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CARDIAC PROGENITOR CELLS AND REGENERATIVE MEDICINE - A CAUTIONARY TALE

By Peter J. Gruber, MD and Karl-Ludwig
Laugwitz, MD

Picture the future. Multipotent cells in a bottle, immunologically privileged, ready for use. Cells that can differentiate into the cell type of choice, guided in this direction by either environment or physician's design. Cells that functionally integrate into host tissue (heart) to provide the missing mechanical or electrical components; cells that maintain these properties in a stable fashion throughout life. In short, cells with a definable plasticity, function, and phenotypic stability.

Now, remember the past: the early 80's. A new technology appeared on the scientific landscape that was received with tremendous expectation and rapidly put into clinical use with early hope. The public's hope (and money) was stimulated by early promising results in selected diseases. The biology was not completely understood, however the promise was too great to ignore, or wait, or so many thought. This was gene therapy. Once the poster child of molecular medicine and the darling of biotechnology ran into problems. A combination of scientific, medical, and public relations errors led to a fiasco. The same frenzy that brought gene therapy to the stage brought it down just as quickly. These lessons must be remembered, since cellular therapy appears to be on path, repeating our historical errors of only 10-15 years ago.

One of the first hints that there may be some cellular plasticity was when human heart transplant patients were examined. Male donor hearts (XX) grafted into female (XY recipients) were explanted after death and examined for the presence of cells

that harbored a Y chromosome. Although all cells in the graft were presumably XX, there were rare cells that were Y chromosome positive (Quaini, Urbanek et al. 2002). Further reports suggested that these were not in fact myocytes, but rather smooth muscle and endothelial cells (Glaser, Lu et al. 2002). Next, a series of reports suggested that bone marrow had the ability to differentiate into cardiac tissue as well as functionally repair the myocardium after infarction (Orlic, Kajstura et al. 2001). However, there have now been a number of subsequent reports that question the findings of the original papers (Balsam, Wagers et al. 2004; Murry, Soonpaa et al. 2004).

More recently, work by two independent labs have found tissue derived progenitor cells that may be of more promise (Oh, Bradfute et al. 2003; Laugwitz, Moretti et al. 2005). These cells are multipotent, but reside among fully differentiated cells. How they arise, what triggers their differentiation, and what possible roles they may play in development and repair are unclear. Especially promising are results from the Chien lab which for the first time show high frequency differentiation of progenitor cells from unspecified cardioblasts to fully differentiated, striated cardiac myocytes with functional characteristics of heart muscle cells. They exist in multiple species (mouse, rat and human) and are the closest cell type yet to satisfy all the requirements of bona fide cardiac progenitor cells (Parmacek and Epstein 2005). The existence of these novel cardiac precursors provides a potential explanation for cardiac abnormalities in humans and model organisms in which specific segments of the heart are underdeveloped or completely deleted, leaving the remainder of

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the heart unaffected. These discoveries shed new light on our understanding of congenital heart defects not as a defect in a specific gene or transcription factor, but actually as a cellular defect in a cardiac precursor cell population.

How will this affect the diagnosis and treatment of congenital heart disease? It is not yet clear, but there are at least three promising possibilities. First, progenitor cells may be able to be harvested, expanded, differentiated, and re-inserted in hearts suffering from an insufficient number of cells (e.g. heart failure). Secondly, they may be of use in the diagnosis of cardiac diseases since the cells can be differentiated into bona fide cardiac cells, which would allow for the study of patient-specific disease in vitro- e.g. a library of cardiac disease. Third, the ability to transfer nuclei from these progenitor cells to enucleated oocytes via somatic cell nuclear transfer may allow another route to a renewable source of cardiac cells. All of these technologies have tremendous potential, but we cannot jeopardize the long term value of this technology by prematurely promising undeliverables to the public or a technology that is not yet safe.

In the earlier days, the concept of regenerating the heart was radical and met with considerable skepticism. Today, using stem/progenitor cells to rebuild the heart from its component parts is an experimental concept. Like most researchers in this field, we are optimistic that this approach will eventually lead to therapeutic approaches in the clinic. However, it is also worth sounding a note of caution. This field is moving extremely quickly, and expectations within the public and the scientific community are high. Cell therapy must not follow the trajectory of clinical gene

"In the earlier days, the concept of regenerating the heart was radical and met with considerable skepticism. Today, using stem/progenitor cells to rebuild the heart from its component parts is an experimental concept."

therapy, as outlined above, where serious clinical complications set the field back for many years. The heart is not likely to be regenerated in one fell swoop, but more likely, we will repair the heart in smaller steps, perfecting our cells and interventions over many years.

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SCREENING OF STUDENT ATHLETES FOR SUDDEN CARDIAC DEATH

By Keith M. Weiner, MD

Sudden cardiac death (SCD,) can occur in association with a variety of diseases including hypertrophic cardiomyopathy (HCM,) structural or acquired coronary abnormalities, and various dysrhythmia syndromes. The causes of SCD associated with exercise appear to be age-related. Acquired coronary artery disease is the leading cause of SCD in athletes over 30 years of age, while



Derek Para, 2002 Olympic Gold Medalist receives cardiac screening at the Cathy Turner Celebrity Gold Tournament in Rochester, NY to benefit AHFS.

congenital cardiac abnormalities account for the majority of deaths in athletes less than 30 years of age, with HCM and structural coronary anomalies accounting for the vast majority of those deaths. The true incidence of SCD among children and adolescents is unknown, but a reasonable estimate may be in the range of 1.3/100,000 patient-years. Although SCD in student athletes may be an uncommon occurrence, identification of these at-risk athletes prior to SCD on the athletic field affords the only opportunity to

preserve their lives. This article reviews our experience with the largest student-athlete screening program reported to date.

