HeartWATCH

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A Newsletter Produced by the Texas Heart Institute

Texas Heart® Institute

at St. Luke's Episcopal Hospital

Cellular Housekeeping May Underlie Reverse Remodeling of Mechanically Supported Failing Hearts

Abstract: Reverse remodeling of mechanically unloaded hearts may involve a novel balance between protein synthesis and degradation in cardiomyocytes.

Mechanical unloading of the failing heart with a left ventricular assist device (LVAD) has become an accepted clinical practice. LVADs are now used for short-term support of patients in cardiogenic shock, as bridges to transplantation, and as destination therapy. Another evolving use for LVADs is bridging to recovery.

An LVAD eases the work of the failing heart by decreasing the blood pressure, heart rate, cardiac output, and cardiac size. This results in ventricular remodeling, which is sometimes maintained even after the LVAD is removed. Numerous investigators have noted reverse remodeling in patients with advanced dilated cardiomyopathy whose hearts have been mechanically supported long-term, thus challenging the common notion that end-stage heart failure is irreversible and must end in death or transplantation.

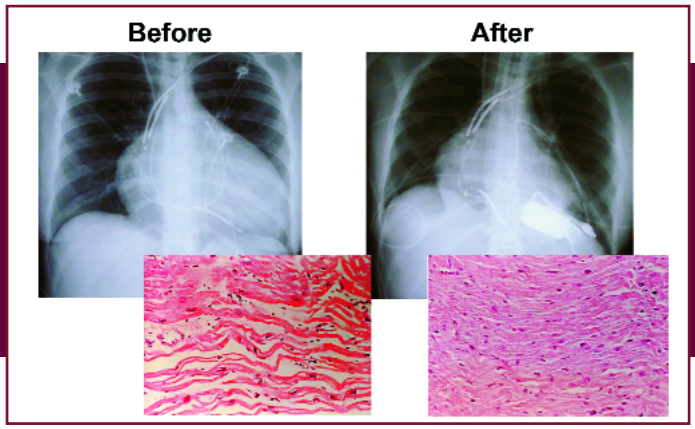
Although the biological mechanisms responsible for reverse remodeling and improved myocardial function are still unclear, many investigators believe that these mechanisms involve adaptive responses inside and outside individual cardiomyocytes. LVAD-supported hearts have been shown to undergo changes in the expression of key regulators of myocyte morphology, extracellular matrix, calcium homeostasis, energy metabolism, inflammation, and programmed cell death (*Cardiology* 2002;98:167–74).

Researchers affiliated with the Texas Heart Institute at St. Luke's Episcopal Hospital (THI/SLEH) have been using a rat model of atrophic cardiac remodeling involving heterotopic or "piggyback" transplantation to search for novel gene and protein expression pathways that may facilitate reverse remodeling. Leading the team is Heinrich Taegtmeyer, MD, DPhil, a research scientist at THI/SLEH and co-director of the division of Cardiology at The University of Texas Medical School at Houston. One hypothesis behind the team's work is that mechanical support of enlarged failing hearts for long periods induces signaling pathways that ultimately regulate the turnover of 2 proteins important to cellular health: ubiquitin and the so-called mammalian target of rapamycin (mTOR) (*Circulation* 2003;108:2536–41).

"Ubiquitin is a protein that basically cleans the cellular house by trashing defective, unneeded, or unwanted proteins," says Peter Razeghi, MD, a cardiology fellow at THI/SLEH and a research scientist on Dr. Taegtmeyer's team. "mTOR tidies up the cells by helping to restore proteins necessary for cell survival and remodeling. We believe that an intricate balance between the expression of these 2 proteins, which is lost in the cardiomyopathic heart but regained in the mechanically unloaded heart, creates a feedback mechanism that prevents cardiomyocytes from shrinking too much and dying, thus controlling heart size."

To confirm their findings in the rat model, Dr. Taegtmeyer and his colleagues are now testing their hypothesis in tissue samples taken from failing human hearts before and after LVAD support.

