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Computer model for testing heart-disease drugs developed

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UC Davis researchers have developed an accurate computer model to test the effects of medications for arrhythmia, or abnormal heart rhythm, before they are used in patients.

The new tool -- described in the Aug. 31 issue of the journal *Science Translational Medicine* -- will help scientists screen anti-arrhythmia medications early in the drug-development pipeline and eventually guide physicians in prescribing those interventions to patients who could benefit the most.

"Drug development for arrhythmia has failed because it is difficult to anticipate how drugs will alter the heart's intricate electrical behavior prior to clinical trials," said Clancy, an associate professor of pharmacology at UC Davis and senior author of the study. "We developed a novel approach to solve this problem -- a computational framework for making early predictions about the effects of medications on cardiac rhythms."

In the 1980s, the Cardiac Arrhythmia Suppression Trial (CAST) study came to an abrupt halt when scientists discovered that the arrhythmia medication flecainide, used to treat abnormally fast heart rhythms, more than tripled the risk of sudden cardiac death compared to placebo in patients with irregular heartbeats.

"No one ever knew exactly why this happened, and we used our model to find out," said Clancy. "CAST gave us the clinical starting point for our

study."

To further prove the model's utility, Clancy and her team also used it to test lidocaine, an anti-arrhythmia medication with a strong safety profile and sufficient clinical outcomes data.

In conducting the study, Clancy, a biophysicist who specializes in using high-performance computing to understand diseases arising from abnormal excitability, started with existing models that simulate the behavior of heart cells during both normal heart rhythms and arrhythmia. She then devised mathematical formulas to describe the interactions of flecainide and lidocaine with their specific cellular targets -- tiny pores in cell membranes called ion channels that are the foundation for cardiac electrical activity. She and her team used these models in a simulation study to predict the effects of these drugs on cardiac rhythms in a 3-D virtual heart.

The results can be seen as videos showing that in the setting of extra heartbeats, flecainide causes arrhythmia, the condition it was developed to treat. Arrhythmia was not observed with lidocaine, confirming this drug is a safer alternative.

"An additional benefit of this model is that we could see exactly how flecainide causes arrhythmia," Clancy said.

The test showed that flecainide detaches from ion channels very slowly, causing it to build up in cells. This drug action led to a loss of heartbeats in some portions of the heart but not others - a condition that can set the stage for arrhythmia.

According to the study's lead author, Jonathan D. Moreno, a major benefit of the computer-based drug-testing approach is that it allows researchers to follow many processes simultaneously.

"We can test treatments under a range of conditions, including various heart rates, drug concentrations and arrhythmia triggers," said Moreno, who was a graduate student in Clancy's lab when the study was conducted. "It could even be used to mix and match drugs to create multidrug regimens."

To confirm the results, Clancy and her team treated rabbit hearts with the two drugs and found that the simulation correctly predicted the heart rates and concentrations at which the adverse effects were seen with the computer model.

The researchers hope their model will provide the foundation for a virtual drug-testing system that could streamline the current approach, which is limited to just a few drugs and biological processes at a time. Clancy also hopes her research will lead to quicker discoveries of new arrhythmia therapeutics.

"Millions of people each year are affected by cardiac arrhythmias that don't respond well to medications or that must be controlled with implantable defibrillators that can reduce quality of life," said Clancy. "Our model will hopefully speed the discovery of new options."

More information: "A Computational Model to Predict the Effects of Class I Anti-Arrhythmic Drugs on Ventricular Rhythms," *Science Translational Medicine*.

Provided by University of California - Davis