A Heart for Sports (AHFS) is a 501 (c) (3) nonprofit California Public Benefit Corporation dedicated to saving young lives from sudden cardiac death through early detection and increased public awareness. AHFS conducts free community-based cardiac screenings for high school and college student athletes in an effort to identify those individuals at risk for sudden cardiac death and to strengthen collaborative relationships among health professionals who care for cardiac conditions. Originally developed with a primary focus on HCM, AHFS expanded its program in 2003 to include an electrocardiogram in addition to the history and echocardiogram used in the screening process. The primary goal of AHFS is to make cardiac screenings available free of charge to as many student-athletes as possible without creating the misperception that cardiac screenings are a definitive tool to exclude SCD.

AHFS screenings are performed by AHFS sonographers, technicians and volunteers under the supervision of cardiologists. With the advancement of technology and the development of the hand-carried echocardiogram devices, AHFS can provide community-based cardiac screenings.

Since September 2001, more than 4500 student-athletes have undergone AHFS screening in over 17 different cities spanning both coasts of the United States. The process as currently implemented begins with the school athletic director,

who identifies the student-athletes and provides them with an AHFS consent form and history questionnaire to take home. All such student-athletes have already obtained medical clearance to participate in school athletics, and their primary care provider information is included in this paperwork. Prominent written disclaimers indicate the limitations of the screening process. On the screening date, student-athletes with completed paperwork signed by their legal guardian undergo a 12-lead ECG and limited echocardiogram. The screenings occur on site at the school campus using portable equipment. Data analysis occurs off-site, with review of the ECG, history form, and digitized echo images by volunteer cardiologists with expertise in electrophysiology and cardiomyopathy.

Following off-site analysis, student-athletes with negative screens receive a post-card indicating that no abnormalities have been detected by this limited screening process. Student-athletes whose results appear abnormal are flagged, and the reason(s) for concern are relayed to their primary care provider, who is then responsible for either clearing the students for ongoing athletics or for obtaining additional testing.

“Although SCD in student athletes may be an uncommon occurrence, identification of these at-risk athletes prior to SCD on the athletic field affords the only opportunity to preserve their lives.”



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LA Laker Greg Foster at the screening to open The Tommy Lasorda Heart Institute.

Our preconception in developing the history questionnaire was that student-athletes would be generally unwilling to report symptoms that could potentially disqualify them from athletic participation. This has turned out to be a misperception. At our most recent screening of 600 student-athletes in a southern California school district, about 10% of respondents reported feeling excessively tired or developing dyspnea, palpitations, or chest pain on exertion. When these symptoms correlate with abnormalities on ECG or echocardiogram, it appears prudent for the athlete to undergo more comprehensive medical evaluation. In this recent screening, cardiac ultrasounds were judged abnormal in five students (0.8%). Abnormalities included mitral valve prolapse with mitral regurgitation in one, bicuspid aortic valve in two, symmetric left ventricular hypertrophy in one, and asymmetric left ventricular hypertrophy in one case. Electrocardiograms requiring further evaluations were identified in 2.4% of the studies. Isolated conduction delays were not considered a criterion for further evaluation. Significant dysrhythmias or STT changes comprised the bulk of ECGs that merited student referral back to their primary care provider.

Analysis of the aggregate data may be the subject of a future publication. Generally speaking, only a few athletes have been disqualified from sports participation as a result of problems first suspected during this screening process. The remainder, with diagnoses such as bicuspid aortic valve or MVP with regurgitation, have been identified and are now followed for treatable conditions not previously recognized in general or pre-sports evaluations. We believe this is a service to student-athletes, not a loss to high school athletic programs

or inappropriate restriction of budding athletic careers. Our screening program has undergone legal review. Our malpractice insurer has concluded that with the screening procedures and disclaimers in place, and in the setting of volunteer cardiology supervision and data review, there is such a minimal liability risk that physician participation in the screening program is supported without surcharge.

Screening programs to reduce the risk of SCD on athletic fields remain quite controversial. It is valid to argue the costs and benefits of any screening program in a world where demand outstrips resources. The program described herein operates predominantly with donated equipment and supplies, and volunteer medical staff. False parental reassurance has been cited as an argument against SCD screening. The parents of these student athletes have already been reassured as to their children's health by the pre-sports evaluations completed prior to athletic participation. While a screening program such as this one cannot begin to approach 100% sensitivity and specificity, our experience with positive tests in student athletes who have already passed pre-sports examinations by medical professionals suggests that

this type of screening provides supplemental benefit in disease detection.

In a society where sports participation is highly valued, and excellence in performance is highly emphasized, physicians have an obligation to serve as advocates for the health and safety of our children. While other diseases may be more prevalent than SCD, few of them are heralded by such a terminal event. The development of portable screening tools and volunteer organizations to provide access to these tools promotes the delivery of health care to our student-athletes. For those interested in more information, www.heartforsports.org.

