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Non-surgical Septal Reduction Procedure in Down's Syndrome with Hypertrophic Obstructive Cardiomyopathy - A Case Report

By Shanthi Sivanandam, MD and James H. Moller, MD

Keywords: Hypertrophic Cardiomyopathy, Alcohol septal reduction, Down's syndrome
Running title: Alternative treatment for Hypertrophic Obstructive Cardiomyopathy

The authors have no potential conflicts of interest, real or perceived, to report with regards to this work.

Introduction

We report our experience of Non-surgical septal reduction procedure in Down's Syndrome with Hypertrophic Obstructive Cardiomyopathy.

A 21-year old male, with Down's Syndrome, mental retardation had been followed for a number of years for a small ventricular septal defect. When last seen five years ago he was asymptomatic. Echocardiogram obtained in 1997 demonstrated a small pressure restrictive perimembranous ventricular septal defect. Interventricular septal thickness (IVS) was 7mm; left ventricular posterior wall (LVPW) was 7mm. In 2003 he was noted to have shortness of breath, diaphoresis with activity, decreased exercise tolerance and was

becoming more sedentary with New York Heart Association (NYHA) Class III symptoms.

Physical examination showed typical features of Down's Syndrome. Cardiovascular examination revealed a grade 2/6 high-pitched midsystolic murmur best heard along the lower left sternal border. Electrocardiogram showed left ventricular hypertrophy with strain (Figure 1). Echocardiogram showed marked asymmetric septal hypertrophy measuring 25mm; Left ventricular posterior wall measuring 15mm, consistent with hypertrophic cardiomyopathy (HCM) (Figure 2). Continuous wave Doppler estimated a 70mm Hg sub-aortic gradient due to dynamic systolic anterior motion of the mitral valve with septal contact. Thus, the diagnosis hypertrophic obstructive cardiomyopathy was made. Medical management with beta blockers was ineffective in controlling symptoms. There was no change in his exercise capacity and he continued to be in NYHA Class III. Due to progressively worsening symptoms, Non-surgical septal reduction procedure (NSRP) was considered for this patient to reduce outflow obstructive symptoms and was successfully performed.

Methods and Result

A non-surgical septal reduction procedure with intracoronary (septal) ethanol injection to



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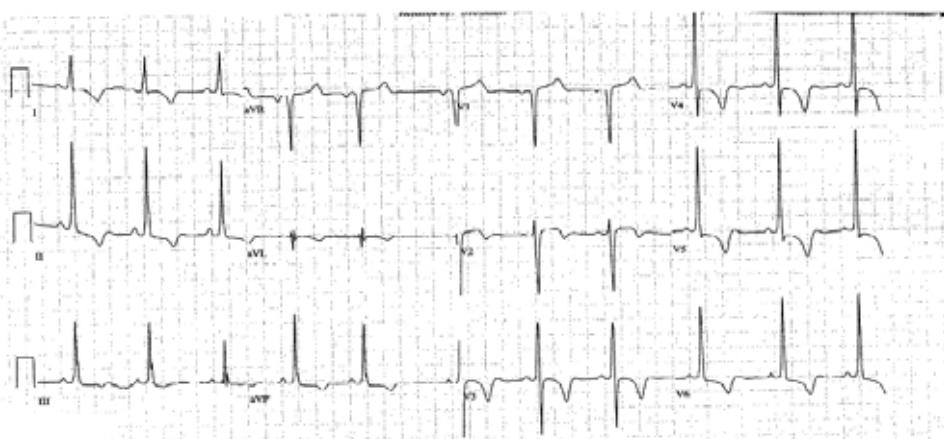
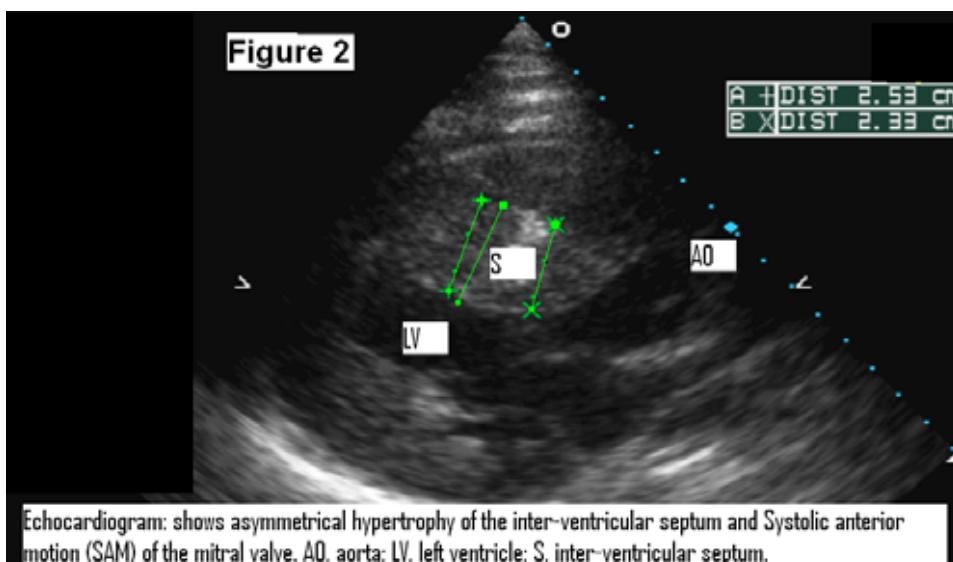


Figure 1: Pre procedure ECG showing left ventricular hypertrophy with strain.



Echocardiogram: shows asymmetrical hypertrophy of the inter-ventricular septum and Systolic anterior motion (SAM) of the mitral valve. AO. aorta; LV. left ventricle; S. inter-ventricular septum.

Figure 2: Echocardiogram shows asymmetrical hypertrophy of the inter-ventricular septum and Systolic anterior motion (SAM) of the mitral valve.

reduce the left ventricular obstruction was performed. Prior to NSRP he underwent a prophylactic pacemaker and defibrillator because of the high incidence of sudden death induced by ventricular tachycardia and ventricular fibrillation in hypertrophic obstructive cardiomyopathy. In brief, a high fidelity Radi pressure wire was placed into the LV through a 6 Fr catheter. The

catheter was withdrawn to the aorta and simultaneous pressures were continuously recorded in the left ventricle and aorta. Coronary angiography was performed to exclude atherosclerotic coronary arterial disease and identify the septal perforators. A 2.0/15 Crosssail balloon catheter was introduced into the first septal branch of the left anterior descending coronary artery.

