

# CONGENITAL CARDIOLOGY TODAY

Timely News and Information for BC/BE Congenital/Structural Cardiologists and Surgeons

Volume 9 / Issue 4

April 2011

North American Edition

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#### **Adult Congenital Heart Association's Sixth National Conference**

April 28-May 1, 2011 Los Angeles, CA  
<https://secure.lenos.com/lenos/conferencedirect/ACHA2011/>

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May 4-5 2011; Tel-Aviv, Israel  
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Editorial and Subscription Offices

16 Cove Rd, Ste. 200  
Westerly, RI 02891 USA  
[www.CongenitalCardiologyToday.com](http://www.CongenitalCardiologyToday.com)

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## Congenital Heart Disease in Neonates and Infants in a Developing Country: Patterns and Constraints

By Samia H. Osman, MD, Ghada Sh. Mohamed, MD; Osama A. Mohammed, SSMB; Sulafa K. Ali, FRCPCH, FACC

### Introduction

Congenital Heart Disease (CHD), which is an abnormality in cardio circulatory structure,<sup>1</sup> has a prevalence of about 0.5-0.8%.<sup>2-5</sup> In addition to unique diagnostic and management problems, CHD affects ongoing well-child care, and can complicate bonding, feeding, growth and development. Delayed diagnosis and limited surgical facilities in developing countries increase the risk of mortality, morbidity and handicap.<sup>6</sup>

### Patients and Methods

We retrospectively reviewed records of 180 neonates and infants with CHD at the Cardiology Clinic in Gafaar Ibn Auf Specialized Hospital, a central referral hospital in Khartoum, Sudan, for the period January 2009 to January 2010. Echocardiography was performed using Easote MyLab™ 30 echocardiography machine equipped with a 2.5–5.0 MHz transducer. Data was

analyzed by software SPSS Version 13 software.

### Results

The total number of patients seen was 900. One-hundred-eighty (20%) of them were neonates and infants with congenital heart disease. Males were 55% of the total, and females were 45%. Most of the patients (49%) presented after four months of age, and only 14% presented in the neonatal period. Figure 1 shows cause of referral for echocardiography. The majority of the patients had symptoms and signs of heart failure; a few had cyanosis. Figure 2 shows the distribution of

Fig. 1 Cause of Referral for Echocardiography

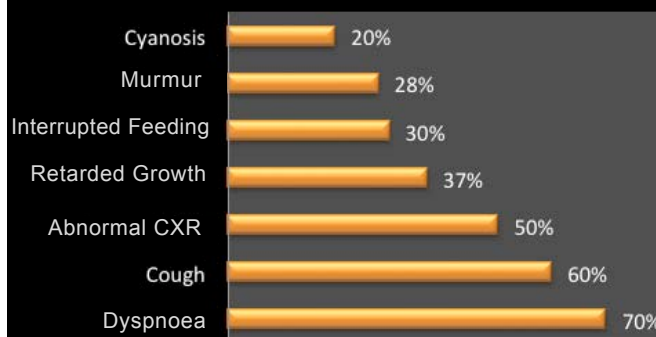


Figure 1: Cause of referral for echocardiography and including symptoms and signs in 180 cases.

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Fig. 2 Distribution of Acyanotic Cardiac Lesion (no =135)

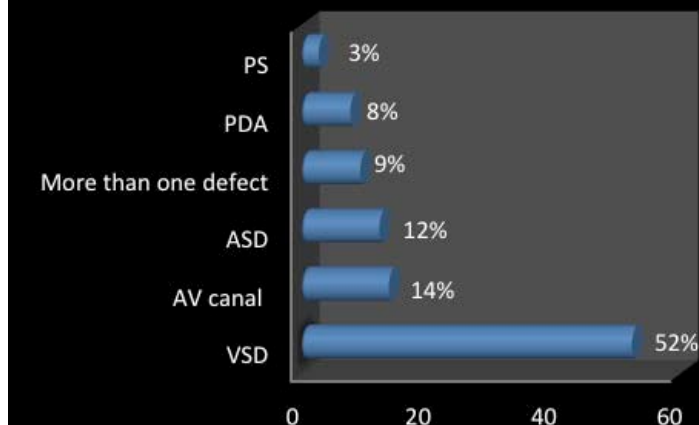


Figure 2: Distribution of 135 cases with acyanotic cardiac lesion based on echocardiography. (PS Pulmonary stenosis, PDA patent ductus arteriosis, ASD atrial septal defect, VSD ventricular septal defect, AV atrioventricular).

Table 1. Distribution of Cyanotic Heart Disease in 45 Patients Based on Echocardiography

Type of Cyanotic Lesion	No. of Patients	Percentage
Tetralogy of Fallot	23	51%
Transposition of Great Arteries	14	31%
Complex Lesions	7	16%
Tricuspid Atresia	1	2%
<b>Total</b>	<b>45</b>	<b>100%</b>

135 cases with acyanotic cardiac lesion. Seventy-one (52%) cases were Ventricular Septal Defect (VSD); seventeen (12%) cases were Atrial Septal Defect (ASD); eleven (8%) cases were Patent Ductus Arteriosis (PDA); nineteen (14%) cases were AV canal; four (3%) cases were PS; and thirteen (9%) cases had more than one defect. Table 1 shows distribution of 45 cases with cyanotic cardiac lesions: twenty-three (51%) cases of cyanotic CHD were Tetralogy of Fallot (TOF), fourteen (31%) cases were Transposition of the Great Arteries (TGA), one case (2%) was Tricuspid Atresia (TA), and seven (16%) cases were complex cardiac lesion. Figure 3 shows the recommended management of patients: 0.94% of the cases were treated conservatively, 65% of the patients were scheduled for surgery in Sudan, 34% of the patients needing surgery were sent abroad, and 4% were scheduled for catheterization.

