Termination of perioperative atrial fibrillation with epicardial cooling in the oblique sinus: A first-in-human feasibility study

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BACKGROUND Postoperative atrial fibrillation (AF) is associated with prolonged hospitalization, stroke and expense. We have previously demonstrated the effectiveness of cooling the oblique sinus to terminate AF in animal models.

OBJECTIVE The study sought to determine whether cooling can terminate intraoperative AF in humans undergoing cardiac surgery.

METHODS Patients presenting for clinically indicated cardiac surgery with a history of atrial fibrillation were enrolled. During surgery, before bypass, AF was induced if not present, and a 1 × 1 inch cooling device was placed in the oblique sinus that cooled to 5 to 10 °C at the device-tissue interface. Due to the pandemic, remote, real-time monitoring was used.

RESULTS Four patients (all women, mean age 69.3 years) underwent 8 AF inductions. Five (63%) of 8 episodes were terminated with cooling, with average time to termination (after 30 seconds of sustained arrhythmia) of 21 seconds. Of the 3 failed episodes, 1 may have been a type II termination, 1 organized to flutter, and 1 failed to cool for technical reasons. There were no procedure-related complications.

CONCLUSION Termination of perioperative atrial fibrillation with epicardial cooling in the oblique sinus is feasible and appears safe in this very early first-in-human study.

KEYWORDS Postoperative atrial fibrillation; Epicardial cooling; Oblique sinus; First-in-human feasibility study; Stroke

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Introduction

Postoperative atrial fibrillation (AF) following cardiac surgery is common, with an incidence ranging from 30% to 50%.[1–4] It is also common in the early and intermediate postoperative period following surgery for atrial arrhythmias, during lesion maturation. Postoperative AF typically peaks on the second postoperative day and is associated with adverse short- and long-term outcomes, increased length of stay, and cost.[1,5–7] Patients who develop postoperative AF on average incur $10,000 to $20,000 in additional hospital costs, have hospitalizations that are 2 to 5 days longer, and experience a 2-fold increase in mortality. Current guidelines recommend anticoagulation for postoperative AF episodes longer than 48 hours and cardioversion for poorly tolerated episodes (class 1 recommendation).[8] It has long been known that "AF begets AF," namely that persistence of the arrhythmia promotes adverse electrophysiologic remodeling that promotes ongoing arrhythmia.[9] Immediate/early termination of AF limits remodeling, may be beneficial after cardiac surgery, and might be more readily applied if it could be performed painlessly at the bedside without the need for general anesthesia.

The oblique sinus has a rich autonomic cardiac innervation and is in juxtaposition to the pulmonary vein ostia, making it an attractive site for antiarrhythmic interventions. Because cardiac channels are temperature sensitive,

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KEY FINDINGS

- In this first-in-human study, cooling in the oblique sinus terminates intraoperative atrial fibrillation in patients with cardiovascular disease undergoing cardiac surgery.
- Arrhythmia termination is temperature dependent (occurred with average temperature below 13 °C) and commonly occurred in under 30 seconds.
- There were no complications associated with cooling.
- This early feasibility study paves the ground for studies in awake, postcardiac surgical patients to test whether cooling painlessly terminates postoperative atrial fibrillation.

nonfreezing hypothermia decreases cardiac action potential velocity and increases its duration, interrupting arrhythmia,[10] without structural cellular injury. Because cooling may interrupt regional pain fiber conduction, it may permit the painless termination of AF by avoiding the muscle twitch and nerve fiber recruitment associated with shocks.

We have previously demonstrated the effectiveness of cooling the oblique sinus to terminate AF in animal models.[11] However, humans undergoing cardiac surgery often have common comorbidities, including advanced age, hypertension, diabetes, and concomitant structural and fibrotic changes, which may impact therapy effectiveness. To determine whether cooling would be effective for the termination of AF in humans, we performed a pilot feasibility study. Due to the pandemic at the time of testing, we further tested the hypothesis that we could perform these surgeries supported by a proctoring site located thousands of miles away in another country by means of real-time 2-way video.