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HIGHLIGHTS FROM THE EASTERN MEDITERRANEAN REGIONAL MEETING ON ESTABLISHING GUIDELINES ON RHEUMATIC FEVER PREVENTION AND CARE, ORGANIZED BY WHO IN YEMEN, MAY 2005

By Oussama Khatib, MD, PhD and Fadi Bitar, MD

Introduction

Between May, 2nd and 4th, 2005, the Eastern Mediterranean Regional Office (EMRO) of the World Health organization (WHO) organized a Regional Consultation on rheumatic fever (RF) prevention and care. The meeting took place in Sana'a, Yemen.

The EMRO covers 22 countries, namely: Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Syria, Sudan, Somalia, Tunisia, UAE, and Yemen. The Human Development Index (HDI) for these countries ranges from an HDI rank of 40 (Bahrain with GDP per capita of 17,170\$) to 154 (Djibouti) and from GDP per capita of 870 \$ (Yemen with HDI rank of 149) to 22,420\$ (UAE with HDI rank of 49). The HDI is a summary composite index that measures a country's average achievements in three basic aspects of human development: longevity, knowledge, and a decent standard of living.

“...rheumatic heart disease (RHD), remains a major public health problem in developing countries, accounting for up to 60% of all cardiovascular disease in children and young adults.”

Just over 20 regional experts in the field of rheumatic fever were invited to the meeting. The aim of the meeting was to discuss the status of RF in the region and to come up with regional guidelines for the prevention and care of rheumatic fever. During the three-day meeting, the attendees discussed various issues relating to RF. The following is a brief review and summary of the various presentations and discussions during the meeting.

Background

Rheumatic fever is a multisystem, immunologically mediated inflammatory disease that occurs as a delayed sequel to group A β -hemolytic streptococcal (GABS) infection. The clinical manifestation of the response and its severity in an individual is determined by host genetic susceptibility, the virulence of the infecting organism, and a conducive environment. Its subsequent complication, rheumatic heart disease (RHD), remains a major public health problem in developing countries, accounting for up to 60% of all cardiovascular disease in children and young adults.

Epidemiology

Worldwide, as many as twelve million new cases occur each year with two million people requiring repeated hospitalization, and one million requiring, often unaffordable, heart surgery in the next five to 20 years. Rheumatic fever and its heart complication cause 400,000 deaths annually mainly among children and young adults.

The epidemiology of RF in developed countries has changed dramatically over the past decades. In developing areas, the prevalence is still high at up to 24 per 1000 population. Rheumatic fever occurs

most frequently among children and adolescents between 5 and 18 years, coinciding with the age distribution of the highest prevalence of streptococcal infections. The disease may cluster in families. In some countries, a shift into older groups may be a trend.

In the United States, while the incidence has declined steadily, mortality has declined even more steeply. Credit may be attributed to improved sanitation and antibiotic therapy. Several sporadic outbreaks in the United States could not be blamed directly on poor living conditions. New virulent strains are the best explanation. The introduction of antibiotics has been associated with a rapid worldwide decline in the incidence of ARF. Now the incidence is 0.23-1.88 patients per 100,000 populations.

Reliable data on the incidence of RF in developing countries are scarce. The prevalence of RHD showed wide variation between countries. The prevalence of RF/RHD in some of the EMR countries among schoolchildren based on local data in as follows: 36/1000 in Yemen, 0.4/1000 in Oman, 10.2/1000 in Sudan, 5.1/1000 in Egypt and 0.7/1000 in Iran. Prevalence had decreased in some regional countries like Oman, which is approaching industrialized countries. Incidence rate of Eastern Mediterranean varies between 27-100/100000 population. In Yemen 60% of cardiac surgery is due to rheumatic heart complications, whereas in Egypt only 5-7% is due to rheumatic complication. In Lebanon, less than 1% of cardiac surgery is due to rheumatic complications.

No clear-cut sex predilection exists for the syndrome in general, but its manifestations seem to be sex-variable. For ex-



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Some of the attendees of the Eastern Mediterranean Regional Meeting on Establishing Guidelines on Rheumatic Fever Prevention and Care, Organized by WHO in Yemen.

ample, predominance for certain clinical manifestations (i.e., chorea and tight mitral stenosis) occurs in women, while men are more likely to develop aortic stenosis.

Pathogenesis

The pathogenic mechanisms involved in the development of RF remain unclear. However, it is evident that an abnormal humoral and cellular immune response occurs. Antigenic mimicry between streptococcal antigens, mainly M-protein epitopes and human tissues, such as heart valves, myosin and tropomyosin, brain proteins, synovial tissue and cartilage has been proposed as the triggering factor leading to autoimmunity in individuals with genetic predisposition. An association has been reported between certain class-II HLA antigens (DR2 in blacks and DR4 in whites).

The first inkling streptococcal infection played a role in RF was the finding that after outbreak GABS; one would find

outbreaks of RF. In military recruits about 3% of individuals developed RF after having streptococcal infection, and in the general population, about 0.3%. A combination of overcrowding, damp conditions, especially during the rainy season in tropical and sub-tropical countries, coupled with poverty and overstretched health services produces fertile ground for circulation of the infection. Asia, Africa, Latin America and the Eastern Mediterranean regions are the four geographical areas that suffer the most.

