CONGENITAL CARDIOLOGY TODAY

RELIABLE INFORMATION IN CONGENITAL CARDIOLOGY

INTERNATIONAL EDITION

Formerly Pediatric Cardiology Today

WWW.CONGENITALCARDIOLOGYTODAY.COM VOL. 3, ISSUE 6 JUNE 2005

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CONGENITAL CARDIOLOGY TODAY
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Potomac, MD 20854 USA
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LONG-TERM ISSUES OF CORONARY ARTERY SEQUELAE IN KAWASAKI DISEASE

By Teiji Akagi, MD, PhD

Kawasaki Disease is not really "congenital heart disease," but this acquired disease is of considerable interest to congenital cardiologists. The importance of Kawasaki Disease is not only the coronary artery aneurysm in the acute phase but also long-term cardiovascular sequelae, which may include risk of early atherosclerotic changes in adolescents or young adults.

Clinically, Kawasaki Disease is an acute, self-limited vasculitis of unknown etiology that occurs predominantly in infants and young children. This vasculitis frequently affects small to mid-size arteries especially coronary arteries. In Japan, 17 nationwide surveys have been conducted (every 2 years since 1970) and more than 180,000 patients have been registered. Although no nationwide outbreak has been observed since the outbreak in 1986, the incidence rate has gradually increased over the past 16 years. The disease also has been reported in more than 60 countries around the world. In the United States, an estimated 4248 hospitalizations associated with Kawasaki disease occurred in 2000, with a median patient age of 2 years. Currently, the incidence of coronary artery abnormalities is about 3 to 5%. This means that nearly 200 children develop coronary artery abnormalities due to Kawasaki Disease in each year in the United States.

The most striking feature of coronary artery abnormalities in Kawasaki Disease is the change of size or shape of aneurysm. About 50% of coronary aneurysms regress within 2 years. On the other hand, coronary artery stenosis occurs in 4% of patients, or in 20% with coronary aneurysms in the follow-up period. In general, coronary artery stenosis does not develop in patients after aneurysms regress .

Does Kawasaki Disease increase the risk of atherosclerosis?

One unanswered question is whether the regressed coronary lesion becomes normal vessel or not. The major mechanism of regression of coronary aneurysms is intimal proliferation derived from the smooth muscle cells of media and regenerated endothelium. Thrombus formation in the aneurysm and calcification of arterial wall may combine in some instances. These findings are similar to atherosclerotic lesions.

Thus, recent long-term studies have focused

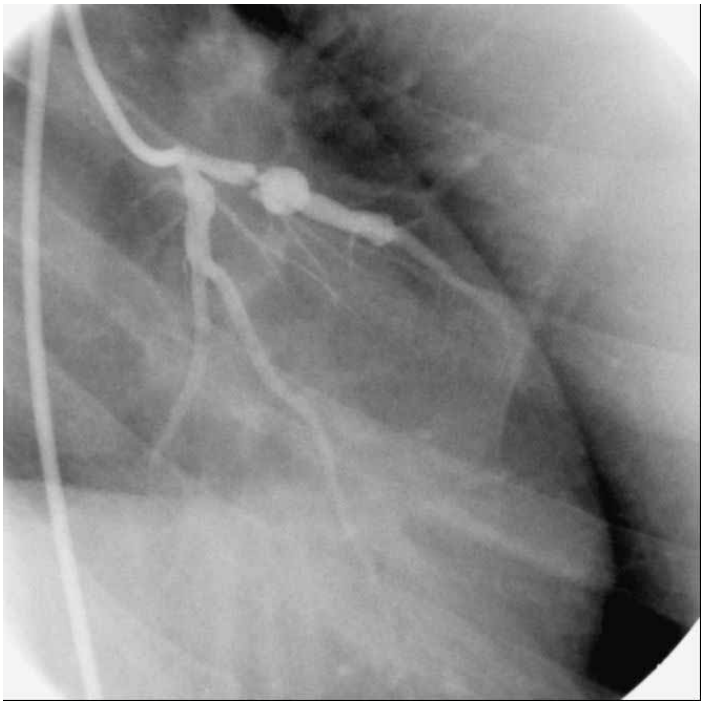

Figure 1. Fifteen-year old boy complained of mild chest pain. Coronary angiography revealed the significant stenosis on his left anterior descending artery.

CONGENITAL CARDIOLOGY TODAY
Formerly Pediatric Cardiology Today

(ISSN 1554-7787 - print; ISSN 1554-049 - online)
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on functional abnormalities of coronary arteries, especially endothelium function. Dhillon and colleagues evaluated endothelial function after Kawasaki Disease using flow mediated dilatation of brachial artery. In response to reactive hyperemia, a measure of endothelium-dependent vasodilation, Kawasaki Disease patients had significant lower vasodilation compared to controls. In response to sublingual glyceryl trinitrate, a measure of endothelium-independent vasodilation, the mean amount of dilatation was similar in the controls. This study suggested that endothelial dysfunction is present, possibly throughout the systemic arterial bed, in patients who have had Kawasaki disease. However, using a similar technique, a group from Toronto reported that there were no significant differences in either flow mediated or nitroglycerine mediated vasodilatation in brachial arteries of Kawasaki Disease patients.

We conducted a study of endothelial function evaluating intracoronary infusion of acetylcholine. The control or normal sites of coronary artery in Kawasaki Disease patients demonstrated significant vasodilatation, whereas the regressed aneurysms or persistent aneurysms revealed vasoconstriction or no changes. These findings suggest impaired endothelial function. Interestingly, patients having more than 4 mm aneurysms in the acute stage of Kawasaki Disease have significantly decreased coronary endothelial function, even if their coronary arteries appear to be completely normal by angiography or echocardiography. Evaluation of Kawasaki Disease patients without coronary artery lesions in the acute stage of illness using intravascular ultrasound imaging revealed normal findings at 10 to 20 years after the onset of disease. Patients whose original aneurismal size was less than 4 mm also had normal intravascular ultrasound findings. However, patients whose original aneurismal size was larger than 4 mm, revealed thickened intima and media. From our studies of pathology with intravascular ultrasound and by pharmacological studies of vascular function, it appears that coronary artery lesions may be long-term coronary risk factors, even in regressed aneurysms. Other coronary risk factors such as hyperlipidemia, smoking or hypertension may accelerate these conditions. Furthermore, a recent study reported that CRP levels were significantly elevated in Kawasaki Disease patients with coronary artery abnormalities compared with those without coronary abnormalities. If the inflammatory response as well as endothelial dysfunction are present late after Kawasaki Disease, anti-inflammatory medication such as aspirin, beta-blocker or statin treatment may be considered in the future.

