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Postpericardiotomy Syndrome After Surgical Ligation of Patent Ductus Arteriosus in an Extremely Premature Neonate

By Praveen Kumar, MD; Mohammed Sabit, MD; Rekha Bandepalli, MD; Huda Elshershari, MD

Abstract

Postpericardiotomy Syndrome is uncommon in infants. We describe a premature neonate who underwent a ligation of patent ductus arteriosus through a median sternotomy approach and developed Postpericardiotomy Syndrome. After initial uneventful postoperative course, the patient was noted to have pericardial effusion on the tenth postoperative day. Steroids were administered and pericardial drainage was indicated due to progressive increase of effusion.

Keywords
- Pericardial effusion
- Complication
- Inflammatory reaction

Introduction

Postpericardiotomy Syndrome is a frequent complication of open-heart surgery that involves opening the pericardium[1]. It occurs secondary to an inflammatory reaction in the pericardium and pleura, and is characterized by fever, chest pain, pericardial and pleural effusion. The exact etiology of Postpericardiotomy Syndrome is unknown and postulated to be an immunologic response to the damaged pericardium. Postpericardiotomy Syndrome is uncommon in infants. We report on a low birth weight extremely premature neonate who developed Postpericardiotomy Syndrome following surgical ligation of patent ductus arteriosus. The pericardial effusion had to be drained due to failure of medical treatment. To the best of our knowledge, there are no previous reports of Postpericardiotomy Syndrome in an extremely premature infant.

Case report

A male infant was born at 24 weeks gestation with a birth weight of 670 grams, and was admitted to the neonatal intensive care unit for treatment and management of extreme prematurity. He was noted to have a patent ductus arteriosus, and failed a trial of indomethacin treatment on Days of Life Four and Five. The infant had increased pulmonary blood flow due to significant

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left to right shunting through the patent ductus arteriosus which resulted in steal from the systemic circulation. These hemodynamic changes caused prolonged ventilator dependence and he developed acute renal failure. Therefore, surgical ligaton of patent ductus arteriosus was indicated and he underwent this procedure on Day of Life 45. The operation was performed intrapericardially through a median sternotomy approach because the infant was on high frequency oscillatory ventilation. The operative procedure was completed without any complications.

Cardiomegaly was noted on the chest x-ray during the first week of postoperative follow-up. An echocardiogram was performed which showed a moderate pericardial effusion, Figure 1. The clinical picture was suggestive of inflammatory etiology. Complete blood count revealed hemoglobin of 10.9 gram/dl, white blood cell 18.1 and platelet of 96 mm3, C-reactive protein 1.5 mg/dl. The patient was stable from a cardiac standpoint without any signs of cardiac tamponade. In view of the low platelets, the patient was started on steroids. Over the course of the next days, serial echocardiograms showed persistence of effusion despite steroid therapy without any change. Due to progressive increase in the size of effusion, percardiocentesis was performed after one week of failed steroid therapy. The fluid was serosanguinous in nature, cell counts and chemistries were not suggestive of infectious etiology, and subsequent viral and bacterial cultures were negative. During follow-up, imaging study showed no recurrence of pericardial effusion, Figure 2.

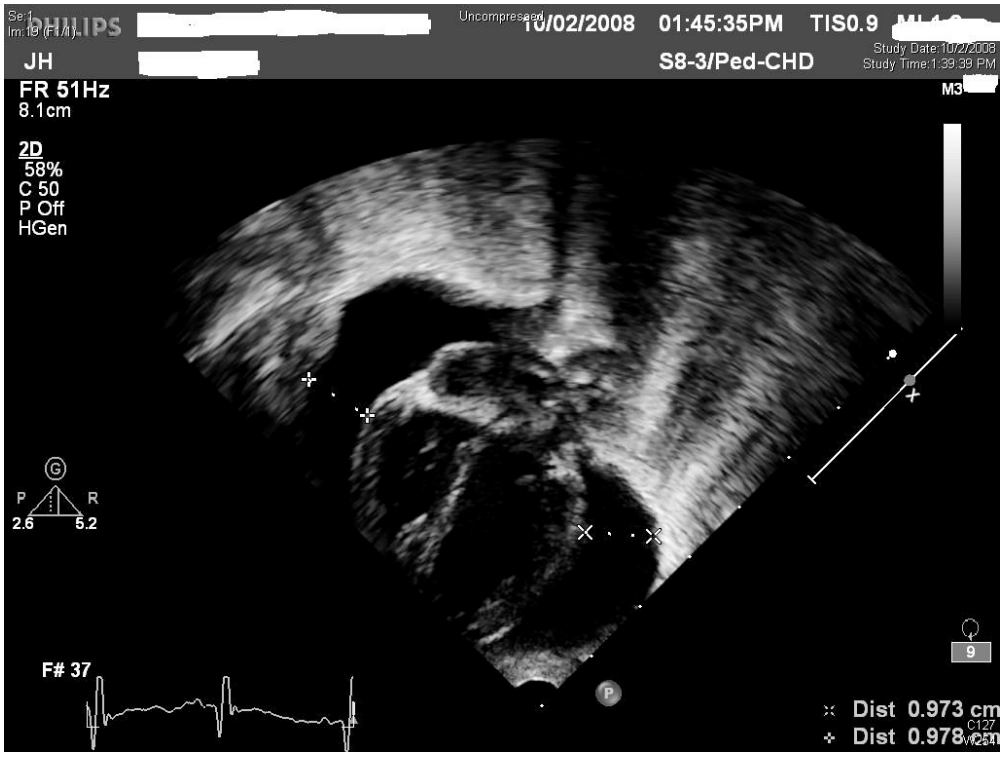

Figure 1. Two-dimensional echocardiogram showed moderate pericardial effusion.

