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45th Annual Meeting of the Association of European Cardiology
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HCMA's 14th Annual Meeting
June 3-5, 2011; Florham Park, NJ USA
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2011 Toronto Cardiac Symposium
June 5-7, 2011; Toronto, ON Canada
<http://www.sickkids.ca/Centres/heart-centre/Cardiac-symposium>

ASE (American Society of Echocardiography) 22nd Annual Scientific Sessions
June 11-14, 2011; Montreal, Quebec Canada
<http://www.asecho.org>

9th Edition of the International Congress on Complications During Cardiovascular Intervention: Management & Prevention
June 15-17, 2011; Lausanne, Switzerland
<http://www.ecc-conference.com>

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Acute Management of Right Coronary Artery Dissection Following Transcatheter Occlusion of a Congenital Right Coronary Artery Fistula – Benefits of a Collaborative Congenital and Structural Heart Program

By Damien Kenny, MD; Clifford Kavinsky, MD, PhD and Ziyad M. Hijazi, MD, MPH

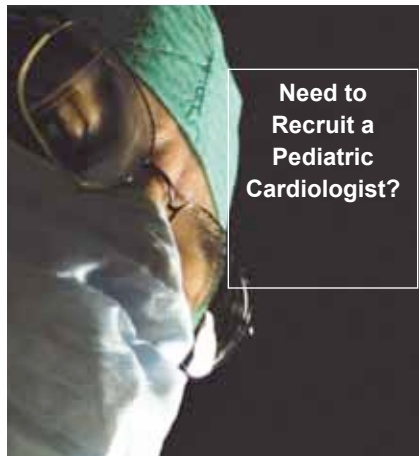
Abstract

This case report outlines acute coronary compromise secondary to dissection of the right coronary artery following transcatheter occlusion of a large proximal coronary artery fistula in a 43 year old female. We use this case to highlight the benefits of joint collaboration between adult and congenital interventional cardiologists in managing these patients.

Introduction

Congenital coronary artery fistulae (CAF) are rare with a reported incidence of approximately 0.5%.¹⁻² Most are small with no clinical implication and, indeed, some regress spontaneously;³ however, larger fistulae may lead to significant left-to-right shunting and symptoms in adult life. Older age at diagnosis and treatment has been associated with higher rates of mortality⁴ and, therefore, current strategies focus on early treatment following diagnosis irrespective of the presence of

symptoms. Prior to the initial description of percutaneous occlusion of a CAF in 1983,⁵ surgical management was the mainstay of treatment. Morbidity and mortality rates were not insignificant⁴ and longer term follow-up demonstrated significant distortion or occlusion of the distal coronary vessels demonstrated by coronary angiography.⁶ Since this time, numerous series describing transcatheter occlusion of CAF have been reported;⁷⁻¹¹ however, detailed longer term follow-up on these patients is sparse. A recent follow-up report of 76 patients over 50 years, demonstrated major complications in 15% of patients, the majority of these being myocardial infarction.⁷ A more recent report from Cleveland described myocardial infarction secondary to coronary thrombosis in 3 of 16 patients (19%) following both surgical and transcatheter closure.⁸ Both of these series did not carry out adequate serial imaging of the coronary arteries and it may be that more subtle abnormalities remain undetected. In both series, propagation of thrombus seems to have been the precipitant for myocardial ischemia; however, coronary artery compromise may occur secondary to the procedure itself. We describe a case of an asymptomatic 43 year old lady with a large fistula originating from the proximal right



