Molecular Markers of Congenital Heart Disease

By Mariam Arabi, MD; Marianne Majdalani, MD; Georges Nemer, PhD and Fadi Bitar, MD

INTRODUCTION
Cardiac abnormalities occur with an incidence of 1 per 100 live births represent 25% of all congenital malformations, and are the leading cause of death in the first year of life. The etiologies of Congenital Heart Disease (CHD) include consanguinity, environmental factors, teratogens and genetic mutations. Yet, 90% of all CHD cases do not have any known etiology. It has been reported that approximately 5 to 8% of patients with CHD have a gross chromosomal defect, usually trisomy 21, 13, 18 and Turner’s Syndrome.

The complexity of heart formation, which integrates different structures and cell types, involves a network of genes regulated by transcription factors. The molecular causes of most CHDs remain unknown, although numerous cardiac regulatory factors have recently been described. Understandably, parents of patients, and increasingly patients themselves, are interested in the risk that future offspring will be affected. In this review, we pursue a discussion of the molecular markers for heart development and diseases that have been discovered during the last decade in numerous organisms.

I. HEART DEVELOPMENT

“Heart development processes including gradient-like expression of some genes, as well as the chamber-specific expression of others, are tightly regulated by combinational interactions of several transcription factors and their cofactors.”

Studies in model organisms from the invertebrates and vertebrates have revealed an evolutionary conserved program of heart development, initiated by specific signaling molecules and mediated by tissue-specific transcription factors. The program, though still not complete due to lack of determina-
CONTEGRA® Pulmonary Valved Conduit

The natural tissue conduit offering the essential features of a homograft with the convenience of a bioprosthesis

This device has been approved as a humanitarian use device in the U.S.

CONTEGRA® Pulmonary Valved Conduit

Indications: See “Humanitarian use device section below. Contraindications: Patients 18 years and older, heart surgery procedures. If, after assessment of the risk to benefit ratio by the physician, superior clinical results are suspected by presently established alternative medical or surgical techniques. Warnings/Precautions: Side Effects: Acceptable clinical performance has been established for the Contegra conduit in pediatric patients under the age of 10. Because of the possibility that complications of the device could become apparent only after extended use, a benefit-risk consideration of the long-term use of the Contegra conduit in pediatric patients over 10 years of age is particularly important. General complications reported with valved conduits and biological tissue valves implanted in the heart include: hemorrhage, bleeding, dissection due to use of anticoagulants, residual or increasing transaortic gradients, progressive neointimal thickening and peeling, progressive stenosis and obstruction, progressive pulmonary hypertension, graft infection, endocarditis, legulation, hemolysis, valve malfunction, physical or chemical deterioration, tricuspid incompetence, thrombus, conduct dislocation. For additional information, please refer to the instructions for use provided with the product. CAUTION: Federal law (USA) restricts this device to sale by, or on the order of, a physician.

*Humanitarian Use Device: Authorized by Federal law for use in patients under 19 years of age for correction or reconstruction of the right Ventricular Outflow Tract (RVOT) in the following congenital heart malformations: Pulmonary Osteitis, Hypertrophy of Pulmonary Arteria, Truncus Arteria, Transposition with Ventricular Septal Defect (VSD), Pulmonary Stenosis. In addition, the Contegra Pulmonary Valved Conduit is indicated for the replacement of previously implanted but dysfunctional pulmonary homografts or valved conduits. The effectiveness of this device for these uses has not been demonstrated.
commitment to valve formation can have a major impact on heart morphogenesis and function and may lead to CHDs.

Factors affecting heart tube formation have been described. In Drosophila, the mutant heartless has permitted the identification of a fibroblast growth factor (FGF) receptor as being essential for the migration of the pre-cardiac cells. In this mutant, the heart is not formed since the pre-cardiac cells do not migrate to the center of the embryo. In mice, the inactivation of the genes encoding Bone Morphogenetic Protein 2 (BMP-2) or BMP-4, the fibronectin, and the GATA-4 transcription factor, causes a phenotype resembling the heartless mutant.

The mechanisms implicated in the looping, and the forces causing it are not yet clarified. The asymmetry at the level of the organs, named situs solitus is inverted in 1 per 7000 of humans (situs inversus), and causes many physiological abnormalities, as well as an increasing predisposition to develop congenital diseases notably at the atrial and ventricular septations. Recent studies have shown that it is caused by mutations in the gene encoding the zinc finger transcription factor Zic3. Retinoic acid (RA) affects cardiac folding in many species. This is the reason why in chicks and in mice, an excess of retinoic acid causes situs inversus.

Myocyte differentiation into two subtypes, atrial and ventricular, will form the different chambers of the mature heart. Members of the basic/helix-loop-helix (bHLH) family of transcription factors have been implicated in regulation of cell fate specification and differentiation in different organisms. In the heart, the two subfamilies which are expressed are the hand proteins (dHand and eHand), and the Hairy protein (Hey 1, 2, and 3). dHand and eHand are asymetrically expressed in the heart: dHand being in the right ventricle and eHand being in the left. This differential expression implies a role in chamber specification and function.

