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FETAL MAGNETOCARDIOGRAPHY-AN EXCITING NEW TECHNIQUE FOR THE DIAGNOSIS AND MANAGEMENT OF FETAL ARRHYTHMIAS

By Joel D. Temple, MD

Fetal arrhythmias are estimated to occur in 1-2% of gestations. The majority of these are PVCs and PACs which are generally considered benign. More serious arrhythmias can occur including SVT, atrial flutter, and VT. Management of fetal arrhythmias has been limited by our inability to effectively monitor and diagnose them. The gold standard has been Doppler M mode echocardiography which can demonstrate the timing of atrial and ventricular contractions. Echo, however, does not give information about the electrical activity of the heart and is labor intensive. The fetal ECG can be obtained from the maternal abdomen but there is significant artifact in the form of both myopotentials and the maternal ECG. Of particular interest, the maternal ECG (based on voltage potential) does not attenuate and is 10-100 times as strong as the fetal signal. In addition, useful signals are difficult to obtain after 27 weeks, probably due to the insulating properties of the vernix caseosa. Fetal magnetocardiography (fMCG) is a new technique that is particularly useful for evaluating fetal arrhythmias.

When an electric or ionic current flows through a conductor, a magnetic field is generated perpendicular to the current. As cardiac tissue depolarizes, small currents are generated across the advancing wave front and consequently an electromagnetic field is generated perpendicular to the current. This field can be detected and is the basis of fMCG. The field generated by the fetal heart is on the order of 0.5-10 pT, or approximately one millionth the strength of the earth's magnetic field. By comparison, the maternal signal is approximately 50 pT. The device used to measure these biomagnetic fields is called a Superconducting Quantum Interference Device or SQUID magnetometer. SQUIDs must be super cooled and shielded from all electromagnetic interference.

One clear advantage of fMCG is that the signal strength is inversely proportional to the square of the distance from the source. Consequently, if the receiver is placed close to the fetus, the maternal signal will

Figure 1. SARA, consisting of 151 gradiometers arranged to comfortably fit the gravid abdomen.