"Clinically, Kawasaki Disease is an acute, self-limited vasculitis of unknown etiology that occurs predominantly in infants and young children."

New therapeutic strategy in Kawasaki disease

During the past decade, the clinical experience with interventional treatment in Kawasaki Disease has been gradually increasing. This includes balloon angioplasty, stent implantation, rotational ablation, and transluminal coronary revascularization. However, the experiences in Kawasaki Disease are still extremely limited compared to coronary intervention in adults. Coronary artery stenosis in Kawasaki Disease commonly involves severe calcifi-

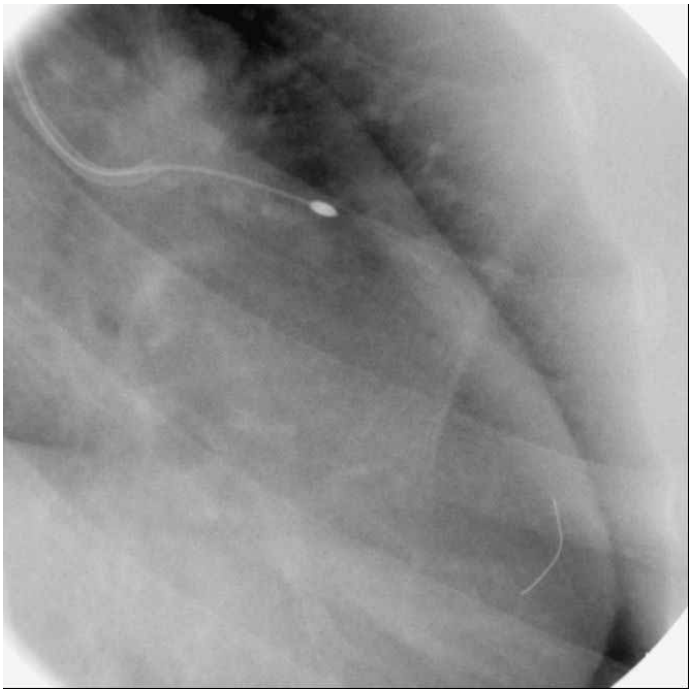

Figure 2. PTCRA using 2.15 mm burr.

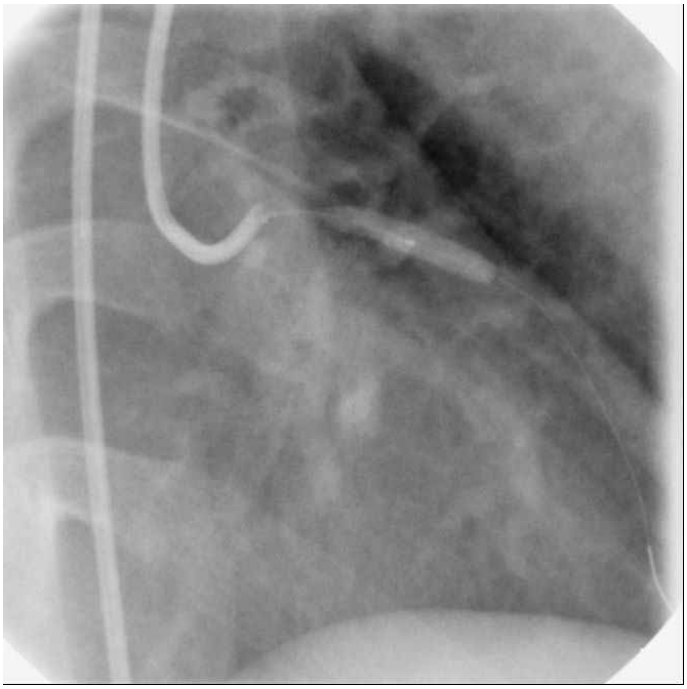

Figure 3. Additional POBA using low pressure (4 mm, 8 atmosphere).

cation, in contrast to adult coronary artery lesions, which consist primarily of atherosclerosis. Therefore, the indications for catheter intervention for adult patients cannot be directly applied in Kawasaki Disease patients, a largely pediatric population. Currently, the fundamental therapeutic regimen for ischemic heart disease after Kawasaki Disease is coronary bypass surgery. However, the long-term coronary graft patency is not satisfactory, even with the use of intrathoracic arterial bypass graft, and especially if the operative age is under 12 years old.

Plain old balloon angioplasty (POBA) is a useful treatment of stenotic lesions with or without mild calcification within 6 years of the onset. Satisfactory acute results were obtained in patients with up to 6 years interval from the onset of the disease and the POBA. However, the incidence of restenosis after POBA was high. Approximately, one quarter of the patients developed restenosis or occlusion. Coronary arteries with thick intimal hyperplasia probably recoil significantly, even if the stenosis has been dilated sufficiently. Stent implantation may prevent the occurrence of restenosis in this situation.

The development of new coronary aneurysms after POBA is a significant clinical concern. The mechanism responsible for this phenomenon is unclear, however intimal and/or medial dissection due to high-pressure balloon inflation could play a role. In this regard, the maximum balloon pressure is recommended to be less than 8-10 atmospheres at the time of POBA in the pediatric population. In resistant coronary artery lesions, (which require greater than 10 atmospheres), rotational ablation or bypass surgery is advisable as alternative procedures. Additionally, when POBA is performed in young children, shorter balloon lengths should be selected.

Experience with use of stent implantation for Kawasaki Disease is still limited. However, acute results with stent implantation have been excellent. Because this procedure relies on balloon dilation, the limitations are similar to those for POBA. The advantages of this procedure include high vascular patency rates in patients with segmental or relatively long stenosis, and the prevention of new aneurysm formation after POBA. Anticoagulation therapy with aspirin and clopidogrel is recommended after the procedure.

Excellent acute results for percutaneous rotational ablation (PTCRA) were observed in previous studies. Although use of this procedure is still limited,

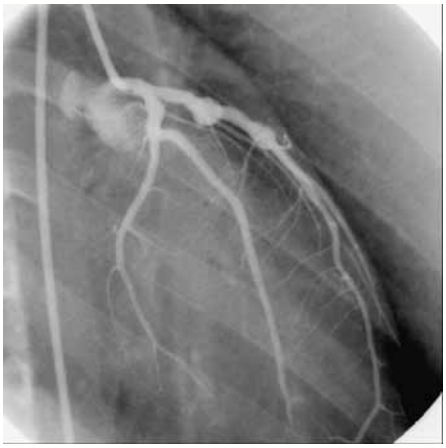

Figure 4. Stenosis was completely resolved.

