MAYO CLINIC

CardiovascularUpdate

Clinical Cardiology and Cardiovascular Surgery News Vol. 10, No. 2, 2012

INSIDE THIS ISSUE

Taking Research to New Heights on Mount Everest

Bruce D. Johnson, PhD

Extreme altitude in many ways simulates the same conditions experienced by patients with heart failure. To that end, Bruce D. Johnson, PhD, a physiologist in the Cardiovascular Health Clinic at Mayo Clinic in Rochester, led a team of Mayo Clinic cardiac researchers to the Mount Everest base camp in April 2012 to perform sophisticated, high-altitude physiologic research (Figure 1). The base camp is located at approximately 18,000 feet, much higher than any mountains in North America. The expedition was cosponsored by *National Geographic*, The North Face, and Montana State University.

Prior to their departure, the Mayo Clinic team performed baseline testing on the expedition climbers. They carried 1,300 pounds of scientific equipment to the base camp.

"The climbing on Mount Everest was difficult this year because of the lack of snow," said Dr

Figure 1. *The Mayo Clinic team ascending to the Mount Everest base camp.*

Johnson. "The team had to deal with falling ice and avalanches."

Data obtained during the trip will be analyzed and compared to data from healthy adults at sea level and heart failure patients (Figure 2).

Sleep Physiology

The periodic breathing experienced by climbers at high altitudes at night simulates sleep-disordered breathing found in many obese individuals and heart failure patients. Oxygen saturation studies were conducted on the climbers during sleep and correlated with sleep quality and external environmental factors. The Mayo team members and the climbers noted frequent awakening during the night, gasping for air due to hypoxia and sleep apnea.

High-Altitude Muscle Loss

Prior studies have demonstrated that climbers lose weight rapidly at high altitude, primarily muscle mass and not fat, irrespective of caloric intake. This same phenomenon is observed in patients with heart failure and other chronic diseases. It is hypothesized that nocturnal hypoxia contributes to this loss of muscle mass. The team traced caloric intake, body mass composition, sleep hypoxia, and sleep quality during the climb. "All of the team members experienced appetite loss and nausea during the expedition," said Dr Johnson.

Pulmonary Edema

High-altitude pulmonary edema has been observed for decades in certain individuals at altitude. The pathophysiology is unclear, mechanisms may have similarities to those noted in patients with heart failure. During the climb, researchers measured pulmonary pressures, and pulmonary gas exchange. One of the *National Geographic* photographers had to be evacuated during the trip because of the development of dyspnea thought to be related to pulmonary edema or pulmonary embolism.

In addition to obtaining physiology data, the Mayo Clinic team tested the performance of monitoring equipment at high altitude. Dr Johnson has lead prior research expeditions to Mount Aconcagua, Argentina, and the South Pole.

Figure 2. *A summary of physiologic changes noted at high altitude.*

RECOGNITION

Stephen L. Kopecky, MD, is the 2012 president of the American Society for Preventive Cardiology. Dr Kopecky is a cardiologist at Mayo Clinic in Rochester and works in Mayo Clinic's Cardiovascular Health Clinic. He has written numerous articles for peer-reviewed journals and has received multiple "Teacher of the Year" awards from Mayo's Division of Cardiovascular Diseases and Department of Internal Medicine. His research interests include the role of inflammation in cardiovascular disease and the role of lifestyle, including diet, exercise, and proper nutrition, in the prevention of cardiovascular disease.

Combined Heart-Liver, Heart-Kidney, and Heart-Liver-Kidney Transplantation at Mayo Clinic in Rochester: A Unique Experience

Following the reports of the first simultaneous combined heart and kidney transplantation (CHKTx) in 1978 and combined heart and liver transplantation (CHLTx) in 1985, both have become viable therapeutic solutions in the treatment of dual vital organ failure. Since 1987, reports to the United Network for Organ Sharing (UNOS) indicate that CHKTx has been performed in 722 patients, and through 2009, CHLTx was performed in 78 patients at 21 centers (only 8 centers with more than 2 cases). Through 2009, combined heart, liver, and kidney transplantation was reported in only 6 patients.

