Perioperative Considerations for Extracorporeal Membrane Oxygenation

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Abstract

Technological advances in health care are improving the survival rates of adults experiencing advanced cardiopulmonary failure. Extracorporeal Membrane Oxygenation (ECMO) is one such advancement allowing for hemodynamic support until organ recovery can take place or an organ transplant becomes available. ECMO presents unique challenges to anesthesia as the patients are critically ill resulting in altered pharmacodynamics. Additionally, formulating an anesthetic plan of care can be challenging due to the complexity of the patient's illness. A general knowledge deficit and limited clinical exposure was identified amongst the AdventHealth University (AHU) Student Registered Nurse Anesthetist's (SRNA) regarding ECMO, therefore a systematic literature review and educational PowerPoint presentation addressing perioperative considerations was developed. The aim of the project was to increase the knowledge base of the AHU SRNA cohort of 2019 which can be applied to the cardiac clinical rotation assisting in a patient centered anesthetic plan. After obtaining informed consent 10 question multiple choice pre-test was administered followed by an educational PowerPoint presentation. After the PowerPoint presentation a posttest (identical to pretest) was administered to assess the knowledge base and effectiveness of the educational PowerPoint presentation. Th aim of the investigator was to assess baseline knowledge gain as evidenced by an increase in Pre and post- test scores. The presentation was effects as shown by an increase in mean increase in pre- test scores 47.72% compared to post- test 93.18%. Indicating that the aim to increase knowledgebase in this population via use of an educational PowerPoint was successful.

Keywords: extracorporeal membrane oxygen, anticoagulation, fluid resuscitation, pharmacodynamics

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Introduction

ECMO devices were first introduced in the 1960s for newborns suffering from cardiopulmonary failure. Gradually, ECMO technology expanded to include long term circulatory support in adults experiencing Acute Respiratory Distress Syndrome (ARDS) in 1972 (Makdisi and Wang, 2015). ECMO can be used in pulmonary, cardiac, or cardiopulmonary failure (Meng, 2017). In addition, ECMO is often utilized as a bridge therapy while patients await transplant (Shekar, 2015). Clinical indications for adult ECMO include respiratory failure caused by hypoxia or hypercapnia, pulmonary hypertension, ARDS, cystic fibrosis, cardiac arrest, unable to wean from cardiopulmonary bypass (CPB), and pulmonary embolism. Relative contraindications include sepsis, age greater than 65 years, multiorgan system dysfunction (MODS), permanent central nervous system (CNS) injury, hemorrhagic stroke, or terminal illness (Meng, 2017).

In ECMO support, blood circulation is taken over by a pump where carbon dioxide and oxygen exchange is accomplished by flow through an oxygenator with a semipermeable membrane. An outflow or drainage cannula removes blood from the patient, circulates it through the device, and oxygenated blood is returned to the patient via an inflow or return cannula (Meng, 2017 & Shekar, 2013). Generally, ECMO cannulation sites and function are identified by the first letter referring to the drainage or outflow cannula (venous = V) and the second letter referring to the inflow or return cannula(s) (venous = V or arterial = A) (Meng, 2017).

Registry reports from the Extracorporeal Life Support Organization (ELSO) reveal in 2017 a total of 98,840 devices were utilized internationally for treatment of neonatal and adult cardiopulmonary failure. Of those cases 68% survived ECMO and 58% were either discharged

home or transferred to follow up care centers. Currently there are 444 ECMO centers registered with ELSO, 233 are centers in the United States, and 18 in Florida (ELSO, 2018).

In February of 2012, AdventHealth Orlando established itself as a leading care provider for patients requiring advanced cardiopulmonary medical therapies as well as a heart and lung transplant program. With the influx of high acuity patients, the need for ECMO availability is necessary. Anesthesia providers not specialized in care of cardiovascular patients may find themselves caring for ECMO patients needing non-cardiac procedures. This scholarly project was developed due to a generalized lack of knowledge and clinical exposure in regard to the purpose and perioperative care of patients on ECMO.

Project Questions

In development of this scholarly project two questions was proposed, using PICO format, to guide the systematic literature review and the goal of the scholarly project.

PICO: Do surgical patients on ECMO (P) require specific anesthetic interventions (I) to maintain cardiovascular stability and pain control (O).

PICO: Will ADU SRNAs (P) who reviewed an 30-minute educational PowerPoint presentation on ECMO and it's anesthetic implications (I) have an increase knowledge base (C) as evidenced by higher mean post-test scores compared to pre-test scores (O)?

Literature Review and Synthesis

According data collected from the United Network of Organ Sharing (UNOS) 3,244 heart transplants and 2,449 lung transplants were performed in the United States in 2017. Coinciding with this specific patient population is often the necessity of ECMO to stabilize and provide hemodynamic support until an opportunity for organ transplantation is made available.

AdventHealth University's NAP students are in a unique position to be exposed to perioperative management of these patients revealing a need for education regarding this specific population. Literature review revealed important implications regarding ECMO include preoperative assessment, anticoagulation, fluid resuscitation, and pharmacodynamics which will be synthesized in this review.