PTCRA may be the most appropriate catheter intervention for Kawasaki Disease. The advantage of PTCRA is the high success rate, even in patients with calcified coronary artery stenosis. The limitation is the need for larger arterial access for the metal burr. For this reason, PTCRA can only be performed in older patients. Using this procedure, the stenotic area can be dilated up to 2.5 mm. Anti-coagulation and anti-platelet medication should be continued at least 2 months after the procedure.

Based on our results, we make the following recommendations: POBA is effective in many situations, particularly in patients without severe calcification or in patients with a relatively short interval (within 6 years) between the onset of the disease and the intervention. POBA may be used even in small children. Therefore, POBA should be the first line procedure in younger children with significant coronary artery stenosis. Stent implantation is preferable to POBA, because it may prevent new aneurysm formation and restenosis. In adolescents and older patients, stent implantation should be considered instead of POBA alone. If patients have severely calcified coronary stenosis, PTCRA may be the only effective treatment. Intravascular ultrasound imaging provides valuable information for the selection of the appropriate interventional procedure and early detection of vascular complications.

Kawasaki Disease is the leading cause of acquired heart disease in children

Compulsive follow-up is required in patients with coronary aneurysms, especially if the original aneurismal size is larger than 4 mm. Early detection of stenotic lesions is essential. Kawasaki Disease is now a worldwide problem, which may cause life-threatening events in children. In Japan and in North America, Kawasaki Disease is the leading cause of acquired heart disease in children. Furthermore, it may develop into coronary artery disease in adults. To elucidate the etiology is essential. Long-term follow-up studies are also important.

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MEDICAL CONFERENCES

Update on Cardiac Care in Neonates, Children, and Young Adults
June 8-11, 2005; Shanghai, China
www.congenitalcardiology.com/2005-ICU-Shanghai.pdf

PEDIRHYTHM-2
June 15-18, 2005; Antalya, Turkey
www.pedirhythm.org

ASE 16th Annual Scientific Sessions
June 15-18, 2005; Boston, MA, USA
www.asecho.org

8th International Workshop Catheter Interventions in Congenital Heart Disease
June 16-18, 2005; Frankfurt, Germany
www.chd-workshop.org

5th International Pediatric Cardiovascular Symposium: Management of Complex Congenital Heart Disease from Infancy to Adulthood
June 23-26, 2005; Amelia Island, FL, USA
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12th World Congress on Heart Disease
July 16-19, 2005; Vancouver, Canada
www.cardiologyonline.com

SIS (Summer in Seattle) 2005
July 19-23, 2005; Seattle, WA, USA
www.summerinseattle.com

New Concepts in Exercise and Pulmonary Hypertension in the Young: Their Interaction at Sea Level and Altitude
August 5-7, 2005; Aspen, CO, USA
Taylor.Amy@tchden.org or
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PICS-IX and ENTICHS-III (9th Pediatric Interventional Cardiac Symposium & Third Emerging New Technologies in Congenital Heart Surgery
Sep. 15-18, 2005; Buenos Aires, Argentina
www.picsymposium.com

The 4th World Congress of Pediatric Cardiology and Cardiac Surgery
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Selected questions and answers may be published in upcoming issues. Names will be withheld upon request.

THE PEDIATRIC HEART NETWORK

By Gail D. Pearson, MD, ScD

When the National Heart, Lung, and Blood Institute (NHLBI) established the Pediatric Heart Network (PHN) in September 2001, it was the beginning of a new era in pediatric cardiovascular research. Relatively few multi-center trials had been undertaken previously, compared to the number in adult cardiovascular disease, and few pediatric academic centers had the infrastructure to conduct multiple trials simultaneously. This discouraging research landscape changed significantly with the advent of the PHN.

The mission of the PHN is to achieve public health advances for children, through the conduct and dissemination of collaborative research leading to evidence-based treatment options and improved outcome for pediatric patients with congenital and acquired heart disease.

The principal governing body of the Network is the Steering Committee, comprised of the 7 clinical center principal investigators, the data coordinating center principal investigator, and the Network Chair. The role of the Network Chair is to provide, with NHLBI, overall management and direction of Network activities.

The PHN had its origins in recommendations made to the NHLBI by pediatric cardiovascular researchers, and in the NHLBI Report of the Task Force on Research in Pediatric Cardiovascular Disease. To establish the PHN, the NHLBI released a Request for Applications – known as an RFA – to which there was a robust response. Applications to establish clinical centers and a data coordinating center were reviewed for technical merit by an independent group of experts convened specifically for this purpose. Clinical center applicants were judged on the scientific merit of the two clinical protocols proposed as well as on their ability to participate in a multi-center trials environment. Data coordinating center applicants were evaluated on the basis of their ability to coordinate complex clinical research, manage large databases, and provide analytical expertise in the execution of clinical protocols and analysis of resulting data. The decision as to which applications to fund, was made on the basis of technical merit, the National Heart, Lung and Blood Advisory Council's recommendations and funds available at the time.

As in other NHLBI Clinical Research Networks, standard oversight committees were established to assist the PHN. The Protocol Review Committee (PRC) is an independent group responsible for peer review of Network protocols. It is appointed by and reports to

The Pediatric Heart Network (PHN) (with Principal Investigators)
Network Chair:
University of Texas Southwestern Medical Center, Dr. Lynn Mahony
Clinical Centers:
Boston Children's Hospital; PI, Dr. Jane Newburger
Children's Hospital of New York; PI, Dr. Welton Gersony
Children's Hospital of Philadelphia; PI, Dr. Victoria Vetter
Duke University Medical Center; PI, Dr. Page Anderson
Medical University of South Carolina; PI, Dr. Phillip Saul
Toronto Hospital for Sick Children; PI, Dr. Brian McCrindle
Utah Primary Children's Hospital; PI, Dr. LuAnn Minich
Data Coordinating Center:
New England Research Institutes; PI, Dr. Lynn Sleeper

Table 1. The Pediatric Heart Network (PHN).

the NHLBI. Although the protocols proposed by the clinical center applicants are peer reviewed during the application process, protocols chosen for further development within the PHN may be considerably modified, and completely different protocols also may be developed. Therefore, an additional level of peer review provided by the PRC is an integral part of NHLBI Networks.

"The mission of the PHN is to achieve public health advances for children, through the conduct and dissemination of collaborative research leading to evidence-based treatment options and improved outcome for pediatric patients with congenital and acquired heart disease."

