Ancillary Effects of Dexmedetomidine

Sedation After Cardiac Surgery

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Preface

Dexmedetomidine is FDA approved for procedural and critical care sedation. It is widely used for this purpose and has an excellent efficacy and safety record. Like any drug, dexmedetomidine presumably has ancillary side effects and benefits. Likely consequences are reduced risk of atrial fibrillation and flutter, reduced postoperative delirium, renal protection or harm, and reduced persistent incisional pain. On the other hand, dexmedetomidine costs more than other sedatives such as propofol. We thus propose to evaluate the ancillary effect of dexmedetomidine sedation, and the cost of dexmedetomidine use.

Our proposed study fully complies with the letter and spirit of the rules for IND exemptions: 1) we will not use study results to support an FDA application for a new indication and labeling; 2) the investigation will not support a change in advertising; 3) the dose, route, and population in this study will be as approved; and, 4) the study will be conducted with IRB approval and dexmedetomidine will not be represented as safe or effective for the outcomes under study.

1. Background

Dexmedetomidine is an alpha-2 adrenoreceptor agonist with known sedative and analgesic properties (1). It also causes reduction in blood pressure, bradycardia, and inhibition of platelet aggregation, renin release and insulin secretion (1). Dexmedetomidine has a chemical structure similar to clonidine, but with a greater affinity for the alpha-2 receptor (36). Dexmedetomidine has been used successfully in anesthesia for neurosurgery, cardiac surgery, and bariatric surgery, as well as for sedation in the intensive care unit (2).

Since its approval by the FDA in 1999, dexmedetomidine has been increasingly used in the Intensive Care Unit (ICU) to facilitate both sedation and analgesia, as it is associated with low respiratory depression (3). Postsurgical patients are often intubated and mechanically ventilated (4). It is a common practice to use a benzodiazepine or propofol for sedation in mechanically ventilated patients and then switch to dexmedetomidine to attempt extubation. However, dexmedetomidine has been increasingly administered as a continuous infusion throughout the ICU admission (64). The dexmedetomidine-induced sleep and non-rapid eye movement sleep mimics normal sleep, i.e. patients can be easily aroused, and thus there are clinical advantages to both the individual and care providers (3).

Hemodynamic effects

Dexmedetomidine is known to have sympatholytic effects on hemodynamics at low doses, however increased peripheral vascular resistance and blood pressure (systemic and pulmonary) can be observed at high doses. In anesthetized dogs, the dexmedetomidine (5) administration lowered heart rate, cardiac index (CI) and systemic oxygen transport index in comparison with the control group. (6) Aortic cross- camping

increased mean arterial pressure (MAP) and systemic vascular resistance index (SVRI) in both groups, but the effects were greater with dexmedetomidine. CI, heart rate, and systemic oxygen transport index were lower, while central venous pressure and pulmonary artery occlusion pressure were higher with dexmedetomidine compared to controls. After aortic unclamping, MAP, CVP and SVRI were maintained higher by dexmedetomidine (6). In a small study in vascular surgery, patients were randomly assigned to achieve three plasma levels of dexmedetomidine (0.15 ng/ml (low dose), 0.30 ng/ml (medium dose), or 0.45 ng/ml (high dose). The medication was administered as a continuous infusion from 1 h before induction of anesthesia until 48 h postoperatively (1). In all subjects heart rate decreased (low dose 11%, medium dose 5%, and high dose 20%) and systolic blood pressure decreased (low dose 3%, medium dose 12%, and high dose 20%). (7) A targeted plasma concentration of 0.45 ng/ml (on average 8.03 micro g /kg (range 5.57 – 9.87 micro g/kg) was found beneficial for stabilizing perioperative hemodynamics in vascular surgery patients, and also for decreasing anesthetic requirements, and decreasing the level of circulating catecholamine's. (7)

Cardiac function and coronary blood flow

In healthy patients, the administration of dexmedetomidine slightly depresses systolic function without altering the diastolic function. This negative inotropic effect may be associated to a reduction in the release of epinephrine and norepinephrine during dexmedetomidine infusion. Moreover, a reduction in the cardiac work and sympatholytic effect is responsible of a substantial decrease in myocardial blood flow, thus coupling between cardiac oxygen demand and supply is maintained. (7) In an animal model of coronary ischemia, dexmedetomidine showed an anti-ischemic effect also related to sympatholysis and improved myocardial oxygen balance with preferred blood flow distribution to the endocardium (5). Therefore, medications that favors or improve coronary blood flow are favorable in the immediate postoperative period of cardiac surgery.

Cardiac Surgery and Dexmedetomidine use

There are many rationales to use dexmedetomidine in cardiac surgery. Jalonen et al. (9) evaluated dexmedetomidine use in patients undergoing coronary artery revascularization they determined that dexmedetomidine decreased the sympathetic tone and attenuated the hyper dynamic response to surgery but increased hypotension. In a recent study (10), with dexmedetomidine infusion HR and MAP were found to be moderately decreased in comparison to baseline values and no severe bradycardia or hypotension requiring intervention was encountered. They determined no response to sternotomy and bypass. Dexmedetomidine can be safely used in CABG operations delivering a stable hemodynamic status throughout the operative period. Furthermore, dexmedetomidine was found to decrease the need of inhalational anesthetics required for cardiac surgery (11). And another recent study demonstrated that dexmedetomidine combined with ketamine had significant cardio protective effects in cardiac surgery compared to inhalational agent combined with opioids (12). Cardiovascular mortality and morbidity can be decreased with the sympatholytic effects of α2-receptor agonists in patients with coronary artery disease, however this was not adequately studied.