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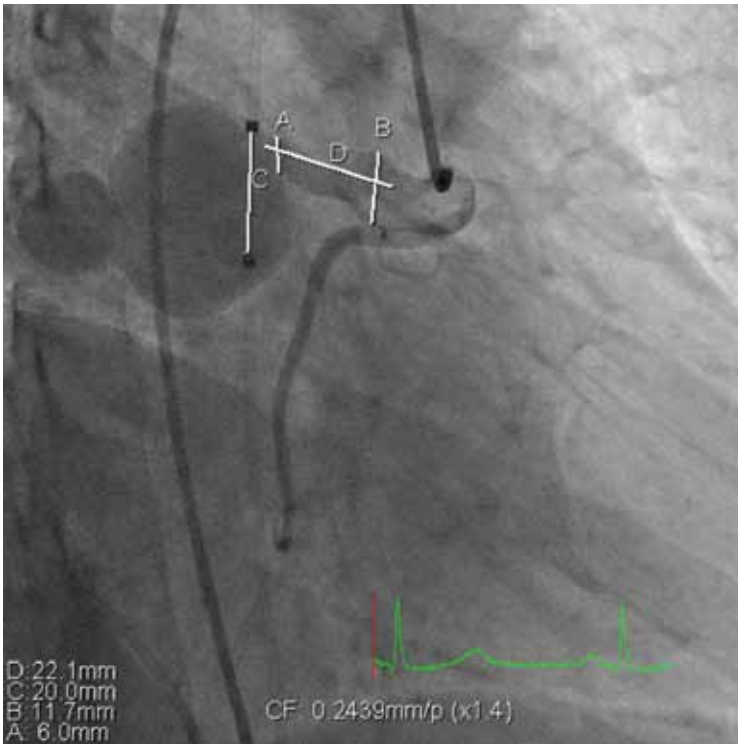
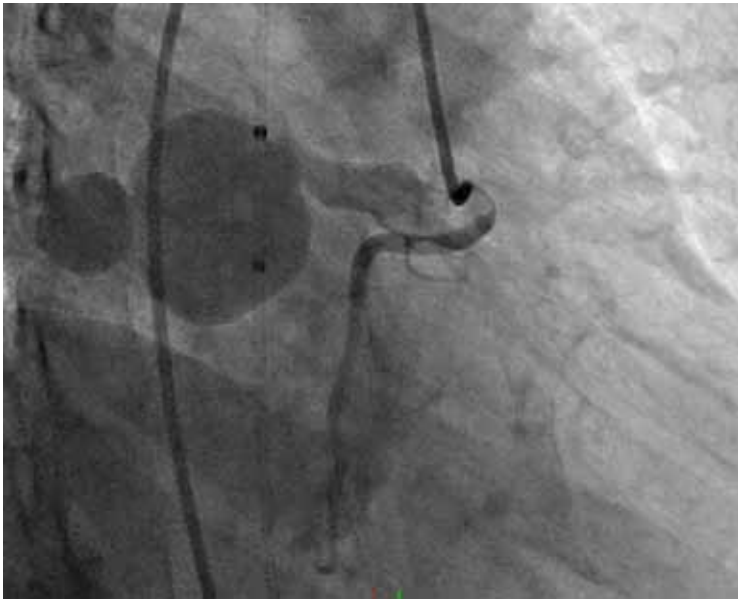


Figure 1 (a)-TOP: Selective right coronary artery angiogram demonstrates dilation of the proximal RCA with a large fistula originating from the proximal artery and evolving into a large bilobed aneurismal portion before draining to the right atrium. (b)-BOTTOM: Measurements confirm the proximal neck of the fistula to be 6mm.

coronary artery (RCA) and draining to the right atrium. Transcatheter occlusion was successfully achieved using a 6mm Amplatzer Muscular VSD Occluder. However, the patient required stenting of the RCA within hours of the initial procedure due to the occlusion secondary to a dissection flap in the RCA. This case highlights the potential for non-thrombotic coronary artery compromise in these cases and the benefits of strong collaboration between coronary and congenital interventionalists.

“Congenital coronary artery fistulae (CAF) are rare with a reported incidence of approximately 0.5%.¹⁻² Most are small with no clinical implication and, indeed, some regress spontaneously,³ however, larger fistulae may lead to significant left-to-right shunting and symptoms in adult life.”

Case Report

A 43 year old lady was referred to our center for consideration for transcatheter closure of a large RCA to right atrial congenital CAF. It was noted that on routine physical examination a number of months earlier, she had a continuous murmur audible along the right sternal border. Subsequent angiographic evaluation at the referring center revealed a large bilobed aneurismal fistula originating from the proximal RCA and draining to the right atrium (Figure 1a). The patient was asymptomatic, exercising regularly with no shortness of breath. The angiographic data were reviewed simultaneously by specialists in both congenital and coronary intervention as part of a collaborative program at our institution and a strategy for transcatheter occlusion was discussed.