The other standing oversight committee is the Data and Safety Monitoring Board (DSMB). The DSMB is also an NHLBI-appointed independent group and is responsible for ensuring human subjects protections and data integrity as protocols are developed and during the conduct of clinical studies. Once studies are under way, a major role of the DSMB is to review adverse events, recruitment, interim findings, and protocol violations. The recent addition of a Medical Monitor to the Network will augment the review of adverse events and any study endpoints that require adjudication.

With this infrastructure in place, the PHN Steering Committee began the arduous task of deciding what research to conduct in September 2001. The Steering Committee began by hearing presentations of the 14 protocols that its members proposed in their grant applications, and soon established a system of protocol evaluation including criteria such as benefit to pediatric patients, scientific merit, and feasibility. After careful deliberation, the Steering Committee settled on two initial protocols: The Relationship Between Functional Health Status and Laboratory Parameters of Ventricular Performance After the Fontan Procedure, and the Trial of Pulse Steroid Therapy in Kawasaki Disease.

The Fontan study was designed as a cross-sectional study to determine the interrelationships between health status and measures of cardiac performance in children 6-18 years old who have undergone a Fontan procedure. The Steering Committee originally set out to design a treatment trial in the Fontan population, but soon discovered that there were not enough published data to select clinically relevant endpoints. The goal of the Fontan study, therefore, was to acquire such data. When enrollment ended in 2004, 546 patients were enrolled. These patients underwent multiple evaluations, including exercise testing, MRI measures of ventricular function and

Figure 1. PHN Logo

"NHLBI will provide funds to support the Pediatric Heart Network for another five years, beginning in September 2006."

mass, echocardiographic assessment of ventricular mechanics, cardiac peptides, and health status using standard questionnaires for children, adolescents, and their families. Central interpretation of echocardiographic, MRI, and serology data was conducted. Several abstracts from this study have already been presented at national meetings, and the main results and additional papers are in preparation.

The Kawasaki trial was undertaken to determine whether a single high dose of methylprednisolone vs. placebo, on the background of standard therapy, affects coronary artery diameter at 6 weeks post-randomization, normalized for body surface area. Secondary endpoints include duration of fever and hospital stay, C-reactive protein levels, and adverse events. This trial also included central interpretation of echocardiographic and serology data. In 2 years, nearly 200 patients were randomized, with recruitment completed in December 2004. Data cleaning and analysis are underway, with the primary results expected soon.

Once these trials were launched, the PHN turned its attention to developing additional protocols. The ability to conduct multiple studies simultaneously is a strength of the Network infrastructure, but it also requires constant mental gear-changing and considerable hard work. To date, the Steering Committee has developed four more proto-

cols. Two are currently recruiting patients, and the remaining two are set to begin recruitment within the next month. These studies are:

- *Trial of ACE Inhibition in Infants with Single Ventricle.* The purpose of this trial is to determine the effect of ACE inhibition (enalapril) on somatic growth in infants with single ventricle physiology who have undergone the first staged surgical procedure.
- *Trial of ACE Inhibition in Children with Mitral Regurgitation after Repair of an AVSD.* This study is evaluating the safety and efficacy of enalapril therapy after repair of an atrioventricular septal defect in children who have at least moderate mitral valve regurgitation.
- *Single Ventricle Reconstruction Trial.* In this trial, the standard Norwood approach for neonates with hypoplastic left heart syndrome and variants will be compared to the right ventricle-to-pulmonary artery conduit surgical strategy.
- *Ventricular Volume Variability Trial.* This is a study of variability in echo measures of ventricular performance, assessed within patients, across time, and between echocardiographers. The purpose is to estimate, in a pediatric cardiac population, the variance of change in ventricular function measures to use for future clinical trial sample size calculations.

In addition to the benefits of the specific research performed, the Network has a number of other advantages. Participation in Network activities and meetings is providing experience in clinical research for many young nurse and physician investigators. PHN protocols offer fertile ground for ancillary studies, which can be proposed by investigators both within and outside the Network. The success of the Network is also fostering increased interest in multi-center clinical trials in pediatric cardiovascular disease.

NHLBI will provide funds to support the Pediatric Heart Network for another five years, beginning in September 2006. The RFA for the next funding cycle was published in early March, and can be found at: http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-05-010.html. Applications are due September 23, 2005.

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RFA-HL-05-010
"Pediatric Heart Network"

This RFA solicits applications in an open competition for clinical centers and a data coordinating center for the next funding cycle of the Network. Current centers and new centers are both invited to apply.

Key Dates:

- Letter of Intent Due: 8/26,/2005
- Applications Due: 9/23/2005
- Peer Review: February-March, 2006
- NHLBI Council Review: 6/5/2006
- Expected Start Date: 9/1/2006

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For complete details see http://grants.nih.gov/grants/guide/notice-files/NOT-HL-05-116.html

PERCUTANEOUS CLOSURE OF A RESIDUAL PERIMEMBRANOUS VENTRICULAR SEPTAL DEFECT AFTER SURGICAL REPAIR

By Carlos AC Pedra, MD; Sérgio C. Pontes, Jr., MD; Simone R.F. Pedra, MD; Juliana Neves, MD; M. Aparecida P. Silva, MD; M. Virginia T. Santana, MD; Valmir F. Fontes, MD

Introduction

Isolated perimembranous (PM) ventricular septal defect (VSD) is one of the most common congenital cardiac malformations.[1] Surgery has been performed safely and effectively and has been regarded as the gold standard method of treatment for this disease.[1,2] Although residual leaks are observed in up to 5-10% of cases, most of them are restrictive and well tolerated.[1,2] Occasionally, they can result in significant left-to-right shunting with persistent left ventricular volume overload, which requires reintervention.[2] Recent publications have reported the feasibility, safety and efficacy of percutaneous closure of native PM VSDs with the use of the Amplatzer membranous VSD occluder (AGA Medical Corporation, Golden Valley, Minnesota).[3-8] Controlled release coils made of a reinforced Nitinol wire (PFM, Cologne, Germany) has also been employed for transcatheter closure of such defects with encouraging results.[9,10] In this paper, we describe a case in which a significant residual leak after surgical repair of a PM VSD was closed using transcatheter techniques.