SEPTEMBER MEETING FOCUS

18th International Parma Echo Meeting - From Fetus to Young Adult
September 16-18, 2009
Parma, Italy
www.unipr.it/arpa/echomeet/

Program Director: Umberto Squarcia, MD, FACC

Program Includes the following and more:

- Standard Echocardiographic measurements of chambers and volumes - D. J. Hagler
- Usefulness of Echographic contrast for chamber size, volume and wall motion measurements - N. Gaibazzi
- Echo vs MRI volume measurements - S. P. Sanders
- 3D Echo Volumes estimates for the LV and RV - G. Shirali
- Current Status of Fetal Echocardiographic diagnosis of CHD - L. Fermont
- Fetal Echocardiographic Predictor for Shone Complex - L. Pasquini
- Standford Experience of Fetal Cardiology - N. Silverman
- Impact of fetal ductus arteriosus anomalies on perinatal outcome - M. Guirgis
- The "Giancarlo Rastelli Lecture" - L. Bokeria
- Congenital Anomalies of the Coronary Arteries and Sudden Death - G. Thiene
- Isolated Congenital Coronary Anomalies. Echocardiographic Diagnosis - A. Bozio
- Advances in Real Time 3D Echocardiographic diagnoses - G. Shirali
- Clinical application of 3D Echocardiographic in our practice - S. P. Sanders
- MRI: Advanced Imaging of Extracardiac Vessels in Congenital Heart Disease - Paul Julsrud
- How does MRI and 3D Echocardiography compare? - S. P. Sanders
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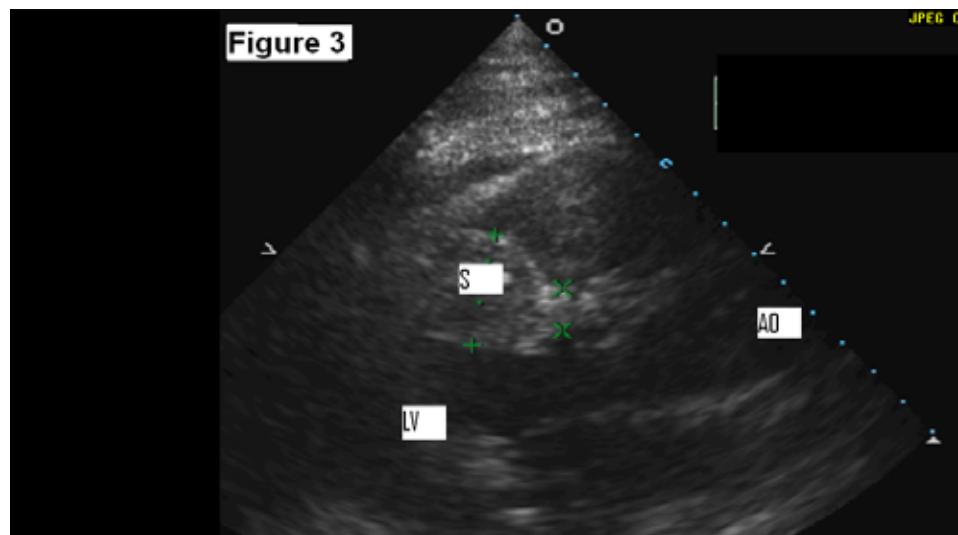
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Figure 3



Echocardiogram after NSRP shows inter-ventricular septum at the level of Left ventricular outflow tract reduced from 25mm to 10mm. AO: aorta; LV: left ventricle; S: inter-ventricular septum.

Figure 3: Echocardiogram after NSRP shows inter-ventricular septum at the level of left ventricular outflow tract reduced from 25mm to 10mm.

	Echo gradient	LVSP(cath)	Aorta(cath)	Cath gradient
2003	70mm Hg			
Resting 2004(cath)		142mm Hg	72mm Hg	70 mm Hg
1st injection (cath)				60 mm Hg
2nd injection (cath)		99mm Hg	83mm Hg	16 mm Hg
2nd injection (cath)				
1 month later	4mm Hg			
1 year later	No gradient			
4 year later	No gradient			

Table: shows LVOT gradient pre and post Nonsurgical septal reduction procedure

After the balloon was inflated, the distribution of the first septal branch was verified by contrast two-dimensional echocardiography after the injection of 2cc of myocardial echo contrast Definity. After confirming which territory of the basal septum contributed to the LVOT obstruction and no other myocardial territory was involved,

a total 1.6 ml of ethanol was injected slowly. The balloon occlusion was maintained for 10 minutes. There was an immediate reduction in LVOT peak systolic gradient to 20mm Hg. After balloon deflation the gradient slowly rose to 60mm Hg. The target septal perforator was again identified and an additional 1.6ml of



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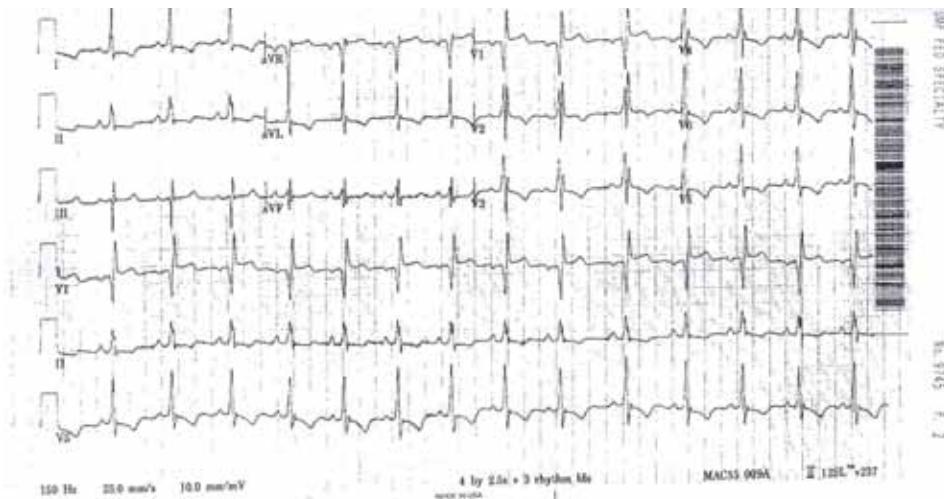


Figure 4: Post procedure ECG showing left ventricular hypertrophy with strain and Right bundle branch block.

ethanol was injected through the inflated balloon resulting in 16mm Hg LVOT systolic peak gradient. The LVOT pressure gradients were measured before and immediately after the procedures by catheter and by two-dimensional echocardiography. LVOT catherization gradient reduced from 70mm Hg to 16mm Hg. His hospital course following the procedure was uneventful, and he was discharged home in less than 2 days. One month after the NSRP echocardiogram revealed a mean gradient across the LVOT of 4mm Hg. One and four year follow-up echocardiograms revealed no LVOT gradient (Table 1). Interventricular septum measured 25mm prior to NSRP. One and four year follow-up revealed IVS measuring 10mm at the level of the left ventricular outflow tract (Figure 3).

Patient remains asymptomatic with no shortness of breath and improved exercise tolerance. He is NYHA class I with no limitation of activities. Since the placement of prophylactic pacemaker and defibrillator, there was no arrhythmia, no heart block, no ventricular tachycardia or ventricular fibrillation. Recent EKG showed normal sinus rhythm, Left ventricular hypertrophy with strain and Right bundle branch block (Figure 4).