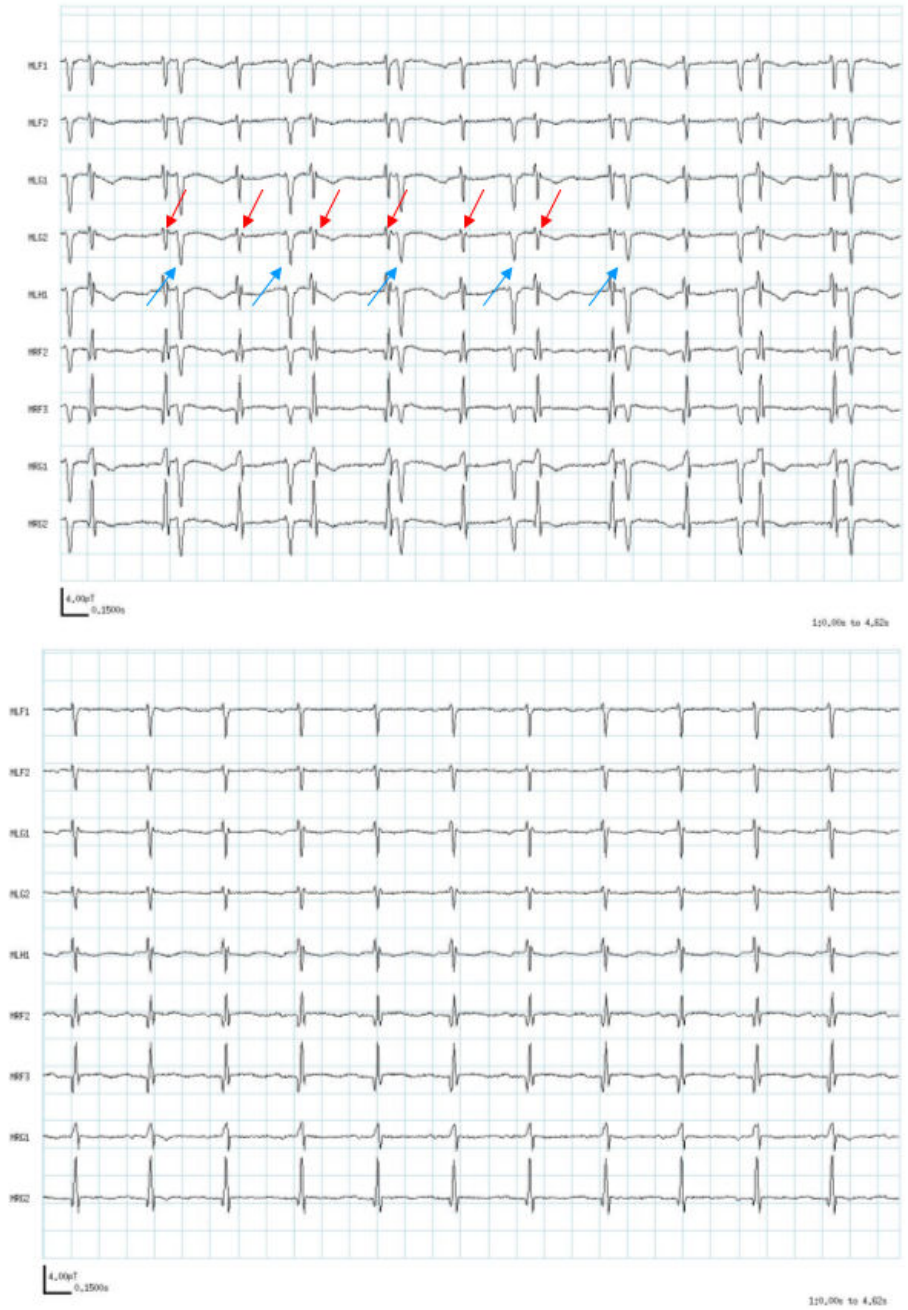

Figure 2. A) Raw tracing demonstrating both fetal and maternal tracings. Maternal signals are marked with blue arrows. Fetal signals are marked with red arrows. B) Fetal signal after attenuation of metrnal signal using orthogonal projection.

be considerably smaller. The University of Arkansas for Medical Sciences has developed a specialized array called SQUID Array for Reproductive Analysis or SARA. SARA consists of 151 magnetometers arranged to fit the gravid abdomen. The patient leans forward onto the array while seated. (Figure 1) There is no trauma to the fetus and minimal discomfort to the mother and extended recording periods are possible.

Background noise is filtered using a first order gradiometer (magnetometer). The maternal signals are identified and averaged using template matching and the maternal signal is attenuated using a technique called orthogonal projection. The result is a signal that is analogous to a surface ECG. (Figure 2) If further resolution is needed, signal averaging can be performed.

"Fetal magnetocardiography is a safe noninvasive technique allowing monitoring of fetal heart rhythm and providing information and a degree of resolution not previously obtainable."

Fetal magnetocardiography offers some exciting possibilities including the more accurate diagnosis of fetal arrhythmias, monitoring for fetal toxicity with drugs such as Flecainide, Sotalol, and Amiodorone leading to safer use of antepartum antiarrhythmics, and prenatal diagnosis of channelopathies such as the Long QT syndrome without the need for amniocentesis.