Effect on cardiac electrophysiology

Dexmedetomidine has prominent effect on the cardiac conduction system. Sinus node and atrial ventricular nodal function is significantly depressed after the administration of dexmedetomidine. (13) The results from a small trial in children undergoing cardiac surgery indicate a potential role in the treatment of acute onset of atrial or junctional tachycardia. Briefly, a rapid bolus of 0.5 to 1 mcg/kg/min in patients with reentry type supraventricular tachycardia converted this rhythm to normal sinus rhythm. (14) In adults, the incidence of tachycardia after cardiac surgery was lower in patients treated intraoperatively with dexmedetomidine compared to placebo. However, the number of patients who developed new onset atrial fibrillation was comparable in both groups. (8) In a recent study in congenital cardiac surgery, dexmedetomidine given intraoperative and postoperatively decreased the incidence of supraventricular arrhythmias from 25% to 6%, without significant adverse effects. (15) In a laboratory study, dexmedetomidine also prevented halothane-epinephrine induced ventricular tachycardia by increasing the dysrrhytmogenic dose and the plasma concentrations at which arrhythmia occurs. (16)

Dexmedetomidine and Inflammation

Cardiac surgery and cardiopulmonary bypass strongly triggers an inflammatory response. Increased levels of pro-inflammatory cytokines can be detected during and after cardiac surgery (17). Atrial fibrillation after cardiac surgery seems to be in response to a pro-inflammatory state. (18) The administration of corticosteroids during cardiac surgery has shown the decrease the incidence of atrial fibrillation. (19) Sepsis and subsequently multi organ dysfunction remains as one the leading cause of death after cardiac surgery and both states are characterized by an uncontrolled inflammatory response. Therefore, the use of immune-modulatory medications may be beneficial.

Pre-clinical studies suggest that dexmedetomidine has anti-inflammatory effects. For instance its administration ameliorates the inflammatory response associated to spinal cord injury. (20) Moreover, the administration of dexmedetomidine improves survival in animals with sepsis. (21) In Humans, dexmedetomidine infusion decreased cytokine production in sepsis at a greater level than midazolam. There were significant decreases in TNF-a [19.5 (5.8) vs 14.6 (4) pg ml21], IL-1b [6.29(2) vs 5 (0.30) pg ml21], IL-6 [455.6 (338.4) vs (212.4) (198.3) pg ml21], at 24 h in the dexmedetomidine group, compared to midazolam (P, 0.05) (22) Similarly, study with propofol and dexmedetomidine demonstrated significant decrease in inflammatory mediators compared to propofol with dexmedetomidine (23). These studies suggest that dexmedetomidine may have a positive impact in controlling the inflammatory response associated to cardiac surgery. And number of studies has demonstrated that giving corticosteroids prophylactically decreases the risk of atrial fibrillation.

Preliminary Results on atrial arrhythmia and Rationale

Previously defined effect on cardiac electrophysiology and inflammation makes dexmedetomidine reasonable preventive drug for post cardiac surgery fibrillation. However, there is no prospective randomized clinical study evaluating this in the literature in adult patient population. Supporting these, in a recent previous retrospective study (24), we used data from the Cleveland Clinic Cardiac Anesthesiology database,

and compared patients who were or were not given dexmedetomidine for postoperative sedation within 3 days after cardiac surgery using a multivariable logistic regression, adjusting for imbalanced covariables. In this study, we evaluated the electronic records of 17,776 patients, including 765 cardiac patients given dexmedetomidine for postoperative sedation in ICU, and 17,011 cardiac patients who did not. After adjusting for imbalanced factors we found that patients given postoperative dexmedetomidine had a decreased odds of for having atrial arrhythmias: 0.74 (95% CI: 0.60, 0.91, P = 0.004). In a recent report (25), dexmedetomidine was started after surgery in ICU and they determined the incidence of atrial fibrillation to be 6 % in dexmedetomidine group compared to 35% in the control group.

There are significant preliminary evidence to support the concept of dexmedetomidine to be effective in prevention of atrial arrhythmias after cardiac surgery, however there are no studies done in adult patient population to evaluate these in a randomized controlled trial.

Preliminary Results on Delirium and Rationale

Studies evaluating delirium after cardiac surgery with dexmedetomidine have mixed results. Maldonado et al. (26) determined that dexmedetomidine after cardiac surgery decreased the incidence of delirium from 50 % to 3%. However, in another study dexmedetomidine was compared with morphine and dexmedetomidine reduced the duration but not the incidence of delirium after cardiac surgery (27). However, these studies are underpowered to determine for certain the effect of dexmedetomidine on delirium after cardiac surgery. Current study with large sample size will bring information about dexmedetomidine and delirium.

Incidence of Atrial fibrillations and Delirium

An estimated 17 million people in world die of cardiovascular diseases, particularly heart attacks and strokes, every year. Heart disease is also the leading cause of death in the United States. In 2007, one-quarter of all deaths (616,000) were from diseases of the heart (27). Heart diseases like ischemic heart disease, congenital or valvular heart diseases require cardiac surgery at some point. As a consequence, coronary revascularization, comprising coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI), are among the most common major medical procedures provided by the US health care system, with more than 7 million procedures performed annually (28). It is also among the most costly with inpatient payments to hospitals for coronary revascularizations exceeded $6.7 billion in fiscal year 2006 for Medicare patients alone, an amount larger than the reimbursement for any other medical or surgical procedure) (29).

Most of the cardiac surgeries require use of cardio pulmonary bypass (CPB), which is responsible for major inflammatory response seen in this surgery. This response is associated with most of the postoperative complications. Recovery period after cardiac surgery is frequently affected with different complications. Furthermore 4-5% of patients will not survive their hospital stay after cardiac surgery. Postoperative atrial arrhythmia and delirium are the most common complications encountered after

CABG surgery. Postoperative atrial arrhythmias affect morbidity, mortality, prolong intensive care unit and hospital stay, and increase costs related to surgery (30,31,32,33). Delirium is an important prognostic determinant of hospital outcomes including poor cognitive recovery, functional decline, nursing home placement and death (34,35). Prevention of atrial arrhythmias and delirium after cardiac surgery has been infrequently studied with some success.

Atrial Arrhythmias after Cardiac surgery

Incidence and Clinical Impact

Postoperative atrial arrhythmias incidence ranges depending on surgery type. The incidence of postoperative atrial arrhythmias specifically atrial fibrillation is between 25-35 % in isolated CABG and higher in valve procedures; the incidence is around 50 % in combined surgeries (36). Incidence is continuously rising, which seems to be related to patients undergoing cardiac surgery are getting older since incidence is very much dependent on age. Atrial fibrillation after cardiac surgery usually occurs between day 2 and 4, however can happen as late as postoperative day 6 (37). There are many factors associated with occurrence; history of atrial fibrillation, gender, left atrium enlargement, renal failure and diabetes are some (38).