Discussion

Patent ductus arteriosus is a common congenial heart defect. Many babies in the neonatal intensive care nurseries may have this as one of their problems. In a premature infant, the patent ductus arteriosus often closes on its own in the weeks after birth. In a full-term infant, a patent ductus arteriosus usually will close within the first few days of life. If the ductus remains and fails to respond to medical management, surgical closure is the last resort. Since the closure of the patent ductus arteriosus is not associated with frequent complications, the condition usually has a good prognosis. Our patient underwent the traditional closure of patent ductus arteriosus due to failure of medical treatment, and was noted to have pericardial effusion on the tenth postoperative day.

Postpercardiotomy Syndrome occurs in 25 to 30% of patients after open heart surgery and cardiac tamponade is reported in 0.7 to 3% of postoperative patients[1]. The etiology and pathogenesis of Postpericardiotomy Syndrome is unclear. There is possible association with viral infections and Autoimmune process[2,3]. In some cases of Postpericardiotomy Syndrome, the viral titers and antimyocardial antibodies were increased. Though, recent investigations had revealed no evidence of viral etiology[4]. The extent of myocardial injury is also implicated as one of the factors for Postpericardiotomy Syndrome. However, Postpericardiotomy Syndrome has been reported after minor cardiac injury; such as permanent pacemaker implantation[5], percutaneous closure of secundum atrial septal defects[6].

A prospective study by Prabhu et al, evaluated the incidence of postoperative pericardial effusions after open-heart surgery in children and showed decreased incidence of postoperative pericardial effusions after cardiac surgery for congenital heart disease[1]. This study composed of 212 patients with median age of 2.4 years (range from 4 months to 18

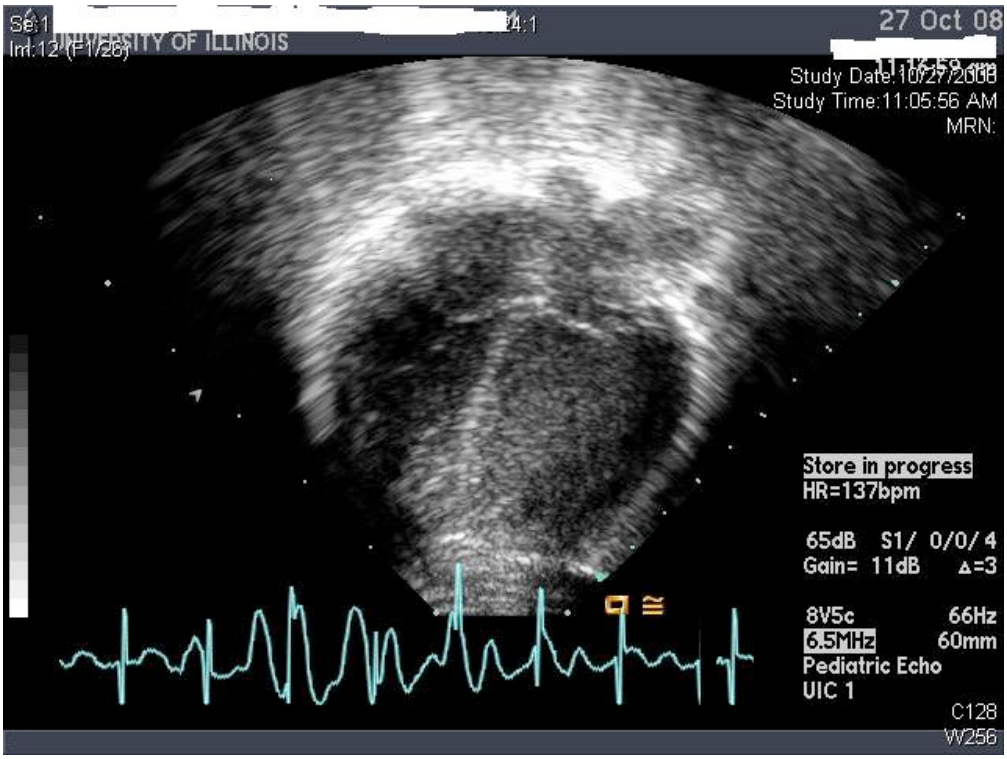

Figure 2. Two-dimensional echocardiogram during follow-up showed no evidence of pericardial effusion.

years). In another study of 15 cases with recurrent pericarditis following atrial septal defect, the age range was from 6.5 years to 16.8 years (Median 11.6 years)[7]. To the best of our knowledge, there is no previous report of Postpericardiotomy Syndrome following ligation of patent ductus arteriosus in extremely premature infant at age of less than 2 month.

The treatment of Postpericardiotomy Syndrome includes the use of non-steroidal anti-inflammatory agents, corticosteroids, colchicine and intravenous immunoglobulins. Aspirin and Ibuprofen are used as first-line therapy[8]. Corticosteroids are preferred if the pericardial effusion is moderate to severe[9]. Cochicine and intravenous immunoglobulins are effective in the treatment of recurrent pericarditis. Patients with recurrent pericarditis resistant to prednisone and colchicine were successfully treated with intravenous immunoglobulins[10].

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The Abstract of this case report was presented at the *33rd Annual Scientific Meeting of the Midwest Pediatric Cardiology Society* that was held in Pittsburgh, PA on October 6-7, 2009.

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SCAI View - A Monthly Column from The Society for Cardiac Angiography and Interventions

By Ziyad M. Hijazi, MD, MPH

Recognizing that the future of interventional cardiology lies in the hands of Fellows-in-Training (FITs), The Society of Cardiovascular Angiography and Interventions (SCAI) will once again be offering its *Annual Congenital / Structural Interventional Cardiology Fall Fellows Course* as part of its greater Interventional Cardiology Fellows Courses programming in Las Vegas, NV, December 5-10, 2010.

