In October 2006, a team of researchers from Mayo Clinic Rochester traveled to Antarctica to begin a 3-year study evaluating human adaptation to the extreme environment at the South Pole, with a particular focus on altitude-related illness. The South Pole is at an altitude of approximately 2,900 meters and has an average “summer” (December through February) temperature of –30°C. Because of the cold and flattening of the atmosphere at the poles attributable to the equatorial bulge, the actual pressure altitude may vary from 2,900 to 3,690 meters. “The McMurdo Station at sea level and the Amundsen-Scott South Pole Station offer a unique opportunity to study adaptation to changes in altitude in conditions of extreme cold and low humidity,” says Bruce D. Johnson, PhD, a scientist in the Mayo Clinic Rochester Division of Cardiovascular Diseases and principal investigator of the study (Figure 1).

Each year, as many as 700 individuals go to the South Pole to work, usually on structured trips that require rapid ascent to the Amundsen-Scott station at 2,900 meters (Figures 2-4). These individuals undergo similar onset and exposure to the altitude and can be studied in a consistent experimental protocol. The goals of this study are 2-fold: to address a recognized need by the National Science Foundation for a more structured assessment of altitude-related problems in this population and to try to identify factors that predict altitude-related symptoms. “This study will focus primarily on finding predictors of mild to moderate altitude-related symptoms typically experienced at the South Pole, rather than the life-threatening syndromes such as high-altitude cerebral edema (HACE) and pulmonary edema (HAPE),” says Dr Johnson. Those mild to moderate symptoms often include headache, dyspnea, nausea, insomnia, fatigue, malaise, peripheral edema, dizziness, and anorexia, alone or in combination; subacute illness may last for weeks or months. To date, the only clear predictors of altitude illness include the rapidity of the ascent, the actual altitude, how active one is at altitude, and the altitude at which one sleeps.

At the sea-level McMurdo Station, researchers on this trip gathered baseline data on 140 individuals who subsequently went on to work at the South Pole. While at the South Pole station, these individuals were reevaluated over 7 to 10 days to try to quantify the incidence, timing, severity, and duration of altitude-related symptoms. The efficacy of the current practice of elective prophylaxis with ginkgo biloba and acetazolamide will be assessed in a subgroup of patients.

The study will try to determine the value of baseline demographic characteristics such as age, sex, and weight in predicting the occurrence of altitude-related symptoms.
illness. Additionally, these researchers are evaluating sleep profiles to assess the predictive value of a history of snoring and sleep apnea. Serum and plasma markers and candidate genes associated with ventilatory drive, fluid regulation, vasoregulation, inflammation, and oxygen-carrying capacity of the blood are also being measured. Two subgroups—the most symptomatic and the least symptomatic individuals—will have gene expression analysis performed to identify additional candidate genes.

The team will collect information about sleep habits and activity levels from subjects using a noninvasive, continuous ambulatory monitoring system (Vivometrics LifeShirt System) and an activity/lifestyle monitoring system (BodyMedia SenseWear). The shirts monitor physiologic activity during sleep such as ventilation, respiratory patterns, oxygen saturation, heart rate, snoring, rapid eye movement, and brain activity. Subjects will wear the shirt 1 night at McMurdo Station and then during their first night at the Amundsen-Scott South Pole Station. The activity monitor is a wearable device placed on the triceps of the right arm. The device, used for long-term, free-living lifestyle monitoring, will precisely record activity levels continuously for up to 2 weeks using a combination of information provided by the device, including skin temperature, heat flux, and movement. The device is then able to calculate resting and active energy expenditure. By correlating degrees of altitude sickness with various physiologic, chemical, and genetic profiles, researchers hope to develop an algorithm that prospectively identifies individual risk of developing altitude sickness. They are hoping also to obtain insight into the differing effects of a hypoxic environment on normal individuals and compare them with those with chronic disease such as pulmonary and cardiac abnormalities.