Previous studies have found that atrial fibrillation after cardiac surgery has significant association with morbidity and mortality (39,40,41,42,43). In a recent study, patients with atrial fibrillation after cardiac surgery had higher rates of 1 year all-cause mortality (40). A meta-analysis evaluating mortality after new onset atrial fibrillation after cardiac surgery included 11 studies with over 40 thousand patients (41). They determined that new onset atrial fibrillation was associated with 50 % increase in short term mortality and almost doubled the risk of dying in 1 and 4 years after surgery. Villareal et al. (6) also found that new-onset atrial fibrillation was associated with a higher risk of in-hospital mortality (OR, 1.5 [95% CI, 1.3–1.8]; P<0.0001). Mariscalco et al. (44) followed 1832 patients (570 with new-onset atrial fibrillation) for up to 6 years and Ahlsson and colleagues (45) followed 1419 patients (419 with new-onset atrial fibrillation) up to 9 years after CABG. A higher number of deaths owing to cerebrovascular events (51/82 vs 20/ 419) was reported by Mariscalco et al., (44) although some of the difference in mortality resulting from cerebral events could be related to how new-onset atrial fibrillation was treated.

Researchers demonstrated increase in need for mechanical support, prolonged ventilator support and renal failure after cardiac surgery. There are also many other complications associated with atrial fibrillation including thromboembolic events, perioperative myocardial infarction gastrointestinal complications, infective complications (e.g., septicemia, mediastinitis and pneumonia), cognitive changes, stroke, hemodynamic issues and ventricular dysrhythmias (41,42,43,44,45). Furthermore, postoperative atrial fibrillation was estimated to prolong hospital stay by almost 4.9 days, and hence, the cost of atrial fibrillation and level of hospital resources was significant (31). Aranki et al (38) reported duration of hospitalization in patients with postoperative atrial fibrillation an average of 3 to 4 days longer than in patients in normal sinus rhythm. Other authors reported similar results, with additional costs attributable to postoperative atrial fibrillation ranging from $5,000 to $12,000 per patient (47,48,49).

Pathophysiology and Mechanisms

The mechanisms behind atrial fibrillation seem to be multifactorial and have not been fully identified. Previous studies have suggested that atrial fibrillation may be result of an existing electrophysiological disturbance that becomes prominent with all the insult to cardiac tissue (50). Mechanisms like pericardial inflammation, autonomic imbalance during the postoperative period, excessive production of catecholamine's, and a fluid shift with resultant changes in volume and pressure, operative trauma, inflammation, autonomic nervous system imbalance are all attributed to the development of postoperative atrial fibrillation (37). These factors alter atrial refractoriness; causing multiple re entry wavelets seems to be the electrophysiological mechanism of postoperative atrial fibrillation (35). In support of this amiodarone has been used with some success in prevention of postoperative atrial fibrillation (51).

Inflammation seems to play significant role in pathogenesis of atrial fibrillation after cardiac surgery. Cardiac surgery causes local and systemic inflammation, which has been shown to be associated with atrial fibrillation and facilitate re entry (52,53). Extracorporeal circulation is the main reason for systemic inflammatory response, and mediators of inflammation like leukocytosis and C-reactive protein (CRP) were found to be the independent predictor of atrial fibrillation (54,55). IL-6 is pro-inflammatory cytokine that is involved in the synthesis of acute phase proteins similar to such as CRP. In patients undergoing cardiac surgery the development of postoperative atrial fibrillation was related to increased levels of IL-6, and linked to polymorphisms in the promoter region of the IL-6 gene (56). Surgical trauma to the atria is associated with local inflammation, which explains why patients undergoing valvular surgery have the highest risk of developing atrial fibrillation (57,58). Because of this, less manipulation of the atria decreases local atrial inflammation, and subsequently, atrial fibrillation. Inflammation is involved in its initiation, and the arrhythmia itself generates an inflammatory response that results in persistence of atrial fibrillation (58). Inflammation also appears to directly alter atrial conduction properties (53). In animal studies atrial inflammation was associated with incidence and duration of atrial fibrillation (52), and inflammation changes distribution of connexin proteins, which have important role in intercellular communication linked to atrial fibrillation (59). Furthermore in support of these corticosteroids, anti-inflammatory drugs like colchicine and statins were found to be effective on postoperative atrial fibrillation probably by decreasing inflammation (60,61,62).

Prevention of Atrial Arrhythmias

Treatment of atrial fibrillation is difficult, requires multiple treatment options and often results in interventions. Prevention is preferred especially in post cardiac surgery atrial fibrillations. Many studies have evaluated the effectiveness of different pharmacologic interventions to prevent or decrease the incidence of atrial fibrillation. Although some of these pharmacological interventions have been shown to decrease the incidence of atrial fibrillation with some success, there is still no accepted single preventive drug that does work for all patients. Long-term outcomes of these interventions for post cardiac surgery atrial fibrillation are also unknown. Furthermore, effect on hospital stay and its associated economic impact also remains controversial. Pharmacological agents used with some success are amiodarone, magnesium and

beta-blocker drugs. There are also some side effects of these interventions and they are not suitable for all patients.

Delirium after Cardiac surgery

Incidence and Clinical Impact

The incidence and prevalence of delirium vary widely between different study populations. The reported incidence of postoperative delirium in a systemic review by Dyer et al. ranged from 0% to 73.5% (36). Ten to 30% of patients admitted to a general hospital develop delirium and a prevalence of up to 60% is recognized in elderly patients (64). Patients in intensive care units are especially at high risk of developing delirium. In a recent study in postoperative elderly patients an incidence of 43% was found (65). However, types of patients, the method of the study and the diagnostic criteria used, influence the incidence reported. Generally, an incidence of 25% is assumed among all hospitalized elderly patients (63).

Patients who undergo cardiac surgery have an increased risk of developing delirium. In a recent study the incidence of delirium following cardiac surgery was found to be 21% and the European System for Cardiac Operative Risk Evaluation could predict a postoperative delirium in patients who underwent elective cardiac surgery (66). In another study the incidence of delirium was 13.5% to 20%, higher in patients 60 years and older (67). In a recent study, the prevalence of postoperative delirium was 41.7% as diagnosed by the psychiatrist based on DSM-IV criteria (68). Two recent studies by Rudolph showed an incidence of delirium after cardiac surgery ranging between 42 and 50% (69,70). Developments in operative and anesthetic techniques have enabled older patients to undergo cardiac surgery. This may be an important cause of the increase in the frequency of delirium in the foreseeable future.