Methods

Patient selection and enrollment

Patients presenting for clinically indicated cardiac surgery, including coronary artery bypass grafting, mitral valve surgery, aortic valve surgery, or other procedure requiring a sternotomy, and who had a history of AF were screened at Mayo Clinic and Presidente Perón Hospital for study inclusion following investigational review board approval at both sites. The study was approved by the institutional review board at both hospitals and adhered to Declaration of Helsinki ethical guidelines, and all enrolled patients provided written informed consent. All of the following criteria were also required at the time of enrollment: age $\geq$18 years; documented paroxysmal or persistent AF with a history of $<$1-year duration; in AF at time of surgery or inducible using manual or electrical stimulation; willingness and ability to provide informed consent; and life expectancy of at least 1 year. Exclusion criteria included long-standing AF ($>$1 year); prior AF ablation; left main coronary artery stenosis $>$70%; critical aortic stenosis (gradient $>$50 mm Hg); inability to induce AF at the time of surgery if not already present; pregnancy; presence of a medical condition or comorbidity that could adversely impact study participation, safety, or conduct of the study; permanent pacemaker or defibrillator; cancer treatment that includes cardiac radiation; and inability to provide informed consent. Here, we report the first 4 patients in a proof-of-concept study.

Study procedures

Patients were brought into the operating room and a sternotomy was performed as per the clinically indicated cardiac surgery. Pacing wires were inserted per usual surgical technique. Prior to commencement extracorporeal circulation, AF was induced via rapid atrial pacing and permitted to sustain for 30 seconds. If it was not induced or did not sustain for the required time, up to 3 attempts were made, changing the durations of the stimulation or site of delivery. Once the qualifying AF was induced, the cooling device was placed in the oblique sinus and the time to termination was recorded (Figure 1). If the rhythm failed to terminate within 180 seconds, cardioversion could be applied. Based on previous animal work,[11] the target cooling temperature was between 5 and 10 °C at the device-tissue interface.

Remote study proctoring

Technical support was provided by 2 of the investigators (P.F., S.A.) with additional support from the industry sponsor (MediCool Technologies).

Due to the pandemic, live proctoring was not feasible. Thus, the lead surgeon (A.T.) and electrophysiologist (B.E.) visited Mayo Clinic to perform an animal experiment in which all the unique procedural characteristics were reviewed, demonstrated, and tested. Additionally, procedural videos, summarizing the use of the novel cooling device and the protocol, were created and made available for training purposes for the entire surgical team (Supplemental Videos 1, 2, and 3). During study procedures performed in Argentina, real-time communication utilizing video conference software (Zoom Communications) displayed real-time patient data, the surgical field, and device parameters to the Mayo Clinic staff and sponsor. Three-way communication allowed for immediate clinical and technical input given the Mayo team's preclinical experience with the novel technology.

Device description

The device consists of a 1 $\times$ 1 inch stainless steel fluid-based cooling module that delivers a specific therapeutic temperature via a Thermo Fisher Scientific SC100-10A lab chiller (Figure 2). The saline was circulated through insulated lines into and out of the cooling device at a rate of 1 L/min via a peristaltic pump attached to the lab chiller. Quick-connect