## Discussion

Slight male predominance was found, male-to-female ratio was 1.2:1; similar results are described in many African countries.<sup>7-8</sup> Most of the patients (86%) were diagnosed after the neonatal period and half of the patients were diagnosed late in infancy, so critical congenital heart disease (CCHD) might be missed. Several studies in many developed countries showed that this delay in diagnosis was responsible for 48% of infant deaths, despite availability of advance life-saving procedures like interventional catheterization and surgery.<sup>9-18</sup> The pattern showed that ventricular septal defect (VSD) was the most common lesion (52.1%) in acyanotic patients, as was also the case (45%) in a similar study from Nigeria and (49%) in Nepal.<sup>7-8</sup> This pattern was noticed in many studies.<sup>7-8</sup> Tetralogy of Fallot (TOF) dominated as the cause of cyanotic lesions among patients in the study, as TOF is known to be the most common cyanotic heart disease,<sup>1</sup> followed by complex lesions. Most of cases were referred for cardiology consultation and echocardiography because of symptoms of heart failure: dyspnoea in 70% of the cases, cough in 60% and cyanosis in 20%. Commonly, cyanosis is poorly recognized in black patients. In our study, large number of patients were referred for surgical treatment (65%) in Sudan and (34%) abroad. This reflects the technical and financial constraints of congenital heart surgery in Sudan especially corrective surgery. Another problem was the late presentation and diagnosis in the majority of patients referred for surgery. This delayed diagnosis is well-known to be associated with increased post-operative morbidity and mortality.<sup>19-25</sup>

## Conclusion

The fact that most of our cases were detected late in infancy stresses the need of improving early detection of CHD. This can be achieved by introduction of fetal echo, which is not available now in Sudan, and proper evaluation of neonates, particularly using pulse oximetry. Once a diagnosis is made, arrangement of a suitable intervention can follow.

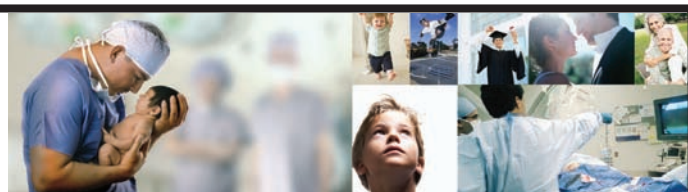
Surgery was indicated in a large number of cases and one third of the patients had to go abroad, so it is obvious that the improvement and extension of the locally available cardio-thoracic surgery service, with the minimum possible cost, is what is really needed.

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**Division of Pediatric Cardiology  
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Saint Louis University, a Catholic, Jesuit institution dedicated to student learning, research, health care, and service is seeking an additional pediatric cardiologist to join an established group within the Division of Cardiology and the Department of Pediatrics at SSM Cardinal Glennon Children's Medical Center. Applicants will be considered at the Assistant/Associate Professor rank, and must be board certified/eligible in Pediatric Cardiology. General responsibilities will include clinical care, teaching, and research.

**Non-Invasive Cardiologist**

We are seeking an additional non-invasive cardiologist to assist our current faculty with the growing number of echocardiographic procedures performed at our institution. Experience in performing and interpreting both transthoracic and transesophageal echocardiograms is required. Fetal echocardiography experience is desired but not mandatory. An interest in clinical research is encouraged. Academic rank will be commensurate with qualifications and experience.

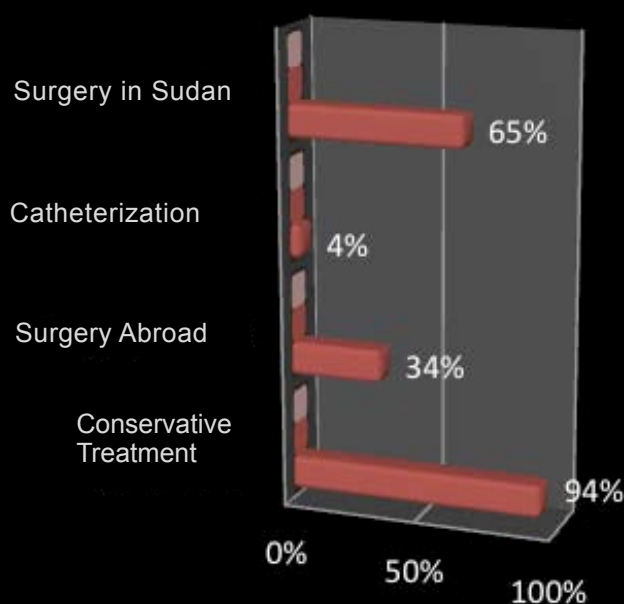
The cardiology division is in a period of significant expansion, with the opening of the Dorothy and Larry Dallas Heart Center within SSM Cardinal Glennon Children's Medical Center in January, 2009. An active congenital heart surgery program exists, and the hospital houses state-of-the-art operating rooms and a new 60-bed neonatal intensive care unit. Construction of a new hybrid cardiac catheterization lab/operating suite is scheduled to begin in 2010. The Doisy Research Center, a new 10-story tower housing the Health Sciences Center Research laboratories, was opened in 2007.