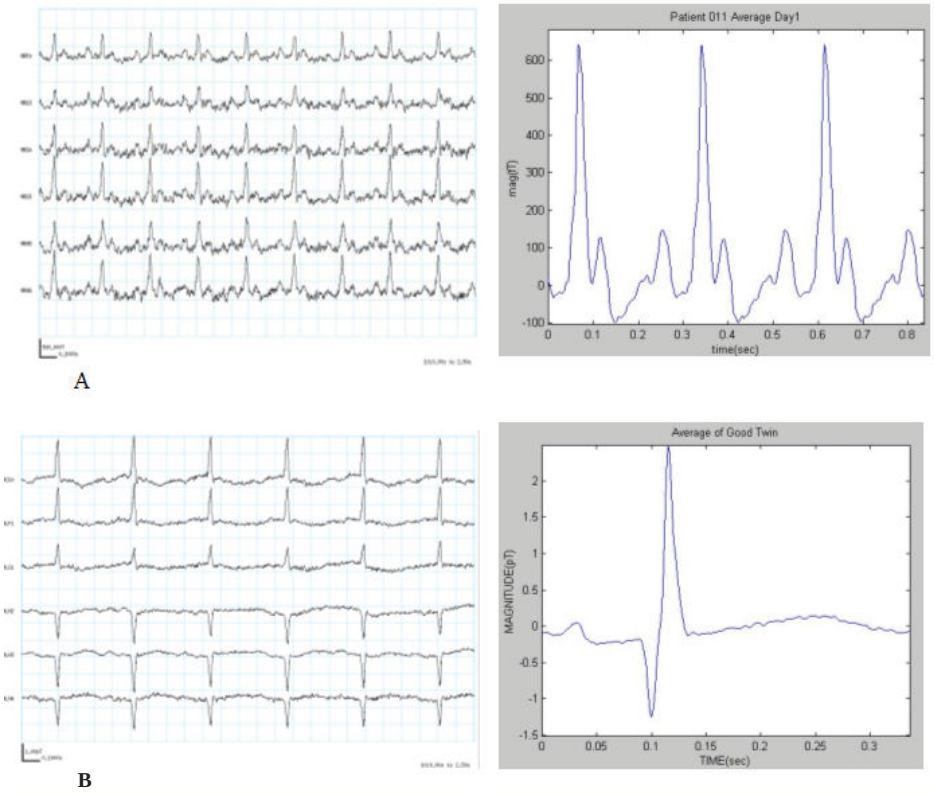

Figure 3. (A) FMCG of twin "A" in atrial flutter with signal averaged ECG. (B) FMCG of twin "B" in sinus. Recordings were obtained simultaneously.

This technology is currently expensive and cumbersome due to the need for super cooling and electromagnetic shielding. However, work is currently under way towards the development of a "high" temperature SQUID that does not require super cooling.

Fetal magnetocardiography is a safe noninvasive technique allowing monitoring of fetal heart rhythm and providing information and a degree of resolution not previously obtainable. (Figure 3) The particular design of SARA allows extended monitoring without apparent harm or discomfort to the mother or fetus. As fMCG becomes more widely available, I believe it will have a significant impact on the way we diagnose and manage fetal arrhythmias.

For comments to this article, send email to: JANJDT@PediatricCardiologyToday.com

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UK MEDICAL WEBSITES

Arrhythmia Alliance
www.arrhythmiaalliance.org.uk/

British Cardiac Society
www.bcs.com

British Heart Foundation
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British Hypertension Society
www.hyp.ac.uk/bhs/

Cochrane Heart Group
www.epi.bris.ac.uk/cochrane/heart.htm

Coronary Heart Disease Collaborative
www.modern.nhs.uk/scripts/default.asp?site_id=23

Best Treatments (BMJ Publishing Group)
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Health Development Agency
www.hda-online.org.uk/

National Electronic Library for Health (NeLH)
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NeLH (National Electronic Library for Health) Cardiovascular Diseases
libraries.nelh.nhs.uk/cardiovascular/

National Institute for Clinical Excellence (NICE)
www.nice.org.uk

Society of Cardiothoracic Surgeons of Great Britain and Ireland
www.scts.org

TRANSCATHETER CLOSURE OF VENTRICULAR SEPTAL DEFECTS

By Yun-Ching Fu, MD, Qi-Ling Cao, MD and Ziyad M. Hijazi, MD

Introduction

Ventricular septal defect (VSD) is the most common congenital heart defect (representing approximately 20% of all defects). VSDs are classified as one of 4 types depending on their location in the septum: perimembranous (70%), muscular (10-15%), supracristal (5-10%), or inlet (5%). VSDs result in left to right shunting which may cause volume overloading of the left atrium and left ventricle, pulmonary hypertension, failure to thrive and/or congestive heart failure. In addition, there is also a significant life-long risk of infective endocarditis. Traditional treatment is surgical repair, which is generally safe. However, surgery involves small risks of complete heart block, chylothorax, phrenic nerve injury, early and late arrhythmia, post-pericardiotomy syndrome and also death. Moreover, the surgical scar may be a cosmetic concern for the patients and their parents. Therefore, the availability of transcatheter device closure has the potential to offer improved safety as well as more desirable cosmetic results.

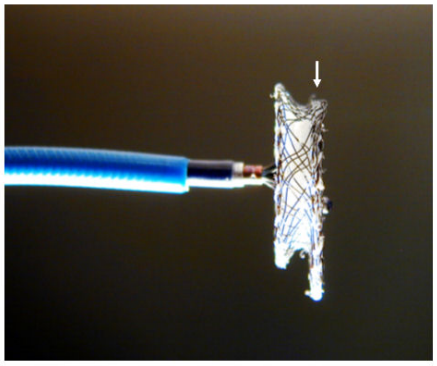

Figure 1. Amplatzer membranous VSD occluder is an asymmetric double disc device with the aortic end of the left ventricle disc only 0.5 mm larger than the waist to avoid impingement on the aortic valve (Arrow).