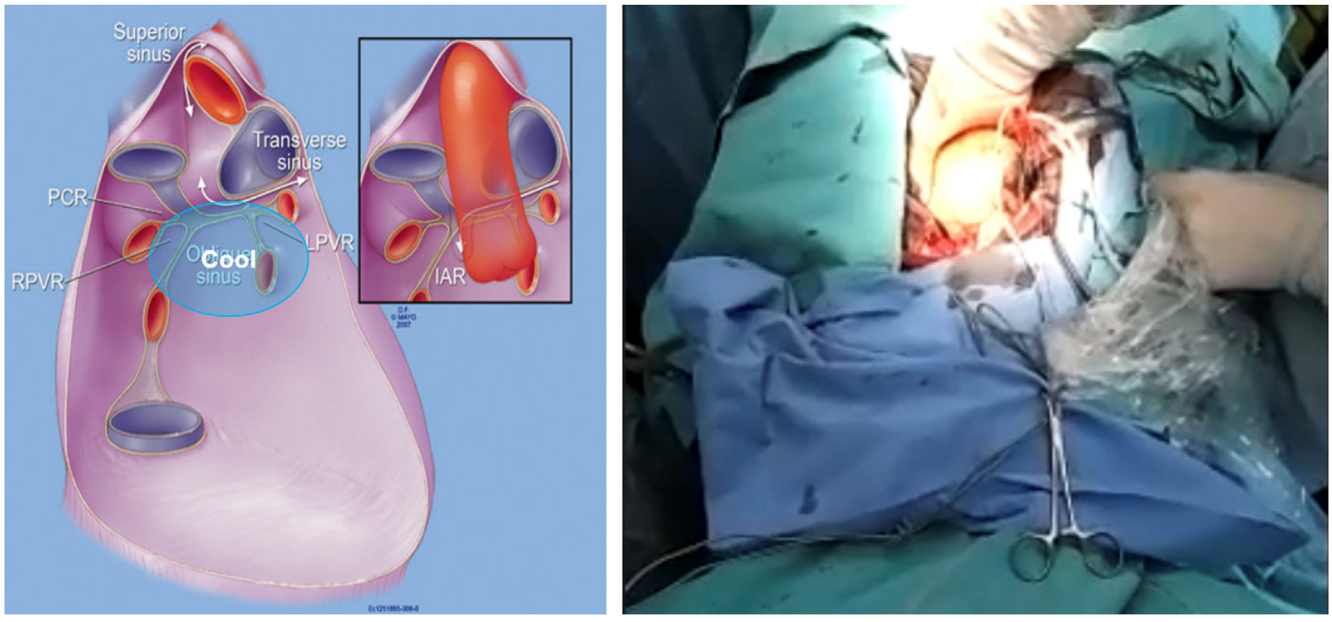

Figure 1 Anatomic location of cooling and surgical placement. (Left) Anatomical depiction of the oblique sinus. The pericardium is shown with the anterior section and heart removed. The region to which cooling was applied is shown with the blue oval labelled "Cool." (Right) Surgical placement of the device in the oblique sinus in one of the patients in the study. Note that the right panel is a captured image from a live, remote transmission, accounting for blurriness. IAR = inferior aortic recess; LPVR = left pulmonary vein recess; PVR = pulmonary vein recess; RPVR = right pulmonary vein recess;

adapters attach the device between the sterile field and the lab chiller in an efficient manner. The saline was maintained in a sterile bag and placed in a chilled bath so that the chilling circuit was sterile throughout its entire circuit, and the cooling device (Figure 2) was sterilized before use. A thermocouple located in the chiller and another one attached to the external surface of the device in contact with the atrial epicardium continuously monitored the temperature on the surface of the cooling device and recorded the device-tissue interface temperature.