The *Fall Fellows Course* is a unique opportunity for congenital or structural interventionalists-in-training to receive final preparation before entering the real world as full-fledged specialists. Offered to 3rd year pediatric cardiology fellows interested in cardiac catheterization as well as 4th year interventional cardiology fellows, the course provides a unique opportunity for fellows to interact with internationally recognized faculty, further their education with guidance from premiere practicing physicians, and learn the latest cutting-edge technology in the field. Fellows attend five days of expense-free hands-on workshops, live-case medical simulations, and clinical case presentations.

Throughout the years we have hosted this course, we have seen 90% of the interventional cardiology fellows from the United States, plus others from around the world. Last year's program attracted over 250 interventional cardiology FITs from 6 continents! Bottom line, if you're a fellow-in-training, and can only attend one fellows course this year, you better be sure it's *SCAI Fall Fellows*. If you are a training program director, please be sure to encourage your fellows to attend.

This year's impressive Congenital / Structural faculty includes: Zahid Amin, MD, FSCAI; Lee Benson, MD, FSCAI; John P. Cheatham, MD, FSCAI; Ted Feldman, MD, FSCAI; Craig Fleishman, MD, FSCAI; William E. Hellendbrand, MD, FSCAI; Eric Horlick, MD, FSCAI; Tom Jones, MD, FSCAI and Shakeel Qureshi, MD, FSCAI, as well as myself. The overall program includes over 30 renowned interventional cardiologists. The faculty prides itself in making time not just for lectures from the podium, but also small-group discussions about how to launch and nurture a career in today's complex healthcare environment.

More information on *SCAI Fall Fellows* is available online at www.scai.org/Fellows.

SCAI PUBLISHES STRUCTURAL HEART DISEASE CORE CURRICULUM

In other exciting news for interventional training directors and FITs, SCAI recently published a first-of-its-kind core curriculum in structural heart disease, defining training and credentialing requirements along with program standards for practitioners who perform interventional structural heart disease procedures. Many thanks for lead author Carlos Ruiz, MD, PhD, FSCAI and his brilliant supporting cast for making this much-needed document happen.

Published in SCAI's official journal, *Catheterization & Cardiovascular Interventions*, the core curriculum outlines specific training recommendations and skill requirements for certification as a structural heart disease practitioner, including:

- Superb basic catheterization skills with the ability to achieve unusual types of vascular access and manipulate various catheters, balloons and other devices.
- The ability to competently handle potential complications resulting from interventional treatment.
- A knowledge base and interventional skills for a variety of complex structural heart diseases including: appropriate device selection, imaging needs, stenting techniques, managing complications and acute and long-term post-procedural care.

Additionally, specific guidelines for adequate structural heart disease training centers include:

- A structural heart center composed of integrated and dedicated faculty members from various specialties, including: anesthesiology, pediatrics, surgery and radiology, among others.
- Staff and faculty dedicated to mentorship.
- Sufficient patient volume with a variety of patient case levels.
- Hybrid procedure rooms, sophisticated imaging equipment and simulation technology.
- Formal didactic sessions, ongoing mentorship opportunities, weekly medical-surgical structural heart disease conferences, inpatient and outpatient consultation services, and clinical follow-up.

"The Fall Fellows Course is a unique opportunity for congenital or structural interventionalists-in-training to receive final preparation before entering the real world as full-fledged specialists."

For more information, just visit www.SCAI.org.

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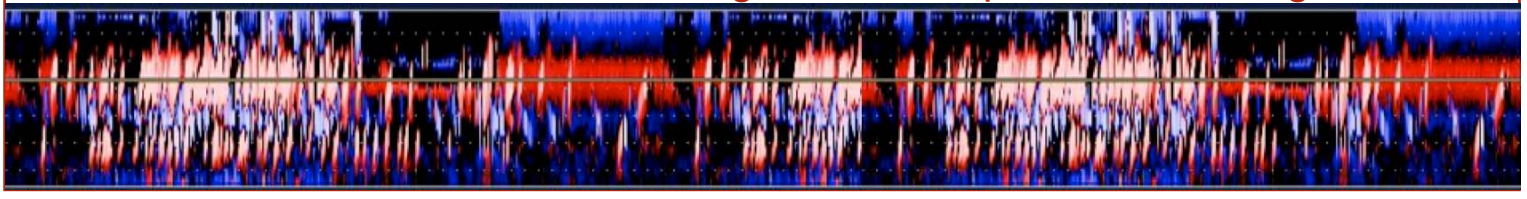

Highlights from Pediatric & Adult International Cardiac Symposium (PICS & AICS 2010)

By Ziyad M. Hijazi, MD, MPH

PICS/AICS 2010 was held in Chicago, IL from July 17th-21st, 2010! It had been 5 years since we had the meeting in Chicago and the feedback we received about the venue and city was unbelievable.

More than 770 attendees from over 55 countries attended the meeting. This year, we introduced for the first time a new pre-meeting symposium *"Imaging In Congenital And Structural Cardiovascular Interventional Therapies*." This symposium was directed by Dr. Frank E. Silvestry from University of Pennsylvania and Dr. Girish Shirali from Medical University of South Carolina and had 30 faculty members. The meeting started in the morning with an overview of imaging modalities, how and which one to choose. After that session, various specific lesions were discussed in more detail, including ASD/PFO and VSD. For each lesion, Dr. Paul Weinberg showed pathological specimens and made correlation to imaging. Then breakout sessions were held in the afternoon where some attendees opted for congenital interventions and others for structural interventions. The day was very well-attended, with more than 350 people. The feedback on that day was very good and we're planning to repeat such an imaging symposium next year.