Discussion

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder characterized by asymmetric left ventricular hypertrophy and dynamic outflow obstruction and is inherited as a Mendelian autosomal dominant trait. HCM can be caused by a mutation in any 1 of 5 genes that encode proteins of the cardiac sarcomere: beta-myosin heavy chain (on chromosome 14), cardiac troponin T (chromosome 1), troponin I (chromosome 19), alpha-tropomyosin (chromosome 15), and cardiac myosin-binding protein C (chromosome 11). In addition, mutations in 2 genes encoding essential and regulatory myosin light chains have been reported in what may be an extremely rare form of HCM. This genetic diversity is further compounded by intragenic heterogeneity, with a total of more than 100 individual disease-causing mutations identified for these genes; the majority represents missense mutations in which a single amino acid residue is substituted with a different amino acid in the globular head or head-rod junction regions of the myosin molecule. The prevalence of HCM in the general population has been estimated as 1:500, higher than was previously postulated.

OCTOBER MEETING FOCUS

Contemporary Questions in Congenital Heart Disease: Heart Failure and Transplantation
October 4-6, 2009
Toronto, Canada
www.sickkids.ca/Centres/heart-centre/Cardiac-symposium

Course Objectives:

- Bring together experts in the field of heart failure and cardiac transplantation in children and adults.
- Explore contemporary understanding of heart development, physiology and pathophysiology on congenital and acquired heart disease.
- Encourage a multidisciplinary approach to the fetal, preoperative, perioperative and late postoperative management.

Program Director:

Andrew Redington

Toronto Team Directors:

Glen Van Arsdell, Steven Schwartz and Erwin Oechslin

Invited Faculty:

Robert Anderson, Leonard Bailey, Barry Byrne, Anne Dipchand, Jean-Claude Fouron, James Huta, Stephen Lipshultz, Sandra Merklinger, W. Robert Morrow, Daniel Penny, Jeffery Robbins, Robert Shaddy, Maully Shah, Lara Shekerdemian, Reeni Soni, Jeffrey Towbin, Stephen Webber and Gil Wernovsky.

All lectures will be recorded and each attendee will receive a DVD shortly after the meeting.

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- Hybrid Stage I Palliation for HLHS PA Bands and PSA Stent
- Intraoperative Aortic Stent for CoA
- Intraoperative LPA Stent Using Endoscopic Guidance
- Creation of ASD after PA Bands & PDA Stent for HLHS in a Preemie
- Perventricular Implant of Edwards Valve Stent in the Pulmonary Position
- High Frequency Ultrasound Creation of ASD
- PmVSD Closure
- Percutaneous Closure of ASD(s) with TEE or ICE Guidance
- Percutaneous Valve Implantation
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Annual mortality for HCM in an unselected population has been reported to be about 1% to 2%, and sudden death represents the most common cause. Sudden death is assumed to be due to idiopathic ventricular arrhythmias, but hemodynamic factors and myocardial ischemia may be involved as well. Long-term consequences of HCM attributable to outflow obstruction have been emphasized, particularly progression of disabling symptoms and death related to heart failure.

Surgical myectomy has been the preferred method of treatment for symptomatic patients with significant hemodynamic outflow tract obstruction (systolic pressure gradient at rest ≥ 50 mm Hg, after provocation ≥ 100 mm Hg) for more than 20 years. Recently introduced non-surgical septal reduction procedure with intracoronary ethanol, however, is a new promising treatment for patients with hypertrophic obstructive cardiomyopathy. This technique avoids a thoracotomy and cardio-pulmonary bypass to remove the excessive myocardium in the left ventricular outflow tract. Ethanol is infused into one or more septal perforator branches of the left anterior descending coronary artery to cause necrosis and the resultant shrinkage of the proximal hypertrophied interventricular septum. The result is akinesis and enlargement of the narrowed LVOT. Myocardial contrast echocardiography (MCE) is used to guide the targeted delivery of ethanol during nonsurgical septal reduction procedure. MCE can provide quantitative assessment of the extent of myocardium supplied by each septal perforator. MCE definition is selectively injected into the septal perforator artery can potentially provide an excellent definition of the vascular bed perfused by this vessel and can delineate the area at risk before induced infarction. MCE localized the septal territory and ensured that balloon inflation prevented retrograde spillage into the left anterior descending coronary artery because the septum was the only opacified wall. Coronary angiography was performed to exclude significant atherosclerotic coronary artery disease.

Non-surgical septal reduction therapy was first performed and reported by Dr. Ulrich Sigwart in 1995. His initial series reported on the first three patients in the world to undergo this new procedure. The procedures were all successful, and there was sustained clinical improvement at 1 year. These excellent results in a small series of patients led the way for more studies of this new procedure.

In the US, the first procedure was performed at the Baylor College of Medicine. In their 1-year follow-up study of 50 patients, there was a mean decrease in the outflow tract gradient from 74 mm Hg at baseline to 6 mm Hg at 1 year.

Eleven patients (22%) in this group required permanent pacemaker implantation secondary to refractory heart block after the procedure. Two patients (4%) died during the follow-up period. Data from 2001 showed regression of left ventricular hypertrophy, septal thickness at the infarction site decreased from 20 mm before to 12 mm at 1 year and 10 mm at 2 years. Wall thickness throughout the left ventricular circumference was significantly reduced after NSRP, along with a preserved EF. Regression of LVH may also

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contribute to symptomatic improvement and is probably related to the fact that the increasing hypertrophy in patients with obstruction contributes to a decrease in LV compliance and impaired exercise tolerance. NSRP essentially eliminated the LVOT gradient and was associated with marked reduction in symptoms and improved exercise tolerance. NSRP also resulted in regression of LVH which may be another beneficial effect, given that the frequency of sudden death in HOCM patients increases with increased LVH. Part of this enthusiasm for NSRP derives, understandably, from the relative ease with which NSRP can be performed in experienced hands compared with surgery, involving shortened postoperative recovery, less discomfort and avoidance of cardiopulmonary bypass.

Although, early studies demonstrated an increased incidence of complete heart block, as the technique has been modified with slower rate of injection ethanol (1 to 1.5ml/min instead of bolus) using intracoronary myocardial contrast echocardiography to help target ethanol to the culprit septal segments, the incidence of complete heart block has reduced to 6.7%. The data by Fernandes et al in 2005 on long-term outcome (follow-up of 5 years with mean follow-up 3.6 ± 1.4 years) of alcohol septal ablation had shown resting left ventricular outflow tract gradient at baseline versus last follow-up visit showed a decrease from 74 ± 30 to 4 ± 13 and the dobutamine-provoked gradient of 88 ± 29 decreased to 21 ± 21 mm Hg. Complications of procedures included death 1.5% (2/130), heart block requiring permanent pacemaker 13% (17/130), and coronary dissection 4.4% (6/130). Alcohol septal ablation decreased symptoms and improved exercise performance, indicating that it is an effective procedure for symptomatic HOCM.

Nielsen et al reported in 2003, 50 alcohol septal ablation procedure on 46 patient using echocardiographic contrast localization, slow alcohol injection, and shorter balloon catheters. There was a decrease in the LVOT gradient from 84.2

(± 30.8) mm Hg at baseline, to 18.5 (± 14.8) mm Hg immediately after alcohol septal ablation. The septal thickness decreased from 2.21cm at baseline, to 1.67cm at 3 months. Three patients (6.7%) of the 45 developed complete heart blocks, requiring permanent pacing.