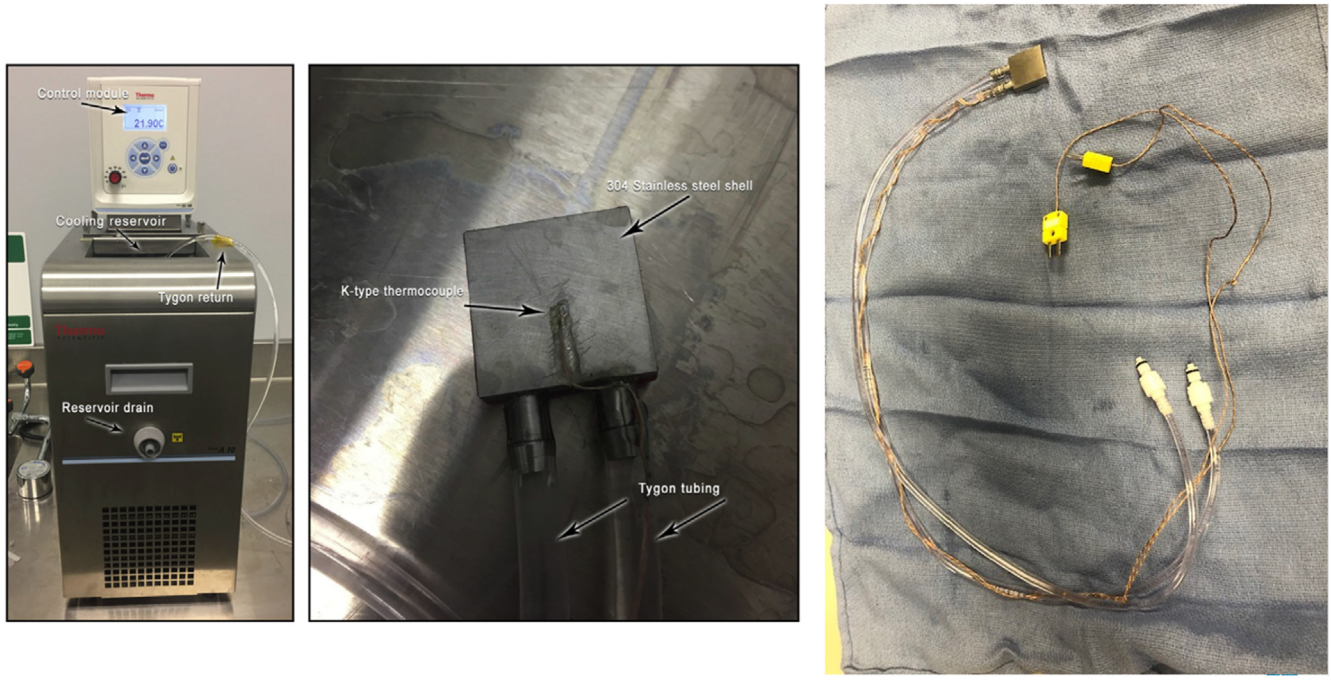

Figure 2 Equipment used to cool the oblique sinus during cardiac surgery. (Left) Chiller kept at bedside that cooled saline and pumped it through the system to maintain a specified temperature at the posterior left atrium. (Middle) Close-up of the cooling element through which saline circulated. (Right) View of the cooling elements with tubing, snap connectors for fluid, and electrical connectors for continuous temperature monitoring. Modified with permission from Witt et al.[11]

Study design and manuscript

The study was designed by the sponsor (MediCool Technologies) with input from investigators (P.F., S.A., A.K., J.C., A.T., and B.E.). The manuscript was drafted by the corresponding author (P.F.) with critical review, revision, and agreement to submit from all the authors, including those employed by the study sponsor (J.R.).

Results

Study enrollment was stopped after 4 patients were enrolled due to the decision to redesign the device by the study sponsor to enable postoperative clinical use in addition to intraoperative use. Thus, 4 patients were included in this early feasibility report, all enrolled at Presidente Perón Hospital.

Patient characteristics are shown in Table 1. There were 4 patients, and surgical indications included aortic valve replacement, mitral valve, and bypass surgery. All patients had a history of paroxysmal AF and all underwent induction as per the protocol to assess cooling termination. As detailed in Table 2, there were 8 inductions in 4 patients. Five (63%) of 8 episodes were terminated with cooling, with an average time to termination (after 30 seconds of sustained arrhythmia) of 21 seconds. (Figure 3) It is noteworthy that all episodes for which the average tissue-device interface temperature was under 13 °C terminated, and all in under 1 minute (all but 1 in under 30 seconds), and in no cases did the temperature drop below 5 °C. Of the 3 failed cases, 1 may have been a type II termination but was classified as a failure due to lack of immediate termination during cooling (patient 1, induction 2), 1 involved a kinked lead and failure to keep the temperature cool (patient 3, induction 2), and 1 organized but did not terminate (patient 4). In both cases in which arrhythmia did not terminate, therapeutic temperatures were not reached. In patient 1, induction 2, bradycardia and ventricular fibrillation developed, prompting study termination. There were no clinical complications in association with this.

In all cases, real-time communication between the teams in North America and South America was maintained (Figure 1, right panel, and Figure 3), which included video feeds of the temperature, rhythm, and surgical field (Figures). Voice communication between the lead electrophysiologist and support team was also maintained, with no interruptions.

All clinically indicated procedures were performed without study-related complications. All procedures were recorded and data were available for postprocedure analysis.

