

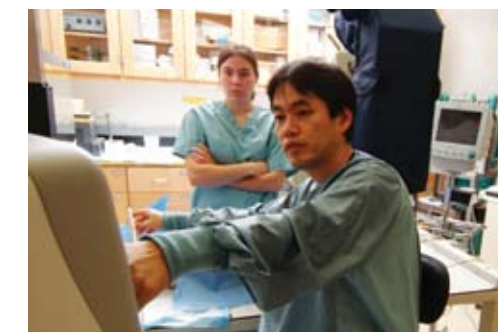


CORNERING SUDDEN DEATH

SUDDEN CARDIAC DEATH (SCD) is a catastrophic disruption of heart rhythm that will cause a seemingly healthy person to collapse and die within minutes. Unlike a heart attack, this deadly fibrillation—which claims approximately 300,000 lives annually in the U.S.—occurs without warning: there is no chest pain and no shortness of breath.

One focus of the center's research is whether statins aid in repair of damaged hearts.

State-of-the-art proteomic research facilities support the work of the center.



Multidisciplinary research looks at molecular pathways, cardiovascular repair actions

Until recently, scientists knew little about the underlying mechanisms that set the stage for SCD because there are no survivors to study.

Groundbreaking and promising research by investigators in the University at Buffalo Center for Research in Cardiovascular Medicine is changing that.

Headed by John M. Canty Jr., Albert and Elizabeth Rekate Professor of Medicine in the UB School of Medicine and Biomedical Sciences, the center brings together physician scientists in cardiovascular medicine and basic scientists in biochemistry, physiology, biophysics, pharmaceuticals, nursing, biostatistics, and bioinformatics to study SCD and related cardiovascular diseases from bench to bedside. The work has garnered approximately \$12.5 million in research dollars since 1996.

Most patients who die suddenly from heart disease do not have a heart attack, but develop a ventricular arrhythmia in a setting of chronically narrowed coronary arteries. They are frequently asymptomatic prior to the event. This silent killer may arise from a remodeling of the heart muscle cells and nerves that develops when the heart is subjected to repetitive episodes of inadequate blood flow.

Canty and colleagues opened an entirely new avenue of investigation into this remodeling by demonstrating a similar cardiac condition in pigs, where the heart develops an adaptation to inadequate blood flow called hibernating myocardium. This condition also is associated with a high rate of lethal ventricular arrhythmias.

The center's basic research projects that have

direct relevance to understanding human disease are carried out with the aid of this innovative animal model. Researchers can identify cellular and molecular changes that occur in the heart's muscle wall (the myocardium) due to ischemia, and track cellular responses after a cardiac event and revascularization. The pig model also is used to test potential therapies for preserving or rejuvenating cardiac tissue threatened or damaged by ischemia.

The research is concentrated in three general areas: chronic adaptive responses of the myocardium, potential new methods of cardiac repair, and the mechanisms underlying sudden cardiac death.

Projects investigating chronic adaptive responses of the myocardium to ischemia focus on intrinsic cellular changes, metabolic remodeling in response to revascularization, and determinants of reversibility and functional improvement.

Researchers in this group, of which Canty is the principal investigator, are employing the university's state-of-the-art proteomic research facilities to conduct concurrent physiological, proteomic, and mitochondrial function studies in the pig model that are translatable to patients. The work couples protein studies with assays of mitochondrial respiration and the activity of specific enzymes.

These investigations are identifying how changes in the molecular pathways responsible for myocardial adaptation to decreased blood flow can be reversed, with the ultimate goal of manipulating these pathways to restore full contractile function.

In the cardiac repair component, Te-Chung Lee, associate professor of biochemistry, and Gen Suzuki, research assistant professor of medicine, are using the pig model to investigate whether transplanting the model's bone marrow-derived mesenchymal stem cells (MSC) into down-regulated tissue (the hibernating myocardium) can change myocardial adaptive responses and improve function. MSCs

have the capacity to develop into blood vessels, as well as other types of tissues. The researchers anticipate that this work will lead to MSC therapeutics that can aid in managing aging and curing disease.

Suzuki and Canty also are investigating the potential of statins, used widely to lower cholesterol, to aid in heart repair. Results to date have shown that high doses of a common statin increase the number of stem cells localized in both normal and ischemic hearts, and improve cardiac function and coronary blood flow in diseased hearts. These new findings raise the possibility that statins may be an effective treatment for heart failure.

Research into mechanisms leading to sudden cardiac death involves both basic and hospital-based studies. Harold C. Strauss, professor and chair in the Department of Physiology and Biophysics, and Randall L. Rasmusson, associate professor in the department, are concentrating on the basic physiology of hibernating cells.

James A. Fallavollita, associate professor of medicine, is leading a four-part investigation of the heart's sympathetic nervous system. Three projects entail injecting a special isotope into the pig model. The isotope is taken up by nerve cells and can be imaged with positron emission tomography (PET), a technology that allows researchers to observe nerve activity in real time.

A fourth component aims to determine if normalizing blood flow in patients improves sympathetic nerve function, and if so, by how much and over what time frame. Michael S. Haka, clinical associate professor of nuclear medicine, and Andrew J. Luisi Jr., assistant professor of medicine, are major investigators on the project.

This research group also has been successful in applying its work on sudden death and hibernating myocardium to patient care, a critical component of translational research. In the recently funded National Institutes of Health PAREPET study (Prediction of Arrhythmic Events with Positron Emission Tomography), Canty and Fallavollita are determining whether PET scans that show alterations in nerves to the heart or the presence of hibernating myocardium can identify patients with established heart disease who have the highest risk of sudden death.

Estimates show that only one in five patients who receive a cardiac defibrillator to normalize aberrant heart rhythm may actually need it. PET scans could be used to better identify those most likely to benefit from implantation of a defibrilla-

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tor and to identify new at-risk patient groups that have relatively preserved levels of heart function. This is the largest prospective study to evaluate the role of cardiac PET in decision-making and requires the unique facilities available in the UB Center for Positron Emission Tomography and the Veterans Affairs Western New York Healthcare System.

In an adjunct study, Mary G. Carey, assistant professor in the School of Nursing, is using 24-hour electrocardiograph (ECG) readings of patients at risk of sudden cardiac death to find new markers of cardiovascular dysfunction. Findings from this research will complement results from the imaging studies.

Additional investigators affiliated with the Center for Research in Cardiovascular Medicine, and their departments, are: Vijay S. Iyer, Qinsong Hu, Michael D. Banas, Sunil Baldwa, Arturo M. Valverde, and Susan P. Graham, from the Department of Medicine's Division of Cardiovascular Medicine; Alan D. Hutson, professor and chair in the Department of Biostatistics in the School of Public Health and Health Professions, and Jeffrey C. Miecznikowski, assistant professor in the department; Steve Toorongian, senior radio chemist in the Department of Nuclear Medicine; Michael J. Morales, clinical assistant professor in the Department of Physiology and Biophysics; Kenneth Blumenthal, professor and chair in the Department of Biochemistry; Norma J. Nowak, director, UB-Roswell Park Cancer Institute microarray facility and director of science and technology in UB's New York State Center of Excellence in Bioinformatics and Life Sciences; and Jun Qu, research assistant professor in the Department of Pharmaceutical Sciences in the School of Pharmacy and Pharmaceutical Sciences.

Canty, chief of the Division of Cardiovascular Medicine in the Department of Medicine in the medical school, also heads the Cardiovascular Disease Group in the Center of Excellence. □

John M. Canty Jr. heads UB's Center for Research in Cardiovascular Medicine.