Case report

This patient was a non dysmorphic 4 year-old boy (weighing 15 kgs) with a large PM VSD who was referred from the countryside to our institution for surgical repair. He was symptomatic and receiving digoxin, furosemide and captopril. Classical findings of significant PM VSD with pulmonary arterial hypertension were encountered on physical examination, chest radiograph and ECG. Transthoracic echocardiography revealed a large PM VSD with inlet extension, measuring 14 mm at its maximal dimension (Figure 1A). There was significant left atrial and ventricular volume overload. Pulmonary arterial pressure was estimated at systemic levels. The child was taken to the catheterization laboratory for further hemodynamic assessment. A routine left and right catheterization was carried out under general anesthesia. Hemodynamics showed the

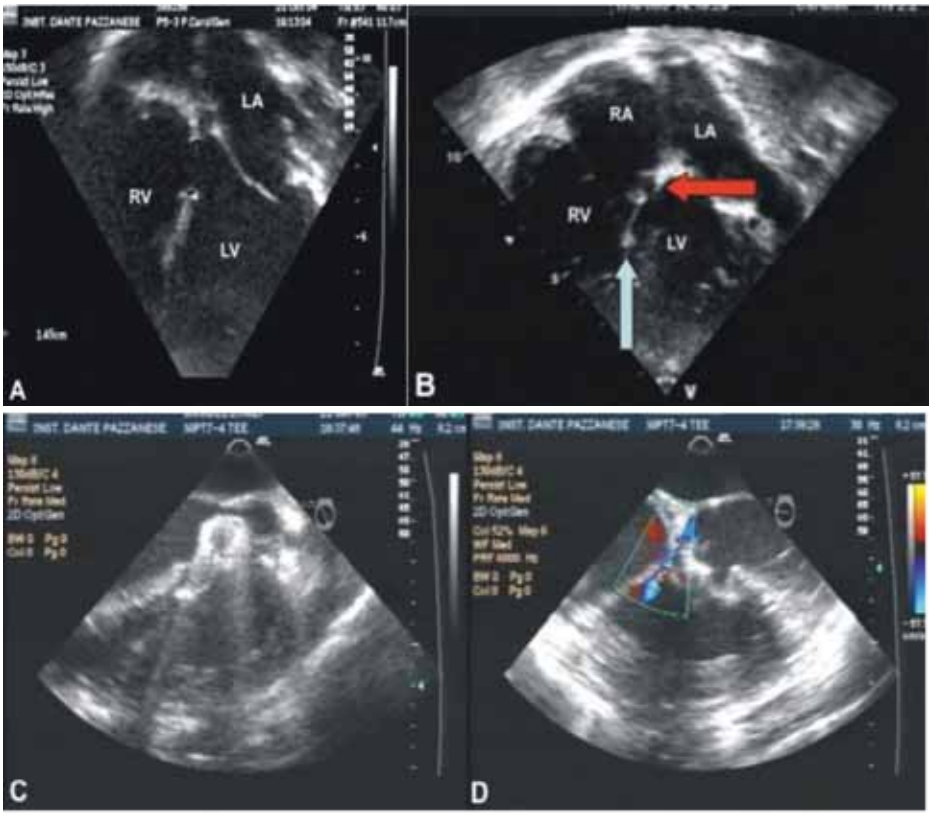

Figure 1. Echocardiographic pictures of the defect. (A) Four chamber view (pre-operative TTE): Large PM VSD with inlet extension measuring 14 mm at its maximal diameter. (B) Modified four chamber view (post-operative TTE): There is a residual VSD (red arrow) measuring 5-6 mm at the superior portion of the patch (light blue arrow), near the crux of the heart and the AV valves. (C) Long axis view (TEE during the percutaneous procedure): The left ventricular loops of the PFM Nitinol coil are protruding into the LVOT. (D) Long axis view (TEE during the percutaneous procedure): The Amplatzer membranous VSD occluder is well positioned after final release. There is a small residual leak through the superior aspect of the device.

following pressures (in mm Hg): RA: 5; RV: 88/6; MPA: 88/31 (mean 58); Ao: 90/58 (mean 71); LV: 90/12. Pulmonary vascular resistance (PVR), Qp/Qs and PVR/SVR were estimated at 3.6 Wood Units, 2.9 and 0.23, respectively. After the administration of NO (40 PPM), PVR was 1.6 U Wood X m-2 , Qp/Qs 4.9 and RVP/RVS 0.11. Left ventriculogram in long axial view showed a large PM VSD, measuring 13 mm at its maximal diameter (Figure 2A). Pulmonary arterial angiogram demonstrated progressive tapering of the pulmonary arteries with satisfactory opacification of the peripheral vessels. The capillary phase was homogeneous and there was rapid return of the contrast media to the LA. The child was subsequently referred to surgery, which was carried out under cardiopulmonary bypass using standard techniques.[2] A pericardial patch was sutured at the edges of the defect with pledgets. The tricuspid valve was not removed for patch closure. Post-operatively, signs of persistent left-to-right shunting were detected invasively (SVC sat: 65%; PA sat: 82%) and confirmed by echocardiography. A 5-6 mm residual VSD was observed through the upper portion of the patch near the AV valves (Figure 1B). On the 8th post-op day the child was reoperated, however, the surgeon was unable to identify the site of the residual leak intra-operatively. After a month, a decision was made to attempt closing the residual leak using transcatheter techniques. Informed consent was obtained from parents. Under general anesthesia, vascular access was obtained with placement of a 5 Fr sheath in the left femoral artery and a 7 Fr sheath in the right femoral vein. Heparin sulfate (150 IU/kg) and Cefazolin (30 mg/kg) were given. Hemodynamics showed the following pressures (in mm Hg): RA: 8; RV: 50/10; MPA: 50/18; Ao: 90/50; LV: 90/15. The Qp/Qs was estimated at 1.8:1. Left ventriculogram confirmed the echocardiographic findings (Figure 2B). Using previously described techniques and under transesophageal echocardiographic guidance (TEE), the residual VSD was crossed retrogradely and an arterial-

