Drug discovered by researchers shows potential life-saving results in treating cardiac arrhythmias

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Scientists at Simon Fraser University (SFU) and the Lankenau Institute for Medical Research (LIMR) near Philadelphia have found that a drug discovered at SFU and patented several years ago may have potential lifesaving results in the treatment of conditions leading to sudden cardiac death.

The drug, known as AR-787, was originally discovered and designed by former Ph.D. student Mena Abdelsayed as a pharmacological solution for arrhythmias.

The so-called J Wave syndromes (JWS), consisting of Brugada syndrome and early repolarization syndromes, occur in about one in 2,000 people and are associated with life-threatening cardiac arrhythmias—complications with the rate or rhythm of the heart.

In some patients, these arrhythmias can lead to sudden cardiac death and, in some cases, may be triggered by hypothermia.

The first line of treatment for high-risk patients often involves the use of an implantable cardioverter defibrillator (ICD), though this route has shown to be problematic, especially for young patients and those experiencing frequent shocks from an ICD.

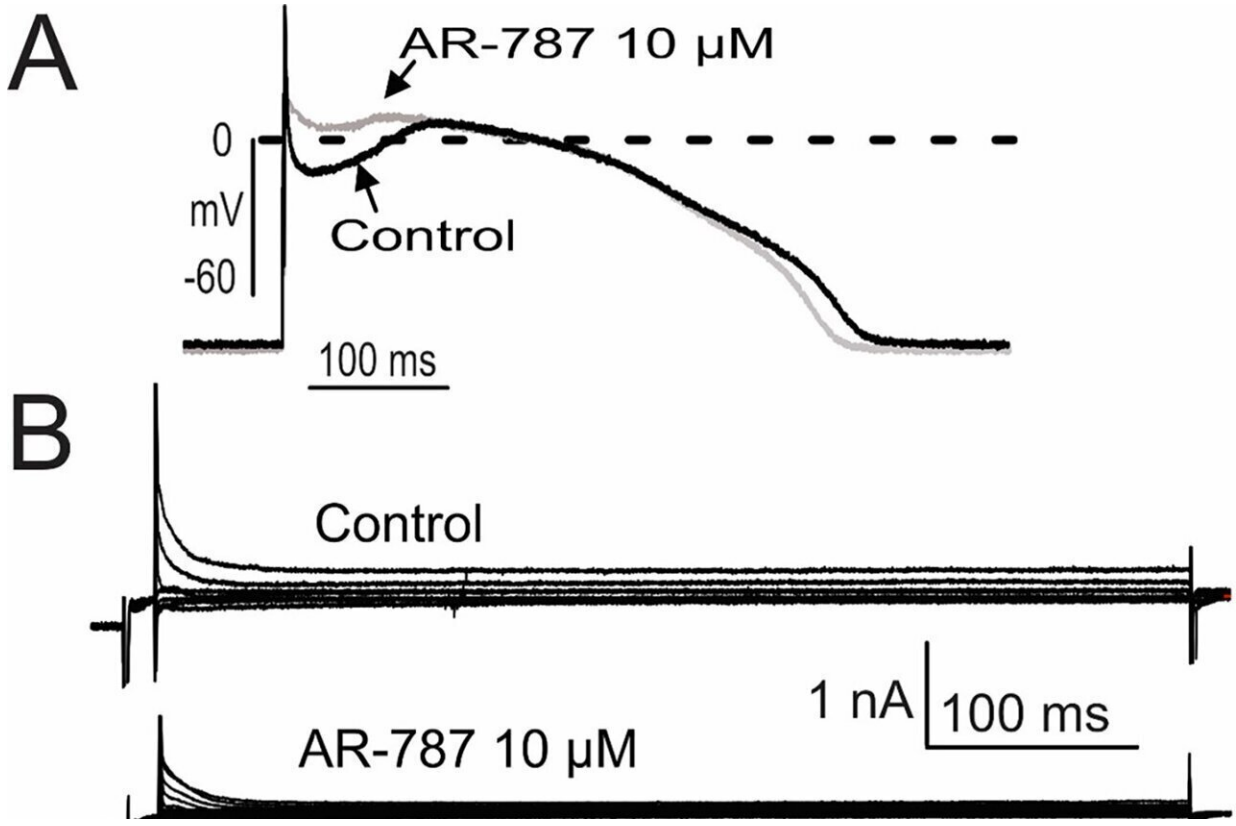
A study recently published in *PLOS ONE* and led by LIMR, involving current and former SFU researchers Mena Abdelsayed, Mohamed Fouda, and SFU biomedical physiology and kinesiology professor Peter Ruben, has shed light on a possible pharmacological approach to treat

arrhythmic activity in the heart caused by JWS.

