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The Use of Core Warming as a Treatment for Coronavirus Disease 2019 (COVID-19): an Initial Mathematical Model

Marcela Mercado-Montoya[1], Nathaniel Bonfanti[2], Emily Gundert[2], Anne Meredith Drewry[3], Roger Bedimo[4], Victor Kostov[5], Konstantin Kostov[6], Shailee Shah[7], Erik Kulstad[8,*]

ORCID IDs

Mercado-Montoya M https:/orcid.org/0000-0002-1453-4690
Bonfanti N https://orcid.org/0000-0002-9564-9536
Gundert E https://orcid.org/0000-0001-5918-9088
Drewry AM https://orcid.org/0000-0001-6899-5196
Bedimo R https://orcid.org/0000-0001-9794-0389
Kostov V https://orcid.org/0000-0003-0150-8597
Kostov K https://orcid.org/0000-0003-3778-5051
Shah S https://orcid.org/0000-0002-1240-5414
Kulstad E https://orcid.org/0000-0002-9331-8266

ABSTRACT

Introduction: Increasing data suggest that elevated body temperature may be helpful in resolving a variety of diseases, including sepsis, acute respiratory distress syndrome (ARDS), and viral illnesses such as SARS-CoV-2, which causes coronavirus disease 2019 (COVID-19). A mechanical provision of elevated temperature focused in a body region of high viral activity in patients undergoing mechanical ventilation may offer a therapeutic option that avoids arrhythmias seen with some pharmaceutical treatments. This study investigated the potential to actively provide core warming to the lungs of patients with a commercially available heat transfer device via mathematical modeling, and examined the influence of blood perfusion on temperature using this approach. **Methods:** Using the software Comsol Multiphysics, the authors modeled and simulated heat transfer in the body from an intraesophageal warming device, taking into account the airflow from patient ventilation. The simulation was focused on heat transfer and warming of the lungs and performed on a simplified geometry of an adult human body and airway from the pharynx to the lungs. **Results:** Simulations were run over a range of values for blood perfusion rate, since the heat capacity and density remain relatively constant. The highest temperature in this case is the device warming water temperature, and that heat diffuses by conduction to the nearby tissues, including the air flowing in the airways. At the range of blood perfusion investigated, maximum lung temperature ranged from 37.6 to 38.6°C. **Conclusions:** The provision of core warming may offer an innovative approach to treating infectious diseases from viral illnesses such as COVID-19, while avoiding the arrhythmogenic complications of currently used pharmaceutical treatments.

KEYWORDS: COVID-19; Body temperature; Mathematical model

1.Universidad de Antioquia – Engineering Faculty – Bioengineering Department – Medellín, Colombia
2.UT Southwestern Medical Center – Departments of Emergency Medicine and Anesthesia/Critical Care – Dallas (TX), USA
3.Washington University – School of Medicine – Department of Anesthesiology – St. Louis (MO), USA
4.VA North Texas Health Care System – UT Southwestern Medical Center – Dallas (TX), USA
5.Walter Payton College Preparatory High School – Chicago (IL), USA
6.Life Science Angels – Chicago (IL), USA
7.Illinois Institute of Technology – Department of Bioengineering – Chicago (IL), USA
8.UT Southwestern Medical Center – Department of Emergency Medicine – Dallas (TX), USA
***Correspondence author:** erik.kulstad@utsouthwestern.edu
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INTRODUCTION

Traditionally, fever has been treated because its metabolic costs were felt to outweigh its potential physiologic benefit in an already stressed host[1]. However, increasing data suggest that fever may be a protective adaptive response that should be allowed to run its course under most circumstances[2,3]. The American College of Critical Care Medicine and the Infectious Diseases Society of America define fever as a body temperature of 38.3°C (101°F) or higher[4]. Although one randomized controlled trial using physical cooling of mechanically ventilated patients with septic shock found a reduction in vasopressor dose and reduced early mortality when treating fever[5], a growing number of studies have found either no clinically important benefit, or harms, in treating fever of infectious origin.

