	
	POD3-4 Match	85	CABG	A		A		D
	POD3-4 Match	80	CABG	A	A	A		
	POD3-4 Match	69	CABG	A	A	D	D	D
	POD3-4 Match	84	AVR	A	A			
	POD3-4 Match	76	CABG	A			D	D
	POD3-4 Match	75	AVR					
	POD3-4 Match	79	CABG+AVR				D	D
	POD3-4 Match	66	CABG			D	D	D
	POD3-4 Match	62	CABG			D	D	D
	POD3-4 Match	75	CABG			D	D	D
	POD5 Match	80	CABG + AVR				A	
	POD5 Match	70	CABG	A	A	A	D	D
	POD5 Match	59	CABG					D
	POD5 Match	83	AVR				D	D

Legend

	Day without AF
A	Day with AF
D	Discharged

Table 4: Comparison of Cases who underwent thoracentesis versus age and procedure matched Controls who had no procedural intervention for non-specific pleural effusion after cardiac surgery. Amongst Cases and Controls, there was no difference in the overall number of days of AF (2.3 ± 1.5 vs. 1.8 ± 0.7, p=0.45), or daily incidence of AF (OR = 0.22, p = 0.13). Where thoracentesis was performed before POD5 (n = 10), there was no incidence of AF in Case patients versus 6 of 10 Control patients (OR = 0, p = 0.01). There was no significant difference in the mean daily dose of amiodarone between Cases and Controls during postoperative stay, 670 ± 1070 mg versus 730 ± 1070 mg, (p = 0.43).

7 Discussion

Non-specific pleural effusion contributes to pulmonary dysfunction after cardiac surgery[4, 8-10]. In the present study, our objectives were to 1) measure the frequency of reduced dyspnea after thoracentesis on cardiac surgery patients with non-specific pleural effusion; and 2) compare clinical outcomes between patients who had thoracentesis versus those who did not have procedural intervention. To our knowledge, this is the first comparative evaluation of outcomes for early thoracentesis in cardiac surgery patients with non-specific pleural effusion.

The observed frequency of improved dyspnea after thoracentesis was 73% as measured by a ≥2 LPM reduction in daily peak supplemental O2 requirement. Although the limited sample size does not allow this rate to be defined precisely, we are reasonably confident that the majority of patients improve after intervention is performed (95% CI 0.45 – 0.92). The median volume of pleural fluid removed from Case patients was 0.50 ± 0.50 L (Range 0.08 – 1.96L). There was no relationship between the volumes of pleural fluid removed and improved dyspnea in our study ($p = 0.59$). The median pleural fluid volume removed from patients by thoracentesis in our study generally correlates with blunting of the costophrenic angles on a chest radiograph[65]. This volume is also at the intervention cut off point in the algorithm proposed by Usta, *et al* for symptomatic patients[65].

We have proposed that non-specific pleural effusion after cardiac surgery is the result of interrelated lung and pleural inflammation; and early reduction of PMN burden in the pleural space with thoracentesis might shorten the duration of symptoms. Most non-specific pleural effusions are thought to spontaneously resolve about a week after uncomplicated cardiac surgery[5]. Whether or not thoracentesis improves dyspnea beyond that which is experienced during the typical day – to – day postoperative course is unclear. The odds ratio for improvement of dyspnea for Cases who had thoracentesis versus age and operation matched Controls was 3.1. But this was not significant for the limited number of patients studied ($p = 0.14$, 95% CI 0.7 – 14.5).

One interpretation of this result could be that thoracentesis doesn't improve dyspnea compared to the typical day – to – day postoperative course. For this interpretation, we would offer that reduction of PMN burden had no impact on dyspnea. Symptomatic improvement after thoracentesis is generally correlated with increasing volumes of pleural fluid removed[11, 12]. If there is no difference between these groups, we might explain this by the small size of effusions encountered (median = 0.5 L). However, an alternative explanation is that the current study was underpowered to detect significant differences between the two groups. The upper limit of the OR 95% confidence interval is 14.5 in the setting of a trend toward statistical significance. This large upper limit leads us to believe that the study was in fact, underpowered to detect a significant difference.

We found no significant difference in LOS for Cases who had thoracentesis versus Controls who did not (6.7 ± 3.2 days versus 5.8 ± 1.6 days, p=0.84). Therefore, we could not substantiate reports made by mid-level providers that cardiac surgery patients experience *fewer* postoperative days in hospital after thoracentesis. Patient LOS at our institution was observed to be shorter than for similar patients in the literature (5-7 versus 9-14 days)[64].

An interesting related observation is that Cases who required thoracentesis had a significantly higher oxygen requirement on POD3 versus matched Controls (mean = 2.7 versus 1.2 LPM, p = 0.02). If patients who had thoracentesis were more symptomatic than matched Controls, but there was no difference in LOS, this raises some questions about the role of thoracentesis in their course of recovery. The mean length of stay from thoracentesis to discharge for Cases was not significantly different versus the equivalent day to discharge for Controls (2.8 vs. 1.9 days, p = 0.84). Linear regression analysis revealed a significant positive correlation between LOS and POD of thoracentesis (Coef. of Variation = 2.5, SE = 0.84, $p < 0.01$). By this trend, we could predict that patients who had thoracentesis on POD3 would stay 4 days, on POD4 would stay 7 days, and POD5 would stay 9 days. Although we cannot say whether or not thoracentesis augmented hospital course, there is an argument that this might have been the case.

We did not observe escalation of care during the study period for either Cases or Controls. Based on our statistical analysis, the probability that our actual rate of escalation of care is ≤10% can be made with >95% confidence (p = 0.04, 95% CI 0.00 – 0.14). Although not explicitly an endpoint, there were no complications of bleeding, infection, or pneumothorax attributable to thoracentesis during the study.

Approximately 30% of inpatient cardiac surgery patients will have postoperative AF[67]. The current study observed a rate of 33% amongst all patients, which is consistent with the literature. There was no significant difference between Cases and Controls for the odds of developing postoperative AF during the present study (3 versus 8 patients, OR = 0.22, p = 0.13). If a patient had postoperative AF, the mean number of days in AF was also not significantly different between Case and Control patients (2.3 versus 1.8 days, p = 0.45). Sensitivity analysis by the POD of thoracentesis demonstrated that the odds of postoperative AF were significantly reduced for Cases (0:11) versus matched Controls (6:5) if intervention was performed before POD5 (p = 0.01). The incidence of AF was also significantly lower for Cases who underwent thoracentesis prior to POD5 (0 of 11 patients) versus *Cases* who underwent thoracentesis on POD5 (3 of 4 patients)(95% CI 0.00 – 0.95, p = 0.05).

The differences in incidence of postoperative AF amongst Cases and Controls might be explained by several factors. These include: 1) inpatient medical management, 2) systemic inflammation, 3) postoperative risk factors, 4) preoperative risk factors, and 5) the study design [e.g. resolution of AF prior to POD3]. First, the cumulative dosage of amiodarone was not significantly different between groups during the inpatient period of study (670 versus 730 mg, p = 0.43). Second, there was no difference observed for markers of systemic inflammation during the study. These included mean WBC (9.8 vs. 9.9 X 10^3 cells/mL, p < 0.46) and the absence of fever during the inpatient period of study in both groups. Third, the highest *postoperative* risk factors for new onset AF after cardiac surgery are pulmonary edema (OR = 5) and pleural effusion requiring thoracentesis (OR = 3)[59]. Although not formally measured, nearly all of the Cases and Controls had some minor component of pulmonary edema on their POD3 chest x-ray. By design, only Cases had been determined to require a thoracentesis during the study. We did not find an increased risk of postoperative AF with the requirement for thoracentesis.

Fourth, the highest *preoperative* risk factor for postoperative AF is a prior history of AF[67]. Although the incidence of AF [e.g. chronic or paroxysmal] in the general population is 2 – 4%, the incidence of preoperative AF for patients undergoing cardiac surgical procedures is approximately 30%[67]. Contributing preoperative risk factors for *new onset* of postoperative AF include age >75 years and history of stroke[59, 67]. The mean age of patients in our study was 75 years but this was not different between Case and Control groups ($p = 0.89$). However, we did not evaluate prior history of AF or stroke to account for differences in the risk of postoperative AF. Perhaps preoperative risk might explain the differences in both incidence and persistence of AF between the two groups after cardiac surgery. Fifth, additional reasons for not detecting postoperative AF would have been resolution prior to POD3 or occurrence after POD7.

