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Fetal Echocardiography II: Congenital Heart Defects and Management

By Monesha Gupta-Malhotra, MBBS

This is the second in a series of two articles. The first article, "Fetal Echocardiography I," was written by Gurur Biliciler-Denktaş, MD, FACC, FAAP of the University of Texas Houston Medical School & Children's Memorial Hermann Hospital, Houston, TX. It was published in the February issue of Congenital Cardiology Today, and is available on the website.

Fetal echocardiography has been an evolving field with an increasing number of congenital heart defects being detected and reported in-utero. The implications for prenatal detection and management of these defects are enormous with two main outcomes: firstly, improvement in the outcomes of congenital heart disease and secondly the burden of early termination of pregnancy based on these diagnoses.¹ By eight weeks of gestation, the development of the heart is complete, and from then onwards the heart grows in size. The American Institute of Ultrasound in Medicine guidelines

for the obstetric ultrasound includes imaging of the 4-chamber view and the left and right outflow tracts of the heart (see Figure 1). The screening obstetric ultrasound at around twenty weeks gestation can detect about 30% of the malformations;^{1,2} this significantly improves in the hands of trained maternal fetal medicine specialists.³ The fetal echocardiogram, however, can provide detailed diagnosis of 80% of heart defects⁴ and can further help in counseling, management and prognostication. The expected survival rate of neonates with prenatal diagnosis is 90%, and that of neonates without prenatal diagnosis is 60% (i.e., 50% improvement in survival with prenatal diagnosis).⁵ Fetal echocardiography diagnoses of congenital heart disease guides in-utero and postnatal management¹ including urgent interventions such as balloon atrial septostomy. Furthermore, fetal echocardiography can help in monitoring cardiovascular status during fetal surgery for non-cardiac congenital anomalies.⁶

The prevalence of congenital heart malformations is higher than previously thought and is about 3-4 per 100 live births.⁷



Figure 1. The four chambers of the heart with left ventricular outflow tract.



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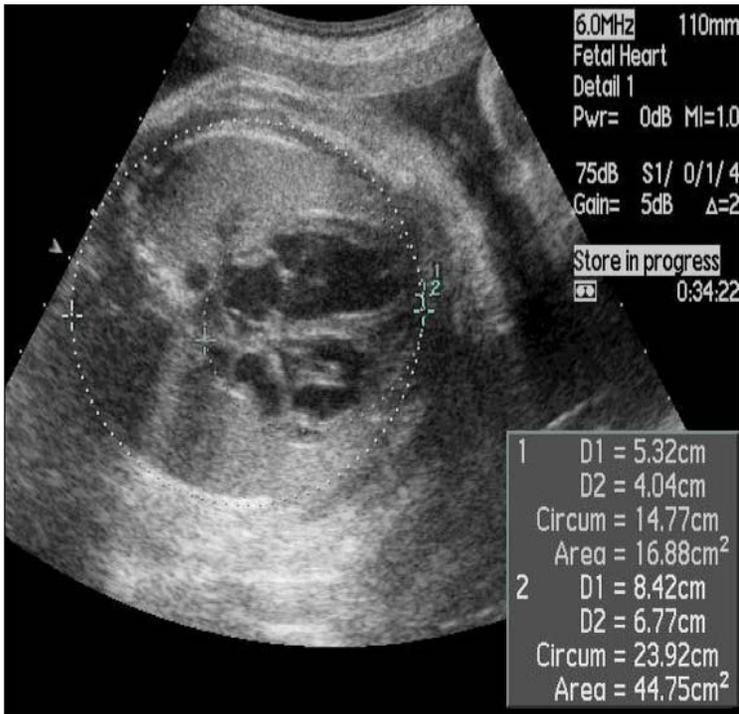


Figure 2. Determining the heart size in the fetus.

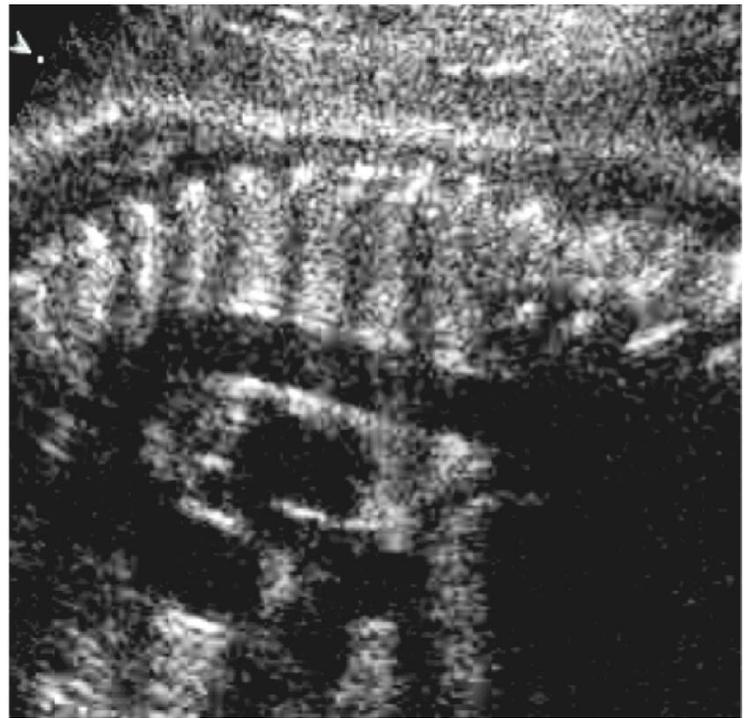


Figure 4. The aortic arch.



Figure 3. The branch pulmonary arteries and pulmonary valve annulus.