Studies have found that higher early fever is associated with a lower risk of death among patients with an ICU admission diagnosis of infection[6,7] and that fever may enhance immune-cell function[8,9], inhibit pathogen growth[10–12], and increase the activity of antimicrobial drugs[13]. Fever potentially benefits infected patients via multiple mechanisms; *in vitro* and animal studies have shown that elevated temperatures augment immune function, increase production of protective heat shock proteins, directly inhibit microorganism growth, reduce viral replication, and enhance antibiotic effectiveness[3,14]. More rapid recoveries are observed from chickenpox[15], malaria[16], and rhinovirus[17] infections with avoidance of antipyretic medication, and many innate and adaptive immunological processes are accelerated by fever[18–20]. Purposefully inducing hyperthermia has been shown to have positive impacts on the immune system[21–27]. In fact, an approach known as "pyrotherapy" was once widespread, with the originator of the idea, Prof. Wagner-Jauregg, receiving the Nobel Prize in Medicine or Physiology in 1927[28,29]. Recently, a pilot study of external warming of septic patients has been completed[30].

A core heat trasnfer device (ensoETM, Attune Medical, Chicago, IL) has been commercially available for several years and is used for a range of temperature management purposes, including postcardiac arrest therapeutic hypothermia[31–34], warming of burn patients[35], warming general surgical patients[36], cooling traumatic brain injury[37], cooling heat stroke[38], and the treatment of central fever[39,40]. The device is a multichambered silicone tube placed in the esophagus and connected to a heat exchanger to provide heat transfer to or from a patient[41].

Because of the apparent heightened sensitivity of 2019-nCoV to temperature, in particular to the potential for viral entry to be inhibited by elevations in temperature, elevations in lung temperature, particularly in afebrile patients typically seen late in the disease course, may decrease viral replication and activity sufficiently to affect an improvement in clinical outcome. This approach also avoids the potential for inducing arrhythmias commonly seen with some pharmaceutical treatments being used for COVID-19, such as chloroquine, hydroxychloroquine, azithromycin, and others[42,43]. This work sought to investigate this approach by developing a mathematical model of core warming to determine the temperature distribution throughout lung tissue at typical physiologic conditions.

METHODS

Mathematical modeling of core warming

The software Comsol Multiphysics was used to model and simulate heat transfer in the body from an intraesophageal warming device, taking into account the airflow from patient ventilation. The simulation was focused on heat transfer and warming of the lungs and performed on a simplified geometry of an adult human body and airway from the

pharynx to the lungs. This symmetry was utilized to reduce the computational cost, so only half of the body was simulated, as shown in Fig. 1.

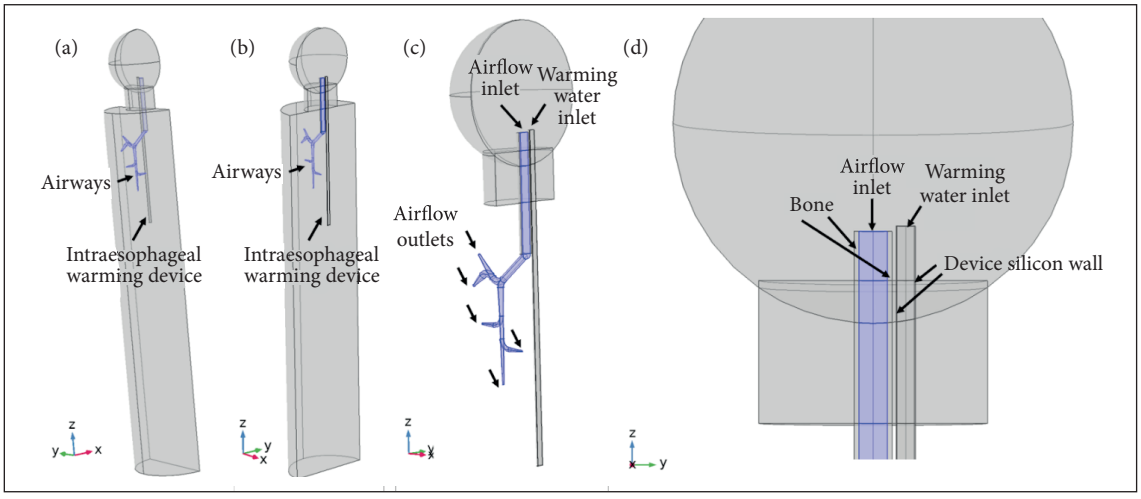

Figure 1. Computational domain. (a) General side view 1, (b) general side view 2, (c) close-up of the airways and intraesophageal warming device, (d) close-up showing details of the relevant domains.