Dissections of the molecular pathways implicated in valve formations have revealed two pathways governing the epithelial-mesenchymal transformation the endocardial cells undergo to form the mature valves. These pathways involve the calcineurin/NFATc pathway whereby the dephosphorylation of the transcription factor NFATc (nuclear factor for activated T-cells) is essential for the transformation, and the Ras proto-oncogene pathways essential for the proliferation of mesenchymal cells.

Numerous mice models in which inactivation of genes encoding transcription factors like Nkx2.5 and Tbx2.5 exhibit septal defects associated with other gross abnormalities in the heart. Atrioventricular node defects are observed in humans and mice with dominant mutations in Nkx2.5 and Tbx5; thus further delineates their role in the formation of a functional conduction system.
Heart development processes including gradient-like expression of some genes, as well as the chamber-specific expression of others, are tightly regulated by combinational interactions of several transcription factors and their cofactors. Transcription factors are proteins involved in the regulation of gene expression that bind to the promoter elements upstream of genes and either facilitate or inhibit transcription. Through this process they control and regulate gene expression. Transcription factors are composed of two essential functional regions: a DNA-binding domain and an activator domain. The DNA-binding domain consists of amino acids that recognize specific DNA bases near the start of transcription. Transcription factors are typically classified according to the structure of their DNA-binding domain, which are of one of the following types: zinc fingers, helix-turn-helix, leucine zipper, helix-loop-helix, and high mobility groups.

II– CONGENITAL HEART DISEASE

We will present a brief description of the various CHDs including an overview of the genes associated or implicated in the development of these defects (Table 1). Moreover, we will review several syndromes associated with CHD, and describe the genes associated with these syndromes.

The improvement in molecular genetic techniques such as PCR and fluorescent in situ hybridization (FISH) can now rapidly identify specific genes and chromosomes. FISH can also reveal abnormalities within individual chromosomes. Labeled gene probes, often derived from animals, can localize genes on chromosomes. A multitude of genes are involved in programming heart development which renders the immediate clinical application somewhat remote. However, molecular genetics is likely to produce in the near future answers about the mechanics involved in abnormal cardiogenesis.

A. Specific Cardiac Defects

1. Ventricular Sepal Defect (VSD)

Mutations in a large number of genes in animal models have been associated with VSDs, usually in association with other cardiac or extra-cardiac abnormalities. Examples of knock-out mice developing VSD are those where Nkx2.5, FOG2, and Hey2 genes are inactivated. Heterozygous mice for the Tbx5 gene also develop VSD. Some human syndromes and sporadic cases of VSD have been associated with Nkx2.5, Tbx5, and GATA4 mutations.

2. Atrial Septal Defect (ASD)

Patients with Holt-Oram Syndrome (HOS) have ASDs in association with limb deformities. This disorder is due to mutations in the T-box transcription factor gene TBX5. Interestingly, mutations in the Nkx2.5 gene which interacts with Tbx5 have also been linked to familial and sporadic cases of ASDs. Recently, mutations in GATA4 were found in two familial cases of ASDs. These findings point to a major role for GATA4 in septation, with both Tbx5 and Nkx2.5 being GATA4 partners, and define a network of cooperative activity that contributes to ASD.

3. Patent Ductus Arteriosus (PDA)

Recent linkage analysis pointed to the 12q24 locus as potentially implicated in PDA. The 12q24 locus includes different potential cardiac genes like Tbx5 implicated in HOS and Shp2 implicated in Noonan Syndrome.

4. Atrioventricular Canal Defects (AVC)

The syndrome most often associated with atrioventricular canal defects in trisomy 21.
6. Aortic Stenosis (AS)
No linkage analysis has been performed in humans and no animal model exists so far in which only aortic stenosis is present.

7. Pulmonary Stenosis (PS)
Recently, isolated cases of PS have been associated with mutations in Jagged-1, which was previously linked to patients with the Alagille Syndrome.

8. Coarctation of the Aorta (CoA)
Studies in Zebrafish show that the gridlock mutation is due to mutations in the Hey2 gene causing coarctation of the aorta resembling that found in humans. In humans, some patients with the neurofibromatosis defect characterized by hematopoetic malignancy, presents a CoA. The mutations in this tumor-

It has been estimated that 22% of people with AVSD who do not have Down Syndrome or heterotaxy have a Mendelian genetic syndrome. Of note the involvement of tyrosine kinase receptors ErbB2 and B3 which binds neuregulin in the formation of the atrioventricular canal in mice.