An alternative explanation for the differences in incidence of AF between Cases and Controls is the early treatment of pleural effusion. Stamou, *et al*, have shown that pleural effusion is a risk factor for new onset AF after cardiac surgery[59]. Pericardial effusion is also a known risk factor for AF and up to 63% of patients maintain a sub-clinical pericardial effusion 1-week after surgery[60]. Vargas, *et al*, have demonstrated that the persistence of pericardial effusion is dependent on the persistence of pleural effusion after myocardial revascularization[61]. Early treatment of pleural effusion in Cases might therefore explain the difference in incidence of AF. We have also proposed that early reduction of PMN burden in the pleural space with thoracentesis might shorten the duration of lung and pleural inflammation. The COPPS-2 trial demonstrated a lower incidence of both pleural effusion and atrial fibrillation with the use colchicine as an anti-inflammatory agent[57]. One of the mechanisms of action for colchicine is reduction in PMN recruitment[57]. It is reasonable to suspect that reducing PMN recruitment with colchicine would have reduced PMN burden in the pleural space. Although not definitive, the present study might provide some evidence that PMN burden in the pleural space is part of the pathogenesis pathway in postoperative AF.

There are several limitations to this study. First, daily peak O2 supplementation was used as a surrogate marker of changes in dyspnea in the absence of a validated instrument. A validated instrument

would have presumably produced more precise results. Second, a small number of patients were thought required to show statistical significance in terms of the major endpoints for this study. We did not power the study appropriately to show differences for our other endpoints and this was a limitation to interpreting some of the results. Third, our findings for postoperative AF are interpreted with some hesitation. We did not evaluate patients for preoperative risk factors for postoperative AF. Preoperative risk could have explained the differences in both incidence and persistence of AF during the study. Lastly, our study design was useful in terms of expeditiously completing a low-cost pilot project but the results might not be readily generalizable to larger populations of cardiac surgery patients.

Several research questions that have emerged from the present study. First, *who* is appropriate for thoracentesis after cardiac surgery? Usta, *et al*, used the size of pleural effusion (> 480mL) estimated by chest x-ray and thoracic ultrasound in symptomatic patients in order to determine who should undergo thoracentesis[65]. For smaller symptomatic effusions, patients in their study received diuretics[65]. In our study, more than half the Cases that improved after thoracentesis had a pleural fluid volume of less than 400mL. Additionally, there is no comparative data to suggest that diuretics are a superior therapy to thoracentesis for patients with smaller effusions. Diuretics increase the concentration of proteins in the pleural space as compared to thoracentesis[71]. This could feasibly promote ongoing inflammation and related pulmonary symptoms after cardiac surgery. Usta's study also suggests that LOS is longer for patients who receive diuretics for small effusions[65]. Perhaps the use of diuretics in these small effusions evolved due to the historically poor complication rate for thoracentesis in the setting of uncertain benefit. If this is the case, its use in smaller effusions might require some reconsideration given the reduced complication rate for thoracentesis with thoracic ultrasound.

Second, does thoracentesis augment the postoperative course of patients with non-specific pleural effusion who require intervention after cardiac surgery? We think that the current report lays some groundwork for such an outcomes study. The goals of our study were to measure frequency of improvement and compare selected outcomes with age and procedure controls. We found that the majority of patients experience some improvement of dyspnea with thoracentesis but these people might have been

sicker after surgery. We have further demonstrated that there are increased odds for improved dyspnea for patients who have thoracentesis versus age and operation matched controls. We did not show significance for this result, likely because the study was not powered to detect it. We have reported that there is no difference for LOS between patients who have thoracentesis. A larger study might have also detected a difference for LOS that favored Controls. Lastly, regression analysis suggested that patients who had thoracentesis later in their course, stayed longer. We think that there might be a beneficial impact for thoracentesis in the postoperative course for certain patients who require intervention. But this has yet to be fully elucidated.

Lastly, is there a role for early thoracentesis (before POD5) in reducing postoperative AF? Designing an ideal study with generalizable results might be challenging at this point. We can, however, offer some considerations based on the learning from our current study. First, a prospective study might enable the use of an instrument that reliably documents preoperative risk factors for postoperative AF. Our current study would have benefited from an accurate account of preoperative risk factors for AF in interpreting our results. Second, we might consider broadening the inpatient period of study to encompass the entire postoperative length of stay. We did not measure postoperative AF prior to POD3 or after POD7 in the current study, which may have biased our results. Third and as suggested above, a better understanding of which patients should have intervention might be helpful in determining selection criteria for an intervention group in a prospective study. Well-defined selection criteria might help determine the limits of generalizability for reported results. In the current study, it was unclear what the selection criteria were for thoracentesis and this impacts the generalizability of our reported outcomes data.

8 Conclusions

The present pilot study suggests that the majority of patients who have symptomatic pleural effusion have some improvement in dyspnea after thoracentesis. This benefit did not translate into reduced length of stay. Our observations also suggest that patients might experience fewer days in AF with thoracentesis, particularly if performed earlier in the course of their postoperative care. These observations were limited to patients with pulmonary symptoms that required thoracentesis based on unclear clinical criteria. We

interpret these results with some hesitation, primarily because preoperative risk factors for postoperative AF could have explained differences detected between Cases and Controls. Future research might focus on better defining the clinical criteria for thoracentesis in non-specific pleural effusion and better understanding the impact of intervention on postoperative course.

9 References

1. Hall, M., et al., *National Hospital Discharge Survey: 2007 Summary*, in *National Health Statistics Reports*. 2010, Naitonal Center for Health Statistics: Hyattsville, Maryland. p. 1-24.
2. Dvir, D., et al., *Transcatheter Aortic Valve Replacement for Degenerative Bioprosthetic Surgical Valves.* Circulation, 2012. **126**: p. 2335-2344.
3. Light, R., *Pleural Effusions Following Cardiac Injury and Coronary Artery Bypass Graft Surgery.* Sem Resp Crit Care Med, 2001. **22**(6): p. 657-663.
4. Labidi, M., et al., *Pleural Effusions Following Cardiac Surgery: Prevalence, Risk Factors, and Clinical Features.* CHEST, 2009. **136**: p. 1604-1611.
5. Light, R., et al., *Prevalence and Clinical Course of Pleural Effusions at 30 Days after Coronary Artery and Cardiac Surgery.* Am J Respir Crit Care Med, 2002. **166**: p. 1567-1571.
6. Light, R., et al., *Large pleural effusions occuring after coronary artery bypass grafting.* Ann Intern Med, 1999. **130**: p. 891-96.
7. Vargas, F., et al., *Relationship Between Pleural Changes after Myocardial Revascularization and Pulmonary Mechanics.* CHEST, 1992. **102**: p. 1333-36.
8. Wynne, R. and M. Botti, *Postoperative Pulmonary Dysfunction in Adults After Cardiac Surgery with Cardiopulmonary Bypass: Clinical Significance and Implications for Practice.* Am J Crit Care, 2004. **13**(5): p. 384-393.
9. Braun, S., M. Birnbaum, and P. Chopra, *Abnormalities in Coronary Artery Revascularization Surgery.* CHEST, 1978. **73**(3): p. 316-320.
10. Van Belle, A., et al., *Postoperative pulmonary function abnormalities after coronary artery bypass surery.* Resp Med, 1992. **86**: p. 1995-199.
11. Gilmartin, J., A. Wright, and G. Gibson, *Effects of pneumothorax or pleural effusion on pulmonary function.* Thorax, 1985. **40**: p. 60-65.
12. Brown, N., N. Zamel, and A. Aberman, *Changes in Pulmonary Mechanics and Gas Exchange following Thoracocentesis.* CHEST, 1978. **74**(5): p. 540-542.
13. Rodriguez RM, et al. *Prevalence and Clinical Course of Pleural Effusion at 30 days post-Coronary Bypass Surgery*. in *American College of Chest Physicians*. 1999. Chicago, IL: American College of Chest Physicians.
14. Vargas, F., et al., *Actue Pleuropulmonary Complications Detected by Computed Tomography Following Myocardial Revascularization.* Rev Hosp Clin Fac Med S Paulo, 2002. **57**(4): p. 135-142.
15. Jensen, L. and L. Yang, *Risk factors for postoperative pulmonary complications in coronary artery bypass graft surgery patients.* Eu J Cardiov Nursing, 2007. **6**: p. 241-246.
16. Brody, W. and B. Reitz, *Topical Hypothermic Protection of the Myocardium.* Ann Thorac Surg, 1975. **20**(1): p. 66-71.
17. Allen, B., et al., *Topical cardiac hypothermia in patients with coronary disease. An unnecessary adjunct to cardioplegic protection and cause of pulmonary morbidity.* J Thorac Cardiovasc Surg, 1992. **104**(3): p. 626-631.
18. Nikas, D., F. Ramadan, and J. Elefteriades, *Topical Hypothermia: Ineffective and Deleterious as Adjunct to Cardioplegia for Myocardial Protection.* Ann Thorac Surg, 1998. **65**(1): p. 28-31.
19. Landymore, R. and F. Howell, *Pulmonary complications following myocardial revascularization with the internal mammary artery graft.* Eur J Cardiothorac Surg, 1990. **4**(156-162).
20. Iverson, L., et al., *Injuries to the phrenic nerve resulting in diaphragmatic paralysis with special reference to stretch trauma.* Am J Surg, 1976. **132**: p. 263-268.
21. Mattison, L., et al., *Pleural Effusions in the Medical ICU: Prevalence, Causes, and Clinical Implications.* CHEST, 1997. **111**: p. 1018-1023.
22. Stark, P. and A. Leung, *Effects of Lobar Atelectasis on the Distribution of Pleural Effusion and Pneumothorax.* J Thorac Imag, 1996. **11**: p. 145-149.
23. Miserocchi, G., *Mechanisms controlling the volume of pleural fluid and extravascular lung water.* Eur Respir Rev, 2009. **18**(114): p. 244-252.
24. Kroegel, C. and V. Antony, *Immunobiology of pleural inflammation: potential implications for pathogenesis, diagnosis, and therapy.* Eur Respir J, 1997. **10**: p. 2411-2418.
25. Wilcox, P., et al., *Phrenic Nerve Function and Its Relationship to Atelectasis After Coronary Artery Bypass Surgery.* CHEST, 1988. **93**(4): p. 693-698.