Then on Sunday, July 18th, 2010, the actual *PICS/AICS* meeting started with a comprehensive workshop on ASDs/PFOs from 8:00 am-1:00 pm. The workshop was very heavily attended. Basically, everything you need to know about ASDs/PFOs was discussed in this workshop. Every available device inside and outside the US was discussed. Update on the stroke and migraine trials was also given.

At about 1:00 pm, Dr. Gerard Martin, Chair of the ACC Section on Pediatric Cardiology and Adult Congenital Heart Disease, gave an excellent talk about the NCDR IMPACT registry, which has been developed to track congenital interventions (outcome/complications/etc). This registry will no doubt be the best and most comprehensive in our field. Hospitals and 3rd party payers will use data from this registry for reimbursement and credentialing.

In the afternoon, oral abstract presentations and "Meet the Expert" sessions were also well attended. This year about 38 of the best-accepted abstracts were selected for oral presentations and all abstracts were published in *Catheterization Cardiovascular Interventions*.

At the end of the day, the exhibit officially opened with 27 exhibitors representing various device/product manufacturing companies and cheese and wine were served.

Monday, July 19th was the official opening day of *PICS/AICS,* and that was an extremely busy day.

Live cases were transmitted from three international venues: From Saudi Arabia, Dr. Tarek Momenah hosted Dr. Shakeel Qureshi as a guest operator/commentator and they have done superb three cases including a percutaneous pulmonary valve implantation using the Edwards Sapien valve and another case using the Melody valve and finally, a coarctation stent case using the CP stent.

From Brazil, Dr. Carlos Pedra and his team performed very good four cases, including ASD/PFO/Coarctation using Occlutech devices and CP stent and an Atrium stent.

From the Heart Hospital in London, Dr. Michael Mullen also performed three excellent cases including: a percutaneous pulmonary valve using the Edwards valve and a PFO and an ASD case using the Coherex Flatstent and the Occlutech device.

At noon on Monday, we had a lunch symposium where we discussed safety in operating rooms/catheterization laboratory and compared our work to aviation safety. Captain Michael Quiello, VP at United Airlines, and Dr. Emile Bacha gave the talks, which were very well-received.

Top, from left-to-right: Dr. Larry Latson (receiving the PICS Achievement Award), Drs. Ziyad M. Hijazi, William E. Hellenbrand and John P. Cheatham.
Bottom, from left-to-right: Dr. John P. Cheatham, Mr. William Cook (receiving the PICS Pioneer Award), Drs. Ziyad M. Hijazi and William E. Hellenbrand.

The afternoon was extremely busy; we had a breakout session for nurses and technologists. This session was very well-attended. Eleven speakers gave excellent presentations, and I heard the most popular one was "Analyze This!" which included hemodynamic traces/fluoro images, etc.

Also, in the afternoon, there was a debate between a cardiologist and a cardiac surgeon regarding aortic valve stenosis; this debate was very good, and both Drs. Phillip Moore and Bacha did an excellent job.

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The last didactic session of the day was a very popular workshop, "Embolization Therapies," supported by a grant from Cook Medical. In this workshop, we heard: Dr. Lee Benson talk about how to stock the cath lab for effective embolization therapy; Dr. Robert White, the world's foremost expert on pulmonary AVMs, talked about how to manage these patients; Dr. Dan Levi discussed AP collaterals; Dr. Benson again discussed coronary AV fistulas; Dr. Don Hagler discussed venovenous collaterals and Dr. Jo DeGiovanni talked about complications encountered during embolization therapy.

Monday evening was the time for two special awards: *The PICS Pioneer Award*! This was the second time we have presented this award. The first one was given to Dr. Terry D. King; this year's recipient was Mr. William Cook, founder of the Cook Group, for his achievements and contributions to our field and others in the last fifty years. Many Cook employees had flown specifically for this occasion. The second award was the conventional *PICS Achievement Award*, which was given this year to Dr. Larry Latson from Cleveland Clinic, for the work he has done over the years to both advance interventional cardiology and to advance our understanding of congenital heart disease.

On Tuesday, live case demonstrations were performed from Chicago (Rush Center for Congenital Heart Disease) where our team performed three cases. The last one I performed ended rather late, and made me miss the Gala Night for the first time in 14 years.

Drs. John P. Cheatham, Ralf Holzer, Alistair Phillips and Ms. Sharon Hill performed very good cases from Nationwide Children's Hospital in Columbus: an interesting case of a small baby undergoing closure of an ASD using the Amplatzer Septal device, and a very nice demonstration of the closure of a PDA using the Amplatzer Duct Occlud.

The didactic sessions started rather early that day at 6:30 am, with the first breakout session "Adults with CHD." There were many didactic sessions including: Vascular Access And Its Complications; Aortic Valve and Arch Diseases; The Ventricular Septum and The RVOT. The second breakout session of the day was dedicated to structural heart disease interventions, where experts in the field gave 8 different talks.

"More than 770 attendees from over 55 countries attended the meeting. This year, we introduced for the first time a new pre-meeting symposium 'Imaging In Congenital And Structural Cardiovascular Interventional Therapies.'"

At the end of the day, all attendees were treated to a beautiful night aboard the ship, the Odyssey, that sailed in Lake Michigan under the blue skies of Chicago; we could not have asked for better weather than that night. This was the 14th Gala, and as I mentioned above, for the first time, I missed this one!

On Wednesday, Drs. Saibal Kar and Raj Makkar performed cases from Cedar Sinai Medical Center in Los Angeles. They performed three very good cases including: alcohol septal ablation, a VSD and an ASD. There was a lot of discussion about the VSD case, and I just recently received a letter from that patient expressing her gratitude to all of us for the discussion we had surrounding her case. She mentioned that over the last few weeks she feels as if she were a new person.