5. Persistent Truncus Arteriosus (PTA)
Micro-deletion of chromosome 22 has been noted in as many as 1/3 of patients with PTA. 22q11 deletions are commonly associated with the DiGeorge Syndrome. The PTA phenotype is also found in numerous engineered mouse models like the ones with inactivation of the genes encoding the BMP2, the Pax3 homeobox transcription factor, and the vasoconstrictor hormone Edn1.
associated with Jagged-1 mutation. Jagged-1 is a ligand to the Notch receptor which has been implicated in different aspects of organogenesis in Drosophila and mammals.

Two recent reports have also linked mutation in the FOG2 and Nkx2.5 genes to isolated cases of Tetralogy of Fallot. FOG2 (friend of GATA) encodes a multizinc fingers protein that interacts specifically with GATA proteins to modulate their transcriptional activity mainly by repressing it. In comparison, the FOG2 null mice which lack both alleles display a tricuspid atresia (TA) phenotype associated with both atrial and ventricular septal defects.

A recent study at our center designed to look at mutation in GATA-4 included 120 patients with various CHD and their families. We identified two patients out of 26 patients with TOF to harbor a missense mutation in exon 2 resulting in E to D substitution at residue 215 of the first zinc finger of GATA-4 (Figure 2). None of the 94 other patients with different phenotypes, nor in 223 healthy individuals had the mutation. The heterozygous mutation results in an amino acid substitution in the first zinc finger of GATA4 that reduced its transcriptional activation of downstream target genes, without affecting GATA4 ability to bind DNA, nor its interaction with ZFPM2. Further studies are needed in this area.

10. Hypoplastic Left Heart Syndrome (HLHS)
No linkage analysis has been performed and no association to a single gene mutation has been documented in humans. Recently inactivation of the gene encoding the cardiac lineage restricted nuclear protein-1 (CLP-1) has produced embryonic lethality in mice due to a severe hypoplastic left ventricle that is in part the result of a differentiation defect of progenitor myocytes.

11. Tricuspid Atresia (TA)
No single gene mutation has been identified so far in humans and no linkage analysis has been performed. In mice, the inactivation of FOG2 (friend of GATA) lead to a phenotype resembling TA associated to both an ASD and VSD.

12. Transposition of the Great Arteries (TGA)
No linkage analysis has been performed on familial cases of TGA, and the animal models that recapitulate TGA have additional embryonic defects besides the heart.

The Pitx2 null mice in particular confirm the role of Pitx2 as the downstream effector of left-right asymmetry along the body axis starting with the heart and embryos lacking Pitx2 display in addition to TGA a wide variety of left-right defects.

Inactivation of genes encoding the type II activin receptor, the Cited2 co-activator, and the transduction cytoplasmic protein Dishevelled2 associated to Wnt signaling, all lead to TGA in addition to cardiac and extra-cardiac phenotypes.

13. Double Outlet Right Ventricle (DORV)
No genes have been yet linked to DORV

Pediatric Cardiac Anesthesiologist

The Congenital Heart Center at the University of Florida has a faculty position opening at the level of Clinical Assistant/Associate Professor in a non-tenure accruing position. This position will coordinate all aspects of pediatric cardiac anesthesia services, including those for the cardiac operating rooms, cardiac catheterization, cardiac MRI, and other related areas for children. This role includes teaching of residents, fellows, medical students and other health care professionals. This position will bring clinical research funding and expertise or develop a clinical research program. This position is for a Board Certified/Board Eligible Anesthesiologist

Applicants should send a letter of application, a C.V., and three letters of reference to:
Mark Bleiweis, M.D, Director
Congenital Heart Center
University of Florida College of Medicine
P.O. Box 100296
Gainesville, FL 32610-0296

Anticipated hiring date is on or before July 1, 2007.
in humans. However, a large number of mouse mutations result in a DORV phenotype. Mutations in the type IIB activin receptor result in complex defects, which include DORV. Over-expression of Pitx2 in transgenic mice leads also to DORV.

B. Syndromes

1. DiGeorge Syndrome

Recently, genetically modified mice with targeted disruption of only one allele of the gene encoding Tbx1 have been generated. In addition to being found at the 22q11 locus in humans, Tbx1 expression pattern matches the organs affected in the DiGeorge Syndrome.

2. Holt-Oram Syndrome

Linkage studies have shown that the syndrome was linked to 12q2. The subsequent identification of mutations in the Tbx5 gene that is found on 12q2 in HOS patients, and the cloning and pattern of expression of its mouse homolog confirmed that Tbx5 is the gene implicated in HOS. The fact that only one Tbx5 allele less in mice is sufficient to mimic HOS correlates well with the fact that in humans mutations are found on one allele in an autosomal dominant manner of transmission and introduces the notion of haploinsufficiency which results in reduction of the total amount of proteins produced.

3. Alagille Syndrome

It is caused by mutations in Jagged-1 (20p12), a ligand for the Notch receptor.

4. Char Syndrome

This is an autosomal dominant trait mapped at 6p12. Linkage analysis in families with this syndrome revealed mutations in the transcription factor AP-2 type B (TFAP2B).