Perioperative Assessment

Preoperative assessment is vital tool in formulating an anesthetic plan for a patient with ECMO. Indications for ECMO are pulmonary failure, circulatory failure, or both (Meng, Bachetta, & Spellman, 2017). The anesthetist should review all laboratory data such as CBC, CMP, and coagulation tests. An investigation into end-organ function should be made along with review of recent echocardiography reports.

Knowing the indication for ECMO should be the initial question from the anesthetist and the cannulation sites are next. Veno-Veno (VV) Cannulation is used for pulmonary failure cases and commonly has one cannulation site, in right Internal jugular (IJ). Blood is pulled from the SVC and IVC oxygenated through the ECMO system and returned through the IJ to the Right Atrium (Meng et al, 2017).

Veno- Arterial (VA) ECMO is indicated for patients experiencing Cardiovascular or combined cardiopulmonary collapse. Cannulation involves pulling blood from the venous system or Inferior Vena Cava (IVC) and returning it to the aorta (Meng et al., 2017). Femoral cannulation is also an option in VA heart failure in which blood is pulled from the circuit from the femoral vein, oxygenated and returned to the femoral artery (Schaheen, Thiele, and Isbell, 2015).

Maintenance of end- organ perfusion is a primary predictor of morbidity and mortality in ECMO patients and should be included in the preoperative assessment. Review of the literature revealed that urine output in the first 24 hours after cannulation was a strong predictor of 30- day mortality ($p < 0.001$) in patients with VA ECMO (Stelmaier et al., 2016). To ensure adequate end-organ perfusion the patient may need hemodynamic support using inotropes and/ or vasopressors (Meng, Bachetta, and Spellman, 2017; Schaheen et al., 2015).

Transesophageal echocardiography (TEE) studies assist in determining underlying heart function and fluid volume status. Including recent results in the pre-operative assessment can help to guide anesthetic choice and serve as a guide to fluid volume resuscitation. Review of literature regarding the use of TEE with ECMO patients indicates that in patients with VA ECMO and severe LV dysfunction, TEEs are invaluable tool in determining valve function and contractility (Meng et al. 2017; Kepoor, 2017). In the case of the aortic valve severe LV dysfunction may keep the valve from opening resulting in distention of LV (Kapoor, 2017).

Anesthetist should be aware that VA circuits cause and increase in afterload and reduction should be considered through use of vasodilation and inotropes to assist in contractility and unloading of the heart. Stasis in the LV can precipitate the development of clots posing a risk for stroke or pulmonary embolus and should be prophylactically treated with anticoagulation (Kapoor, 2017). Schaheen et al. (2015) mentions that and early sign of decreased LV ejection be apparent by a loss in pulsatility of the arterial line and should be investigated with echocardiography.

Anticoagulation

Finding a balance between bleeding and thrombosis can be an issue in management of the ECMO patient. Review of literature indicates that consumptive coagulopathy is created due to

blood exposure to the circuit. Additionally, exposure to the circuit triggers an inflammatory response of the complement cascade, macrophages, and cytokines resulting a hypercoagulable state, making the need for anticoagulation a necessity throughout the course of implantation (Esper, Levy, Waters, & Welsby, 2014; Meng et al. 2017).

The anesthetist must be vigilant to the current coagulation state of the patient especially when patients are needing to undergo invasive procedures like bronchoscopy, endoscopy, or exploratory laparotomy. Unfractionated heparin is typically used to manage anticoagulation needs. Coagulation status via aPTT, ACT, and thromboelastography (TEG), and anti- Xa factor should be monitored to guide heparinization and replacement of coagulation deficiencies (Meng et al., 2017; Espers et al., 2014).

Fluid Resuscitation

Aronson, Nisbet and Bunke (2017), in a cross-sectional study investigated current practice & decision-making in fluid resuscitation and assessed: a) choice of volume expander (crystalloid, colloid [albumin or hydroxyethyl starch (HES)], b) what patient and/or practice attributes guide the choice volume expander, c) does clinical specialty impact choice of volume expander, and d) fluid of choice perfusionists select to prime the circuit.

Anesthesiologists selected TEE as the most important volume indicator (79%) compared to surgeons (26%), a statistically significant difference ($P < .001$). Pulse pressure variation was less important to anesthesiologists (56%) compared to surgeons (26%), a statistically significant difference ($P = .002$). Stroke volume variation was selected least by anesthesiologists (44%) compared to surgeons (15%), a statistically significant difference ($P = .001$) (Aronson, 2017).

Fluid selection varied significantly between anesthesiologists and surgeons (Aronson et al., 2017). Crystalloid and 5% albumin were reported equally as the fluid of choice during

ECMO or VAD support but, 5% albumin was reported more by anesthesiologists (35%) than surgeons (17%), a statistically significant difference ($P < .05$). Surgeons (21%) reported 25% albumin more than anesthesiologists (4%) and surgeons were the only specialty to select HES for volume expansion in ECMO support (Aronson et al., 2017). Further studies with larger sample sizes are needed to make more conclusions and/or recommendations for best practice.