Diagnosis

The American Heart Association (AHA) made a slight revision of the guidelines for diagnosis published more than 50 years ago by T. Duckett Jones. Prior history of a preceding group A streptococcal infection is helpful but not required. In addition, two major manifestations or one major and two minor manifestations must be present. Major manifestations include carditis, polyarthritis,

chorea, erythema marginatum, and subcutaneous nodules. Minor manifestations include arthralgias and fever. Laboratory findings include elevated acute phase reactants (erythrocyte sedimentation rate [ESR] and C-reactive protein) and prolonged PR interval. A prolonged PR interval is not specific and has not been associated with later cardiac sequelae. An exception includes chorea, with another possible exception being indolent carditis. Isolated mitral valve involvement occurs in nearly 60% of patients with carditis, followed in prevalence by combined mitral and aortic valve involvement. When present, Sydenham chorea is seldom evident at the time of initial presentation. Arthritis, which occurs in 80% of patients, usually involves multiple large joints, particularly the knees, ankles, elbows, and wrists. This form of arthritis rarely causes permanent joint deformity. Typically, the first manifestation is a very painful migratory polyarthritis.

Echocardiography Role

The utility of echocardiography is controversial. There are significant advantages in using echocardiography to detect valvulitis. Foremost, is its superior sensitivity in detecting rheumatic carditis, which should prevent patients with carditis from being misclassified as noncarditic. It is reasonable to accept that valvular regurgitation may not always be detected by routine clinical auscultation.

A second advantage of echocardiography is that it should allow the valve structure to be properly delineated. Thus, nonrheumatic causes of valvular dysfunction (e.g. mitral valve prolapse, bicuspid aortic valve) may be detected, and may prevent patients from being mislabeled as cases of rheumatic carditis. On the other hand, there are logistical problems with the universal use of echocardiography to detect RF. This could be ascribed either to the high sensitivity of Doppler echocardiography for diagnosing valvular regurgitation, or to the overdiagnosis of physiological valvular regurgita-



The mystery of the past and the thrill of discovery remain to be experienced when traveling different places in Yemen.

tion as an organic dysfunction, or to both. In developing countries, which withstand the worst of RF disease, it is unlikely that echocardiographic facilities will be widely available. It was agreed that, in areas where appropriate facilities for echocardiography exist, echocardiographic study should be a part of the routine work up of patients with suspected RF.

Approach to Sore Throat

Antibiotics are of limited use for most people with sore throats. Antibiotics can reduce bacterial infections, but communities build resistance to these drugs. They can reduce rheumatic fever in communities where this complication is common. Strategies should be tailored towards local circumstances. Evidence has been presented from a simulation study suggested that the most cost-effective strategy was to treat all pharyngitis patients with penicillin (particularly those at risk), without a strict policy of waiting for the disease to be confirmed by bacterial culture. However, this approach has not been confirmed and cannot be advo-

cated until more thorough studies are carried out. In hospital settings where facilities are available, the "culture and treat" strategy has been shown to be cost-effective. Attendees agreed to consider empirical antibiotics treatment, in the EMR countries with high prevalence of RF, of clinically suspected cases of bacterial pharyngitis in the setting where appropriate laboratory diagnosis of GABS is not available.

Treatment

Treatment strategies can be divided into management of an ARF attack, management of the current infection, and prevention of further infection and attacks.

The primary goal of treating the ARF attack is to eradicate streptococcal organisms and bacterial antigens from the pharyngeal region. Penicillin is the drug of choice in persons who are not at risk for allergic reaction. A single parenteral injection of benzathine benzylpenicillin can ensure compliance. Oral cephalosporins are recommended as an alter-

native in patients who are allergic to penicillin. However, one should be cautious of the 20% cross-reactivity of the cephalosporins with penicillin. Antimicrobial therapy does not alter the course, frequency, or severity of cardiac involvement. Analgesia is optimally achieved with high doses of salicylates, often inducing dramatic clinical improvement. The nonsteroidal anti-inflammatory drug (NSAID) naproxen is also effective and may be easier to use than aspirin. Although many reserve the use of corticosteroids for the treatment of severe carditis, it is our practice and others, to use corticosteroids whenever carditis is present. After 2-3 weeks, the dosage may be tapered, reduced by 25% each week. Overlap with high-dose salicylate therapy is recommended as the dosage of the prednisone is tapered over a 2-week period to avoid poststeroid rebound. In extreme cases, intravenous methylprednisolone may be used. Some reports about potential beneficial effect of the use of intravenous immunoglobulin in the treatment of acute rheumatic carditis have been described. Protracted Sydenham chorea has shown good response to haloperidol. Although Glucocorticoids or salicylates have been reported to have little or no effect on chorea, some recent studies described marked improvement of the involuntary movements with short course of corticosteroids.

No dietary factors are known. All patients should be restricted to bed rest and monitored closely for carditis. When carditis has been documented, a 4-week period of bed rest is recommended.

"In developing countries, which withstand the worst of RF disease, it is unlikely that echocardiographic facilities will be widely available."

Pediatric Cardiac Intensive Care Society (PCICS) and Congenital Cardiac Anesthesia Society (CCAS) present

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Prevention

Attempts to achieve a safe and effective vaccine against group A streptococci are undertaken. Success in developing a vaccine may be achieved in the next 5-10 years. In the meantime and short of an effective vaccine in the near future, the recommended approach can be divided into primary and secondary prevention.