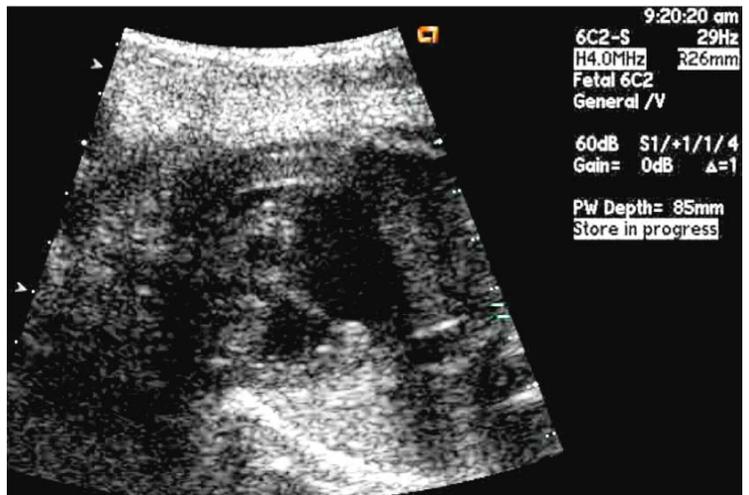


Figure 5. Complete atrioventricular canal defect with mild-left ventricular hypoplasia.

However, in-utero the prevalence is much higher, with high lethality. The congenital heart lesions detected in-utero are myriad and include simple shunt lesions to complex cyanotic heart disease. On fetal echocardiogram, a detailed imaging is performed using 2-dimensional (2-D), M-mode and Doppler ultrasound and recently using 3-D⁸ and 4-D.⁹ Several measurements are made to evaluate the heart size (Figure 2) and function¹⁰. Standard views

are obtained to identify anatomy of the chambers (Figure 1), valves, walls, and vessels of the heart (Figures 3-4).¹¹ Serial studies throughout pregnancy are important to detect development and progression of valve obstruction, hypoplasia or cardiomegaly, rhythm disturbances and heart failure in some of the heart defects. Determining the z-scores of the chambers and vessels is beneficial in determining the degree of hypoplasia or enlargement. The flow across the patent foramen ovale, ductus venosus and ductus



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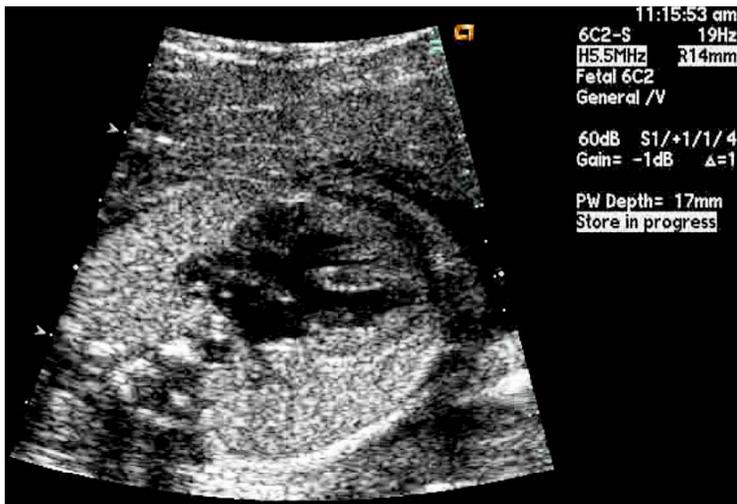


Figure 6. Tetralogy of Fallot with a subaortic ventricular septal defect. Note aorta overriding the interventricular septum.

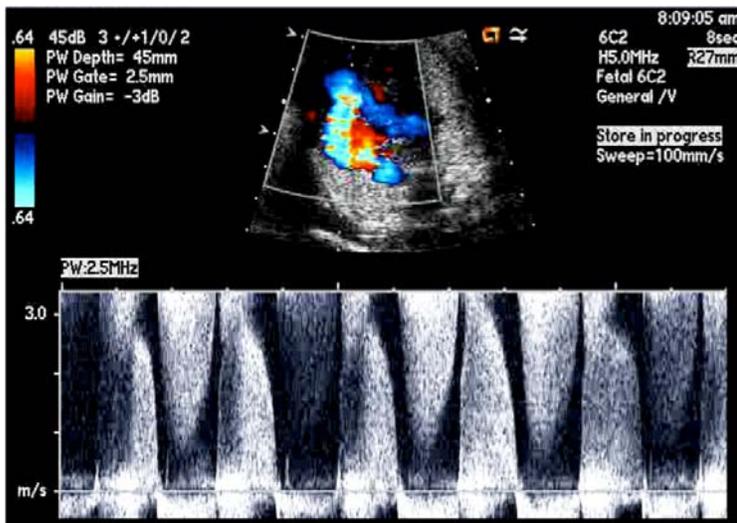


Figure 7. Tetralogy of Fallot with absent pulmonary valve. Note the pulmonary stenosis and pulmonary insufficiency by Doppler interrogation.

arteriosus requires special attention in the presence of congenital heart malformations. Besides congenital cardiac malformations, one can determine other cardiovascular disease, such as: rhythm disturbances, heart failure, hypertrophy of the myocardium, premature ductal constriction, twin-to-twin transfusions, pericardial effusions, and cardiac tumors. The congenital cardiac malformations are several different types and can be divided into following categories for ease in diagnosis: shunt lesions (atrioventricular canal defect), valve lesions (Tetralogy of Fallot, Ebstein's Anomaly), malpositioning of great arteries (d-transposition of great arteries, double outlet right ventricle),