Pharmacokinetics & Pharmacodynamics

Consensus exists that, while on ECMO support, patients generally require larger doses of sedatives and analgesics. This is largely based on clinical experience and a clear, definitive cause has yet to be established (Bhatt & Annich, 2005, Shekar et al., 2012, Ha & Sieg, 2017). Escalating doses of benzodiazepines and opioids have implications for weaning ECMO support and patient morbidity (Lemaitre et al., 2015). The cause is likely multifactorial including (1) drug sequestration into the polyvinyl chloride (PVC) circuit tubing and/or the membrane oxygenator (MO), (2) the circuit and it's components create an additional compartment for drug distribution (Vd) and clearance (CL) resulting in reduced elimination, (3) the clinical impact of critical illness, (4) individual drug characteristics, (5) fluids used prime the circuit, (6) the age of the circuit, and (7) CRRT (Mehta & Annich, 2005, Lemaitre et al., 2015, Ha & Sieg, 2017, Bhatt & Annich, 2005, Shekar et al., 2012).

Drug Sequestration and Drug Characteristics

The majority of available data regarding drug sequestration into the circuit is derived from study models on neonates and/or infants therefore extrapolating these results to adults on ECMO is inappropriate (Ha & Sieg, 2017). Infants, when compared to adults, have a smaller distribution of adipose tissue and larger compartment of total body water resulting in a smaller Vd for lipophillic drugs. Neonatal renal and hepatic systems are immature with inefficient

metabolic pathways. Additional studies on adult models are necessary to make recommendations for appropriate and therapeutic dosing.

Multiple studies have demonstrated that drugs are sequestered into the ECMO circuit, but this may be inadequately described in the literature (Shekar et al., 2012; 2015). In vitro studies conducted by Gillogly et al. (2012), reveal drug characteristics such as lipophilicity, partition coefficient, molecular size, ionization, and affinity for protein binding influence sequestration of drugs into the ECMO circuit. Lipophillic drugs that are highly protein bound, such as midazolam, fentanyl, and propofol, appear to be sequestered the most (Bhatt & Annich, 2005 & Shekar 2012 & 2015) and may explain the need to increase doses as the circuit ages. The age of the circuit appears to be important consideration, it may behoove anesthesia providers to determine the age of the circuit when planning an effective anesthetic for patients on ECMO support.

Midazolam, a benzodiazepine, is 92% protein bound with a lipophilicity (log *P*) of 3.9 (Shekar et al., 2015). Shekar et al (2015) demonstrated, in an adult model, that midazolam was reduced by 50% 1 hour after introduction into the ECMO circuit concluding that initial doses should be higher to reach an appropriate level of sedation. An in vivo study conducted by Shekar (2012) and colleagues support this conclusion and found an 18mg/day increase in midazolam requirements, a 10.2% increase in dose. Lemaitre et al. (2015), in a two-part in vivo and ex vivo adult model, found after 30 minutes only 54% of the baseline midazolam concentration remained and at 24 hours only 11% remained. Providing the amnestic component of an anesthetic may prove to be very challenging for patients on ECMO support for more than 24 hours. Alternative medications such as ketamine, a dissociative-sedative, should be considered if patient comorbidities allow.

Fentanyl, a synthetic opioid, is 85% protein bound and has 3.9 log *P* (Shekar et al, 2015). An ex vivo, adult model, showed fentanyl was significantly sequestered and at 24 hours only 6.3% of the baseline concentration was recovered (Shekar et al., 2012-2015). In another ex vivo study, Mehta and colleagues found concentrations of fentanyl in the ECMO circuit were the same for the first 3 hours but was completely undetectable at 24 hours (Mehta et al., 2007). Other studies have concluded, from these results, that Fentanyl may be useful for short periods of analgesia in patients on ECMO support (Ha & Seig, 2017). Based on these results, anesthetists may be able to use fentanyl to provide adequate analgesia for cases lasting less than 3 hours.

Propofol, a hypnotic-sedative, is 97-99% protein bound with log *P* 3.8 (Shekar et al., 2015). Lemaitre et al. (2015), in a two-part study previously described, found propofol was dramatically sequestered by the ECMO circuit after only 30 minutes with 70% of the baseline drug lost and after 5 hours later only 11% remained, a statistically significant loss ($P < .001$). This study also demonstrated that, after 45 minutes, exposure of the drug to PVC tubing and oxygen decreased propofol concentrations, 85% and 70% respectively (Lemaitre et al., 2015). Increasing propofol doses to maintain appropriate levels of sedation may place already critically ill patients at risk for propofol infusion syndrome (Ha & Sieg, 2017). In a recent prospective study comparing oxygenator exchanges with propofol requirements, Hohlfelder and colleagues (2017), found patients receiving propofol infusions required fewer oxygenator changes ($p < .001$). This contradicts previous studies suggesting the lipophillic characteristics of propofol result in obstruction of the membrane oxygenator resulting in frequent changes resulting in increased cost, potential for infection, and blood loss (Hohlfelder et al., 2017). The authors conclude their findings suggest the duration of propofol exposure to the membrane oxygenator

increases the likelihood of oxygenator exchange not the dose and put forth that propofol is safe for patients on ECMO (Hohlfelder, 2017).