Even in experienced hands alcohol septal ablation may incur morbidity and mortality similar to that of septal myectomy.

Conclusion

NSRP is a promising alternative procedure for selected patients and an important addition to the therapeutic management of hypertrophic obstructive cardiomyopathy. There is a learning curve in the performance of the procedure which affects the success and complication rate. NSRP is efficacious in providing symptom relief and improving exercise tolerance.

CCT

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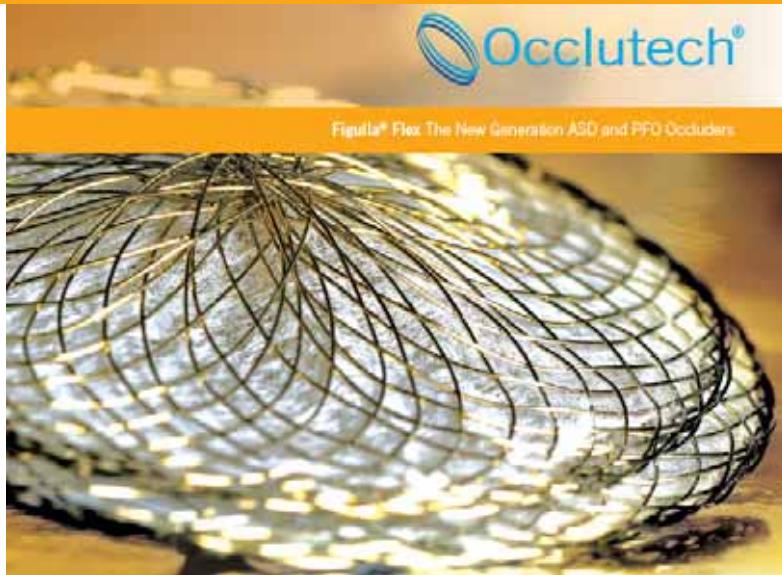
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ISHAC MILANO: From the Joint Meeting of Workshop IPC & ISHAC - March 22nd – 25th, 2009

By John P. Cheatham, MD

For the first time in four years, the International Symposium on the Hybrid Approach to Congenital Heart Disease (ISHAC) left the friendly confines of Nationwide Children's Hospital and Columbus, Ohio, to join the 7th International Workshop on Interventional Pediatric Cardiology (IPC) in beautiful Milano, Italy. On the last day of the joint meeting, March 25th, over 620 attendees participated in lectures, panel discussions, and live cases highlighting the importance of teamwork between interventional cardiology and cardiothoracic surgery in the hybrid therapies for CHD.

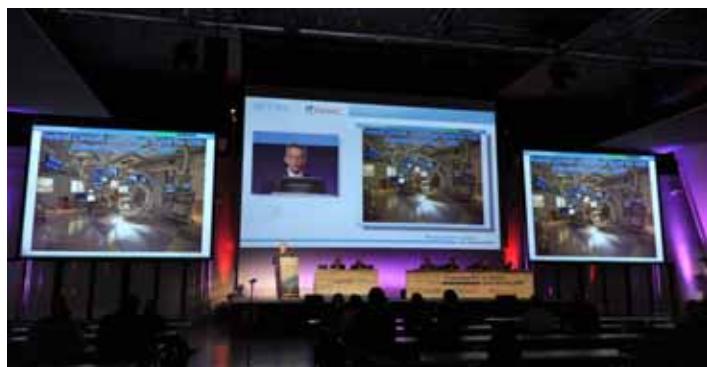
The morning began with a welcome and introduction from the Program Co-Directors, Drs. Mario Carminati, John Cheatham, and Mark Galantowicz. Dr. Cheatham then gave a lecture on how to establish a Hybrid program by overcoming obstacles, suite design, and the teamwork required. The morning session was highlighted by Dr. Ina Michel-Behnke and Dr. Mark Galantowicz updating the audience on the intermediate results of the Hybrid Approach to Hypoplastic Left Heart Syndrome from Giessen and Columbus, respectively. The results were outstanding from these two leading institutions and compared favorably to the Norwood/Sano results of the leading heart centers worldwide. Next, alternative pulmonary artery banding techniques using adjustable external bands and internal flow restrictors were discussed by Dr. Renato Assad from Sao Paulo and Dr. Cheatham. Finally, the choices and techniques for PDA stenting were discussed by Dr. Carlos Pedra, also from Brazil.



A beautiful venue for a meeting.



Welcome - (left to right) John P. Cheatham, Mark Galantowicz and Mario Carminati.



John P. Cheatham lecturing on how to build a Hybrid Program.



Sharon Hill lecturing on transcranial doppler in HLHS.



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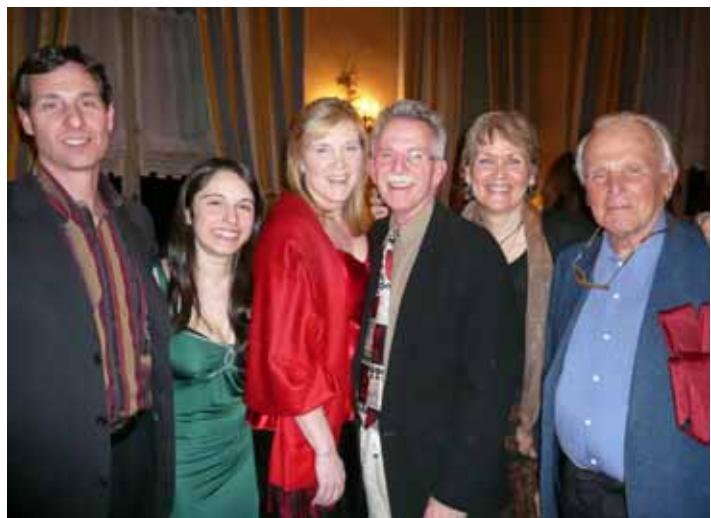
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Zhen Xu lecturing on Histotripsy.

Dr. Shakeel Qureshi showed the tape-recorded live case broadcast of Hybrid PA banding and PDA stent implant in a baby with HLHS variant and aortic valve stenosis from Evelina Children's Hospital in London. With his surgical colleague, Mr. David Anderson, Shakeel then proceeded to perform successful balloon aortic valvuloplasty using a trans-aortic approach through a purse-string sutured sheath. It was a wonderful demonstration of Hybrid techniques and collaborative thinking to achieve the best result for our patients.

The next live case was broadcast from Giessen where Dr. Dietmar Schranz treated the attendees by demonstrating the techniques for PDA stenting in a baby with pulmonary atresia and ventricular septal defect. A brief discussion between the moderators, panelists, operator and attendees followed and resulted in an excellent clinical result. The morning session continued with a long distance lecture by Dr. Ziyad Hijazi from Chicago on how to deal with the atrial septum in babies with HLHS, while Dr. Pedra provided insight on how to treat retrograde aortic arch obstruction when it occurs after Hybrid Stage I

palliation. The final morning lecture, given by Dr. Pedro Del Nido from Boston, focused on "rescuing" the borderline left ventricle by surgical removal of the endocardial fibroelastosis and returning to 2-ventricular physiology...sort of the LV "overhaul" procedure!