Procedure

The procedure was performed in a biplane catheterization laboratory dedicated for congenital/structural interventions under general anesthesia. Following femoral venous and arterial access, the patient was fully heparinized and received IV antibiotics as per unit protocol. A diagnostic evaluation confirmed a significant left-to-right shunt with Qp:Qs of 1.8:1 with normal pulmonary artery pressures. Selective RCA angiography confirmed the findings of the original angiogram, with dilatation of the proximal RCA and a bilobed aneurysm of the fistulous tract which measured 22mm in length. The proximal “neck” of the aneurysm measured 6mm (Figure 1b) and this was identified as the optimal site to occlude the fistula so as to minimize the potential for thrombus formation. An 8 Fr Guide catheter was advanced retrograde from the right femoral artery and the origin of the fistula was engaged. At this point a 0.014” wire was advanced through the fistula into the right atrium. Consideration was given to snaring and exteriorizing the wire to create an arteriovenous loop;



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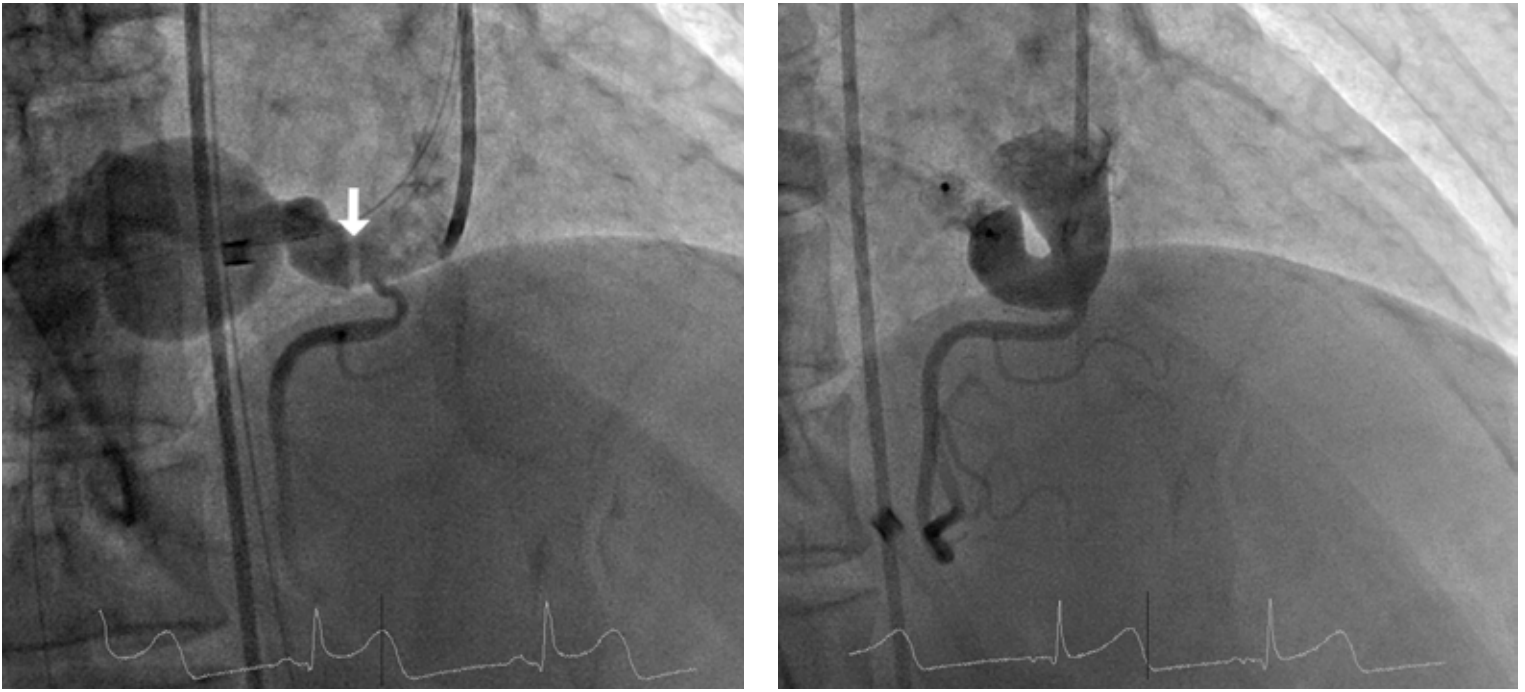