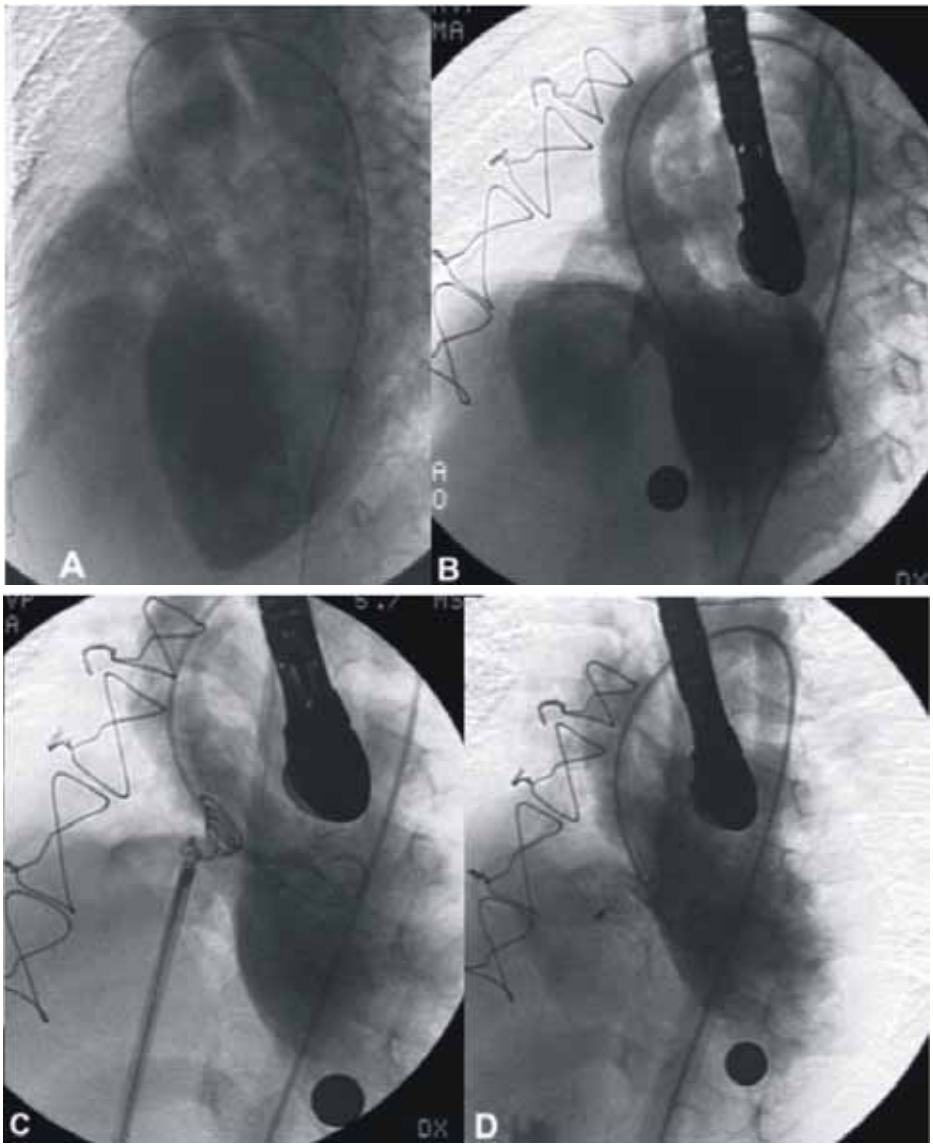

Figure 2. Ventriculograms in long axial or hepatoclavicular views displaying the defect (A) Pre-operative findings: Large PM VSD with inlet extension and conspicuous left-to-right shunt, opacifying the dilated MPA. (B) Post-operative findings during the percutaneous procedure: Moderate left-to-right shunt through the superior portion of the patch, near the AV valves. The residual defect measured 5 mm on angiography. (C) The PFM Nitinol coil remained in a sub-optimal position with the left loops protruding into the LVOT, distant from the patch. (D) Adequate position of the Amplatzer membranous occluder immediately after release. There is a small residual leak at its superior portion.

venous loop established using a 260 cm Glide wire (Terumo Cardiovascular Systems Corporation, Ann Harbor, MI). A 7 Fr long, braided sheath (Flexor; Cook Cardiology, Bloomington, IN) was advanced to the ascending aorta across the VSD from the vein. The latest version of a premounted PFM coil (with reinforced Nitinol wire and Dacron fibers) (12 X 6 mm) was advanced through the long sheath until the tip of the delivery catheter was about 1 cm out of the long sheath. By pushing the core wire, the loops of the coils were exteriorized in the ascending aorta with the last 2 loops remaining inside the delivery catheter. The whole system was carefully brought back as a unit across the aortic valve until the loops abutted the interventricular septum. Keeping a gentle traction on the system and the tip of the long sheath close to the tip of the delivery catheter, the last 2 loops were delivered in the RV by withdrawing the delivery catheter and pushing the core wire. Final position of the coil was assessed by TEE (Figure 1C) and angiography (Figure 2C). Because the left ventricular loops protruded into the LVOT and there was significant residual leak, the device was recaptured inside the long sheath and removed out of the body. A decision was then made to attempt closing the defect using an 8 mm Amplatzer membranous VSD occluder (AGA). The VSD was again crossed in a retrograde fashion and an arteriovenous loop established using a Rope wire (AGA) as described in previous published protocols (6-8). An 8 Fr long sheath (TorqVue, AGA) was advanced to the ascending aorta and subsequently positioned near the left ventricular apex as described before. [6-8] After removal of the Rope wire and dilator, the device was pushed through the long sheath and the left ventricular disc deployed within the left ventricular cavity with the radiopaque marker pointing downwards. The whole system was retracted as a unit until the left disc touched the patch. By pulling the long sheath and advancing the delivery cable, the right disc was deployed on the right side. Good device position was confirmed by both TEE and angiography. Aortic and AV valve function were preserved. After device release, a tiny residual leak was seen through the superior portion of the device (Figure 1D and 2D). The child was awaken in the catheterization laboratory and had an uneventful recovery. He was discharged home the following day on aspirin (5 mg/kg/day). A transthoracic echocardiogram revealed complete closure of the defect after a month. There was no AI or significant TR. The child remained in sinus rhythm with no signs of left or right bundle branch block. Medications were gradually discontinued.

Discussion

A significant residual VSD after surgical repair may occasionally require reoperation, resulting in increased morbidity and hospital stay. Although successful transcatheter closure of PM VSDs has been described recently,[3-8] there is limited experience with this approach for such residual defects. Since it has the potential to avoid a repeat cardiopulmonary bypass run, it may well be a safer therapeutic option. However, the issue of what type of residual defect that is amenable to transcatheter closure, including location, number and size, has yet to be clarified. This will only come with ongoing experience. In the case described herein, the residual defect was single and located at the superior edge of the patch, towards the crux of the heart. Despite being close to the AV valves, we felt there was enough room surrounding the defect to accommodate a device without interfering with AV valve function. Moreover, we decided to attempt the transcatheter approach because the child had undergone surgical repair twice unsuccessfully.