Critical Illness

Adults requiring ECMO are often critically ill compounding the challenge of drug dosing in this population. Pathological processes common in critical illness reduce serum protein levels causing an increase in free, normally protein-bound, drugs (Ha, 2017 & Shekar, 2012). Critical illness may result in alterations in physiologic pH, systemic inflammation, volume shifts, hemodilution, bleeding, and/or transfusion all of which affect distribution, clearance, and uptake of protein-bound drugs (Ha, 2017, Shekar, 2012 & 2015).

ECMO support alters physiologic pH significantly and exposure to circuit induces additional systemic inflammation Shekar, 2012-2015). End organ dysfunction, affects drug metabolism and, is typical in critically ill patients. Many require some form of continuous renal replacement therapy (CRRT) (Shekar, 2013), maintaining therapeutic drug levels during CRRT is vital. This is noteworthy because 50% of patients on VV ECMO and 41% on VA ECMO require CRRT (Shekar, 2012). VA ECMO causes up-regulation of the renin-angiotensinogen system (RASS) due to nonpulsatile flow and reduced glomerular filtration (Ha, 2017). Hepatic perfusion may be also affected. The complex processes of critical illness in the presence of ECMO support represent additional difficulties in determining therapeutic drug levels.

Contribution and Dissemination/ Justification

Successful completion of AdventHealth University's (AHU) Nurse Anesthesia program includes a 5-week specialty rotation in the Cardiovascular operating room. During this time SRNAs will be expected to take part in the intraoperative care of a variety of cardiovascular cases potentially including procedures involving ECMO devices. A prerequisite for admittance to

the Nurses Anesthesia program is experience working on a critical care unit. However, depending on the unit specialty, SRNAs may not have been exposed to ECMO patients.

AdventHealth's heart and lung transplant program is growing meaning that the use of ECMO will increase as well. Due to the high acuity of the population requiring ECMO special anesthetic considerations must be considered to ensure safe effective care. It is an expectation of the ADU NAP to be able to form patient specific anesthetic plans, however limited clinical exposure to patient's on ECMO may make that difficult. Providing education to the group of SRNAs will result in increased awareness and comfort in formulation of an anesthetic plan for patients with ECMO devices. Presentation of this project will take place in the fall semester of 2018.

Project Aims

The aim of this project was to increase the knowledge base of 22 AHU NAP students in the class of 2019 regarding anesthetic management of patients with ECMO devices. This scholarly project was developed to provide education to the SRNA cohort of 2019 with the goal of increasing the comfort of providing anesthesia care to this specific population. Presentation of this scholarly project took place October 18, 2018 during the fall trimester. The dependent variable was the difference between the mean pre and posttest scores and the independent variable is the educational PowerPoint presentation.

Project Methods

This scholarly project was a single group quantitative design, a request for approval or exemption from the SRC and IRB boards was obtained. Upon approval of the proposed topic, a 30-minute educational PowerPoint presentation was given to a convenience sample (n = 22) of the 2019 NAP cohort during clinical conference on October 18, during the fall trimester of 2018.

Prior to presentation of the 30- minute educational PowerPoint presentation, the cohort of 2019 was invited to participate in this scholarly project. Informed consent and signatures were obtained from participants before presentation of the topic. Inclusion criteria to participate in the research project included, currently enrolled senior ADU NAP students who read and signed the informed consent indicating willingness to participate in data collection. Exclusion criteria included those who do not sign the informed consent, were tardy, or absent on the day of the presentation. Students who arrived late and missed the pre-test were able to watch the presentation, however, will be excluded from the study.

A pretest was administered prior to the presentation of the scholarly project. This scholarly project incorporated a 30-minute educational PowerPoint presentation. After the presentation the students were given an identical posttest to evaluate the effectiveness of the presentation. Both tests were returned to the SRNA investigator prior to leaving the presentation room.

Participant's privacy was protected by making the pre and posttests anonymous, multiple choice, and no personal identifiers used. Paper data was stored in a locked file cabinet at the investigator's home. Tests results were logged into the password protected laptop of the researcher. Access to the data was be limited to members of the scholarly project including the investigator, project mentor, project chair and data analyst Roy Lukman PhD.

Results of the test were submitted to Roy Lukman PhD (AHU statistician) via Excel spreadsheet and analysis will be performed using SPSS for statistical analysis. After conclusion of the scholarly research project all data was deleted from the investigator's laptop and paper documents shredded.

Timeline

Initiation of the scholarly project began in May of 2018 and extended through June of 2018. Data collection began at the start of May and the project proposal was submitted to the project mentor and chair on May 20, 2018. CITI modules were completed by May 13, 2018 and submitted to the drop box along with the project chairs modules. An appointment was made for the AHU writing center to review the scholarly project paper and revisions completed and submitted by June 4, 2018 with final revisions submitted to mentor and chair on June 7, 2018. On June 9, 2018 one email was sent to the project chair with attached revised project, Scholarly project concept/ Plan approval form signed by mentor, and ADU SRC/ IRB application form with attached mandatory documents. On Monday July 16, 2018 the web based scholarly project application was completed and submitted to SRC/ IRB/ GMC review. Approval by SRC/IRB was received on October 5, 2018. SRC feedback and a completed copy of all completed due dates to the assigned drop boxes was submitted on October 5, 2018. Presentation of the scholarly project was implemented on October 18, 2018.