Figure 2 (a) LEFT: Angiogram of the RCA fistula following acute ST elevation on the accompanying single lead ECG recording. There is a proximal filling defect (white arrow) seen in the fistula with some attenuation of the proximal true RCA. (b) RIGHT: Following release of the Amplatzer Muscular Occluder, there is abolition of distal flow to the fistula. There is no persisting filling defect and the right coronary artery fills well. The ST segment elevation is resolving compared to that seen in Figure 2a.

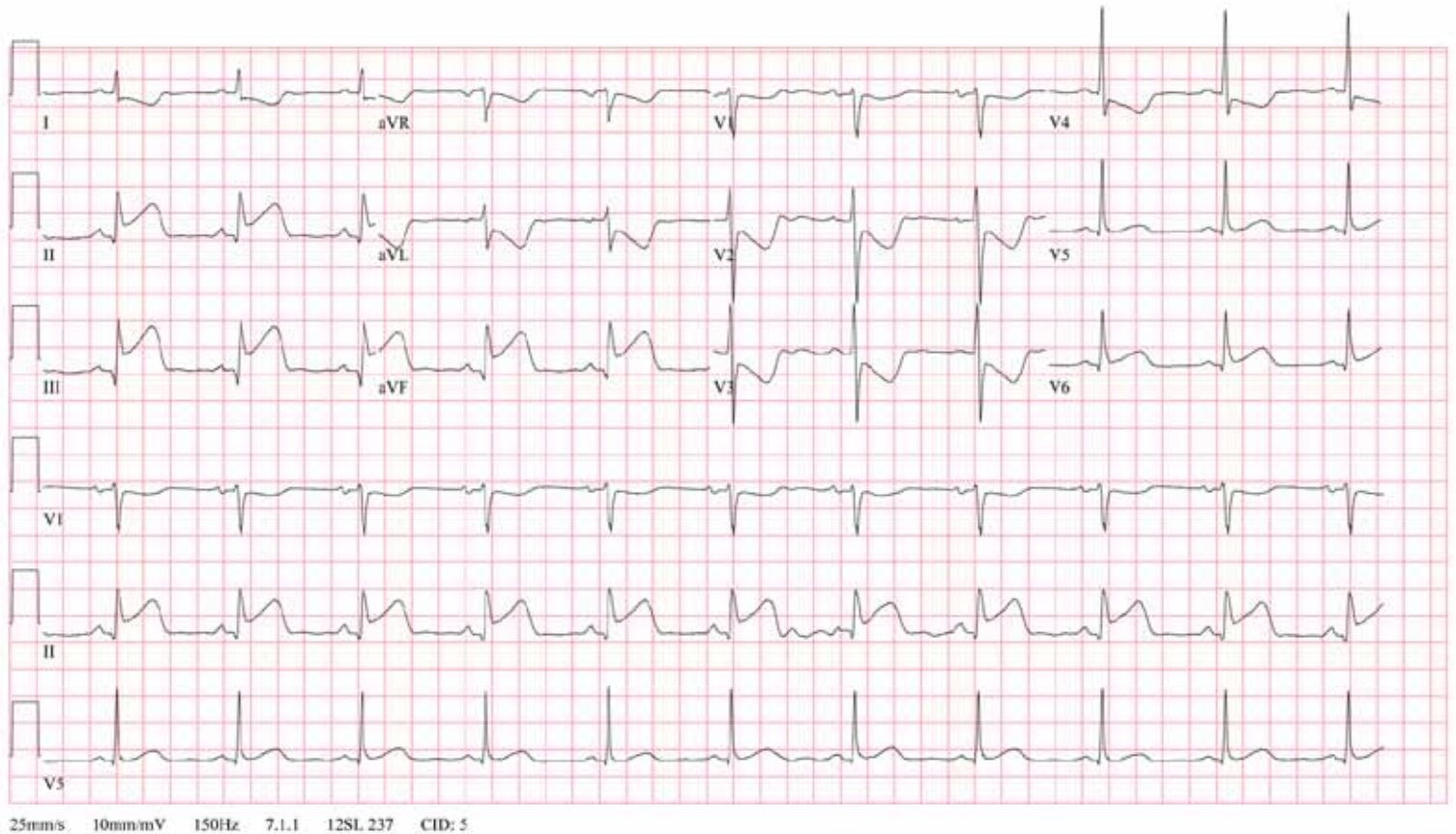


Figure 3. Electrocardiogram two hours following the procedure demonstrates significant ST segment elevation in the inferolateral leads (II, III and aVF) with T wave inversion in the mid precordial leads.

however, as the plan was to occlude the fistula proximally, it was decided to attempt to advance the Guide catheter to the ostium of the proximal aneurysm. Multiple attempts were made with varying wires to advance a suitable catheter from this retrograde approach; however, stable catheter position for delivery of an occlusion device could not be achieved. Thus, the aneurysm was recrossed with a 0.014" wire and snared in the pulmonary artery from the femoral vein to create an arteriovenous loop. An 8 Fr Mullins sheath was advanced over the wire and whilst attempting to enter the neck of the proximal aneurysm, the patient developed widespread ST segment elevation without hemodynamic compromise. Immediate angiography revealed a small filling defect just distal to the origin of the true RCA (Figure 2a) with no significant filling defect within the true RCA. Over the course of a few minutes, the ST segment elevation improved and repeat angiography demonstrated this filling defect was less prominent. Therefore, a 6mm Amplatzer Muscular VSD Occluder (AGA Medical, Plymouth, MN) was prepared and advanced through the long sheath with the coronary wire still in position to ensure access to the fistula was not compromised, and deployed in a good position across the neck of the aneurysm. Following release, angiography demonstrated the device in an optimal position with the proximal disk separated from the lumen of the true RCA, negligible residual leak and no residual filling defect in the fistula (Figure 2b). Groin hemostasis was achieved in the femoral artery using a Perclose device (Abbott Vascular, Abbott Park, IL) and the femoral vein using a figure-of-eight suture. Prior to transfer from the catheter laboratory, the ST segments had normalized. The patient was transferred to the coronary care unit, due to start a Heparin infusion later that evening as a bridge to Warfarin therapy due to previous experience with myocardial infarction in this setting secondary to propagation of clot from the blind end of the occluded fistula.¹² Elective electrocardiogram was also planned for two hours post procedure to confirm resolution of the abnormality seen during catheterization.

Post-Procedural Course

The patient recovered well from the procedure with no complaints of chest pain or shortness of breath. However, she complained about right arm numbness and weakness that was thought to be related to praxis of the brachial nerve plexus secondary to the protracted length of the procedure. An elective electrocardiogram was performed and demonstrated significant ST segment elevation in the inferolateral leads (Figure 3). The patient was asymptomatic, although it was unclear if residual opioids were masking chest discomfort; therefore, the patient was brought immediately to the adult coronary catheterization suite for coronary angiography. Initial selective RCA angiography demonstrated TIMI 1 flow with a possible dissection flap seen within the proximal RCA. (Figure 4a). There was no suggestion of propagation of clot from the proximal portion of the occluded fistula. The flap was crossed carefully with a 0.014" coronary wire and three bare metal coronary stents (Driver RX, Medtronic Inc, Fridley, MN) were implanted along the RCA with intravascular ultrasound assessment to ensure the flap was covered completely. Final angiography demonstrated excellent distal flow to the RCA with no residual filling defects noted (Figure 4b). The patient recovered well and, although an acute rise in cardiac enzymes was noted, this resolved and a transthoracic echocardiogram prior to discharge did not suggest any regional wall abnormality. Right arm function returned to normal prior to discharge two days later.

Discussion

This case highlights three important points in dealing with complex congenital cases:

1. The possibility of non thrombotic coronary artery compromise when attempting to occlude CAF via the retrograde approach.