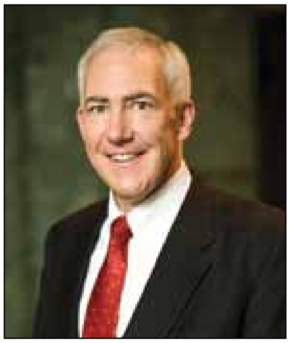
The Heart Transplantation Program at Mayo Clinic in Rochester started in June 1988, and 446 heart transplantations have been performed to date; 46 (10.3%) were multiple organ transplants involving the kidney, liver, or both. Twenty-two procedures were CHLTx procedures, 21 were CHKTx procedures, and 3 were combined heart-liver-kidney transplants. Each of these series represents the largest collection of such procedures performed by a single institution. The frequency of these multiple organ transplants has been increasing over time, with 41 of the 46 procedures being performed since 2000 (Figure 1). Furthermore, of the 91 patients who are currently on the heart transplant waiting list, 16 are listed for multiple organs, 8 are listed for combined heart-liver and 8 are listed for combined heart-kidney. Additionally, combined heart-lung and heart-lung-liver have been performed in a few instances, but are not included in this update.

Overall survival after heart transplantation alone at Mayo Clinic in Rochester since 1988 is 93% at 1 year, 81% at 5 years, and 65% at 10 years (Figure 2). Over the same time period, the Mayo outcomes were superior to survival reported by UNOS and the International Society of Heart and Lung Transplantation (ISHLT) at 1 year (UNOS: 89%; ISHLT: 82%) and 3 years (UNOS: 80%; ISHLT: 75%). Outcomes of specific combined organ transplants are presented below.

Combined Heart-Liver Transplantation

The most common indication for CHLTx is familial amyloidosis (FA), a fatal autosomal-dominant disease caused by deposition of an abnormal mutant protein, transthyretin. FA is associated with progressive peripheral and autonomic neuropathy and dysfunction of the cardiac, gastrointestinal, and urinary systems. The prognosis for symptomatic cardiac amyloidosis is poor, with a median survival of 6 months after diagnosis; only 6% of patients survive 3 years. The worldwide experience of CHLTx is limited, and fewer than 15 cases have been reported in the literature, of which 11 were performed for FA. The experience at Mayo Clinic in Rochester, 22 CHLTx procedures, exceeds that in the world literature. FA was the indication for CHLTx in 18 patients, and indications for the other 4 CHLTx procedures were hemochromatosis, restrictive cardiomyopathy, congenital heart disease, and primary pulmonary hypertension; the last 3 of these patients had advanced cirrhosis due to chronic congestive heart failure. Median waiting time for patients with FA who underwent CHLTx at Mayo

John M. Stulak, MD



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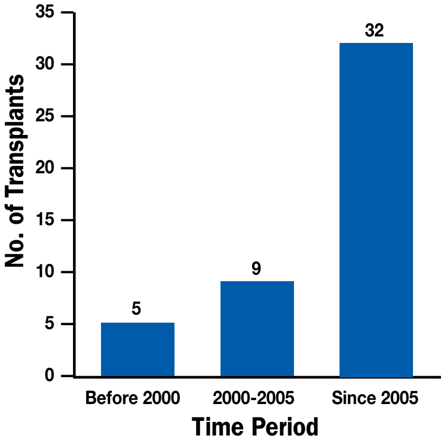


Figure 1. *The increasing frequency of combined heart with simultaneous liver and/or kidney transplants at Mayo Clinic in Rochester since 1988.*

