Noteworthy Literature Published in 2016 for Cardiothoracic Critical Care

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Abstract
In 2016, demand for the presence of cardiothoracic anesthesiologists outside of the cardiac operating rooms continues to expand. This article is the second in this annual series to review relevant contributions in postoperative cardiac critical care that may impact the cardiac anesthesiologist. We explore the use of extracorporeal membrane oxygenation (ECMO), management of postoperative atrial fibrillation, coagulopathy, respiratory failure, and role of quality in cardiac surgery.

Keywords
critical care, atrial fibrillation, ECMO, coagulopathy, respiratory failure

Introduction
This article is the second in the annual series in Seminars in Cardiothoracic and Vascular Anesthesia highlighting important publications for cardiothoracic anesthesiologists.¹ We would like to thank the editor-in-chief Dr Weitzel and the editorial board for the opportunity to review several important scientific areas related to the postoperative care of the cardiothoracic surgical patient in 2016. This article is not meant to serve as a comprehensive review of all facets of postoperative cardiac critical care but a discussion of selected, high-quality articles for reference for those caring for a cardiac surgery patient in the postoperative period. As cardiac anesthesiologists continue to expand their scope of services outside of the cardiac operating rooms, caring for patients in the intensive care unit remains a logical extension and the need to stay abreast of the latest knowledge remains paramount. In this yearly update, we focus on the latest trends in coagulation and transfusion, management of respiratory failure and atrial fibrillation after cardiac surgery, use of extracorporeal life support, and the emerging quality indicator in the intensive care unit-failure to rescue.

Coagulation and Transfusion
Factor Concentrates
Prothrombin complex concentrate (PCC) and human fibrinogen concentrate (HFC) continue to be used off-label in cardiac surgery patients for the management of post–cardiopulmonary bypass (CPB) bleeding. In 2016, several studies added to an already growing body of literature. In a cohort of 22 patients undergoing proximal aortic arch replacement, Hanna and colleagues² measured plasma fibrinogen levels at baseline, immediately prior to separation from CPB and after administration of 70 mg/kg of HFC. In this study, mean fibrinogen levels were 235 ± 39 mg/dL before separation from CPB and rose to 331 ± 41 mg/dL after administration of HFC. The study was not powered to look at bleeding, but did demonstrate that fibrinogen levels are low in aortic surgery patients immediately prior to separation from CPB and that administration of 70 mg/kg of fibrinogen concentrate restores them to baseline values.

In a randomized trial that included 48 coronary artery bypass graft (CABG) patients with baseline plasma fibrinogen levels below 380 mg/dL, Jeppsson and colleagues³ assigned patients to receive either placebo or 2 g of HFC prior to surgery. Their primary end-point was postoperative blood loss during the first 12 hours after surgery. In this study, there was no difference in postoperative bleeding or

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Among cardiac surgery patients, the question of whether to continue aspirin perioperatively has remained controversial. In 2016, Fabbro et al., in a study of CABG patients, found no difference in the composite outcome of death or thrombotic complications (myocardial infarction, stroke, etc) within 30 days after surgery. Its principal finding was that there was no difference in the perioperative period in cardiac surgery patients (CPB >90 minutes) where administration of HFC after protamine administration decreased postoperative bleeding.

An important study about the safety of off-label PCC use was also published in 2016. One major concern with off-label PCC use is the potential for thromboembolic events. In a recent review by members of the Food and Drug Administration, PCC use was associated with a 7-fold increase in same or next day thrombotic events. In an in vitro study of dilutional coagulopathy, Mitrophanov et al. helped shed light on how PCC administration without antithrombin supplementation can lead to supranormal levels of thrombin generation, which may increase the risk for thromboembolism. The authors suggested that PCC administration with antithrombin supplementation might be a more “balanced” approach than PCC alone since it restores thrombin generation toward baseline values and not to supranormal values.