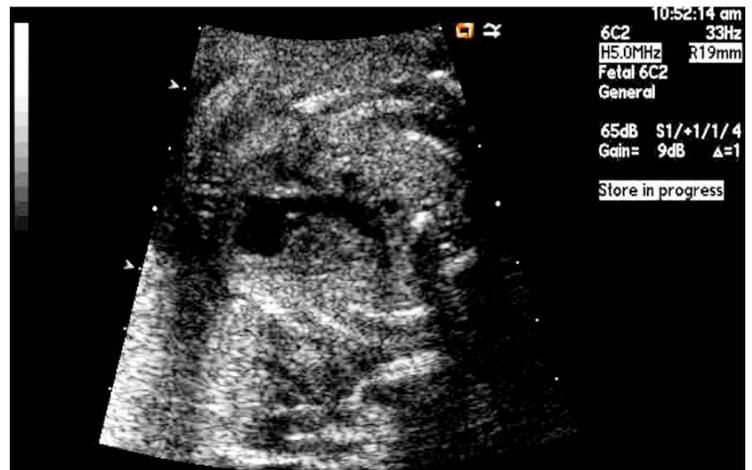


Figure 8. D-transposition of great arteries. Note aorta coming off from the right ventricle.

univentricular hearts (Hypoplastic Left Heart Syndrome, tricuspid atresia), arch anomalies (interrupted aortic arch), venous anomalies (total anomalous pulmonary venous return), and cardiopulmonary syndromes. The following are a few examples of heart defects routinely detected in-utero by fetal echocardiography.

Atrioventricular Canal Defects (AVC)

AVC defects can be diagnosed easily by a 4-chamber view (Figure 5) and have high risk of in-utero demise.¹² It is important to determine whether it is a balanced AVC or unbalanced AVC with hypoplasia of one of the ventricles. Color flow mapping can determine the degree of atrioventricular valve regurgitation, which is crucial as significant valve regurgitation can lead to non-immune hydrops fetalis. Heart blocks and fetal arrhythmias are associated with this lesion. In addition, these defects are associated with abnormal karyotype, in particular, Trisomy.²¹

Tetralogy of Fallot (TOF)

TOF is the most common cyanotic congenital heart malformation and is associated with an overriding aorta in relation to the ventricular septum (Figure 6) and some degree of right ventricular outflow obstruction and pulmonary valve hypoplasia. An important finding is an abnormal ratio of the diameter of the aortic to the pulmonary valve.¹³ In most cases the pulmonary valve velocity is normal or mildly increased and can be determined by spectral Doppler. Severe stenosis and atresia can develop over time.¹³ Very rarely, the pulmonary valve is rudimentary and hypoplastic, resulting in significant pulmonary insufficiency and stenosis or Tetralogy with absent pulmonary valve syndrome (Figure 7). The branch pulmonary arteries can be hypoplastic in varying degrees in TOF to aneurysmal in absent pulmonary valve syndrome. These defects are seen in association with 22q11 deletion and the fetus should be evaluated for other non-cardiac malformations and thymic hypoplasia.¹⁴



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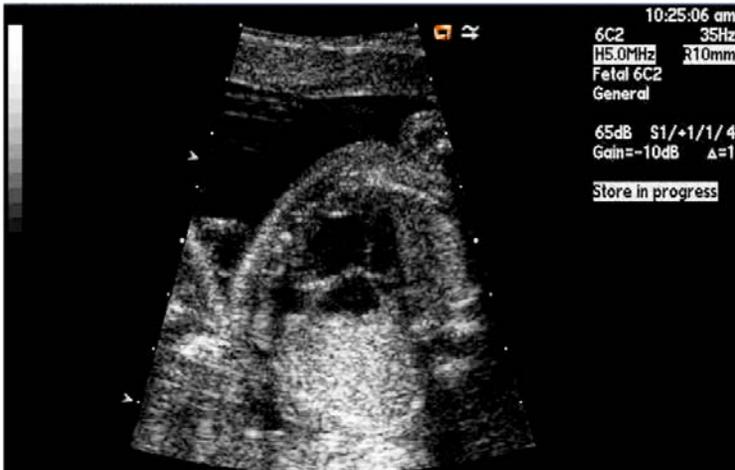


Figure 9. Hypoplastic Left Heart Syndrome. Note hypoplasia of the left atrium as well.

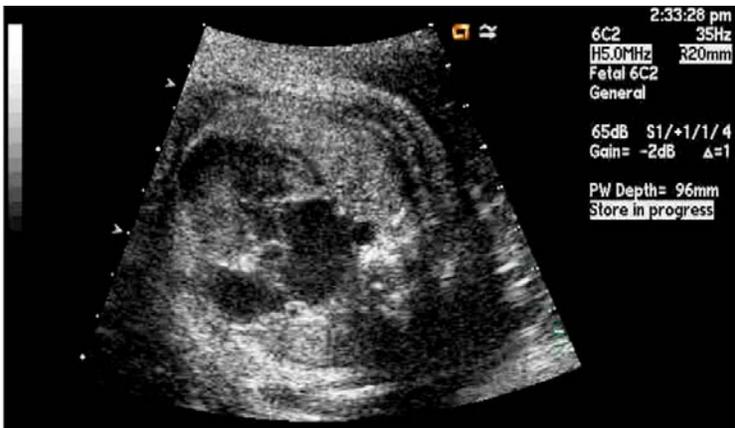


Figure 10. Tricuspid atresia with hypoplastic right ventricle.

D-Transposition of Great Arteries

The diagnosis of D-Transposition of the Great Arteries is made by demonstrating ventriculoarterial discordance¹⁵ in the presence of atrioventricular concordance (Figure 8). In the absence of a non-restrictive ventricular septal defect, defining the patency of the foramen ovale is of utmost importance in this lesion, as restriction at the atrial level could result in prenatal¹⁶ or postnatal demise. Early identification and emergent balloon atrial septostomy can thus be planned. The fetal diagnosis of d-TGA has improved the clinical status of the child before surgery¹⁷ and outcomes post-surgery.^{17,18} Double outlet right ventricle is a type of heart defect with a variety of cardiac configurations and can be associated with malpositioning of great arteries, including d-malpositioning.¹⁹