Delirium is an important independent prognostic determinant of hospital outcomes including nursing home placement, functional decline, and death (35,36). Postoperative delirium increases postoperative complications and prolongs hospital stays (44-47). Even brief episodes of postoperative delirium can impact significantly on the patient's ability to live independently after hospital discharge (48). In addition to functional decline and dementia, delirium is associated with increased mortality. Hospital mortality in patients with delirium has been estimated to be between 10% and 65%(49). This is significantly higher than that in patients without delirium and can be compared with patients with perioperative myocardial infarction. Mortality after hospital discharge is also higher for those who had delirium, estimated to be 22–76% during the months following surgery (50). In a prospective study of 921 patients age 65 or older who underwent surgery for hip fracture, Edelstein found that those who had postoperative delirium had a significantly longer mean length of hospitalization (P<0.001) and significantly higher rates of mortality at 1 year (odds ratio = 2.4; 95% CI 1.1-4.9; P=0.02)(44).

Pathophysiology and Mechanisms

The fundamental pathophysiological mechanism of delirium remains unclear. The etiology of postoperative delirium seems to be multifactorial and includes pain (51-53),

sleep deprivation (54-59), surgical stress, anesthetic effects, concomitant medications (53-58) and the inflammatory response to surgery. Further supportive of an inflammatory etiology is Rudolph's recent identification of atherosclerosis score as a significant risk factor for postoperative delirium in cardiac surgery patients (42). Dexmedetomidine has anti-inflammatory properties, decreases use of opioids and benzodiazepines that are blamed for delirium, and provides sedation very similar to natural sleep that can attenuate delirium seen after cardiac surgery.

Renal Function and Dexmedetomidine

Acute kidney injury and kidney problems are recognized complication of cardiovascular surgery and associated with high mortality and costs-of-care. The pathogenesis is multifactorial and involves hemodynamic, inflammatory and nephrotoxic components. (87) The effect of dexmedetomidine on the renal function has been inadequately studied. There are multiple mechanisms that dexmedetomidine can influence kidney functions;

Effect on Blood Flow

Cardiac surgery activates sympathetic nervous system; dexmedetomidine-induced sympatholysis might attenuate harmful hemodynamic events resulting in prevention of acute kidney injury. In a small prospective study, administration of the alpha agonist clonidine at a rate of 4 micrograms/kg iv over a period of 15 min, 1h before induction of anesthesia preserved postoperative creatinine clearance in comparison to controls, where it reduced with 30 ml/min. (88) This may suggest a significant influence even when administered for a short time. A randomized controlled trial that compared the sedative effect of dexmedetomidine with propofol found higher urinary output without the need of high doses of diuretics. (89) In another small study (n=28) in thoracic surgery, dexmedetomidine infusion in addition to epidural analgesia suggested a beneficial effect on glomerular filtration measured by increased urinary output and preserved creatinine levels and higher creatinine clearance, whereas in controls there was a 21 % reduction of creatinine levels. (90). Conversely, dexmedetomidine could worsen kidney function via hypotension.

In case series of CABG surgery patients, plasma BUN and creatinine levels did not increase on the postoperative period in the dexmedetomidine group in contrast to the control group. (91) A study in vascular surgery did not report any laboratory differences between the three target blood levels of dexmedetomidine, which may not suggest a dose effect, but renal function was not the main objective of the study. (92) A recent study in cardiac surgery patients determined no harmful effect but increase in urinary output suggesting beneficial effect (93).

Cellular effects

Ischemia-reperfusion injury is one of the most serious causes of acute renal failure. (94) In a recent animal model of ischemic kidney, the kidneys of untreated animals showed tubular cell swelling, cellular vacuolization, pyknotic nuclei, medullary

congestion, and moderate to severe necrosis. On the opposite treatment with dexmedetomidine showed normal glomeruli and only slight edema of the tubular cells. (95)

Postoperative Cognitive Deficit and Dexmedetomidine

Postoperative cognitive deficit (POCD) is an important and common complication of cardiac surgery with and without cardiopulmonary bypass. (95) In a study by Newman and colleagues a significant cognitive decline, defined as a 20% reduction from baseline, occurred in 53% of patients at discharge, 36% at 6 weeks, 24% at 6 months, and 42% at 5 years. (96) Some other studies also report an incidence ranging from 8% to 40% (97). Cognitive impairment causes lower general health after cardiac surgery with important implications for future care of these patients undergoing cardiac surgery (98). Inflammation plays and important role in POCD. Cardiac surgery with or without Bypass causes an enormous release of inflammatory mediators to the circulation. The effect of dexmedetomidine on POCD has not been studied previously, although there are ongoing trials looking at the effect of dexmedetomidine on delirium but not on POCD. There are compelling reasons to believe that dexmedetomidine can prevent delirium and POCD after cardiac surgery.

Chronic Pain-Cardiac Surgery and Dexmedetomidine

A potential adverse outcome of surgery is the development of persistent postoperative incisional pain. Persistent postoperative pain is defined as incisional pain developing after a surgical procedure that lasts at least three months for which other causes (i.e., malignancy or chronic infection) have been excluded. (99) There are number of factors involved in this chronic pain formation, most importantly injury caused by surgery which produces intense pain signals. These signals are emitted from the peripheral nerves and tissues and sensitize the nociceptive pathways in the central nervous system (CNS)(100,101), which leads to restructuring and central sensitization in the CNS — which is then amplified by ongoing peripheral input. (102) Once established, persistent incisional pain is difficult to control or eliminate; pain persisting after surgery is likely to be permanent.

Persistent postoperative pain is common; a number of retrospective and a few prospective studies have defined the incidence in certain surgical populations. The incidence of chronic chest wall, breast, or scar pain ranges from 11 to 57%; phantom breast pain is reported by 13–24% of mastectomy patients, while 12–51% report arm or shoulder pain. (103) The reported incidence of thoracotomy pain varies from 30 to 50% (104-106); however this is less well established after cardiac surgery. The prevalence of chronic pain reported after cardiac surgery varies from 11% to 61%. Taillefer et al (107) in a retrospective survey study determined that the incidence of non-anginal persistent postoperative pain affected 23% of patients after cardiac surgery. These reports demonstrate that cardiac surgery is associated with increased chronic pain.