5. Marfan syndrome

Mutations in the fibrillin gene (15q21.1) which encodes an extracellular matrix protein result in Marfan’s syndrome.

6. Noonan Syndrome

Fifty percent of patients with the Noonan Syndrome have been linked to mutations in the gene encoding the protein-tyrosine phosphotase Shp2(or Ptnm11) on 12q24. Mice models with inactivation of the Shp2 gene have been generated and they recapitulate phenotypically the syndrome.

7. Williams Syndrome

It is caused by a very small chromosomal deletion on the long arm of chromosome 7 (Figure 3). The deleted region includes the elastin gene, which encodes a protein that gives blood
vessels its elasticity and strength. (Role of FISH assay in the diagnosis of Williams Syndrome; Courtesy of the University of Utah, Genetic Science Learning Center).

III. Conclusion

In spite of the amazing success during the past half-century in diagnosis and treatment of congenital heart disease, very little is known with regard to its causes. However, a genetic cause has been clearly established for many forms of cardiovascular disease, and new understandings in the molecular genetics of congenital heart disease will provide further insight. The availability of complete genome sequences for humans and model organisms should revolutionize our understanding of cardiac development.

References


~CCT~

### Table 1.
Cardiac phenotypes associated with mutations in genes encoding transcription factors

<table>
<thead>
<tr>
<th>Genes</th>
<th>Species</th>
<th>Phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cited2</td>
<td>Mouse</td>
<td>ASD, VSD, DORV, PTA</td>
</tr>
<tr>
<td>Isl1</td>
<td>Mouse</td>
<td>RV and Atrial hypoplasia</td>
</tr>
<tr>
<td>Gata4</td>
<td>Mouse, Human</td>
<td>ASD, VSD, TOF, cardiabifida</td>
</tr>
<tr>
<td>Hand1</td>
<td>Mouse</td>
<td>Looping abnormality</td>
</tr>
<tr>
<td>Hand2</td>
<td>Mouse</td>
<td>RV hypoplasia, Ao arch hypoplasia</td>
</tr>
<tr>
<td>HoxA3</td>
<td>Mouse</td>
<td>CT abnormalities</td>
</tr>
<tr>
<td>NFATc</td>
<td>Mouse</td>
<td>Valve defects, VSD</td>
</tr>
<tr>
<td>Nkx2-5</td>
<td>Mouse, Human</td>
<td>ASD, VSD, TOF</td>
</tr>
<tr>
<td>COUP-TFII</td>
<td>Mouse</td>
<td>Atrial hypoplasia, ASD</td>
</tr>
<tr>
<td>Pax3</td>
<td>Mouse</td>
<td>PTA, CT defects</td>
</tr>
<tr>
<td>HF-1b</td>
<td>Mouse</td>
<td>Conduct system defect</td>
</tr>
<tr>
<td>Pitx2</td>
<td>Mouse</td>
<td>Laterality, AVSD, PTA, TGA, DORV</td>
</tr>
<tr>
<td>RAR/RXR</td>
<td>Mouse</td>
<td>VSD, PTA, DORV, CT Defects</td>
</tr>
<tr>
<td>Sox4</td>
<td>Mouse</td>
<td>AVSD, TGA, valve defects, PTA</td>
</tr>
<tr>
<td>Tbx1</td>
<td>Mouse, Human</td>
<td>DiGeorge Syndrome</td>
</tr>
<tr>
<td>Tbx5</td>
<td>Mouse, Human</td>
<td>Holt-Oram Syndrome, atrial hypoplasia</td>
</tr>
<tr>
<td>TEF-1</td>
<td>Mouse</td>
<td>Noncompaction, trabecular abnormality</td>
</tr>
<tr>
<td>FOG2</td>
<td>Mouse, Human</td>
<td>TA, ASD, VSD, PS, TOF, AVSD</td>
</tr>
<tr>
<td>MEF2C</td>
<td>Mouse</td>
<td>RV and LV hypoplasia</td>
</tr>
<tr>
<td>Hey2</td>
<td>Mouse, Zebrafish</td>
<td>Ao Coarctation, VSD, TOF</td>
</tr>
<tr>
<td>TFAP2B</td>
<td>Human</td>
<td>PDA</td>
</tr>
<tr>
<td>Gata5</td>
<td>Zebrafish</td>
<td>Cardia Bifida</td>
</tr>
<tr>
<td>Zic3</td>
<td>Mouse, Human</td>
<td>TGA, laterality</td>
</tr>
</tbody>
</table>

Corresponding Author:

Fadi Bitar, MD  
Professor of Pediatrics  
Director, Pediatric Cardiology Program  
Coordinator: External Programs: Medicine  
AUBMC  
Riad El Solh, P.O. Box: 11-0236 A#22  
11072020, Beirut, Lebanon  
Fax: 011-961-1-342517  
Email: fadi.bitar@aub.edu.lb

Corresponding Author:

Georges Nemer, PhD  
Assistant Professor of Biochemistry  
Director of the CHD Genetics Program  
AUBMC  
Email: gn08@aub.edu.lb

Mariam Arabi, MD  
First Year Fellow in Pediatric Cardiology  
American University of Beirut-Medical Center (AUBMC)

Marianne Majdalani, MD  
Assistant Professor of Pediatrics  
Director, Pediatric Intensive Care Unit  
AUBMC

---

kids play. worries rest. fun happens!