Hypoplastic Left Heart Syndrome

The finding of hypoplastic left-sided structures can help in making the diagnosis of this syndrome (Figure 9).²⁰ The lesions are usually progressive with a range of disease leading to mild hypoplasia and multiple levels of left heart obstructive disease (Shones anomaly) to true Hypoplastic Left Heart Syndrome with ductal dependent circulation. The prenatal prognosis for this lesion is usually poor.²¹ Right ventricular function²² and tricuspid regurgitation should be followed closely. Atrial level flow should be assessed by evaluating the foramen ovale and the pulmonary venous Doppler for restriction.^{23, 24}

Hypoplastic Right Ventricle

Tricuspid and pulmonary valve obstruction can result in a variety of heart defects including pulmonary atresia with intact ventricular septum and tricuspid atresia. Tricuspid atresia (Figure 10) has several different configurations with malpositioning of the great arteries. Again, the atrial and ductal level shunts need to be closely monitored along with the growth of the structures including the branch pulmonary arteries. Ebstein's anomaly can also lead to right ventricular and pulmonary hypoplasia and has a high degree of lethality in-utero.²⁵

Total Anomalous Pulmonary Venous Return

If the pulmonary venous return is obstructed, this defect is one of the remaining true pediatric cardiac emergencies if the pulmonary venous return is obstructed. It requires not only urgent diagnosis, but also an emergent surgery in a matter of hours after birth. Hence, in-utero diagnosis would be the key to management of this defect, but the defect is seldom recognized in fetal life by an obstetric ultrasound,¹ and not usually referred for a fetal echocardiogram. Furthermore, it can be a difficult diagnosis by fetal echocardiogram as well.²⁶ The growth of the left heart structures should be monitored carefully and evaluation for associated lesions such as cardiopulmonary syndromes should be made.

Aortic Arch Anomalies

Arch anomalies can be a challenging diagnosis in utero and coarctation of the aorta can develop over days even after birth with closure of the ductus. Hypoplasia of the isthmus and transverse arch are considered the most definitive signs of coarctation of aorta.²⁷ The fetus should be evaluated for associated lesions such as a bicuspid aortic valve with obstruction. Right aortic arch and double aortic arch can also be determined by a careful scan.²⁸

Cardiosplenic Syndromes

The viscerotransverse situs is routinely ascertained by fetal echocardiograms and any discrepancy along with congenital heart malformations is suggestive of Heterotaxia.²⁹ A stomach-distance ratio has been proposed in the diagnosis of right atrial isomerism by one study²⁹. There is a high incidence of dextrocardia and venous anomalies; however, some cardiopulmonary syndromes can be very subtle and can be missed in-utero.

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Management of Fetus with Congenital Heart Defect

A. Multidisciplinary approach: There is a high association rate of extracardiac and chromosomal anomalies with congenital heart malformations which requires a multidisciplinary team effort including consults from neonatologist, geneticist and pediatric surgery.³⁰ Congenital cardiac malformations are a multifactorial disease, and a detailed maternal history is often necessary to determine the causative factors, although often none are found. Controlling maternal blood glucose levels is very important in prevention of congenital heart malformations. Every effort should be made to avoid preterm delivery as immature lungs often can complicate the prognosis in complex congenital heart defects.

B. Medical Management: Maternal transplacental digitalization can help with fetal cardiac failure and hydrops;³¹ however, the risk of intrauterine demise remains high once hydrops fetalis has occurred. Direct fetal therapy with drugs such as furosemide and digoxin has proven to be successful in certain cases.³² Pharmacological management of rhythm disturbances and early delivery, where hemodynamically significant and persistent rhythm disturbances occur, is also crucial as certain rhythms such as complete heart block in presence of congenital heart disease can be lethal if not treated early.³³

C. Intrauterine Cardiac Procedures: Fetoscopic surgery and transcatheter management such as in-utero treatment with balloon angioplasty and septostomy are being routinely considered by some centers in concert with maternal fetal medicine and the perinatal cardiologist. Fetal balloon valvuloplasty is being offered for critical aortic stenosis and pulmonary atresia with intact ventricular septum and balloon atrial septostomy for d-transposition of great arteries and Hypoplastic Left Heart Syndrome^{34, 35} in order to alter postnatal outcomes. In-utero pericardiocentesis can be helpful in the presence of large effusions.^{36, 37}

D. Postnatal Management: The delivery can be planned according to the congenital heart malformation, i.e., delivery at a tertiary care center for finding of d-transposition of great arteries. Very rarely is emergent

delivery needed for heart defects unless there is evidence of fetal compromise or sustained hemodynamically significant arrhythmia. Neonatology, pediatric cardiology and pediatric cardiac surgery should be involved in postnatal period. Most infants with congenital heart malformations require routine care; however, a small number require emergent intervention after birth which can be predetermined by the perinatal cardiologist.³⁸

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Medical News, Products and Information

Children's Hospital of Philadelphia Bypass Procedure used During Infant Heart Surgery Does Not Impair Later Neurological Outcomes

Congenital heart defects (CHD) are the most common birth defects in humans, affecting 8 per 1000 live births, with one third of affected children requiring intervention in early infancy. Increasing numbers of survivors combined with developmental expectations for independence, behavioral self-regulation and academic achievement have led to a growing identification of neurobehavioral symptoms in some survivors. A study now suggests that a cooling technique often used in heart operations does not impair neurological outcomes.

Congenital heart disease and its treatment were originally thought to potentially increase neurologic injury in these patients. The technique of deep hypothermic circulatory arrest (DHCA) is used in order to repair these congenital cardiac defects by providing a bloodless surgical field, which may facilitate completion of the best physiologic repair, and decrease the duration of blood exposure to the bypass circuit. However, it involves a period of reduced blood flow in the brain. Cooling is a protective mechanism to reduce metabolism of the brain and other organs during periods of low blood flow.

