Research points to way to improve heart treatment

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Current drugs used to treat heart failure and arrhythmias (irregular heartbeat) have limited effectiveness and have side effects. New basic science findings from a University of Iowa study suggest a way that treatments could potentially be refined so that they work better and target only key heart-related mechanisms.

The team, which included researchers from Vanderbilt University, showed in theory that it might be possible to use drugs that maintain the positive effects on heart function of a known enzyme called calmodulin kinase II (CaM kinase) while reducing its negative effects. The findings were published the week of March 1 in the Early Online Edition of the *Proceedings of the National Academy of Sciences*.

anderson"CaM kinase helps regulate calcium, which is essential to heart function, but CaM kinase's calcium connection also can play a role in electrical problems that lead to irregular heart beats and cell death. This new finding suggests a specific way to keep the wanted CaM kinase effects but at the same time eliminate the bad effects," said Mark E. Anderson, M.D., Ph.D., professor and head of internal medicine at the University of Iowa Roy J. and Lucille A. Carver College of Medicine.

Anderson said that heart failure is among the most common discharge diagnoses for patients leaving hospital. "Most patients with heart failure are at risk of sudden death. Figuring out how and why heart failure happens is a major goal for academic medicine," Anderson said.

CaM kinase adds phosphate groups to other proteins -- a process known as phosphorylation. This process can activate proteins and set in motion or sustain cell activity.

"The study showed, surprisingly, the importance of CaM kinase's effect on two particular amino acid targets among the thousands of amino acids that make up protein targets for phosphorylation by CaM kinase. Controlling these targets might prevent the 'ripple effect' of other molecular events that result in arrhythmia and cell death," said Anderson, who also is a member of the University of Iowa Heart and Vascular Center and holds the Francois Abboud Chair in Internal Medicine.

Using rabbit heart cells, which behave much like human heart cells, the team showed that if CaM kinase is prevented from interacting with a protein that regulates calcium channels, negative effects, including cell death, do not occur. Specifically, they showed it was possible to either block the specific site on the protein where CaM kinase binds or block the ability of CaM kinase to perform phosphorylation on the protein.

In both cases, blocking the action of CaM kinase prevented too much calcium activity, which can be harmful.

"CaM kinase is needed to maintain calcium channel function, which allows the heart to contract. But too much CaM kinase, and consequently too much calcium entry into heart cells, causes electrical instability and other downstream molecular problems that can lead to cell overload and cell death, which causes heart failure," Anderson said.

Anderson said a next step is to try to develop drugs to prevent the unwanted CaM kinase effects.

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