"Even under normal conditions, muscle is destroyed and rebuilt all the time," notes Dr. Taegtmeyer. "What our findings in the rat model show, and what our findings in the human heart samples should confirm, is that this is also true under the abnormal conditions presented by the enlarged failing heart. If the cardiac muscle is stressed or given a chance to rest, the cycle of destruction and rebuilding changes accordingly."



Chest radiographs (top) and histologic specimens of myocardial cells (bottom) before and after LVAD support in a patient with cardiomyopathy. Note the decrease in both heart and myocardial cell size with support.

"Teasing out the molecular and cellular processes involved in reverse remodeling is difficult and tedious but worthwhile," says Dr. Taegtmeyer. "Once identified, however, those processes can conceivably be targeted. This gives hope that, one day, targeted medical therapies might be developed that can prod failing hearts into remodeling themselves without the need for an implanted device." ●

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Heart Failure Center Offers Gamut of Treatment Options for Chronic Heart Failure

Abstract: Besides offering patients control over their own cardiovascular health, the heart failure center at THI/SLEH also delivers cutting-edge therapies when heart failure worsens.

Regardless of heart failure's underlying cause—usually coronary artery disease, cardiomyopathy, hypertension, or valve disease—the end result is the same. Even with treatment, the affected heart may grow progressively larger and beat progressively faster until it can no longer pump enough blood throughout the body. Ultimately, fluids begin to back up into the lungs and other tissues, leading to a cascade of cardiovascular, renal, and other problems.

Approximately 5 million Americans have chronic heart failure, and over half a million new cases are added each year. Those who seek treatment at the Texas Heart Institute at St. Luke's Episcopal Hospital (THI/SLEH) enter the Heart and Lung Transplant and Treatment Center's heart failure program, which, since its establishment in 1997, has reduced unnecessary hospitalizations and medical costs while significantly improving quality of life.

"The primary goal is to teach our patients to recognize their symptoms, use their medications to best effect, and make healthy lifestyle choices, all in the hope of keeping them out of the hospital, leading productive lives," says Frank Smart, MD, cardiologist and director of Advanced Heart Failure/Cardiac Transplantation at THI/SLEH. "But when these efforts are no longer effective, we are equipped to offer other cutting-edge treatment options designed to ease the workload of the failing heart."

Besides maintaining its world-renowned transplant program and conducting high-profile trials such as the ongoing AbioCor total artificial heart feasibility study and the stem cell therapy trial recently approved by the Food and Drug Administration (FDA), the center is involving its patients in a number of other innovative studies. One concerns an oral recombinant atrial natriuretic peptide (ANP) called caperitide. This drug, already approved for use in Japan, belongs to a novel class of powerful, naturally occurring vasodilators and diuretics called natriuretic peptides. In the United States, only the brain-derived form of natriuretic peptide is approved by the FDA for clinical use.

Greg Poulin, RN, reviews a treatment plan with a patient in the Heart and Lung Transplant and Treatment Center.

"In heart failure patients, the blood, atria, and ventricles usually produce more ANP than normal, which suggests that ANP helps the failing heart compensate for its increased workload," says Dr. Smart. "If oral caperitide can be shown to heighten this compensatory effect, it will become an important addition to the medical armamentarium against heart failure."

Also underway is a multicenter medical trial concerning the chronic inflammation that contributes to heart failure. The idea is that cardiac function may be improved by subjecting blood cells from heart failure patients to oxidative stress. Once a month, a 10-mL sample of blood is drawn, mixed with a small amount of oxygen and ozone to stimulate the production of anti-inflammatory substances, and then injected back into the patient.

"A preliminary clinical study of this experimental immunomodulatory therapy has already shown that it can safely and effectively reduce hospitalizations and deaths and improve quality of life," says Dr. Smart. "The worst side effect appears to be infection at the injection site."

The center is also conducting trials of cardiac resynchronization therapy in patients whose failing hearts are so electrically incompetent that no amount of medical therapy can help them respond to the cardiovascular demands of normal daily activities such as exercise.