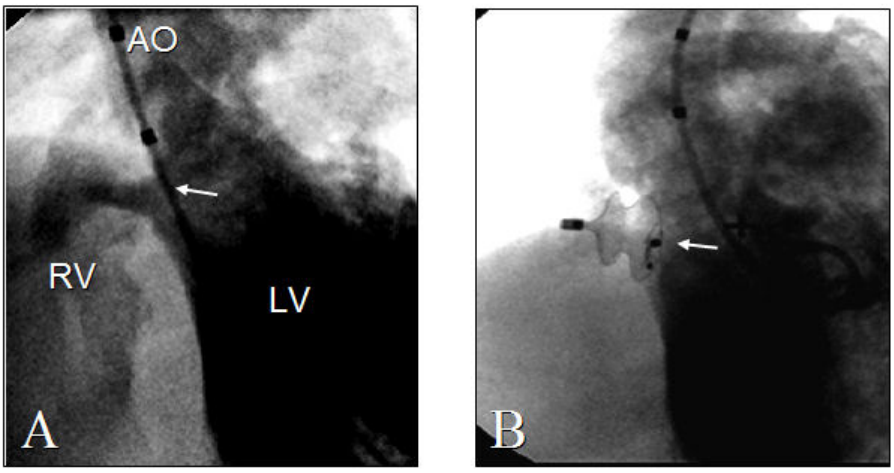

Figure 2. Left ventriculography in the left anterior oblique view demonstrates the perimembranous VSD (A). Final left ventriculography indicates good device position without residual shunt (B). AO: aorta, LV: left ventricle, RV: right ventricle.

Because of the proximity to the aortic and atrioventricular valves, supracristal and inlet VSDs are not amenable to device closure. Perimembranous and muscular VSDs have been occluded using the Buttoned and the Rash kind devices. However, these devices are cumbersome to deploy and are associated with a high incidence of residual shunts. To date the Amplatzer VSD Occluders (AGA Medical Corporation, Golden Valley, MN) are the most popular and most efficacious devices for VSD closure.

Perimembranous/membranous VSD

The Amplatzer membranous VSD occluder is a self-expandable double-disc device made from a nitinol wire mesh (Fig. 1). Dacron polyester patches are sewn into each disc and the connecting waist to increase the thrombogenicity of the device. The device is asymmetric and specifically designed for the perimembranous VSD. The aortic end of the left ventricle disc is only 0.5 mm larger than the waist to avoid impingement to the aortic valve. "The other end of the left ventricle disc is 5.5 mm larger than the waist. It has a platinum marker, which is used to guide device orientation. The right ventricle disc is 2 mm larger than the waist. The device waist is 1.5 mm long, and devices are sized according to the waist diameter (from 4 to 18 mm).

In addition to the general indications for VSD closure, the prerequisites for use of the Amplatzer occluder are body weight larger than 8 kg and the subaortic rim larger than 2 mm. The procedure is preferably performed under general endotracheal anesthesia with transesophageal echocardiographic (TEE) guidance. Access is obtained in the femoral artery (4-5 Fr sheath) and the femoral vein (7-8 Fr sheath). Heparin is given to keep an activated clotting time of greater than 200 seconds. Routine right and left heart catheterization is performed to assess the degree of shunting and to evaluate the pulmonary vascular resistance. Left ventriculography in the left anterior oblique view defines the location and size of the VSD (Fig. 2). The appropriate device size is chosen to be the same or 1-2 mm larger than the VSD size measured by TEE (Fig. 3) or ventriculography. The closure procedure is performed as follows: First, with the assistance of 0.035-in Terumo glide wire, a 4 or 5 Fr Judkins right coronary catheter crosses the VSD from the left ventricle to the right ventricle and then is placed into the branch pulmonary artery or superior vena cava. Second, the glide wire is exchanged for a long noodle wire, which is exteriorized out the femoral vein using a gooseneck snare. Third, over the wire, a long sheath is advanced into the left ventricle apex. After that the device is loaded and advanced to the tip of the sheath. Fourth, the sheath is retracted and the left disc is deployed in the left ventricle. The whole system is retracted to the septum and the right disc is deployed in the right ventricle. The whole system is retracted to the septum and then the right disc is deployed in the right ventricle. Finally, the device is released after proper position is confirmed by TEE and ventriculography. The patients are usually discharged the following day. Aspirin (3-5 mg/kg/day) is administered for 6 months

"The Amplatzer muscular VSD occluder, unlike the membranous VSD occluder, is a symmetric double-disc device."