Data Collection Plan

Informed consent process was conducted with all prospective participants and signed consent was required prior to receiving the pre-test. The pre- and post-tests were identical and consisted of 10 multiple choice questions. The tests were disseminated to the participants directly from the investigators. All pre- and post-tests were be numbered, completely de-identified, and counted upon return to confirm that all participants completed each test. The investigator interacted with participants 6 times passing out consent forms, handing consent forms back to investigator, passing out pre-tests, handing pre-tests back to investigator, passing out the post-tests, and handing the post-tests back to the investigator.

Evaluation Plan

The effectiveness of the educational PowerPoint presentation was evaluated by comparing the mean scores of the pre- and post-tests. This was accomplished by using a paired t-test. The collected data was recorded on Excel spreadsheet and presented to, ADU statistician, Dr. Roy Lukman who used an SPSS program to perform a paired t-test on the data collected.

Limitations

Limitations of this study included use of a small, convenience, homogenous sample of 2 participants. One person was absent therefore excluded from the final sample. Timing between the pre-test, presentation, and the post-test being given immediately after the presentation which may limit ability to assess knowledge retention.

Results and Findings

The pre-test mean score was 47.72% with a standard deviation of 19.7% and a standard error mean of 4.2%. The post-test resulted in a mean score of 93.18% with a standard deviation of 7.26%, and a standard error mean of 1.52% Therefore, the average mean percentage scores increased by 45.46%. The paired samples t test revealed a mean of -45.45, with a standard deviation of 20.40, and a standard error mean of 4.35. The t value was -10.44 and is associated with a p value of $p < .001$. (See Appendix D)

Conclusions and Limitations

As demonstrated by the pre-test students initial understanding of Anesthetic considerations of patients on ECMO was limited with an average score of 47.72%. Comparison of pre and post-test scores revealed an increase in knowledge regarding the topic after the presentation, this was evidenced by an average percentage increase in pre and post- test scores of 45.46%. With a p value of <0.001% indicating a clear statistical significance. The aim of this project was to

enhance SRNA knowledge base regarding the anesthetic considerations for patients requiring ECMO for hemodynamic support. As evidenced by an increase in mean post-test scores compared to pre-test scores the aim of the project was achieved. Statistical analysis additionally revealed that the PowerPoint presentation was an effective tool in increasing knowledge base of the topic.

There were known limitations to this study. One limitation was the short amount of time between pre and post- testing. In order to truly prove retention of information the post test would ideally have been given several days to a week after the pre-test and presentation of the material. Another limitation to the scholarly project was the small homogenous sample, only including 22 senior SRNA students attending AdventHealth University. A stronger study would have included a larger sample size involving students from other Nurse Anesthesia programs. By enlarging the sample size, the results of the study would have included a larger heterogenous sample and revealed statistics would have been stronger.

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Appendix A

ADU NAP CAPSTONE PROJECT – INFORMED CONSENT

My name is Elizabeth Paige Gore, and I am a MSNA student in the Nurse Anesthesia Program (NAP) at Adventist University of Health Sciences (ADU). I am doing a Capstone Project called *Perioperative Considerations for Extracorporeal Membrane Oxygenation*. This project is being supervised by Steven Fowler DNP. We would like to invite you to participate in this project. The main purpose of this form is to provide information about the project so you can make a decision about whether you want to participate.

WHAT IS THE PROJECT ABOUT?

The purpose of this project is to increase the knowledge base of ADU SRNAs as it pertains to important considerations when providing safe anesthesia care to patients on ECMO devices.

WHAT DOES PARTICIPATION IN THIS PROJECT INVOLVE?

If you decide to participate in this project, you will be asked to complete an anonymous pre-assessment, attend a classroom presentation, and then complete an anonymous post-assessment. The assessment will address important anesthetic considerations for ECMO patients. Your participation by attendance at the presentation and completion of the survey is anticipated to take approximately 45 minutes.

WHY ARE YOU BEING ASKED TO PARTICIPATE?

You have been invited to participate as part of a convenience sample of students currently enrolled in the ADU NAP. Participation in this project is voluntary. If you choose not to participate or to withdraw from the project, you may do so at any time.

WHAT ARE THE RISKS INVOLVED IN THIS PROJECT?

Although no project is completely risk-free, we don't anticipate that you will be harmed or distressed by participating in this project.

ARE THERE ANY BENEFITS TO PARTICIPATION?

We don't expect any direct benefits to you from participation in this project. The possible indirect benefit of participation in the project is the opportunity to gain additional knowledge about anesthetic care of patients with ECMO

HOW WILL THE INVESTIGATORS PROTECT PARTICIPANTS' CONFIDENTIALITY?

The results of the project will be published, but your name or identity will not be revealed. To maintain confidentiality of assessments, the investigator will conduct this project in such a way to ensure that information is submitted without participants' identification. Data will be kept anonymous by numbering the pre/ posttest with corresponding numbers to allow for data evaluation. All information gathered for the purpose of this research project will be stored on the researchers locked laptop or in a locked file cabinet at the researcher's home. At the end of the project data collected will be either shredded or deleted from the researcher's laptop. Thus, the investigator will not have access to any participants' identities.