“Studying the adaptive and maladaptive processes that are associated with altitude-related symptoms at the South Pole holds broad relevance to the area of altitude medicine and altitude physiology,” says Dr Johnson. “Careful studies on large numbers of subjects going to altitude in an identical and uniform fashion offers an ideal setting to study mild to moderate symptoms.”

To read more about the study, Altitude Symptoms at the South Pole (ASAP), visit http://mayoresearch.mayo.edu/mayo/research/asap/.
Amyloidosis is a pathogenic process involving the deposition of insoluble proteins as fibrils in organs and tissues, resulting in organ failure and death. The most common classification is based on the chemistry of the amyloid fibrils and includes the following:

- Primary amyloidosis or AL (monoclonal κ or γ chains)
- Secondary amyloidosis or AA (protein A)
- Familial amyloidosis (γ-transthyretin mutation)
- Dialysis-associated amyloidosis (β2-microglobulin)
- Senile amyloidosis (wild-type transthyretin)

Cardiac protein deposition and resultant dysfunction occur most commonly in patients with primary amyloidosis and familial amyloidosis. “Physicians and scientists at Mayo Clinic Rochester have a long history of research and clinical expertise in the diagnosis and treatment of amyloidosis,” says Christopher G. A. McGregor, MD, director of the William J. von Liebig Transplant Center. “We are now exploring cardiac transplantation as a treatment for patients with selected subtypes of amyloidosis.”

**Primary Amyloidosis**

Primary amyloidosis, a plasma cell dyscrasia related to multiple myeloma, is a relatively rare disease, with 1,275 to 3,200 new cases diagnosed annually in the United States. Once symptoms occur, the disease is rapidly progressive, and the median survival is 13.2 months. Diagnosis is often made late in the course of the disease, and cardiac failure is the most common cause of death.

In patients whose ventricular septal thickness is more than 15 mm, left ventricular ejection fraction is less than 40%, or a presenting symptom is heart failure, median survival is less than 6 months (Figure 1). Chemotherapy may increase survival by 12 months. Early experience with autologous blood stem cell transplantation has resulted in medium-term survival in highly selected patients with primary amyloidosis. Cardiac transplantation initially was performed in rare patients in whom amyloid involvement was limited to the heart. Early to intermediate survival was achieved in the few reported cases with occasional long-term success. Systemic and donor heart amyloid disease recurrence was increasingly reported so that transplantation was contraindicated in patients with primary amyloidosis.

At Mayo Clinic, 140 patients with primary amyloidosis have been referred for evaluation for heart transplantation; 43 were accepted onto the transplantation waiting list, and 22 have received donor hearts. Challenges are to identify those patients with a poor prognosis, exclude myeloma, and assess the severity of the systemic disease to estimate the noncardiac prognosis. Bradycardia or electromechanical dissociation resulting in patient death on the waiting list supports early pacemaker insertion. The case for defibrillator insertion remains uncertain.

Ten patients are currently alive at 1, 2, 14, 27, 34, 85, 90, 103, and 106 months after transplantation. Twelve patients have died. Two patients developed nephrotic syndrome and underwent kidney transplantation 24 and 54 months after heart transplantation and remained alive and well for 40 and 114 months after kidney transplantation. Recurrence or progression of primary amyloidosis necessitates continued therapy for the disease, including autologous peripheral stem cell transplantation. Eleven patients underwent stem cell transplantation, and 6 are currently alive at 8, 11, 23, 29, 73, and 95 months. In these 6 patients, the mean 24-hour urine protein is 1,297 mg (range, 61-2,852 mg). The mean±SD 1-, 5-, and 10-year survival after transplantation is 85.0%±8.0%, 61.3%±11.7%, and 29.1%±15.0%, respectively, compared with 93.3%±1.5%, 84.2%±2.4%, and 70.2%±3.6%, respectively, in patients without amyloidosis under-
Cardiac Amyloidosis

- Increased jugular venous pressure with rapid Y descent and peripheral edema may occur as a manifestation of “restrictive cardiomyopathy” and is the most common clinical presentation of cardiac amyloidosis.

