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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 af-

ter 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 differenti-

***"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."***

ate 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

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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 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 suffer-

*“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.”*

*“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.”*

ing 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



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extremely quickly, and expectations within the public and the scientific community are high. Cell therapy must not follow the trajectory of clinical gene 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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~CCT~



**Corresponding Author:**

Peter J. Gruber, MD, PhD  
 Attending surgeon  
 Assistant professor of Surgery,  
 University of Pennsylvania School of  
 Medicine  
 The Children's Hospital of Philadelphia  
 34th St and Civic Center Blvd.  
 Philadelphia PA, 19104 USA  
 gruber@email.chop.edu



Karl-Ludwig Laugwitz, MD, PhD  
 University of California - San Diego  
 La Jolla, CA 92093 USA

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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  $\beta$ -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-

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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.

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

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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~



**Corresponding Author:**

*Fadi F. Bitar, MD*  
 Associate Professor of Pediatrics  
 Director, Pediatric Cardiology Service  
 American University of Beirut, Lebanon  
 Phone: 961-3-310844  
 Fax: 011-961-1-342517 or  
 011-961-1-345325  
 saad@aub.edu.lb

*Oussama Khatib, MD, PhD*  
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## PFM DEVICE CLOSES PERIMEMBRANOUS VSDs

By John W. Moore, MD

Closure of the perimembranous VSD is the latest challenge for transcatheter devices. To date, the Amplatzer Perimembranous VSD Occluder (Amplatzer Medical Corporation, Golden Valley, MN) has been the only device available. Recent events in Brazil appear to have opened up the field.

In Rio de Janeiro, on January 15th and 16th Dr. Trong Phi-Le and Dr. Luis Carlos Simoes implanted some of the first pfm (Productke fur die Medicine, Cologne, Germany) devices designed to close perimembranous VSDs. In Rio de Janeiro, six patients were catheterized. Their defects were all restrictive, but hemodynamically significant. The defects ranged from 4 mm to 8 mm minimum diameter, most with some aneurysm formation. None had aortic cusp prolapse or aortic insufficiency. The distance from the superior rim of the defects to the aortic valve annulus ranged from 2 to 4 mm. These VSDs were similar to those reported in Amplatzer closures.<sup>1-3</sup>

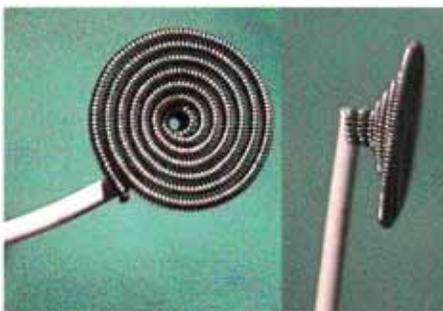


Figure 1. Nit-Occlud PDA Occluder. Photograph courtesy of Dr. Le.

Dr. Le has a track record in closing VSDs using the pfm Nit-Occlud device. The Nit-Occlud device is a nitinol coil with a cone-in-cone configuration, designed for PDA closure. It is available in most of the world without restrictions, and it is currently finishing a Phase 2 FDA clinical trial in the United States. Dr. Le has performed closure of perimembranous and muscular VSDs using the Nit-Occlud coil with surprisingly good results: achieving greater than 90% complete closure in muscular VSDs, and almost 80% in perimembranous defects by 6 months after implant. Furthermore, in more than 40 patients there have been no deaths and no major complications. Dr. Le expects that the modified Nit-Occlud device will perform even better than the earlier VSD device.

The Nit-Occlud VSD device, like the PDA device, is made of nitinol coils and has a cone-in-cone configuration. The device has been modified by adding additional larger, reinforced coil loops on both the left ventricular and the right ventricular ends of the coil. Perhaps more importantly, polyester fibers have been added to the left ventricular cone. The fibers are placed between the tightly spaced primary coils of the device, much like the synthetic fibers in a standard Cook Gianturco coil. Several prototype devices have been built, the largest being the 14 x 8 device. (The device nomenclature refers to the sizes of the largest diameter left ventricular coil, followed by the largest diameter right ventricular coil.) The 14 x 8 device has a maximum left ventricular coil diameter of 14



Figure 2. Nit-Occlud Perimembranous VSD Occluder. Photograph courtesy of Dr. Le.

mm and a maximum right ventricular coil diameter of 8 mm.