WILL IT COST ANYTHING OR WILL I GET PAID TO PARTICIPATE IN THE PROJECT?

Your participation will cost approximately 45 minutes of your time but will require no monetary cost on your part. You will not be paid to participate.

VOLUNTARY CONSENT

By signing this form, you are saying that you have read this form, you understand the risks and benefits of this project, and you know what you are being asked to do. The investigator will be happy to answer any questions you have about the project. If you have any questions, please feel free to contact E. Paige Gore (386-801-6904) or elizabeth.p.lambert@my.adu.edu. If you have concerns about the project process or the investigators, please contact the Nurse Anesthesia Program at (407) 303-9331.

_____ **Date** _____

Participant Signature/ Participant Name (PRINTED LEGIBLY)

_____ **Participant Name (PRINTED LEGIBLY)**

Appendix B

Pretest/ Post Test

Perioperative Considerations for Extracorporeal Membrane Oxygenation Devices

1. T/F- VV ECMO is typically cannulated at one site- Right Internal Jugular

2. With a VA Circuit the anesthetist should expect:
   a. Increase in Afterload reduction in contractility
   b. Decrease in Afterload and increase in contractility
   c. No hemodynamic change
   d. Increase in SBP

3. Anticoagulation is necessary in the ECMO patient because:
   a. The blood becomes more viscous in the circuit
   b. The ECMO circuit triggers an inflammatory response and a hypercoagulable state
   c. RBC adhesion
   d. Disseminated Intravascular Coagulation

4. T/F- An early sign of decreased LV ejection can be a loss in pulsatility of the arterial wave form.

5. Pharmacodynamics and Pharmacokinetics is altered in the ECMO patient because (select all that apply)
   a. Drug sequestration into the polyvinyl chloride circuit
   b. An additional compartment is created by the circuit itself increasing volume of distribution
   c. Critical illness
   d. Drug characteristics
   e. Hemodilution
   f. CRRT
   g. Age of the Circuit
   h. All the above

6. T/F – lipophilic drugs are significantly sequestered in the ECMO circuit

7. Critical illness can alter the pharmacodynamics of protein bound anesthetics such as:
   a. Propofol
   b. Fentanyl
   c. Midazolam
   d. All the above

8. T/F- VA ECMO causes in upregulation in renin- angiotensinogen system (RASS) and decreased glomerular filtration (GFR) due to nonpulsatile flow from the circuit.

9. T/F- According to Aronson et al (2017) volume status via Transesophageal Echocardiography is the most important volume status indicator in comparison to SVV or pulse pressure variation.

10. In VA ECMO (select all the apply):
    a. Blood is pulled from the SVC/ IVC and returned to the right atrium
    b. Typically, has one cannulation site
    c. Blood is pulled from the SVC/ IVC and returned to the aorta
    d. Can either be centrally cannulated or peripherally cannulated (Femoral- Femoral)

Appendix C

Perioperative Considerations for Extracorporeal Membrane Oxygenation.

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PROJECT CHAIR: DR. STEVEN FOWLER, DNP, CRNA
PROJECT MENTOR: DR. ALA HADDADIN, MD, FCCP, FACC

Objectives

The objective of this scholarly project is to enhance the knowledge regarding anesthetic considerations in caring for the patient utilizing Extracorporeal Membrane Oxygenation Support.

PICO Questions

Do surgical patients on ECMO (P) require specific anesthetic interventions (I) to maintain cardiovascular stability and pain control (O).

Will ADU SRNAs (P) who reviewed an 30-minute educational PowerPoint presentation on ECMO and it's anesthetic implications (I) have an increase knowledge base (C) as evidenced by higher mean post-test scores compared to pre-test scores (O)?

Case Scenario

A 48 year old man currently requiring VA ECMO support post Myocardial Infarction with emergency Coronary Artery Bypass to LAD and RCA. The patient was unable to be weaned from bypass post-operatively. The decision was made to place VA ECMO and transfer to the ICU in hopes of slowly weaning ECMO support. Today is POD #10 and the patient is scheduled for endoscopy for GI bleed.

ECMO History

- First introduced during the 1960s for neonates experiencing cardiopulmonary failure.
- In 1972 the first successful case of ECMO use in a adult patients with acute respiratory failure.
- CESAR Randomized control trial (2001-2006)
  - ECMO for adults with reversible Acute Respiratory Distress Syndrome
  - 180 participants
  - 90 were treated with ECMO- 63% had 6 month survival rate
  - 90 received conventional treatments- 47% had 6 month survival rate

(Peek et al, 2009)

Why is this Important?

- According to the Extracorporeal Life Support Organization (ELSO): 98,840 devices were utilized internationally for treatment of neonatal and adult cardiopulmonary failure in 2017.
  - 68% survived to discharge home or tertiary care centers.
- 444 ECMO Centers worldwide
  - 233 in the United States
  - 18 in Florida

Why is this important continued…

- In 2012 Florida Hospital started its heart and lung transplant program.
- 2017 Florida Hospital Orlando reported:
  - 60 heart transplants
  - 20 lung transplants
  - 95 patients utilized ECMO technology
- 2018 Florida Hospital Orlando opened a specialized ECMO unit.