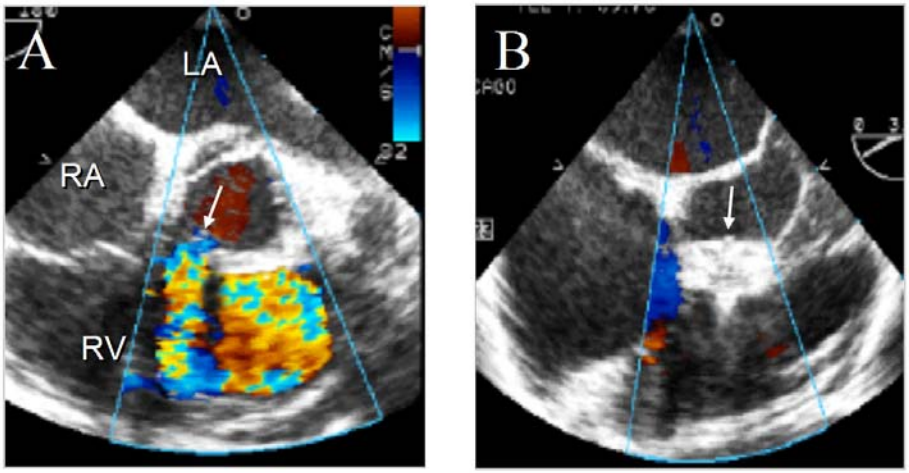

Figure 3. Color Doppler transesophageal echocardiography in short axis view reveals the perimembranous VSD with a left to right shunt (A). Final echocardiography shows no residual shunt (B). LA: left atrium, RA: right atrium, RV: right ventricle.

In 2002, we reported the initial use of the Amplatzer membranous VSD occluder in 6 patients who all achieved immediate complete closures[2]. In the 2004 American Heart Association meeting in New Orleans, Louisiana, Holzer et al. reported a successful procedure rate of 92.7% (89/96) with 0% mortality[3]. Only two patients had major complication of complete heart block. Left ventricular end-diastolic dimension decreased from a median of 42 mm prior to device closure to a median of 39 mm the day after the procedure. The above result shows that transcatheter closure of perimembranous VSD using the Amplatzer membranous VSD occluder is safe and effective.

Muscular VSD

Muscular VSDs are frequently hidden within the coarse right ventricular trabeculations and is difficult to localize through the standard surgical approach via the right atrium. Therefore, surgical repair still poses a remarkable challenge and carries certain morbidity and mortality.

The Amplatzer muscular VSD occluder, unlike the membranous VSD occluder, is a symmetric double-disc device (Fig 4). The connecting waist is 7 mm long and the left and right ventricle discs are 8 mm larger than the waist. The procedure is similar to that of membranous VSD occlusion except that a right internal jugular

"Ventricular septal defect (VSD) is the most common (approximately 20%) of congenital heart defect."

Figure 4. The Amplatzer muscular VSD occluder is a symmetric double disc device.

venous access is needed for defects located in the mid/apical or posterior septum. If the infant is small, precluding safe percutaneous closure, or if the VSD is associated with other defects requiring surgical repair, closure of the VSD can be achieved perventricularly in the operating room prior to initiation of cardiopulmonary bypass. Briefly, after the chest and pericardium are opened, an 18-gauge needle is used to puncture the right ventricle free wall pointing toward the VSD. Under the TEE guidance, a 0.035-in short guide wire is passed through the VSD into the left ventricle. The needle is taken out, leaving the wire in position. Over the wire, a proper size short sheath is advanced to the left ventricle. Once the short sheath is well positioned in the left ventricle, closure steps are similar to those of percutaneous closure with emphasis on the TEE to guide the steps.

In 2004, the US registry of the Amplatzer Muscular VSD occluder reported 83 procedures in 75 patients with a median age of 1.4 years who underwent percutaneous (70 patients) or perventricular (6 patients) closure of hemodynamically significant congenital muscular VSDs[4]. The device was implanted successfully in 72 of 83 (86.7%) procedures. Major procedure- or device- related complications occurred in 10.7% of patients. Closure rates were excellent and increased from 47.2% 24-hours post-procedure to 92.3% at 12 months' follow-up. These results compare favorably with the surgical results.

Conclusions

Transcatheter closure of perimembranous and muscular VSDs using the Amplatzer perimembranous and muscular VSD occluders is safe and effective with very rare complications. It has no scar, less pain, shorter hospital stay, and less cost compared to the open heart surgery.

References

1. Hijazi ZM. *Device closure of ventricular septal defects.* Catheter Cardiovasc Interv. 2003;60:107-114.

2. Hijazi ZM, Hakim F, Haweleh AA, et al. *Catheter closure of perimembranous ventricular septal defects using the new Amplatzer membranous VSD occluder: initial clinical experience*. Catheter Cardiovasc Interv. 2002;56:508-515.

3. Holzer R, Hijazi ZM, Wilkinson J, el al. Circulation 2004;110(supp);III-565

4. Holzer R, Balzer D, Cao QL, Lock K, Hijazi ZM; *Amplatzer Muscular Ventricular Septal Defect Investigators. Device closure of muscular ventricular septal defects using the Amplatzer muscular ventricular septal defect occluder: immediate and mid-term results of a U.S. registry*. J Am Coll Cardiol. 2004;43:1257-1263.