Primary prevention: Eradicate streptococcus from the pharynx, which generally entails administering a single intramuscular injection of benzathine benzylpenicillin.

Secondary prevention: The AHA Committee on Acute Rheumatic Fever recommends a regimen consisting of benzathine benzylpenicillin at 1.2 million units intramuscularly (or 600,000 IU for children weighing less than 27 kg.) every 4 weeks. However, in high-risk situations, administration every 2-3 weeks is justified and advised. High-risk situations include patients with heart disease who are at risk of repetitive exposure. Although some published studies reported ineffective penicillin levels after two weeks of long acting penicillin injection, it was agreed among the attendees to recommend 2-3 weeks in the Eastern Mediterranean Region.

Oral prophylaxis, which is less reliable, consists of phenoxymethylpenicillin (penicillin V) or sulfadiazine. These can be used in compliant patients. If penicillin allergy is suspected, oral cephalosporins or erythromycin should be used; however, prevalence of macrolide erythromycin resistant GABS must be taken in account in some countries

In the EMR countries, the attendees agree that prophylaxis should be continued as follows: continue for 5 years after the first attack; continue indefinitely for patients with established heart disease; continue indefinitely for those who are

frequently exposed to streptococci, are less than optimal, and difficult to monitor. However, the decision to withdraw the antibacterial drugs should be individualized after carefully assessing the risk of repetitive exposures.

Infective Endocarditis (IE) poses a special threat for individuals with chronic RHD and whom have a prosthetic valve implanted because of RHD. Appropriate prophylaxis for prevention of IE in patients with rheumatic valvular heart disease should be emphasized.

Potentially, the most cost-effective strategy for ameliorating the impact of RF and RHD on the economies and health-care systems of developing countries is the secondary prevention of RF. Patients on irregular or no secondary prophylaxis have a high recurrence rate (5.5 to 25.0% of patient-years) and severe RHD.

Prevention Programs

Attendees discussed various ways to develop guidelines for prevention of RF. The importance of mounting school education campaigns both for teachers and for their pupils was addressed. The need for better training of health personnel at the local health centres and in laboratories was also discussed. Suggestions for prevention and planning/implementation of national programs included the following:

- Community Awareness and Public Education through feasible programs (Radio/TV, etc..) in addition to including political commitments.
- RF/RHD Registry and National surveillance; Reliable data collection and epidemiology studies.
- Upgrade the role and training of primary care takers , i.e. nurses and physicians in early recognition and appropriate treatment of GABS.
- Reduce occurrence and severity of GABS.

- Encourage countries to develop adequate microbiological laboratory at national and peripheral facilities.
- Appropriate primary and secondary treatment.
- Specialized referral clinics for RHD
- A valid monitoring processes to insure implementation.
- Improvement in access to medical care and standards of living.

~CCT~



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MEDICAL NEWS, NEW PRODUCTS AND INFORMATION

Jeffrey Smallhorn, MBBS, FRACP, FRCP(C)
Presented with the Founder's Award from ASE at
the 16th Annual Scientific Sessions in Boston

The American Society of Echocardiography's 16th Annual Scientific Sessions was held June 15 through June 18 at the Hynes Convention Center in Boston, Mass. Attendance was estimated at 3,400 professionals.

The ASE Pediatric Echocardiography Council Luncheon was held during the Scientific Sessions on Thursday, June 16. During this luncheon, Dr. Tal Geva, the chair of the ASE Pediatric Council Board gave the State-of-the-Pediatric Counsel Address which included initiatives new and old. He also presented Jeffrey Smallhorn, MBBS, FRACP, FRCP(C) from the Hospital for Sick Kids in Toronto, Canada with the Founder's Award. Dr. Smallhorn lecture was titled "How to Mix a Successful and Sustained Career with a Fulfilling Personal Life."

Based in Raleigh, NC, the American Society of Echocardiography is a professional organization of physicians, cardiac sonographers, nurses and scientists involved in echocardiography, the use of ultrasound to image the heart and cardiovascular

system. The organization was founded in 1975 and has more than 9,800 members nationally and internationally. Next year, ASE 2006 will be held in Baltimore, Maryland from June 4-8, 2006. For more information on ASE, visit www.asecho.org.

Children's Anxiety Prior to Surgery Linked to Behavioral Changes

A child's level of anxiety prior to surgery is predictive of whether they will experience post-surgical delirium and maladaptive behavioral changes, including anxiety, nighttime crying, and bedwetting, according to a Yale study published in the *Journal of Anesthesia & Analgesia*.

"This finding is of importance to the clinician, who can now better predict the development of adverse postoperative phenomena in children based on the child's pre-operative anxiety," said Zeev Kain, MD, professor in the Department of Anesthesiology at Yale School of Medicine and principal investigator of the study.

Kain and his colleagues found children whose anxiety before surgery increased 10% based on the Yale Operative Anxiety Scale were 10% more likely to experience delirium after surgery. Children with delirium also were more likely to have one or more new maladaptive behavioral changes following surgery when compared to children with no delirium. In addition, children with a 10% increase in anxiety scores had a comparable increase in the likelihood that they would have one or more new maladaptive behavioral changes following surgery, among them separation anxiety and temper tantrums.