Discussion

In this first-ever human feasibility study, we found that cooling in the oblique sinus to terminate perioperative AF is feasible and appears safe. Specifically, we found that lowering the average temperature below 13 °C successfully terminated AF, most commonly in under 30 seconds, and in all cases in under 1 minute. In no cases did

Table 1 Patient demographics

Patient number	Procedure date	Age (y)	Sex	Type of surgery	AF history	Coronary disease history	Hypertension	Diabetes mellitus	Creatinine	Ejection fraction (%)
1	October 15, 2021	76	F	LIMA to LAD; aortic valve replacement	PAF	Yes	Yes	No	0.77	64
2	October 20, 2021	78	F	Aortic valve replacement	PAF	Yes	Yes	No	0.89	60
3	December 15, 2021	47	F	MV replacement	PAF	Yes	Yes	No	1.6	60
4	September 21, 2022	76	F	Aortic valve replacement	PAF	Yes	Yes	No	0.9	65

AF = atrial fibrillation; AV = atrioventricular; F = female; HBP = high blood pressure; LAD = left anterior descending artery; LIMA = left internal mammary artery; MV = mitral valve; PAF = paroxysmal atrial fibrillation.

Table 2 Results of cooling to terminate AF

Patient number	Cooling device application number	AF initiation	Initial temperature at device-tissue interface (°C)	Average device temperature (°C)	Result	Time to termination (s)	Observations
1	1	Induced	8.7	7.8	Success	4	—
1	2	Induced	2.7	6.5	Failure	—	Device removed early for bradycardia; rhythm terminated (type II vs failure)
2	1	Induced	6.6	12.1	Success	30	
2	2	Induced	7.8	12.3	Success	37	
3	1	Induced	14.1	12.5	Success	23	
3	2	Induced	12.8	13.5	Failure	N/A	Kinked lead
3	3	Induced	12.7	12.1	Success	11	When cooled from 2
4	1	Induced	9.6	14.5	Failure	N/A	Organized

AF = atrial fibrillation; N/A = not applicable.

the temperature drop below 5 °C, and there were no findings to suggest any temperature-related injury. Importantly, 13 °C is a temperature at which no intracellular ice crystals or long-term damage to cardiomyocytes or surrounding tissues occur. All patients underwent the planned subsequent cardiac surgery without study-related complications. These early feasibility findings suggest that cooling may be a reasonable means to terminate perioperative AF.

The use of cold has an established safety and efficacy history over decades for the treatment of arrhythmias. Rapid cooling to temperatures below –40 °C leads to formation of intracellular and extracellular ice crystals, resulting in cellular dehydration and mechanical disruption of cell membranes.[12] This process has been used to irreversibly modify substrate for the surgical and transcatheter treatment of epicardial accessory pathways and AF.[13,14] Cold has also been used to terminate arrhythmias without lasting structural damage, including the surgical injection of saline to confirm the site of arrhythmogenesis prior to delivering structure-altering therapy.[15] In the present study, temperatures above freezing were used; these are capable of arrhythmia termination with no lasting cellular injury. These observations support the concept that cooling could be safely used to terminate perioperative atrial arrhythmias.

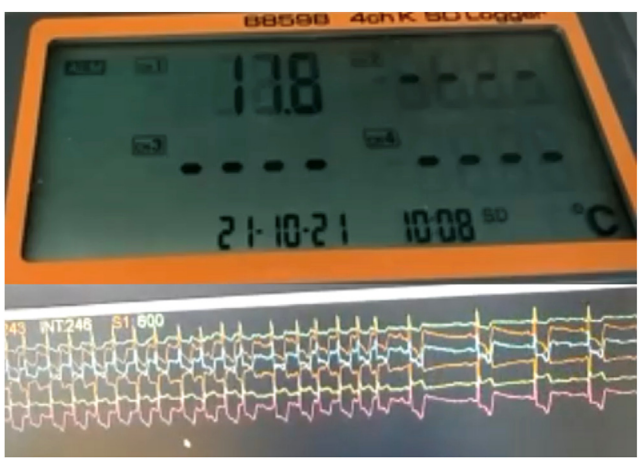

Figure 3 Example of intraoperative termination of atrial fibrillation with cooling (images as seen remotely). Note that these are capture images from a live, remote transmission, accounting for blurriness. Top: real-time temperature monitoring at the time of AF termination. Bottom: real-time ECG showing termination of AF to normal rhythm.

