



INQUIRIES

into
THE heart

Story by Elizabeth Kumru • Photos by JoAnne Erick

The heart is one of the strongest and most vital organs of the body. A little larger than your fist, your heart “beats” 100,000 times and pumps about 2,000 gallons of blood each day. The blood flows through a network of blood vessels that, if laid end-to-end, would encircle the earth more than twice.

The system was designed perfectly, yet there is so much that can go wrong. More than 41 diseases and conditions are associated with the heart and its supporting circulatory system. These diseases cause one or more forms of cardiovascular disease (CVD) in 58.8 million Americans.

All of this makes cardiovascular disease the No. 1 killer in the United States and a major focus for a group of researchers at the University of Nebraska Medical Center. Researchers are looking at the cause of chronic heart failure with the hope of developing therapies for the future.

“Too much of a good thing can be bad.”
You can almost hear mother say it.
Of course, she was probably talking about ice cream and not your body’s “fight-or-flight” reaction to stress.

Cardiovascular researchers at UNMC are discovering that the motherly advice holds true.

Fight or flight — a reaction of our sympathetic nervous system (SNS) that triggers adrenaline release and can save our life under certain circumstances. The reaction normally dissipates, but when it doesn’t, it can eventually damage the heart.

Irving Zucker, Ph.D., professor and chairman of physiology and biophysics, and his team of more than 20 scientists are looking at what role the sympathetic nervous system plays in chronic heart failure from three different perspectives.

The SNS is comprised of specialized nerve fibers that release a chemical substance called norepinephrine, or noreadrenaline. This chemical increases the heart rate and constricts blood vessels in times of stress — fight or flight — on the cardiovascular system. Under normal circumstances, the sympathetic nervous system works for a short time and then shuts down, Dr. Zucker said.

“The problem that occurs in heart failure is that a weak heart attempts to adjust cardiac function back to normal. Instead, the heart begins a vicious cycle that leads to additional heart failure when the SNS is activated.

“The harder the heart works the more oxygen it needs. In the case of coronary artery disease, there’s no way to deliver more oxygen. The blood vessels can’t get bigger,” he said.

One of the current strategies for breaking the cycle in heart failure is to block the SNS with drugs, such as beta blockers, ACE inhibitors and digitalis, which block the influence of norepinephrine on the heart. Beta-blockers relax the heart and cause it to beat more slowly, allowing it to stabilize.

“We want to understand what causes the SNS to be activated initially in patients who have heart failure and why SNS continues over time.”

His team recently received an \$8.2 million five-year program project grant from the National Heart, Lung and Blood Institute of the National Institutes of Health to answer those questions.

Program project grants are typically larger than grants

“The best way is to find a mechanism that causes the heart to function at a better level... That’s what we’re trying to find.”

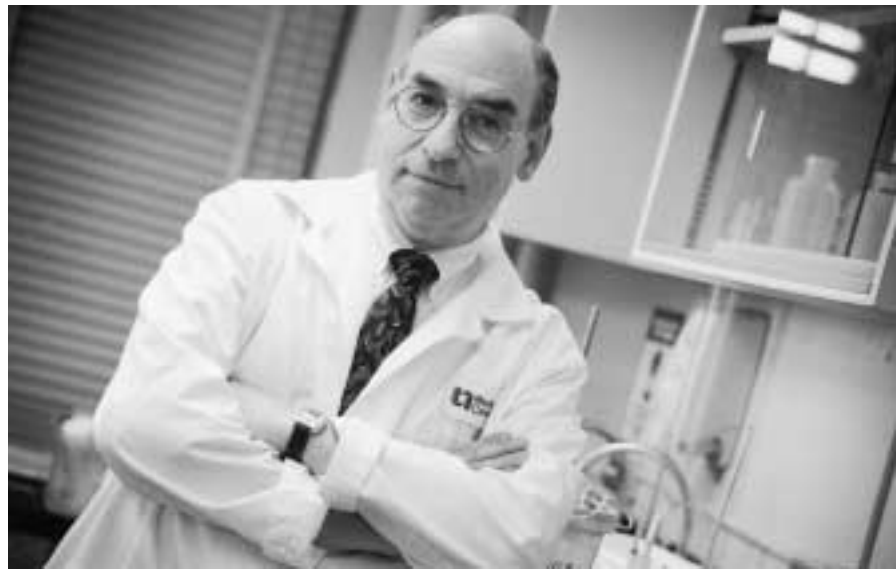
awarded to individual scientists, as they bring together a group of researchers who will collaborate to study a narrow theme. Due to the large value of program project grants, they are extremely competitive. The only other such grant at UNMC is for cancer research.

Research into the sympathetic nervous system is not new.

“Clinical studies have shown that the higher the level of plasma norepinephrine, the worse the prognosis is for the patients who have been diagnosed with heart failure,” he said.

A rough scale exists. Patients with plasma norepinephrine above 800 picograms (pg-ml) have a poor prognosis for five-year survival. Patients with plasma norepinephrine levels below 400 pg-ml, statistically have a much better chance of recovery.