"Co-authors include Alison Caldwell-Andrews, Inna Maranets, MD, Brenda McClain, MD, Dorothy Gaal, MD, Linda Mayes, MD, Rui Feng, and Heping Zhang, all of Yale.

"We identified characteristics of children who are at high risk of developing all of these clinical issues: they are younger, more emotional, more impulsive, and less social," Kain said. "In addition, the parents of these children are significantly more anxious in the holding area and more anxious on separation to the operating room. This underscores the importance of finding ways to ease this



Dr. Tal Geva (right) presents Dr. Jeffrey Smallhorn (left) with the ASE Founder's Award.



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Interventional Catheterization

The Division of Pediatric Cardiology at the University of Utah School of Medicine is recruiting a pediatric cardiologist at the Assistant or Associate Professor level with a major interest in interventional catheterization. The candidate must have advanced training and/or experience in interventional catheterization. Our division is very busy clinically and academically productive with all subspecialty areas represented. In 2004, we performed approximately 650 catheterization procedures including a full spectrum of interventions. We expect to open 2 brand new cath labs in 2007 ensuring the continued growth of our interventional program. Opportunities exist for wide ranging clinical and bench-top collaboration both locally and nationally within both academics and industry.

In addition to expertise in interventional catheterization, applicants should have a sound clinical background in all areas of pediatric cardiology. The current division staff is composed of individuals with significant professional experience and expertise. There will be protected time for clinical research, with mentoring available within the division for clinical research studies. The division has a very active clinical research program and is one of the participating centers in the Pediatric Heart Disease Clinical Research Network funded by the NIH.

The successful candidate will receive a faculty appointment at the University of Utah. The pediatric cardiology division is based at Primary Children's Medical Center, a tertiary referral center for a three state area, which is located on the hills overlooking Salt Lake City. The area offers an excellent quality of life with immense cultural and recreational opportunities close and available. The University of Utah is an Equal Opportunity Employer and welcomes applications from minorities and women and provides reasonable accommodations to the known disabilities of applicants and employees.

Interested individuals should contact: Robert E. Shaddy, Professor of Pediatrics, Division Chief of Pediatric Cardiology, University of Utah School of Medicine, 100 North Medical Drive, Salt Lake City, Utah 84113. E-mail: robert.shaddy@ihc.com

Interventional Electrophysiologist

The Division of Pediatric Cardiology at the University of Utah School of Medicine is recruiting a pediatric cardiologist at the Assistant or Associate Professor level with a major interest in interventional electrophysiology. The candidate must have advanced training and/or experience in interventional electrophysiology. This will include electrophysiology studies, radiofrequency ablation of complex arrhythmias, and device placement. Additional training and experience in cardiac resynchronization therapy is encouraged. Our division is clinically very busy and academically productive with all subspecialty areas represented. We have a large and growing volume of arrhythmia and device patients. A new faculty member would join two other faculty members in the area of electrophysiology. We are opening two brand new catheterization laboratories (one of which is an electrophysiology laboratory) in 2007, to ensure the continued growth of our interventional program.

In addition to expertise in electrophysiology, applicants should have a sound clinical background in all areas of pediatric cardiology. The current division staff is composed of individuals with significant professional experience and expertise. There will be protected time for clinical research, with mentoring available within the division for clinical research studies. The division has a very active clinical research program and is one of the participating centers in the Pediatric Heart Disease Clinical Research Network funded by the NIH.

The successful candidate will receive a faculty appointment at the University of Utah. The pediatric cardiology division is based at Primary Children's Medical Center, a tertiary referral center for a three state area, which is located on the hills overlooking Salt Lake City. The area offers an excellent quality of life with immense cultural and recreational opportunities close and available. The University of Utah is an Equal Opportunity Employer and welcomes applications from minorities and women and provides reasonable accommodations to the known disabilities of applicants and employees.

Interested individuals should contact: Robert E. Shaddy, Professor of Pediatrics, Division Chief of Pediatric Cardiology, University of Utah School of Medicine, 100 North Medical Drive, Salt Lake City, Utah 84113. E-mail: robert.shaddy@ihc.com



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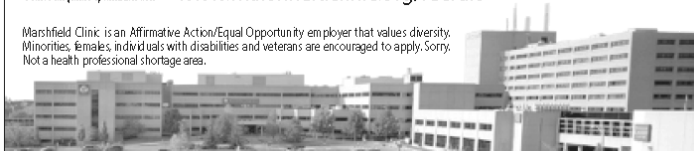
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782-8581 extension 19774, or fax to (715) 221-9779; E-mail: treichel.mary@marshfieldclinic.org Check out our web site to learn more about Marshfield Clinic at: www.marshfieldclinic.org/recruit



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parental anxiety, for example, by developing preoperative preparation programs directed at parents."

For more information: www.med.nyu.edu.

Biosound Esaote Introduces MyLab™50, Expands Offerings for the Cardiovascular Laboratory

Biosound Esaote, a global leader in ultrasound technology, unveiled the MyLab™ 50, the newest member of the MyLab™ family of advanced ultrasound systems at the American Society of Echocardiography (ASE) meeting, June 15-18, in Boston, MA USA.