Meanwhile, the heart failure program continues to build on THI/SLEH's decades of experience in the development and use of implantable ventricular assist devices by actively conducting trials of second-generation devices. In 2 such studies, continuous-flow left ventricular assist devices—the HeartMate II (Thoratec Corp., Pleasanton, CA) and the Jarvik 2000 (Jarvik Heart, Inc., New York, NY)—are being used as bridges to transplantation. Both of these small, relatively quiet pumps have enhanced the quality of life of recipients by reducing infections and other complications, even permitting some patients to return home to await a transplant.

"What we primarily offer our patients is greater control over their own cardiovascular health," says Dr. Smart. "Whenever it careens beyond their control, we are ready to provide a continuity of care that is unmatched in scope and unsurpassed in expertise." ●

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Contents

Surgical and Endovascular Interventions for Brachiocephalic Artery Disease

Abstract: Surgical and endovascular interventions for brachiocephalic artery disease are associated with similar short-term outcomes, but the surgical approach may offer better long-term effectiveness.

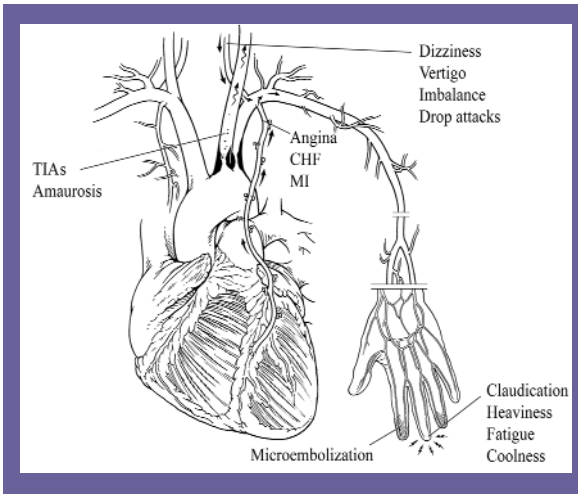
At the sites where the brachiocephalic arteries (i.e., the brachiocephalic, or innominate, artery; the subclavian arteries; and the common carotid arteries) arise from the aortic arch, atherosclerosis can restrict blood flow to the head and upper extremities. Though less common than coronary or carotid atherosclerosis, brachiocephalic disease (BCD) can cause strokes, transient ischemic attacks (TIAs), vertigo, fainting, cognitive problems, visual disturbances, or cramps and weakness in the arm, depending on the site and severity of the blockage and on the development of collateral circulation.

"Once we suspect BCD," says Denton A. Cooley, MD, president and surgeon-in-chief of the Texas Heart Institute at St. Luke's Episcopal Hospital (THI/SLEH), "we can use several tests—including ultrasonic duplex scanning before and after arm exercise, and standard radiographic techniques, with positional change when necessary—to confirm the diagnosis and to determine the location and extent of the patient's lesions."

With this information, surgeons and cardiologists can then decide what treatment approach to take.

"The choice of intervention for BCD depends mainly on the extent of the disease and the character of the lesion," explains George J. Reul, MD, associate chief of Surgery at THI/SLEH, who has performed hundreds of operations to revascularize blocked brachiocephalic arteries. "In patients with multivessel BCD, surgical bypass grafting is necessary to restore blood flow. However, if the lesion is simple, non-ulcerated, and confined to one artery, then either surgical bypass or percutaneous angioplasty and stenting with embolic protection can be used."

For patients with multivessel BCD, surgery is usually performed through either a transthoracic or an extrathoracic approach. Transthoracic techniques involve direct revascularization with bypass grafts from the ascending aorta to the stenotic arteries. This is typically done via a median sternotomy or a thoracotomy, although minimally invasive incisions for complete revascularization from the ascending aorta to its arch vessels are gaining in popularity. On the other hand, extrathoracic surgery involves performing an arterial bypass without entering the thorax itself, utilizing aortic arch vessels as inflow sites.



Brachiocephalic disease can cause a variety of symptoms, depending on the location and severity of the blockage. CHF, congestive heart failure; MI, myocardial infarction; TIA, transient ischemic attack.

A recent review of 157 multivessel BCD operations performed at THI/SLEH over the past 35 years has shed some light on the advantages and disadvantages of each approach.