**Interested candidates must submit a cover letter, application, and current CV to <http://jobs.slu.edu>. Other correspondence regarding this position can be sent to:**

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**Fig. 3 Recommend Management for the Cases (n = 180)**



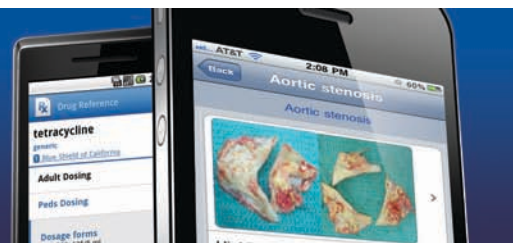
*Figure 3: Shows the recommended management of the cases.*

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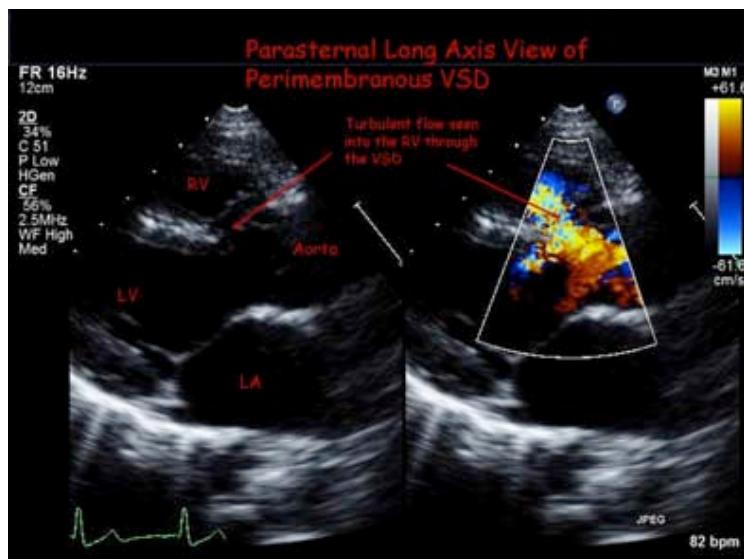


Figure 4: Echocardiography of a large perimembranous VSD. 2D and colour flow showing turbulent flow from left ventricle to the right ventricle of an eight-month old infant.

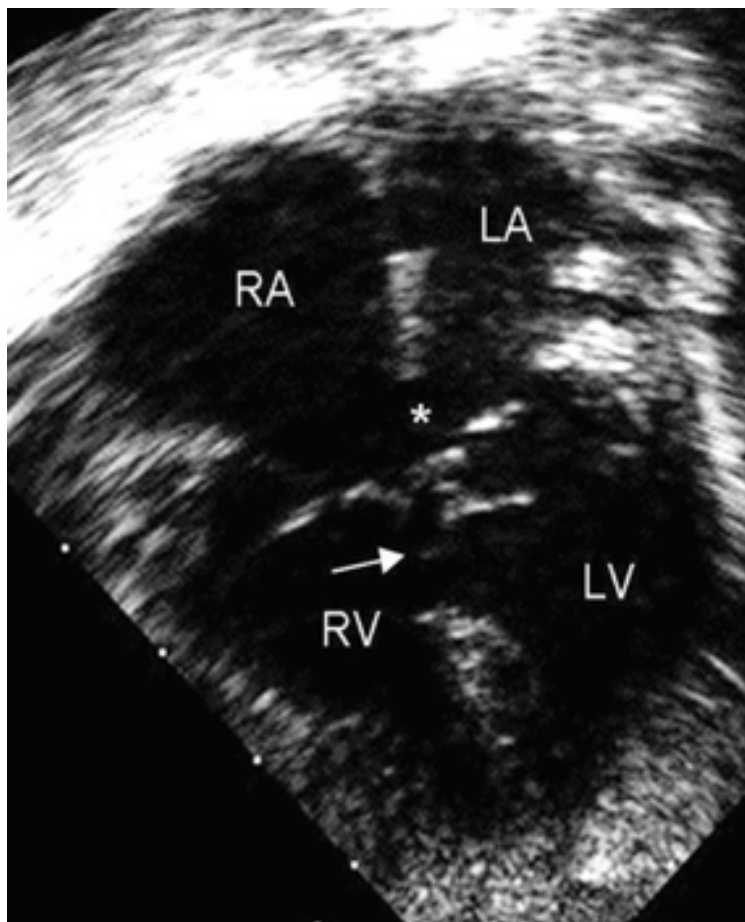


Figure 5: 2D Echocardiography of a four-month old infant with Down's Syndrome showing Atrioventricular septal defect. (\*) primum septal defect. (Arrow) inlet ventricular septal defect.

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## Recruiting Physician Leader for PEDIATRIC ECHOCARDIOGRAPHY CORPUS CHRISTI, TEXAS

Driscoll Children's Hospital is advancing a comprehensive Heart Center to meet the healthcare needs of congenital heart patients in South Texas. The Heart Center is seeking to develop a formal echocardiography laboratory and is recruiting a physician leader. Experience or advanced training in diagnostic imaging (i.e., echocardiography, TEE, and fetal) is necessary; experience administering a laboratory is preferred. Sub-specialty board eligible and/or certification is required.