Stephanie Fuller, MD, a cardiothoracic surgeon at The Children's Hospital of Philadelphia, presented these research findings yesterday in the prestigious J. Maxwell Chamberlain Lecture at the annual meeting of the Society of Thoracic Surgeons in Fort Lauderdale, FL. According to the study, DHCA does not impair language skills, attention, and other neurocognitive abilities in school-age children.

Dr. Fuller and colleagues from Children's Hospital and the University of Washington assessed the use of DHCA as a predictor of neurodevelopmental outcomes in children who had cardiac surgery as infants. The infants were enrolled in a prospective study of apolipoprotein-E (APOE) polymorphisms and neurodevelopmental outcome after cardiac surgery and underwent formal neurodevelopmental testing at four years of age.

Neurodevelopmental testing was completed in 238 out of 307 eligible patients. The surgeons used DHCA in 92 of those infants as deemed necessary to provide better operative exposure with a bloodless and less cluttered surgical field and therefore a shorter total cardiopulmonary support time. Use of DHCA was not predictive of worse performance for any neurodevelopmental outcome. Significant

predictors of worse outcome included lower socioeconomic status, preoperative mechanical ventilation and babies that were younger and smaller at the time of first operation. Neurodevelopmental assessment included cognition, language skills, attention, impulsivity, executive function, social competence, and visual-motor and fine-motor skills.

"Selective use of DHCA during cardiac surgery in infancy may facilitate operative repair and is not associated with impaired neurodevelopmental outcomes," said Dr. Fuller. "Despite added risk factors, the selective use of DHCA during infancy for repair of congenital heart disease without an obstruction in the aorta was not predictive of worse performance at four years of age."

Dr. Fuller added "use of DHCA as a support technique during cardiac surgery in infancy has many advantages; it is not necessary to sacrifice these advantages merely to avoid use of DHCA. Our study adds to the growing literature showing no adverse influence of limited periods of DHCA. New support techniques must be carefully evaluated prior to wide-spread acceptance to confirm they are not inferior to conventional management strategies."

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Genetic Link Between Cardiac Arrhythmias and Thyroid Dysfunction Identified

Newswise — Genes previously known to be essential to the coordinated, rhythmic electrical activity of cardiac muscle -- a healthy heartbeat -- have now also been found to play a key role in thyroid hormone (TH) biosynthesis, according to Weill Cornell Medical College researchers.

The authors' findings, published online this week by the peer-reviewed journal *Nature Medicine*, suggest that mutations of either of two gene products -- proteins called KCNE2 and KCNQ1 -- already known to be involved in human cardiac arrhythmias, could also cause thyroid dysfunction.

"It has long been known that the thyroid influences cardiac function and cardiac arrhythmias," says study senior author Dr. Geoffrey W. Abbott, Associate Professor of Pharmacology in medicine at Weill Cornell Medical College, "but our findings demonstrate a novel genetic link between inherited cardiac arrhythmia and thyroid dysfunction."

Additionally, it is the authors' suggestion that assessment of the thyroid status of patients

with KCNE2- and KCNQ1-linked cardiac arrhythmias could, in some cases, reveal a potential endocrine component to their cardiac arrhythmias that may not have been previously determined. This, in turn, could indicate treatment of the thyroid condition, with potentially beneficial effects on cardiac function.

KCNQ1 and KCNE2 were each recognized more than a decade ago as forming potassium channels in cardiac muscle that help end each heartbeat in a timely fashion. Inherited mutations in KCNQ1 and KCNE2 cause ventricular and atrial cardiac arrhythmias, previously presumed to be due entirely to the role of these proteins in cardiac muscle. The researchers have now discovered that KCNQ1 and KCNE2 also form a potassium channel in the thyroid gland.

"When the thyroid does not produce enough TH, a person may experience symptoms such as fatigue and a lowered heart rate, but there is also a more complex interplay between thyroid function, cardiac structure and cardiac arrhythmias. Our new findings may begin to explain some of these interrelationships," explains Dr. Abbott.

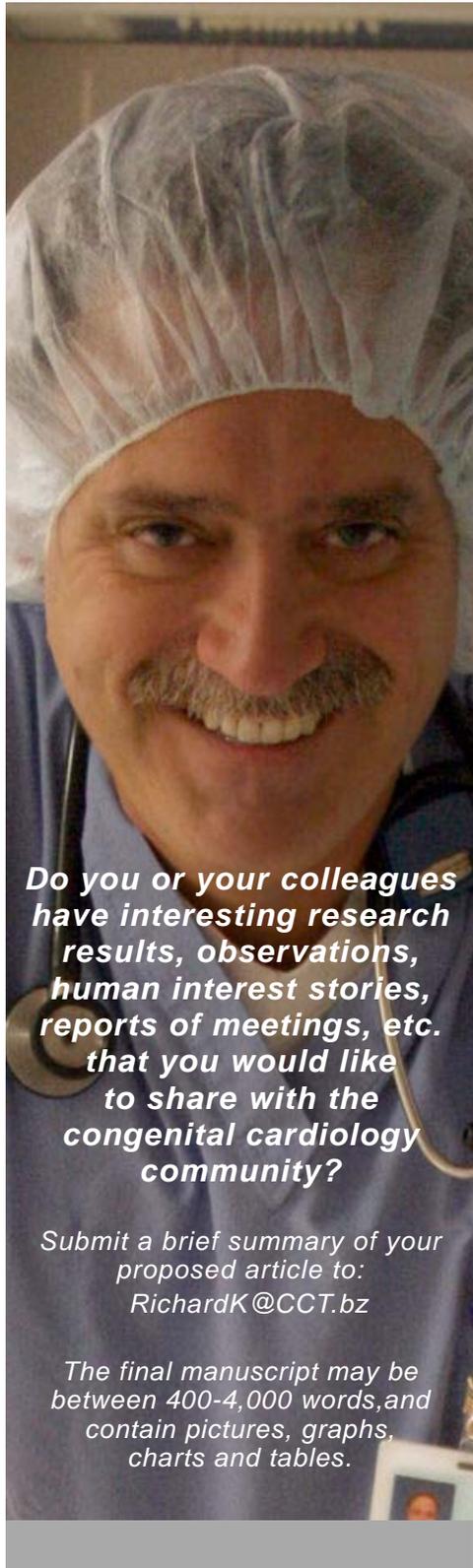
While studying mice that had the KCNE2 gene removed from their genome, the researchers observed that the animals developed symptoms of hypothyroidism, especially during pregnancy, and gave birth to pups with dwarfism, alopecia (baldness) and cardiomegaly (enlarged heart).