"The transthoracic approach is more invasive," says Dr. Cooley, "so it may cause greater morbidity, and other institutions have associated it with high rates of postoperative mortality. However, our series had a low 30-day mortality for both the 113 patients who had transthoracic surgery (2.7%) and the 44 patients who had extrathoracic procedures (2.3%). Furthermore, the 10-year patency rate was 94% with the transthoracic approach versus 60% with the extrathoracic approach."

To explore the relative effectiveness of surgical and endovascular approaches to single-vessel BCD, the results of 229 open surgical procedures and 169 endovascular interventions performed over the same period were compared.

"Endovascular treatment is obviously less invasive than surgery," says Dr. Reul, "and our review showed that it is somewhat less expensive—about $8800 less per initial procedure. The 30-day mortality was less than 1% for both the surgical and the endovascular patients. However, the 5-year patency rate was 92.7% for the patients who had surgical repair but only 83.9% for the patients who had endovascular repair."

Drs. Cooley and Reul say that the results of the 2 studies are not surprising.

"The trade-off between invasiveness and long-term patency is a recurrent theme in the vascular literature," Dr. Cooley explains. "Whether you're dealing with the brachiocephalic arteries, the coronary arteries, or the carotid arteries, more invasive techniques allow more complete revascularization and promote greater patency. However, given the undeniable advantages of less invasive procedures, choosing the best treatment is still very much a matter of what will work best for each particular patient." ●

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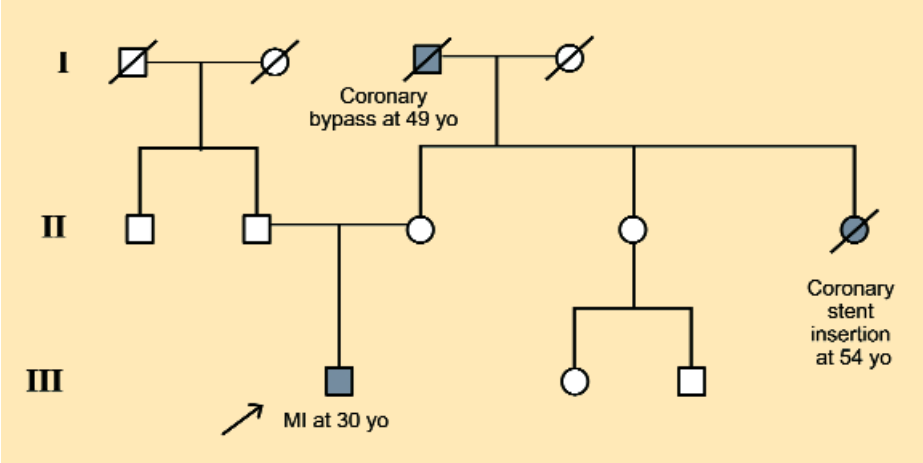
Genetics Project Underway to Examine Familial Clustering of Premature Myocardial Infarction

Abstract: Clinical researchers at THI/SLEH have begun gathering genetic and demographic data for investigations into the familial clustering of premature myocardial infarction.

According to the American Heart Association, an estimated 700,000 Americans suffer a first myocardial infarction (MI) each year. In 5–10% of cases, the MI is considered premature because it occurs in a patient less than 50 years old. While medical treatment of acute MI has improved in recent years, the morbidity and mortality remain high. Moreover, it is now clear that traditional cardiovascular risk factors such as tobacco use, diet, exercise, age, and hypertension cannot explain all cases of MI or the coronary artery disease that often underlies it and that genetic risk factors must be involved as well.



Representative family tree of a patient who has had a premature myocardial infarction.

"The normally functioning heart expresses certain genes and proteins that are essential for its health and optimal performance," says James T. Willerson, MD, director of Cardiology Research and president-elect of the Texas Heart Institute at St. Luke's Episcopal Hospital (THI/SLEH). "These include genes that raise high-density lipoprotein levels, prevent programmed cell death, prevent blood clots, and prevent restenosis after stenting. Any disruption of their normal expression may induce coronary disease, so it is very important to understand the genetics and resulting protein activity associated with this disease."