The drug, known as ARumenamide-787, or AR-787 for short, was designed by Abdelsayed in an SFU laboratory led by Ruben. AR-787 has now proven to be effective in a series of lab trials at LIMR and SFU.

AR-787 was designed to directly interact with a protein in the heart called the cardiac sodium channel, which is essential for electrical impulse conduction that triggers contraction of the heart muscle.

More importantly, it interacted with the transient outward current channels in the heart, acting to suppress arrhythmic activity associated with JWS.



Effect of AR-787 on the transient outward current (I^{to}), inward calcium current (I_{Ca}) and action potential recorded from canine right ventricular epicardial myocytes. (n = 6) A: Representative action potential traces recorded in the absence (Control) and presence of AR-787 (10 μM) at a frequency of 0.5 Hz. B and C: Representative traces of Ito and ICa recorded in Control and following exposure to AR-787 (10 μM). D and E: I-V relationships for peak Ito and ICa recorded under control conditions and following exposure to AR-787. F: Molecular structure of Arumenamide-787 (AR-787). All data were obtained at 37°C. Credit: *PLOS ONE* (2023). DOI: 10.1371/journal.pone.0281977

While he was a graduate student in Ruben's lab, Abdelsayed (now a postdoctoral fellow at Stanford University) designed AR-787 based on his knowledge about the structure of sodium channels.

Abdelsayed designed different drug structures with computer modeling programs to select and visualize the results of his designs, adjusting them until they rendered the desired result.

Working in Ruben's SFU lab, his research team, including Abdelsayed, Fouda, and Dr. Dana Page, proved the drug's effectiveness in altering sodium channel current characteristics by performing tests on sodium channel genes artificially inserted into human embryonic kidney cells.

Still, they had yet to verify the drug's effectiveness in the muscle cells of a real heart. That is when they tapped into the expertise of one of the world's most recognized researchers in heart arrhythmia, Charles Antzelevitch, Ph.D., a distinguished professor emeritus and executive director of cardiovascular research at LIMR, which is part of the Main Line Health system outside Philadelphia.

Dr. Antzelevitch's team—consisting of Drs. José Di Diego, Héctor Barajas-Martínez, Robert Cox, Victoria M. Robinson, and Bence

Patocskai, and joined by Joseph Jung—supported the research by conducting AR-787 trials on mammalian hearts in LIMR's laboratory.

They tested the effect of the drug on the sodium channel current as well as additional ion channels within the heart. They found that AR-787 not only augments sodium channel activity, but was effective in inhibiting a particular cardiac potassium channel that contributes importantly to the development of life-threatening arrhythmias, in experimental models of Brugada and early repolarization syndromes.

"I've been researching J-Wave syndromes for 35 years and have shown that inhibition of the transient outward potassium current can prevent the development of lethal arrhythmias related to JWS regardless of the genetic cause of the syndromes," says Dr. Antzelevitch.

"Twenty-four years ago, we reported that a drug called quinidine blocks that channel and is effective in suppressing the development of JWS-related cardiac arrhythmias. Quinidine has since been used worldwide in the treatment of JWS.

"More recently, we reported that a natural product from the safflower plant, called acacetin, also blocks the transient outward potassium current. Much of our work in recent years has been focused on finding a drug with similar features but that would dissolve better than acacetin in blood, and is free of quinidine's adverse side effects. We're optimistic that AR-787 may be the drug we've been looking for."

The team has since patented the drug and hopes that their research will inspire interest within the pharmaceutical industry to take AR-787 to the next step, by testing its long-term safety and efficacy, and eventually, conducting clinical trials. "Our hope is that this drug will save lives," says Ruben.

More information: José M. Di Diego et al, Mechanisms underlying the antiarrhythmic effect of ARumenamide-787 in experimental models of the J wave syndromes and hypothermia, *PLOS ONE* (2023). DOI: 10.1371/journal.pone.0281977