Clinical and epidemiologic evidence for an association between influenza virus infection and cardiovascular events is growing. Research has shown that influenza can trigger heart attacks and that vaccination against influenza reduces the risk of recurrent myocardial infarction in patients with prior myocardial infarction by 66%. The cardiovascular repercussions associated with the influenza virus may originate from the ability of the virus to contribute to atherosclerosis—a possibility that challenges the conventional belief that the virus does not infiltrate extrapulmonary tissues. Thus, researchers are working to determine whether the influenza virus can directly infect the arterial wall and promote the development of atherosclerotic plaque.

Mohammad Madjid, MD, MSc, Senior Research Scientist at the Texas Heart Institute at St. Luke’s Episcopal Hospital (THI at St. Luke’s), has led a study exploring the effects of influenza A/Hong Kong (H3N2) virus on the vascular system of mice (Atherosclerosis 2010;208:90-6). After intranasally administering the virus to 4 different strains of mice, including atherosclerosis-prone and wild-type mice, the researchers analyzed various tissues for the presence of the influenza virus after 7 days. Using the reverse transcription polymerase chain reaction (PCR) and immunofluorescence, they detected influenza virus RNA and its antigens in the lung and aortic tissues of H3N2-infected mice but not in the tissues of uninfected mice or control mice infected with respiratory syncytial virus. Dr. Madjid and his associates, Drs. Ward Casscells and Mehran Haidari, were also able to determine that live influenza virus could be consistently recovered from the lung, aorta, and heart tissue of influenza-infected mice but not often from the blood, ruling out viremia as a source of virus in these tissues.

“Few microbial agents have been cultured reproducibly from atherosclerotic lesions,” states Dr. Madjid. “The presence of viable influenza virus, its RNA, and its antigens in the hearts and aortas of infected mice has important implications regarding the mechanisms that connect the virus with cardiovascular events.”

Dr. Madjid and his team also found that by using transmission electron microscopy, they could visualize the replication of influenza viruses in human coronary endothelial and smooth muscle cells, indicating that these cell types harbor the virus.

To further assess the local and systemic inflammatory effects of the influenza virus in mice, the researchers used real-time PCR to quantify the expression of various antiviral genes, chemokines, cytokines, and inflammatory markers. They observed increased expression of chemokines such as monocyte chemotactic protein (MCP)-1 and RANTES, as well as inflammatory mediators, including interleukin (IL)-6 and IL-1B, in the aorta and blood of influenza-infected mice. Furthermore, the number of macrophages was significantly higher in the atherosclerotic plaque of infected mice than in the plaque of uninfected mice, a finding confirmed by immunohistochemical and quantitative real-time PCR studies.

The results of this study raise important questions regarding the mechanism by which the influenza virus reaches the arteries, how the virus evades the innate immune response, and how longer-lasting infections may promote the formation of atherosclerotic plaque—topics that will receive attention in future studies.

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Biologic Sex Differences Play a Role in Cardiovascular Disease

Abstract: As more studies shed light on the role of biologic sex differences, they may begin to change how physicians diagnose and treat women with heart disease.

Cardiovascular diseases account for approximately half of all deaths in women. Although the underlying pathophysiologic processes leading to the development of heart disease (ie, atherosclerosis and inflammatory processes) are similar between men and women, death and other clinical end points often occur later in women. Reasons for the sex differences remain a matter of debate, but many physicians agree that hormones play a role, largely because manifestations of heart disease are somewhat rare in premenopausal women.

Awareness of biologic sex differences may begin to change how physicians diagnose and treat women with heart disease. Perhaps the most striking differences between men and women with heart disease are heart attack symptoms and severity. Many women who have a heart attack do not know it, yet heart attacks in women are often more severe. Women are twice as likely to die in the first year after a heart attack and twice as likely to have a second heart attack in the first 6 years after their first one.

“Many times, women have atypical symptoms,” says Stephanie Coulter, MD, a cardiologist at the Texas Heart Institute at St. Luke’s Episcopal Hospital (THI at St. Luke’s). “Instead of having typical chest pain, women may have jaw pain, arm pain, or simply shortness of breath or nausea. Alarming, 4 out of 5 physicians are unaware that cardiovascular disease is the leading cause of death in women.”

However, sex differences with regard to heart disease do not stop with symptoms. For years, physicians have recommended the preventive use of low-dose aspirin in people who have never had a heart attack or stroke. Recently, the guidelines have been tailored to match cardiovascular risk factors, which include sex and age (Ann Intern Med 2009;150:396-404). The new guidelines reflect that aspirin appears to be more effective for preventing heart attack in men but for preventing stroke in women.