“There is a clear relationship between severity of the



Dr. Irving Zucker

disease and the activation of the SNS,” Dr. Zucker said.

But, because it’s a chemical measurement, SNS activity never has been recorded continuously from blood samples. As long as a patient’s symptoms of heart failure continue, the SNS will remain activated unless that patient is treated and heart failure is effectively reversed. In patients with the most severe types of heart failure, the only treatment that can normalize the sympathetic nervous system is a heart transplant.

“Most cardiologists believe that cardiac transplantation will not be the future salvation for this disease, because it’s unlikely we’ll have enough donors and wide-scale xenotransplantation (organs from animals) is still pretty far on the horizon. Many people believe that animals will be genetically engineered so that their organs will not be rejected by humans. That seems like a reasonable way to go. I think most cardiologists still believe there are other kinds of therapies that might be better.”

While the majority of patients with heart failure are

Cardiovascular research breakthroughs

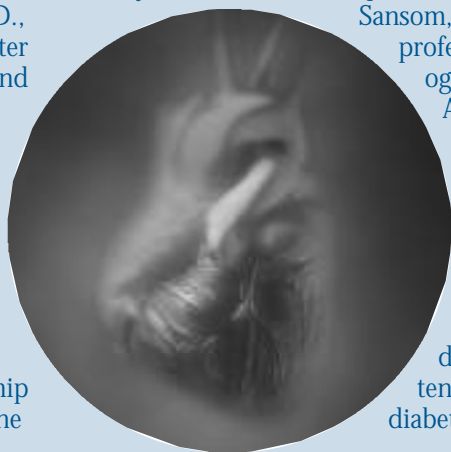
Scientists and physicians across the UNMC campus have made exciting breakthroughs in cardiovascular research. Here are a few.

- Folic acid protects against certain defects, but researchers don't know why. Tom Rosenquist, Ph.D., chairperson and professor of cell biology and anatomy, and Richard Finnel, Ph.D., director of UNMC's Center for Molecular Genetics and professor of cell biology and anatomy, have proposed two possibilities. This work, recently funded by the National Institutes of Health, will look at a direct effect of low folic acid on embryo growth, and also at the relationship between folic acid and the

amino acid, homocysteine. Homocysteine causes congenital heart and neural tube defects, and folic acid reduces homocysteine levels.

- The mechanisms that are responsible for filtering of blood by the kidneys are being studied by Pamela K. Carmines, Ph.D., professor, and Steven C. Sansom, Ph.D., associate

professor, both of physiology and biophysics. Alterations in this filtration process represent both a major cause and a consequence of cardiovascular disease. This research should help in understanding diseases such as hypertension, heart failure, diabetes and atherosclerosis.



- The mechanisms by which chronic alcohol ingestion alters the reactivity of cerebral blood vessels, a major factor in stroke, was defined by William Mayhan, Ph.D., professor of physiology and biophysics.

- A novel vaccine delivery system using the group B coxsackieviruses to prevent heart disease was developed by Steven Tracy, Ph.D., professor, and Nora Chapman, Ph.D., associate professor of pathology and microbiology.

- A new method of ultrasonic imaging of the heart and coronary arteries using microbubbles was developed by Thomas Porter, M.D., associate professor of cardiology. This method, which also determines blood flow to the heart and the delivery of cardiac specific drugs, is becoming part of the standard research protocol in clinics and laboratories throughout the world.

treated with medication, there are procedures, such as coronary artery bypass surgery, and implantation of devices, such as the left ventricular assist device, that help the heart regain strength.

"The best way is to find a mechanism that causes the heart to function at a better level, to reverse whatever the disease mechanism is. That's what we're trying to find," he said.

Dr. Zucker began preparing to apply for his program project grant in 1989 when he became chairman of the department. He began by recruiting a critical group of researchers that would develop the project. In addition, a \$100,000 grant from UNMC's College of Medicine allowed Dr. Zucker's team to gather preliminary data for the application.

"A program project grant is the crowning achievement in an investigator's career. It allows him to get much more productivity by interacting with other faculty on a common theme. The whole is greater than the sum of the parts. Even if we didn't get it funded, it would have been a worthwhile exercise to do because it brought this group together," he said.

Fortunately, his group was successful in obtaining the grant and now the three teams are busy with experiments.

Project 1

One group, led by Dr. Zucker and Kaushik Patel, Ph.D., professor, physiology and biophysics, is attempting to control the sympathetic nervous system activity by modulating two hormones.

They hypothesized that a substance called angiotensin II (Ang II) activates the SNS and another substance, nitric oxide, inhibits the SNS. In their preliminary studies, the

researchers demonstrated that nitric oxide production is decreased and Ang II production is increased when heart failure is induced in animals.

"By using different drugs, such as ACE inhibitors and Ang II receptor antagonists, we can shift the balance back and forth and alter SNS activity," Dr. Zucker said.

To get this information, Drs. Zucker and Patel developed a novel way to record the electrical activity of SNS in rabbits with heart failure while they are awake.

Electrical sensors are implanted around the SNS nerves entering the kidney and sealed from moisture inside the experimental animals. Wires from the sensors lead outside the animal and are attached to an amplifier and other recording equipment to monitor SNS activity.