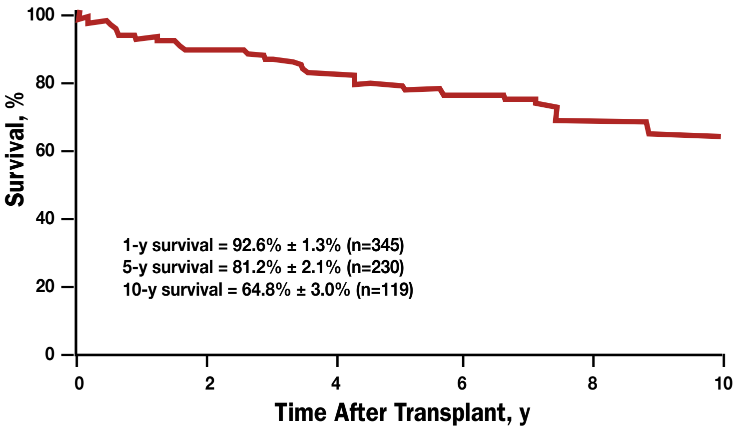


Figure 2. *Outcome after isolated heart transplants at Mayo Clinic in Rochester from June 1988 through April 2011.*

Clinic was 201 days (range, 45-443 days). Currently, 12 patients are alive at a mean time of 4.3 years (maximum, 13 years) after CHLTx, and 2 patients have survived 5 and 8 years after combined heart-liver-kidney transplantation performed for the indication of FA.

One major issue in the long-term follow-up of these patients is progression of peripheral neuropathy, which is part of the clinical spectrum of FA; the extent of neuropathy must be considered during evaluation for CHLTx. Of the 12 late survivors after CHLTx performed for FA, 5 have evidence of progressive neuropathy. Importantly, survival rates at 1 month, 1 year, 5 years, and 10 years after CHLTx were comparable to survival rates after both isolated heart transplant and isolated liver transplant (Figure 3). Interestingly, freedom from cardiac allograft rejection was significantly higher at 10 years (*P*=.02) after CHLTx (83%) compared with that after isolated heart transplant (32%).

Combined Heart-Kidney Transplantation

Chronic kidney disease following cardiac transplantation is a major source of morbidity and mortality. When patients present with extensive coexisting cardiac and renal disease, the presence of severe, irreversible renal dysfunction is a contraindication for isolated heart transplant. CHKTx has become an accepted treatment option for patients with this challenging clinical scenario. Success has been documented after simultaneous or staged CHKTx. The criteria for consideration of combined organ transplant include a glomerular filtration rate (measured using iothalamate clearance corrected for body surface area) less than 40 mL/min, despite hemodynamic optimization. All 21 CHKTx procedures performed to date at Mayo in Rochester were done as a simultaneous procedure; 2 were done for FA.

Postoperatively, intensive care unit and hospital stay did not differ significantly between CHKTx patients and those undergoing isolated heart transplantation. Two early deaths occurred, and late survival for hospital survivors is 100% at follow-up extending to 5 years. Early cardiac allograft dysfunction was present in 2 patients, but late cardiac allograft function was normal in all patients. Four patients had delayed kidney allograft function, necessitating temporary dialysis, and 1 of these went on to have permanent graft dysfunction. Survival rates for CHKTx recipients were similar to those achieved after isolated heart transplantation (Figure 4). Similar to the observations after CHLTx, the incidence of cardiac rejection was less frequent after CHKTx than in patients receiving isolated heart transplants. Although the time to first rejection did not differ significantly, 1 year after transplantation rejection episodes were virtually absent in CHKTx recipients but were still present in isolated heart transplant recipients.

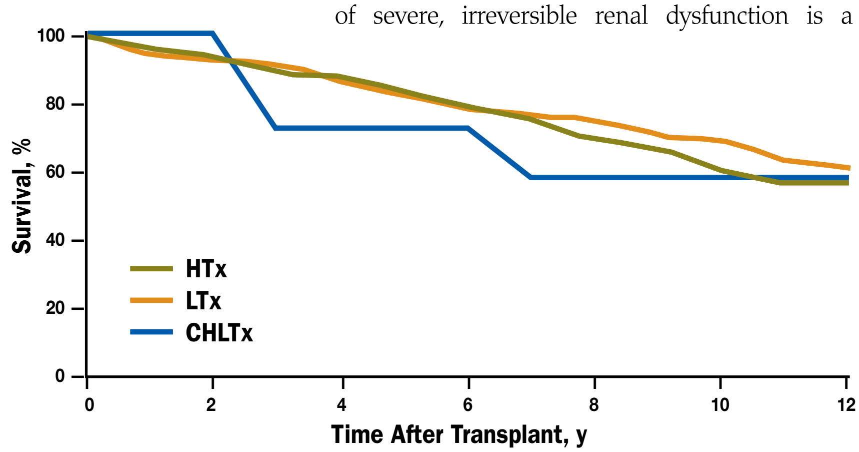


Figure 3. *Survival for CHLTx (n=15), isolated heart transplant (HTx) (n=258), and isolated liver transplant (LTx) (n=1,201).*