Camp Odayin provides residential, day and family camp experiences for children with heart disease from all around the world. The camp offers the opportunity to strengthen self-confidence, gain independence, develop life skills, and meet other young people with similar health, emotional and social concerns.

www.campodayin.org
Hemorrhagic Pericardial Effusion in Two Siblings

By Arkadi Yakirevitch, MD and Nathan Roguin, MD

Introduction

Although in one third of the cases pericarditis is idiopathic, in these instances pericardial effusion is rarely life-threatening. The two cases we report are in siblings from an Arabic family without any history of congenital pathology and are of interest because of the hemorrhagic nature and large amount of pericardial fluid. To the best of our knowledge, idiopathic hemorrhagic pericarditis in siblings has not been described in the English literature.

Case reports

Case 1

A one and a half year old girl, born to healthy parents after a normal pregnancy, vaccinated against poliomyelitis, hepatitis B, measles, mumps and rubella, was referred with a four day history of cough and shortness of breath. On admission, pallor, severe dyspnea and consciousness deterioration were revealed. Laboratory data showed normal electrolytes and blood count with the exception of mild lymphocytosis and thrombocytosis of 626,000/L and a mild increase of the erythrocyte sedimentation rate (28 mm per hour). Electrocardiogram showed ST and T wave changes and chest roentgenogram demonstrated an enlarged heart silhouette. Echocardiography revealed significant amounts of pericardial fluid with pressure on the right atrium and right ventricle.

Urgent open pericardial drainage was performed through a subxiphoid approach. Six-hundred-twenty ml of sanguineous fluid were withdrawn and a pericardial biopsy was also taken.

Fluid analysis revealed glucose 97 mg/dl, total protein 5.9 g/dl, lactate dehydrogenase 662 U/L. Cytologically, the fluid contained mesothelial cells and granulocytes with no anaplastic cells. Virus isolation from pericardial fluid for echovirus, coxsackie A and B, and herpes simplex was negative. Blood and pericardial fluid cultures were sterile.

Pericardial biopsy showed fibrin deposits, fibroblasts, and isolated granulocytes with no evidence of tuberculosis or malignancy.

Tuberculin skin test was negative.

The girl was treated with aspirin and cefazolin.

On the fourth postoperative day the pericardial drain was removed. The patient convalesced satisfactorily and was discharged on the ninth hospitalization day and required no further medications.

Eleven years later at thirteen years of age she remains in good health; hemoestasis screening tests and blood count, including platelets, are normal; electrocardiogram is within normal ranges. Echocardiogram demonstrates normal cardiac contractility and absent pericardial effusion. Serologic tests carried out were negative for immunoglobulin M antibodies and positive for immunoglobulin G antibodies to cytomegalovirus and toxoplasma.

Case 2

A fifteen-year-old, usually healthy boy, vaccinated against poliomyelitis, measles and rubella, elder brother of the first patient, was admitted with epigastric pain, vomiting, subfebrile fever, mild dyspnea and fatigue. Electrocardiogram showed sinus tachycardia with inverted T waves in all the leads. Chest X-ray demonstrated marked cardiac enlargement without any lung findings. Blood count revealed only mild thrombocytosis of 569,000/L; electrolytes, cardiac and liver enzymes levels and thyroid function tests were normal though the erythrocyte sedimentation rate was elevated (74 mm per hour).

With echocardiographic evidence of massive pericardial effusion subxiphoid puncture had been performed under X-ray control and with the help of introducer to minimize pericardial trauma. 750 ml of hemorrhagic fluid was removed followed by rapid clinical improvement.

Despite aspirin and ceftriaxone treatment by the fourth hospitalization day the patient’s condition worsened, and a follow-up echocardiogram demonstrated considerable pericardial effusion. Repeated puncture yielded 1200 ml of hemorrhagic fluid. Its analysis showed pH 7.44, glucose 99 mg/dl, total protein 6.2 g/dl. Cytologically it was normal and negative for Ziehl-Neelsen staining.

Serologic studies for antibodies to Epstein-Barr, coxsackie A and B, echo, herpes simplex virus, parvovirus and mycoplasma were negative. Studies for immunoglobulin M antibodies to cy-
Pediatric Cardiology

We are looking for a non-invasive Pediatric Cardiologist for the Orlando Florida area. Established in 1994, we serve the Central Florida area with outpatient clinics, inpatient consults, fetal echo’s and cardiac catheterizations.