After allowing the mouse pups to drink milk only from mothers without the genetic alteration, the pups' symptoms were alleviated. The healthy mothers' milk contains normal levels of TH -- essentially acting as a TH replacement therapy. The symptoms were also treated by direct TH supplementation of pups or mothers.

"We then wanted to test what the mechanism was in the mice that caused deletion of the KCNE2 gene to have negative consequences for the thyroid," says Dr. Abbott.

Using micro positron emission tomography (microPET), Dr. Abbott and his team visualized the accumulation in the mouse thyroid of an iodine radioisotope in real-time. They found that absorption of the radioisotope in the thyroid was greatly impaired in mice lacking the KCNE2 gene. They believe that, normally, the KCNQ1-KCNE2 potassium channel helps another protein (the sodium/iodide symporter) to transport iodide into the thyroid.

Without the KCNQ1-KCNE2 potassium channel, the efficiency of iodide absorption by



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the thyroid is greatly reduced. Because iodide is an essential component of TH, this means that KCNE2 deletion also impairs TH production.

Future studies will now center on determining how applicable the research team's findings in the mouse are to the human population.

"While we have identified KCNQ1 and KCNE2 in both mouse and human thyroid, much additional work is required before we can fully understand how inherited mutations in the genes coding these proteins affect human thyroid function, how this in turn influences the health of human heart and other tissues, and how useful our discoveries will be in developing therapies to treat thyroid and thyroid-related human disease," explains Dr. Abbott.

Cardiac arrhythmias affect up to three million people in the US. The majority of these suffer from atrial fibrillation, a chronic arrhythmia most often observed in the aging population. Ventricular arrhythmias account for the large majority of the 300,000 cases of sudden cardiac death annually in the US. Thyroid dysfunction is estimated to affect 1-4% of the world's population.

Additional co-authors include: Torsten K. Roepke, Elizabeth C. King and Kerry Purtell from Weill Cornell; Daniel J. Lerner from CV Ingenuity, San Francisco, CA; and Andrea Reyna-Neyra, Monika Paroder, Wade Koba, Eugene Fine and Nancy Carrasco from the Albert Einstein College of Medicine, The Bronx, NY.

The study received support from the National Institutes of Health and the American Heart Association.

Growth Factor Hit by Cancer Drugs Also Protects the Heart

Newswise — A growth factor that is a common target of cancer drugs also plays an important role in the heart's response to stress, researchers at The University of Texas M. D. Anderson Cancer Center report online this week in the *Journal of Clinical Investigation*.

In many cancers, the body makes too much platelet-derived growth factor receptor (PDGFR), a type of protein that controls cell growth, allowing cancer cells to increase uncontrollably. Several chemotherapy

agents, including Sutent® (sunitinib), Nexavar® (sorafenib) and Gleevec® (imatinib), work by targeting and inhibiting PDGFR. This slows the growth of cancer - as well as angiogenesis, which is the growth of new blood vessels.

"Recently, some of these targeted anti-cancer drugs have been associated with heart failure," said Aarif Khakoo, MD, Assistant Professor in M. D. Anderson's Department of Cardiology and corresponding author on the study, said. "But the role of PDGFR signaling in the heart has been largely unexplored until now."

In this study, Khakoo and his colleagues showed that, while PDGFR-inhibiting agents may slow the growth of cancer cells, they also may impair the heart's ability to respond to stress. Since these agents also often cause elevated blood pressure, this causes a double bind of added stress to the heart and lessened capacity to deal with this stress.

Limiting PDGFR causes heart failure in mice

Using special laboratory mice with limited cardiac PDGFR and mice with normal PDGFR signaling, researchers performed transverse aortic constriction (TAC), a procedure widely used to study heart disease in which a band is placed at the aortic arch, resulting in acute pressure overload. The mice with limited PDGFR had heart failure.

"We showed that cardiomyocyte PDGFR expression and activation in heart muscle cells rises dramatically in response to pressure overload stress," Khakoo said. "Furthermore, we showed that knockout of PDGFR in heart muscle results in cardiac dysfunction, heart failure and a marked defect in stress-induced cardiac angiogenesis."

They also demonstrated that PDGFR signaling is crucial in the creation of new blood vessels that help the heart respond to stress.

High blood pressure may put patients who receive these drugs at even greater risk.

"Since these drugs also cause vascular stress in the form of severe high blood pressure in a significant numbers of patients, our findings suggest the double hit of high blood pressure and the blockade of PDGFR signaling may play a key role in



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heart problems when patients are treated with anti-cancer agents whose targets include PDGFR," Khakoo said.

Khakoo said the study suggests aggressive control of high blood pressure may significantly reduce cardiac toxicity caused by these agents.

This study opens the door to studying additional effects of PDGFR-inhibiting drugs

on the heart, as well as ways to prevent damage to the heart.

"Patients with pre-existing heart disease may be at increased risk for cardiomyopathy and heart failure associated with these drugs," Khakoo said. "If we can confirm this, it might help develop a tool to determine the individual risk for cancer patients being considered for treatment with PDGFR

inhibitors and to develop strategies to prevent heart damage."