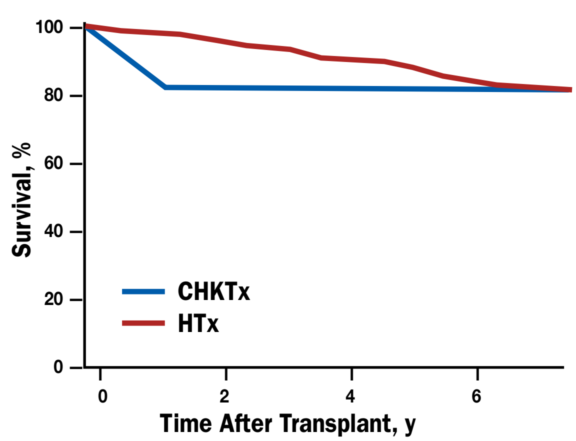


Figure 4. *Survival for CHKTx (n=12) and isolated heart transplant (HTx) (n=183).*

Summary

Approximately 10% of all heart transplantation procedures performed at Mayo Clinic in Rochester since 1988 were combined with simultaneous liver (n=22) or kidney (n=21) transplantation and, in some instances, both (n=6). Furthermore, almost 20% of all patients currently awaiting heart transplants are listed for combined organ transplants. This is consistent with our observation that the frequency of combined organ transplants has significantly increased in the past decade, especially in the past 5 years. Late survival after combined organ transplantation is similar to that after isolated heart transplantation, and freedom from cardiac allograft rejection and dysfunction is improved following combined organ transplantation compared with isolated heart, liver, or kidney transplantation. The success of Mayo Clinic's program is owed to the strong collaboration of a wide multidisciplinary group that participates in preoperative selection and optimization, surgical procedure, postoperative care, and long-term follow-up.

Treatment of Hypertension With Catheter-Based Radiofrequency Renal Artery Sympathetic Denervation

Issam D. Moussa, MD

Rajiv Gulati, MD, PhD

The effects of systemic hypertension on public health and the beneficial effects of antihypertensive drug therapy are unquestionable. Antihypertensive drug therapy, however, is not without limitations. A significant minority of patients continue to have poor blood pressure control (resistant hypertension) despite multiple drugs (3 or more medications); other patients cannot tolerate multidrug therapy due to the drugs' adverse effects. Recently, catheter-based interventional strategies that interrupt the renal sympathetic nervous system have shown promising results in providing better blood pressure control in patients with resistant hypertension.

The role of systemic sympathetic activity in causing hypertension is well known. Historically, surgical sympathectomy has been used to improve blood pressure control. This procedure, however, was abandoned because of its high operative morbidity and mortality. Building on this knowledge base, subsequent experimental and clinical studies demonstrated that the renal sympathetic nervous system also plays a major role in the pathogenesis of systemic hypertension. In spontaneously hypertensive rats, bilateral renal sympathetic denervation delayed and reduced the severity of hypertension. In patients with end-stage renal disease and those with kidney transplants, bilateral nephrectomy of native kidneys improved or normalized blood pressure.

The renal sympathetic nervous system has 2 components: 1) An efferent network supplies the kidneys with noradrenergic sympathetic fibers and raises the blood pressure by a direct effect on the kidney, promoting salt and water retention. 2) An afferent network of sympathetic fibers returns signals to the central nervous system. Both efferent and afferent nerve fibers are located in the adventitia of the renal arteries, making them a potentially modifiable target.