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CRYOABLATION: THE LATEST TECHNOLOGY IN PEDIATRIC ARRHYTHMIA ABLATION

By Kathryn K. Collins, MD

Cryoablation, which has been approved by the FDA within the last year (Cryocath Technologies, Inc, Montreal, Quebec), is the newest technology in pediatric ablation and the biggest advancement in ablative technologies in the last decade. Many pediatric electrophysiology centers have acquired this technology and have used it for the treatment of specific arrhythmias.

Since ablation for arrhythmias began in the late 1990s, radiofrequency energy has been the gold standard for interventional treatment of pediatric arrhythmias. The recent findings of the multicenter Prospective Assessment of Pediatric Catheter Ablation study have shown a high overall procedural success rate of 95.7% for diverse arrhythmia substrates and a low complication rate of 4%[1]. The risk of atrioventricular block was reported as 2.1% with atrioventricular nodal reentry and 3% with septal accessory pathways.

"Cryoablation technology also allows for temporary test lesions, which is an advantage over radiofrequency applications that create only permanent lesions."

How does one improve on this current gold standard? The answer may come in the safety of cryoablation - to decrease the risk of atrioventricular block when the arrhythmia arises from a location near the atrioventricular node. Cryoablation eliminates the risk of catheter dislodgement as the catheter freezes to the cardiac tissue and effectively adheres at that location. The analogy is the 'tongue on the pole' phenomenon in freezing temperatures. The catheter only moves once it is re-warmed. Cryoablation technology also allows for temporary test lesions, which is an advantage over radiofrequency applications that create only permanent lesions. By freezing to –30 degrees Celsius, cardiac conduction is only temporarily interrupted. The effects of the lesion can be assessed, with respect to the freezing on the arrhythmia location and also on the effect on the atrioventricular node, before freezing further to create a permanent lesion. By freezing to –70 degrees, permanent damage to the cardiac tissue is then created.

Permanent cryoablation lesions are smaller than those created by radiofrequency, and are therefore less likely to damage structures such as the coronary arteries when freezing on the atrioventricular groove. Another advantage of cryoablation is the ability to apply freezing in very tight locations, such as within the coronary sinus an impedance rise, or the inability to deliver adequate power is often a problem. Finally, with cryoablation compared to radiofrequency, the endothelium is not as disrupted and there may be less risk of thrombus formation at the ablation site.

The drawbacks of cryoablation are that the catheter size is a 7 French and thus cannot be utilized easily in the very small patient. The cryoablation catheter is somewhat stiff and catheter manipulation can be challenging. Also, in adult populations, initial reports have shown a higher chance of recurrence of the arrhythmia. Some of this recurrence risk has been ascribed to the 'learning curve' with any new technology, with hopes of improvement with operator experience.

Will cryoablation replace radiofrequency? The answer is likely no, because of the current high success and low complication rate from radiofrequency, and also because of the limits of the cryoablation system. Cryoablation is likely to be utilized along the septum, in locations near the atrioventricular node,

"The drawbacks of cryoablation are that the catheter size is a 7 French and thus cannot be utilized easily in the very small patient."

MEDICAL CONFERENCES

5th Annual International Symposium on Congenital Heart Disease: Controversies of Single Ventricles
February 11-15, 2005; St. Petersburg, FL
www.CHIF.us/conferences

Cardiology Update 2005 (Foundation for Cardiovascular Research)
February 14-18 2005; Davos, Switzerland
www.cardiologyupdate.ch

Cardiology 2005: 8th Annual Postgraduate Course in Neonatal and Pediatric Cardiovascular Disease
Feb. 16-20, 2005; Lake Buena Vista, FL
www.chop.edu/cme/#c2005

4th Annual Charleston Mini-Symposium on Pediatric Cardiology
Feb. 25-27, 2005; Charleston, SC
www.pediatrics.musc.edu/pedscard

ACC (American College of Cardiology) 54th Annual Scientific Session 2005
March 6-9, 2005 Orlando, FL
www.acc.org

10th Vail Symposium on Pediatric Cardiac Disease
March 13-16, 2005; Veil, CO
www.thechildrenshospital.org

2005 SIR (Society of Interventional Radiology) 30th Annual Scientific Meeting
March 31 - April 5, 2005; New Orleans, LA
www.sirweb.org

AATS (American Association for Thoracic Surgery) 85th Annual Meeting
April 10 – 13, 2005; San Francisco, CA
www.aats.org/annualmeeting/

28th Annual Scientific Sessions and Melvin P. Judkins Cardiac Imaging Symposium
May 4-7 2005; Ponte Vedra, FL
www.scai.org

2005 PAS (Pediatric Academic Societies) Annual Meeting
May 14 –17, 2005; Washington, DC
www.pas-meeting.org

and in tight or unusual places such as the coronary sinus. Initial reports of cryoablation used in pediatric arrhythmias have been reported only in brief, but have been promising [2-4]. More experience is necessary to assess the short and long term implications of this new technology.