“Thanks to results from women-specific studies, physicians can look closer at the influence of sex and how it may affect treatment,” says Dr. Coulter. “The changes to the aspirin guidelines are just one example of how a ‘one-size-fits-all’ strategy for both sexes may not be the best approach.”

The Women’s Ischemia Syndrome Evaluation (WISE) was initiated by the National Institutes of Health to develop accurate diagnostic approaches for detecting ischemic heart disease in women, to better understand how heart disease develops in women, and to evaluate the influence of hormones on the development and diagnosis of heart disease. The investigators found that women are more likely than men to have coronary microvascular syndrome, in which atherosclerotic plaque does not build up to block the main coronary arteries but, instead, spreads evenly throughout the arterial wall. Diagnostic coronary angiography often reveals that these women have “clear” arteries, incorrectly indicating a low risk.

Other studies have shown that women have 50% more adverse drug reactions and that tobacco affects women’s hearts and lungs much differently than men’s. In fact, smoking a pack of cigarettes a day increases a woman’s heart attack risk sixfold, as opposed to threefold in men.

“Much of our understanding of heart disease and heart attack and the basis for our standard methods of diagnosis and treatment are the result of research conducted on men,” says Dr. Coulter. “Too often, women’s heart disease is ignored by primary care physicians, emergency room staff, and women themselves. Physicians are now beginning to understand that heart disease may manifest differently in women than in men and that diagnostic tests and treatment options may need to be used differently.”

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Erythropoietin Protects Stem Cells Against a Cytotoxic Environment

Abstract: In myogenic cardiac stem cells, erythropoietin reduces tumor necrosis factor-α–induced apoptosis by means of multiple mechanisms.

Cell-based therapy is a promising treatment option for enhancing cardiac repair after acute myocardial infarction (AMI) if the transplanted cells can survive in the harsh postinfarction environment. When the heart is damaged by ischemia, multiple proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, are released by infiltrating cells, leading to widespread apoptosis (programmed cell death) and reduced function. Thus, protecting cells from potentially lethal inflammatory stimuli may increase the benefits of cardiac cell-based therapy.

Under the direction of Yong-Jian Geng, MD, PhD, Director of the Heart Failure and Stem Cell Research Laboratory at the Texas Heart Institute at St. Luke’s Episcopal Hospital (THI at St. Luke’s) and Professor of Medicine at The University of Texas Health Science Center (UTHSC) at Houston, investigators at THI at St. Luke’s and UTHSC are studying erythropoietin (Epo), a hormone-like protein, as a potential cardioprotective molecule that may help prevent inflammation-associated apoptosis of stem cells in the heart. Epo belongs to a superfamily of growth factors and has multiple biologic functions, including promoting red blood cell production, maintaining cell viability, and reducing the effects of inflammation.

Dr. Geng’s group isolated myogenic stem cells from immature dog hearts and treated the cells with TNF-α to mimic the in vivo inflammatory milieu of the heart after AMI. They examined the effects of Epo on cell death–associated signaling components in the TNF-α–stimulated stem cells (Exp Cell Res 2009;315:2921-28). To determine how Epo in- terrupts the apoptotic cascade, the researchers studied several proteins involved in the complex pathways leading to cell death.

“Overall, Epo protected cells against the cytotoxic effects of TNF-α. We saw fewer changes in cell morphology and significantly reduced apoptosis in cell cultures treated with Epo before TNF-α exposure [see Figure],” says Rosalinda Madonna, MD, of The Center for Cardiovascular Biology and Atherosclerosis Research at UTHSC, the Institute of Cardiology at Gabriele d’Annunzio University in Chieti, Italy, and the Heart Failure Laboratory at THI at St. Luke’s, who was a lead researcher in the study. “More specifically, apoptosis requires cleavage of the caspase-3 protein into an activated form. We found that Epo decreases this cleavage step, potentially preventing caspase-3 activation.”

Another possible target for the protective effects of Epo is inducible nitric oxide synthase (iNOS), which is produced in response to proinflammatory cytokines. After infarction, excessive levels of iNOS in the heart lead to over-production of nitric oxide, which, in turn, increases apoptosis and inhibits cell differentiation. The THI investigators showed that Epo reduces TNF-α–induced iNOS activity, suggesting that Epo protects cells by regulating the intracellular expression of iNOS.

“After cytokine exposure, transcription of iNOS requires binding of the nuclear transcription factor NF-κB. So we isolated nuclear proteins from the cardiac myoblasts and studied the effect of Epo on the binding of NF-κB to the DNA for inflammatory gene expression,” explains Dr. Geng. “As expected, stimulation with TNF-α caused increased binding. However, overnight treatment with Epo reduced the binding of NF-κB to nuclear proteins, again supporting a regulatory role for Epo in iNOS expression.”