Pediatric Cardiology has been an integral part of Driscoll Children's Hospital since 1962. The Hospital and the Heart Center are committed to bringing state-of-the-art technology and quality service to 31 counties in South Texas. In 2009, the Heart Center saw 9,500 outpatient and satellite visits and performed 3,569 echocardiograms (157 TEE and 116 Fetals). The Center has a thriving fetal echocardiogram service, and in 2010 we anticipate to perform 250 fetal studies. Driscoll Children's Hospital is associated with two pediatric cardiothoracic surgeons who deliver all aspects of surgical service including hybrid procedures.

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### **Pediatric Cardiologist**

The Department of Pediatrics at the University of Chicago is expanding its section of Pediatric Cardiology. We are currently recruiting a BC/BE pediatric cardiologist (open rank) as our director of the pediatric echocardiography laboratory. Preference will be given to candidates with a strong background in fetal echocardiography. Join us in our comprehensive efforts to expand our care of patients with congenital heart defects.

The successful candidate will have an M.D., or M.D./ Ph.D., and hold or be eligible for licensure in Illinois and Indiana. Candidates should be able to demonstrate excellent teaching skills. Academic appointment and salary will be commensurate with experience. Research opportunities are available for appropriately qualified candidates. The section has research opportunities in the field of interventional biodegradable stent development and cardiac morphogenesis as well as various clinical aspects of congenital heart disease. This position will have responsibility for teaching students, residents and fellows. Outpatient and inpatient venues are included.

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# SCAI Monthly Column - Plenty of Time to Make Plans to Attend SCAI 2011

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The year's program will feature an expanded *Congenital Heart Disease (CHD) Symposium* delivering three days of clinical trials, brain-teasing case studies, in-depth symposia, and plenty of information for cardiologists who treat congenital heart disease in pediatric and adult patients.

## Cardiovascular Thrombosis in Children

New to the *CHD Symposium at SCAI 2011* is a workshop on cardiovascular thrombosis in the pediatric patient. This problem accounts for many complications in infants and children who have long-term indwelling lines because of a serious illness, even those without CHD.

Pediatric interventionists are often called upon to take care of vessels that have clotted off in the cardiovascular system of sick children. A topic not seen at other meetings, this session will address: the clinical scenarios that increase the risk of clotting in children, the basic science that explains why pediatric patients may be predisposed to thrombosis, and transcatheter treatment options for acute and chronic thrombosis.

## Dr. John Cheatham to Deliver Mullins Lecture Focusing on Hybrid Procedures

John P. Cheatham, MD, FSCAI, knows a successful hybrid procedure when he sees one. In May he'll deliver the Mullins Lecture at the *SCAI 2011 Scientific Sessions*, exploring how hybrid procedures are flourishing in the treatment of congenital heart disease.

These procedures blend interventional cardiology and cardiothoracic surgery, creating a hybrid approach that — just as in the botanical world — is both stronger and more adaptable than what came before.

Dr. Cheatham, who directs cardiac catheterization and interventional therapy at Nationwide Children's Hospital in Columbus,

OH, traces his own introduction to hybrid procedures to 1999, when he and Mark Galantowicz, MD, now Chief of Cardiothoracic Surgery at Nationwide Children's, began working together to establish a new heart center in Orlando, FL. While the new cath lab was being built, all cardiac catheterization procedures were performed in the surgical suite.

Working in close proximity gave each physician a better appreciation for the strengths and obstacles of treating complex congenital heart disease with surgical and interventional techniques. Out of this mutual respect came the idea that it would be easier and perhaps improve patient outcomes to combine the scalpel with specialized catheters and devices — and sometimes avoid cardiopulmonary bypass altogether.

Initially, hybrid procedures focused on stage I palliation in babies with Hypoplastic Left Heart Syndrome. This involved surgical placement of left and right pulmonary artery bands through a median sternotomy, along with direct catheter access through the pulmonary artery to place a stent in the patent ductus arteriosus. Later, balloon atrial septostomy was added.

Over the years, many new hybrid procedures have evolved. These include a less traumatic way to treat large muscular ventricular septal defects, as well as techniques for the early recognition and treatment of significant vascular obstruction after congenital heart surgery. Today high-risk patients undergo "exit angiography" in the hybrid suite, immediately followed by pulmonary artery or aortic stenting if needed.

In addition to detailing the past and present, Cheatham will also preview what's still to come in the evolving realm of hybrid therapies. For more information on the Mullins Lecture and the *CHD Symposium*, please visit [www.scai.org/SCAI2011](http://www.scai.org/SCAI2011).

CCT



## Academic Interventional Cardiologist

The Division of Cardiology at Children's Hospital Los Angeles and the Keck School of Medicine at the University of Southern California is recruiting an individual with advanced experience in interventional cardiac catheterization techniques. This includes experience and certification in transcatheter valve implantation and extensive experience in hybrid catheterization-surgical procedures. The candidate must have a track record of academic success, participation in multi-center clinical trials as well as eligibility for NIH funding. The successful candidate will join a team of 2 highly-experienced interventional cardiologists and an established hybrid program.