26. Zupancich, E., et al., *Mechanical ventilation affects inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: A randomized clinical trial.* J Thorac Cardiovasc Surg, 2005. **130**(2): p. 378-383.
27. Paparella, D., T. Yau, and E. Young, *Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update.* Eu J Cardio Thorac Surg, 2002. **21**: p. 232-244.
28. Bellomo, R., J. Raman, and C. Ronco, *Intensive Care Unit Management of the Critically Ill Patient with Fluid Overload after Open Heart Surgery.* Cardiology, 2001. **96**: p. 169-176.
29. Hachenberg, T., et al., *Thoracic intravascular and extravascular fluid volumes in cardiac surgical patients.* Anesthesiology, 1993. **79**(5): p. 976-984.
30. Massoudy, P., et al., *Evidence for Inflammatory Responses of the Lungs During Coronary Artery Bypass Grafting with Cardiopulmonary Bypass.* CHEST, 2001. **119**(1): p. 31-36.
31. Conti, V., *Pulmonary Injury After Cardiopulmonary Bypass.* CHEST, 2001. **119**(1): p. 2-4.
32. Wan, S., J. LeClerc, and J. Vincent, *Inflammatory Response to Cardiopulmonary Bypass: Mechanisms Involved and Possible Therapeutic Strategies.* CHEST, 1997. **112**: p. 676-692.
33. Roth-Isigkeit, A., et al., *Inter-individual differences in cytokine release in patients undergoing cardiac surgery with cardiopulmonary bypass.* Clin Exp Immunol, 2001. **125**: p. 80-88.
34. Gehlbach, B. and E. Geppert, *The Pulmonary Manifestations of Left Heart Failure.* CHEST, 2004. **125**(2): p. 669-682.
35. Wiener-Kronish, J., et al., *Relationship of Pleural Effusions to Increased Permeability Pulmonary Edema in Anesthetized Sheep.* J Clin Invest, 1988. **82**: p. 1422-1429.
36. Wiener-Kronish, J. and M. Matthay, *Pleural Effusions Associated with Hydrostatic and Increased Permeability Pulmonary Edema.* CHEST, 1988. **93**(4): p. 852-858.
37. Sadikot, R., et al., *Pleural Fluid Characteristics of Patients with Symptomatic Pleural Effusion After Coronary Artery Bypass Graft Surgery.* Arch Intern Med, 2000. **160**: p. 2665-2668.
38. Gilbert, T., G. Barnas, and A. Sequeira, *Impact of pleurotomy, continuous positive airway pressure, and fluid balance during cardiopulmonary bypass on lung mechanics and oxygenation.* J Cardiothorac Vasc Anesth, 1996. **7**: p. 844-849.
39. Taggart, D., et al., *Respiratory Dysfunction After Uncomplicated Cardiopulmonary Bypass.* Ann Thorac Surg, 1993. **56**: p. 1123-1128.
40. Utley, J., *Pathophysiology of Cardiopulmonary Bypass: A Current Review.* AustralAs J Thorac Surg, 1992. **1**(2): p. 46-52.
41. Martin, W., et al., *Respiratory dysfunction and white cell activation following cardiopulmonary bypass: comparison of membrane and bubble oxygenators.* Eu J Cardio Thorac Surg, 1996(10): p. 774-783.
42. Hurlbut, D., et al., *Pleuropulmonary morbidity: internal thoracic artery versus saphenous vein graft.* Ann Thorac Surg, 1990. **50**(6): p. 959-964.
43. Ali, I., P. Lau, and C. Kinley, *Opening the pleura during internal mammary artery harvesting: advantages and disadvantages.* Can J Surg, 1996. **39**: p. 42-45.
44. Jain, U., et al., *Radiographic pulmonary abnormalities after different types of cardiac surgery.* J Cardiothorac Vasc Anesth, 1991. **5**(6): p. 592-595.
45. Porcel, J. and R. Light, *Diagnostic Approach to Pleural Effusion in Adults.* Am Fam Physician, 2006. **73**: p. 1211-1220.
46. Ali, H., et al., *Spontaneous Hemothorax: A Comprehensive Review.* CHEST, 2008. **134**: p. 1056-1065.
47. Medzhitov, R., *Origin and physiology roles of inflammation.* Nature, 2008. **454**(24): p. 428-435.
48. Cailhier, J., et al., *Resident pleural macrophages are key orchestrators of neutrophil recruitment in pleural inflammation.* Am J Respir Crit Care Med, 2006. **173**(5): p. 540-547.
49. Murai, N., et al., *Concurrent evolution and resolution in an acute inflammatory model of rat carrageenin-induced pleurisy.* J Leuk Bio, 2003. **73**: p. 456-463.
50. Murphy, K., *Janeway's Immunobiology*. 8th ed. 2012, London, England and New York, NY: Garland Science, Taylor and Francis Group, LLC.
51. Lo, C., et al., *IL-6 Trans-Signaling in Formation and Progression of Malignant Ascites in Ovarian Cancer.* Cancer Res, 2010. **71**(2): p. 424-434.
52. Mutsaers, S., *Mesothelial cells: Their structure, function, and role in serosal repair.* Respirology, 2002. **7**: p. 171-191.
53. Mutsaers, S., et al., *Pathogenesis of pleural fibrosis.* Respirology, 2004. **9**: p. 428-440.