Why some patients develop persistent incisional pain remains unknown. But one theory is that severe acute pain, such as a scalpel blade cutting through skin, provokes activation of high-threshold peripheral sensory neurons which signal the presence, location, and intensity of the injury. Normally, peripheral sensory neuron activation fades once the stimulus is removed. Inflammatory pain is the heightened pain sensitivity that

occurs in response to tissue injury and inflammation and is termed peripheral sensitization. Peripheral sensitization results from the local action of inflammatory mediators, including prostanoids released from injured and inflammatory cells, on the peripheral terminals of high-threshold nociceptor sensory neurons. Inflammatory pain persists until the surgical wound has healed. If a focus of ongoing inflammation persists, so will the pain. But peripheral pain can also provoke central sensitization, which is an increase in the excitability of spinal neurons because of persistent nociceptive afferent input from peripheral neurons. It thus seems likely that good control of acute postoperative pain and inflammation by aggressive early pain management reduces the risk of persistent incisional pain by blunting central sensitization (100,101).

Dexmedetomidine has anti-inflammatory and analgesic properties. Anti-inflammatory properties of dexmedetomidine have been previously described. Clonidine, an α2-adrenergic receptor (α2-AR) agonist, has been widely used as an analgesic adjuvant in perioperative conditions and chronic pain therapy (108). Dexmedetomidine comes from same family of drugs with clonidine using the same receptors with different affinity. Intraoperative dexmedetomidine (bolus dose of 0.5-1 µg/kg, with or without continuous infusion of 0.5-2 µg/kg per hour) causes a significant reduction in the need for both intraoperative and postoperative analgesics in adults (109) and in children (110). Although elimination half-life of dexmedetomidine is short (i.e., 2-3 hours), the analgesic-sparing effect observed after a preoperative or an intraoperative administration usually lasts up to 24 hours, with the anxiolytic and sedative properties implicated as being partly responsible for this effect (110,111). Dexmedetomidine when added to intravenous patient-controlled analgesia morphine improved postoperative analgesia and decreased postoperative morphine consumption by 30%, as well as decreasing morphine-induced side effects like nausea, without additional sedation (112). α2-AR agonists and opioids act by different mechanisms and thus their combination produces a synergistic analgesic effect without increasing the respiratory depression that is often associated with opioid use (108).

Literature in regards to effect of dexmedetomidine on chronic postoperative pain does not exist. There are nonetheless good pathophysiological reasons to believe that dexmedetomidine will be effective in prevention of chronic pain. For example, dexmedetomidine can be effective on persistent postoperative pain formation either by decreasing inflammation which plays a crucial role in maintaining of peripheral sentisation and/or providing better acute pain control which is blamed as an important factor in chronic pain formation.

Pharmaco-economics

The impact of postoperative atrial fibrillation is significant from not only a clinical standpoint but from an economic standpoint. The additional cost attributable to atrial fibrillation has not been well defined but is estimated between $10,000-$11,000 per patient in the US. Considering current rates, the extra cost of postoperative atrial fibrillation for the US is conservatively estimated at around $2 billion per year.

Increased length of stay is the greatest contributor to additional costs attributable to post operative atrial fibrillation. The increased length of stay has been estimated around 4.9 days. This additional length of stay is costly to patients but extremely costly

to hospitals. As the proportion of fixed payment patients including Medicare per hospital increases with time and the influx of baby boomers, the cost to hospitals will only increase. In addition, in line with Affordable Care Act, reimbursements for complications such as postoperative atrial fibrillation will be limited and therefore have further financial impacts for a hospital.

One barrier to using dexmedetomidine in the postoperative period is that it is relatively expensive compared to other sedative drugs. However, the complications including atrial fibrillation associated with other cheaper sedative drugs are extremely costly. The costs of using Dexmedetomidine for preventing atrial arrhythmias as compared to the cost of cheaper sedatives and the costs of treating the associated complications has not been addressed. Therefore, assessing the cost-effectiveness of Dexmedetomidine needs to be investigated as well.

2. Study Objectives

Our goal is to evaluate the effects of intraoperative and postoperative dexmedetomidine sedation (versus placebo) on a variety of important outcomes in patients recovering from cardiac surgery. Specifically, we will use dexmedetomine as a sedative in the FDA-approved dose, by the approved route, and in the approved population. The proposed research will have the following aims:

Primary Aims; We will have two primary aims in current study.

Primary Aim 1. To assess whether dexmedetomidine sedation decreases the incidence of atrial arrhythmias.

<u>*Hypothesis.*</u> Our first primary hypothesis is that the incidence of new-onset atrial arrhythmia (any of atrial flutter and atrial fibrillation) is reduced in patients given dexmedetomidine.

Primary Aim 2. To assess whether dexmedetomidine sedation reduces postoperative delirium.

<u>*Hypothesis.*</u> Our second primary hypothesis is that, in patients given dexmedetomidine, the incidence of delirium is reduced during the initial five postoperative days.

Secondary Aims;

Secondary Aim 1. To assess whether dexmedetomidine sedation reduces kidney injury.

<u>*Hypothesis.*</u> Kidney function evaluated by RIFLE score is better preserved in patients given dexmedetomidine.

Secondary Aim 2. To assess whether dexmedetomidine sedation reduces persistent incisional pain.

<u>*Hypothesis.*</u> The incidence of incisional pain 3 months after cardiac surgery is reduced in patients given dexmedetomidine sedation.

Specific Aim 3. To assess the cost-effectiveness of dexmedetomidine after cardiac surgery.

<u>*Hypothesis.*</u> Dexmedetomidine reduces the cost of care.

3. Method

We propose to assess atrial arrhythmias, delirium, kidney function, persistent pain, and health economics in patients having cardiac surgery who are randomly assigned to dexmedetomidine sedation or placebo.

Type of Study

This study is a multicenter, randomized, double-blind placebo controlled trial of dexmedetomidine sedation in adults having cardiac surgery.   The participating institutions are as follows:

- Cleveland Clinic, Cleveland, Ohio
- Ohio State University, Columbus, Ohio
- Northwestern University, Evanston, Illinois
- Florida Hospital Winter Park, Winter Park, Florida
- University of Maryland Medical Center, Baltimore, Maryland
- University of California, Los Angeles, California
- Flagler Hospital, St. Augustine, Florida

Setting and Population

Inclusion criteria:
(1) 18-85 years old;
(2) Scheduled for cardiac surgery with bypass (CABG, valve, or combined);
(3) Able to provide a written informed consent;
(4) Hemodynamically stable (heart rate>= 50).

