Comparison of propofol and sevoflurane as a primary anesthetic for cardiac ablation of atrial fibrillation

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Protocol

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A. SPECIFIC AIMS

The primary aim of this study is to compare two commonly used anesthetic techniques (propofol and sevoflurane) during atrial fibrillation ablation cases. Of greatest interest is to compare the time to awaken the patients after the procedure. Also of interest is the duration of the ablation procedure. The hypothesis of this investigation is that patients who receive propofol will require a longer time to removal of the endotracheal tube after the end of the procedure than patients anesthetized with sevoflurane.

B. BACKGROUND AND SIGNIFICANCE

The incidence and prevalence of atrial fibrillation continues to rise in our country. Currently, the incidence is predicted to double from 1.2 million cases in 2010 to 2.6 million cases in 2040. Atrial fibrillation prevalence is projected to increase from 5.2 million in 2010 to 12.1 million in 2030. [1] As the rates of atrial fibrillation cases increase, treatments such as catheter-based ablation will also increase.

Ablation procedures require the administration of general anesthesia. A wide variety of general anesthesia techniques have been used since the inception of the ablation procedure, but there are few comparative studies of anesthetic techniques. The lack of evidence comparing two widely used anesthetic techniques means that choice of a primary anesthetic is based on personal preference or local custom. In a recent review of Ablation Procedures and Anesthetic implications the authors state: “The literature regarding the best choice for anesthetic technique in ablative procedures is still scarce and the decision ultimately depends on the patient’s clinical condition, the anesthesiologist’s judgment, and the electrophysiologist’s comfort level.”[2] For this reason a study comparing two of the commonly employed techniques is warranted.

Propofol is a sedative hypnotic agent used as an infusion as a general anesthetic at a recommended dose of between 100 and 200 mcg/kg/min. In a continuous infusion, the distribution half-life of propofol is 1 to 3 hours in a 2-compartment model and 30 to 70 minutes in a 3-compartment model. The context-sensitive half time for infusions of up to 8 hours is 40 minutes. [1]

Propofol produces myocardial depressant effects and decreased systemic vascular resistance; these are both dose and concentration dependent. Propofol has also been found to alter the baroreflex mechanism, which causes a smaller increase in heart rate for a given decrease in blood pressure.

Propofol is commonly used as a general anesthetic agent for many different types of surgical procedures, including atrial fibrillation ablations. Propofol is used as a general anesthetic for cardiac ablation procedures because it has no known effects on the cardiac conduction system.

Sevoflurane is a volatile anesthetic, which is administered via inhalation. A concentration of 2% is typically used as a general anesthetic dose of sevoflurane. Sevoflurane undergoes very little metabolism by the body, rather once the vaporizer is turned off and the patient breathes off the gas, the anesthetic effects are gone. Like other inhaled anesthetics, sevoflurane is very rapid acting. This ability to quickly increase or decrease anesthetic levels as necessary aids in efficiency and also increases the margin of error for this drug.

Sevoflurane, and other volatile anesthetics, are the most commonly used general anesthetic agents in use today, both for their confirmed safety profile and also the ease of titrating the drugs. Sevoflurane is used in some centers for ablation procedures. Our institution has also used Sevoflurane for atrial fibrillation ablations in the past when there has been a shortage of propofol.

At our institution a total intravenous anesthetic (TIVA) with propofol is used during atrial fibrillation ablation cases. Sevoflurane is used at other centers, such as UCLA. Due to sevoflurane's shorter half life and the fact that it is not metabolized as much as propofol by the body, patients may have the breathing tube removed in a shorter period of time after the procedure is over and also be more awake and alert in the recovery room than if they had undergone the procedure using propofol as the primary anesthetic. Propofol has been shown to have no effect on cardiac conduction[4] and preliminary evidence shows that sevoflurane may similarly have no effect.[3] Because shorter wake-up time could reduce hospital costs and improve efficiency, it is important to compare these two techniques focusing on time for extubation.

There have been no head to head comparisons of total intravenous anesthesia (TIVA) versus sevoflurane for ablation procedures. By conducting a randomized blinded study of these two anesthetics, new and important knowledge can be generated for this increasingly commonly performed procedure.

A side effect of other volatile anesthetics, such as isoflurane and desflurane, is enhanced automaticity, accounting for secondary atrial pacemakers. [5] Volatile anesthetics also have varying effects on the AV node and His-Pukinje system.[6] These agents also prolong the QT interval[6] and, for this reason, volatile anesthetics as a group have at times been avoided for atrial fibrillation ablation. However, sevoflurane does not seem to have the effects shown for other volatile anesthetics on cardiac conduction, based on preliminary evidence.[3] Sharpe, et al suggested with results from a 15 patient study that Sevoflurane had no effect on the refractoriness of the normal or accessory atrioventricular pathway and also no clinically significant effects on sinoatrial node function or intraatrial conduction.[3] Though the aforementioned study's population consisted of patients with Wolff-Parkinson-White (WPW) syndrome, the concerns with how the anesthetic drugs affect the conduction system are the same with WPW as they are for atrial fibrillation cases. Some institutions, such as UCLA, now use sevoflurane as the primary anesthetic for atrial fibrillation ablation cases.