From Seattle Children's Hospital, Dr. Tom Jones performed three cases with a lot of discussion and debate that was truly informative.

The didactic sessions were very educational that day, and included: breakout session on hybrid & fetal interventions; the RVOT; the PDA, and another breakout session on structural heart disease interventions.

The last session of the day was, "Futuristic Things." Drs. Bonhoeffer, Levi, Cheatham, Forbes and Fish presented this session. They talked about what they are working on, a sort of "glimpse into the future." Despite being the last session of the day and the last one of the meeting, this session was very well-attended.

PICS/AICS closed after five days of intense education, where people met and shared their experiences. It is the only course of its kind in the U.S. dedicated to the field of intervention for congenital and structural heart disease in children and adults.

Next year's course will take place July 24-27, 2011 at the Westin Boston Waterfront in Boston, MA. *PICS* started in Boston in 1997, and we will celebrate our 15th anniversary there.

One last update, after 14 years of dedication to *PICS*, Dr. William Hellenbrand decided to retire his role as a course director. We want to thank Bill for his service all these years. His leadership has been very clear, and we wish Bill the very best. He will be always on the *PICS/AICS* cover as Director Emeritus. To fill his position, the course directors choose Dr. Thomas Jones from Seattle Children's Hospital to be the fourth director of the course. "Tom, welcome aboard; we look forward to working with you. You have been a very active faculty member for all these years and no one deserves this role more than you."

Please visit *PICS* website for more details and update for next year's program: www.picsymposium.com.

Hope to see you in Boston!

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Unique Conference on Barth Syndrome Showcases Progress, Including a Knockdown Mouse Model of This Rare Disease

By Matthew J. Toth, PhD

During the last week in July, the Renaissance Orlando, Florida SeaWorld Hotel hosted one of the truly unique meetings that deals with a rare disease. Barth Syndrome is a rare, but serious genetic disorder characterized by: cardiomyopathy (dilated or hypertrophic, often with left ventricular noncompaction and/or endocardial fibroelastomosis), growth delay, exercise intolerance or extreme fatigue, neutropenia, and cardiolipin abnormalities. On July 29th-30th, 2010, over 65 scientists, physicians, and healthcare professionals met to hear 26 speakers, and to discuss the progress in Barth Syndrome research, and how it may lead to better treatments. In a separate, but parallel set of meetings, over 40 Barth Syndrome individuals with their families also met to discuss issues of specific importance to their situation. The informal mixing of scientists, physicians, patients, and patient families at common meals, at the poster session, and at the social function, is an invigorating, valuable, and traditional part of this conference series.

This is the fifth conference that has been hosted by the Barth Syndrome Foundation (BSF), an international, non-profit, patient-advocacy organization which also sponsors a research grant program every year. The year 2010 marks the 10th anniversary of the founding of the BSF by family members. Many of the speakers at this conference were previous grant recipients. This year a keynote lecture, "The Pathophysiology of Mitochondrial Disease," was delivered by Professor Douglas C. Wallace, Director of the Center of Mitochondrial and Epigenomic Medicine, Children's Hospital of Philadelphia and the University of Pennsylvania. The scientific and medical sessions of the 2010 conference were funded, in part, by grants from the Office of Rare Disease Research and the National Heart, Lung and Blood Institute of the NIH.

Animal models of Barth Syndrome led off the scientific/medical sessions, and the initial reports of the Tafazzin knockdown mouse (provided by the BSF to all interested researchers) were quite encouraging. Tafazzin is the gene which, when defective, is responsible for Barth Syndrome. Previous efforts in several laboratories to make a knockout mouse model have been unsuccessful for unknown reasons. Zaza Khuchua (Cincinnati Children's Hospital Medical Center) and colleagues, and Michael Kiebish (Washington University School of Medicine) revealed that this knockdown mouse model possesses the cardiolipin abnormalities expected. Interestingly, Dr. Khuchua showed left ventricular dilation and muscle mass loss in 8-month-old mice which were unremarkable for this at 2 months of age. Dr. Khuchua also showed abnormal mitochondrial morphology and other ultrastructural abnormalities in various striated muscle tissue samples. Genevieve Sparagna (University of Colorado, Boulder) showed that linoleic acid diet supplementation increased tetralinoleic cardiolipin levels in a rat model of heart failure (Spontaneously Hypertensive and Heart Failure rat model: SHHF), resulting in an extended lifespan. Carol Moreno-Quinn (Medical College of Wisconsin) updated the group about making a Tafazzin knockdown rat model. Using exercise as therapeutic treatment, Mark Tarnopolsky (McMaster University) showed how mitochondrial DNA deletions in elderly people can be reversed by exercise and what this may mean for Barth Syndrome, a unique mitochondrial disease. Todd Cade (Washington University School of Medicine) is now testing this idea of supervised aerobic exercise training (cardiac rehabilitation) to determine its effects on Barth Syndrome individuals.

Todd Cade along with Carolyn Spencer and Amy Roberts (both at Children's Hospital of Boston) presented the unique physiological characteristics of Barth Syndrome individuals (such as the dramatically increased respiratory exchange ratio and stable blood oxygen saturation levels with an increasing exercise gradient). The Barth Syndrome Medical Database & BioRepository, which is supported by the BSF and now by Children's Hospital of Boston, will collect and store these data and other relevant medical information for interested researchers to use.

Colin Steward (Royal Children's Hospital, Bristol, England) has found many unrecognized cases of Barth Syndrome in the Bristol area by pursuing the neutropenia aspect of the disease and following up on unexplained male fetal deaths in family histories. Dr. Steward related his experiences of setting up a National Specialized Service for Barth

Syndrome in the UK, and provided insights for establishing a similar group in the US.