Exclusion criteria:
(1) Sick sinus syndrome or Wolff-Parkinson-White syndrome;
(2) Atrio-ventricular block;
(3)Hypersensitivity or known allergy to dexmedetomidine
(4) Hepatic disease, e.g. twice the normal level of liver enzymes;
(5) AF within 1 preoperative month;
(6) Permanent pacemaker;
(7) Use of amiodarone or dexmedetomidine within the last 30 days;
(8) Patients with an ejection fraction under 30% or who had severe heart failure;
(9) Myocardial infarction in the previous 7 days;
(10) Body mass index >= 40 (BMI= mass (kg) / height (m)2);
(11) Those taking clonidine within last 48 hours.

Protocol

Patients must meet all inclusion and exclusion criteria to be eligible for the study. After eligibility is confirmed, the patients will receive complete information about the study both verbally and in writing. Informed consent must be obtained from the patients

prior to randomization and study-specific procedures. Once all eligibility criteria are fulfilled (including informed consent), the patients may be randomized, and treatment allocation will be performed. Key baseline patients characteristics, as well as patient's eligibility criteria, will be collected on case report forms.

The anesthetic management will follow pre-established clinical and institutional guidelines. Patients will be premedicated, and induced per institution routine according to attending anesthesiologist discretion. Prophylactic antibiotics will be given per surgical routine. Patients will be randomly assigned to dexmedetomidine or placebo groups (normal saline administration matching dexmedetomidine rate of infusion) after they have met the inclusion/exclusion criteria and consented to the study. Randomization will be web-based and out of the control of any investigator.

Dexmedetomidine infusion, without a bolus dose, (or a comparable volume of placebo) will be initiated before the surgical incision at a rate of 0.1 µg/kg/hr; at the end of bypass, the dose will be increased to 0.2 µg/kg/hr. However, the anesthesiologists may modify the dose as clinically indicated based on hemodynamic and other physiologic responses. Patients with hypotension will be treated first with vasopressors and fluids according to clinical standards; if not responding the dose of the study medication will be adjusted at the discretion of the anesthesiologist.

Intraoperative opioids and benzodiazepines will be left to discretion of the anesthesiologist. Additional midazolam and opioids will be titrated to facilitate extubation. In patients who remain intubated, anesthesia will be further supplemented with fentanyl or any other opioid of choice.

Postoperatively, patients will continue to receive the study medication at a rate of 0.4 µg/kg/h,. Adjustments in the study medication and in the administration of other rescue sedative and analgesic agents will be made according to standard cardiac intensive care unit sedation and analgesia protocols. This may involve propofol, opioids and benzodiazepines according to attending ICU staff physician discretion. The study medication infusion will be continued for a total of 24 hours from the initial administration time intra-operatively. Use of prophylactic amiodarone after surgery is not accepted.

Measurements

Clinical evaluators for the outcomes will be blinded to group allocation and clinical research fellows not involved in evaluations will prepare the study drugs.

Demographic data to be obtained includes height (cm), weight (kg), age (yr), gender, (ASA) physical status, and self-declared ethnicity. Patients will be questioned for social history (tobacco) and medical history (pulmonary disease, kidney disease, diabetes mellitus, neurological disease, chronic pain conditions, illegal drug usage, alcohol abuse, myocardial infarction, and previous surgery or stent placement.

Available preoperative laboratory tests and current medications (according to

classes) will be recorded. Data obtained from medical records will include following but not limited to; euroscore, operation time, perfusion time, number of grafts, anesthesia induction agents, operating room returns, ICU readmissions, length of ICU stay, time to extubation and re-intubations, will be recorded.

Baseline RIFLE, creatinine and AKIN scores will be determined. Pain catastrophizing scale, Brief Pain Inventory, and SF 12 will also be completed before surgery.

Primary Aims

Primary Aim 1;

New onset atrial arrhythmia:

Patients in cardiac ICU (CICU) will have continuous electrocardiogram monitoring with both electronic and clinical diagnosis of atrial arrhythmias. Diagnosis of atrial arrhythmias will be made by clinicians in ICU and recorded. Upon discharge from the CICU, twelve-lead electrocardiograms will be recorded morning and evening until the earlier of hospital discharge or five days in unmonitored patients. A cardiologist or anesthesiologist blinded to randomized group allocations will identify types of atrial arrhythmias in each ECG. Presence of the following arrhythmias will be recorded, and the primary outcome is defined as the presence of any of these in a patient (versus none) from ICU admission to hospital discharge or 5 days, whichever occurs first:

Atrial flutter and atrial fibrillation will be defined by: 1) clinician diagnosis; 2) documented arrhythmia lasting at least 5 minutes; or, 3) presence of either arrhythmia on ECGs in unmonitored patients.

For the evaluation of dexmedetomidine following hemodynamic parameters will be collected and evaluated; Intra-postoperative period will be evaluated for hemodynamic changes every 15 minutes heart rate, blood pressure, and the following parameters will be noted as significant hemodynamic changes, treatments (total vasopressor, anti-hypertensive, opioid, anesthetic, blood and FFP transfusion, total colloid and crystalloid use) will be recorded intra-postoperatively. Requirement of intra-aortic balloon pump, low cardiac output, open chest, permanent pacemaker, heart block or cardio version will also be recorded.

All other complications seen in intraoperative or postoperative period will be recorded from medical records. These will include but not limited to; fungemia, bacteremia, sepsis, septic shock, empyema, endocarditis, mediastinitis, sternal wound infections, pneumonia, ARDS, atelectasis, respiratory failure, ileus, pancreatitis, multiple organ failure and mortality.

Preoperative and postoperative cardiac enzymes (troponin, BNP, CK M) will be recorded from available medical records and compared.

Primary Aim 2

Postoperative delirium;

Our second <u>primary outcome</u> will be presence of delirium at any time point within the earlier of hospital discharge and 5 days after surgery, as determined by CAM-ICU.

Delirium will be assessed with the Richmond Agitation and Sedation Scale to assess the level of possible sedation, and the Confusion Assessment Method for the ICU. The Richmond Agitation and Sedation Scale (RASS) is a validated, commonly used scale assessing sedation depth (113,114). Measurements will be made twice daily by research assistants. The evening assessment will be made after 5 PM.