54. Heidecker, J. and S. Sahn, *The Spectrum of Pleural Effusions After Coronary Artery Bypass Grafting Surgery.* Clin Chest Med, 2006. **27**: p. 267-283.
55. Imazio, M., *The post-pericardiotomy syndrome.* Curr Opin Pulm Med, 2012. **18**(4): p. 366-74.
56. Imazio, M., *Diagnosis and Management of the Postpericardiotomy Syndrome.* Clin Pulm Med, 2014. **21**(5): p. 220-4.
57. Imazio, M., et al., *Colchicine for Prevention of Postpericardiotomy Syndrome and Postoperative Atrial Fibrillation: The COPPS-2 Randomized Clinical Trial.* JAMA, 2014. **312**(10): p. 1016-2023.
58. Molad, Y., *Update on Cochicine and It's Mechanism of Action.* Curr Rheum Rep, 2002. **4**: p. 252-256.
59. Stamou, S., et al., *Atrial Fibrillation After Beating Heart Surgery.* Am J Cardiology, 2000. **86**: p. 64-67.
60. Ikaheimo, M., et al., *Pericardial effusion after cardiac surgery: Incidence, relation to the type of surgery, antithrombotic therapy, and early coronary bypass graft patency.* Am Heart J, 1988. **116**(1): p. 97-102.
61. Vargas, F., et al., *Relationship Between Pleural Effusion and Pericardial Involvement After Myocardial Revascularization.* CHEST, 1994. **105**(6): p. 1748-1752.
62. Gibson, A. and M. Segal, *A study of the routes by which protein passes from the pericardial cavity to the blood in rabbits.* J Physiol, 1978. **280**: p. 423-433.
63. Bartter, T., et al., *Lower Risk and Higher Yield for Thoracentesis When Performed by Experienced Operators.* CHEST, 1993. **103**: p. 1873-76.
64. Lichtenstein, D., et al., *Comparative Diagnostic Performances of Auscultation, Chest Radiography, and Lung Ultrasonography in Acute Respiratory Distress Syndrome.* Anesthesiology, 2004. **100**: p. 9-15.
65. Usta, E., M. Migdat, and G. Ziemer, *Ultrasound estimation of volume of postoperative pleural effusion in cardiac surgery patients.* Interactive CardioVasc and Thor Surg, 2010. **10**: p. 204-207.
66. Amar, D., et al., *Clinical Prediction Rule for Atrial Fibrillation After Coronary Artery Bypass Grafting.* J Amer Coll Cardio, 2004. **44**(6): p. 1248-1253.
67. Almassi, G., et al., *Atrial fibrillation after cardiac surgery: a major morbid event?* Ann Surg, 1997. **226**(4): p. 501-513.
68. Tremblay, A. and G. Michaud, *Single-Center Experience with 250 Tunnelled Pleural Catheter Insertions for Malignant Pleural Effusion.* CHEST, 2006. **129**: p. 362-368.
69. Payne, M., et al., *Left Pleural Effusion After Coronary Artery Bypass Decreases With a Supplemental Pleural Drain.* Ann Thorac Surg, 2002. **73**: p. 149-152.
70. Hibbert, R., et al., *Safety of Ultrasound-Guided Thoracentesis in Patients with Abnormal Preprocedural Coagulation Parameters.* CHEST, 2013. **144**(2): p. 456-463.
71. Romero-Candeira, S., et al., *Influence of Diuretics on the Concentration of Proteins and Other Components of Pleural Transudates in Patients with Heart Failure.* Am J Med, 2001. **110**: p. 681-686.

10 Appendix A

10.1 Data Abstraction Form

Perioperative Intervention for Post-pericardiotomy Pleural Effusion

Unique Identifier: _____

10.1.1 Baseline Data and Assessment

1. **Patient meets all criteria for study inclusion:** ☐ Yes (1) ☐ No (0)

Inclusion Criteria
Patients with radiographically diagnosed pleural effusion are considered. Subjects must meet all of the following inclusion criteria to be entered into the study:

- Post-primary open cardiac surgery (CABG, valve, CABG + valve, etc.)
- Age 40-85 years
- Diagnosis of postoperative pleural effusion in the perioperative period (< POD7)

2. **Patient meets criteria for study exclusion:** ☐ Yes (1) ☐ No (0)

Exclusion Criteria
Any of the following will exclude the subject from study:

- Prior cardiac surgery
- History of pleurodesis
- Patients with pleural effusion known to be associated with non-surgery related etiology (e.g. pancreatitis, malignancy, etc.)
- Surgical complications (e.g. intraoperative bleeding)
- Maintenance of a (contralateral) chest tube or Pleurex® catheter at diagnosis of pleural effusion
- INR > 2.5 at the time of thoracentesis

3. **Case or Control Subject** ☐ Case (1) ☐ Control (0)

4. **Case Matched Control Number (if Case)** _____

5. **Age (years)** _____

6. **Surgical Procedure**

☐ CABG (0)
☐ Valve (1)
☐ CABG + Valve (2)
☐ Other (3)
If Other, Please Specify:
_____

10.1.2 Cardiopulmonary Recovery

Postoperative Day (POD)	Max Requirement for Supplemental O2	Atrial Fibrillation	Dose of Amiodarone	Fever (T>38.3° C)	WBC	Platelets
POD 3	7. ☐ 0 L/min (No Reqmnt) (0) ☐ > 0, ≤ 2L/min (1) ☐ > 2, ≤ 4L/min (2) ☐ > 4, ≤ 6L/min (3) ☐ > 6, ≤ 8L/min (4) ☐ > 8, ≤ 10L/min (5) ☐ > 10L/min (6)	8. ☐ Yes (1) ☐ No (0)	9. Cum 24-hr Dose *(if none, write 0)* _____mg	10. ☐ Yes (1) ☐ No (0)	11. _____ X 10^3 cells/mL	12. _____ X 10^3 cells/mL
POD 4	13. ☐ 0 L/min (No Reqmnt) (0) ☐ > 0, ≤ 2L/min (1) ☐ > 2, ≤ 4L/min (2) ☐ > 4, ≤ 6L/min (3) ☐ > 6, ≤ 8L/min (4) ☐ > 8, ≤ 10L/min (5) ☐ > 10L/min (6)	14. ☐ Yes (1) ☐ No (0)	15. Cum 24-hr Dose *(if none, write 0)* _____mg	16. ☐ Yes (1) ☐ No (0)	17. _____ X 10^3 cells/mL	18. _____ X 10^3 cells/mL
POD 5	19. ☐ 0 L/min (No Reqmnt) (0) ☐ > 0, ≤ 2L/min (1) ☐ > 2, ≤ 4L/min (2) ☐ > 4, ≤ 6L/min (3) ☐ > 6, ≤ 8L/min (4) ☐ > 8, ≤ 10L/min (5) ☐ > 10L/min (6)	20. ☐ Yes (1) ☐ No (0)	21. Cum 24-hr Dose *(if none, write 0)* _____mg	22. ☐ Yes (1) ☐ No (0)	23. _____ X 10^3 cells/mL	24. _____ X 10^3 cells/mL
POD 6	25. ☐ 0 L/min (No Reqmnt) (0) ☐ > 0, ≤ 2L/min (1) ☐ > 2, ≤ 4L/min (2) ☐ > 4, ≤ 6L/min (3) ☐ > 6, ≤ 8L/min (4) ☐ > 8, ≤ 10L/min (5) ☐ > 10L/min (6)	26. ☐ Yes (1) ☐ No (0)	27. Cum 24-hr Dose *(if none, write 0)* _____mg	28. ☐ Yes (1) ☐ No (0)	29. _____ X 10^3 cells/mL	30. _____ X 10^3 cells/mL
POD 7	31. ☐ 0 L/min (No Reqmnt) (0) ☐ > 0, ≤ 2L/min (1) ☐ > 2, ≤ 4L/min (2) ☐ > 4, ≤ 6L/min (3) ☐ > 6, ≤ 8L/min (4) ☐ > 8, ≤ 10L/min (5) ☐ > 10L/min (6)	32. ☐ Yes (1) ☐ No (0)	33. Cum 24-hr Dose *(if none, write 0)* _____mg	34. ☐ Yes (1) ☐ No (0)	35. _____ X 10^3 cells/mL	36. _____ X 10^3 cells/mL
Discharge	37. ☐ 0 L/min (No Reqmnt) (0) ☐ > 0, ≤ 2L/min (1) ☐ > 2, ≤ 4L/min (2) ☐ > 4, ≤ 6L/min (3) ☐ > 6, ≤ 8L/min (4) ☐ > 8, ≤ 10L/min (5) ☐ > 10L/min (6)	38. ☐ Yes (1) ☐ No (0)	39. Cum 24-hr Dose *(if none, write 0)* _____mg	40. ☐ Yes (1) ☐ No (0)	41. _____ X 10^3 cells/mL	42. _____ X 10^3 cells/mL