MyLab 50 is the latest Biosound Esaote cardiovascular system to provide premium performance with advanced features like integrated contrast acquisition, Tissue Velocity Mapping (TVM) and high resolution multiplane TE imaging for diagnostic confidence with even the most difficult patients.



"MyLab 50 will, along with MyLab 30 CV, allow Biosound Esaote to offer a full range of high performance ultrasound systems for the cardiovascular laboratory," stated Jim Chapman, Director of Product Marketing. "From the private practice office to the hospital environment, the MyLab™ Family is capable of satisfying any diagnostic requirement in cardiovascular scanning, from pediatric to adult."

"The MyLab 50 offers a system geared towards those practices not requiring the extreme portability provided by the MyLab 30 CV, but who require premium performance in a console based system which is still relatively small and very ergonomic," added Claudio Bertolini, President of Biosound Esaote. "The introduction of the MyLab 50 allows us to offer a full range of technology options to meet any clinical challenge."

Biosound Esaote, headquartered in Indianapolis, Indiana, is a market leader in diagnostic portable ultrasound systems with real-world applications for mobile and outreach services and private practice cardiovascular offices. For more information, visit www.biosound.com.



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HIGHLIGHTS FROM UPDATE ON CARDIAC INTENSIVE CARE FOR NEONATES, CHILDREN AND YOUNG ADULTS, JUNE 8-11, 2005 AT SHANGHAI CHILDREN'S MEDICAL CENTER, SHANGHAI, CHINA

By Lin Hua Tan, MD and Anthony C. Chang, MD, MBA

With the increasing successes of palliative and reparative surgeries and catheter interventions in most countries in Asia, survival of pediatric patients with congenital heart disease has steadily improved similar to the West. However, current challenges presented to cardiologists, cardiac surgeons, intensivists, anesthesiologists, and nurses include how to manage pediatric patients with complex congenital heart disease and reduce the morbidity and mortality. Asian cardiac caretakers have a myriad of additional challenges such as lack of resources and late referrals.

The conference, Update on Cardiac Intensive Care for Neonates, Children and Young Adults was held in Shanghai, China from June 8th to 11th 2005, and was sponsored by the Shanghai Children's Medical Center and Project Hope. This four-day conference gathered Asian colleagues in pediatric cardiology, cardiac surgery, intensive care, and nursing and had over 200 representatives from more than 10 countries. The multidisciplinary faculty from United States, Canada, Japan, Korea, and Thailand were invited to the conference and gave lectures on a wide range of topics in cardiac intensive care.

The entire conference included sessions on low birth weight neonates with congenital heart disease, fetal and neonatal interventional catheterization, transposition of great arteries, hypoplastic left

heart syndrome, congestive heart failure and therapies, update on pulmonary hypertension, cardiopulmonary interaction in cardiac intensive care, adults with congenital heart disease, cavopulmonary anastomosis, and mechanical support of

birth weight (LBW) infant who carries a higher mortality and morbidity risk compared to the overall population of neonates with congenital heart disease. Dr. Spray pointed out the mortality for the SGA infant was lower than that for in-



Drs. Andrew Redington and Anthony Chang, two of the conference faculty members, posing with three of the attendees.

the myocardium. Multiple speakers presented 10-minute discussions on the same topics to give a broad perspective.

Among the highlights:

The first session opened with a presentation by Dr. Thomas L. Spray from Children's Hospital of Philadelphia describing the effects of cardiac surgery in the low

birth weight (LBW) infant who carries a higher mortality and morbidity risk compared to the overall population of neonates with congenital heart disease. Dr. Spray suggested that current surgical mortality in the LBW neonate is acceptable and improving particularly in the hypoplastic left heart syndrome subgroup. Dr. Anthony C. Chang from Texas Children's Hospital delineated the differences in cardiopulmonary pathophysiology between LBW and normal birth weight neonates and



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promoted early repair of congenital heart disease in LBW neonates whenever feasible. This lecture was followed by a presentation by Dr. Tae-Gook Jun describing the results of cardiac surgery in the LBW neonates in Samsung Seoul Hospital, Seoul, Korea. The next speaker was Dr. Hirakasu Sakai, who came from National Center for Child Health and Development, Tokyo, Japan. Dr. Sakai concluded that LBW neonates are apparently more susceptible to stress and can deteriorate even with minimum surgical intervention, based on his experience as an intensivist.

Another session was a provocative one that focused on fetal and neonatal interventional catheterization. Dr. Andrew N. Redington of Toronto Sick Kids provided an overview of interventional catheterization in congenital heart disease. Dr. Kun Sun presented the role of echocardiography in the intervention of congenital heart disease in fetus and neonates. Dr. Zhaokang Su described his experience with fetal cardiac surgery in an animal model.