The delirium assessment will start with the Richmond Agitation and Sedation Scale to assess the level of possible sedation, followed by the Confusion Assessment Method for the ICU. The Richmond Agitation and Sedation Scale (RASS) is a validated, commonly used scale assessing sedation depth. (113,114)

The Confusion Assessment Method is a validated and reliable tool for diagnosing delirium. (115) It demonstrates sensitivity and specificity in excess of 90% compared to a psychiatrist-rated diagnosis of delirium as well as excellent reliability between clinician raters. A study by Zou et al. showed that, compared with the Confusion Assessment Method and multiple observation points, clinical diagnosis by a psychiatrist had a lower sensitivity (89% versus 73%) and specificity (100% versus 93%). (116) Systematic assessment of delirium using validated rating scales has therefore been regularly advised.

The Confusion Assessment Method is considered the best diagnostic tool. It is the most widely used and studied tool. The CAM-ICU incorporates the same 4 key features of the current DSM-IV-TR criteria for the diagnosis of postoperative delirium. (115) The 4 features are cardinal elements of the DSM criteria for delirium:

1. Acute onset of mental status changes or fluctuating course
2. Inattention
3. Disorganized thinking
4. Altered level of consciousness

Delirium is diagnosed when both Features 1 and 2 are positive, along with either Features 3 or 4. See Appendix 1 for the complete CAM-ICU.

In 2007, an international group of anesthetists and neuropsychologists formed an advisory board to create a new quality of recovery scale. It is called the Postoperative Quality Recovery Scale (PQRS). Six domains of recovery are identified: physiological, nociceptive (pain and nausea), emotive (anxiety and depression), functional recovery (return of activities of daily living), self assessed recovery, and cognitive recovery. The scale is completed prior to surgery to provide baseline values, and then repeated after surgery. The conduct of the test takes approximately 5 to 10 min on each occasion. Whilst in hospital, the scale is conducted via faced-to-face interview. The PQRS will be conducted at baseline (at time of recruitment), in hospital will be repeated at days 3 and before discharge.

Secondary Aims

Secondary Aim 1;

Kidney function

Primary outcome for kidney function will be change overtime in RIFLE classifications from baseline to discharge. Kidney function will be evaluated at baseline prior to surgery, and daily if biochemical tests are done by using RIFLE and AKIN classifications (117). BUN and creatinine values will also be recorded daily if available. If more than one value was obtained, the highest will be recorded. Renal complications such as anuria and dialysis will be recorded.

Figure 1. Rifle Criteria.

Secondary Aim 2;
Postoperative pain

Primary pain outcome: persistent chronic pain will be presence of persistent incisional pain (i.e., any pain) at 3 months after surgery. Patients will be evaluated postoperatively by phone at 3 months for quality of life using SF-12 Health Survey (SF-12), and evaluated for persistent incisional pain (yes/no). If the patient indicates any incisional pain they will be asked to rate their pain using a numeric rating pain scale (0-10).

Secondary chronic pain outcomes will include,the modified brief pain inventory (BPI), Sleep Interference scale and the Neuropathic Pain Questionnaire Short Form (NPQ-SM), evaluated at 3 months after surgery.

The BPI is a practical method of evaluating pain severity and its impact on patient function. The Neuropathic Pain Questionnaire, a clinical tool with the ability to differentiate neuropathic from other types of pain.(119,120) The Sleep Interference

scale will describe how the pain will interfere with the patient's sleep during the previous 24 hours.

Acute pain and early opioid consumption. The total amount of opioid administration during surgery, and for the first 3 postoperative days will be recorded. Pain scores will be evaluated for the first 5 postoperative days. Besides assessing the effects of dexmedetomidine on acute pain score and opioid consumption, we will also correlate these measures with chronic persistent pain.

Specific Aim 3;

Cost-effectiveness of Dexmedetomidine after cardiac surgery

Billing data for all patients will be collected. These will include billing data of patients receiving dexmedetomidine and those not receiving the medication. Additionally, the billing data of those within each treatment group with and without atrial fibrillation will be compared. This data will enable the costs directly attributable to the use of Dexmedetomidine to be compared. To further validate the results, clinical outcomes including LOS (ICU and floor), discharge destination, QOL from the SF12 and mortality will be collected and valued in line with Medicare reimbursement rates and societies willingness to pay for a quality adjusted life year (QALY) (125).

Limitations

A limitation of the current study design relates to the arbitrarily chosen dose of the dexmedetomidine. However, the dose we have selected according to the most preferred regimens used in the literature and also in preliminary studies. Furthermore, surgical and anesthesia team are very worried with side effects related to dexmedetomidine due to hemodynamic effects. While research personnel blinded to group assignments will collect intra-post operative data, they may recognize the randomized drug due to prominent hemodynamic effects. We will ensure the blindness of the research personnel who will be doing the follow-ups by not getting them involved with other parts of the study.

Data Analysis

Randomized groups will be compared for balance on all potentially confounding baseline variables using descriptive statistics and the standardized difference, which is the difference in means or proportions divided by the pooled standard deviation. Criterion for balance will be an absolute standardized difference less than sqrt(2/n), where n is the number of patents per group.(126) Any imbalanced baseline variables will be adjusted for in all analyses below. Data transformations will be made or non-parametric analyses used to meet model assumptions, as appropriate. Analyses will be intent to treat, with a significance level of 0.05 for each hypothesis.

Specific Primary Aim 1. *New onset atrial arrhythmia*. We will assess the relative efficacy of dexmedetomidine to placebo on incidence of any new onset atrial arrhythmia (the primary outcome, as defined above) using either Pearson chi-square test or logistic

regression if there is a need to adjust for baseline imbalance in potentially confounding variables. In either case, the relative risk of developing any arrhythmia during the follow-up period and its 95% confidence interval will be estimated.

Specific Primary Aim 2. *Delirium.* We will compare the randomized groups on the presence of delirium detected at any time before hospital discharge as determined by CAM-ICU using either Pearson chi-square test or else logistic regression if there is a need to adjust for any baseline imbalance in potentially confounding variables. In either case, the relative risk of developing delirium and its 95% confidence interval will be estimated.

Specific Secondary Aim 1. *Kidney function.* We will compare the randomized groups on the change in RIFLE classification from baseline to hospital discharge using a generalized linear mixed effects model with random slope over time and using a cumulative logit link function to model the ordinal nature of the RIFLE data. In essence we will compare the randomized groups on the mean slope over time in kidney function status as measured by the RIFLE classification while adjusting for baseline RIFLE classification as a covariate, along with any baseline imbalanced variables.

