Researchers find how specialized pacemaker works at biological level to strengthen failing hearts

September 14 2011

Heart specialists at Johns Hopkins have figured out how a widely used pacemaker for heart failure, which makes both sides of the heart beat together to pump effectively, works at the biological level. Their findings, published in the September 14 issue of *Science Translational Medicine,* may open the door to drugs or genetic therapies that mimic the effect of the pacemaker and to new ways to use pacemakers for a wider range of heart failure patients.

All sides of the heart's left ventricle (the main pumping chamber) need to beat in concert with one another in order for the heart to pump blood effectively to the rest of the body. In many people who suffer from heart failure, the right and left sides of the ventricle are out of sync, with one side contracting while the other is relaxed.

Several years ago, Johns Hopkins researchers helped develop a modified pacemaker that synchronizes the heart beats and restores normal contractions. That treatment, called cardiac resynchronization therapy (CRT), was approved by the Food and Drug Administration in 2001 and is widely used today to improve symptoms and enable people to live longer. However, the reasons why it worked at the biological level were unknown until now.

David Kass, M.D., professor of medicine and biomedical engineering at the Johns Hopkins University School of Medicine, who led the

development of CRT, is senior author of the new study. "We have revealed a key and important underlying biological mechanism that helps us understand how CRT works. With this information, we can work to develop completely new treatments, such as a drug or gene therapy, to essentially have a kind of 'pacemaker in a bottle' to help a wide variety of patients with a failing heart," says Kass, who is also a cardiologist at the Johns Hopkins Heart and Vascular Institute.

When investigating the changes that were occurring with CRT at the basic science level, Kass and his colleagues found that resynchronizing the heart makes the heart muscle more responsive to adrenaline, which stimulates pumping ability.

"What we learned," says Kass, "is that the modified pacemaker used in CRT raises the levels of regulator of G-protein-signaling (RGS) proteins in the heart. The RGS proteins direct the activity of G proteins, which are messengers that tell the heart and other organs what to do."

In heart failure, levels of a particular G protein, known as Gi, go up. Gi inhibits heart muscle pumping, getting in the way of another protein—Gs—that stimulates the heart muscle, thereby preventing Gs from doing its job. CRT restores the normal balance of Gi and Gs.

Kass uses a car analogy to explain the process. The Gs proteins represent the accelerator. The Gi proteins represent the brake. In heart failure, it's like driving with one foot on the gas and the other on the brake. He says that CRT takes the foot off the brake, inhibiting the Gi proteins, so that not only does the entire left ventricle pump in a coordinated fashion, but the heart muscle now responds to hormones, such as adrenaline, more like a healthy heart.

While the typical pacemaker only has one wire that goes to the right side of the heart, the modified CRT pacemaker that Kass and his colleagues

first helped develop has two wires. The second lead goes to the surface of the left ventricle, so that both sides of the heart are stimulated at the same time.

Usually, translational research begins at the laboratory bench, in cellular, molecular or animal models, and then discoveries are tested in people. However, with CRT, the modified pacemakers were developed first and offered to patients suffering from severe heart failure. The results were significant: helping hearts become stronger and healthier. In published studies, the majority of patients receiving CRT had less fatigue and shortness of breath, and better long-term survival.

"This was remarkable," notes Kass, "since CRT also made the heart do more work, and we had never had a heart failure treatment that made the heart work more, while also decreasing mortality." The next step for Kass and his colleagues was to go into the basic science lab to try to understand why and how CRT worked.

The majority of people with heart failure are not offered CRT because the two sides of their heart are beating in sync. Out of six million heart failure patients in the United States, an estimated one million have the type of disease that CRT was designed to treat. However, in another part of the study, the researchers discovered in animal models that if a heart that beat in synch was temporarily forced to beat out of sync, then was resynchronized, the heart muscle improved, Gi declined and the response to adrenalin was better.

"That finding gives us yet another avenue to explore," says Kass. "By temporarily putting a heart out of sync and then letting it go back, we may be able to trigger the type of biological effect that CRT produced. This theoretically could be applied to patients sooner than developing a drug or gene therapy. Kass and his colleagues are actively pursuing both gene therapy and modified pacing approaches.

Provided by Johns Hopkins Medical Institutions