A number of mechanisms that might account for the ability of cold to terminate AF. Cardiomyocyte membrane channels responsible for electrical wavefront propagation are temperature dependent, with conduction velocity slowing during hypothermia.[16–18] Previous animal models have demonstrated the termination of fibrillation with cooling in tissue preparations.[10] Because the cooling heat-exchange module was placed over the dome of the left atrium, it is possible that a critical mass of tissue was excluded from fibrillation during cold application, terminating the arrhythmia. The oblique sinus subtends the pulmonary veinous ostia posteriorly, which are a common source of AF triggers; cooling may have suppressed triggering discharges. Additionally, autonomic ganglionated plexi have been implicated in the initiation and maintenance of AF.[19] The oblique sinus is rich in these plexi, and cooling may have modified their activity, facilitating arrhythmia termination.

This human feasibility study extends the findings of previous experiments that demonstrated effective termination of AF with the application of cold in the oblique sinus in animal models.[11] Importantly, unlike in animal models, the patients in our study were advanced in age, had structural heart disease, and likely had microscopic fibrosis, macrospcopic structural derangements, and changes in cardiac conduction associated with the pathophysiology of their cardiac lesions. Confirming the feasibility of cooling to terminate AF in this context is an important advance.

Our long-term goal is to effectively treat AF painlessly. The postoperative population is a particularly important cohort, given that over 30% of patients undergoing cardiac

surgery develop postoperative AF in most series, and that its development is associated with short- and long-term complications, including stroke, heart failure, prolonged hospitalization, and substantial financial expense.[9] Because we initially delivered the therapy during ongoing general anesthesia, we cannot confirm whether cold application is painless. However, several observations suggest that it may be painless. First, recruitment of skeletal and nonskeletal muscle by a shock is an important part of pain associated with defibrillation, and such recruitment is absent with cooling. Second, direct stimulation of unmyelinated pain fibers during cardioversion may further promote shock pain, and it is likely absent during cooling; indeed, because there is significant overlap in membrane channels between neurons and cardiomyocytes, pain fiber transmission is slowed,[20] hence the common remedy of applying cold to injuries. Cold has been observed to increase the threshold of painful stimuli and increase tolerance to pain, prompting its use in first aid.[21] Additionally, due to the thermodynamics within the body, cold application is very localized, without the widespread electric field effects associated with shocks. However, only testing in awake individuals can directly address this question.

Cooling in postoperative cardiac surgical patients offers several unique advantages. First, nearly all postcardiac surgical patients receive chest tubes, and cooling elements could be affixed to the terminal end of the chest tube, enabling therapy delivery via a commonly used device. Additionally, the addition of sensing electrodes to the device would enable the tool to provide both the immediate diagnosis of postoperative fibrillation, as well as its immediate therapy. This stands to potentially further shorten intensive care unit stays by enabling monitoring in any medical environment.

Our study is best understood in the context of its limitations. As this was a very early feasibility study, the number of observations is small, and there is no control group. A larger study with control individuals is necessary to confirm safety, efficacy, and impact on clinical outcomes. Nonetheless, on the basis of these preliminary findings, such a study is being planned, and an updated device is in development to permit persistence of the device in postoperative patients. AF induced with rapid atrial pacing may be different than clinical AF and may be transient in nature (self-terminating). This may confound the findings related to the efficacy of oblique sinus cooling.

Conclusion

Termination of perioperative AF with epicardial cooling in the oblique sinus was feasible and safe in this small, first-in-human study.

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Disclosures: Jeff Rynbrant is employed by MediCool, the manufacturer of the equipment. Paul Friedman and Samuel Asirvatham are coinventors of the technology. They, along with their employer, the Mayo Clinic, may benefit from its commercialization.

Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: All enrolled patients provided written informed consent.

Ethics Statement: The study was approved by the institutional review board at both hospitals and adhered to Declaration of Helsinki ethical guidelines.