For over 2 years now, Dr. Willerson and other clinician researchers at THI/SLEH have been actively involved in the search for genetic risk factors in patients with cardiovascular disease, especially premature MI. This work has been conducted as part of the Texas Medical Center Genetics (TexGen) project, which was launched in 2001 by a consortium of institutions in the Texas Medical Center (TMC), including The University of Texas Health Science Center at Houston, The University of Texas M. D. Anderson Cancer Center, and Baylor College of Medicine, to encourage and facilitate genetic and medical research on cancer, cardiovascular disease, and stroke. The ultimate aim of the project is to build and maintain a repository of genetic, clinical, and demographic data from the approximately 50,000 patients treated for these diseases at the TMC each year.

In the fall of 2002, THI/SLEH became the first of several TMC hospitals to begin collecting TexGen-related blood samples for laboratory tests and DNA analysis, as well as demographic and lifestyle information, from patients with cardiovascular disease. Early on, Dr. Willerson and his group began to focus on patients who had had a premature MI; this has led to a substudy concerned with the clustering of premature MI among the parents and siblings of those patients.

"A family history of premature coronary artery disease is a known risk factor for a heart attack," says Dr. Willerson. "Therefore, the data we are gathering should prove useful in devising strategies for predicting and theoretically preventing a premature MI in individuals with clinically asymptomatic coronary artery disease."

So far, more than 80 patients treated for premature MI at THI/SLEH have been recruited for this familial clustering study, and contacts are being initiated with their first- and second-degree relatives. Meanwhile, more potential participants are being recruited prospectively from the approximately 50 patients with cardiovascular disease who continue to be enrolled in the original TexGen project at THI/SLEH each week. All enrolled patients and family members will be followed up 1 year after entering the study.

"Several genes that may contribute to heart attacks and strokes have been identified in groups of unrelated patients," notes Dr. Willerson, "but it is important to begin gathering our familial clustering data now in order to show within the next few years which of these genes are operative in families. In the battle against cardiovascular disease, we must use the genetic information we acquire in these studies to develop new molecular weapons that will lead to the prevention of heart attacks and strokes in patients at increased risk." ●

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Vaccine Shortage Offers Unique Chance to Study Public Awareness and Cardiovascular Benefits of Flu Vaccination

Abstract: This year's uncertain supply of flu vaccine offers a unique chance to study vaccination's effects on flu-related cardiovascular complications and on public awareness of its cardiovascular benefits.

In the past few years, researchers have accumulated substantial evidence that influenza can cause serious long-term complications, including the acute (and often fatal) complications of atherosclerosis such as heart attack and stroke. Analyses of 20th-century disease patterns have suggested that increased influenza activity is generally followed by increased cardiovascular morbidity and mortality.

A leading expert on the cardiovascular effects of influenza is Mohammad Madjid, MD, a senior research scientist at the Texas Heart Institute at St. Luke's Episcopal Hospital. He and his colleagues have found that up to a third of myocardial infarctions are preceded by an upper respiratory infection. Such infections tend to occur during the winter months, usually peaking in February.

"For many individuals, especially the elderly, winter is a vulnerable period, owing to an increased incidence of heart attacks and arrhythmias," says Dr. Madjid. "Influenza activity has been suggested as an explanation for this phenomenon. Our group has shown that in patients with coronary artery disease, a flu shot reduces the risk of a myocardial infarction during the subsequent influenza season by 67%."

Dr. Madjid has worked to raise public awareness of the cardiovascular benefits of an annual flu shot. However, now that this message has begun to get out, uncertainty about the supply of vaccine available this flu season may have kept many patients from following the best medical advice.

"The projected shortage of vaccine arose from contamination at the Liverpool, England–based vaccine manufacturing facility of Chiron Corporation, 1 of only 2 companies licensed to provide inactivated influenza vaccine to the US," says Dr. Madjid. "The affected vaccine stock represented a supposed 46–48 million doses, or about half of this season's US supply. Because flu vaccines take almost an entire year to develop, manufacture, and distribute, it was too late to simply make more."