Competitive salary and benefits, including paid health, disability, malpractice insurance and CME allowances.

Come enjoy Florida with its beautiful beaches, lakes, great outdoor activities, and many cultural and sporting events. The Orlando area boasts ‘A’ schools and a prominent local University.

For a glimpse into our practice visit our website at: www.carson-appleton.com

Please contact: Thomas Carson, M.D. for more details on this great opportunity via email at: reddvet@aol.com or our office at 407-902-2866.

Submit your CV via fax to 407-902-2585.

tomegalovirus and toxoplasma were negative, and positive for immunoglobulin G antibodies to cytomegalovirus and toxoplasma. Pericardial fluid and blood cultures were sterile.

Tuberculin skin test was negative.

By the tenth day the patient was asymptomatic. Repeated echocardiograms demonstrated a small amount of pericardial fluid and the boy was discharged on aspirin treatment which was discontinued two weeks after discharge.

After 6 year follow-up, the patient is in good health, has normal hemostasis tests and complete blood count. Electrocardiogram shows minimal residual ST and T wave changes in leads III, aVF and V3. Echocardiogram demonstrates normal cardiac contractility with no signs of residual pericardial effusion.

Discussion

Hemorrhagic pericardial effusions are infrequent, especially in children, and are usually caused by tuberculosis, tumors, rheumatic fever, uremia and cardiac injury. During the past decade the incidence has been reduced even more due to reduction of bacterial causes so that currently the most common cause is iatrogenic disease, namely, secondary to invasive cardiac procedures [1].

We presented two cases of massive hemorrhagic pericardial effusion that had been observed in two siblings in separate occasions. In both cases there was no history of trauma, no evidence of tuberculosis, coxsackie A or B, echo, herpes simplex virus or bacterial infection. Cases of hemorrhagic pericarditis due to mycoplasma pneumoniae [2], cytomegalovirus [3] and toxoplasma [4] infections have been reported. These three causations were ruled out in the case of the elder sibling. In the younger sister’s case, which was actually studied retrospectively, we are not able to exclude these etiologic agents. Nonetheless, they were unlikely taking into account the clinical picture. It is worth mentioning, that in our region the prevalence of antibodies against Toxoplasma gondii among the Arab population reaches 20.5% in the first decade of life with a gradual increase up to 74% at age 40 [5].

On the other hand, the familial nature of these cases can be hardly ignored. In this connection familial Mediterranean fever [6,7] and porphyria [8] could be suspected but hemorrhagic pericardial effusion is not typical for them; the history of familial Mediterranean fever is absent in this family and both cases didn’t have a clinical picture of porphyria.

Therefore, we consider these two familial cases of hemorrhagic pericarditis to be idiopathic, though an infectious origin of the first one cannot be entirely ruled out.

References

4. Sano J, Saitoh H, Kobayashi Y, Ikeda M, Kodani E, Takayama M et al. Toxoplasma pericarditis without immunosuppressant disorder detected by polymerase chain reaction of pericardial...


---

**Corresponding Author:**
Arkadi Yakirevitch, MD
Department of Cardiology
Western Galilee Hospital
Nahariya Technion Faculty of Medicine
Haifa, Israel

Emek Dotan Str. 14/5
Ramat Gan 52621
Israel
Tel: 972-3-6355324
Fax: 972-3-5305387
E-mail: arkadiyak@gmail.com

---

**MARCH SYMPOSIUM FOCUS**

6th International Workshop on Interventional Pediatric Cardiology
March 28th-31st, 2007
Crowne Plaza Hotel, San Donato Milanese (Milan, Italy)
Tel. +39 02.93790014
Fax +39 0293572845
www.workshopIPC.com
email: info@workshopIPC.com

**Course Director:** Mario Carminati
**Course Co-Directors:** Gianfranco Butera, Massimo Chessa

**San Donato Pediatric Cardiology Team:**
- Mario Carminati, Gianfranco Butera, Massimo Chessa, Carmelo Arcidiacono,
- Viasta Fesslova, Angelo Micheletti, Diana Negura, Luciane Piazza, Luca Rosti

**Objective:** State of the art and future perspectives on catheter interventional procedures for the treatment of congenital heart disease from fetal life to adulthood.

**Workshop Overview:** The mission of this workshop is to provide education through demonstration. All lectures and live transmissions performed by the experts will focus on giving an overview of the latest techniques’ state of the art and the status of the management of congenital heart disease. At the end of the workshop all participants should be able to: (1) know the indications for treatment of endovascular procedures for congenital heart defects, (2) identify the proper device to be used, and (3) discuss the pre- and post-procedural management of patients. The official language will be English; simultaneous translation provided.