Lunch time was jam-packed with the announcement of the recipients of the 2nd Fung-Wexner Award for international scientific collaboration within The Heart Center at NCH. Dr. Zhen from Fuwai Cardiovascular Institute, Beijing, China, and Dr. Wold from Nationwide Children's Hospital received the award for their continued work in establishing an International Tissue Bank for CHD. After a delicious and healthy Italian cuisine was served, the attendees prepared for the Perventricular Approach Session by sipping Italian coffee and eating scrumptious pastries. Dr. Gianfranco Butera from San Donato, Milano began the afternoon session by describing the challenges of percutaneous closure of muscular VSD, while Dr. Hijazi compared the technique to perventricular closure of those defects in newborns and small infants. Dr. Del Nido then educated the interventional cardiologists that surgeons have a few tricks up their sleeves by demonstrating live 3-D echo guided closure of muscular VSD using perventricular approach. The session ended with Dr. Shengshou Hu from Fuwai Hospital in Beijing describing their innovative work in the perventricular approach to R-sided obstructive CHD, avoiding CP bypass.

The third live broadcast of the day from Giessen demonstrated the pre Comprehensive Stage II cardiac catheterization after successful PA bands, PDA stent, and balloon atrial septostomy. This nicely led into the 3rd major topic at ISHAC where intraoperative stents were discussed. Dr. Galantowicz lead off by explaining that surgical removal of endovascular stents is just a


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ISHAC faculty and program directors at the Gala



Live case from Columbus - Ralf Holzer and Alistair Phillips showing periventricular MVSD closure.

matter of attitude...a thought not shared by many cardiac surgeons! Next, Dr. Evan Zahn described the techniques of implanting intraoperative pulmonary artery and aortic stents using both endoscopic and fluoroscopic guidance, once again emphasizing the need for collaboration! Following this lecture, Drs. Ralf Holzer and Alistair Phillips performed the fourth live case broadcast, demonstrating periventricular closure of a muscular VSD, as well as endoscopic-guided intraoperative PA stent implantation from the Cardiovascular Research Surgical Suites in Columbus.

The final session of ISHAC and the Grande Finale of the joint meeting centered on future materials, techniques, and research. Dr. Felix Berger from Berlin gave a preview of new biodegradable stents and polymers. Then Dr. Zhen Xu from the University of Michigan Biomedical Engineering Department dazzled the audience with histotripsy...using therapeutic ultrasound bubble clouds that act as microscopic scalpels. She showed both the surgeons and interventional cardiologists why we may be out of jobs someday!

Dr. Loren Wold from the Center for Cardiovascular and Pulmonary Research Center, Nationwide Children's Hospital, reported the importance of future tissue banking and genetic biomarkers in unraveling some of the mysteries of congenital heart disease. The final lecture from Sharon L. Hill, ACNP, at NCH stressed the importance of determining neurodevelopmental outcomes after HLHS palliation and the future use of transcranial Doppler analysis to determine cerebral blood flow...before, during, and after each staged-procedure. This may provide insight into an important aspect of our patients' care.

ISHAC and Workshop IPC came to a close and Program Co-Directors, John Cheatham and Mark Galantowicz reminded everyone that ISHAC 2010 returns to Columbus, Ohio, September 1st – 3rd with a 2-day Symposium and 1-day special hands-on Skills Workshop. Our Keynote Speakers will be Professor Philipp Bonhoeffer from Great Ormond Street and Mr. Marc de Leval from the International Congenital Cardiac Centre, London, UK. Rumor even has it that an Ohio State University Buckeye football game may be a part of the meeting...stay tuned! Then, Drs. Gianfranco Butera and Massima Chessa, on behalf of Dr. Carminati and the entire program staff from Ab Medica, thanked everyone for attending, the faculty, and the sponsors and welcomed them to the 8th IPC Workshop scheduled for 2011 in Milano, Italy.

CCT

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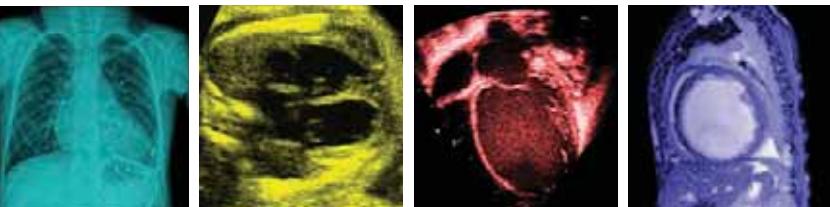


CONTEMPORARY QUESTIONS IN CONGENITAL HEART DISEASE HEART FAILURE AND TRANSPLANTATION

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Experience with a Novel Miniaturized Multi-plane Transesophageal Echocardiographic Transducer

By Eric M. Graham, MD and Girish S. Shirali, MBBS

With the advances in cardiac surgery, anesthesia and post operative care and the manifest advantages of correcting abnormal cardiac physiology early, there continues to be a growing trend towards complete repair of complex intracardiac operations undertaken in smaller and smaller patients. Transesophageal echocardiography (TEE) has been shown to be safe and cost effective in the intraoperative period and has become standard of care in many institutions.¹⁻³ Prior to starting the operation, TEE can confirm or further delineate the cardiac anatomy. Prior to separating from cardiopulmonary bypass TEE can assure adequate intracardiac de-airing, lowering the risk of air emboli. After separation from cardiopulmonary bypass TEE can confirm the adequacy of repair, assess atrioventricular and arterial valvar competency and assess ventricular filling and function prior to leaving the operating room. Confirming the adequacy of a repair prior to leaving the operating room is important because inadequate repairs can be immediately corrected. Whereas, patients leaving the operating room with significant residual defects have experienced increased morbidity, mortality and financial cost.³⁻⁶ Despite the advantages of TEE there are some potential disadvantages. These include esophageal or gastric trauma or perforation, left atrial, aortic or airway compression resulting in hemodynamic or ventilation compromise, and inadvertent tracheal extubation. Despite these potential concerns, several studies have shown a low rate of complications, predominantly airway compression and inability to pass the transducer.² Neonates and small infants are

particularly at risk for the potential complications given their small size

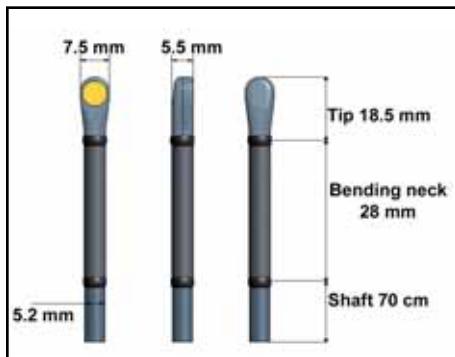


Figure 1: This demonstrates the dimensions of the micro-multiplane TEE probe.

compared to the transducer size.^{1, 2} Despite current reports that clinically significant hemodynamic and ventilation compromise is infrequent even in children as small as 2-5 kg, concerns remain.^{7, 8} These have led to reluctance to use TEE in small infants and neonates. Paradoxically, it is the small neonate undergoing intracardiac repair that probably has lower tolerance for residual defects, and thus more to gain from intraoperative TEE.