"...percutaneous closure of a residual PM VSD after surgical repair using an Amplatzer membranous device was feasible, safe and effective in the selected patient presented herein. More experience is warranted before the widespread use of this technique is recommended."

In regards to the types of devices used in this case, the PFM coil was employed initially under a study protocol to assess its safety and efficacy. Even acknowledging that clinical experience with it is still very limited [9,10] (about 20 implantation procedures with the latest version; unpublished data; Dr. Trong-Phi Le, personal communication), it has theoretical and potential advantageous features. It requires lower profile sheaths (6 or 7 Fr) for implantation; due to the flexible central portion of the device, it can be exteriorized in the ascending aorta and pulled back safely across the aortic valve, with no need to place the long sheath near the left ventricular apex; and it is se-

cured within the defect without exerting radial forces. Although it seems to work well for small to moderate defects, especially those associated with aneurysm formations, it may be unsuitable for larger defects. In the case described herein, the PFM coil remained in an inadequate position, protruding into the LVOT, probably because it approached the septum (patch) from above, coming from the aorta. If we had delivered the LV loops close to the left ventricular apex, it might have been possible to engage it within the patch, in a more favorable course towards the defect itself. Possible entanglement with the mitral valve apparatus could be an issue employing this approach. Coil recapturing and removal was feasible and safe, keeping in mind that the long sheath had to be kept close to the delivery catheter tip to avoid entanglement with the tricuspid valve apparatus. Subsequent use of the Amplatzer membranous occluder was a natural choice. Initial clinical experience with this device has been encouraging.[3-8] The rate of complete closure is high (>90%) and aortic and tricuspid valve function are preserved, at least in the short-to-mid term.[3-8] However, complete heart block seems to occur with an incidence of 1-2%.[11] Whether this is related to the radial forces exerted by the central waist of the device onto the defect edges or due to the endothelialization process is speculative. Other factors such as younger age, inlet extension of the VSD and crossing the VSD from the RV side may play a role in the development of this complication. In our experience, complete heart block did occur between 3-6 months after the procedure in a single case out of 33 implantation procedures (unpublished personal data). In the case presented herein, the Amplatzer device worked nicely because it approached the patch at a proper angle, coming from the LV apex. Besides, the longer inferior portion of the LV disc engaged well within the patch with the waist remaining inside the residual defect itself, which was probably responsible for complete closure. Improvements on the design of this device and delivery system have been made by placing a female screw in the center of the left ventricular disc and a male screw at the tip of the rope wire.[12] This enables to position the device more precisely because of the through-and-through cable-to-device-to-rope wire system, creating traction from both the venous and arterial sides. We anticipate that this system can be useful in difficult cases, such as some residual VSDs after surgical repair.

In conclusion, percutaneous closure of a residual PM VSD after surgical repair using an Amplatzer membranous device was feasible, safe and effective in the selected patient presented herein. More experience is warranted before the widespread use of this technique is recommended.

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MEDICAL NEWS AND INFORMATION

Study Points to Link Between Risks of Congenital Heart Defects and Alterations in Maternal Plasma Biomarkers

Findings from a study lead by Dr. Charlotte Hobbs, director of the Arkansas Children's Hospital Research Institute's Center for Birth Defects Research and Prevention, point to the link between babies with congenital heart defects and the presence of certain plasma biomarkers.

The study measured biomarkers of the folate-dependent methionine/homocysteine pathway among 314 women. Two hundred and twenty four of the subjects had children with congenital heart defects, and 90 had children who were unaffected. All of the women who had children with heart defects had higher average concentrations of homocysteine and lower average concentrations of methionine.

The findings were published in the January 2005 issue of American Journal of Clinical Nutrition, (www.ajcn.org) and while they will still need to be verified through subsequent tests, this study is the first to show the association between these biomarkers and congenital heart defects.

"This is important, because it is the first step in identifying a specific metabolic profile in women who have an increased risk of producing children with congenital heart defects," Hobbs said. 'If we can do that, we may be able to identify women who are at higher risk of having pregnancies affected by congenital heart defects before they even conceive. We could then prescribe a targeted clinical intervention that would increase their chances of having a healthy pregnancy."

Congenital heart defects are the most prevalent birth defect in the United States where 11 in 1,000 children are born with some form of the condition. While it is the most common birth defect, it also is one of the least understood. Only about 15% of heart defects can be attributed to a known cause.

At this time, the best tool to manage these defects is for an expectant mother to have an ultrasound during her second trimester.

"Even with this tool, we can only identify that the problem exists and make plans for the birth to occur in a center where the defect can be treated immediately," Hobbs said. "These new findings could be used to prevent the defect from occurring in some cases."

The study is funded through a five-year, $4.5 million grant from the National Institute of Child Health and Human Development. Dr. Hobbs is an associate professor Pediatrics, University of Arkansas for Medical Sciences College of Medicine.

For more information: www.archildrens.org or www.ajcn.org

U.S. Patent & Trademark Office Issues Patent No. 6,830,584 to CoreValve for Its 'Device for Replacing a Cardiac Valve by Percutaneous Route'

PARIS, FRANCE & IRVINE, CA, USA.--(BUSINESS WIRE)

CoreValve S.A. has announced that the United States Patent & Trademark Office has issued Patent No. 6,830,584 to CoreValve, thus protecting the Company's 'device for replacing a cardiac valve by percutaneous route'--i.e., the CoreValve Percutaneous ReValving System.™

With ReValving,™ heart valve replacement can be performed 'non-surgically' in a cardiac 'cath lab' just like angioplasty and stenting, resulting in less trauma to the patient and substantial cost-savings to the healthcare system compared to open-heart surgery to replace diseased heart valves.

"U.S. patent protection for ReValving is critically important, of course--particularly in light of the fact that we already have clinically established that ReValving is feasible to non-surgically treat the widest possible range of diseased heart-valve patients, including traditional surgical-candidates," said Jacques Seguin, MD, chairman and CEO of Core-

At the University hospital of Muenster
an interdisciplinary center for Grown-up Congenital Heart Disease (GUCH) is being established with support from an external sponsor (http://www.emah.de/).

For this center, the Medical Faculty invites applications for the newly created
Hella Hueck Endowed Professorship (W2) for
"Grown-up Congenital Heart Disease (GUCH)"

for the duration of 5 years within the Department of Cardiology and Angiology (Head: Univ.-Prof. Dr. Günter Breithardt). The future holder of the position (male/female) must fully represent the subject with regard to research and teaching.