Figure 4 (a) - TOP: Initial selective right coronary angiogram demonstrates two proximal circumferential filling defects within the RCA, with minimal distal flow. The ST segment elevation is again noted on the electrocardiogram. (b)-BOTTOM: Following stenting of the RCA with three bare metal stents, there is excellent recanalization of the RCA with return of complete distal perfusion and resolution of the ST segment elevation on ECG tracing.

2. The arguable benefits of joint collaboration between adult coronary and congenital interventionalists in treating patients with these conditions.
3. The importance of attention to brachial plexus neuropraxis when using biplane angiography in protracted cases.

“... this case highlights the procedural challenges in dealing with complex transcatheter coronary artery fistula occlusion. Complications in this setting may be difficult to avoid and, therefore, access to acute coronary intervention is recommended in centers treating these patients.”

To date, most cases of coronary compromise in the setting of either surgical or transcatheter occlusion of a congenital CAF have been attributed to coronary artery thrombosis.^{7,8,12} This case demonstrates that procedure-related damage to the coronaries may also occur. It is likely that advancement of the Mullins sheath (despite the guide wire rail) into the coronary artery fistula lead to the development of a small intimal flap at the junction of the fistula and the true RCA. This initially lead to ST segment elevation, but this resolved quickly with no evidence of persisting filling defect on the final angiogram. Early electrocardiogram may be prudent following these procedures, particularly when residual analgesia may mask symptoms. It is unclear if approaching the fistula from the venous side, thus avoiding engagement of the coronary artery, may have reduced potential for this complication; however, this would have involved distal placement of an occlusion device leaving a significant blind ending aneurismal pouch with high risk for thrombus formation. The pertinent point here is that early recognition within a center providing acute coronary intervention (by the coronary interventionalist involved in the initial case) lead to rapid appropriate treatment, and minimization of longer term myocardial damage. This approach provides the foundation of a congenital and structural program at our center ensuring patient benefit from the expertise of adult and congenital trained cardiologists. This collaboration is likely to become more beneficial in the future as transcatheter therapies continue to evolve with percutaneous valve implantation in younger patients with and without congenital heart disease. Indeed, until established guidelines for assessment of those training in the evolving field of structural heart disease are agreed upon,¹³ dissemination of knowledge and skills across the fields of adult and congenital interventional cardiology should be supported.

The last point worth commenting on in this case is the potential for brachial plexus injury because of prolonged fixed posture during anesthesia. Elevation of the arms is necessary for biplane imaging which is essential in these complex cases and reports in congenital cases have previously published.^{14,15} Fortunately, many deficits are superficial and permanent neurovascular deficits are rare but devastating, particularly considering this complication is avoidable. Since this case we have instigated a protocol for arm repositioning on an hourly basis in protracted

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“In conclusion, this case highlights the procedural challenges in dealing with complex transcatheter coronary artery fistula occlusion. Complications in this setting may be difficult to avoid and, therefore, access to acute coronary intervention is recommended in centers treating these patients.”

cases using biplane angiography with the hope that this may avoid such complications in the future.

In conclusion, this case highlights the procedural challenges in dealing with complex transcatheter coronary artery fistula occlusion. Complications in this setting may be difficult to avoid and, therefore, access to acute coronary intervention is recommended in centers treating these patients.

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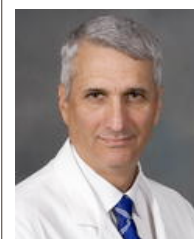
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SCAI Monthly Column - Help SCAI Improve Quality of Care, One Cath Lab at a Time

SCAI is inviting YOU to join the interventional cardiology community in tackling continuous quality improvement (CQI) in pediatric and adult cardiac cath labs. SCAI will launch its eagerly anticipated Quality Improvement Toolkit (SCAI QIT) on Thursday, May 5th, at SCAI 2011 Scientific Sessions in Baltimore, MD, will explain in detail several tools, including:

- Guidelines;
- Peer review conferences;
- Random case selection;
- National database participation;
- Pre-procedure checklists;
- Data collection; and
- Inventory management

The beauty of SCAI QIT is that it is flexible and can be customized for each user. Even better, you will lead the way at your own institution, using its practical tools to document your strengths, identify opportunities for improvement, and prepare for government-mandated "Pay-for-Quality" initiatives.

