The Overworked Heart

Research suggests molecular mechanisms for heart failure

By KATHLEEN FACKELMANN

Almost 5 million people in the United States suffer from congestive heart failure. Although this medical term conjures up images of a heart suddenly stopping, it in fact refers to a progressive weakening of the organ. It gradually loses its ability to pump enough blood to nourish the body's tissues. People with congestive heart failure suffer from shortness of breath, fatigue, and swelling of the legs and ankles. Many eventually die of the disorder.

Researchers don't know what causes congestive heart failure. Drugs can slow or even reverse the damage it causes. For many people with heart failure, such treatment eases symptoms and may prolong life, but for only a few years.

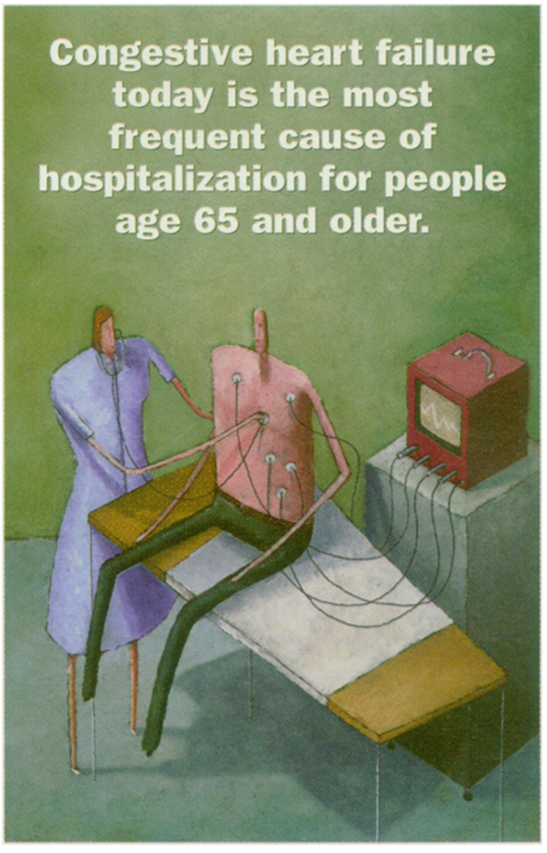
Several groups of researchers are working to improve that prospect. By determining what causes the heart damage, they hope to find ways to intervene. Such work "identifies the important elements that lead to progression of the failing heart," says cardiologist Michael R. Bristow of the University of Colorado Health Sciences Center in Denver.

Some of the research groups are tracking an inflammatory protein that they suspect is a culprit in the disease. Others are focusing on an enzyme that participates in the heart's response to hormones.

Studies of such molecular components may one day provide scientists with novel drugs aimed at treating heart failure. "In fact, interrupting some of these pathways may actually reverse the abnormal [heart] function," Bristow says.

Such drugs would not only aid the people diagnosed with congestive heart disease but might also rescue the hearts of many others who suffer from an early, undetected form of heart failure, says James B. Young, a cardiologist at the Cleveland Clinic Foundation. Such people rarely notice any symptoms, even though their hearts are growing weaker with every beat, he says.

All told, drugs that fight heart failure could benefit "millions and millions of patients," Young says.



The inflammatory protein called tumor necrosis factor-alpha (TNF) may play a lead role in congestive heart failure. White blood cells produce TNF as part of the body's normal response to injury. Researchers recently discovered that heart muscle cells, myocytes, also make this protein.

Normally, myocytes rev up production of TNF after any injury to the heart—for example, a blood clot that abruptly reduces blood flow. The brief release of TNF helps the injured heart tissue to heal. Trouble may arise, however, when the myocytes continue to crank out TNF. This protein may cause tissue damage when produced in large amounts over an extended period.

To test the theory that TNF plays a central role in congestive heart failure, Brett Giroir and Debora Bryant of the University of Texas Southwestern Medical Center in Dallas and their colleagues studied 30 mice that had been genetically engineered to make extra TNF in their heart tissues.