Drs. Le and Simoes implanted the Nit-Occlud VSD devices using techniques similar to those employed for the Amplatzer device. Typically, the VSD was assessed by transesophageal echocardiography and long axis oblique angiography. The defect was crossed retrograde using a Judkins right coronary catheter and a floppy wire. The wire was advanced into the pulmonary artery, with care to avoid the moderator band and the tricuspid apparatus. The wire tip was snared in the pulmonary artery by a loop snare introduced in the femoral vein. The wire end was externalized and a "rail" established. The Judkins catheter was advanced through the VSD along the rail into the inferior vena cava. A 7 French long sheath (Cook Flexor or Cordis Brite Tip) was introduced into the femoral vein, and advanced on the rail until the dilator "docked" with the tip of the Judkins catheter introduced in the femoral

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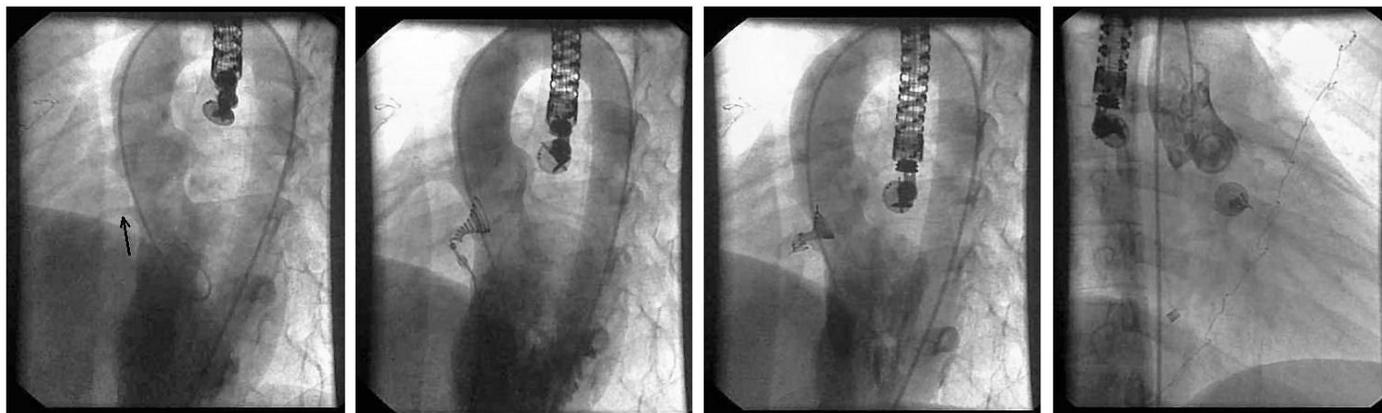


Figure 3 (A-D). (A) VSD prior to device closure; (B) Nit-Occluder device in VSD prior to release; (C) Nit-Occluder device in VSD after release; (D) Nit-Occluder device does not interfere with aortic valve function. Courtesy of Dr. Simoes.

artery. Clamps were attached to both ends of the wire securing a tight docking of dilator and Judkins catheter. The sheath was advanced as the Judkins was withdrawn, until the sheath passed through the VSD and was com-



Figure 4. Drs. Simoes and Le confer prior to VSD Closure.

fortably into the ascending aorta. The Judkins catheter was removed and a pigtail catheter was advanced from the femoral artery along the wire until it met the dilator. Subsequently, the dilator was removed and the pigtail catheter was advanced into the sheath to the level of the hepatic portion of the IVC, this maneuver to prevent sheath kink-

ing. The Nit-Occlud delivery catheter was introduced into the sheath and advanced to the tip of the pigtail catheter. The delivery catheter was further advanced into the ascending aorta as the pigtail catheter was withdrawn from the sheath. The delivery catheter was extended outside the long sheath, and the distal cone of the device was formed by pushing the coil outside the catheter. The distal cone was gently pulled to the level of the aortic sinuses and allowed to fall through the aortic valve into the left ventricular outflow tract. Once in the outflow tract, the distal coil cone was gently pulled into the VSD, guided by echocardiography and fluoroscopy. The largest one or two loops remain opposed to the left ventricular rims of the defect. The remainder of the coil cone is within the defect. Finally, the reverse cone of the device is developed to anchor the device. This is done carefully in order to avoid entrapping tricuspid valve structures. Angiography and echocardiography are employed to verify good device position, and the device is detached.