Pediatric TEE probes that are in general usage are equipped with either a biplane or multiplane transducer. The biplane probe has 64 elements in each transducer, an output frequency of 5.5 or 7.5 MHz and a tip dimension of 9.1 x 8.8 mm. The multiplane probe has a 48 element transducer with a center frequency of 6 MHz (range 4 to 7 MHz) and a tip dimension of 10.7 x 8.0 mm.⁹ Improving technology has led to a new miniaturized multiplane TEE. We report our experience with the world's smallest

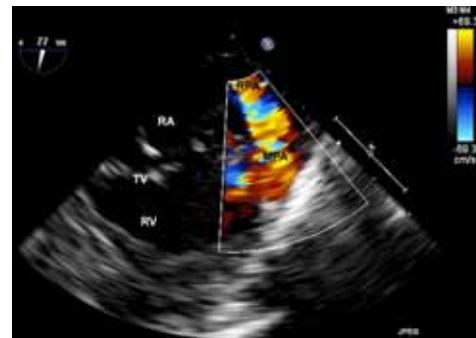


Figure 2: Color flow Doppler imaging of the right ventricular inflow – outflow view in a 2.5 kg patient who was undergoing surgery for a large membranous ventricular septal defect. MPA, main pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle.

multiplane TEE probe, the micro-TEE transducer (Philips Medical, Andover, MA, USA). The shaft width is 5.2 mm with a transducer tip width of 7.5 mm and height of 5.5 mm (Figure 1, Table 1). The micro-TEE is a 32 element phased array multiplane TEE transducer complete with 2D, color, pulse wave, Hi PRF and continuous wave Doppler, MMode and CF MMode. It has a center frequency of 6 MHz (range 3.2 MHz to 7.4 MHz). The controls on this probe are identical to those on the minimultiplane TEE that is in general usage. Specifically, there is a 180 degree manual image plane control with angular display, anterior and posterior articulation and an articulation brake. The transducer has tip temperature sensing and display for added safety.

Patients are currently being enrolled at the Medical University of South Carolina's Institutional Review Board approved study evaluating image quality of this probe in neonatal and pediatric TEE. To date, over 20 patients have been studied, primarily in the operating room but also in the catheterization suite under general anesthesia. Probe insertion has been attempted in patients 1.7 kg and above. All insertions have been successful and well-tolerated. High-quality diagnostic images have been obtained consistently (Figure 2-4).

This advance enables us to provide the small neonate and infant with intra-

Table 1 Transducer comparison

	Tip Length (mm)	Tip Width (mm)	Tip Height (mm)	Shaft (mm)	Pt Wt (kg)
X7-2t	40	16.6	13.1	10	30
Mini-mTTE	27	10.6	8	7.5	3.5
Micro-mTEE	18.5	7.5	5.5	5.2	?

operative TEE imaging, thus optimizing repairs and outcomes.

Acknowledgments: The authors thank the faculty and fellows of the Divisions of Pediatric Cardiology, Cardiothoracic Surgery, and Cardiothoracic Anesthesia, and the Pediatric Cardiology sonographers for their assistance with this project.

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Figure 3: This image was obtained in a 3 month old, 5 kg infant with atrioventricular septal defect and severe left-sided AV valve regurgitation. In addition to closing the 'cleft', the surgeon created a double-orifice left AV valve. This is a 60-degree image of the surgically-created double-orifice mitral valve, demonstrating prograde flow through both orifices. LA, left atrium; LV, left ventricle.



Figure 4: Simultaneous 2D and color flow Doppler in a 4 month old, 5.4 kg infant undergoing repair of tetralogy of Fallot. The asterisk marks the severely anteriorly malaligned outlet septum. There is right to left flow across the VSD. Note the long-segment stenosis of the right ventricular outflow tract, pulmonary valve and main pulmonary artery. MPA, main pulmonary artery; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract; VSD, ventricular septal defect.

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Medical News, Products & Information

Toshiba Launches InTouch Flex Service Agreement

To further its commitment to providing innovative, quality customer solutions, Toshiba America Medical Systems, Inc. has launched the new InTouch™ Flex Service Agreement, offering customers unparalleled flexibility, security and value. Considered the first of its kind in the diagnostic imaging industry, the InTouch Flex Service Agreement allows customers to secure fixed price points for both the full service and partnership agreements at the point of purchase and after the warranty, convert the agreement back and forth between a full service security agreement and a partnership agreement, as needed. This flexible service approach enables customers to adapt service plans throughout the lifetime of the agreement to match real-time needs.

"Toshiba's InTouch Flex Service Agreement provides us a flexible, cost-effective service arrangement to meet our changing needs today and in the future," stated George Morley, director of Biomedical Engineering at PinnacleHealth, a premier nonprofit healthcare system with in-house service staff already under the new InTouch Flex Service Agreement. "The flexibility offered by Toshiba is unmatched in the service marketplace. It allows us to utilize our in-house staff effectively, but also rely on Toshiba Service when additional support or expertise is required."

PinnacleHealth, serving Central Pennsylvania, is the first healthcare system to take advantage of the InTouch Flex Service Agreement. Under the InTouch Flex Service Agreement, service problems are first handled by PinnacleHealth's in-house service team through diagnosis remotely via phone or by a service team member on site. Receiving the same training as Toshiba engineers, PinnacleHealth service staff can troubleshoot issues quickly and order product equipment for repairs directly from Toshiba. If PinnacleHealth's service team needs additional assistance, a service engineer from Toshiba arrives within two hours to address the customer's needs. This one-of-a-kind service partnership results in a situation where the customer's interests are at the forefront for both PinnacleHealth service staff and Toshiba.

PinnacleHealth purchased more than \$14.5 million of Toshiba medical imaging equipment as part of a five-year strategic business agreement, most of which is serviced under the new InTouch Flex Service Agreement. PinnacleHealth sources 85 percent of its new medical imaging systems from Toshiba's leading product portfolio including CT, MR, Vascular X-ray, X-ray and Ultrasound.

As the service needs of hospitals, IDNs and imaging centers change over time, Toshiba's InTouch Flex Service Agreement enables these facilities to adjust their service agreement to meet these needs. The InTouch Flex Service Agreement allows

customers to switch between the following existing full service and partnership agreements:

- InTouch Full Security Agreement - the ideal full-service solution, providing a blend of security and flexibility. This offering provides full protection for imaging systems, risk-free and fixed-price support, customized service solutions and unmatched technical support.
- InTouch Partnership Agreement - the ideal partnership solution giving healthcare providers the flexibility to balance fixed and variable service costs while benefiting from special discounted rates on parts and labor. InTouch Partnership Agreements are a shared-risk solution allowing the customer to adjust service levels to optimize patient care while controlling costs.

Under the InTouch Flex Service Agreement, the customer's in-house service support team receives extensive in-person training from Toshiba. Additionally, customers have access to immediate applications and technical support through Toshiba's InTouch Center, when needed.