Co-authors with Khakoo are first author Vishnu Chintalgattu, PhD; Di Ai, MD, PhD; Jianhu Zhang, PhD; Tiffany Shih, Iyad Daher, MD and Shalin Patel, all of M. D. Anderson's Department of Cardiology; Robert Langley, PhD of M. D. Anderson's Department of Cancer Biology; James Bankson, PhD, of M. D. Anderson's Department of Imaging Physics; Anilkumar Reddy, PhD; Jennifer Pocius; George Taffet, MD and Mark Entman, MD of Baylor College of Medicine's Department of Medicine; Kevin Coombes, PhD, of M. D. Anderson's Department of Bioinformatics and Computational Biology; Shibani Pati, MD, PhD of The University of Texas Health Science Center at Houston Center for Translation Injury Research; and L. Maximilian Buja, MD of The University of Texas Medical School at Houston Department of Pathology and Laboratory Medicine.

This work was supported in part by a Howard Hughes Medical Institute Physician-Scientist Early Career Award, a Physician-Scientist Award from M.D. Anderson Cancer Center, a Michael and Marriet Cyrus Scholar Award, a postdoctoral fellowship from the American Heart Association, the National Institutes of Health and the Wanamacker Foundation.

Early Cooling in Cardiac Arrest May Improve Survival

Rapidly cooling a person in cardiac arrest may improve their chance of survival without brain damage, according to research presented at the American Heart Association's Scientific Sessions 2009.

"We now have a method that is safe and can be started within minutes of cardiac arrest to minimize damage during this very critical period," said Maaret Castrén, MD, lead author of the study and Professor of Emergency Medicine at the Karolinska Institute in Stockholm.

For years, people hospitalized after cardiac arrest have been cooled to reduce injury to the brain and other tissues that occurs when the blood supply returns after being temporarily halted.

In the PRINCE (Pre-Resuscitation Intra-Nasal Cooling Effectiveness) investigation, Castrén and colleagues at 14 other centers across Europe used a new tool, RhinoChill, that cools the brain during ongoing cardiopulmonary resuscitation (CPR).

Researchers randomized 200 adults going into witnessed cardiac arrest to receive either standard resuscitation or resuscitation with cooling started as soon as possible during the arrest, with ongoing CPR. All patients who survived to hospitalization were further cooled



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according to standard criteria. Eighteen patients were excluded from the analysis because a 'do-not-resuscitate' order was found or there was a non-cardiac reason for their cardiac arrest.

In the 182 patients reported, 83 (average age 66 years, 71% male) were randomized to receive nasal cooling (although two were not cooled because of user or device problems) and 99 (average age 64.8, 78% male) received standard care.

RhinoChill is a non-invasive device that introduces coolant through nasal prongs. The system is battery-powered and requires no refrigeration, making it suitable for emergency medical technicians in the field to use while a person is receiving CPR.

The patients in each group were similar in their initial heart rhythms, how much time lapsed before CPR was started and whether CPR restored a pulse. The median time between arrest and the initiation of cooling was 23 minutes. On arrival at the hospital, the cooled patients' temperatures (measured at the eardrum) were significantly lower (average 34.2°C, 93.56°F) than those receiving standard care (35.5°C, 95.9°F, $p = 0.0001$).

In the total group:

- 46.7% of those cooled survived to hospital discharge, compared with 31% of those receiving standard care;
- 36.7% of those cooled were in good neurological condition on hospital discharge, compared with 21.4% of those receiving standard care. In the 137 patients in whom resuscitation efforts began within 10 minutes of cardiac arrest:
 - 59.1% of those cooled survived to hospital discharge, compared with 29.4% of those receiving standard care;
 - 45.5% of those cooled were neurologically intact at hospital discharge, compared with 17.6% of those receiving standard care ($p=.01$).

"Our results show that the earlier you can do the cooling, the better," Castrén said. "When resuscitation efforts were delayed, there was no significant difference in survival."

In a time analysis, patients who received a combination of early CPR started within six minutes of collapse and cooling had the best outcomes.

Patients with ventricular fibrillation (VF), whose heart chambers aren't pumping blood because they are twitching rapidly and erratically instead of fully contracting, are the subgroup of cardiac arrest patients most likely to survive. In this study, of the 56 patients who had VF:

- 62.5% of those cooled survived to hospital discharge, compared with 47.6% of those who received standard care;
- 50% of those cooled were neurologically intact at hospital discharge, compared to 28.6% of those who received standard care.

"RhinoChill is easy and safe to use during a cardiac arrest outside of the hospital," said Denise Barbut, MD, senior author of the study and President and Chairman of BeneChill, Inc., maker of the device.

"Although the study was not powered to look at outcomes, there seemed to be a significant benefit relative to survival and neurologically intact survival, specifically in those treated within 10 minutes."

Eighteen adverse reactions were reported after the treatment, including three nosebleeds and 13 nasal discolorations. Coloring spontaneously returned to normal in all patients who survived. Serious adverse events, such as seizure or repeat cardiac arrest, occurred in seven cooled patients and 14 controls.

RhinoChill has been approved for marketing in Europe, and the company expects to start selling the device there in March 2010.

Other authors are Per Nordberg, MD; Didier Desruelles, MD; Frank Eichwede, MD; Pierre Mols, MD, PhD; Leif Svensson, MD, PhD; Fabio Taccone, MD; Jean-Louis Vincent, MD, PhD; Hans-Jörg Busch, MD; Michael Vergnion, MD; Christian Storm, MD; Antonio Pesenti, MD, PhD; Fabien Guérisse, MD; Thomas Elste, MD; Markus Roessler, DEAA; Harald Fritz, MD; and Pieterjan Durnez, MD.

Study Finds New Causes of Heart Disease That Leads to Sudden Death

A new study on a significant cause of heart failure and sudden death raises questions about previously assumed genetic causes of this disease and may prevent potentially tragic outcomes due to incomplete genetic screening.