This study, a partnership between anesthesia and electrophysiology cardiologists, will be the first study to compare these two commonly used anesthetic techniques. The primary end-point of this study is the time interval from the end of the procedure to tracheal extubation. We will also measure the length of procedure, any differences in hemodynamics, patient alertness in the immediate postoperative period, as well as the rate of postoperative nausea and vomiting to see if there is a difference between the two anesthetics. At 3 month and 6 months, medical records will be examined to see if there is any difference in the recurrence of atrial fibrillation. Although our study is not powered for this, we will examine for this due to the theoretical risk of recurrence with Sevoflurane.

The significance of this study is that it will be the first study to compare two commonly used anesthetic techniques in the setting of atrial fibrillation ablation. There is currently no comparative evidence available to determine which technique is superior in this setting and as a result clinical practice is based on custom and familiarity rather than evidence of superiority.

C. PRELIMINARY STUDIES

There have not been any blinded randomized studies comparing volatile anesthetics to TIVA for atrial fibrillation ablations. By performing this study, we can demonstrate if one anesthetic is superior to another for time of extubation and note any other differences in measured variables including the patient's satisfaction in the immediate post- operative period.

D. RESEARCH DESIGN AND METHODS (including data analysis)

Patients with persistent and paroxysmal atrial fibrillation, undergoing their first ablation, will be invited to participate in the study during their pre-operative visit if the patient is scheduled for one, but otherwise during their pre-operative anesthesia work up in the holding room. Once informed consent is obtained, the participant will be randomized via computer-generated randomization into one of two groups. Group A will receive propofol 100-150mcg/kg/min; Group B will receive sevoflurane 2% end tidal concentration as their primary, general anesthetic for the procedure. Doses of each drug will be titrated to effect in order to obtain general anesthesia. The electrophysiologist performing the procedure will be blinded as to which drug the patient is receiving. Data will be collected from the patient's electronic medical record postoperatively. Our primary endpoint is time from procedure end until the time that the endotracheal tube is removed (wake-up time.) Data will be analyzed using an independent 2-sample t-test.

We will also measure and compare duration of the procedure, postoperative nausea and vomiting, hemodynamic differences during the case, and patient alertness postoperatively using a short questionnaire to be filled out on the morning of POD 1 by a trained study team member. Following their first clinic visit with their cardiologist and for a total of 6 months postoperatively, we will view their medical record to look for recurrence of atrial fibrillation.

Analysis plan, sample size and power:

The primary outcomes are procedure duration and time to extubation. Both outcomes will be analyzed using an independent 2-sample t-test.

Propofol infusion is the most common primary anesthetic at MUSC for patients undergoing cardiac ablation for atrial fibrillation. The primary outcome is time from procedure end to extubation between the two groups that will be compared using a two-sample t-test approach. Sixty-three patients per group (126 total) provides 80% detection an effect size of 0.5 between the two groups using a two-sided t-test at significance level $\alpha = 0.05$. The statistical assumptions will be checked graphically and the non-parametric Wilcoxon rank sum test will be used if assumptions are violated.

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics

To account for a 6% attrition rate, we plan to enroll 134 participants who are ages 18 and over and have paroxysmal atrial fibrillation undergoing their first ablation.

Targeted/Planned Enrollment Table

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
	Sex/Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	3	3	6
Not Hispanic or Latino	64	64	134
Ethnic Category: Total of All Subjects*	126		
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	21	21	42
White	46	46	92
Racial Categories: Total of All Subjects*	67	67	134

**The "Ethnic Category: Total of All Subjects" must be equal to the"Racial Categories: Total of All Subjects".*

All eligible participants who volunteer for the study will be enrolled regardless of gender, race, or ethnicity. It is difficult to estimate the proportion of gender or ethnicity representation in the study population as this is

predetermined by the surgical schedule, but every effort will be made to enroll participants from both genders and a variety of racial/ethnic backgrounds. The only reason for exclusion based on ethnic category is the inability to speak English. Our interpretters' services are limited in time and availability.

b. Sources of Materials

Once informed consent is obtained, the participant will be randomized via computer-generated randomization into one of two groups. Group A will receive propofol as their primary, general anesthetic for the procedure and Group B will received sevoflurane as their primary, general anesthetic for the procedure.

The following data will be obtained from the participant's electronic medical record: overall length of procedure, time from procedure end to extubation, side effects (nausea, vomiting, hemodynamic differences during the case) and patient alertness.