**Antiplatelet Drugs**

Whether to continue aspirin during the perioperative period in cardiac surgery patients is controversial. In 2016, a large randomized controlled trial published by Myles et al. (ATACAS investigators) assigned CABG patients to receive either 100 mg of aspirin prior to surgery or placebo. Patients in the study were either not taking aspirin before surgery or stopped taking aspirin at least 4 days prior to surgery. The study’s primary outcome was all-cause mortality or thrombotic complications (myocardial infarction, stroke, etc) within 30 days after surgery. Its principal finding was that there was no difference in the composite outcome of death or thrombotic complications between groups and there was no difference in perioperative bleeding. Based on these results, it seems likely that the question of whether to continue perioperative aspirin in cardiac surgery patients will remain controversial.

**Extracorporeal Membrane Oxygenation and Left Ventricular Assist Device**

Bleeding is a frequent complication in patients on extracorporeal membrane oxygenation (ECMO) and in left ventricular assist device (LVAD) patients. With increasing use of adult ECMO, understanding risk factors for bleeding and its epidemiology has become increasingly important. In a single center study that examined ECMO patients over a 3.5-year period, 56% of patients experienced at least one bleeding complication and the rate of bleeding was approximately 10 events per 100 days. The mechanisms for bleeding in patients with mechanical circulatory support remain somewhat unclear, although bleeding appears to be in part due to loss of large von Willebrand factor multimers, platelet dysfunction, and overanticoagulation. Grosman-Rimon and colleagues published a novel study in 2016 demonstrating that plasma cyclic guanosine monophosphate (GMP) levels are highly correlated with gastrointestinal bleeding in patients with continuous flow LVADs. The authors hypothesized that high levels of cyclic GMP and nitric oxide may impair normal platelet activation. Cyclic GMP can lower intracellular calcium levels in platelets impairing their function. Future studies are needed to confirm whether cyclic GMP is directly involved in the pathophysiology of LVAD bleeding or is simply a marker associated with bleeding.

The current standard for long-term anticoagulation in LVAD patients is warfarin. In 2016, one of the first case reports was published of an LVAD patient who received long-term anticoagulation with a novel oral anticoagulant (NOAC), apixaban. In this report, the authors described a patient who had recurrent gastrointestinal bleeding while taking warfarin. The patient was switched to apixaban 2.5 mg twice per day and had no further gastrointestinal bleeding for over a year. More studies are needed to determine whether NOACs will have a role in LVAD patients and whether they may be superior to warfarin. This question is becoming more important as recently developed drugs (andexanet alfa and idarucizumab) can rapidly reverse the effects of NOACs offering a potential rapid reversal strategy for patients with LVAD bleeding.

**Coagulation Monitoring**

Coagulation monitoring during cardiac surgery varies by center and best practices continue to evolve as new coagulation assays are validated and become more widely available. Some centers have adopted point of care platelet function testing, but their use remains somewhat controversial. In a study by Mahla et al., 149 patients that were taking dual antiplatelet therapy and presented for urgent CABG were evaluated using a number of platelet function assays, including light transmittance aggregometry (LTA) and impedance aggregometry. In this study, LTA, using adenosine diphosphate (ADP) as an agonist, was highly predictive of bleeding after surgery, suggesting that this assay might be used to determine which patients will benefit from platelet transfusion during surgery.

Many centers use viscoelastic tests to guide transfusion and in 2016, Fabbro and colleagues added an important study to a growing body of literature about thromboelastography (TEG) use in cardiac surgery. In their study, 51 cardiac surgery patients had Clauss method fibrinogen
levels measured at baseline, during rewarming, and after protamine administration. All patients also had functional fibrinogen levels measured using TEG at the same time points. The important findings of the study were that (1) TEG functional fibrinogen values had poor correlation with Clauss method fibrinogen levels (differing by approximately 92.5 mg/dL) and (2) rewarmed fibrinogen levels were very similar to postprotamine fibrinogen levels, suggesting that these values could be used to order cryoprecipitate at a much earlier time point (approximately 45 minutes earlier while on CPB).

A large meta-analysis was also performed in 2016 examining the impact of viscoelastic tests on bleeding outcomes in cardiac surgery patients. This analysis included 17 trials (9 randomized controlled trials and 8 observational studies) and a total of 8332 patients. The main findings were that viscoelastic tests decreased the odds of allogeneic transfusion (odds ratio [OR] = 0.63), reexploration due to bleeding (OR = 0.56), acute kidney injury (OR = 0.77), and thromboembolic complications (OR = 0.44). The authors concluded that viscoelastic guided transfusion therapy is superior to the current standard of care for coagulation management.