The bioheat transfer interface of Comsol was used for the modeling and simulation of heat transfer, considering the heat generated by the blood perfusion, and known tissue thermal properties[44]. The bioheat transfer governing equations are given by Eq. 1, where T is the temperature and is the dependent variable, ρ is the density, C_p the heat capacity, k the thermal conductivity, u the velocity field (which is obtained from the fluid flow in the airways) and Q_{bio} is the heat generation term with "b" being a subscript corresponding to blood. As the intraesophageal device temperature is higher than the blood temperature in this simulation (Tb = 37 °C), this term has a negative sign, making it a heat consuming term.

$$\underbrace{\rho C_p \frac{\partial T}{\partial t}}_{Transient} + \underbrace{\rho C_p \boldsymbol{u} \cdot \nabla \mathrm{T}}_{Convection} + \underbrace{\nabla \cdot (-k \nabla \mathrm{T})}_{Diffusion\ or\ Conduction} = \underbrace{Q_{bio} = \rho_b C_{p,b} \omega_b (T_b - T)}_{Blood\ Perfusion\ Heat\ Generation} \quad (1)$$

The temperature boundary condition at the warming device inlet was set to 42 °C, the maximum operating temperature of the device. The surrounding air at 20 °C (emulating a hospital environment) was not considered in the model, but replaced with a convection boundary condition at the skin boundaries.

The airflow was modeled using the turbulent flow, k-ε interface considering a stationary study with the RMS value of 0.5 m/s of a presumed sinusoidal behavior of the airflow velocity at the inlet of the trachea at the throat level (Fig. 2).

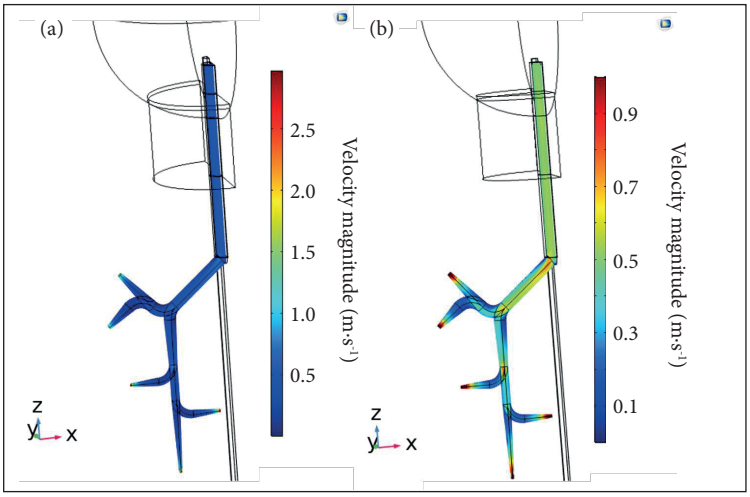

Figure 2. Airflow velocity profile in an xz plane at the center of the airways. (a) Original range and (b) modified range for better visualization.

The boundary condition in the airflow outlets was set to pressure of -1 mmHg. The warming water flow was directly defined to be 120 L/h in the negative z-axis direction, which corresponds to the actual flow rate in the clinical use of the device.

RESULTS

Simulations were run considering a range of values for the blood perfusion rate, which is a parameter expected to have high influence in the heat consumption term in Eq. 1, since the heat capacity and density remains almost constant. The values considered for the blood perfusion rate were 1e-3[1/s] to 6e-3[1/s] with a step of 1e-3[1/s].

The simulation results show a temperature distribution which agrees with the expected clinical experience, with the skin surface at a lower temperature than the rest of the body due to convective cooling in a typical hospital environment; however, most of the torso is at 37 °C in the healthy-condition body temperature. The highest temperature in this case is the device warming water temperature, and that heat diffuses by conduction to the nearby tissues, including the air flowing in the airways. With the effective (RMS) value considered for the airflow, warmed air moves through the lungs, and the intraesophageal warming device leads to an increment in the core temperature, as well as in the bronchi from the trachea to the lungs.