The Division of Cardiology and Heart Institute at Children's Hospital Los Angeles include a 24 bed dedicated pediatric cardiac intensive care unit, a faculty and referral network of 36 pediatric cardiologists, 5 staff pediatric cardiac surgeons and a regional referral base of 12 million people. Two, dedicated full-time state of the art catheterization laboratories will commence operation in July 2011.

Academic appointment with the Keck School of Medicine of the University of Southern California and salary will be commensurate with experience. USC is an Equal Opportunity / Affirmative Action Employer.

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# Book Review: Illustrated Field Guide to Congenital Heart Disease and Repair, Third Edition

By John W. Moore, MD, MPH

Even if you have the First or Second Editions, take a serious look at the *Illustrated Field Guide to Congenital Heart Disease and Repair*. The Third Edition is now available, and it takes this useful guide to a new level!

The Third Edition improves on the previous editions with new chapters on Hybrid Procedures and Percutaneous Valve Implantation. Every chapter has been revised and up-dated, especially the ICU and the Pharmaceutical chapters. The art work, one of the Guide's strongest features, just gets better, with over one hundred new or modified diagrams and a more realistic style. Like earlier editions, the Third Edition is published by Scientific Software Solutions, Inc. in Charlottesville, Virginia. ([www.pedHeart.com](http://www.pedHeart.com))

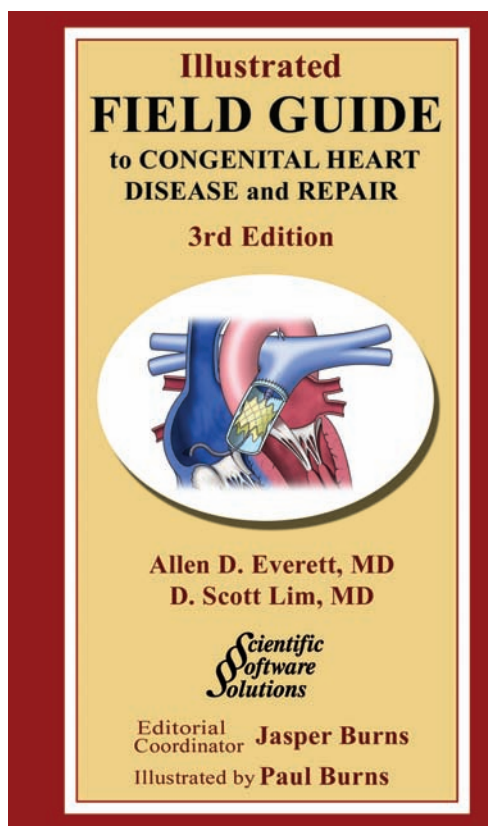
***"Like most of you reading this review, I remain 'in the field' most of my professional time. This Guide looks more useful than ever to me, so I plan to get the Third Edition for my lab coat pocket and some copies of the larger edition for the Rady Children's Hospital Cardiology Clinic."***

with large print and diagrams suitable for use in the office or clinic for education of patients and families, and for medical education. Both sizes are sturdy ring-bound paperbacks.

The *Illustrated Field Guide to Congenital Heart Disease and Repair*, Third Edition is highly versatile and fills several important educational niches. For patients and families, it is an excellent reference and an aid to their understanding of the heart defect and the clinical approach that cardiologists and surgeons are taking to treat it. For nurses, technologists, medical students, and residents, it provides easy-to-access essential educational material about congenital heart disease and clinical practice. This allows them to "get up to speed" with the clinical dialogue and treatment of patients they encounter in the clinic or on the ward, and to converse intelligently with cardiovascular physicians. For "adult" cardiologists, pediatricians, internists, and other practicing physicians; it provides a quick updated review of congenital heart defects and current clinical practice. This may be helpful in their general care of patients with congenital heart disease, and in communication with congenital cardiovascular specialists.

Like most of you reading this review, I remain "in the field" most of my professional time. This Guide looks more useful than ever to me, so I plan to get the Third Edition for my lab coat pocket and some copies of the larger edition for the Rady Children's Hospital Cardiology Clinic. I'm also thinking about giving a copy to our new fellows as they arrive for orientation.

**CCT**



The principle authors are Allen Everett and Scott Lim, and the illustrations are by Paul Burns. Contributing authors include the following: Marcia Buck, Jane Crosson, Howard Gutgesell, Luca Vricella, Stacie Peddy, Marshall Jacobs, David Cooper and Jeffrey Jacobs. There are ten chapters: The Normal and Fetal Heart, Congenital Heart Defects, Echocardiography, Catheterization Lab Interventions, Percutaneous Valve Insertion, Hybrid Therapies, Congenital Heart Surgeries, Cardiac ICU Topics, Electrophysiology, and Cardiac Pharmaceuticals. The chapters are quick reads and provide essential information, as well as many important details about congenital heart disease and clinical practice.

The drawings, illustrations and diagrams continue to be the single outstanding feature of the Field Guide! They are accurate, numerous, and attractive to view. They are well-labeled and simple to understand. Also, the colors reinforce the relevant cardiovascular physiology. The echo still-frames are relatively few, but of adequate quality; however, the few angiogram stills are low quality and need improvement.

The Field Guide continues to be available in pocket size, which fits easily in your lab coat pocket for use on rounds and quick reference on the run. It is also available in a larger size

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# Medical News, Products & Information

## Ground-Breaking Technology Will Revolutionize Blood Pressure Measurement for First Time in Over a Century

In a major scientific breakthrough, a new blood pressure measurement device is set to revolutionise the way patients' blood pressure is measured.