**CME hours:** Currently undergoing evaluation for CME accreditation by the Italian Ministry of Health, EBAC and UEMS.

More than 40 International Faculty including:
- Z. Amin-Chicago (USA);
- R.H. Anderson-London (UK);
- L. Benson-Toronto (Canada);
- P. Bonhoefer-London (UK);
- G. Butera-San Donato (Italy);
- J.P. Cheatham-Orlando (USA);
- W.E. Hellenbrand-New York (USA);
- A. Ludomirsky-St. Louis (USA);
- Z.M. Hijazi-Chicago (USA);
- S.A. Qureshi-London (UK);
- J.F. Piéchaud-Paris (France);
- M. Ranucci-San Donato (Italy);
- H. Sievert-Frankfurt (Germany);
- M. Tynan-London (UK), to mention a only a few.

---

**The Barth Syndrome Foundation**

P.O. Box 974, Perry, FL 32348
Tel: 850.223.1128 info@barthsyndrome.org www.barthsyndrome.org

**Symptoms:** Cardiomyopathy, Neutropenia, Muscle Weakness, Exercise Intolerance, Growth Retardation

www.CongenitalCardiologyToday.com
First in a Series from PICS
Watch Doctors Eric Horlick and Lee Benson of Toronto General Hospital perform a Percutaneous Valve Implantation on a 46-year old male with Tetrology of Fallot.

Watch this 30 minute video in its entirety.

Produced by
Pediatric and Adult Interventional Therapies for Congenital and Valvular Disease (PICS)
To register or learn more about PICS 2007: www.picsymposium.com

If you would like to be notified of other videos in the series, please send an email to: PICS@CHDvideo.com

Video Live Cases Hosted by Congenital Cardiology Today

PICS 2007 JULY 22-25, 2007
Bellagio, Las Vegas

www.picsymposium.com
Remote Device Allows Cardiologist to Monitor Patients at their Homes

An easy-to-use in home monitoring device for patients is changing the way doctors monitor the health of patients with implanted defibrillators. Rush University Medical Center is participating in a pilot study of the LATITUDE® Patient Management system to determine if the wireless home monitoring system can decrease hospitalizations for heart failure.

A mini-antenna built into the implanted defibrillator sends data to a wireless system placed in the patient’s home. The data is automatically transmitted to a secure Internet server where the physician can access this medical information anytime, from anywhere.

Unlike other remote devices which only transmit data if certain parameters are out of range, the LATITUDE system uploads health information that can help physicians monitor the day-to-day changes in patients. In addition to the data stored before, during and after an arrhythmia, the system employs a wireless weight scale and blood pressure monitor to record vital statistics crucial for the management of cardiac failure patients. An abrupt change in weight could indicate worsening heart failure.

“This sophisticated system allows physicians to manage the patient much more closely. The same information that would normally require a visit to the office every few months can now be downloaded to the physician at anytime without the patient ever leaving home,” said Dr. Kousik Krishnan, a cardiac electrophysiologist at Rush.

Arkansas Children’s Hospital, Little Rock, AR
PEDIATRIC TRANSPLANT CARDIOLOGIST

The Department of Pediatrics, Section of Cardiology, of the University of Arkansas for Medical Sciences College of Medicine located at Arkansas Children’s Hospital in Little Rock, Arkansas, seeks candidates for an Assistant Professor (tenure track) position in the clinical-scientist pathway. M.D. degree and board eligibility/board certification in Cardiology is required. The position is available immediately, starting date is negotiable.

Cardiology offers state-of-the-art procedures and comprehensive post operative care to patients from Arkansas and the region. The Cardiac Catheterization team performs a variety of procedures including atrial septal defect closure, angioplasty with stent implantation, and blade and balloon atrial septostomy. Inpatient Cardiology and Intensive Care provides attending coverage of the cardiac intensive care service including post-operative care. The Cardiac Transplant program is recognized at one of the leading cardiac transplant programs in the United States. Cardiology Clinics and Outreach conduct monthly patient clinics in Fayetteville, Fort Smith, Texarkana, and Jonesboro.

The UAMS Department of Pediatrics employs over 195 faculty members and 75 residents. Arkansas Children’s Hospital is among the largest children’s hospitals in the United States. Located in the foothills of the Ozark Mountains, Little Rock offers Midwestern family values combined with the friendliness of the South, affordable housing, quality school options, a mild climate, excellent cultural and artistic venues, professional minor league sports, world class hunting, fishing and other outdoor recreational opportunities plus extraordinary natural beauty. With a population in excess of 500,000, Greater Little Rock offers the most desirable features of large cities without sacrificing ease of access and convenience. For more information, please see our website: www.uams.edu/pediatrics.