Magnetic resonance imaging of the mice revealed a severe decline in the heart's ability to pump blood. The researchers focused on the ventricular ejection fraction, which measures the proportion of blood ejected from the heart's pumping chambers, or ventricles, with each beat. Normal mice have an ejection fraction of about 65 percent, but the pumping power of the genetically altered mice was 20 percent or less.

A similarly low ejection fraction is seen in patients suffering from heart failure, Giroir says.

Another symptom observed in people with congestive heart failure is that the normally fist-sized heart more than doubles in size. The researchers also found that the genetically engineered mice had "huge, inefficient hearts—that's a definite indicator of heart failure," Bryant told SCIENCE NEWS.

"And they do die of heart failure—we've proven that," Bryant says. "They are all dead by about 3 months of age." The researchers detailed their evidence in the April 14 CIRCULATION.

The progression of heart failure marched in step with the rise in TNF, lending weight to the idea that the protein causes this disease, at least in part.

Still, the researchers don't know whether TNF directly injures the heart cells or recruits other cells to do the damage. Several teams of researchers have evidence that TNF can prompt heart cells to commit suicide.

The research by Bryant, Giroir, and their colleagues supports the idea that "TNF is a biochemical mediator for disease progression," says Douglas L. Mann, chief of cardiology at the Veterans Administration Medical Center in Houston. In the same issue of CIRCULATION that reports the Dallas study, Mann and his

colleagues provide further evidence for the TNF theory of heart failure.

In their study, Mann and his team continuously infused rats with TNF for 15 days at concentrations equivalent to that found in human heart-failure patients. The treatment produced in the rats several characteristics of human heart failure, notably a ballooning of the ventricles and a marked decrease in pumping power.

"Bigger is not better in terms of the heart," Mann says, noting that enlarged hearts pump inefficiently, in some cases allowing blood to spill back into the ventricle instead of being forced forward.

In another set of experiments, the researchers infused rats with TNF for 7 days, then injected a single dose of an experimental drug that blocks TNF's effects. This procedure completely reversed the pumping abnormalities, Mann says. It did not, however, shrink the hearts of the rats. Mann notes that such structural changes may take longer to reverse.

The blocking compound, manufactured by Immunex Corp. of Seattle, acts as a decoy that lures TNF away from heart cells. The drug tricks TNF into binding to it rather than to TNF receptors on the heart cells. Once TNF attaches to the experimental compound, it cannot damage the heart, Mann says.

In an early safety study, Mann and his colleagues gave the drug to 12 people with congestive heart failure. At the American Heart Association's 70th Scientific Sessions held in Orlando, Fla., last year, the team reported a moderate improvement in pumping ability after the patients had received a single infusion. "That drug is very promising," says Young.

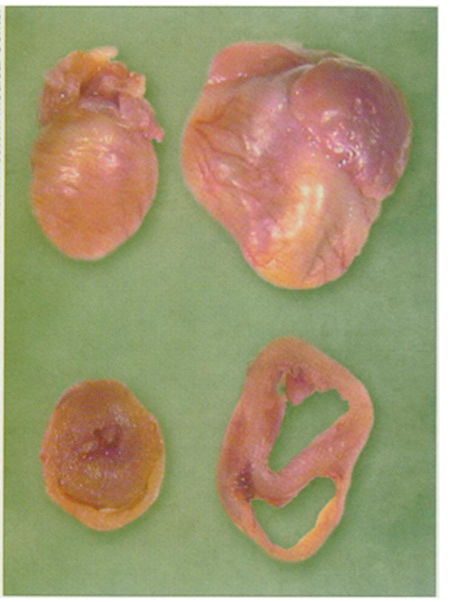
No adverse side effects were reported. Mann warns, however, that this test was just a pilot and much larger studies, now being planned to begin next fall, need to be completed before solid conclusions can be drawn about the drug.

Young adds that the Immunex compound isn't the only one that may block TNF's deleterious effect on the heart. Another drug, vesnarinone, lowers TNF production. Yet, a clinical trial of that drug produced disappointing results, Bristow noted in a commentary accompanying the Bryant paper.