Clinical Indications

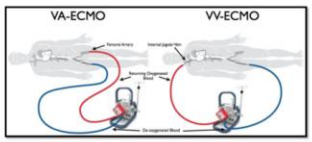
- Hypoxic or hypercapnic respiratory failure
- Pulmonary Hypertension
- Acute Respiratory Distress Syndrome (ARDS)
- Cystic Fibrosis
- Failure to wean from Cardiopulmonary Bypass
- Severe Myocardial infarction requiring hemodynamic support
- Pulmonary Embolism
- Bridge to Transplant

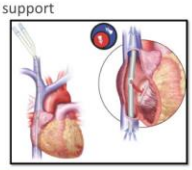
What is ECMO?

- Physiologic blood circulation is taken over via machine
  - Pump facilitates the exchange of CO2 and O2 via semipermeable membrane
- Outflow Cannula- drains blood from the body to the Oxygenator
- Inflow Cannula- returns oxygenated blood to the body.

Types of ECMO Cannulation

- Veno- Venous (VV)- primary function is pulmonary support
- Veno- Arterial (VA)- Complete cardiopulmonary support





Cannulation continued…

- VV Cannulation
  - Cannulation trough 2 venous vessels
  - **Commonly a single cannulation site an be utilized by a double lumen cannula in the right jugular**
  - Allowing for patient mobilization
- VA Cannulation
  - **Central or peripheral sites**
  - **Blood is pulled from venous circulation (IVC/SVC) through ECMO and returned to arterial circulation (aorta)**
  - Patients typically too hemodynamically unstable to mobilize

Circuit Components

- Cannula
  - Polyvinyl Chloride (PVC)
- Centrifugal pump
  - Suspended magnetically
  - Impeller spins propelling blood towards the membrane oxygenator
  - Design allows for decreased risk for blood stasis and thrombosis

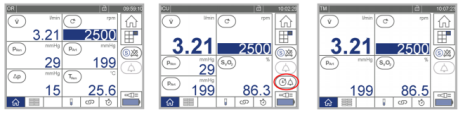
Circuit components continued…

- Membrane Oxygenator
  - Hollow Fiber polymethyl pentene
  - Mechanism for Oxygenation and Carbon Dioxide removal
- Thermoregulation is achieved by a heat exchange machine attached to the membrane oxygenator
- ECMO Circuits are designed with a 1 hour back up battery life
- Manual crank is located on the ECMO machine in case of power failure

Machine settings

- Blood flow rate- Calculated by the amount of venous blood being pulled from the patient oxygenated through the machine and returned to the body.
  - VA ECMO- To achieve a Cardiac Index of 2.4 l/min/m2 the pump needs to be circulating at 60 ml/kg/min
  - VV ECMO- Flow rates can be lower and titrated to patient oxygenation needs
    - 1L/min minimum to prevent stasis

Cardiohelp Display Screens



Anesthetic Considerations

Preoperative Assessment

- Imperative tool in developing an anesthetic plan for a patient needing surgical interventions
  - What type of ECMO does the patient have?
  - What is the goal of ECMO?
  - Where are the cannula sites?
- All pertinent laboratory data should be reviewed.
  - CBC
  - CMP
  - Coagulation studies

Preoperative Assessment Continued…

- Diagnostic Data
  - Transesophageal Echocardiography- diagnostic of fluid volume status, valve function, and contractility
  - Chest X-ray
- Invasive Hemodynamic monitoring
  - **Arterial line**
    - **Loss in pulsatility is an early indicator of a loss in LV contractility**
  - Swan Ganz

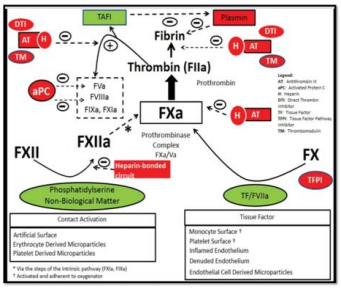
Preoperative Assessment Continued…

- Consider End- Organ Dysfunction
  - Urine output
- Hemodynamic Support
  - Vasopressors
  - Inotropes
- **VA ECMO circuits can increase afterload and decrease contractility of the heart**
  - **Patients may require afterload reduction and increased contractility supported with vasodilators and inotropes** (Meng et al. 2017; Kapoor, 2017)

Anticoagulation

- Anticoagulation is an important aspect of ECMO management.
- Consumptive coagulopathy occurs with blood exposure to the circuit
- **Inflammatory Response to circuit creates a hypercoagulable state**
  - Compliment Cascade activation
  - Macrophage activation
  - Cytokine activation

Esper et al., 2014 & Meng et al., 2017



Anesthesia & Analgesia118(4):731-743, April 2014.