Because the Barth Syndrome is a mitochondrial disease, there were several presentations about how defects in this subcellular organelle could influence the symptoms of patients. Charles Hoppel (Case Western Reserve University) provided an overview of mitochondrial diseases by focusing on oxidative phosphorylation defects. John Lynn Jefferies (Texas Children's Hospital) spoke about the cardiomyopathy found in Barth Syndrome, while Quan He (Henry Ford Hospital) showed how the knockdown of Tafazzin by siRNA in rat neonatal cardiac myocytes caused hypertrophy.

Robert Jensen (Johns Hopkins University) illuminated the important parallels between Barth Syndrome and Dilated Cardiomyopathy with Ataxia (DCMA), and how mitochondrial protein transport may link the common symptoms of these two genetically distinct, but similar, rare conditions. On a research angle, Christopher McMaster (Dalhousie University) used a systematic genome-wide analysis to identify genes that interact with the yeast Tafazzin gene which included several involving mitochondrial protein import and protein stability. Interestingly, Dr. McMaster is adapting his system to analyze pharmaceutical compounds that interact with the same yeast Tafazzin mutant which could lead to relevant drug discovery situations.

In addition to the above presentations, a small poster session was held that was well received by both the science/medicine attendees and by the families of Barth Syndrome individuals. The interactions between these two groups are extremely important, as both groups get to know and appreciate the details and the problems each face—a perspective that often is lacking in other science/medicine-oriented meetings.

The Varner Award for Pioneers in Science and Medicine was presented to Daniela Toniolo and posthumously to Peter Vreken. Dr. Toniolo (Research Director, National Research Council of Italy, DIBIT-San Raffaele Research Institute, Milan, Italy) was recognized for her discovery of the Tafazzin gene, and the late Dr. Vreken (Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands) was recognized as the first to publish on the cardiolipin deficiency of Barth Syndrome individuals.

Also unique to this conference is the "clinic" or information gathering session hosted by Barth Syndrome physicians and researchers. This "clinic" serves at least two purposes: it allows the efficient collection of historical information and physiological data about this rare disease, and it provides opportunities for patients and patient family members to hear from physicians who have substantial experience in treating Barth Syndrome individuals. In 2010 several distinct IRB-approved protocols were performed with the participation of many of the Barth Syndrome individuals who attended the conference. Most of the information collected is expected to lead to publications or to be available through the Barth Syndrome Medical Database & BioRepository which is open to all interested researchers.

The 2010 conference hosted the greatest number of speakers in its history of which only a few are mentioned here. The meeting was packed with new information and new developments. The individual presentations, for both the scientific/medical sessions and the family sessions, were recorded on DVDs, and will soon be available for a nominal cost by contacting the BSF (www.barthsyndrome.org). Given the breadth and quality of the work presented at this latest conference, the next meeting in 2012 is sure to reveal even more progress towards a specific treatment for this rare disease.

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Medical News, Products and Information

Marfan, a 'Look-Alike' Disorder, or Neither?

Johns Hopkins researchers have compiled what they believe are reliable lists of tell-tale physical signs to help doctors recognize children with Marfan and Loeys-Dietz Syndromes. Timely and early diagnosis of both genetic disorders can mean the difference between life and death, but some of the most common physical features are also found in people with neither of the syndromes, which can cause confusion.

Published as two separate studies in the August issue of the *Journal of Bone and Joint Surgery*, the two lists enumerate physical features that in certain combinations are highly suggestive of either Marfan or Loeys-Dietz syndromes, connective tissue disorders similar in presentation, but caused by different genetic glitches. Many of the signal features of these disorders involve the face, skull, joints and spine, making them easy to spot during a physical exam, but not always easy to sort out.

"The beauty of our lists is that they require no fancy imaging tests and most of the signs are right there for the pediatricians and the orthopedic surgeons to see," says co-investigator Paul Sponseller, MD, MBA, Director of Orthopaedics at Johns Hopkins Children's Center. "All they have to do is see the forest for the trees. The lists will help them do so."

According the investigators, if diagnosed in childhood, both disorders can be managed with drugs or surgery to head off the most life-threatening complications — arterial aneurysms or enlargement and rupture of the aorta.

"We miss that prevention opportunity in people diagnosed as adults," Sponseller says.

Both Marfan and Loeys-Dietz syndromes affect the connective tissue of the heart, spine, joints and eyes, but Loeys-Dietz is also marked by twisted arteries that are prone to aneurysms, a feature absent in Marfan. And because people who have Loeys-Dietz tend to experience tearing of the aorta earlier than Marfan patients, they often need earlier and more aggressive treatment, including surgery.

Marfan

Starting out with a comprehensive list of 20 or so classic Marfan features, including long tapering fingers, a spinal curvature and a long narrow face, the researchers examined how often they occurred in 183 Marfan and 1,250 non-Marfan patients seen at Hopkins. The researchers calculated the diagnostic potential of each feature based on two factors: how common it was among Marfan patients and how well it could help differentiate between patients with the disorder and those without it. The strongest diagnostic predictor of Marfan in the study was the combination of certain facial features with a very long thumb. With a diagnostic accuracy index of 0.97, this combination correctly predicted Marfan in 97 out of 100 every patients.

A patient with any two of the following signs with high diagnostic potential should be sent to a Marfan specialist:

- One or more cranial or facial signs including a long lean skull, downward slanted eyes, a receding jaw (diagnostic accuracy 0.93).
- An extra long thumb: when folded inside the clenched fist of the hand, the thumb reaches the outer rim, past the pinkie (diagnostic accuracy 0.87).
- Wrist test: A thumb that covers the entire nail of the same-hand pinky finger when encircling the wrist of the opposite hand (diagnostic accuracy 0.83).