Of the six procedures performed in Rio de Janeiro, five were successful with 4

patients achieving total occlusion prior to departing from the catheterization laboratory. One patient had good device position, but had a small amount of leaking at the time of the last angiogram. The unsuccessful patient, interestingly, had the smallest defect (4 mm) and the least aortic side rim (about 2 mm). Dr. Le felt that an 8 mm maximum aortic coil diameter was appropriate. The smallest available device had a 10 mm coil diameter. Closure with a smaller Nit-Occlud PDA device was attempted, without success. This coil was removed. There were no complications



Figure 5. Dr. Le and Dr. Simoes perform a VSD Closure.



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in these six patients. Early follow up shows that all five with device implants were totally closed at their first follow-up echocardiograms.

Dr. Le later traveled on to Puerto Alegre and Sao Paulo, and the Rio de Janeiro experience was repeated in the labs of Dr. Raul Rossi Filho and Dr. Carlos Pedra. From there he traveled to Vietnam, presumably to implant additional devices.

Certainly, these anecdotal results look promising. We should look forward to Dr. Le's data from the first series of pfm Nit-Occlud VSD device implants. Many of our colleagues will get to observe the procedure soon because Dr. Carlos Pedra is planning to perform a live case demonstration at PICS in Buenos Aires this September. Stay tuned!

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~CCT~



John W. Moore, MD, MPH, FACC  
 Director of the Pediatric Cardiac Catheterization Laboratory  
 Mattel Children's Hospital at UCLA  
 Los Angeles, CA USA

[jwmoore@mednet.ucla.edu](mailto:jwmoore@mednet.ucla.edu)



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# HIGHLIGHTS FROM THE PEDIRHYTHM II (PEDIATRIC RHYTHM CONGRESS) IN ANTALYA, TURKEY

By Alpay Çeliker, MD

Building on the success of our first Pediatric Rhythm Congress (Pedirhythm I) held in Istanbul in 2003, Pedirhythm II was held in on the Mediterranean Coast of Turkey



Figure 1. Dr. John Triedman at Opening Ceremony.

in Antalya, from June 15-18 and attracted international interest



Figure 2. Drs. Michael Schaffer, Sema Ozer and Eric Rosenthal at welcome reception.

(Figure 1-3). A total of 98 physicians and other health care professionals attended from Turkey, East-



Figure 3. Faculty members and attendants at one of breaks.

ern and Western Europe, and North America. The faculty, drawn from three continents, brought a high level of participation to the conference, giving a series of didactic lectures and workshops, as well as being actively involved in the discussions following each didactic and abstract presentation. Following the opening Keynote Address by Dr. Ali Oto, the President of the Turkish Cardiology Society, addressing the problem of atrial fibrillation, the main Congress kicked off with a series of pacing related topics, talks on a series of "hot topics" in pediatric electrophysiology, including cryoablation and 3-D navigation systems and a session covering the treatment of chronic arrhythmias such as PJRT and ectopic atrial tachycardia (Figure 4). On the second day of the Congress, there was a session devoted to the

difficult problem of ventricular arrhythmias in pediatrics. Six workshops were presented in a "Meet the Experts" format and covered such topics as syncope, ICD programming and lead extraction. A special symposium was devoted to various aspects of ICD use in pediatric patients. The third day ended with symposia devoted to post operative arrhythmias, and on the latest information concerning genetic arrhythmia syndromes.

The international faculty included Drs. Ali Oto, Bulent Ozin, Kamil Adalet, Remzi Karaoguz, and Alpay Çeliker from Turkey, John Papagiannis from Greece, Isabelle Denjoy from France, Eric Rosenthal from the U., Margreet Bink-Boelkens from the Netherlands, Urs Bauersfeld from Switzerland, Narayamswami Sreeram from Germany, and Barbara Deal, John Triedman,



Figure 4. Drs. George Van Hare and John Triedman on one of the panels.

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Figure 5. Drs. Barbara Deal and Margreet Bink-Boelkens at lunch break.

Richard Friedman, Michael Shaffer and George Van Hare from the USA (Figure 5). Unfortunately, Dr. Elizabeth Villain, from France, was not able to come due to a family emergency.