References

1. Caldonazo T, Kirov H, Rahouma M, et al. Atrial fibrillation after cardiac surgery: a systematic review and meta-analysis. J Thorac Cardiovasc Surg 2023; 165:94–103.e24.
2. Greenberg JW, Lancaster TS, Schuessler RB, Melby SJ. Postoperative atrial fibrillation following cardiac surgery: a persistent complication. Eur J Cardiothorac Surg 2017;52:665–672.
3. Halonen J, Kärkkäinen J, Jäntti H, et al. Prevention of atrial fibrillation after cardiac surgery: a review of literature and comparison of different treatment modalities. Cardiol Rev 2024;32:248–256.
4. Muehlschlegel JD, Burrage PS, Ngai JY, et al. Society of Cardiovascular Anesthesiologists/European Association of Cardiothoracic Anaesthetists practice advisory for the management of perioperative atrial fibrillation in patients undergoing cardiac surgery. Anesth Analg 2019;128:33–42.
5. LaPar DJ, Speir AM, Crosby IK, et al. Postoperative atrial fibrillation significantly increases mortality, hospital readmission, and hospital costs. Ann Thorac Surg 2014;98:527–533. discussion 533.
6. Bianco V, Kilic A, Yousef S, et al. The long-term impact of postoperative atrial fibrillation after cardiac surgery. J Thorac Cardiovasc Surg 2023;166:1073–1083.e10.
7. Bramer S, ter Woorst FJ, van Geldorp MW, et al. Does new-onset postoperative atrial fibrillation after coronary artery bypass grafting affect postoperative quality of life? J Thorac Cardiovasc Surg 2013;146:114–118.
8. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2024;149:e1–e156.
9. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995;92:1954–1968.
10. Yamazaki M, Honjo H, Ashihara T, et al. Regional cooling facilitates termination of spiral-wave reentry through unpinning of rotors in rabbit hearts. Heart Rhythm 2012;9:107–114.
11. Witt CM, Dalton S, O'Neil S, et al. Termination of atrial fibrillation with epicardial cooling in the oblique sinus. JACC Clin Electrophysiol 2018;4:1362–1368.
12. Erinjeri JP, Clark TW. Cryoablation: mechanism of action and devices. J Vasc Interv Radiol 2010;21:S187–S191.
13. Guiraudon GM, Klein GJ, Sharma AD, Jones DL, McLellan DG. Surgery for Wolff-Parkinson-White syndrome: further experience with an epicardial approach. Circulation 1986;74:525–529.
14. Melby SJ, Schuessler RB, Damiano RJ Jr. Ablation technology for the surgical treatment of atrial fibrillation. ASAIO J 2013;59:461–468.
15. Kowlgi GN, Arghami A, Crestanello JA, François CJ, Friedman PA, Killu AM. Direct intramyocardial ethanol injection for premature ventricular contraction arising from the inaccessible left ventricular summit. JACC Clin Electrophysiol 2021;7:1647–1648.
16. Liu B, Arlock P, Wohlfart B, Johansson BW. Temperature effects on the Na and Ca currents in rat and hedgehog ventricular muscle. Cryobiology 1991;28:96–104.
17. Herve JC, Yamaoka K, Twist VW, Powell T, Ellory JC, Wang LC. Temperature dependence of electrophysiological properties of guinea pig and ground squirrel myocytes. Am J Physiol 1992;263:R177–R184.
18. Kiyosue T, Arita M, Muramatsu H, Spindler AJ, Noble D. Ionic mechanisms of action potential prolongation at low temperature in guinea-pig ventricular myocytes. J Physiol 1993;468:85–106.
19. Stavrakis S, Nakagawa H, Po SS, Scherlag BJ, Lazzara R, Jackman WM. The role of the autonomic ganglia in atrial fibrillation. JACC Clin Electrophysiol 2015;1:1–13.
20. Kiernan MC, Cikurel K, Bostock H. Effects of temperature on the excitability properties of human motor axons. Brain 2001;124:816–825.
21. Hsu JR, Mir H, Wally MK, Seymour RB. Clinical practice guidelines for pain management in acute musculoskeletal injury. J Orthop Trauma 2019; 33:e158–e182.