"Cryoablation, which has been approved by the FDA within the last year, is the newest technology in pediatric ablation and the biggest advancement in ablative technologies in the last decade."

References:

1. Van Hare GF, Javitz H, Carmelli D, Saul JP, Tanel RE, Fischbach PS, Kanter RJ, Schaffer M, Dunnigan A, Colan S, Serwer G; Pediatric Electrophysiology Society. *Prospective assessment after pediatric cardiac ablation: demographics, medical profiles, and initial outcomes.* J Cardiovasc Electrophysiol. 2004 Jul;15(7):759-70.

2. Kirsh JA, Gross GJ, O'Connor S, Hamilton RM. *Transcatheter cryoablation of tachyarrhythmias in children: Initial experience from an international registry.* J Am Coll Cardiol, in press.

3. Miyazaki A, Kriebel T, Broistedt C, Saul JP, Paul T, Blaufox AD, Zentrum H. *Combined cryotherapy/RF energy approach to ablation of supraventricular tachycardia in pediatric patients.* (A) Heart Rhythm 1(1S):S51, 2004.

4. Gaita F, Antonio M, Riccardi R, Giustetto C, Grossi S, Caruzzo E, Bianchi F, Vivalda L, Gabbarini F, Calabro R. *Cryoenergy catheter ablation: a new technique for treatment of permanent junctional reciprocating tachycardia in children*. J Cardiovasc Electrophysiol. 2004 Mar;15(3):263-8.

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FDA Approval Letter:
www.fda.gov/cdrh/pdf3/p020045a.pdf

MEDICAL NEWS

New Database Provides Doctors and Patients Unprecedented Access to Clinical Study Information for Marketed Medicines

The pharmaceutical industry has inaugurated a central, easily accessible database to better communicate the results of clinical studies of marketed drugs. The database, available at http://www.clinicalstudyresults.org, contains the results of all controlled clinical trials (mainly Phase III and IV studies), both positive and negative, completed since October 2002 for PhRMA member company drug products approved in the United States. This includes both published articles and unpublished study summaries. The free, comprehensive Internet database is publicly available.

"Two years ago, the pharmaceutical industry committed to communicating meaningful results of clinical studies, regardless of outcome, by adopting the PhRMA Principles for the Conduct of Clinical Trials and Communication of Clinical Trial Results. This new database reflects the pharmaceutical industry's ongoing commitment to help educate practicing physicians and patients about marketed prescription medicines," said Alan F. Holmer, PhRMA president and CEO. "Doctors will now have centralized access to the important and meaningful information they need."

"The database contains an unprecedented amount of easily accessible clinical trial information and will be a valuable resource to doctors seeking the latest information about a marketed medicine," said Caroline Loew, Ph.D. PhRMA Vice President for Scientific and Regulatory Affairs.

The information in the database is presented in a standard format that includes the sponsoring company's name, the proprietary and generic names of the drug, a link or reference to the FDA-approved drug label, the studied indication or disease, a bibliography of published studies together with a link (where available) to the printed articles, and a standardized summary of unpublished studies. The standardized summary includes information about the study center; the design of the trial, the number of patients studied, the dose and mode of administration, and a summary of conclusions and outcomes -- whether positive or inconclusive.

For more information: www.clinicalstudyresults.org

Embryonic Stem Cells Correct Congenital Heart Defect in Mouse Embryos

A study published in the October 8, 2004 issue of Science, describes a previously unsuspected capacity of embryonic stem cells to influence neighboring defective cells and restore their capacity to function normally.

Researchers at Memorial Sloan-Kettering Cancer Center report that 15 embryonic stem cells injected into early embryos of mice, whose hearts were genetically predisposed to develop a lethal defect, rescued the heart from developing the disorder by not only producing normal daughter cells that were incorporated into the defective embryonic heart, but also by releasing biological factors into the nearby vicinity. This prevented neighboring heart cells from developing into defective tissue.

Drs. Benezra (left) and Fraidenraich (right)

"In other words, stem cells act like nurses, restoring 'sick' cells to health" said Robert Benezra, PhD, a Member in the Cancer Biology and Genetics Program at Memorial Sloan-Kettering Cancer Center and the study's senior author. "The result was that fifty-percent of the mice fated to die in the womb were born with healthy hearts."