A patient with three or four of the following should be sent to a specialist:

- Cranial and facial features described above.
- High-arched palate.
- Hollow chest.
- Severely flat feet, with or without deformity.
- Arm span more than 1.5 times longer than the total height.

Another potent combination was the pairing of scoliosis (a curvature of the spine) with either facial features or an extra long thumb. Commonly seen in people without Marfan, scoliosis by itself is not a reliable predictor of the disorder, the researchers say.

The researchers warn their tool is not perfect — no screening test is — and may miss some Marfan patients with "silent" syndrome, while raising suspicion about some who don't have the disorder. Indeed, one in five Marfan patients in the study had none or only one physical feature, while 13% of the non-Marfan patients had two skeletal features suggestive of the syndrome.

Loeys-Dietz

Researchers reviewed the charts of 65 Loeys-Dietz patients sent to Johns Hopkins after a diagnosis elsewhere. Investigators say primary-care pediatricians and orthopedic surgeons should be on the lookout for Marfan-like features in all patients, but consider Loeys-Dietz syndrome if they also notice any of the following signs that are not found in Marfan:

- Widely spaced eyes.
- Club foot.
- Translucent skin that bruises easily.
- Bi-forked or split uvula, the dangling protrusion seen in the back of the throat.
- Cleft palate • Scoliosis with isolated deformities of the upper spine.

Other investigators included Hal Dietz, Gurkan Erkula, Richard Skolasky, Kristen Venuti, Laura Paulson and Gretchen Oswald, all of Hopkins, and Bart Loeys of Ghent University in Belgium.

A Heart Beats to a Different Drummer

Scientists at Case Western Reserve University and Vanderbilt University found that pulsed light can pace contractions in an avian embryonic heart, with no apparent damage to the tissue. The work, "Optical pacing of the embryonic heart," was published in the online issue of *Nature Photonics*, Aug. 15, 2010.

According to the scientists, this non-invasive device may prove an effective tool in understanding how environmental factors that alter an embryo's heart rate lead to congenital defects. It may also lead to investigations of cardiac electrophysiology at the cellular, tissue and

organ levels, and possibly the development of a new generation of pacemakers.

"The mechanisms behind many congenital defects are not well known. But, there is a suspicion that when the early embryonic heart beats slower or faster than normal, that changes gene regulation and changes development," said Michael Jenkins, a postdoctoral researcher in biomedical engineering at Case Western Reserve.

"If we can precisely control pacing, we could figure out how structure, function and gene expression all work together," said Michiko Watanabe, PhD, Professor of Pediatrics, Genetics and Anatomy at Case Western Reserve School of Medicine.

Jenkins came up with the idea to try the infrared laser on an embryonic heart. He stumbled on an obscure paper from the 1960s in which researchers found that continuous exposure to visible light accelerated the heart rate of an embryonic chicken. He also knew of the success that Eric D. "Duco" Jansen, a professor of Biomedical Engineering at Vanderbilt University, had using an infrared laser to stimulate nerves. He then hypothesized that pulsed infrared light may enable pacing of the embryonic heart.

Case Western Reserve explained the proposed experiment to Jansen, who agreed to collaborate.

How does the laser make the heart beat? The investigators believe a pulse of infrared light creates a temperature gradient in heart tissue that opens ion channels in a cascade along a heart cell. This effect spurs along an electrical impulse that makes the heart contract.

It's early in the research, "but we think this has exciting implications, especially if we can extend this into the adult heart," said Andrew Rollins, Professor of Biomedical Engineering at Case Western Reserve.

Rollins' lab is now experimenting with adult heart tissue, to determine whether the laser could be used as an implantable pacemaker or to pace an adult heart during surgery or other clinical work.

Watanabe, who specializes in heart development and has studied heart conduction in the developing heart, said the findings could lead to the development of a pacemaker for a child's or baby's heart or even in utero. However, many more studies have to be done to show it would work and be safe. In a young heart, electrodes can cause damage and long-term use of traditional pacemakers can lead to heart failure, she said.

Spinal Muscular Atrophy May Also Affect the Heart

Along with skeletal muscles, it may be important to monitor heart function in patients with spinal muscular atrophy (SMA). These are the findings from a study conducted by Nationwide Children's Hospital and published online ahead of print in Human Molecular Genetics. This is the first study to report cardiac dysfunction in mouse models of SMA.

SMA is a debilitating neurological disease that leads to wasting away of muscles throughout the body. Historically, scientists and physicians believed that SMA only affected skeletal muscles; however, new data suggests that this genetic disease may also impact the heart.

"A few studies regarding SMA patients have implicated the involvement of the cardiovascular and the autonomic nervous system," said the study's co-author Brian Kaspar, PhD, principal investigator in the Center for Gene Therapy at The Research Institute at Nationwide Children's Hospital. "However, there have been few to no highly powered and controlled studies to determine how common these cardiovascular anomalies are in these patients."

The reports of altered blood flow and slowed heart rate in some SMA patients prompted Kaspar's team to examine whether a cardiac deficit is present in a mouse model of severe SMA, developed by Arthur Burghes, PhD, Professor of Molecular and Cellular Biochemistry at The Ohio State University College of Medicine, which is routinely used for drug and therapeutic-based screening.

They analyzed the heart structure of the SMA mice compared with normal mice, and found that there were significant structural changes occurring in the heart of the SMA mice, along with severely impaired left-ventricular function. SMA mice also had significantly lower heart rates. After examining the underlying structure of the mouse heart cells they found it similar to the cellular structure of a heart biopsy from patient with type 3 SMA.

Kaspar's team recently developed a gene therapy approach shown to successfully deliver the missing SMN protein to SMA mice and improve neuromuscular function. Next, the team studied whether the discovered heart defects could be corrected by this gene delivery treatment. Results showed that restoring SMN levels completely restored heart rates and prevented the early development of dilated cardiomyopathy.