43. Cases: POD of Thoracentesis POD: _____

44. Cases: Pleural Fluid Volume Removed Volume: _____ mL

10.1.3 Postoperative Course

45. Length of Postoperative Inpatient Stay: _____ Days

46. Requirement for Escalation of Care:
- ❑ Yes (1)
- ❑ No (0)

47. Discharge O2 Requirement: _____ L/min
(if none, write 0)

10.1.4 Post-Discharge Course

48. Diagnosis of post-pericardiotomy syndrome:
- ❑ Yes (1)
- ❑ No (0)

49. Death (within 30-days):
- ❑ Yes (1)
- ❑ No (0)

50. Requirement for hospital re-admission:
- ❑ Yes (1)
- ❑ No (0)

51. Requirement for outpatient procedural management of pleural effusion:
- ❑ Yes (1)
- ❑ No (0)

11 Appendix B

11.1 STATA Do-Command Program for Data Analysis

Study: Thoracentesis in Cardiac Surgery Patients with Non-Specific Pleural Effusion

Written by David R. Kull, MPH

```
* Start Program

window stopbox rusure "WARNING: The following program
is designed to run in a specific file structure on one specific
computer.  Continue?"

clear

* System Memory Allocation

set memory 1000000

* Clear Data in Memory and Settings
clear all
capture log close
set more off

* Save Data and Log

log using "/Users/davidkull/Desktop/Pericardiotomy - Pleural
Effusion MGMT/DATA/ppcpe.log", replace

* Import PPCPE CSV Delimited TXT File

insheet using "/Users/davidkull/Desktop/Pericardiotomy -
Pleural Effusion MGMT/DATA/PPCPE.csv"

* Label Imported Variables

label var id_case "Case ID"
label var age_case "Case Age"
label var proc_case "Case Procedure"
label var pod2_o2_case "Case POD2 O2 Requirement"
label var pod3_o2_case "Case POD3 O2 Requirement"
label var pod3_af_case "Case POD3 Atrial Fibrillation"
label var pod3_amio_case "Case POD3 Cumulative
Amiodarone Requirement"
label var pod3_fev_case "Case POD3 Fever"
label var pod3_wbc_case "Case POD3 White Cell Count"
label var pod3_plts_case "Case POD3 Platelets"
label var pod4_o2_case "Case POD4 O2 Requirement"
label var pod4_af_case "Case POD4 Atrial Fibrillation"
label var pod4_amio_case "Case POD4 Cumulative
Amiodarone Requirement"
label var pod4_fev_case "Case POD4 Fever"
label var pod4_wbc_case "Case POD4 White Cell Count"
label var pod4_plts_case "Case POD4 Platelets"
label var pod5_o2_case "Case POD5 O2 Requirement"
label var pod5_af_case "Case POD5 Atrial Fibrillation"
label var pod5_amio_case "Case POD5 Cumulative
Amiodarone Requirement"
label var pod5_fev_case "Case POD5 Fever"
label var pod5_wbc_case "Case POD5 White Cell Count"
label var pod5_plts_case "Case POD5 Platelets"
label var pod6_o2_case "Case POD6 O2 Requirement"
label var pod6_af_case "Case POD6 Atrial Fibrillation"
label var pod6_amio_case "Case POD6 Cumulative
Amiodarone Requirement"
label var pod6_fev_case "Case POD6 Fever"
label var pod6_wbc_case "Case POD6 White Cell Count"
label var pod6_plts_case "Case POD6 Platelets"
label var pod7_o2_case "Case POD7 O2 Requirement"
label var pod7_af_case "Case POD7 Atrial Fibrillation"
label var pod7_amio_case "Case POD7 Cumulative
Amiodarone Requirement"
label var pod7_fev_case "Case POD7 Fever"
label var pod7_wbc_case "Case POD7 White Cell Count"
label var pod7_plts_case "Case POD7 Platelets"
label var dis_o2_case "Case Discharge O2 Requirement"
label var dis_af_case "Case Discharge Atrial Fibrillation"
label var dis_amio_case "Case Discharge Cumulative
Amiodarone Requirement"
label var dis_fev_case "Case Discharge Fever"
label var dis_wbc_case "Case Discharge White Cell Count"
label var dis_plts_case "Case Discharge Platelets"
label var pod_int_case "Case POD Intervention"
label var case_vol_case "Case Volume Pleural Fluid"
label var los_case "Case Length of Stay"
label var escal_case "Case Escalation of Care"
label var dis_o2req_case "Case Discharged on O2"
label var ppcs_case "Case Post Pericardiotomy Syndrome"
label var death_case "Case Death"
label var readmit_case "Case Readmission"
label var out_mgmt_case "Case Req for Outpatient
Management"
label var id_control "Control ID"
label var age_control "Control Age"
label var proc_control "Control Procedure"
label var pod2_o2_control "Control POD2 O2 Requirement"
label var pod3_o2_control "Control POD3 O2 Requirement"
label var pod3_af_control "Control POD3 Atrial Fibrillation"
label var pod3_amio_control "Control POD3 Cumulative
Amiodarone Requirement"
label var pod3_fev_control "Control POD3 Fever"
label var pod3_wbc_control "Control POD3 White Cell
Count"
label var pod3_plts_control "Control POD3 Platelets"
label var pod4_o2_control "Control POD4 O2 Requirement"
label var pod4_af_control "Control POD4 Atrial Fibrillation"
label var pod4_amio_control "Control POD4 Cumulative
Amiodarone Requirement"
label var pod4_fev_control "Control POD4 Fever"
label var pod4_wbc_control "Control POD4 White Cell
Count"
label var pod4_plts_control "Control POD4 Platelets"
label var pod5_o2_control "Control POD5 O2 Requirement"
label var pod5_af_control "Control POD5 Atrial Fibrillation"
label var pod5_amio_control "Control POD5 Cumulative
Amiodarone Requirement"
label var pod5_fev_control "Control POD5 Fever"
label var pod5_wbc_control "Control POD5 White Cell
Count"
label var pod5_plts_control "Control POD5 Platelets"
label var pod6_o2_control "Control POD6 O2 Requirement"
label var pod6_af_control "Control POD6 Atrial Fibrillation"
label var pod6_amio_control "Control POD6 Cumulative
Amiodarone Requirement"
label var pod6_fev_control "Control POD6 Fever"
label var pod6_wbc_control "Control POD6 White Cell
Count"
```

```
label var pod6_plts_control "Control POD6 Platelets"
label var pod7_o2_control "Control POD7 O2 Requirement"
label var pod7_af_control "Control POD7 Atrial Fibrillation"
label var pod7_amio_control "Control POD7 Cumulative
Amiodarone Requirement"
label var pod7_fev_control "Control POD7 Fever"
label var pod7_wbc_control "Control POD7 White Cell
Count"
label var pod7_plts_control "Control POD7 Platelets"
label var dis_o2_control "Control Discharge O2
Requirement"
label var dis_af_control "Control Discharge Atrial
Fibrillation"
label var dis_amio_control "Control Discharge Cumulative
Amiodarone Requirement"
label var dis_fev_control "Control Discharge Fever"
label var dis_wbc_control "Control Discharge White Cell
Count"
label var dis_plts_control "Control Discharge Platelets"
label var pod_int_control "Control POD Intervention"
label var case_vol_control "Control Volume Pleural Fluid"
label var los_control "Control Length of Stay"
label var escal_control "Control Escalation of Care"
label var dis_o2req_control "Control Discharged on O2"
label var ppcs_control "Control Post Pericardiotomy
Syndrome"
label var death_control "Control Death"
label var readmit_control "Control Readmission"
label var out_mgmt_control "Control Req for Outpatient
Management"
label var mean_wbc_case "Mean WBC Cases"
label var mean_wbc_control "Mean WBC Control"

* Label Data from Imported Variables

capture label drop proc_lbl
label define proc_lbl 0 "CABG" 1 "Valve" 2
"CABG+VALVE" 3 "Other"
label values proc_case proc_lbl