An afternoon session focused on transposition of great arteries (TGA) and hypoplastic left heart syndrome (HLHS). Dr. Apichai Khong from Bangkok described his experience with the rapid two-stage arterial switch operation for treatment of late referral patients with TGA/IVS. As late referrals are not uncommon in Asia and ventricular assist devices are not readily available, the two-stage option is often utilized. Dr. Shunji Sano from Japan described the outcome of 74 neonates with TGA/IVS who underwent arterial switch operation in Okayama University Hospital from January 1991 to February 2004, with a hospital mortality of 1%. The next speaker was again Dr. Spray, who presented the option for surgical treatment of TGA with left ventricular outlet tract obstruction. In the HLHS ses-

sion, Dr. Shunji Sano gave a literature review on results of Norwood procedure for HLHS patients and described safeguards and pitfalls in the management of patients undergoing stage I palliation using the RV-PA shunt. Dr. Chang emphasized the importance of decreasing systemic vascular resistance as being more efficacious than increasing pulmonary vascular resistance to optimize oxygen delivery. Dr. Spray concluded from the Children's Hospital of Philadelphia experience that no significant difference was found in the stage I morbidity and mortality as well as mid-term survival between the classic Norwood and the RV-PA conduit operation (Sano). Patients with the RV-PA conduit operation, however, required more interim period interventions and returned earlier for the bidirectional Glenn.

The second day provided a lively discussion with regard to congestive heart failure and therapies. Dr. Chang began the session with review of the pathophysiology of chronic heart failure and updated the diagnostic technique and the new emerging therapeutic drugs for heart failure. Dr. Redington went on to describe the relatively little evidence for the clinical benefit of the drugs commonly used in children with heart failure such as digoxin, ACE inhibitors, and beta blockers etc. Dr. Hirokazu Sakai presented the basics of mechanical ventilation as a therapy for congestive heart failure with respect to balance between oxygen supply and demand. A senior cardiologist from Shanghai, Dr. Shubao Chen, concluded from his clinical study that BNP and NT-proBNP improved the accuracy in the diagnosis of heart failure in pediatric patients and that NT-proBNP was more sensitive than BNP to differentiate these patients.

In a pulmonary hypertension session, Dr. Redington reviewed the studies on silde-

nafil, a PDE5 inhibitor, and described its likely efficacy in resistant or rebound postoperative pulmonary hypertension; this benefit was associated with, however, possible increase in intrapulmonary shunting. Dr. Kritvikrom Durongpisitkul from Siriraj Hospital, Thailand, known in Asia for his work on pulmonary hypertension, presented data from his 2 recent studies. Data on outcomes of 326 patients who had acute vasodilator testing with prostacyclin, 100% O₂ and inhaled NO suggested postoperative death was associated with lack of pulmonary vascular reactivity with prostacyclin. His other study showed beraprost treatment in patients who continued to have pulmonary hypertension that resulted in improvement of 6 minute walk test.

Following a presentation Dr. Redington, who described the pathophysiology of cardiopulmonary interaction and emphasized the heart and lungs as a single hemodynamic unit, Dr. Zhenying Shi, Yanping Zhou, and Qin Cui, all from China, presented their topics on evaluation perioperative changes of respiratory function in neonates and infants with congenital heart disease, ventilatory strategies and use of non-invasive positive pressure ventilation after cardiac surgery.

This meeting also included sessions on the adults with congenital heart disease, which emerged as a new challenge, both to the developed and the developing countries. Drs. Chang, Redington, Sano, Nanbin Zhang, and Haibo Zhang presented their works on management of adults with congenital heart disease. In the West, adults with congenital heart disease who interface with the health care system are usually postoperative patients while these patients in Asia are typically previously undiagnosed patients or those who could not have surgery at an earlier time in their lives. Dr. Zhang

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and her data on the postoperative course of over 500 adults with Tetralogy of Fallot were most memorable.

In the cavopulmonary anastomosis session, Dr. Chang focused on the current concept that an interim bidirectional Glenn procedure (BDG) preceding the Fontan operation improves ventricular energetics after total cavopulmonary connection (TCPC). Dr. Chang also pointed out the possible etiologies of cyanosis and how to manipulate cerebral and pulmonary blood flow after BDG. Dr. Spray described the hemiFontan procedure and completion to lateral tunnel Fontan while Dr. Sano concluded that there were no differences in mortality and morbidity between lateral tunnel and extracardiac TCPC.

The highlights of the meeting include the final session on mechanical support on the myocardium. Dr. Spray described mechanical support as a bridge to heart transplant or recovery and Dr. Chang provided an update on the different short-term and long-term mechanical support types used in children. Dr. Chang pointed out that indications and contraindications for acute and chronic mechanical support continue to evolve for children. The results of acute mechanical support are encouraging and ventricular assist devices are ideally suited for fulminant myocarditis. Dr. Chang concluded that axial type devices are better suited for longer-term mechanical support for children because of its smaller size and summarized the experience with the pediatric DeBakey device.

The conference included bedside rounds in the 24-bed cardiac intensive care unit of Shanghai Children's Medical Center in the afternoon everyday after the meeting. The symposium was an excellent opportunity for Asian colleagues to present their experiences on neonates, infants

and young adults with congenital heart disease, and for Western physicians to learn about differences with patients and management between the West and the East.

Immediately after the conclusion of the meeting, a planning committee met and organized the First Asian-Pacific Pediatric Cardiology and Cardiac Surgery Symposium to be held in late fall of 2006 in Shanghai.

~CCT~



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Interested candidates should forward correspondence and curriculum vitae to Robert E. Lynch, MD, PhD, Chair, Cardiology Search Committee, Professor and Director, Pediatric Critical Care, Department of Pediatrics, Saint Louis University School of Medicine, 1465 South Grand Blvd, St. Louis, MO 63104. Tel: (314)577-5395; Fax: (314) 268-6459; email: lynchre@slu.edu

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