- Systemic blood pressure is usually normal or low, often with narrow pulse pressure. Think of cardiac amyloidosis whenever a previously hypertensive patient becomes normotensive, without other explanation. (Cardiac amyloidosis is one of the natural “cures” of systemic hypertension.)

- Orthostatic hypotension can be found in approximately 10% of cases, as a manifestation of autonomic neuropathy associated with amyloidosis.

- Syncope is common in patients with amyloidosis, is multifactorial in origin, is a dire prognostic sign, and may be a harbinger of sudden cardiac death.

Familial Amyloidosis

Familial amyloidosis results from liver production of a number of abnormal proteins attributable to gene mutations principally for transthyretin. Combined simultaneous liver and heart transplantation is indicated to treat the hepatic genetic disorder and replace the affected heart. Liver transplantation has also resulted in improvements in symptoms of peripheral neuropathy. Surgeons at Mayo Clinic Rochester have performed 10 such combined heart-liver transplants for familial amyloidosis. Nine men and 1 woman received these combined transplants. Their mean age was 55.6 years (range, 44-63 years). Eight are currently living at 2, 9, 15, 26, 50, 77, 114, and 115 months after transplantation. Mean±SD 1- and 5-year survival is 100.0±0.0% and 83.3±15.2%, respectively (Figure 3). “Symptomatic relief has been good,” says Dr McGregor, “but we believe heart transplantation should be offered to highly selected patients with end-stage cardiac amyloid disease in centers with extensive experience in the management of amyloidosis.”

UNDER THE STETHOSCOPE

by Clarence Shub, MD

Cardiac Amyloidosis

In this series, heart transplantation for primary amyloidosis achieved improved longevity and quality of life in at least the intermediate time frame. Outcomes were significantly less favorable in patients with nonprimary amyloidosis undergoing heart transplantation than in transplant patients with primary amyloidosis (Figure 2). Aggressive treatment of systemic amyloidosis after heart transplantation with peripheral stem cell transplantation is indicated. “Selection criteria remain uncertain and continue to evolve,” says Dr McGregor, “but we believe heart transplantation should be offered to highly selected patients with end-stage cardiac amyloid disease in centers with extensive experience in the management of amyloidosis.”

Michael J. Ackerman, MD, PhD, has been elected president of the of Sudden Arrhythmia Death Syndromes Foundation (SADS).
Mayo Clinic Jacksonville celebrated 20 years of caring in October 2006.

Mayo Clinic Announces New Trial for Migraine Sufferers

Mayo Clinic Rochester is participating in a new trial for selected patients with severe migraine headaches and patent foramen ovale (PFO). Led by Guy S. Reeder, MD, principal investigator and a cardiologist at Mayo Clinic Rochester, the trial will evaluate continued medical therapy versus PFO closure in the treatment of migraine. PFO closure, which takes about an hour, will be performed percutaneously in the cardiac catheterization laboratory. Coinvestigators at Mayo Clinic Rochester include pediatric cardiologist Donald J. Hagler, MD, and neurologist John D. Bartleson, MD.

Retrospective studies have shown an association between migraine headache and PFO. “One hypothesis is that a PFO with right-to-left intracardiac shunting may allow vasoactive substances to bypass the lungs and gain access to the brain circulation,” says Dr Reeder. “These substances could be responsible for stimulating migraine attacks in susceptible individuals.”

In smaller studies, PFO closure has reduced migraine frequency; however, investigators hope that larger, randomized trial results will provide conclusive data. If PFO closure can be shown to reduce the frequency of migraine headaches in even a subset of patients with migraine, it will be an important new therapy for many afflicted patients.

For inclusion, patients must be between 18 and 55 years old, have 6 to 14 migraine headaches per month, and have tried and failed 2 or more preventive migraine medications. Additionally, candidates must have evidence of right-to-left intracardiac shunting by transcranial Doppler examination.

Exclusion criteria are overuse of acute migraine treatments (more than 10 treatment days per month using ergots, triptans, narcotics, and/or butalbital), history of stroke or transient ischemic attack, contraindication to antiplatelet therapy, current warfarin therapy, or inability to receive a PFO occluder device.