label values proc_control proc_lbl

capture label drop yn_lbl
label define yn_lbl 0 "No" 1 "Yes"

label values pod3_af_case yn_lbl
label values pod3_af_control yn_lbl
label values pod3_fev_case yn_lbl
label values pod3_fev_control yn_lbl

label values pod4_af_case yn_lbl
label values pod4_af_control yn_lbl
label values pod4_fev_case yn_lbl
label values pod4_fev_control yn_lbl

label values pod5_af_case yn_lbl
label values pod5_af_control yn_lbl
label values pod5_fev_case yn_lbl
label values pod5_fev_control yn_lbl

label values pod6_af_case yn_lbl
label values pod6_af_control yn_lbl
label values pod6_fev_case yn_lbl
label values pod6_fev_control yn_lbl

label values pod7_af_case yn_lbl
label values pod7_af_control yn_lbl
label values pod7_fev_case yn_lbl
label values pod7_fev_control yn_lbl

label values dis_af_case yn_lbl
label values dis_af_control yn_lbl
label values dis_fev_case yn_lbl
label values dis_fev_control yn_lbl

label values escal_case yn_lbl
label values escal_control yn_lbl

label values ppcs_case yn_lbl
label values ppcs_control yn_lbl

label values death_case yn_lbl
label values death_control yn_lbl

label values readmit_case yn_lbl
label values readmit_control yn_lbl

label values out_mgmt_case yn_lbl
label values out_mgmt_control yn_lbl

capture label drop o2_lbl
label define o2_lbl 0 "No O2 Requirement" 1 ">0, <=2 L/min
O2 Requirement" 2 ">2, <=4 L/min O2 Requirement" 3 ">4,
<=6 L/min O2 Requirement" 4 ">6, <=8 L/min O2
Requirement" 5 ">8, <=10 L/min O2 Requirement" 6 ">10
L/min O2 Requirement"

label values pod3_o2_case o2_lbl
label values pod4_o2_case o2_lbl
label values pod5_o2_case o2_lbl
label values pod6_o2_case o2_lbl
label values pod7_o2_case o2_lbl
label values dis_o2_case o2_lbl

label values pod3_o2_control o2_lbl
label values pod4_o2_control o2_lbl
label values pod5_o2_control o2_lbl
label values pod6_o2_control o2_lbl
label values pod7_o2_control o2_lbl
label values dis_o2_control o2_lbl

* Generate and Label Pre- post-Intervention Daily Peak O2
Requirement for Cases

capture drop o2_pre_case
gen o2_pre_case = 0
label var o2_pre_case "Case pre-Intervention Peak O2
Requirement"
replace o2_pre_case = pod2_o2_case if pod_int_case==3
replace o2_pre_case = pod3_o2_case if pod_int_case==4
replace o2_pre_case = pod4_o2_case if pod_int_case==5
replace o2_pre_case = pod5_o2_case if pod_int_case==6
replace o2_pre_case = pod6_o2_case if pod_int_case==7

capture drop o2_post_case
gen o2_post_case = 0
label var o2_post_case "Case post-Intervention Peak O2
Requirement"
replace o2_post_case = pod4_o2_case if pod_int_case==3
replace o2_post_case = pod5_o2_case if pod_int_case==4
replace o2_post_case = pod6_o2_case if pod_int_case==5
replace o2_post_case = pod7_o2_case if pod_int_case==6

capture drop o2_diff_case
gen o2_diff_case = ((o2_post_case - o2_pre_case)*2)
label var o2_diff_case "Case Pre-/Post-Int Peak O2
Supplement Difference"

label values o2_pre_case o2_lbl
label values o2_post_case o2_lbl
```

```
capture drop o2_status_case
gen o2_status_case = 0
label var o2_status_case "Case Pre-/Post-Int Status Change"
replace o2_status_case = 0 if (o2_post_case -
o2_pre_case)==0
replace o2_status_case = 1 if (o2_post_case - o2_pre_case)<0
replace o2_status_case = -1 if (o2_post_case -
o2_pre_case)>0
label define imp_lbl 0 "No Change" 1 "Improved Dyspnea" -
1 "Worsened Dyspnea"
label values o2_status_case imp_lbl

capture drop wdyspnea_case
gen wdyspnea_case = 0
replace wdyspnea_case = 1 if (o2_post_case -
o2_pre_case)>0
label var wdyspnea_case "Worsened Dyspnea"

capture drop ncdyspnea_case
gen ncdyspnea_case = 0
replace ncdyspnea_case = 1 if (o2_post_case -
o2_pre_case)==0
label var ncdyspnea_case "No Change"

capture drop idyspnea_case
gen idyspnea_case = 0
replace idyspnea_case = 1 if (o2_post_case - o2_pre_case)<0
label var idyspnea_case "Improved Dyspnea"

* Generate and Label Pre- post-Intervention Daily Peak O2
Requirement for Controls

capture drop o2_pre_control
gen o2_pre_control = 0
label var o2_pre_control "Control pre-Intervention Peak O2
Requirement"

replace o2_pre_control = pod2_o2_control if
pod_int_control==3
replace o2_pre_control = pod3_o2_control if
pod_int_control==4
replace o2_pre_control = pod4_o2_control if
pod_int_control==5
replace o2_pre_control = pod5_o2_control if
pod_int_control==6
replace o2_pre_control = pod6_o2_control if
pod_int_control==7

capture drop o2_post_control
gen o2_post_control = 0
label var o2_post_control "Control post-Intervention Peak O2
Requirement"

replace o2_post_control = pod4_o2_control if
pod_int_control==3
replace o2_post_control = pod5_o2_control if
pod_int_control==4
replace o2_post_control = pod6_o2_control if
pod_int_control==5
replace o2_post_control = pod7_o2_control if
pod_int_control==6

capture drop o2_diff_control
gen o2_diff_control = ((o2_post_control -
o2_pre_control)*2)
label var o2_diff_control "Control Equiv. Peak O2
Supplement Difference"

label values o2_pre_control o2_lbl
label values o2_post_control o2_lbl

capture drop o2_status_control
gen o2_status_control = 0
label var o2_status_control "Control Pre-/Post- Equiv. Status
Change"
replace o2_status_control = 0 if (o2_post_control -
o2_pre_control)==0
replace o2_status_control = 1 if (o2_post_control -
o2_pre_control)<0
replace o2_status_control = -1 if (o2_post_control -
o2_pre_control)>0
label values o2_status_control imp_lbl

capture drop wdyspnea_control
gen wdyspnea_control = 0
replace wdyspnea_control = 1 if (o2_post_control -
o2_pre_control)>0
label var wdyspnea_control "Worsened Dyspnea"

capture drop ncdyspnea_control
gen ncdyspnea_control = 0
replace ncdyspnea_control = 1 if (o2_post_control -
o2_pre_control)==0
label var ncdyspnea_control "No Change"

capture drop idyspnea_control
gen idyspnea_control = 0
replace idyspnea_control = 1 if (o2_post_control -
o2_pre_control)<0
label var idyspnea_control "Improved Dyspnea"

*  Generate Mean LOS after Intervention (or Equiv) for
Cases and Controls

capture drop mlos_case
gen mlos_case = los_case - pod_int_case
label var mlos_case "Post Intervention Length of Stay
(Case)"

capture drop mlos_control
gen mlos_control = los_control - pod_int_control
label var mlos_control "Equivalent Length of Stay (Control)"

* Generate and Label POD_INT + 1d (or Equivalent)
Variables for Cases and Controls

capture drop pod_equiv_o2_case
gen pod_equiv_o2_case = 0

capture drop pod_equiv_af_case
gen pod_equiv_af_case = 0

capture drop pod_equiv_amio_case
gen pod_equiv_amio_case = 0

capture drop pod_equiv_fev_case
gen pod_equiv_fev_case = 0

capture drop pod_equiv_wbc_case
gen pod_equiv_wbc_case = 0

capture drop pod_equiv_plts_case
gen pod_equiv_plts_case = 0

replace pod_equiv_o2_case = pod4_o2_case if pod_int_case
== 3
replace pod_equiv_af_case = pod4_af_case if pod_int_case
== 3
replace pod_equiv_amio_case = pod4_amio_case if
pod_int_case == 3
```

```
replace pod_equiv_fev_case = pod4_fev_case if
pod_int_case == 3
replace pod_equiv_wbc_case = pod4_wbc_case if