A second view of heart failure brings another molecule to the fore. Howard A. Rockman, a Howard Hughes investigator at the University of North Carolina at Chapel Hill School of Medicine, says that he has "dramatic" evidence implicating an enzyme in the saga of heart failure.

Previous studies had demonstrated that heart failure patients show elevated concentrations of beta-adrenergic receptor kinase (BARK) in their heart tissues. Rockman and his colleagues knew that this enzyme shuts down certain receptors on the surface of cardiac cells. These receptors can then no longer interact with the hormones epinephrine and norepinephrine.

These hormones, which are central to the body's fight-or-flight response, cause the heart to beat faster and more forcefully. Indeed, they allow an athlete to run faster and jump farther. However, a heart that is faltering also triggers release of these hormones made by the adrenal gland. They continue to spur the heart long after it is exhausted. To put the brakes on, the heart releases BARK.



John Shelton and James Richardson/Univ. of Texas Southwestern Medical Center

The normal-size heart (top left) taken from a healthy mouse is dwarfed by the heart (top right) from a mouse suffering heart failure. That animal had been genetically engineered to make an excess of tumor necrosis factor-alpha. Cross-sections of the same two hearts show the compact healthy heart (bottom left) and the enlarged, inefficient ventricles (bottom right) underlying the heart failure.

"It's a compensatory mechanism," Rockman notes, that is beneficial in the short-run. But for people with underlying damage to the heart, the body continues to crank out excessive amounts of the heart-boosting hormones and the regulatory BARK in a destructive spiral.

To test this theory, Rockman and his colleagues looked at mice that had been genetically engineered to develop heart failure at an early age. They modified them further, creating two groups of mice. Those in the first group were altered to reduce BARK's efficiency.

By means of a method called echocardiography, the researchers used sound waves to visualize the heart and probe its structure and function. The mice with the less efficient BARK, they discovered, retained normal-size ventricles and heart function, thereby avoiding the heart failure that they had been bred to develop.

The second group of mice had heart cells with 100 times more hormone receptors than normal. These mice, which showed normal BARK activity, had unusually large ventricles, and their heart-pumping-power steadily declined. The researchers speculate that the excess hormone receptors provide more docking sites for epinephrine and norepinephrine and multiply the message to the heart to beat faster. Ultimately, the heart fails.

The team describes these findings in the June 9 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

Next, the researchers want to see if they can use a BARK inhibitor to improve already diminished heart function in mice. Such an experiment would more closely address how drugs would be used in the human population. Doctors generally don't see patients until they are already experiencing the signs of heart failure, Rockman notes. Ultimately, researchers need to develop a drug that can reverse such damage in the human heart.

Is there any connection between the two views of heart failure? "I think there are multiple signaling pathways," Rockman suggests. TNF may represent one path and BARK another, he adds.

Both TNF and BARK production may represent beneficial, short-term mechanisms that helped early humans.

"The idea was to survive the attack by the saber-toothed tiger. Yet as people lived longer lives, these systems began to respond to chronic stressors, such as long-lasting injury to the heart.

"These are mechanisms that evolved to get people through the reproductive years—not to support elderly people," Bristow says. Congestive heart failure today is the most frequent cause of hospitalization for people age 65 and older.

Scientists have made great strides in the treatment of heart failure with a variety of drugs, including beta-blockers and angiotensin-converting enzyme (ACE) inhibitors. A few patients see their heart function return to normal with current treatments, Bristow says. For many more, however, the disease continues to progress.

"There's no cure around the corner," Mann cautions, noting that it takes years for experimental drugs to wend their way through the regulatory system.

Yet the hope is that drugs aimed at TNF, BARK, or other molecular targets will provide some relief for congestive heart disease. "There's a huge, huge need for understanding the molecular mechanism that causes the heart deterioration," Rockman says.

Inhibiting BARK "worked wonders for the mouse," he adds. If the same strategy works for humans, "I would expect to see a tremendous survival benefit." □