The new approach, invented by scientists at the University of Leicester and in Singapore, has the potential to enable doctors to treat their patients more effectively because it gives a more accurate reading than the current method used. It does this by measuring the pressure close to the heart – the central aortic systolic pressure or CASP.

Blood pressure is currently measured in the arm because it is convenient; however, this may not always accurately reflect what the pressure is in the larger arteries close to the heart.

The new technology uses a sensor on the wrist to record the pulse wave and then, using computerised mathematical modelling of the pulse wave, scientists are able to accurately read the pressure close to the heart. Patients who have tested the new device found it easier and more comfortable, as it can be worn like a watch.

Being able to measure blood pressure in the aorta which is closer to the heart and brain is important because this is where high blood pressure can cause damage. In addition, the pressure in the aorta can be quite different from that traditionally measured in the arm. The new technology will hopefully lead to better identification of those who will most likely benefit from treatment by identifying those who have a high central aortic systolic pressure value. This will be especially important for younger people in whom the pressure measured in the arm can sometimes be quite exaggerated compared to the pressure in the aorta.

A key question is whether measurement of central aortic pressure will become routine in clinical practice. Professor Williams said: "it is not going to replace what we do overnight but it is a big advance. Further work will define whether such measurements are preferred for

everybody or whether there is a more defined role in selective cases to better decide who needs treatment and who doesn't and whether the treatment is working optimally"

The University's close collaboration with the Singapore-based medical device company HealthSTATS International ("HealthSTATS") has led to the development of this world-first technique for more accurate blood pressure measurement.

The research work carried out by the University of Leicester was funded by the Department of Health's National Institute for Health Research (NIHR). The NIHR has invested £3.4million with a further £2.2 million capital funding from the Department of Health to establish a Biomedical Research Unit at Glenfield Hospital, Leicester, dedicated to translational research in cardiovascular research. The work, led by Professor Bryan Williams, Professor of Medicine at the University of Leicester and consultant physician at University Hospitals of Leicester NHS Trust, has the promise to change the way we measure blood pressure.

Professor Williams, who is based in the University of Leicester's Department of Cardiovascular Sciences at Glenfield Hospital, said, "I am under no illusion about the magnitude of the change this technique will bring about. It has been a fabulous scientific adventure to get to this point and it will change the way blood pressure has been monitored for more than a century. The beauty of all of this, is that it is difficult to argue against the proposition that the pressure near to your heart and brain is likely to be more relevant to your risk of stroke and heart disease than the pressure in your arm."

"Leicester is one of the UK's leading centres for cardiovascular research and is founded on the close working relationship between the University and the Hospitals which allows us to translate scientific research into patient care more efficiently. Key to our contribution to this work has been the support from the NIHR without which we would not have been able to contribute to this tremendous advance. The support of the NIHR has been invaluable in backing us to take this project from an idea to the bedside. Critical to the success of this project has been the

synergies of combining clinical academic work here with HealthSTATS and their outstanding medical technology platform in Singapore. This has been the game-changer and I really do think this is going to change clinical practice."

## Skin Cells Help to Develop Possible Heart Defect Treatment in First-of-its-kind Stanford Study

Using skin cells from young patients who have a severe genetic heart defect, Stanford University School of Medicine scientists have generated beating heart cells that carry the same genetic mutation. The newly created human heart cells - cardiomyocytes - allowed the researchers for the first time to examine and characterize the disorder at the cellular level.

In a study published online Feb. 9 in *Nature*, the investigators also report their identification of a promising drug to reverse the heart malfunction — for which there are currently no decent treatments — after using these newly created heart cells to check the effects of a plethora of compounds.

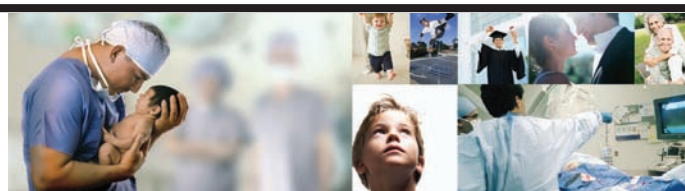
The new approach involved converting skin cells to heart cells in a dish by reprogramming them to an embryonic-stem-cell-like state, so that the cells are capable of "differentiating" into a multitude of cell types. The scientists then chemically coaxed these induced pluripotent stem cells to become heart cells. The iPS-cell approach represents a big advance because no good alternative methods for studying human heart malfunction at the cellular level now exist.

"This may be the first time this noninvasive 'disease-in-a-dish' technique has been used successfully to screen for drugs in heart disorders," said Ricardo Dolmetsch, PhD, Associate Professor of Neurobiology and senior author of the study. The study's first author is Masayuki Yazawa, PhD, a postdoctoral researcher in Dolmetsch's lab.

The human heart is a pump made of muscle and consisting of four compartments, or chambers: left and right ventricles and two corresponding atria. These chambers must contract in a coordinated sequence to ensure



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orderly blood flow. That coordination is mediated by electrical signals from cardiac nodes, which are to the heart's chambers what sparkplugs are to a car engine's pistons. In the aggregate, signals among heart cells generate electromagnetic waveforms that can be visualized on an electrocardiogram.