The disease is Arrhythmogenic Right Ventricular Cardiomyopathy, an inherited heart muscle disorder where damaged heart muscle is gradually replaced by scar tissue and fat. ARVC often requires heart transplantation and can cause heart failure and sudden death, particularly in young people.

In a study published online February 2 (February 9, 2010 issue) in the *Journal of the American College of Cardiology*, researchers found that the genetic basis of ARVC is not related only to a single gene, known as PKP2, but may include multiple mutations in a single gene or in many genes at the same time - particularly those in "cell junctions" where cells are held tightly together. The Cincinnati Children's Hospital Medical Center study also revealed that individuals known to carry a single mutated gene may show no clinical evidence of the condition.

"Cell junctions are the final common pathway for ARVC," said Jeffrey A. Towbin, MD, Executive Co-Director of the Cincinnati Children's Heart Institute and senior author of the multicenter study. "This study has a significant impact on clinical genetic testing, as simple single-gene analysis, particularly for PKP2 alone, is too narrowly defined and the potential for inaccurate interpretation high. Furthermore, the moderate number of genes that encode for the primary working components of cell junctions strongly suggests that all genes in this pathway should be screened in all subjects."

Dr. Towbin and his research colleagues identified 21 variants in PKP2 in 38 of 198 (19%) of those with ARVC and their families. Of those 38 subjects, nine had two or more mutations in the PKP2 gene; while mutations in additional desmosomal genes, those that form where two cells adhere, were identified in 16 of the 38 subjects with PKP2 mutations who were studied. In 14 of all 198 subjects, mutations occurred in non-PKP2 genes encoding cell junction proteins.

"Unless all genes are screened, individuals may have a non-disease-causing gene variant mistakenly assigned as disease-causative, and 'at-risk' family members may be either mistakenly diagnosed with a causative mutation or inappropriately be given a negative result," says Dr. Towbin. "In the latter case, this could lead to discharge from follow-up despite actually carrying a disease-causing mutation in another gene that wasn't analyzed. This could lead to tragic outcomes."

ARVC may cause abnormal electrical heart rhythms and weakening of the pumping action of the heart. In many cases, the disease does not limit the quality or duration of life. A proportion of people with ARVC, however, develop complications, all of which are treatable. Left untreated, sudden death may occur, particularly in young, healthy and athletic individuals. This is why evaluation and follow-up by a cardiologist knowledgeable about ARVC is recommended.

The study included researchers from Baylor College of Medicine, Houston; the University of Padua Medical School, Italy; Beth Israel Deaconess Medical Center, Harvard University, Boston; University of Rochester Medical Center, NY; Johns Hopkins School of Medicine and ARVD Program, Baltimore; and the University of Arizona, Tucson.

The study was funded in part by grants from the National Heart, Lung and Blood Institute of the National Institutes of Health.

Blood Pressure Control Abnormal in Newborns of Smoking Mothers

Newborns of women who smoked during pregnancy show signs of circulatory dysfunction in the first few weeks of life that get worse throughout the first year, Swedish researchers reported in *Hypertension: Journal of the American Heart Association*.

The blood pressure response to tilting the infants upright during sleep — a test of how the body copes with repositioning — was dramatically different in infants born to smoking mothers compared to those born to nonsmoking parents.

Infants not exposed to tobacco experienced only a 2% increase in blood pressure when they were tilted upright at one week of age and later a 10% increase in blood pressure at one year. Infants of smoking mothers had the reverse — a 10% increase in blood pressure during a tilt at one week and only a 4% increase at one year. At three months and one year, the heart rate response to tilting in the tobacco-exposed infants was abnormal and highly exaggerated, researchers reported.

"Babies of smokers have evidence of persistent problems in blood pressure regulation that start at birth and get worse over time," said Gary Cohen, PhD, lead author of the study and senior research scientist in the Department of Women and Child Health at the Karolinska Institute in Stockholm, Sweden. "This study reveals for the first time that early life exposure to tobacco can lead to long-lasting reprogramming of infant blood pressure control mechanisms."

The study included 19 infants of nonsmoking couples and 17 infants of women who smoked on average 15 cigarettes a day. Infants were normal weight at birth and breast fed. All infants had blood pressure and heart rates taken while sleeping and tilted up at a 60 degree angle during the first weeks, at three months and one year. They were then lowered back to the supine position.

Researchers also found:

- When tobacco-exposed babies were tilted semi-upright at one week, the rise in blood pressure was double that of controls, but at one year it had fallen dramatically and was only half that of age-matched controls.
- Reversing the posture from upright to horizontal - similar to suddenly lying down - normally causes blood pressure to fall back to normal; however, in infants of smokers the maneuver resulted in a surge in blood pressure.
- When infants were sleeping undisturbed, diastolic blood pressure in the smoke-exposed infants was higher at three months and their heart rate was slower by 20% at one year than in infants born to nonsmoking parents.

Normally, when a person stands, the heart rate increases and the blood vessels constrict to keep blood flow to the heart and brain.

"Infants of smokers have a hyper-reactive system in the first weeks of life because the blood pressure increases too much when they are tilted up, but at one year they under-react and are less effective in adapting to an upright position," Cohen said. "Tobacco-exposed infants have a different profile. It's surprising how early in life these functional abnormalities can be detected in the babies of smokers. The re-programming of the cardiovascular function is present at birth and is still present and even more dramatic at one year."

The researchers plan to continue to follow these children further to determine whether this re-programming creates problems when they become older.

"The seeds of many diseases probably are sown very early in life," Cohen said. "Babies of smokers may already be showing signs that they are more likely to develop high blood pressure later in life."

Identifying early markers could have broad public health implications — possibly leading to diagnosing, treating and preventing cardiovascular disease earlier, he said.

Co-authors are Hugo Lagercrantz, MD, PhD.; Miriam Katz-Salomon, PhD; and Heather Jeffrey, PhD, MPH. NR10 – 1007 (Hypertension/Cohen).

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