The airflow velocity profile is as expected, being around 0.5 m/s in the trachea and getting higher as the diameter of the airway decreases (Fig. 2). From Fig. 3, it is evident that the blood perfusion rate affects the temperature distribution, with the heat transfer from the warming device increasing, and the skin temperature decreasing, with a reduced blood perfusion rate. This is seen in Fig. 4, where heat diffuses to the air in the trachea more rapidly, and the temperature has higher values,

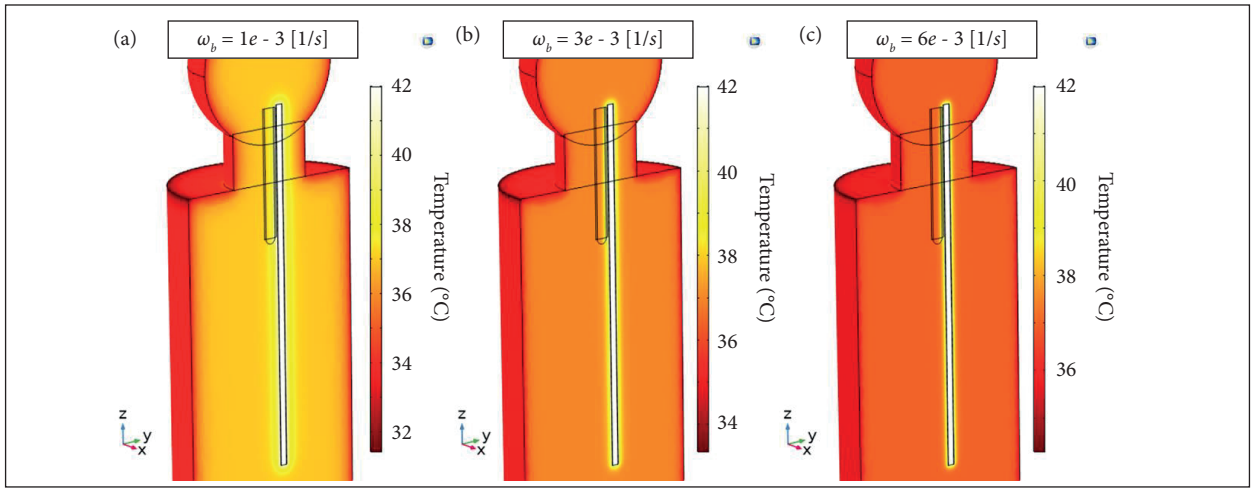

Figure 3. Surface plot of the temperature profile for different blood perfusion rates: (a) 1e-3[1/s], (b) 3e-3[1/s] and (c) 6e-3[1/s]

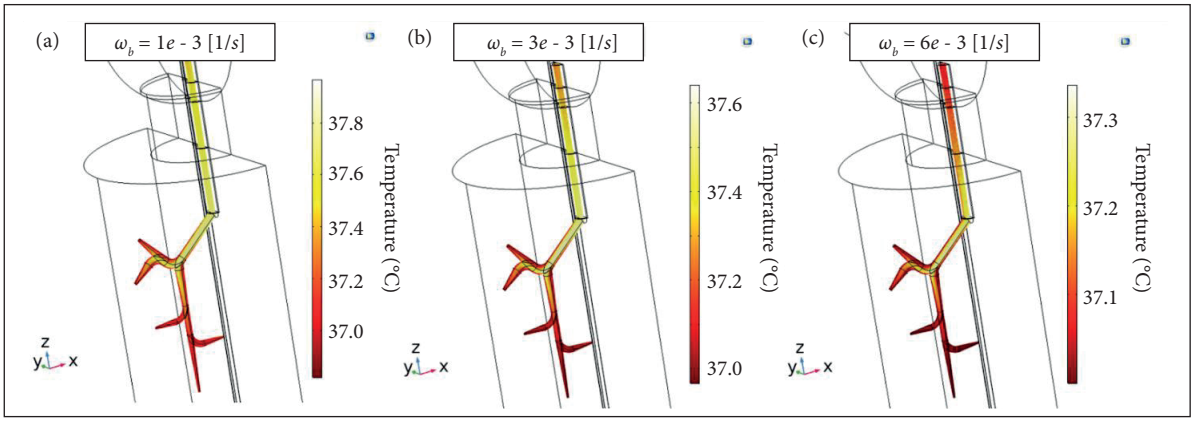

Figure 4. Temperature profile in an xz plane at the center of the airways at different blood perfusion rates: (a) 1e-3[1/s], (b) 3e-3[1/s] and (c) 6e-3[1/s].

at lower blood perfusion rates. The relationship between both the maximum and average temperatures with respect to the blood perfusion rate is exponential in the airways (Fig. 5) as well as in the lungs (Fig. 6). These results are expected given that the blood perfusion heat generation term is a heat consumption term in the warming case considered (Eq. 1).