Nearly a dozen genetic mutations identified in humans are known to cause disruptions in this signaling pattern, resulting in a condition called Long QT Syndrome. (The name reflects an elongated interval between two portions of the waveform typically observed in an electrocardiogram.) People with LQTS suffer from arrhythmias, or irregular heartbeats, and are vulnerable to ventricular fibrillation, an often fatal state in which heart cells contract chaotically.

Genetically caused LQTS occurs in only about one in 7,000 people. But LQTS is also an all-too-common side effect of numerous approved drugs. It's the reason the popular painkiller Vioxx (rofecoxib) was removed from the market in December 2006, although it's not clear why.

For their *Nature* study, Dolmetsch and his colleagues turned to patients with Timothy Syndrome, one genetic mutation known to cause LQTS. Patients with Timothy Syndrome are highly susceptible to ventricular fibrillation and often die at an early age. Another hallmark feature of Timothy Syndrome is autism, which is the primary focus of Dolmetsch's research.

The defective gene in Timothy Syndrome encodes a protein called a calcium channel. This channel controls the flow across a cell's membrane of calcium, which is crucial to many cellular processes but is especially important in nerve cells, where it modulates electrical signals' propagation over long distances, and in muscle cells including heart cells, where it induces contractions.

Exactly why calcium-channel malfunction in Timothy Syndrome patients causes cardiac arrhythmia has not been known. One big reason research into both the causes of and treatments for LQTS in general has lagged is that it's hard to study heart cells, said Dolmetsch. "It would be dangerous and unethical to extract heart cells from a living person with or without cardiac disease," he said. In theory, the gene defect tied to Timothy Syndrome could be reproduced in a laboratory mouse, whose heart could then be studied. But in practice, this is a non-starter. While a healthy person's resting heart rate is about 60 beats per minute, a mouse's heart thumps at a rate of 500 times a minute, making the organ useless for analyzing timing deficits that afflict human hearts.

The study marks an exciting use of iPS cells, a relatively new technology that was first introduced in 2006. Dolmetsch and his associates reprogrammed skin cells from two Timothy Syndrome patients and five normal individuals first into iPS cells, then into cardiomyocytes. Three distinct varieties of cardiomyocytes — atrial, ventricular and nodal cells — were generated in this way from both diseased as well as normal subjects. The three cell subtypes spontaneously clumped into miniature heart-like organs resembling a one-chambered heart.

It was apparent that, in contrast to the average 60 beats per minute of the "miniature hearts" derived from normal subjects' skin cells, those of Timothy Syndrome patients beat at about a 30-per-minute rate and showed substantial irregularities. The investigators dissected these tiny

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organs into their constituent cells and showed that each was composed of atrial, ventricular and nodal cells.

Significantly, Dolmetsch's group found that in the Timothy Syndrome-derived ventricular cells, but not atrial or nodal cells, the calcium channels encoded by the mutant gene opened normally to allow calcium flow but stayed open longer than those of normal cells. With special dyes that mirror calcium concentrations, Dolmetsch and his team were able to visually inspect calcium flow in heart cells prepared from Timothy Syndrome patients' skin.

"We found that their ventricular cells, although not their atrial or nodal cells, had impaired calcium flow" compared with like cells from normal subjects, said Dolmetsch.

The investigators examined the response of these irregular-beating cells to different drugs that have been reported to affect heartbeat rhythms. When they added one of these drugs — roscovitine, currently in clinical trials for an unrelated indication — to the cell-culture medium at the right dose, the deficient calcium flow was restored, and so was the regular heartbeat.

Dolmetsch cautioned that at this point roscovitine should not be considered an adequate treatment for LQTS — it hasn't been tested for this purpose in living animals, let alone humans, and may have pronounced side effects. Still, he said, it's a promising compound for further drug development. Stanford's Office of Technology Licensing has applied for US patents related to the discovery, and Dolmetsch is starting a new company that intends to license those patents once they're granted.

The study was funded by the National Institutes of Health, the Simons Foundation, the Japan Society for the Promotion of Science, the American Heart Association Western States, and Mrs. Linda Miller, Ben and Felicia Horwitz and Mr. and Mrs. Michael McCaffrey. Other co-authors are Brian Hsueh and Xiaolin Jia, former undergraduate students in Dolmetsch's lab now at Princeton University and Baylor College, respectively; Jonathan Bernstein, MD, PhD, Clinical Assistant Professor of Pediatrics; and Joachim Hallmayer, MD, Associate Professor of Psychiatry and Behavioral Science.

## Drug Could Help Preserve Brain Function After Cardiac Arrest

Research published in the March 2nd issue of *The Journal of Neuroscience* showed an experimental drug that targets a brain system that controls inflammation might help preserve neurological function in people who survive sudden cardiac arrest, new research suggests.

Survival rates for sudden cardiac arrest are low, but recent medical advancements have improved the chances for recovery. Many people who do survive suffer a range of disorders that relate to neurological deficits caused by loss of blood flow to the brain when their heart stops.

The researchers, led by a team at Ohio State University, believe these neurological problems might relate to inflammation and brain-



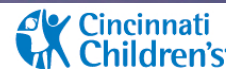
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cell death. The study revealed how the brain is damaged during cardiac arrest, as well as how a drug might counter those effects.