**Hypoxemic Respiratory Failure After Cardiac Surgery**

Hypoxemic postoperative respiratory insufficiency commonly occurs in patients recovering after cardiac surgery and is known to increase morbidity and mortality. Treatment strategies for hypoxemic respiratory failure most often involve oxygen therapy and positive pressure ventilation. Oxygen can be delivered through low flow systems (which are able to deliver up to 15 L/min of flow); however, these flows are typically lower than the inspiratory flow required of a patient with acute respiratory failure. Ventilation at low oxygen flows can entrap room air; thus, diluting the fraction of inspired oxygen (FiO2). Therefore, high flow systems may have greater benefit in the treatment of acute hypoxemic respiratory failure.

High-flow nasal cannula (HFNC) is able to deliver heated, humidified, high flow oxygen through nasal prongs. This system includes a heated single-limb circuit able to deliver high flows (typically up to 60 L/min), a blender, oxygen sensors, and humidification and temperature control systems. Currently, there are high flow nasal cannula systems with electronic controls that allow users to adjust different settings in clinical use.

In cardiothoracic surgical patients, HFNC has been shown to increase end-expiratory lung volume and reduce respiratory rate as well as improve dyspnea scores when compared to conventional oxygen therapy (COT). In patients with mild to moderate hypoxemic respiratory failure postoperatively, HFNC patients needed noninvasive ventilation less often and had significantly less desaturations. In 2013, Parke et al published a randomized controlled trial of 340 cardiac surgery patients randomized to HFNC or COT from extubation until postoperative day 2. There were no differences in oxygenation on day 3 after surgery but there was less need for escalation of respiratory support.

In 2015, Stéphan et al published a noninferiority, randomized clinical trial comparing HFNC versus bilevel positive airway pressure (BiPAP) in cardiothoracic surgery patients in 6 French intensive care units (ICUs). Hemodynamically stable post–cardiac surgery patients with no history of sleep apnea, delirium, nausea or vomiting, bradypnea or impaired consciousness were eligible. Inclusion criteria were (1) failure of spontaneous breathing trial (SBT): SaO2 <90% on 12 L/min of oxygen during T-piece trial or PaO2 <75% at FiO2 50% during low pressure support; (2) successful SBT but risk factors for postextubation acute respiratory failure: body mass index >30 kg/m2, left ventricular ejection fraction <40%, history of failed extubation; (3) Successful SBT followed by failed extubation: PaFiO2 <300, respiratory rate <25 breaths per minute for 2 hours, use of accessory muscles or paradoxic respiration. A total of 830 patients who developed acute respiratory failure after cardiac surgery were randomized to HFNC or BiPAP. SpO2 goal was 925 to 98% as per physician discretion in both groups. The HFNC group was started at a flow of 50 L/min and 50% FiO2 and the BiPAP group was started at FiO2 50% with pressure support to achieve 8 mL/kg exhaled tidal volume, positive end-expiratory pressure was added to achieve goal SpO2; BiPAP was given for at least 1 hour every 4 hours.

The primary outcome was treatment failure defined as: need for reintubation, crossover, or study treatment discontinuation. Predefined criteria for reintubation were followed. Secondary outcomes were changes in respiratory variables at 1 hour and between 6 and 12 hours, dyspnea and comfort scores, and need for bronchoscopy among others. The design of the noninferiority trial assumed a 20% failure rate of BiPAP and a noninferiority margin of 9%. Secondary outcomes were not included in the noninferiority analysis. In fact, HFNC was hypothesized to be superior than BiPAP for secondary outcomes. Intention to treat analysis was performed. There were 414 patients randomized to HFNC and 416 patients randomized to BiPAP. The treatment failed in 21% (95% CI, 17.2% to 25.3%) of patients in the HFNC group versus 21.9% (95% CI, 18.0% to 26.2%) of patients in the BiPAP group. The absolute risk difference was 0.9% (95% CI, −4.9% to 6.6%). The median time to intubation was 1 day in both groups. Reintubation was performed in 13.7% patients on BiPAP and 14% patients on HFNC (P = .95). Crossover occurred in 7.9% BiPAP group and 10.8% HFNC group (P = .15). Premature discontinuation of treatment was noted in 3.5%
BiPAP patients and 1.5% HFNC patients ($P = .04$). There was no difference in mortality (6.8% HFNC vs 5.5% BiPAP; $P = .66$).