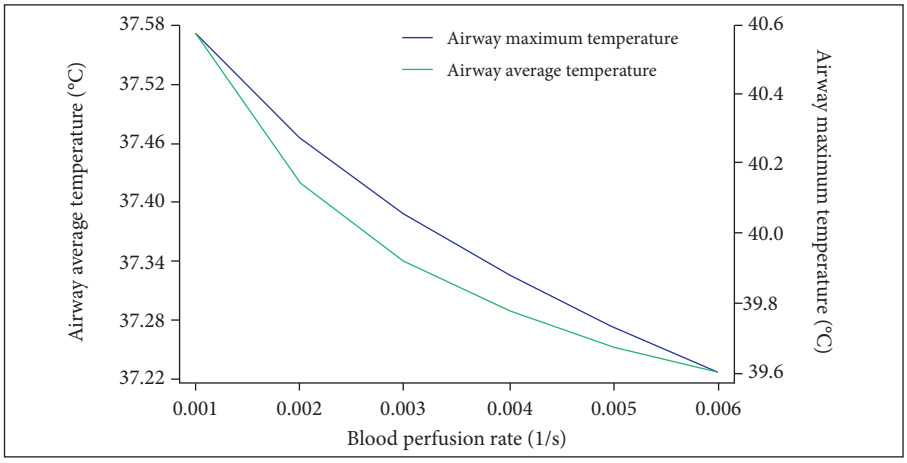

Figure 5. Airway average and maximum temperature as a function of blood perfusion rate.

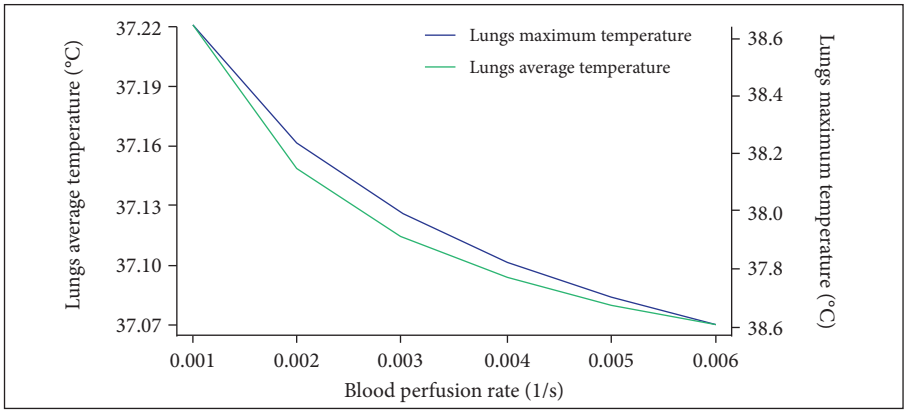

Figure 6. Lungs average and maximum temperature as a function of blood perfusion rate.

DISCUSSION

At the expected ranges of perfusion in the patient requiring critical-care, this work shows that the temperature of lung tissue, including vasculature and airways, can be elevated to a range that may be sufficient to offer therapeutic benefit. Because currently used pharmaceutical treatments for COVID-19 carry a concerning risk for serious arrhythmias[42,43], a nonpharmaceutical approach to treatment may be particularly appealing. Multiple randomized control trials evaluating the impact of antipyretic therapy on outcomes in critically ill patients suggest either no benefit, or harm, from treatment[45–51]. Early in acute respiratory distress syndrome (ARDS), fever is associated with improved survival rates; for every 1 ˚C increase in baseline temperature, the odds of death decrease by 15% (odds ratio, 0.85; 95% CI, 0.73-0.98, p = 0.03)[52].

A retrospective cohort study of 1,264 patients requiring mechanical ventilation initiated found that high fever (≥ 39.5˚C) was associated with increased risk for mortality in mechanically ventilated patients; however, in patients with sepsis, moderate fever (38.3–39.4˚C) was protective, and antipyretic medication was not associated with changes in outcome[53]. An open, parallel-group pilot randomized clinical trial (the FEVER pilot trial) enrolled 87 pediatric intensive care unit patients who were randomly assigned to permissive (antipyretic interventions only at ≥ 39.5 ˚C) or restrictive groups (antipyretic interventions

at ≥ 37.5 °C) whilst on respiratory support, and found that length of stay, duration of organ support and mortality were similar between groups, and no prespecified serious adverse events occurred[18]. The UK National Institute for Health and Care Excellence (NICE) now recommend not using antipyretic agents "with the sole aim of reducing body temperature in children with fever."[18,54].