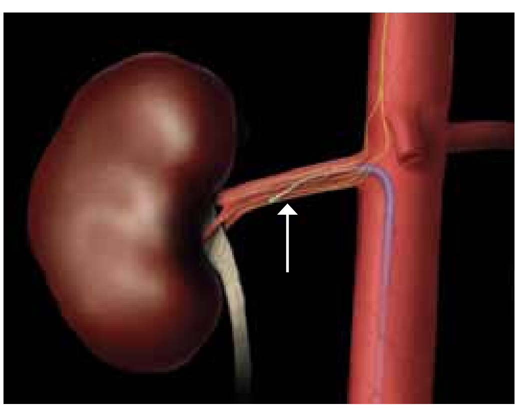


Figure 1. *Diagram of positioning of guide and catheter (arrow) within the renal artery for radiofrequency ablation of renal artery nerves.*

Percutaneous renal artery sympathetic denervation has already been used in patients with resistant hypertension, initially in clinical trials and subsequently in clinical practice in Europe (the procedure remains investigational in the United States). The therapeutic catheter has a steerable tip and is connected to a console that delivers radiofrequency energy. The level of energy delivered is monitored with a sensor at the tip of the catheter so that excessive tissue injury is avoided. The technique involves introducing a 6F femoral artery sheath and a 6F guide catheter to engage the renal arteries and subsequently deliver the radiofrequency catheter into the renal arteries to perform circumferential radiofrequency ablation (Figure 1). This procedure requires administration of anticoagulation and analgesics for control of abdominal pain during the ablation.

Two clinical trials evaluating this therapeutic modality have been conducted and the results published: Symplicity HTN-1 (Catheter-based renal sympathetic denervation for resistant hypertension: a multicenter safety and proof-of-principle cohort study) and Symplicity HTN-2 (Renal sympathetic denervation in patients with treatment-resistant hypertension). In the Symplicity HTN-1 study (a single-arm proof of concept study), 45 patients with drug-resistant hypertension underwent bilateral application of radiofrequency to the renal arteries. Significant blood pressure reduction was observed at 1 month, followed by a sustained response at 12 months (Figure 2). In the Symplicity HTN-2 trial (a randomized controlled trial), 106 patients with resistant hypertension were randomly assigned in a 1-to-1 ratio to receive catheter-based therapy in addition to conventional antihypertensive medications or to receive antihypertensive medications only. The primary end point was systolic blood pressure at 6-month follow-up. There was a significant difference in blood pressure changes from baseline between patients treated with catheter-based renal sympathectomy and those treated medically (Figure 3).

Although this procedure can be associated with complications, the experience thus far suggests a low rate of occurrence. In Symplicity HTN-1, 2 patients had complications—1 renal artery dissection, which was treated with stenting, and 1 femoral artery pseudoaneurysm. In Symplicity HTN-2, only 1 patient had a complication—a pseudoaneurysm at the femoral access site.

Although the results of these trials are encouraging, they lack the power to provide unequivocal proof to support a change in clinical practice. Mayo Clinic has begun screening and enrollment in the pivotal Symplicity HTN-3 trial. In this study, 545 patients will be randomly assigned in a 2-to-1 ratio to receive catheter-based therapy in addition to conventional antihypertensive medications or to receive antihypertensive medications only. The primary end point is systolic blood pressure at 6-month follow-up. The results of this trial may lay the groundwork for a change in how patients with drug-resistant hypertension are treated.

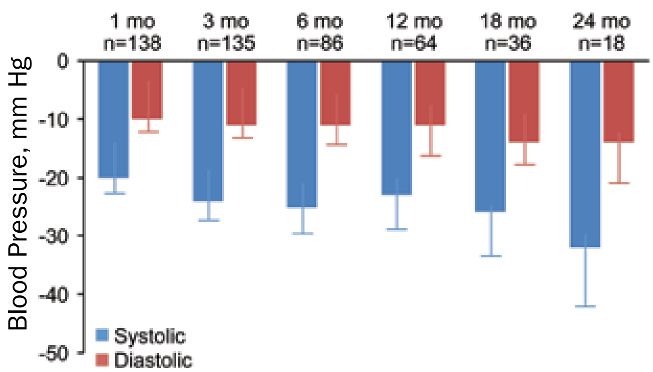


Figure 2. *Mean blood pressure changes after renal sympathetic denervation over 24 months of follow-up. Error bars indicate 95% confidence intervals. Adapted, with permission, from* Hypertension *2011;57:911-7.*