All participants will undergo right heart catheterization as part of the study protocol, regardless of whether a PFO occluder device is placed. All participants will be followed for 5 years. For more information, please contact the study coordinator at 507-255-4502 or fountain.rebecca@mayo.edu or visit the study Web site, http://clinicaltrials.mayo.edu/clinicaltrialdetails.cfm?trial_id=100389.
Few Heart Disease Trials Report Sex-Specific Results

Heart disease differences in men and women continue to be poorly understood because women are included in clinical trials far less than men. Even when women are included, study results are not reported by sex, according to a study in the February 2007 issue of Mayo Clinic Proceedings. The study shows that three-fourths of clinical cardiovascular trials published in leading general medical and cardiology journals during the last 6 months of 2004 did not provide sex-based analyses.

In a review of 645 cardiovascular clinical trials published from July 1 through December 31, 2004, only 153 provided sex-specific reporting, which was defined as reporting results for women and men in a format that allows data to be specifically extracted for each sex. In addition, the authors found that 7% of the studies did not report the participants’ sex, and 3% included no women, despite studying conditions that affect both sexes.

“Heart disease is the No. 1 threat to a woman’s health, and we need to be able to tell women whether the diagnostic tests we order are accurate and how treatments will affect them, but today we don’t have enough data specific to women,” says Sharonne Hayes, MD, an author of the collaborative study and director of Mayo Clinic’s Women’s Heart Clinic. “We hope this analysis will drive the behavior of researchers. If more women are included in trials and the results are reported by sex, it will help physicians provide the best care possible to both men and women.”

Policy changes in 1986 by the National Institutes of Health (NIH) were aimed at increasing participation by women and minorities in research. Little progress was made until 1993, however, when NIH-funded research required by law that women and minorities be included in trials unless a clear reason was given for exclusion. The law required inclusion of women and minorities but did not require reporting the data. While sex-based reporting has increased as a result of the NIH requirement, the authors challenge journal editors to create a similar policy of reporting sex-based results, regardless of the funding source.
Researchers at Mayo Clinic Rochester Study New Approach to Percutaneous Stent Management

The Mayo Clinic Rochester. Although drug-eluting stents have reduced the risk of early restenosis, recent reports of late thrombosis and the prospect of long-term dual antiplatelet therapy have prompted researchers to reevaluate the approach to percutaneous interventions. Delayed or absent endothelialization at the site of stent placement is believed to play a role in the development of stent thrombosis. Prior attempts to coat stents with endothelial cells or their progenitors have had limited success. Researchers at Mayo Clinic Rochester have developed a technique of magnetically attaching endothelial cells to vascular grafts and stents.

“This novel technique may allow us to target local or regional areas for cell-based therapy,” says Gurpreet S. Sandhu, MD, PhD, a cardiologist at Mayo Clinic Rochester and lead author of the study, published recently in the Journal of the American College of Cardiology.

Mononuclear cells are collected from peripheral blood and cultured to isolate endothelial outgrowth cells, which are then labeled with iron-based paramagnetic microspheres. Commercially available coronary artery stents do not retain a strong magnetic charge; therefore, a thin layer of nickel is coated on standard steel stents to improve their magnetic properties. These prototype stents were used successfully to demonstrate cell capture in a large-animal model (Figure). The magnetized stents attracted several times more microsphere-containing endothelial cells than did nonmagnetized control stents. This facilitated endothelialization of vascular stents and grafts could reduce the risk of thrombosis and may reduce restenosis by enhancing the healing of implanted intravascular devices. Biocompatible stents that have satisfactory mechanical and magnetic properties are being developed. The long-term local vascular effects on treated vessels are unknown and await further studies.

This technique has many potential applications but is still in the early stages of preclinical development. Nevertheless, researchers believe this may be a viable technique for the treatment of not only vascular disease but other diseases as well. “Virtually any cell could be magnetically targeted to deliver cell- or gene-based treatments to a specific vessel or tissue,” says Dr Sandhu.
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Phone: 800-748-5052; e-mail: HRS@cdsreg.com; Web: www.heartrhythm2007.org

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