Anticoagulation Continued…

- Unfractionated Heparin is most commonly used to manage anticoagulation needs
- Angiomax may be used in the presence of heparin intolerance such as Heparin Induced Thrombocytopenia (HIT)
- Coagulation status should be monitored
  - ACT
  - aPTT
  - Thromboelastography (TEG)
  - Anti- Xa factor

Fluid Resuscitation

- Crystalloid
  - Lactated Ringers
  - 0.9% Normal Saline Solution
- Colloid
  - Albumin
- Invasive monitoring Interpretation to guide volume resuscitation
  - **TEE – according to Aronson et al., anesthesiologist found TEE to be the most sensitive predictor of fluid volume status**
  - SV
  - SVV
  - Pulse pressure variation
  - CVP

Pharmacokinetics & Pharmacodynamics

- Alterations in drug distribution and metabolism
- Effect of ECMO circuit on medication management
- **Alterations in pharmacokinetic and pharmacodynamics due to**
  - **Drug sequestration**
  - **Circuit creating an additional compartment**
  - **Hemodilution**
  - **Physiologic impact of critical illness**
  - **Age of Circuit**
  - **CRRT**

Mehta & Annich, 2005, Lemaitre et al., 2015, Ha & Sieg, 2017, Bhatt & Annich, 2005, Shekar et al., 2012

Drug Sequestration

- Sequestration in the PVC tubing and Membrane oxygenator account for a significant loss of plasma drug levels
- **Drug Characteristics with the greatest sequestration in ECMO circuits are**
  - **Lipophilic**
  - **Highly protein bound**

Midazolam

- Benzodiazepine which is 92% protein bound
- Ex Vivo studies revealed:
  - Plasma concentration of Midazolam was reduced by 50% one hour after the first dose (Shekar et al., 2015).
  - Lemaitre et al. (2015) 30 minutes only 54% of the baseline midazolam concentration remained and at 24 hours only 11% remained

Fentanyl

- Lipophilic Narcotic
- 95% protein bound
- Significantly sequestered and at 24 hours only 6.3% of the drug was able to be detected (Shekar et al., 2015)
- Mehta et al., (2007) Plasma levels of fentanyl remained unaltered for the first 3 hours of study but dropped significantly there after and were completely undetectable at 24 hours.

Propofol

- Sedative- hypnotic
- 97-99% protein bound
- 10% lipid emulsion
- With in 30 minutes of propofol dosing 70% of the baseline dosing was lost with in the circuit and only 11% of drug remaining with in 5 hours (Lemaitre et al., 2015).
- Previous studies reported concerns that lipophilicity of propofol would increase the need for oxygenator exchange. However, Hohlfelder et al., 2017 suggest that propofol use did not increase the need for oxygenator exchanges

Morphine

- Narcotic Analgesic
- 30-40% protein binding
- Primarily hepatic excretion
- Morphine levels are well preserved in the used of ECMO patients (Mheng et al., 2007 & Ha et al, 2017)
  - Samples taken to measure drug concentration after 23 hours were virtually the same as baseline

Ketamine

- NMDA receptor antagonist
- Protein binding 27% , Lipophilic
- Several studies suggested the need to study ketamine and its changes in pharmacokinetics and the use of ECMO
  - Case studies revealed a decrease in opiate, sedative, vasopressor requirements

Ha et al., 2017

Volume of Distribution

- Volume of Distribution is increased during initiation of ECMO
  - Primed with Isotonic solution
  - Blood Transfusions
  - Fluid boluses
- Hydrophilic drugs have increased Vd
- Highly protein bound drugs have increased Vd due to hemodilution and decrease in serum protein levels

Critical illness

End Organ Dysfunction

- Renal
  - Renal dysfunction is common with 50% of VV ECMO and 41% of VA ECMO patients requiring continuous renal replacement therapy.
  - **Non-pulsatile flow causes an increase in renin- angiotensin system activity**
  - **Decreased GFR**
- Hepatic- Perfusion/ Ischemia

Ha et al, 2017 & Shekar et al., 2013

Final Thoughts

A limitation to this review was that much of the date regarding drug metabolism was that many studies were preformed ex vivo or on neonates.

- Making further studies on the adult population necessary to fully understand the physiologic effects of drug sequestration in ECMO circuits.

Questions?

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Appendix D

Paired Sample Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pe-test	.4772	22	19.74403	4.20944
	Post -test	.9318	22	7.1623	1.52701

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	PreTest - PostTest	-45.45455	20.40711	4.35081	-54.50255	-36.40654	-10.447	21	.000

Pre Test

Test #	Correc	Incorre	Grade (%)
1	6	4	60
2	6	4	60
3	9	1	90
4	7	3	70
5	5	5	50
6	5	5	50
7	2	8	20
8	4	6	40
9	3	7	30
10	6	4	60
11	4	6	40
12	4	6	40
13	3	7	30
14	2	9	20
15	7	3	70
16	6	4	60
17	3	7	30
18	2	8	20
19	3	7	30
20	4	6	40
21	7	3	70
22	7	3	70

Post Test

Test #	Correc	Incorre	Grade (%)
1	9	1	90
2	9	1	90
3	10	0	100
4	10	0	100
5	10	0	100
6	10	0	100
7	10	0	100
8	10	0	100
9	7	3	100
10	9	1	90
11	8	2	80
12	10	0	100
13	9	1	90
14	10	0	100
15	9	1	90
16	8	2	80
17	9	1	90
18	8	2	80
19	9	1	90
20	9	1	90
21	9	1	90
22	10	0	100