Finally, the researchers examined the mechanism by which Epo may prevent the translocation of NF-κB into the nucleus to initiate gene transcription. The inactive form of NF-κB is found in the cytoplasm, bound to inhibitory proteins such as IκB-α. After cytokine stimulation, IκB-α is rapidly phosphorylated, targeting it for degradation. Once IκB-α is degraded, NF-κB can translocate into the nucleus and activate iNOS transcription.

“We found that Epo treatment decreases the cytosolic accumulation of phosphorylated IκB-α in TNF-α–stimulated stem cells, thus reducing the amount of NF-κB that gets into the nucleus to trigger transcription of proapoptotic genes,” says Dr. Madonna. “Our in vitro study sets the stage for in vivo studies of Epo-induced cardioprotection. By attenuating postinfarction apoptosis, Epo may eventually be used to prolong the life of transplanted stem cells, improving the benefits of cell-based therapy.”

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Peripheral vascular disease (PVD) is characterized by blockage of circulatory flow in the arteries and veins. Because PVD may cause severe complications, prompt diagnosis is important. Sophisticated noninvasive vascular imaging techniques, such as ultrasonography or Doppler analysis, can detect PVD at an early stage, before devastating complications occur.

The Peripheral Vascular Laboratory at St. Luke's Episcopal Hospital (St. Luke's) is one of the foremost facilities in the United States for noninvasively diagnosing PVD and assessing the results of its treatment. The Laboratory was established in 1981 by George J. Reul, MD, who has remained its Medical Director ever since. Dr. Reul is also Associate Chief of Surgery at the Texas Heart Institute (THI) at St. Luke's and is Co-Director of the Peripheral Vascular Disease Service at THI at St. Luke's.

In 1994, the laboratory became one of the first such facilities in Texas to be accredited by the Intersocietal Commission for the Accreditation of Vascular Laboratories (ICAVL) for meeting that commission's high national standards for the noninvasive diagnosis of PVD. The laboratory recently received its fifth consecutive 3-year ICAVL accreditation.

“Originally, the laboratory was located in a single small room and was staffed by its first Technical Director, Susan Olson, BSRN, RVT, who used what would now be considered rather primitive, portable devices to visualize vascular anatomy at the patient’s bedside or in the outpatient clinic,” says Dr. Reul. “Today, we have 12 specially trained staff members, who perform nearly 10,000 peripheral vascular examinations per year with state-of-the-art equipment [see Figure]. These procedures help establish an accurate diagnosis, facilitate decision-making about treatment options, and provide follow-up assessment after treatment.”

Brenda Kazee, RVT, the present Technical Director, is a multi-modality sonographer who oversees the facility’s day-to-day operation.

“One of the most important examinations that we perform,” she explains, “is venous duplex imaging, which uses Doppler ultrasonography to detect deep venous thrombosis. This may result from trauma to an extremity or stasis from prolonged immobility or surgery. Venous ultrasonography can image the entire venous circulation from the upper groin to the small vessels in the calf, where blood clots usually manifest first. By detecting a clot early, physicians can prevent it from developing into a life-threatening complication such as a pulmonary embolism.”

“Other beneficiaries of our services include kidney failure patients who need to have an arteriovenous fistula created surgically to facilitate kidney dialysis,” adds Ms. Kazee. “By evaluating the vessels preoperatively, physicians can determine in advance the optimal type of vascular access for each patient.”

Another focus of the laboratory is carotid stent research. Staff members are following up patients postoperatively to gather information about the outcomes of carotid stenting, as well as stroke prevention in these patients.

Because of its high volume, the laboratory recently expanded to include 2 additional locations at outpatient centers (Kirby Glen and O’Quinn Towers). It also acquired 5 new ultrasound units (iU22 Ultrasound System; Philips Healthcare, Andover, MA), which offer the most up-to-date imaging technology available.

“We are one of the few vascular imaging laboratories to offer around-the-clock service,” says Ms. Kazee. “Our experienced personnel are available 24/7 for urgent requests, whether these requests come from the emergency room or from an inpatient source.”

“Our laboratory offers the most accurate noninvasive techniques available for the diagnosis and evaluation of PVD,” adds Dr. Reul. “Because of increased awareness of the consequences of PVD and the advancing age of our patients, the need for the laboratory’s services will increase even more in the future.”

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Comorbid Obesity and Renal Insufficiency Are Associated With Poorer Outcomes After Coronary Artery Bypass Grafting

Abstract: For patients who undergo coronary artery bypass grafting, concomitant obesity and renal insufficiency may increase the risk of postoperative myocardial infarction and other adverse outcomes.