In previous studies, Dr. Benezra and colleagues demonstrated a relationship between the presence of a specific protein called Id during embryonic growth and the normal development of capillaries and blood vessels. Mice engineered without this protein, called Id "knock-out" mice, display severe cardiac defects and die at mid-gestation.

"In this current study, with the repair of congenital heart defects in our Id knockout embryos, we observed that the stem cells provided normal signals to themselves and also to their neighbor cells to correct the organ as a whole," explained Diego Fraidenraich, PhD, the study's lead author.

The researchers also found a relationship between the Id protein and stem cells. "We found that stem cells are critically dependent on the Id protein for self-renewal and differentiation," added Dr. Benezra. "A reduction of just 15-20% of the Id protein impairs the stem cells' ability to rescue these embryonic mouse heart cells. These cells are very powerful, but also apparently very delicate."

To understand the molecular basis of the rescue, the authors identified two important molecules implicated in signaling from the ES cells to the Id knock-out cells. These molecules are insulin-like growth factor 1 (IGF-I) and WNT5a. The former molecule is a long-range acting factor, and the latter is a short-range factor and a member of the family of WNT proteins. Both molecules are implicated in heart development and cancer.

The authors demonstrated that IGF-I injected into the mother can cross the placenta and influence fetal cardiac development in the Id knock-out embryo. The Id knock-out embryos were born, but with partial rescue of cardiac defects and abnormal gene expression profiles. As a result, Id knock-out pups whose mothers were manipulated bypassed mid-gestation lethality, although they died during the first two days of life. On the other hand, WNT5a had the ability to correct the abnormal gene expression profiles of the Id knock-out hearts to normal levels. These two mechanisms (long- and short- range action) in conjunction may account for the full correction of the cardiac defects.

The study was co-authored by Elizabeth Stillwell, PhD, Elizabeth Romero and Katia Manova, PhD from Memorial Sloan-Kettering Cancer Center, and Craig T. Basson, MD, PhD and David Wilkes, PhD from Weill Medical College of Cornell University.

The National Institutes of Health has supported this research, by funding Dr. Diego Fraidenraich through a mentored minority faculty development award (Heart, Lung and Blood Institute) and Dr. Robert Benezra (National Cancer Institute). For more information: www.mskcc.org

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Research Team Discovers Possible Genetic Mechanism Behind Congenital Heart Defects

Researchers at The Hospital for Sick Children (Sick Kids) and Mount Sinai Hospital (MSH) have discovered a possible genetic mechanism behind congenital heart defects. This finding has implications for understanding how congenital heart defects occur, and may lead to genetic tests for certain defects,


Dr. Benoit Bruneau

such as proteins that determine how genes are expressed. This also opens new insights into how general chromosome properties can relate to specific disease processes. This research was reported in the November 4, 2004 issue of the scientific journal, Nature.

"It was previously believed that all cells during development contained the same chromatin remodeling proteins that unwind DNA, a process that is important for genes to be turned on. However, we identified one of these proteins, called Baf60c, that is expressed specifically in the developing heart," said Dr. Benoit Bruneau, the study's co-principal investigator, a Sick Kids scientist and an assistant professor of Molecular and Medical Genetics at the University of Toronto (U of T).

"When we completely suppressed the function of the Baf60c protein, there were dramatic cardiovascular defects. When we suppressed just half of the protein, the result was a defect that resembled one seen in infants," added Dr. Bruneau, also Canada Research Chair in Developmental Cardiology and member of U of T's Heart & Stroke/Richard Lewar Centre of Excellence.

"This new protein may provide new diagnostic tools and insights into how to treat cardiovascular problems," said Dr. Janet Rossant, the study's co-principal investigator and a senior investigator at the Samuel Lunenfeld Research Institute at MSH, as well as a professor of Molecular and Medical Genetics at U of T.

Other members of the research team include the study's co-lead authors Dr. Heiko Lickert of the Samuel Lunenfeld Research Institute at MSH and Dr. Jun Takeuchi of the Sick Kids Research Institute, Dr. Ingo von Both, Dr. Jeffrey Wrana, Dr. Fionnuala McAuliffe and Dr. S. Lee Adamson, all from the Samuel Lunenfeld Research Institute at MSH, and Dr. Mark Henkelman and Dr. Johnathon Walls from Sick Kids.

This research was supported by the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Ontario, the March of Dimes Birth Defects Foundation, the National Cancer Institute of Canada, the Canada Foundation for Innovation, the Ontario Innovation Trust, the Ontario Research and Development Challenge Fund, and Sick Kids Foundation.

For more information: www.sickkids.ca

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