"We pride ourselves on viewing service as a collaboration, listening to our customers' needs and providing unique customized solutions," said Ted Nemetz, Vice President, Service Business Unit, Toshiba. "Whether a customer requires a partnership agreement with the majority of service handled by their in-house staff or a full service agreement with Toshiba service specialists handling the workload, the service agreement pricing never exceeds the original point of purchase pricing."

Toshiba's Service Business Unit has been recognized for its approach through various industry recognitions. In IMV's 2008 ServiceTrak™ Imaging on CT system service, Toshiba received more top rankings than any other imaging vendor. In fact, Toshiba CT received the top ranking in 21 out of 34 service attributes, including overall OEM service performance, overall satisfaction with a manufacturer, reliability of hardware and overall value.

PinnacleHealth is a non-profit healthcare system serving Central Pennsylvania. For a complete list of services, visit www.pinnaclehealth.org.

With headquarters in Tustin, Calif., Toshiba America Medical Systems markets, sells, distributes and services diagnostic imaging systems, and coordinates clinical diagnostic imaging research for all modalities in the United States. Toshiba Medical Systems Corp., an independent group company of Toshiba Corp., is a global leading provider of diagnostic medical imaging systems and comprehensive medical solutions, such as CT, Cath & EP Labs, X-ray, Ultrasound, MRI and information systems. For more information, visit www.medical.toshiba.com.



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New Potential Therapeutic Target Discovered for Genetic Disorder – Barth Syndrome

Newswise — Researchers at NYU Langone Medical Center may have discovered a new targeted intervention for Barth Syndrome (BTHS). BTHS, a sometimes fatal disease, is a serious genetic disorder occurring predominantly in males that leads to infection or heart failure in childhood. The new study entitled, "Role of calcium-independent phospholipase A2 in the pathogenesis of Barth syndrome", was recently published in the *Proceedings of National Academy of Sciences*, shows the benefits of targeted intervention with an iPLA2-VIA inhibitor that prevents a major symptom of the disease- cardiolipin deficiency.

"Our research has established a causal role of cardiolipin deficiency in the pathogenesis of Barth Syndrome and identified an important enzyme in cardiolipin degradation called iPLA2-VIA as a potential target for therapeutic intervention of the disease," said Mindong Ren, PhD, lead investigator of the study and Assistant Professor of cell biology at NYU Langone Medical Center.

BTHS is an X-linked genetic cardioskeletal muscle disease resulting in muscle weakness and fatigue in patients. The debilitating disorder is caused by a mutation in the genetic coding of tafazzin, an enzyme of the cardiolipin pathway. Cardiolipin is an essential lipid in the inner membrane of mitochondria responsible for normal cell structure and energy production. BTHS patients exhibit defects in cardiolipin metabolism which help fight infections. The various symptoms of BTHS, in addition to cardiolipin deficiency, include cardiomyopathy (weakness in heart muscle), neutropenia (a reduction in neutrophils or white blood cells that fight bacterial infections), muscle weakness & fatigue (caused by cellular deficiency), growth delay, and increase of organic acids in urine.

In a previous study, NYU researchers documented the characteristics of a tafazzin-deficiency in a Drosophila (fruit fly) model of the disease, showing low and abnormal cardiolipin concentration, abnormal mitochondria, and poor motor function. In this new study researchers documented that tafazzin or cardiolipin deficiency in Drosophila disrupts the final stage of spermatogenesis causing male sterility. Using this fly model, the study showed that this trait of cardiolipin deficiency can be genetically suppressed by inactivating calcium-independent phospholipase A2, which prevents the degradation of cardiolipin. This method keeps cardiolipin levels normal. Researchers were also able to show that treatment of BTHS patients lymphoblasts within a tissue culture with the iPLA2-VIA inhibitor BEL partially restored the tissue cultures cardiolipin homeostasis.

"Taken together, our two findings establish a causal role of cardiolipin deficiency in the pathogenesis of Barth syndrome and identify iPLA2-VIA as a very important enzyme," said Michael Schlame, MD, Associate Professor of Anesthesiology and Cell Biology, NYU Langone Medical Center. "This is good news for patients since this enzyme is now a potential target for therapeutic intervention."

According to researchers, although this has not been tested in humans, the successful restoration of these mutated cells with BEL shows promise for continued BTHS research, patients and their families. There are no treatments for Barth syndrome at this time.

This study was funded in part by grants from the Barth Syndrome Foundation, the United Mitochondrial Disease Foundation, and NIH.

Link to full article published in *Proceedings of the National Academy of Sciences*:

<http://www.pnas.org/content/106/7/2337.full?sid=14754cf1-3343-490f-a418-ef589e10e510>

First-Degree Relatives of Patients with the Most Common Cardiac Birth Defect Should be Screened for Larger-Than-Normal Aortas

Bicuspid Aortic Valve (BAV), a condition in which patients' aortic valves have just two leaflets instead of the normal three, is the most common cardiac anomaly, affecting up to two percent of the general population. The defect can result in calcification deposits on the heart valve, leakage of the valve and may result in a feeling of tightness in the chest, as well as shortness of breath. The condition is easily diagnosed; often physicians can hear a "click" or a murmur when they listen to a BAV patient's heart with a stethoscope.

Studies have shown that BAV is likely genetic, although the gene has not been identified, and in some families, incidence of this defect could run as high as 20%.

A new study, published in the *Journal of the American College of Cardiology*, suggests that nearly a third of first-degree relatives (siblings, children or parents) of BAV patients are likely to have enlarged aortas, a potentially serious condition that can only be detected by undergoing transthoracic echocardiograms. This was found even in the absence of any abnormalities of the heart valve itself.

According to the study, 32% of first-degree relatives with no heart valve abnormality had significantly larger aortas than expected for age, gender and body size as compared to no enlargement seen in control patients. Also, the study found that the aortas of the first-degree relatives had abnormal stiffness similar to the patients with congenital bicuspid valve. Generally, when aortas are 50 millimeters in diameter, surgery is recommended in order to prevent a rupture of the aorta.

"If you know that a relative does have bicuspid aortic valve, then you know that you should be screened," said study author Kirsten Tolstrup, MD, Assistant Director of the Cardiac Noninvasive Laboratory at the Cedars-Sinai Heart Institute. "BAV appears to be a genetic condition that has many different manifestations, so we will be studying the genes."

Kirsten Tolstrup, MD, Assistant Director of the Cardiac Noninvasive Laboratory at the Cedars-Sinai Heart Institute, is available to discuss the study's findings and provide additional details.

This study, conducted among 54 patients with bicuspid aortic valve and 48 first-degree relatives of those patients as well as 45 matched controls found:

- 32% of apparently healthy first-degree relatives have enlarged aortas
- 53% of BAV patients had enlarged aortas
- 9.4% of first-degree relatives had BAV

The findings suggest that patients with bicuspid aortic valve and their first-degree relatives should have a screening echocardiogram to be evaluated for dilated aorta and bicuspid aortic valve.