At first, the available vaccine was being limited to high-risk groups (*JAMA* 2004;292: 2206), specifically children aged 6–23 months and persons older than 65 years; pediatric patients (aged 6 months to 18 years) receiving long-term aspirin therapy; anyone else with a chronic underlying medical condition (including heart disease); women who would be pregnant during the flu season; nursing-home and long-term care communities; persons caring for babies younger than 6 months old; and health care personnel with direct patient contact. However, as governmental agencies began to obtain vaccine from other sources, the supply began to increase, and the demand paradoxically decreased.

"The main advantage of vaccination is not a decrease in the overall number of uncomplicated flu cases," Dr. Madjid adds, "but rather a decrease in flu-related hospitalizations and deaths. Therefore, we would expect the latter to increase in the face of this year's shifting supply and demand."

Because the flu virus is spread mainly through coughing and sneezing, the risk of infection is reduced by avoiding close contact with flu victims, washing the hands frequently, and refraining from touching the nose and mouth.

"For unvaccinated persons who do get the flu," says Dr. Madjid, "help is available from the antiviral prescription drugs amantadine, rimentadine, zanamavir, and oseltamivir. If taken within 2 days after exposure to the virus, these agents (especially oseltamivir) can reduce symptoms and shorten the duration of the flu."

Although the vaccine shortage has raised concerns, it offers unique research opportunities.

"We had already conducted a national telephone survey of 1,200 persons before the projected shortage became apparent, and we are now conducting another," says Dr. Madjid. "By comparing the before and after data, we can assess the effects of the shortage on the public's attitudes toward flu vaccination and awareness of its cardiovascular benefits. Also, when the epidemiological data become available, we should also be able to compare the flu-related morbidity and mortality this year with those in previous years when the supply of vaccine was not in doubt." ●

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View the CME Archives Online

Selected Texas Heart Institute–sponsored physician education programs are now available for viewing online. To visit, go to www.texasheartinstitute.org/cmeonline.html.

New presentations will be added on a regular basis. The following are now available:

- **The Implantable Left Ventricular Assist Device: From Concept to Clinical Reality** (from Houston, May 21–22, 2004)
- **Advancing the Standard of Care: New Perspectives, New Approaches** (from New Orleans, March 6, 2004)
- **Mechanical Support of the Failing Heart for the Cardiologist** (from New Orleans, March 6, 2004)
- **5th Symposium on Cardiac Arrhythmias: New Pharmacologic and Interventional Strategies** (from Houston, February 14, 2004)
- **Advancing the Standard of Care: Exploring New Frontiers** (from Orlando, November 8, 2003)

Sleep Centers May Benefit Cardiovascular Patients Who Experience Sleep Apnea

Abstract: As evidence grows for a link between sleep apnea and cardiovascular disease, sleep centers are poised to benefit at-risk patients through diagnosis and treatment.

As the overall US population grows older and more obese, diagnoses of sleep apnea and cardiovascular disease are on the rise, and evidence continues to suggest that these conditions may be intimately linked (*Mayo Clin Proc* 2004;79:1036–46; *Minerva Med* 2004;95:257–80).

"Both obesity and sleep apnea increase the risk of cardiovascular morbidity and mortality," says Clinton H. Doerr, MD, ABSM, a pulmonologist in the department of Pulmonary Diseases at St. Luke's Episcopal Hospital (SLEH) and a sleep specialist in SLEH's Sleep Center. "This combination may be deadly, especially for obese men with congestive heart failure, who have a high prevalence of abnormal breathing during sleep."

Associations between sleep disturbances, obesity, and cardiovascular events have been well documented in the longitudinal Wisconsin Sleep Cohort Study (*N Engl J Med* 2000;342:1378–84). Patients with obstructive sleep apnea had a 1.5-fold higher rate of myocardial infarction, arrhythmia, heart failure, and stroke than did those without such apnea. In addition, patients with moderate-to-severe sleep apnea were 3 times more likely to become hypertensive than were those with less severe apnea.

"In reality, apnea-related hypertension may be even more prevalent than once thought," says Dr. Doerr, "since the threshold for diagnosing and treating sleep apnea has been lowered in recent sleep medicine guidelines."