Upon enrollment, subjects will be assigned a randomized numerical identifier for the remainder of the study. This number will be used to label charts and paperwork associated with the subject. An electronic enrollment log will link patient name and MRN with his/her study ID number. All paper information will be kept in a locked cabinet in a locked office. All electronic data will be kept on MUSC's password protected server.

c. Potential Risks

The two anesthetics that could be given are both commonly used and investigators are familiar with both. Side effects of each drug are typically only seen when the medications are given, or in the immediate postoperative period. However, the risk associated with each medication is as follows:

Propofol Risks:

<u>Less Than 5%:</u>

Slower heart rate	Decrease in muscle tone	Muscle pain
Breathing difficulty	Temporary loss of feeling/sensation	
Allergic reaction	Increased saliva	
Fainting	Rash	
Changes in heart rhythm	Cloudy urine	

Transient decrease in vision in the immediate postoperative period

<u>Less Than 20%:</u>

Burning or stinging at IV site

Low blood pressure

Sevoflurane Risks:

<u>Less Than 5%:</u>

Low blood pressure	Slower heart rate
Tightening of airway	Holding breath
Increased in saliva	

Less Than 20%:

Agitation Cough

Although both medications may cause patients to stop breathing, this is not a concern in these procedures as patients have a breathing tube inserted and are on a ventilator for the duration of the procedure when the drugs are being administered.

The risk of decreased efficacy of the ablation procedure is theoretical, however if one medication would cause the ablation to be less efficacious, a repeat ablation may be necessary.

There is a risk of loss of confidentiality, as we will be accessing the medical records of patients. However, all paper information will be kept in a locked cabinet in a locked research office and all electronic data will be kept on MUSC's password protected server. The research team will decrease this risk as much as possible by following confidentiality standards.

Randomization risk: Participants will be assigned to a general anesthetic medication by chance. The anesthetic that is in turn given, may prove to be less effective or to have more side effects than the other study medication.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

Inclusion Criteria: All patients who are 18 years of age or older, have persistent and paradoxical atrial fibrillation, and are undergoing their first ablation will be invited to participate in the study during their pre-operative anesthesia work up in the holding room.

Exclusion Criteria: Patients will not be eligible for the study if they are unable to speak English or if the patient is cognitively incapable of providing their understanding of and consent for the study.

Patients who have contraindications to either study drug, such as an allergy or history of malignant hyperthermia, will also be excluded from the study.

Once the patient agrees to enroll in the study he or she will be asked to sign a written informed consent. An anesthesia study team member will obtain the consent. The participant will be given time to read the consent and have any questions answered about their procedure and the study.

b. Protection against Risk

All participants will be monitored during the procedure per MUSC's policy.

All paper information will be kept in a locked cabinet in a locked office. All electronic data will be kept on MUSC's password protected server.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

The participant may or may not benefit from the study procedures. The knowledge gained from this study could help future patient's undergoing this procedure have the best anesthesia treatment.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

The study may demonstrate whether one anesthetic provides any benefit over another for this relatively long procedure. If the study shows no difference, or the superiority of sevoflurane, patient outcome and overall cost may decrease. This is the first comparative study of these two techniques and will provide anesthesiologists with evidence regarding the choice for one or the other.

5. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

Data and safety monitoring will be performed by the research study committee in the Department of Anesthesia and Perioperative Medicine on a annual basis. The committee is comprised of an MUSC Professor of Anesthesia (Dr. Orin Guidry), an emuritus dean of medicine (Dr. Gerald Reves), Professor Kenneth Catchpole & a Research Instructor Kent Armeson. Any adverse effect on the time of the ablation will also be closely assessed during DSMB meetings. The study will not go on if there has been prolongation of this procedure that is believed to be study related. Furthermore, if there are any identified study related complications, participants will be switched to receive standard treatment for the duration of the case. Though adverse events are not anticipated, any adverse events will be reported to the DSMB committee in real time for evaluation, as well as to MUSC's IRB, per protocol. Of note, these adverse events are no different than what could be seen clinically. The possibility of decreased ablation efficacy via the use of sevoflurane is purely theoretical.

F. REFERENCES/LITERATURE CITATIONS

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G. CONSULTANTS

Where applicable, attach electronic versions of appropriate letters from all individuals confirming their roles in the project. Go to the application under "additional uploads" to attach this information.

H. FACILITES AVAILABLE

Describe the facilities available for this project including laboratories, clinical resources, etc.

MUSC's Research Offices, Library, & the Department of Anesthesia and Perioperative Medicine.

I. INVESTIGATOR BROCHURE

If applicable, attach the electronic version of the investigator brochure. Go to the application under "additional uploads" to attach this information.

J. APPENDIX

Attach any additional information pertinent to the application, such as surveys or questionnaires, diaries or logs, etc. Go to the application under "additional uploads" to attach this information.