pod_int_case == 3
replace pod_equiv_plts_case = pod4_plts_case if
pod_int_case == 3

replace pod_equiv_o2_case = pod5_o2_case if pod_int_case
== 4
replace pod_equiv_af_case = pod5_af_case if pod_int_case
== 4
replace pod_equiv_amio_case = pod5_amio_case if
pod_int_case == 4
replace pod_equiv_fev_case = pod5_fev_case if
pod_int_case == 4
replace pod_equiv_wbc_case = pod5_wbc_case if
pod_int_case == 4
replace pod_equiv_plts_case = pod5_plts_case if
pod_int_case == 4

replace pod_equiv_o2_case = pod6_o2_case if pod_int_case
== 5
replace pod_equiv_af_case = pod6_af_case if pod_int_case
== 5
replace pod_equiv_amio_case = pod6_amio_case if
pod_int_case == 5
replace pod_equiv_fev_case = pod6_fev_case if
pod_int_case == 5
replace pod_equiv_wbc_case = pod6_wbc_case if
pod_int_case == 5
replace pod_equiv_plts_case = pod6_plts_case if
pod_int_case == 5

replace pod_equiv_o2_case = pod7_o2_case if pod_int_case
== 6
replace pod_equiv_af_case = pod7_af_case if pod_int_case
== 6
replace pod_equiv_amio_case = pod7_amio_case if
pod_int_case == 6
replace pod_equiv_fev_case = pod7_fev_case if
pod_int_case == 6
replace pod_equiv_wbc_case = pod7_wbc_case if
pod_int_case == 6
replace pod_equiv_plts_case = pod7_plts_case if
pod_int_case == 6

capture drop pod_equiv_o2_control
gen pod_equiv_o2_control = 0

capture drop pod_equiv_af_control
gen pod_equiv_af_control = 0

capture drop pod_equiv_amio_control
gen pod_equiv_amio_control = 0

capture drop pod_equiv_fev_control
gen pod_equiv_fev_control = 0

capture drop pod_equiv_wbc_control
gen pod_equiv_wbc_control = 0

capture drop pod_equiv_plts_control
gen pod_equiv_plts_control = 0

replace pod_equiv_o2_control = pod4_o2_control if
pod_int_control == 3
replace pod_equiv_af_control = pod4_af_control if
pod_int_control == 3
replace pod_equiv_amio_control = pod4_amio_control if
pod_int_control == 3
replace pod_equiv_fev_control = pod4_fev_control if
pod_int_control == 3
replace pod_equiv_wbc_control = pod4_wbc_control if
pod_int_control == 3
replace pod_equiv_plts_control = pod4_plts_control if
pod_int_control == 3

replace pod_equiv_o2_control = pod5_o2_control if
pod_int_control == 4
replace pod_equiv_af_control = pod5_af_control if
pod_int_control == 4
replace pod_equiv_amio_control = pod5_amio_control if
pod_int_control == 4
replace pod_equiv_fev_control = pod5_fev_control if
pod_int_control == 4
replace pod_equiv_wbc_control = pod5_wbc_control if
pod_int_control == 4
replace pod_equiv_plts_control = pod5_plts_control if
pod_int_control == 4

replace pod_equiv_o2_control = pod6_o2_control if
pod_int_control == 5
replace pod_equiv_af_control = pod6_af_control if
pod_int_control == 5
replace pod_equiv_amio_control = pod6_amio_control if
pod_int_control == 5
replace pod_equiv_fev_control = pod6_fev_control if
pod_int_control == 5
replace pod_equiv_wbc_control = pod6_wbc_control if
pod_int_control == 5
replace pod_equiv_plts_control = pod6_plts_control if
pod_int_control == 5

replace pod_equiv_o2_control = pod7_o2_control if
pod_int_control == 6
replace pod_equiv_af_control = pod7_af_control if
pod_int_control == 6
replace pod_equiv_amio_control = pod7_amio_control if
pod_int_control == 6
replace pod_equiv_fev_control = pod7_fev_control if
pod_int_control == 6
replace pod_equiv_wbc_control = pod7_wbc_control if
pod_int_control == 6
replace pod_equiv_plts_control = pod7_plts_control if
pod_int_control == 6

label var pod_equiv_o2_case "Case - Peak O2 Req."
label var pod_equiv_o2_control "Control - Peak Equiv O2
Req."

label values pod_equiv_o2_case o2_lbl
label values pod_equiv_o2_control o2_lbl

label values pod_equiv_af_case yn_lbl
label values pod_equiv_af_control yn_lbl

label values pod_equiv_fev_case yn_lbl
label values pod_equiv_fev_control yn_lbl

*  Generate and Label Days of AF for Cases and Controls

capture drop daf_case
gen daf_case = pod3_af_case + pod4_af_case +
pod5_af_case + pod6_af_case + pod7_af_case
label var daf_case "Case Days in AF"

capture drop daf_control
gen daf_control = pod3_af_control + pod4_af_control +
pod5_af_control + pod6_af_control + pod7_af_control
label var daf_control "Control Days in AF"
```

```
*  Generate and Label Pre- and Post-Intervention Days of AF for Cases and Controls

capture drop daf_post_case
gen daf_post_case = 0
replace daf_post_case = pod4_af_case + pod5_af_case + pod6_af_case + pod7_af_case if pod_int_case==3
replace daf_post_case = pod5_af_case + pod6_af_case + pod7_af_case if pod_int_case==4
replace daf_post_case = pod6_af_case + pod7_af_case if pod_int_case==5
replace daf_post_case = pod7_af_case if pod_int_case==6

capture drop daf_post_control
gen daf_post_control = 0
replace daf_post_control = pod4_af_control + pod5_af_control + pod6_af_control + pod7_af_control if pod_int_control==3
replace daf_post_control = pod5_af_control + pod6_af_control + pod7_af_control if pod_int_control==4
replace daf_post_control = pod6_af_control + pod7_af_control if pod_int_control==5
replace daf_post_control = pod7_af_control + dis_af_control if pod_int_control==6

capture drop daf_pre_case
gen daf_pre_case = 0
replace daf_pre_case = daf_case - daf_post_case + pod3_af_case if pod_int_case==3
replace daf_pre_case = daf_case - daf_post_case + pod4_af_case if pod_int_case==4
replace daf_pre_case = daf_case - daf_post_case + pod5_af_case if pod_int_case==5
replace daf_pre_case = daf_case - daf_post_case + pod6_af_case if pod_int_case==6
replace daf_pre_case = daf_case - daf_post_case + pod7_af_case if pod_int_case==7

capture drop daf_pre_control
gen daf_pre_control = 0
replace daf_pre_control = daf_control - daf_post_control + pod3_af_control if pod_int_control==3
replace daf_pre_control = daf_control - daf_post_control + pod4_af_control if pod_int_control==4
replace daf_pre_control = daf_control - daf_post_control + pod5_af_control if pod_int_control==5
replace daf_pre_control = daf_control - daf_post_control + pod6_af_control if pod_int_control==6
replace daf_pre_control = daf_control - daf_post_control + pod7_af_control if pod_int_control==7

label var daf_post_case "Case Days AF post-Intervention"
label var daf_pre_case "Case Days AF pre-Intervention"
label var daf_post_control "Control Days AF post-Intervention"
label var daf_pre_control "Control Days AF pre-Intervention"

* Generate and Label Post-Intervention Cumulative Doses of Amiodarone
capture drop amio_post_case
gen amio_post_case = 0
replace amio_post_case = pod4_amio_case + pod5_amio_case + pod6_amio_case + pod7_amio_case if pod_int_case==3
replace amio_post_case = pod5_amio_case + pod6_amio_case + pod7_amio_case if pod_int_case==4
replace amio_post_case = pod6_amio_case + pod7_amio_case if pod_int_case==5
replace amio_post_case = pod7_amio_case if pod_int_case==6

capture drop amio_post_control
gen amio_post_control = 0
replace amio_post_control = pod4_amio_control + pod5_amio_control + pod6_amio_control + pod7_amio_control if pod_int_control==3
replace amio_post_control = pod5_amio_control + pod6_amio_control + pod7_amio_control if pod_int_control==4