Specific Secondary Aim 2. *Persistent incisional pain.* We will compare the randomized groups on presence of persistent incisional pain (i.e., any pain) at 3 months after surgery using either Pearson chi-square test or else logistic regression if there is a need to adjust for any baseline imbalance in potentially confounding variables. In either case, the relative risk of having persistent incisional pain and its 95% confidence interval will be estimated.

Randomized groups will further be compared on the secondary chronic pain outcomes using either t-tests or analysis of covariance to adjust for imbalanced baseline variables.

Specific Secondary Aim 3.

A decision analytic model will be built using TreeAge to compare the cost-effectiveness of Dexmedetomidine in cardiac surgery as compared to existing practice. The model will be developed from two perspectives; the payer perspective and the societal perspective. The payer perspective model will include all costs (positive and negative) with an impact to the payer. The model will include the entire study population and be extrapolated to hospital level and US population level. The model will also incorporate 5 year time horizon changes to reflect the changes in the population and payer mix due to the increasing number of Medicare beneficiaries and healthcare changes with the Affordability Care Act.

The societal perspective model will include all costs (positive and negative) with an impact to society. This model will use parameters including discharge destination, QOL and mortality. This model will also include the entire study population and be extrapolated to the hospital level, US population level and forecast for a 5-year time horizon. Sensitivity analysis on both models will be performed to ensure robustness of the results to changes within the model parameters.

Interim analyses. At each 17% of the maximum enrollment of N=965 patients, an interim analysis will be conducted in which we assess for efficacy and futility of dexmedetomidine versus placebo on each of the outcomes in Aims 1-4. However, decision making to stop or continue the trial will be based on the primary outcome in Aim 1. We will use the gamma spending function (129) with parameters -3 and -1 for alpha (efficacy) and beta (futility), respectively.

SAS statistical software, Cary, NC, and East interim monitoring software, Cytel Inc, will be used for all analyses.

Sample Size Considerations. Sample size is based on the primary outcome in Aim 1, atrial arrhythmia. According to previous reports and our own cardiac registry data we expect approximately 30% of the patients having CABG and 40% of the patients having valvular surgery to develop an atrial arrhythmia. We therefore assume an incidence of approximately 0.35 in the control group for calculating a sample size for Aim 1. Based on our preliminary study we expect a 30% relative reduction in the percent of patients developing atrial arrhythmias with dexmedetomidine infusion. With a **maximum** sample size of **N=965** patients we will have 90% power at the 0.05 significance level to detect a relative risk of 0.70 or stronger given a control group incidence of 0.35. The **expected** sample size following the above-specified group sequential design with 6 interim analyses is **N=591** patients.

Table 1 below gives the P-value boundaries under the null (H0) and alternative (H1) hypotheses in columns 5 and 6. The last 3 columns give the boundary crossing probabilities. For example, if the specified treatment effect is the true treatment effect in the population sampled, the probabilities of crossing either and efficacy or futility boundary are listed in the column "Under H1", and would be a cumulative 6%, 21%, 46%, 71%, 89% and 100% for interim analyses 1 through 6, corresponding to total N of 328, 483, 644, 805 and 965. In other words, there is a very large probability of crossing a boundary and thus stopping the trial before the maximum sample size, and 71% chance by N=644. If either the treatment effect of the incidence of atrial arrhythmias are larger than planned, the probability of crossing an earlier boundary will increase accordingly.

Table 1. P-value boundaries and boundary-crossing probabilities

Information Fraction	Cumulative Accrual	Alpha Spent	Beta Spent	P-value Boundaries		Boundary Crossing Probabilities		
				H0	H1	Under H0	Under H1	Under H1/2
0.167	161	0.002	0.011	0.0017	0.9703	0.031	0.055	0.031
0.333	328	0.005	0.023	0.0032	0.8978	0.101	0.158	0.081
0.5	483	0.009	0.038	0.0061	0.661	0.278	0.243	0.178
0.667	644	0.017	0.055	0.0114	0.3117	0.334	0.249	0.242
0.833	805	0.029	0.076	0.0211	0.1232	0.178	0.189	0.246
1	965	0.05	0.1	0.0383	0.0383	0.078	0.105	0.221

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APPENDIX 1

CAM-ICU Worksheet

	Positive	Negative
Feature 1: Acute Onset or Fluctuating Course Positive if you answer 'yes' to either 1A or 1B.		
1A: Is the pt different than his/her baseline mental status? Or **1B:** Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (e.g. RASS), GCS, or previous delirium assessment?	Yes	No
Feature 2: Inattention Positive if either score for 2A or 2B is less than 8. 　Attempt the ASE letters first. If pt is able to perform this test and the score is clear, record this score and move to Feature 3. If pt is unable to perform this test or the score is unclear, then perform the ASE Pictures. If you perform both tests, use the ASE Pictures' results to score the Feature.	Positive	Negative
2A: ASE Letters: record score (enter NT for not tested) Directions: Say to the patient, *"I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand."* Read letters from the following letter list in a normal tone. **S A V E A H A A R T** Scoring: Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."	Score (out of 10): _____	
2B: ASE Pictures: record score (enter NT for not tested) Directions are included on the picture packets.	Score (out of 10): _____	
Feature 3:Disorganized Thinking Positive if the combined score is less than 4	Positive	Negative
3A: Yes/No Questions (Use either Set A or Set B, alternate on consecutive days if necessary): 　　　　**Set A**　　　　　　　　**Set B** 　1. Will a stone float on water?　　1. Will a leaf float on water? 　2. Are there fish in the sea?　　　2. Are there elephants in the sea? 　3. Does one pound weigh more than　3. Do two pounds weigh 　　two pounds?　　　　　　　　　more than one pound? 　4. Can you use a hammer to pound a nail?　4. Can you use a hammer to cut wood? Score ____(Patient earns 1 point for each correct answer out of 4) **3B:Command** Say to patient: "Hold up this many fingers" (Examiner holds two fingers in front of patient) "Now do the same thing with the other hand" (Not repeating the number of fingers).　*If pt is unable to move both arms, for the second part of the command ask patient "Add one more finger) Score____(Patient earns 1 point if able to successfully complete the entire command)	**Combined Score (3A+3B):** _____ (out of 5)	
Feature 4: Altered Level of Consciousness Positive if the Actual RASS score is anything other than "0" (zero)	Positive	Negative
Overall CAM-ICU (Features 1 and 2 and either Feature 3 or 4):	Positive	Negative