Coronavirus disease 2019 (COVID-19) and its causative virus (SARS-CoV-2) were first identified in December 2019, with mortality initially estimated at 5.7%[55]. The surface glycoprotein of an earlier SARS coronavirus (SARS-CoV), SARS-S, consists of two components: S1, which contains the receptor binding domain (RBD); and S2, which contains the fusion peptide. Permissive host alveolar epithelial cells are initially bound to the SARS virus at the glycosaminoglycan heparan sulfate. Heparan sulfate expression increases viral density, facilitating the SARS-S predilection for the cell surface receptor angiotensin converting enzyme 2 (ACE2)[56,57]. Following these binding steps, SARS CoV undergoes endocytosis into low pH endosomes, where viral RNA replication initiates. ACE2 is a membrane associated enzyme expressed in human endothelial cells identified in 2000, found in heart, kidneys, testis, and the lungs[58,59].

Most isolates of human rhinovirus, the common cold virus, replicate more robustly at the cool temperatures found in the nasal cavity (33–35 °C) than at core body (lung) temperature (37 °C)[60]. Rhinovirus replicates preferentially at cooler nasal cavity temperature due, in part, to a less efficient antiviral defense response of infected cells at cool temperature, raising the possibility that inhaling cool air might diminish resistance to respiratory virus infections by lowering the temperature of potential host cells lining the nasal cavity[60].

Influenza B virus viral hemagglutinin exhibits higher expression at 33 °C (a temperature required for membrane fusion), indicating pronounced adaptation to the mildly acidic pH and cooler temperature of human upper airways[61]. Specifically, protein expression of influenza B virus viral hemagglutinin proved to be temperature dependent, with expression highest at 33 °C and gradually decreasing at higher temperatures[61]. More recently, simulations of the receptor binding domain (RBD) of 2019-nCoV found that it is more flexible than SARS CoV, especially near the binding site, suggesting that the RBD will have a higher entropy penalty upon binding angiotensin-converting enzyme II (ACE2) compared to the RBD of SARS-CoV[62]. Consequently, 2019-nCoV may be more temperature-sensitive in terms of human infection than SARS-CoV[62].

A study investigating the distribution of SARS-CoV-2 in different tissues of 205 patients with laboratory confirmed COVID-19 disease found that while lower respiratory tract samples were more likely to be positive, nasal swabs had the lowest mean RT PCR cycle threshold value of 24.3 (or 1.4×10^6 copies/mL), indicating higher viral loads than all other specimen types including sputum, pharyngeal swabs and bronchoalveolar lavage fluid, which all had a cycle threshold of over 30 (< 2.6×10^4 copies/mL)[63]. Higher viral loads were also detected in the nose than in the throat in 17 symptomatic patients in Wuhan[64]. In a study of the stability of SARS CoV virus at different temperatures and relative humidity on smooth surfaces, virus viability was rapidly lost (>3 log10) at higher temperatures and higher relative humidity (e.g., 38 °C, and relative humidity of >95%)[65].

In summary, core warming appears to be feasible, and existing knowledge of immune system function and viral physiology suggests this may approach be of clinical benefit. A proposed protocol has recently been posted[66].

CONCLUSION

The provision of core warming via technology commonly utilized in the intensive care unit, emergency department, and operating room can increase regional temperature of lung tissue and airway passages. The characteristics of many viruses, and in particular, the temperature sensitivities of SARS-CoV-2, combined with increasing evidence of potential benefits of elevated body temperature in treating infectious conditions suggests that core warming may offer a novel treatment option while avoiding the arrhythmogenic complications of many currently used pharmaceutical treatments.

CONFLICT OF INTEREST

Erik Kulstad and Konstantin Kostov declare equity interest in Attune Medical; Marcela Mercado-Montoya performs consulting for, and Shailee Shah has served as an intern for, and now serves as Operations and Quality Engineer for Attune Medical.

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