Patients with hypertension, obesity, and cardiovascular disease who may also have sleep apnea are often referred to sleep centers like the one at SLEH. Established 12 years ago, SLEH's Sleep Center currently has 3 sites—1 in the Texas Medical Center and 2 others in the outlying community—that feature advanced diagnostic facilities and a wide range of equipment for treating sleep disorders.

Sleep apnea requiring treatment is diagnosed on the basis of a supervised sleep study that lasts for at least 2 hours. Treatment may be warranted if apnea or hypopnea occurs at least 15 times per hour. In patients with documented hypertension, ischemic heart disease, a history of stroke, or symptoms of apnea (i.e., excessive daytime sleepiness, cognitive impairment, mood disorders, or insomnia), this threshold is lowered to 5 or more occurrences per hour.

Detail of a sleep-study polysomnogram showing an instance of obstructive sleep apnea in a heart failure patient.

"Currently, the standard treatment for sleep apnea is the application of continuous or bilevel positive airway pressure, commonly known as CPAP or BiPAP, respectively, through a mask worn over the nose during sleep," says Dr. Doerr. "In congestive heart failure patients, CPAP may improve cardiac function and other outcomes by increasing intrathoracic pressure and lowering the afterload, thereby enhancing optimal drug therapy. CPAP may also decrease the sympathetic drive associated with apneic events, thereby decreasing mean and systolic blood pressures."

"Despite optimal therapy, many patients with severe heart failure continue to experience shortness of breath, poor sleep, and daytime fatigue," says Mark J. Schnee, MD, a cardiologist at the Texas Heart Institute at SLEH who sees a number of obese patients in his clinical practice and refers many of them to the Sleep Center. "Also, as recent studies have shown, patients with arrhythmia or atrial fibrillation may have similar problems, particularly during exercise if they are obese. All such patients may benefit from a sleep study."

"Hypertensive patients who have effort-induced shortness of breath or blood pressure that is poorly controlled despite multiple drug therapy may see their sleep and blood pressure improve with CPAP," adds Dr. Doerr.

"Given the prevalence of obesity, hypertension, cardiovascular events, and sleep apnea in the general population," concludes Dr. Schnee, "cardiac patients with sleep-disordered breathing should be strongly considered for evaluation by a certified sleep specialist." ●

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Cover: Detail of vase donated by Bering's for the Celebration of Hearts display in the Wallace D. Wilson Museum of the Texas Heart Institute at St. Luke's Episcopal Hospital—The Denton A. Cooley Building.

Calendar of Events

Texas Heart Institute Continuing Medical Education Symposia

Texas Heart Institute Sixth Symposium on Cardiac Arrhythmias

New Pharmacologic and Interventional Strategies
February 19, 2005 • Houston, Texas
Program Director: Ali Massumi, MD

American College of Cardiology 54th Annual Scientific Session Satellite Symposium

Current Issues in Cardiology
March 5, 2005 • Orlando, Florida
Program Directors: James J. Ferguson III, MD; James T. Willerson, MD; R. David Fish, MD

Texas Heart Institute Advances in the Treatment of Cardiovascular Disease

April 22–23, 2005 • South Padre Island, Texas
Program Director: Reynolds M. Delgado III, MD

The Society for Cardiovascular Angiography and Intervention 28th Annual Scientific Sessions Satellite Symposium

Stem Cell Therapy for the Treatment of Heart Disease
May 7, 2005 • Ponte Vedra, Florida
Program Directors: Emerson C. Perin, MD, PhD; Guilherme V. Silva, MD

Selected Upcoming National and International Meetings

American College of Cardiology 54th Annual Scientific Session

March 6–9, 2005 • Orlando, Florida

International Society for Heart and Lung Transplantation 25th Annual Meeting and Scientific Sessions

April 6–9, 2005 • Philadelphia, Pennsylvania

American Heart Association Scientific Sessions 2005

November 13–16, 2005 • Dallas, Texas
Abstract submission begins: March 15, 2005
Abstract submission ends: May 27, 2005

For information about the CME activities listed above, please e-mail cme@heart.thi.tmc.edu or call 832.355.2157. To view selected CME presentations and other physician resources online, please visit www.texasheartinstitute.org/doctors1.html.

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