This study has several important limitations. The active control was defined as use of noninvasive positive pressure ventilation (NIPPV) intermittently; however, use of NIPPV in this setting can be considered contradictory. The study would have been easier to interpret if it was designed as a superiority trial and compared with usual care (which could have included NIPPV). Also, use of a noninferiority margin of 9% leads to results that yield wide confidence margins ($−4.9$% to 6.6%). Thus, use of HFNC could potentially result in a 6.6% absolute reduction of treatment failure or a 4.9% absolute increase in treatment failure, a worse outcome, compared with NIPPV. The study noted, however, a trend toward lower nursing interventions to address device adjustments (6 daily interventions for BiPAP vs 1 intervention for HFNC).

**Preemptive Use of HFNC**

Current evidence indicates that the preemptive use of HFNC to prevent postextubation failure seems more effective than the use of HFNC in already established hypoxic respiratory failure patients. A recent randomized clinical trial indicates 24 hours of HFNC following extubation in low-risk patients decreases postextubation failure. Despite concerns for increased mortality of failed HFNC therapy, a recent study by Maggiore et al. suggests that HFNC could be used for longer than 24 hours to provide maximum benefit to some patients without increase in mortality. In contrast, HFNC used in established hypoxic respiratory failure does not result in lower intubation rates when compared with COT or NIPPV.

The role of HFNC in patients at high risk of postextubation failure has been recently addressed in a noninferiority randomized clinical trial. High-risk patients were defined as having at least one of the following criteria: older than 65 years, heart failure as primary indication for mechanical ventilation, moderate to severe chronic obstructive pulmonary disease, APACHE score $>12$ on extubation day, body mass index $>30$ kg/m², airway patency problems, prolonged weaning, $>2$ comorbidities, and intubated for $>72$ hours. Patients were randomized to either NIPPV or HFNC if they were intubated for at least 12 hours, were considered at high risk, had passed a spontaneous breathing trial (SBT) and were ready for extubation. The trial excluded patients with tracheostomy, DNR orders, hypercapnia during SBT, accidental extubation, or self-extubation. Interventions were started immediately after elective extubation, titrated to SpO₂ $>92$% and continued for 24 hours. The HFNC group was started at flow 10 L/min and titrated up by 5 L/min for up to 24 hours and then switched to COT. The BiPAP group was started at pressure support titrated to respiratory rate $<25$ breaths per minute. The primary outcome was reintubation within 72 hours after extubation and postextubation respiratory failure. Follow up was performed throughout hospital stay. Secondary outcomes were respiratory infection, sepsis, or multiple organ failure, ICU and hospital length of stay, mortality, and reason for failure. A noninferiority margin of 10% and power of 80% on an assumed reintubation rate of 20% to 25% for each therapy required 300 patients in each group. A noninferiority margin was established for between-group difference was less than 10%. Analysis was based on both intention-to-treat and per-protocol. A total of 604 patients were randomized: 324 received NIV and 290 HFNC. Sixty-two patients in HFNC (22.8%) versus 60 (19.1%) in the NIPPV did not require reintubation (absolute difference, $-3.7$; 95% CI, $-9.1$ to $\infty$). A total of 78 patients (26.9%) in HFNC versus 125 (39.8%) in the NIPPV group experienced postextubation respiratory failure (risk difference, 12.9%; 95% CI, 6.6% to $\infty$). Median time to reintubation did not significantly differ but median ICU length of stay was lower in the HFNC group, 3 days (interquartile range 2-7 days) versus 4 days (interquartile range 2-9 days; $P = .048$). Other secondary outcomes were similar between the 2 groups.

**Atrial Fibrillation**

Atrial fibrillation remains a common problem ranging in incidence from 20% to 50% that increases length of stay and is associated with higher mortality in patients after cardiac surgery. Until this year, it was unclear whether a rhythm or rate control strategy should be performed, and many institutions pursue aggressive rhythm control therapies to reduce the number of patients requiring anticoagulation, and presumably to reduce the consequences of atrial fibrillation. This strategy of rhythm control exposes patients to amiodarone and various other agents with significant toxic side effect profiles with little evidence of added benefit.