The scientists identified in a mouse model how the loss of blood in the brain sets off a process that attracts inflammatory compounds and kills brain cells. The study showed that these damaging effects were associated with alteration of the cholinergic system – an area of the brain that sends signals using the neurotransmitter acetylcholine to regulate inflammation.

Mice that were treated with an experimental drug called GTS-21, which activates acetylcholine, had lower levels of inflammatory chemicals and reduced damage to brain cells in the days following a surgically induced cardiac arrest and subsequent resuscitation.

"This is a drug that has been used safely in humans in clinical trials, so we think our findings have significant clinical potential," said Courtney DeVries, Professor of Neuroscience and Psychology at Ohio State University and senior author of the study. "Another very important aspect of the study is that the drug was not given until 24 hours after resuscitation, and yet it was successful at reversing inflammatory effects in the brain. So there would be a large therapeutic window of time if this could eventually be used clinically."

Cardiac arrest is not the same as a heart attack, which occurs when blood flow to the heart is interrupted. In sudden cardiac arrest, the heart's electrical system malfunctions and blood flow stops altogether. The American Heart Association estimates that fewer than 8% of people who suffer cardiac arrest in a home or community setting will survive, and that brain damage can occur within four to six minutes after the heart has stopped. Lasting effects of this brain damage can include physiological problems as well as memory loss and increased anxiety and depression.

In this study, the researchers surgically induced cardiac arrest in groups of anesthetized mice and then revived them eight minutes later using cardiopulmonary resuscitation. The scientists then analyzed brain tissue in mice three and seven days after the heart stoppage. Some mice received the drug beginning 24 hours after resuscitation, and some did not.

Within three days after the cardiac arrest, the untreated animals' brain tissue showed increased levels of immune cells in the central nervous system that indicate neurons are under attack. In addition, there were signs of high activity in the brain associated with the creation of compounds linked to inflammation. These compounds included tumor necrosis factor-alpha, interleukin-1 beta and interleukin-6 (IL-6) – all members of a family of proteins called cytokines, chemical messengers that cause inflammation, most often to fight infection or repair injury. When these proteins are circulating without an infection to fight, the body part hosting them – in this case, the brain – experiences excess inflammation.

By day seven after cardiac arrest, some untreated mice also had elevated levels of IL-6 in their bloodstream, a sign that excessive inflammation was present in other parts of the body.



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"The higher IL-6 levels in the blood are important, because this cytokine is also a marker of inflammation in humans," DeVries said.

The researchers also observed reduced activity levels of the enzyme that generates the neurotransmitter acetylcholine, suggesting that chemical signaling that protects the brain by regulating inflammation had been severely altered in mice that had experienced cardiac arrest.

"The cholinergic system is important for maintaining an appropriate balance between inflammation in the central nervous system and throughout the body," said DeVries, also an investigator in Ohio State's Institute for Behavioral Medicine Research. "Though the presence of cytokines can be beneficial in limited amounts, the huge inflammatory response in these mouse brains became detrimental to the survival of the neurons."

Twenty-four hours after cardiac arrest and resuscitation, some of the mice received daily treatments of the experimental drug GTS-21. This drug can reverse these signaling malfunctions and restore the anti-inflammatory properties of the cholinergic system.

Mice that received this treatment had lower levels of pro-inflammatory compounds in their brains three days later and fewer inflammation markers in their blood seven days later than did untreated mice. In addition, fewer brain cells died in these mice compared to mice that did not receive any treatment after cardiac arrest and resuscitation.

When the researchers simultaneously introduced a drug that can counter the GTS-21, the mice showed none of the improvements associated with the treatment.

"This confirmed for us that we were targeting the appropriate system to reduce inflammation in the brain," DeVries said. "Essentially, what we were trying to do is provide balance to the cholinergic system. GTS-21 replaced a signal that was missing,

which in turn reduced the inflammatory response to levels that are not as damaging to neurons."

DeVries also noted, however, that cardiac arrest disrupts the cholinergic signaling at multiple points. So restoration of one part of the system appears to reduce damaging effects on some, but not all, responses to the blood loss in the brain.

She also said her lab is continuing research in this area to further explore the link between inflammation in the brain that follows cardiac arrest and resulting neurological problems.

"The cognitive effects are one of the biggest patient concerns. If these symptoms are related to increased inflammation that occurs after cardiac arrest, this drug might have potential benefits that go far beyond control of inflammation; they might also help improve other symptoms," DeVries said.

GTS-21 is currently being tested by other researchers as a potential treatment for Alzheimer's Disease, schizophrenia and nicotine addiction. It can cross the blood-brain barrier, so it can be given intravenously.

This work was supported by the National Institute of Neurological Disorders and Stroke, the National Institutes of Health, the American Heart Association and the J. Parker and Kathryn Webb Dinius Fellowship at Ohio State.

Co-authors include: Greg Norman (now at the University of Chicago), John Morris, Holly Brothers and Gary Wenk of Ohio State's Department of Psychology; Kate Karelina, Zachary Weil and Ning Zhang of Ohio State's Department of Neuroscience; and Yousef Al-Abed, Valentin Pavlov and Kevin Tracey of the Feinstein Institute for Medical Research at North Shore-LIJ Health System in Manhasset, NY.

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  - Implications of Advanced Therapies & Interventions in ACHD patients with Pulmonary Hypertension.

### CONGENITAL CARDIOLOGY TODAY

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