The QIT initiative is FREE and SCAI will be also be hosting a webinar this summer for those unable to attend SCAI 2011. To get updates on this webinar and to enlist as a Quality Champion at your facility simply visit www.SCAI.org/QIT.

Let's Get to Work on
QUALITY,
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Society Joins Patient Groups in Requesting Congress for Funding of CHD Research

SCAI has joined several Congenital Heart Disease (CHD) patient advocacy groups including Mended Little Hearts, Children's Heart Foundation, and March of Dimes in urging Congress to provide FY 2012 funding to conduct surveillance of CHD at the Centers for Disease Control and Prevention (CDC) and provide resources for research on CHD at the National Heart, Lung and Blood Institute (NHLBI).

The groups are requesting Congress to:

- Provide \$3 million in FY 2012 to the CDC to support data collection to better understand CHD prevalence and assess the public health impact of CHD. This level of funding will support a pilot adult surveillance system (\$1.75 million) and allow for the enhancement of the existing birth defects surveillance system (\$1.25 million).
- Support the NHLBI's efforts to expand research targeted to the diverse life-long needs of individuals living with CHD.

Find out more at www.SCAI.org/CHD.

Call for Unique CHD Angiogram Submissions

SCAI recently launched a "Special Interest Page" specific to interventional therapies for Congenital Heart Disease at www.SCAI.org/CHD and we need your help!

As part of this project being spearheaded by Makram R. Ebeid, MD, FSCAI, and Russel Hirsch, MD, FSCAI, SCAI is currently building a comprehensive library of angiograms of unique lesions (single ventricle, heterotaxy, pulmonary atresia, etc.). Have an interesting angiogram that might be a valuable resource for our community? Please send your images or AVI files, with a bit of background info, into us at egrammer@scai.org.

Remember to remove any personal identifiers. We'll be recognizing the very best images in an Interesting Image of the Week feature on the site.

SCAI Introduces New Education Program

"SCAI recently launched a "Special Interest Page" specific to interventional therapies for Congenital Heart Disease at www.SCAI.org/CHD and we need your help!"

Focusing on Structural Heart Disease

What do you get when you combine University of Miami's MIRS (*Masters in Repair of Structural Heart Disease*) and SCAI's MOTA (*Meeting of the Americas*) education meetings and hold both established programs jointly on Miami Beach? Answer: *M3 Intercontinental Cardiovascular Conference*, a unique combination of up-to-date information on structural heart, coronary and endovascular therapies.

With the active involvement of Latin American faculty, and participation from the Latin American professional societies, the content will be uniquely tailored to physicians focusing on adult congenital interventions from all over the Americas.

Taking place October 5th-7th at the Fontainebleau Miami Beach, and organized by Eduardo de Marchena, MD, FSCAI and Robert M. Bersin, MD, FSCAI, this program will feature focused presentations, interactive case discussions, and plenty of opportunities for one-on-one interactions – all designed to help attendees develop a clearer understanding of the latest techniques and advances in interventional therapies for structural heart disease.

To view the full agenda and learn more about registration, please visit www.SCAI.org/M3.

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Medical News, Products & Information

Study of 143,000 Children Shows Reference Heart Rate and Breathing Rate Ranges Differ Widely from Published Guidelines

A new analysis of 69 studies comprising some 143,000 children has produced new reference ranges that differ widely from existing published guidelines. The findings are in an article published in *Online First* by *The Lancet*. Existing guidelines should be updated, say the authors, led by Dr. Matthew Thompson, Oxford University, UK, and colleagues.

The researchers identified 69 studies with heart rate data for some 143,000 healthy children and respiratory rate data for almost 4000 children. Their new reference ranges (centile charts) show decline in respiratory rate from birth to early adolescence, with the steepest fall apparent in infants under 2 years of age; decreasing from a median of 44 breaths per min at birth to 26 breaths per min at 2 years.