Many abstracts were submitted from all the countries represented, some of which were presented orally, and others as posters. The faculty judged the oral presentations on the basis of scientific quality, skill of the presentation and discussion, and enthusiasm, and awarded first prize to Dr. Zual

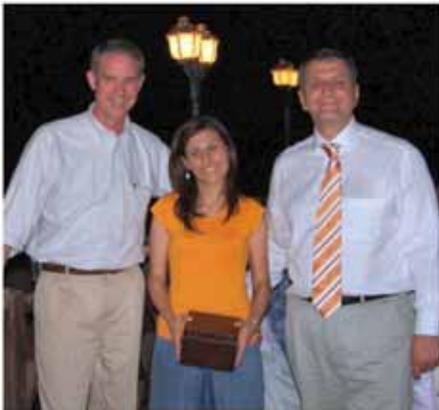


Figure 6. Drs. George Van Hare and Alpay Çeliker with Dr. Zual Ulger of Izmir of Turkey.

Ulger of Izmir, Turkey, for her abstract entitled "Assessment of tilt test results and the effect of  $\beta$ -blocker treatment in children with neurocardiogenic syncope" (Figure 6).

On the evening of the second night, we all attended a Gala Dinner, where we ate, drank and danced under the stars, with a gentle and warm Mediterranean breeze (Figure 7). Following the conclusion of the Congress, many faculty and partici-



Figure 7. Scene from gala dinner.

pants stayed for a tour of the region which included a visit to Aspendos, an ancient town with a spectacularly well-preserved Roman amphitheater. At the end of the tour, we said "goodbye" and began planning for Pedirhythm III, tentatively to be held in Istanbul in October 2007. Don't miss it!

The principal sponsor of Pedirhythm II was Medtronic, with additional sponsorship from Phillips, St. Jude, Medes, Schiller, Guidant, Johnson & Johnson and Spectranetics. Continuing Medical Education accreditation was provided by the European Board for Accreditation in Cardiology ([www.ebac-cme.org](http://www.ebac-cme.org)) with 15 points.

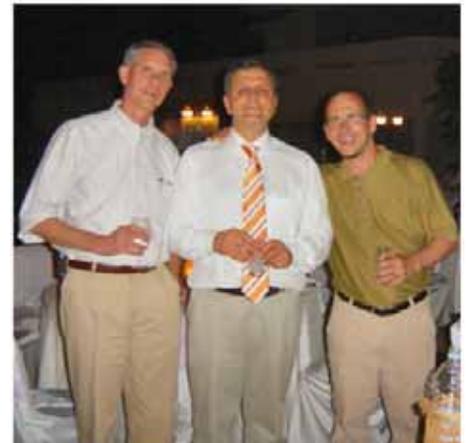


Figure 8. Pedirhythm Co-Directors - Drs. George Van Hare, Alpay Çeliker and John Triedman.

Alpay Çeliker, MD, George Van Hare, MD, and John Triedman, MD Congress Co-Directors (Figure 8).

For more information on Pedirhythm III, go to: [www.pedirhythm.org](http://www.pedirhythm.org)

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Alpay Çeliker MD  
Hacettepe University  
Department of Pediatric  
Cardiology  
06100 Sıhhiye  
Ankara, Turkey  
Tel: 90 312 3104258  
Fax: 90 312 3090220  
GSM: 90 532 2921015

[aceliker@hacettepe.edu.tr](mailto:aceliker@hacettepe.edu.tr)

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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

tation 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



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

care, adults with congenital heart disease, cavopulmonary anastomosis, and mechanical support of 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 presen-

population of neonates with congenital heart disease. Dr. Spray pointed out the mortality for the SGA infant was lower than that for infants born AGA. 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

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Texas Children's Hospital delineated the differences in cardiopulmonary pathophysiology between LBW and normal birth weight neonates and 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 session, 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 effica-

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*“Asian cardiac caretakers have a myriad of additional challenges such as lack of resources and late referrals.”*

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cious 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 sildenafil, 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% O<sub>2</sub> 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



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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,

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*“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.”*

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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 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 evening 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~



**Corresponding Author:**

*Anthony C. Chang, MD, MBA  
Chief, Critical Cardiology,  
Director, Cardiac Intensive Care  
Service  
Texas Children’s Hospital  
Baylor College of Medicine  
6621 Fannin Avenue, MC19345C  
Houston, TX 77030 USA  
Phone: +1-832-826-5640 / 5671  
acchang@texaschildrenshospital.org*



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Associate Professor & Director,  
Surgical Intensive Care Unit, Children’s  
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