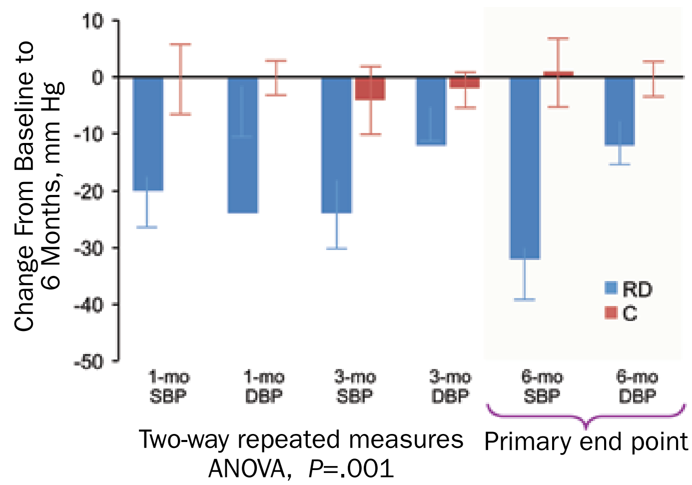


Figure 3. *Paired changes in office-based blood pressure measurements at 1, 3, and 6 months after renal denervation (RD). C indicates control. Adapted, with permission, from* Lancet *2010;376:1903-9.*

IN THE NEWS

Sleep Deprivation May Contribute to Obesity

Sleep deprivation is a growing problem, with almost 30% of adults in the United States getting 6 or fewer hours of sleep nightly. Researchers from Mayo Clinic in Rochester have demonstrated that sleep-deprived adults consume an average of 540 calories more daily than study participants who had normal sleep. The study lead author, Mayo Clinic cardiologist Virend Somers, MD, PhD, noted that lack of sleep was associated with higher levels of leptin and lower levels of ghrelin, hormones associated with hunger and satiety. While this study suggests sleep deprivation may be an important and preventable cause of weight gain and obesity, Dr Somers noted that it was a small study conducted in a hospital's clinical research unit and that larger studies conducted under home sleeping and eating conditions will be needed to confirm their findings. The study was presented at the American Heart Association's Epidemiology and Prevention/Nutrition, Physical Activity and Metabolism 2012 Scientific Sessions.

IN THE NEWS

Mayo Clinic Collaboration With theheart.org

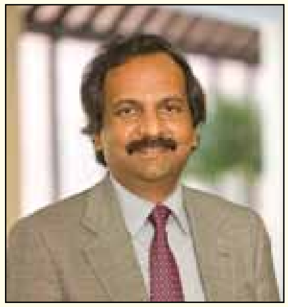
Mayo Clinic's divisions of cardiovascular disease and divisions of cardiovascular and thoracic surgery have embarked on a formal collaboration with theheart.org, a worldwide cardiology news source with 85,000 physician subscribers. Through this partnership, Mayo Clinic will be able to interact with a large pool of physicians and communicate with them more directly.

The first phase of this collaboration includes a Mayo Clinic page on theheart.org site, consisting of

- "Leaders' Perspective," video messages from leaders at all 3 Mayo Clinic sites, Rochester, Minnesota, Jacksonville, Florida, and Scottsdale/Phoenix, Arizona
- On-site expert "Roundtable Reviews" at select professional meetings moderated by a Mayo Clinic expert
- "Mayo Clinic Talks," a radio show on theheart.org radio, including interviews with experts on hot topics, moderated by Bernard Gersh, MD, PhD, a cardiologist at Mayo Clinic in Rochester
- Links to speak with or refer a patient to a cardiovascular specialist; cardiovascular CME; and Cardiovascular E-Update

Additional content and features will be added in the coming year. Visit the Mayo Clinic page at http://www.theheart.org/article/1357777.do.