Applicants should possess a M.D. degree, be board-certified adult, and should have an outstanding record of clinical experience and scientific achievements in the field of grown-up congenital heart disease. Prerequisite for the application are scientific achievements as a junior professor; alternatively, scientific achievements can result from a post-doctoral lecture qualification (habilitation), work as a research scientist at a school of higher education/university, non-university institute, industry, administration, or other fields of society within or outside Germany. Please pay attention to §46 "Hochschulgesetz NRW". All applicants should have proven teaching experience and will be required to take part in the preparation and implementation of undergraduate and postgraduate courses. In the case of applications from foreign countries or other exceptional cases qualification can be replaced with equivalent scientific achievements. Furthermore, the candidate must document educational suitability, engagement, and teaching experiences.

The successful candidate is going to head the section of grown-up congenital heart disease within the Department of Cardiology and Angiology. He/she is expected to closely collaborate with the Departments of Cardio-Thoracic Surgery, of Paediatric Cardiology, and of Anaesthesiology and Surgical Intensive Care Medicine as well as with referring office-based physicians and hospitals. The aim is to improve the care of adults with congenital heart disease on a supra-regional level.

Candidates are expected to participate in existing and planned joint research programs of the Medical Faculty, such as the "Interdisciplinary Center for Clinical Research" (IZKF), the Coordination Center for Clinical studies (KKS), the Collaborative Research Programmes (Sonderforschungsbereiche) and the just founded Max-Planck-Institute for Molecular Biomedicine.

Applications of women are specifically invited. In the case of similar qualification, competence, and specific achievements, women will be considered on preferential terms within the framework of the legal possibilities.

Handicapped candidates with equivalent qualifications will be given preference.

Documents in support of an application, enclosing CV, scientific career, structured catalogue of publications, acquired third-party funds and reprints of the six most important publications should be submitted to the Dean of the Faculty of Medicine, University of Münster, Domagkstrasse 3, 48129 Münster, Germany, by June 24th 2005.

For further information, please contact Prof. G. Breithardt,
Department of Cardiology and Angiology
(phone: +49-251–83 47617; g.breithardt@uni-muenster.de)

Valve. "Indeed, CoreValve's ReValving approach has potential universal applicability to percutaneously treat the two most prevalent diseases of the aortic valve--stenosis and regurgitation," added Professor Seguin.

About CoreValve

Privately held CoreValve, S.A., headquartered in Paris, France, has developed a proprietary delivery system for percutaneous heart valve replacement, based on a novel catheter-and-self-expanding-stent approach on a beating heart, thus avoiding open-heart surgery. The CoreValve procedure--with the proprietary CoreValve Percutaneous ReValving System™ --can be performed in a cardiac "cath lab" just like angioplasty and stenting, resulting in less trauma to the patient and substantial cost-savings to the healthcare system.

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Rare Childhood Genetic Syndrome Identified: Multiple Problems Include Cardiac Arrhythmias and Atypical Autism

Researchers at Children's Hospital Boston, Howard Hughes Medical Institute and the University of Utah have identified a rare, previously undiscovered genetic syndrome that is often fatal by the second year of life, but which may be treatable with calcium channel-blocking drugs. Findings were reported in the October 1, 2004 issue of the journal, Cell.

The disease, named Timothy Syndrome after one of the paper's authors, is characterized by a variety of problems including heart arrhythmias, congenital heart abnormalities, webbed

hands and feet, a weakened immune system, cognitive abnormalities, and, surprisingly, autism. The researchers have identified 17 children with the syndrome, seven of whom were living.

Despite the complexity and severity of Timothy Syndrome, the researchers show that it arises from a single, spontaneous, very subtle gene mutation in the mother's egg or father's sperm - substitution of a single base pair. The reason so many body systems are affected is that mutation impairs a very fundamental molecule, a type of calcium channel, that is found in many tissues and organs.

Calcium channels control how much calcium can get inside a cell. Calcium is one of the body's most important signaling molecules, and normally, cellular calcium levels are tightly regulated. Dr. Mark Keating, senior author of the study and a Howard Hughes Medical Institute investigator at Children's Hospital Boston, likens the calcium channel to a screen door.

"After you go through the screen door, it automatically closes," he says. “This mutation dismantles the automatic closing mechanism, so the door just stays open."

As a result, cells are overwhelmed by an influx of calcium. Because calcium-channel blocking drugs can ameliorate calcium overload, these medications may be useful for treating arrhythmia and cognitive deficits in individuals with Timothy Syndrome, Keating says.

Experiments also showed that the gene encoding the calcium channel was active not only in heart muscle cells, but in tissues of the gastrointestinal system, lungs, immune system, smooth muscle, testes, and brain - including brain regions that are known to show

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for the duration of 5 years within the Department of Cardio-Thoracic Surgery (Head: Univ.-Prof. Dr. Hans-H. Scheld). The future holder of the position (male/female) must fully represent the subject with regard to research and teaching.

Applicants should possess a M.D. degree, be board-certified cardiac surgeons, and should have an outstanding record of clinical experience and scientific achievements in the field of surgical treatment of grown-up congenital heart disease, also in adults. Prerequisite for the application are scientific achievements as a junior professor; alternatively, scientific achievements can result from a postdoctoral lecture qualification (habilitation), work as a research scientist at a school of higher education/university, non-university institute, industry, administration, or other fields of society within or outside Germany. Please pay attention to §46 “Hochschulgesetz NRW”. All applicants should have proven teaching experience and will be required to take part in the preparation and implementation of undergraduate and postgraduate courses. In the case of applications from foreign countries or other exceptional cases qualification can be replaced with equivalent scientific achievements. Furthermore, the candidate must document educational suitability, engagement, and teaching experiences.

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For further information, please contact Prof. H.-H. Scheld, (phone: +49-251–83 47401/ 2; h.h.scheld@ukmuenster.de).

abnormalities in autism. Keating notes, however, that autism is a complex disorder with many different causative factors.

The study was led by Igor Splawski, PhD, in the Cardiovascular Research Division at Children's Hospital Boston in collaboration with the University of Utah and the Boston University School of Medicine. The researchers will continue to treat patients with Timothy Syndrome and evaluate their response to calcium-blockers. They will also continue to look for arrhythmia genes and other calcium channels that might be involved in arrhythmia, and try to determine whether this calcium channel is involved in other forms of autism.

Children's Hospital Boston is the nation's leading pediatric medical center, the largest provider of health care to Massachusetts' children, and the primary pediatric teaching hospital of Harvard Medical School.

For more information:
www.childrenshospital.org

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