replace amio_post_control = pod6_amio_control + pod7_amio_control if pod_int_control==5
replace amio_post_control = pod7_amio_control + dis_amio_control if pod_int_control==6

label var amio_post_case "Case Total Post-Intervention Amiodarone"
label var amio_post_control "Control Total Post-Intervention Amiodarone"

*  Data Generation and Labeling Complete; Ready for Endpoints

window stopbox rusure "Variable Generation and Labeling Complete.  Display Endpoints?"

*****************************
** Demographic and Baseline **
*****************************

tab proc_case

ttest age_case==age_control

window stopbox rusure "Demogrpahic and Baseline Results Generated.  Click Yes to Continue or No to Review"

**********************
** Primary Endpoint **
**********************

* Frequency of Improved Dyspnea Following Thoracentesis
tab o2_status_case
tab o2_status_control

* Binomial Expansion Test for Improvement >50%
bitest idyspnea_case == 0.5
ci idyspnea_case, binomial

* POD of Intervention
tab pod_int_case pod_int_control

* Regression for Pleural Fluid Removed
summarize case_vol_case, detail
regress case_vol_case los_case
regress case_vol_case o2_diff_case

* Fisher's Exact Test on Improvement Status
tabulate o2_status_case o2_status_control, exact

* Difference in O2 Requirement after Thoracentesis for Cases and Controls

window stopbox rusure "Primary Endpoint Results Generated.  Click Yes to Continue or No to Review"

************************
** Secondary Endpoint **
************************
```

```
* Summary of Data
summarize los_case los_control

* Total Days in Hospital by Group
tab los_case
tab los_control

* Paired T-test of Hospital LOS
ttest los_case==los_control

* Regression Analysis of LOS by POD of Thoracentesis
regress los_case pod_int_case

* Mean LOS from Intervention to Discharge (Cases Only)
sum mlos_case
sum mlos_case if pod_int_case<5

window stopbox rusure "Secondary Endpoint Results
Generated.  Click Yes to Continue or No to Review"

**********
** Tertiary Endpoint **
**********

ttest escal_case==escal_control

window stopbox rusure "Tertiary Endpoint Results
Generated.  Click Yes to Continue or No to Review"

*****************************
** Other Endpoint Summaries **
*****************************

*************************
** Atrial Fibrillation **
*************************
* Days in AF
tab daf_case pod_int_case

summarize daf_case if daf_case>0
summarize daf_control if daf_control>0

* Days in AF if POD of Thoracentesis <5
summarize daf_case if daf_case>0 & pod_int_case<5
summarize daf_control if daf_control>0 & pod_int_case<5

*  Requirement for Amiodarone After Thoracentesis

ttest amio_post_case==amio_post_control
ttest amio_post_case==amio_post_control if pod_int_case<5

* Markers of SIRS or Acute Phase Reaction

summarize mean_wbc_case, detail
summarize mean_wbc_control, detail
ttest mean_wbc_case==mean_wbc_control

ttest pod_equiv_wbc_case==pod_equiv_wbc_control

* Requirement for Readmission or Outpatient Pleural
Effusion MGMT

ttest readmit_case==readmit_control

ttest out_mgmt_case==out_mgmt_control

* Incidence of Post Pericardiotomy Syndrome

ttest ppcs_case==ppcs_control

* 30-day Mortality

ttest death_case==death_control

* Pre- Post- Thoracentesis Oxygen Requirement for Cases

ttest o2_pre_case==o2_post_case if pod_int_case>=4

* Save Data
save "/Users/davidkull/Desktop/Pericardiotomy - Pleural
Effusion MGMT/DATA/ppcpe_dataset", replace
set more off


**************************
** Automated Key Figures **
**************************
* Primary Endpoint Graph 3

graph twoway (scatter case_vol_case los_case) (lfit
case_vol_case los_case)
graph export "/Users/davidkull/Desktop/Pericardiotomy -
Pleural Effusion MGMT/DATA/Graphs/dysp3.tif", replace


* Secondary Endpoint Graph

graph box los_case los_control, ytitle(Days) ytick(##10)
ymtick(##2) ylabel(#10)
graph export "/Users/davidkull/Desktop/Pericardiotomy -
Pleural Effusion MGMT/DATA/Graphs/los.tif", replace


* Primary Endpoint Graph 1

clear
insheet using "/Users/davidkull/Desktop/Pericardiotomy -
Pleural Effusion MGMT/DATA/PPCPE2.csv"
label var case_status "Case or Control"
label var dysp_status "Dyspnea Change"
label var mean "Proportion"
label var n "Number of Patients"

capture label drop case_lbl
label define case_lbl 1 "Case" 2 "Control"
label values case_status case_lbl

capture label drop dysp_lbl
label define dysp_lbl 1 "Improved Dyspnea" 2 "No Change"
3 "Worsened Dyspnea"
label values dysp_status dysp_lbl

generate hidysp = mean + (invttail(n-1,0.025)*(sd / sqrt(n)))
generate lodysp = mean - (invttail(n-1,0.025)*(sd / sqrt(n)))
replace hidysp = 0.9108 in 1
replace lodysp = 0.4483 in 1
replace hidysp = .7258 in 2
replace lodysp = .2228 in 2
replace hidysp = .7258 in 4
replace lodysp = .2228 in 4
replace hidysp = .4162 in 3
replace lodysp = .0234 in 3
replace hidysp = .4162 in 5
replace lodysp = .0234 in 5
replace hidysp = .3397 in 6
replace lodysp = .0035 in 6

generate rank = case_status      if dysp_status == 1
replace  rank = case_status+2    if dysp_status == 2
```

```
replace  rank = case_status+4    if dysp_status == 3
sort rank
list rank dysp_status case_status, sepby(case_status)

graph twoway (bar mean rank if case_status==1) (bar mean
rank if case_status==2)(rcap hidysp lodysp rank),
legend(row(1) order(1 "Case" 2 "Control")) xlabel( 1.5
"Improved Dyspnea" 3.5 "No Change" 5.5 "Worsened
Dyspnea", noticks) xtitle("Changes in Dyspnea")
ytitle("Proportion of Patients")
graph export "/Users/davidkull/Desktop/Pericardiotomy -
Pleural Effusion MGMT/DATA/Graphs/dysp.tif", replace

save "/Users/davidkull/Desktop/Pericardiotomy - Pleural
Effusion MGMT/DATA/ppcpe_dataset_graph1", replace
set more off

* Primary Endpoint Graph 2
clear
insheet using "/Users/davidkull/Desktop/Pericardiotomy -
Pleural Effusion MGMT/DATA/PPCPE3.csv"
label var case_status "Case or Control"
label var pre_post "Pre or Post"
label var mean "Mean"
label var sd "Standard Deviation"
label var n "n"

capture label drop case_lbl
label define case_lbl 1 "Case" 2 "Control"
label values case_status case_lbl

capture label drop pre_post_lbl
label define pre_post_lbl 1 "Pre-Intervention or Equiv" 2
"Post-Intervention or Equiv"
label values pre_post pre_post_lbl

generate hici = mean + (invttail(n-1,0.025)*(sd / sqrt(n)))
generate loci = mean - (invttail(n-1,0.025)*(sd / sqrt(n)))

graph twoway (bar mean rank if pre_post==1) (bar mean
rank if pre_post==2)(rcap hici loci rank), legend(row(1)
order(1 "Pre-Intervention or Equiv" 2 "Post-Intervention or
Equiv")) xlabel( 1.5 "Cases" 3.5 "Controls", noticks)
xtitle("Grouping") ytitle("Daily Peak O2 Requirement")
graph export "/Users/davidkull/Desktop/Pericardiotomy -
Pleural Effusion MGMT/DATA/Graphs/dysp2.tif", replace


* Close log
log close

* Save Data
save "/Users/davidkull/Desktop/Pericardiotomy - Pleural
Effusion MGMT/DATA/ppcpe_dataset_graph", replace
set more off
```