Obesity is a risk factor for many diseases, including atherosclerotic coronary artery disease. This may be partially due to the fact that adipose tissue secretes adipokines and adipocytokines, which have elevated plasma levels in obese persons. Circulating levels of adipokines and adipocytokines also tend to be heightened in patients with chronic renal disease, probably because the disease slows the elimination of these substances from the bloodstream.

Because adipokines and adipocytokines are proinflammatory, and because inflammation is associated with adverse outcomes after coronary artery bypass grafting (CABG), Wei Pan, MD, staff cardiothoracic anesthesiologist at the Texas Heart Institute at St. Luke’s Episcopal Hospital (THI at St. Luke’s) and Assistant Professor of Anesthesiology at Baylor College of Medicine, and Charles D. Collard, MD, Chief of the Division of Cardiovascular Anesthesiology at THI at St. Luke’s and Professor of Anesthesiology at Baylor College of Medicine, and their colleagues theorized that CABG patients with concomitant obesity and chronic renal disease have a particularly high risk of adverse outcomes.

To test this hypothesis, the investigators reviewed the medical records of more than 10,000 patients who underwent isolated CABG with cardiopulmonary bypass at THI at St. Luke’s. Those with a body mass index (BMI) of 30 kg/m² or greater were classified as obese, and those with a BMI of 18.5 to 29.9 kg/m² were classified as non-obese. (Patients with a BMI of <18.5 kg/m² were deemed underweight and were excluded from the study.) Patients were considered to have preoperative renal insufficiency if diagnosed with renal insufficiency or failure before surgery, or if their serum creatinine level was 2.0 mg/dL or higher on the day of the operation; about 13% of both the obese and the non-obese patients met this criterion. The results of this study were published in the Journal of Thoracic and Cardiovascular Surgery (2009;138:873-9).

In patients without preoperative renal insufficiency, obesity was an independent predictor of postoperative sternal wound infection and leg wound infection but not of any other adverse perioperative outcomes examined (such as mortality, stroke, myocardial infarction, prolonged hospital stay, need for mediastinal reexploration, and ventilator dependence). In fact, obese patients were less likely than non-obese patients to have a postoperative stroke or need mediastinal reexploration.

“Our findings suggest that obesity and renal insufficiency have a synergistic deleterious effect on outcomes in CABG patients.”
—Wei Pan, MD, staff anesthesiologist

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THI at St. Luke’s Receives Grant for Combined Stem Cell and Heart Assist Device Therapy

THI at St. Luke’s recently received a grant for $1.5 million from the National Institutes of Health for a Cardiac Translational Research Implementation Program (CTRIP). This grant will fund a study that THI investigators hope will ultimately result in the use of combined mesenchymal stem cell (MSC) and left ventricular assist device (LVAD) therapy to treat patients with end-stage heart failure. The THI team, led by Igor Gregoric, MD, Biswajit Kar, MD, and Emerson C. Perin, MD, PhD, believes that combination therapy may enhance myocardial recovery in some bridge-to-transplant or destination-therapy patients, leading to removal of the device without a need for transplantation or further device support.

Patients who undergo LVAD implantation as a bridge to transplantation also provide a unique opportunity for studying the possible mechanisms of myogenesis and angiogenesis involved in cell transplantation. Direct injection of MSCs into the heart at the time of LVAD implantation will allow histologic and immunologic study of the effects of cell therapy in the explanted hearts of patients who later undergo transplantation. These findings may help determine which therapies have the greatest potential for enhancing regional blood flow and improving myocardial function.

The grant provides funding for the 2-year Stage 1 CTRIP program, during which THI investigators will develop the best techniques for mapping target sites for injection and for delivering stem cells in a sheep model of heart failure with an implanted LVAD. This effort and other preliminary work will be used to complete an Investigational New Drug application for a clinical study, which would be conducted after approval of a Stage 2 application.
Approval of the HeartMate II LVAS for Destination Therapy Broadens the Patient Population Eligible for Treatment

Abstract: The HeartMate II Left Ventricular Assist System was recently approved for destination therapy in patients with advanced heart failure who are not eligible for heart transplantation.