The Cardiac Surgical Trials Network (CTSN) has added to it sentinel research by answering the age-old question of whether outcomes are different in patients undergoing cardiac surgery who have rate or rhythm control strategies. This study randomized over 695 patients with new postoperative atrial fibrillation at 23 sites in Canada and the United States to a rate or rhythm control regimen. Patients in the rhythm control group could cross over to rate control to improve hemodynamic status or alleviate symptoms. Patients in the rhythm control group received amiodarone and direct current cardioversion if atrial fibrillation remained after 24 to 48 hours.

The results were surprising to some, because there was no difference hospital length of stay (rate control 5.1 days
vs rhythm control 5.0 days, \( P = .76 \), in the rate of death or serious adverse events (\( P = .64 \)), or hospital readmission (\( P = .99 \)). Since the authors designed the study to anticoagulate all patients who remained in atrial fibrillation 48 hours after randomization, there was no statistical difference in the number of patients discharged on anticoagulation. Finally, there was no difference in the rate of atrial fibrillation between groups at 60 days (rhythm control 86.9% vs rate control 84.2%, \( P = .41 \)). We expect this to potentially affect management styles across the continuum of cardiac surgical care.

### Extracorporeal Life Support

In cardiac surgery, extracorporeal life support (ECLS) remains an important intervention to study and many questions abound on topics as simple as who should get ECLS and when should a team consider withdrawal. After a patient has been on ECLS for more than a couple of weeks, this topic will be raised by everyone who is asked to consult in their care. Polslusnzy and colleagues\(^25\) at Michigan attempted to shed some light on the outcomes of patients on prolonged duration of ECLS. The authors analyzed almost 1000 patients who had been treated with ECLS for respiratory failure from 1989 to July 2013. Overall, the ECLS survival was 45.4%, but survival was significantly higher in when comparing patients cannulated from 1989 to 2006 to patients cannulated between 2007 and 2013 (36.6% vs 48.9%, \( P < .001 \)). Even more helpful is the outcome that survival declined as ECMO duration became more prolonged. For patients on ECLS runs >6 weeks in duration, survival was 40.9%, and for 16.4% for patients on ECLS >60 days. This information can be crucial in discussions with families and consultant eager for prognostic information.

Dr Combes and colleagues\(^26\) recently published their analysis of patients undergoing venoarterial ECLS for acute myocardial infarction complicated by cardiogenic shock. The authors reviewed 138 patients at 2 French university ICUs. Sixty-five patients survived to ICU discharge and 57 survived to 6 months after ICU discharge. Using data such as age >60 years, sex, body mass index, serum lactate, creatinine, prothrombin activity, and serum Glasgow coma score, the authors were able to generate a predictive scoring system called the ENCOURAGE score, which will need to be prospectively evaluated. This scoring system is one among many now available to ECLS physicians hoping to predict outcome, including the SAVE score, the GRACE model, the SHOCK Trial and Registry scoring system, and the SAPS II and SOFA ICU scores.

Dr Aubin and associates\(^27\) shocked the ECLS community by publishing their results utilizing mobile venoarterial ECLS to salvage patients with refractory circulatory failure. The Dusseldorf network offers 24/7 ECLS even in patients receiving cardiopulmonary resuscitation compared with the standard method of offering ECLS to patients with cardiogenic shock and transporting these patients to high volume centers to get ECLS. After stabilization on ECLS and transfer the patient undergoes a standard diagnostic and treatment algorithm, including cannula implantation for limb perfusion, cardiac catheterization and whole body computed tomography scan. The results of this group are astounding with 115 patients receiving venoarterial ECLS support between July 2011 and October 2014 with 44% survival to discharge and 33% survival at 1.5 years' follow-up. Furthermore, the vast majority (97%) reported a favorable neurologic outcome. This type of program would require significant investment to support a 24/7 mobile team to serve a region.