The study abstract can be accessed at: <http://content.onlinejacc.org>

For additional information, call Sandy Van at 800-880-2397 or Sally Stewart at 310-248-6566.

Citation: *Journal of the American College of Cardiology, June 8, 2009, "Aortopathy is Prevalent in Relatives of Bicuspid Aortic Valve Patients"*

Comprehensive Cardiogenetic Testing for Families of Sudden Unexplained Death Victims Can Save Lives

Relatives of a young person who dies suddenly should always be referred for cardiological and genetic examination in order to identify if they too are at risk of sudden death, a scientist told the annual conference of the European Society of Human Genetics in May. Dr. Christian van der Werf, a research fellow at the Department of Cardiogenetics, Academic Medical Centre, Amsterdam, The Netherlands said that, although his team's research showed that inherited heart disease was present in over 30% of the families of sudden unexplained death (SUD) victims, the majority of such relatives were currently not being referred for examination.

When an individual aged 1-50 years dies suddenly, autopsy reveals an inheritable heart disease in the majority of the victims. But in approximately 20%, autopsy does not reveal cause of death. "We thought that cardiological and genetic examination of surviving first degree relatives of these SUD patients might reveal an inherited heart disease," said Dr. van der Werf.

In the largest such study to date, the team looked at the outcome of first degree relative screening in 127 families who had suffered an SUD and where either there had been no autopsy (53.8%), or the autopsy did not reveal a cause of death. The average age at death of the SUD victims was only 29.8 years old.

The initial examination of the relatives consisted of taking personal and family medical history and a resting ECG. A second cardiac autopsy of the SUD victim

was undertaken if tissue had been stored and was available. Additional cardiological examinations of the relatives were performed where necessary. Genetic analysis of the associated candidate gene(s) was performed in material obtained from the deceased person or in those relatives who showed clinical abnormalities.

The researchers found inherited heart disease in 36, or 32% of the families. These results meant that doctors were able to treat affected relatives and try to prevent their succumbing to sudden cardiac death. "The scale of heart disease that we found in such families underlines the necessity for general practitioners to refer first degree relatives of SUD victims to a specialised cardiogenetics department as soon as possible," said Dr. van der Werf. "Currently we estimate that only 10% of SUD families are being examined for inherited heart conditions.

The study is the second report from the registry of families who attended the Amsterdam centre's cardiogenetics department because of unexplained sudden death of a relative aged 1-50 years. The scientists intend to continue to report the yield of family screening in an increasing number of families.

"At present we are conducting a study to stimulate general practitioners and other involved physicians to request autopsy and DNA-storage for SUD patients and to refer relatives to a cardiogenetics department after a case of sudden death at young age. We hope this will lead to identification of more families at risk of sudden cardiac death, in which preventive measures then can be taken" said Dr. van der Werf.

"Relatives of young sudden death victims are often referred to cardiologists for cardiological examination. We believe relatives should instead be referred to cardiogenetics departments, where clinical geneticists, cardiologists and psychosocial workers cooperate. These professionals specialise in inherited heart diseases and their clinical and psychosocial implications, and can provide a better quality of care. Additionally, cardiologists should receive more education in inherited heart diseases. By taking these measures we can save lives and avoid further distress for families who have already suffered enough," he said.

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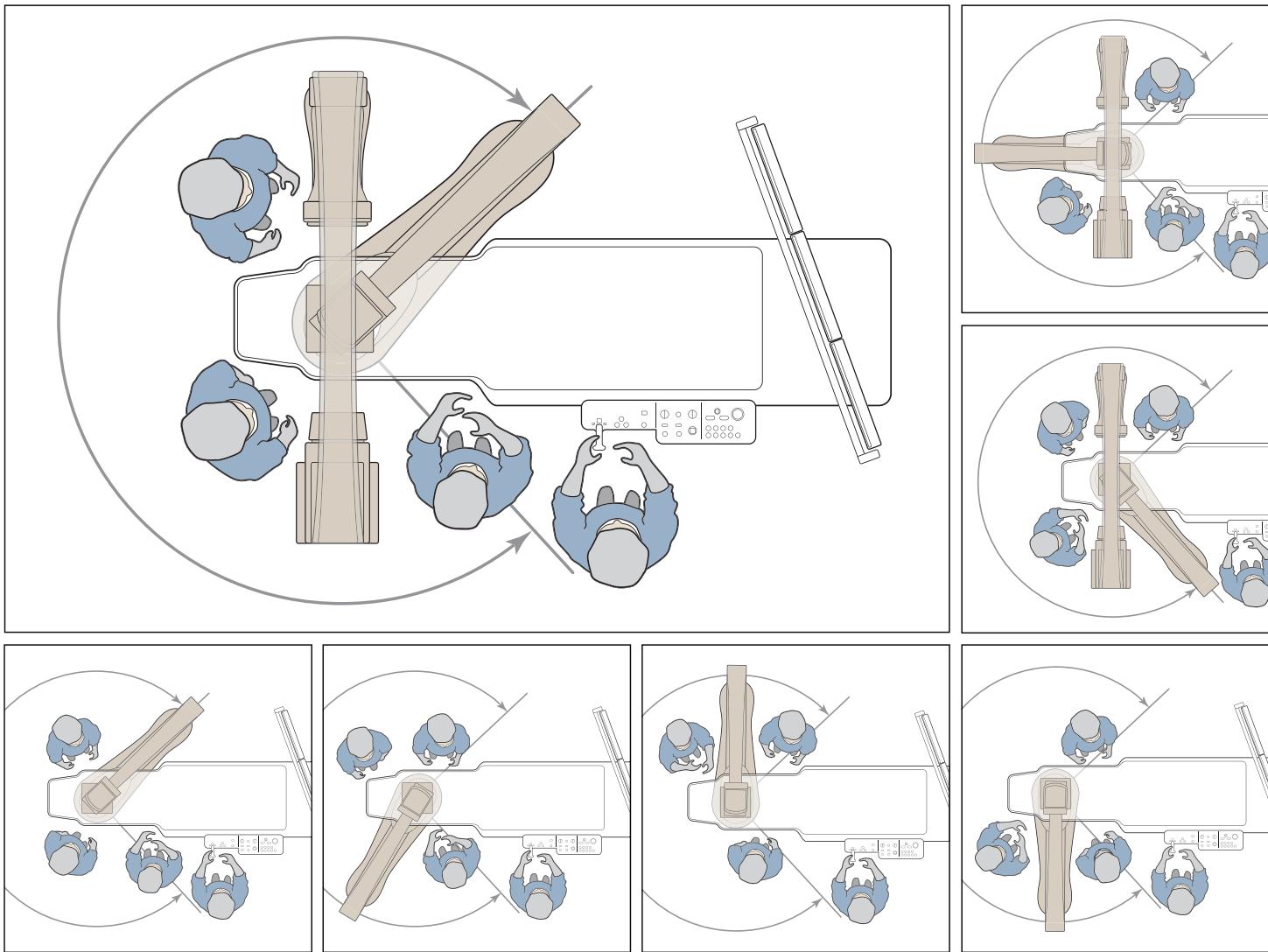
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