In January 2010, the HeartMate II Left Ventricular Assist System (Thoratec Corporation, Pleasanton, CA), a second-generation blood pump that has undergone extensive laboratory and clinical testing at the Texas Heart Institute at St. Luke’s Episcopal Hospital (THI at St. Luke’s), received US Food and Drug Administration (FDA) approval for use as destination therapy. (The same device was approved for use as a bridge to transplantation in April 2008.) This approval allows the HeartMate II to be used in patients with New York Heart Association (NYHA) class IIIB or IV end-stage left ventricular heart failure who have received optimal medical therapy for at least 45 of the previous 60 days and who are not candidates for cardiac transplantation. The approval was granted partially on the basis of data from a 2-year, randomized study involving 200 patients enrolled at 38 centers, including THI at St. Luke’s, comparing the continuous-flow HeartMate II with the pulsatile-flow HeartMate vented electric (XVE) left ventricular assist device (N Engl J Med 2009;361:2241-51). O. H. Frazier, MD, Director of the Center for Cardiac Support at THI at St. Luke’s, has been involved since the 1980s with the development of both the HeartMate II and the HeartMate XVE and was one of the investigators for the multicenter collaborative study.

“I implanted the first of these pumps in November 2003, and I now have more than 65 patients who are pursuing normal lives while being supported by the HeartMate II,” says Dr. Frazier. “This pump has become so widely used that more than 2000 patients worldwide are currently supported by it on an outpatient basis.”

One important finding of the collaborative study was that more than 2000 patients worldwide are currently supported by it on an outpatient basis.”

One important finding of the collaborative study was that more than 2000 patients worldwide are currently supported by it on an outpatient basis.”

HeartMate II recipient Allyssa Smith and Dr. O. H. Frazier at the 2010 Denton A. Cooley Leadership Award dinner. The HeartMate II’s system controller, usually worn in a shoulder holster or a waist pack, is inconspicuously hidden in Ms. Smith’s purse.

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Denton A. Cooley Cardiovascular Surgical Society and Michael E. DeBakey International Surgical Society to Hold Historic First Joint Meeting

This June 10-13, the 17th Symposium of the Denton A. Cooley Cardiovascular Surgical Society and the 18th Congress of the Michael E. DeBakey International Surgical Society will be held as a single joint meeting. Program Directors Denton A. Cooley, MD, and Joseph S. Coselli, MD, have invited 32 expert faculty to speak in 6 sessions dealing with a variety of topics in cardiothoracic surgery. Francisco G. Cigarroa, MD, Chancellor of the University of Texas System, will give the keynote address; other special sessions will feature prominent thoracic surgeons Kenneth L. Mattox, MD, and W. Roy Smythe, MD, and biomedical ethicist Baruch A. Brody, PhD. For the complete program, visit www.texasheart.org/cme.
Calendar of Events

TEXAS HEART INSTITUTE CONTINUING MEDICAL EDUCATION SYMPOSIA

Joint Session
Denton A. Cooley Cardiovascular Surgical Society 17th Symposium
Michael E. DeBakey International Surgical Society 18th Congress
Barton Creek Conference Center
June 10–13, 2010 • Austin, Texas
Program Directors: Denton A. Cooley, MD, and Joseph S. Coselli, MD
www.cooleysociety.com
www.mediss.org/inmemoriam.html

SELECTED UPCOMING LOCAL, NATIONAL, AND INTERNATIONAL MEETINGS

American Surgical Association 130th Annual Meeting
April 8–10, 2010 • Chicago, Illinois
www.americansurgical.info

International Society for Heart and Lung Transplantation 30th Anniversary Meeting and Scientific Sessions
April 21–24, 2010 • Chicago, Illinois
www.ishlt.org

Society of Cardiovascular Anesthesiologists 32nd Annual Meeting and Workshops
April 24–28, 2010 • New Orleans, Louisiana
www.scahq.org

American Association for Thoracic Surgery 90th Annual Meeting
May 1–5, 2010 • Toronto, Ontario, Canada
www.aats.org

Heart Rhythm Society 31st Annual Scientific Sessions
May 12–15, 2010 • Denver, Colorado
www.hrsonline.org

Western Thoracic Surgical Association 36th Annual Meeting
June 23–26, 2010 • Ojai, California
www.westernthoracic.org

American Society of Echocardiography 21st Annual Scientific Sessions
June 12–15, 2010 • San Diego, California
www.asecho.org

International Society for Stem Cell Research 8th Annual Meeting
June 16–19, 2010 • San Francisco, California
www.isscr.org

For information about Texas Heart Institute CME activities, please e-mail cme@heart.thi.tmc.edu or call 832.355.2157. To view or complete selected online CME courses (certificates are available online), please visit www.texasheart.org/cme. New courses are added regularly.

For 19 consecutive years, the Texas Heart Institute at St. Luke’s Episcopal Hospital has been ranked among the top 10 heart centers in the United States by U.S. News & World Report’s annual guide to “America’s Best Hospitals.”