### Failure to Rescue

Traditionally, surgical quality markers focus on mortality as a benchmark. The incomplete assessment of quality achieved by looking only at risk of death has shifted quality metrics toward examining the entire perioperative system treating surgical patients; in particular, cardiac surgical patients. Rates of complications are commonly reported, in addition to simple mortality data. Furthermore, complications and mortality are no longer seen only as a report card for surgeons, but are increasingly linked to ranking and reimbursement for entire hospital systems.

The term failure to rescue first appeared in 1992 in an article titled “Hospital and Patient Characteristics Associated With Death After Surgery.”\(^28\) In it the authors reviewed 2 elective, intermediate risk surgeries (cholecystectomy and transurethral prostatectomy) to compare overall mortality versus mortality following a complication, newly coined “failure to rescue” (FTR). The authors presented an elegant mathematical proof to show that death after a complication or FTR, allows distinctions to be made between high-performing hospitals (all of which had low, relatively similar mortality rates) compared to a simple mortality rate. In addition, FTR methodology puts an emphasis on the entire medical system by eliminating deaths that occurred before a complication, which may be more attributable to surgical error or other rare event.

In 2016, Edwards et al\(^29\) explored the Society of Thoracic Surgeons Adult Surgery Database to examine the FTR rates after coronary bypass grafting. The authors examined the database for CABG patients over a 4-year period, yielding over 600 000 patients and over 1100 centers; making it the largest FTR study to date. FTR was defined in the study as death after 1 or more of 4 particular complications: stroke, renal failure, reoperation, or prolonged ventilation. Of the total population, 78 611 (13%) patients experienced one or more adverse events. Overall, there were 8228 deaths after complication, yielding an
overall FTR rate of 10.5%. The majority of patients had an isolated complication (78.5%), with an FTR rate of 5.9%. The occurrence of a second complication increased mortality to 18.6%, and 3 complications resulted in 24.7% death rate. The few, unfortunate patients with all 4 complications died 58.3% of the time.

In order to further examine the potential system factors associated with variation in FTR, centers with more than 150 CABG procedures per year were grouped into terciles according to total mortality, hospital volume and overall complication rates. The average overall rate of mortality ranged from the lowest to highest tercile (1.1% vs 3.1%). The complication rates similarly increased in parallel to overall mortality (11.4% vs 15.7%). Yet the FTR rate had the most dramatic difference with a more than doubling of the FTR rate between the lowest and highest mortality centers (6.8% vs 13.9%).

Interestingly, when the patients were regrouped by complication rate, there was an inverse relationship between the complication tercile and the FTR rate, with the highest complication group demonstrating the lowest FTR. This conflicting finding was attributed to the variable patient populations regularly encountered by different centers. The authors assert that centers accustomed to caring for high-risk patients encounter more complications and have built more robust systems for managing such events.

Other studies have examined the utility of FTR to evaluate quality within a single institution. Chu et al. evaluated the effectiveness of various quality improvement implementations by traditional methods (mortality and morbidity rates) as well as FTR rates. The authors were able to demonstrate a significant reduction in the number of adverse events (both complication or mortality) after the quality improvement implementations from 20.2% to 10.7%. However, the FTR rates for all major complications (reoperation for bleeding, deep sternal wound infection, stroke, ventilation >24 hours, pneumonia, renal failure, dialysis) as well as a composite of those complications showed no difference before or after the intervention. What is striking about these FTR studies is that in a single center (despite a 4-year review including 3000 patients), the incidence of each complication was associated with variation in FTR, centers with more than 150 CABG procedures per year were grouped into terciles according to total mortality, hospital volume and overall complication rates. The average overall rate of mortality ranged from the lowest to highest tercile (1.1% vs 3.1%). The complication rates similarly increased in parallel to overall mortality (11.4% vs 15.7%). Yet the FTR rate had the most dramatic difference with a more than doubling of the FTR rate between the lowest and highest mortality centers (6.8% vs 13.9%).

Conclusion
The past year has seen significant advances in the postoperative management of patients undergoing cardiovascular surgery. Expanded indications for the use of ECLS, refinement in the treatment of atrial fibrillation and coagulopathy, improved outcomes with management of respiratory failure, and greater attention to quality improvement in cardiac surgery should hopefully improve outcomes in this population.

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