Through this method, researchers can determine how much the SNS is activated and how it responds to changes in blood pressure or blood gases.

In humans, the SNS is measured by inserting a small electrode through the skin and into a bundle of nerve fibers that have high SNS activity. Dr. Zucker's project, however, will not measure SNS activity in humans.

Project 2

Since the sympathetic nervous system activity originates in the brain, the second project focuses on a neurotransmitter called gamma amino butyric acid (GABA). SNS activity is reduced when GABA is released. Dr. Patel is leading this project that will look at the relationship between GABA and nitric oxide in rats with chronic heart failure. Researchers know that nitric oxide can cause the release of GABA, but don't know exactly why.

"We need to study the mechanisms in the brain that are responsible for SNS activation. Once those mechanisms are known, then new drugs can be designed to target specific sites," Dr. Zucker said.

Project 3

A third research team is trying to figure out what happens inside the cells of chemoreceptors, tiny nerve receptors in arterial blood vessels, when a person has heart failure. This team is led by Harold Schultz, Ph.D., professor, George Rozanski, Ph.D., associate professor, Wei Wang, M.D., Ph.D., assistant professor, and Shu-Yu Sun, Ph.D., instructor, all from physiology and biophysics.

Under normal circumstances, when chemoreflex receptors sense a drop in oxygen, they immediately tell the body to increase ventilation and increase blood pressure. The body increases blood pressure by activating the sympathetic nervous system.

Because the SNS is already activated in a person with heart failure, the response is even greater. Receptors found in the carotid artery are particularly sensitive and, as Dr. Schultz has found, contain less nitric oxide under this condition. Nitric oxide is important for reducing the sensitivity of the chemoreflex. It is his theory that the loss of nitric oxide is key to turning these oxygen sensors into a hyper-sensitive system.

Exercise components are included in all three projects as well. UNMC researchers want to know if exercise can be used as a strategy for altering SNS activity in heart failure.

"Exercise training has been used over the past several years as a treatment modality for patients with heart failure, especially patients with less severe heart failure. Data coming out now shows that it is beneficial in improving the quality of life and reducing symptoms in patients with heart failure.

"But, nobody understands why. I believe one component involved is the reduction in SNS outflow. We actually have data in rabbits to show that this occurs," Dr. Zucker said.

Other principal investigators are Kurtis Cornish, Ph.D., associate professor of physiology and biophysics, who is in charge of the animal model core and Shyamal Roy, Ph.D., associate professor of OB/GYN, who directs the molecular biology and histology core of the grant.

"We'll know in four years if this work paid off when we evaluate our findings and submit for a grant renewal," Dr. Zucker said.

"Then we'll also know if we're any closer to solving some mysteries of the heart and to helping people with chronic heart failure." *d*

CREATING images from heart signals

Like a stone thrown into a pond creating ripples in the water, beats of the heart send waves of electrical signals to the body's surface.

Left undisturbed, the ripples gradually reach the shore. But, if a boulder in the water blocks the ripples, the pattern is disrupted.

Similar to the boulder in the pond, scar tissue from previous heart attacks disrupts the electrical signal.

John Windle, M.D., associate professor of cardiology, is working to map those signals into a four-dimensional image that will identify the precise location of that scar tissue. Once the scar tissue is located, surgeons can eliminate it using radio-frequency ablation, a minimally invasive procedure.

He is working with Robert Throne, Ph.D., associate professor of electrical engineering who has a focus on biomedical research, and Lorraine Olson, Ph.D., professor of mechanical engineering and mathematician at the University of Nebraska-Lincoln.

"This has the potential of curing a life-threatening rhythm problem before a person ever has an episode," Dr. Windle said.

Each year, 250,000 Americans die from life-threatening heart problems. Sudden cardiac death is a major cause of premature death and it's all due to a short-circuit in the heart.

"We now know which patients are high risk and, in the past two years, we've been able to prevent their first sudden death episode with implantable defibrillators.

Those episodes were 90 percent fatal with the first manifestation. With these devices, we have the opportunity to make an impact in that life-threatening process," he said.

The problem is that implantable defibrillators cost \$25-\$30,000 and the battery needs replacing every five years. Also, it only treats arrhythmia, it doesn't cure the problem.

Dr. Windle's group wants to fix the short-circuit.

They have expanded the science of electrocardiography into mathematical models. Instead of using the routine 12 EKG electrode leads to measure signals, the researchers attach 128 electrodes to the body. They call it inverse electrocardiography.

Using magnetic resonance imaging scans, EKG signals and a computer program, Dr. Windle's group can create a four-dimensional image to show exactly where the scar tissue is located. This will help pinpoint the real target — the tissue next to the scar.

"Usually, a critical piece of tissue supports this abnormal heart rhythm. If you can go in and destroy that critical tissue, you can cure the patient of that problem," he said.

The group is now working with animals and expects to develop models for humans in the next few years.

"It's our hope that once we establish our guidelines, physicians will only need an EKG to map their patient's heart. This research has the potential of curing heart disease, saving lives and lowering health-care costs," he said.



Dr. John Windle