Percutaneous Autonomic Neural Modulation: A New Approach to Treating Cardiac Arrhythmias



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Atrial fibrillation (AF) and ventricular fibrillation (VF) are common cardiac arrhythmias that do not have a uniformly efficacious or curative approach for their clinical management. Two-year efficacy rates with pharmacologic and/or ablative treatment are between 50% and 70%. There is a pressing need for superior techniques to effectively treat these arrhythmias. AF affects more than 2.5 million patients annually and is associated with serious morbidity (stroke) and a $6.65-billion cost to the US health care system. VF is the most common cause of death in the United States, affecting more than 450,000 patients annually.

As a result of suboptimal arrhythmia management techniques, the cardiac autonomic nerves have been intensely studied and clinically targeted to treat malignant arrhythmias. Prior to the development of antianginal medications, coronary artery bypass grafting, and percutaneous coronary interventions, sympathectomy was noted to relieve chronic anginal pain. Patients who have undergone heart transplantation with autonomic denervation of the heart do not develop AF, and cervical sympathectomy is an increasingly successful management option for VF, especially in patients with genetic arrhythmias. Several procedures have been developed to target the autonomic cardiac nerves, but all involve either cardiac surgery or endocardial ablation during which the cardiac muscle lying between the ablation energy source and the epicardial nerves is unnecessarily destroyed.

Physicians at Mayo Clinic in Rochester and in Florida are evaluating percutaneous techniques developed in animal models to modulate the autonomic ganglia located on the epicardium. A series of prototype catheters and devices have been developed.

Next steps include a first in-human study of efficacy and safety of the approach and prototype catheters in patients undergoing open-chest cardiac surgery who have a high incidence of postsurgical arrhythmia. If successful, these preliminary clinical studies will lead to subsequent human studies using newly developed catheters and equipment via a percutaneous approach and compare their efficacy with existing techniques that attempt to decrease AF and VF.

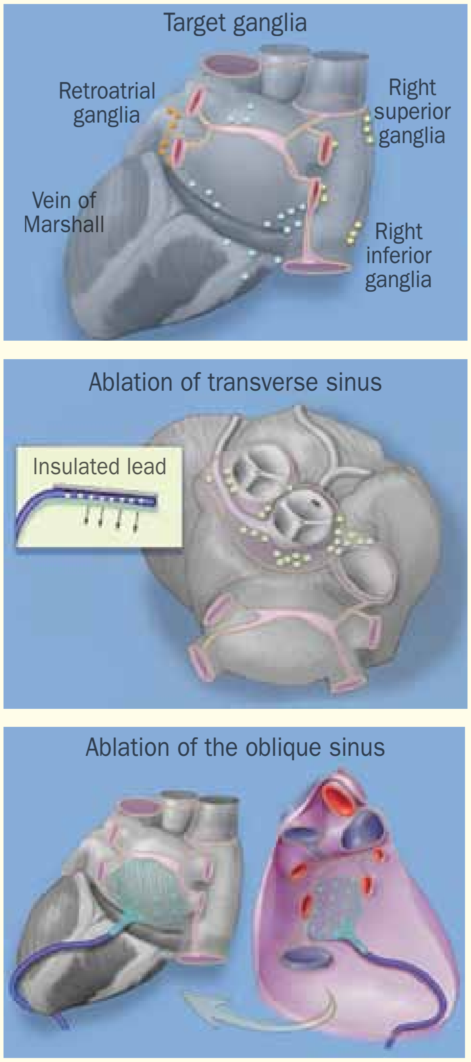

Figure. *A complex but well-defined network of cardiac nerves and ganglia surround the epicardial surface of the heart (top panel). Evidence from heart transplant patients and present surgical and ablative techniques targeting the ganglia have shown arrhythmia treatment efficacy. However, these approaches either require open surgery or destroy the surrounding cardiac muscle from radiofrequency ablation and thermal injury. The technique currently under investigation targets the pericardiac autonomic nerve tissue without the need for surgery and without cardiac tissue damage. Locations of prototype catheters for the transverse and oblique sinus are shown in the middle and bottom panels.*

RECOGNITION

Issam D. Moussa, MD, chair of the Division of Cardiovascular Diseases at Mayo Clinic in Florida, has been named chair of the Steering Committee of the National Cardiovascular Data Registry of the American College of Cardiology CathPCI registry.