Pam Lucchesi, PhD, Director of the Center for Cardiovascular and Pulmonary Research at The Research Institute at Nationwide Children's Hospital and study co-author, says it is still not clear which mechanisms are fully responsible for the heart deficits seen in the SMA mice, but data suggests that neuronal, autonomic and developmental components all may play a role.

"Our gene delivery strategy has unique advantages in that it targets neurons within the central and peripheral nervous system as well as the cardiac tissues," said Lucchesi, also a faculty member at The Ohio State University College of Medicine.

More research is needed to determine whether the cardiac deficits are unique to the mouse or whether SMA patient of various severities have or will develop similar issues. Still, Kaspar, also on the faculty at The Ohio State University College of Medicine, says clinicians should be acutely aware of potential heart dysfunction in a subset of SMA patients.

"Increasing reports of autonomic dysfunction together with our current findings warrant increased attention to the cardiac status of SMA patients, and potentially highlights the need to investigate cardiac interventions alongside neuromuscular treatments," said Kaspar.

This research was funded in part by a 2009 American Recovery & Reinvestment Act grant from the National Institutes of Health.

Structural Defects Precede Functional Decline in Heart Muscle

The disruption of a structural component in heart muscle cells, which is associated with heart failure, appears to occur even before heart function starts to decline, according to a new study by researchers at the University of Iowa Roy J. and Lucille A. Carver College of Medicine.

The structure is a highly organized network of grooves in heart muscle membrane called T-tubules. This network is essential for transmitting electrical signals to the cell's interior where they are translated into contractions that make the heart beat.

It was previously known that T-tubules become very disorganized during heart failure. The new study, published in the Aug. 20th issue of the journal, *Circulation Research*, showed that this disorganization starts well before heart failure occurs during a stage known as compensated hypertrophy, when the heart muscle is enlarged but still able to pump a normal amount of blood around the body.
"Although heart function appears normal during compensated hypertrophy, we found that there already is structural damage," said Long-Sheng Song, MD, senior author of this paper and UI Assistant Professor of Internal Medicine. "Our study suggests that things are going wrong very early in the process, and if we could prevent or slow this damage, we might be able to delay the onset of heart failure."

The researchers used a state-of-the-art imaging technique called laser scanning confocal microscope to visualize these structural changes in an animal model of heart failure. The study compared T-tubule structure and heart function at different stages of heart disease, and found that the more disorganized the T-tubule network becomes, the worse the heart functions.

Moreover, the researchers found that T-tubule disorganization was also accompanied by a reduction in levels of a molecule called junctophilin-2, which is thought to be involved in formation of T-tubule networks. In cell experiments, loss of this molecule led to reduced T-tubule integrity.

Although the new findings are not ready to be applied in a clinical setting, understanding how T-tubule disruption occurs may lead to new ways to diagnose or treat heart failure.

In addition to Song, UI researchers involved in the study included: Sheng Wei; Ang Guo; Biyi Chen; William Kutschke; Yu-Ping Xie; Kathy Zimmerman, Robert Weiss; and Mark Anderson. The team also included Heping Cheng from Peking University, Beijing, China.

The study was funded in part by grants from the National Institutes of Health, the American Heart Association and Chinese Scholarship Council. In addition, gifts from the Albaghdadi family of Clinton, Iowa, contributed to the purchase of the laser scanning confocal microscope used in the study.

Teaching Doctors to Treat the Individual

Doctors can be taught to listen better to individual circumstances that may affect patient care, according to researchers at the University of Illinois at Chicago College of Medicine. The findings were reported in the Sep. 15th issue of *JAMA*.

In a previous study the investigators had shown that doctors are not good at picking up clues to details in their patients' personal lives that may affect their treatment -- what the researchers call "context." The current study was designed to see if doctors could be taught to think about context when examining patients.

Fourth-year medical students from the UIC College of Medicine for the last two years were divided into two groups. One group attended four short workshops training them to recognize and respond to contextual clues during patient examinations. The second group did not attend the workshops.

The two groups were compared by having them see four standardized patients -- actors who are trained to portray patients the same way every time. The students acted as doctors to these patients, making a diagnosis and developing a treatment plan.

All the students saw the same four cases. The investigators were able to score the interactions with the standardized patients to determine how well the students individualized care for patients who had unique contexts.

In one of the cases, for example, a patient came in with worsening asthma.

Such a patient may simply need to have his inhaler dose increased, says Alan Schwartz, Associate Professor of Medical Education and Pediatrics at UIC College of Medicine and first author of the study. "But if the patient tells their doctor that they've lost their job, it may be that the patient isn't using their medication properly because they can't afford it -- and increasing the dosage wouldn't help."

In this case, Schwartz said, the doctor needs to ask if there is a problem with insurance or paying for the medication, and perhaps should be prescribing a cheaper alternative inhaler.

In the control group, students correctly treated the contextually complicated patients about 25% of the time. In the group that attended the workshops, students correctly identified and appropriately treated the contextually complicated patient two thirds of the time. All students did equally well at treating other kinds of patients.

"Our workshop was not only effective at improving students' abilities to individualize care, but it focused specifically on that ability without affecting their other abilities as a doctor," said Schwartz. "Individualized care is something that can be taught and should be part of training doctors."

The project was funded in part by a National Board of Medical Examiners Edward J. Stemmler, MD, Medical Education Research Fund grant. Dr. Saul Weiner, Associate Professor of Medicine and Pediatrics at UIC and staff physician at the Jesse Brown VA Medical Center; Ilene B. Harris, Professor and Interim Head of Medical Education at UIC; and research associate Amy Binns-Calvey co-authored the study.

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