Interested individuals should contact:
W. Robert Morrow, MD
Professor of Pediatrics
David and Stephanie Clark Chair in Pediatric Cardiology
UAMS College of Medicine
Arkansas Children’s Hospital
800 Marshall, Slot 512-3
Little Rock, AR 72202-3591
Phone: (501) 364-1479; Fax: (501) 364-3667
morrowwilliamr@uams.edu

The State of Arkansas has a Conrad 30 program and the University of Arkansas for Medical Sciences is an equal opportunity employer.
According to Krishnan, the LATITUDE system provides added peace of mind for the patient. The physician can remotely check if the defibrillator is working correctly and assess battery life. If the patient feels the defibrillator activate, he or she can transmit the rhythm information immediately. The physician can quickly analyze the data and determine if the shock was appropriate or if the patient needs to go to the hospital.

“Now with patient information available weekly, or even daily if needed, we can better monitor our patients,” said Dr. Krishnan. “We can pick up abnormalities sooner and act on those before they become serious.”

Rush is one of only 18 centers in the country participating in the LATITUDE Inductive Pilot Program which offers remote monitoring for all Boston Scientific/Guidant devices.

35 % of 49 Young People Who Died Suddenly Had Genetic Heart Defects

In 49 young people who died suddenly and inexplicably at an average age of 14, conventional autopsies found no cause of death. But when Mayo Clinic researchers conducted a sophisticated form of postmortem genetic testing — known as a molecular autopsy — they found that more than one-third died due to potentially heritable genetic defects that impair the heart’s rhythm center.

The defects were caused by mutations, which can be thought of as spelling errors in the genetic code. The defects produced one of two abnormal heart rhythm conditions: Long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT). Both syndromes can declare their presence silently and catastrophically with a sudden death episode as the first symptom. Because they leave no structural or physical clues, the defects can’t be detected with conventional autopsy methods — so families have been left with the additional grief of wondering what caused the premature death.

Mayo Clinic’s molecular autopsy is a detailed examination at a molecular level of heart function. Molecular autopsies can help lessen grief burden of families because data show that they exposed the lethal mutations as the cause of death in 35 percent of cases in which conventional autopsies could not ascertain cause of death. “The fact that conventional autopsy fails to provide an answer is, in fact, a key clue that the killer may be LQTS or CPVT,” says Michael J. Ackerman, MD, PhD, the study’s chief author who heads the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory.

“To prevent further tragic, premature deaths, the standard of care for the evaluation of sudden unexplained death must now change. Surviving members in a family in which there’s been this tragedy should receive medical attention that is equal to a ‘full-court press,’” Dr. Ackerman says. “It must involve a careful and sleuth-like search for these inherited glitches in the heart’s electrical system.”


**Significance of the Mayo Clinic Research**

These results identify a tragic situation that could, with increased medical surveillance, potentially be prevented in many cases. To do so requires physicians and families to work astutely together to take a careful multigenerational heart history. Dr. Ackerman says that to identify at-risk relatives, all immediate family members of the person who died inexplicably must undergo comprehensive cardiac evaluation that includes, at a minimum, an electrocardiogram and an exercise stress test as initial screens for LQTS and CPVT. If evidence of heart problems is found, family members need to act immediately by
getting screened for the lethal mutations, and treated, if necessary, he says.

“Families who have lost a loved one to sudden unexplained death should now know that they can do more if the coroner or medical examiner is unable to provide an explanation for their loved one’s sudden and unexplained death,” Dr. Ackerman says. “Postmortem genetic testing could be performed on the victim of sudden death in search of the cause. Now, one-third of the time, we can find the cause.”

Although all deaths in the study were officially categorized as unexplained, the medical histories showed that nearly half of those with the lethal mutations had experienced a warning sign prior to death. The warning signs of possible mutation-linked heart abnormality include:

- sudden fainting or a sudden seizure.
- evidence of unexplained death in the family history, such as a motor vehicle accident for which no plausible cause can be found.
- a distant relative with an unexplained death.

With proper recognition of key warning signs, some sudden unexplained deaths may be preventable, Dr. Ackerman says.


Collaboration and Support

Also involved in the study was David Tester, senior research technologist of the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory. Funding came from the Mayo Clinic Foundation for Biomedical Research, the Dr. Scholl Foundation, the Hannah Wernike Memorial Foundation, the CJ Foundation for SIDS, the American Heart Association, and the National Institutes of Health (NIH).

For more information: www.mayo.edu.
MyLab™30 CV.
Taking high performance into any environment.

When there is no room for compromise, MyLab™30 CV delivers even more.
Whether for private practice or hospital environments, high-performance cardiovascular scanning is what you really need. From scheduling to final report, MyLab™30 CV provides go-anywhere diagnostic scanning, reporting and networking—all with high end results. And with enhanced connectivity, advanced workflow tools and a broad range of transducers, including multiplane TE, MyLab™30 CV offers the adaptability needed in today’s clinical environment without compromising the clinical performance necessary to provide the highest levels of patient care.

At Biosound Esaote, we have been developing innovative ultrasound solutions for over 25 years. And our factory-trained technicians and customer service representatives ensure that your investment is a solid one.