Mayo Clinic
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CARDIOLOGY BOARD REVIEW COURSES

Pediatric Cardiology Board Review Course
Aug 26-31, 2012, Laguna Beach, CA

Electrophysiology for Boards and Recertification (Transseptal and Epicardial Workshop)
Sep 27, 2012, Rochester, MN

Electrophysiology Review for Boards and Recertification
Sep 28-30, 2012, Rochester, MN

Mayo Clinic Cardiovascular Review Course for Cardiology Boards and Recertification
Sep 29-Oct 4, 2012, Rochester, MN

9th Annual Mayo Clinic Interventional Cardiology Board Review
Oct 12-14, 2012, Rochester, MN

Cardiology Update in Sedona
Aug 2-5, 2012, Sedona, AZ

NEW LOCATION **Success With Heart Failure: Heart Failure for Clinical Practice**
August 12-15, 2012, Tahoe, NV

Echocardiography for the Sonographer
Sep 8-9, 2012, Rochester, MN

2012 Advanced Catheter Ablation Course: New Tips, Techniques and Technologies for Complex Arrhythmias
Sep 8-11, 2012, Chicago, IL

First International Biological Valve Symposium
Sep 12, 2012, Rochester, MN

Internal Medicine Review for Nurse Practitioners, Physician Assistants and Primary Care Physicians
Sep 12-14, 2012, Rochester, MN

Challenges in Clinical Cardiology
Sep 14-16, 2012, Chicago, IL

Ventricular Function in Congenital and Acquired Heart Disease: From Doppler to Deformation—State of the Art in 2012
Oct 5-6, 2012, Rochester, MN

28th Annual Echocardiography in Adult and Pediatric Congenital Heart Disease
Oct 7-10, 2012, Rochester, MN

22nd Annual Cases in Echocardiography, Cardiac CT and MRI
Oct 24-27, 2012, Napa, CA

Southwest Electrophysiology Course: Bridging the Gap Between Specialist and Internist
Oct 25-27, 2012, Phoenix, AZ

Coronary Artery Disease: Prevention, Detection, and Treatment
Nov 15-17, 2012, Las Vegas, NV

Echo on Marco Island: Case-Based Approach
Dec 6-9, 2012, Marco Island, FL

The Heart Beat of Cardiology: Practical Application of Echocardiography
Dec 13-15, 2012, Chicago, IL

Case Studies in Structural Heart Disease
Jan 24-27, 2013, Miami, FL

Arrhythmias and the Heart: A Cardiology Update
Jan 28-Feb 1, 2013, Maui, HI

Hawaii Heart 2013: Echocardiography and Multimodality Imaging: Case-Based Clinical Decision Making
Feb 4-8, 2013, Kauai, HI

18th Annual Cardiology at Cancun
Feb 25-Mar 1, 2013, Cancun, Mexico

20th Annual Echocardiographic Workshop on 2-D and Doppler Echocardiography at Vail
Mar 11-14, 2013, Vail, CO

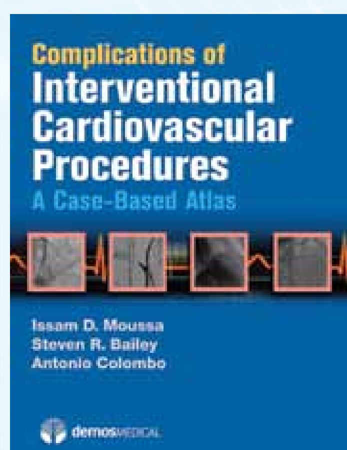
Other Education Courses

European Society of Cardiology
Aug 25-28, 2012, Munich, Germany
Website: www.escardio.org

ESC—Satellite Education Program Illustrative Case Discussion: Multivessel Coronary Disease and Atrial Fibrillation: Current Management Options
Aug 27, 2012, Munich, Germany
Website: www.escardio.org

AHA—Satellite Education Program
Nov 3-7, 2012, Los Angeles, CA
Website: www.accscientificsession.org

NEW



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