Heart rate shows a small peak at age 1 month, and median heart rate increases from 127 beat/min. at birth to a maximum of 145 beats/min. at about 1 month, before decreasing to 113 beats/min. by 2 years of age. Comparison of the new centile charts with existing published reference ranges for heart rate and respiratory rate which are used for paediatric assessment and resuscitation show striking disagreements, with limits from published ranges often completely different. For children 10 years of age for example, the existing reference range classifies about half of healthy children as having an abnormal heart rate or respiratory rate.

The authors concluded, "Our centile charts of respiratory rate and heart rate in children provide new evidence-based reference ranges for these vital signs. We have shown that there is substantial disagreement between these reference ranges, and those currently cited in international paediatric guidelines. For clinical assessment of children, our findings suggest that current consensus-based reference ranges for heart rate and respiratory rate should be updated with new thresholds on the basis of our proposed centile charts, especially for those age groups where there are large differences between current ranges and our centile charts, indicating that many children are likely to be misclassified."

In a linked comment, Dr. Rosalind L. Smyth, Institute of Translational Medicine, University of Liverpool and Alder Hey Children's Hospital, Liverpool, UK, says that it is surprising the study does not include differences between sexes, in light of normal differences between the heart rates of women and men; she also cautions that other factors such as pain or distress (ie, factors not related to infection) can raise heart rate. She concludes, "These centile charts should initiate important new studies to establish where the clinical boundaries should be set for different ages, to assist clinicians to distinguish between normal and abnormal heart and respiratory rates. These studies will lead to revised algorithms, risk scores, and guidelines, which will incorporate these limits. Such instruments will then need to be extensively validated in different settings and populations before they can be incorporated into clinical practice."

Do All Student Athletes Need Heart Screenings?

Seemingly every year there are reports of a young, apparently healthy athlete dying on the court or playing field.

The sudden death of Wes Leonard, a junior at Fennville High School, who died of cardiac arrest from an enlarged heart on March 3rd, may have parents and coaches wondering if enough is being done to identify athletes at risk for dying suddenly.

"We would like to develop a better screening program to help prevent sudden cardiac death, but there is not enough rigorous data to support what that should look like," says Sanjaya Gupta, MD, clinical lecturer in the Division of Electrophysiology at the University of Michigan Health System.

Some communities have begun programs to perform more extensive heart testing, including electrocardiograms and sometimes echocardiograms on students before they compete. Yet, a task force organized by the American Heart Association to evaluate pre-participation screening practices has not supported such community programs due to a lack of evidence that they are able to reduce the number of sudden deaths.

A large trial recently completed in Israel concluded that mandatory ECG testing of

athletes prior to sports participation did not reduce the number of deaths from sudden cardiac arrests.

"One of the major obstacles to developing a better screening process is that no one heart test is the best," says Mark Russell, MD, a pediatric cardiologist at the University of Michigan's C.S. Mott Children's Hospital. "There are a number of different heart conditions that can cause sudden death in a young athlete."

"For some heart conditions, the ECG is the best test. For other heart problems, an echocardiogram is required," Russell says. "Unfortunately, both tests are usually normal in some individuals whose heart problem can only be diagnosed with an exercise stress test."

Furthermore, some conditions such as hypertrophic cardiomyopathy, a thickening of the heart, or dilated cardiomyopathy, the cause of death of the Fennville, Michigan teen, can develop over time. A single screening may not detect the condition.

As many as 10 to 12 million young athletes in the US participate in competitive athletics, identifying which of those athletes is at significant risk of sudden death is a bit like finding a needle in a haystack, doctors say.

How can you responsibly identify the student who is at risk without excluding thousands of other students from participating in sports?

The most important step may be to ensure that the screening process outlined by the AHA is being performed as recommended. The AHA recommendations require that the screening form document 12 specific aspects of the student's personal medical history, his/hers family medical history and a physical exam. If any concerns are identified based on the initial screen, then referral to a cardiologist is recommended.

Unfortunately, until very recently, the pre-participation screening form approved by the state of Michigan only covered five of the 12 topics recommended by the AHA. Russell and other colleagues from U-M were involved in updating the Michigan pre-participation physical form available from the Michigan Department of Community Health. The



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updated form conforms to the AHA guidelines and will help improve the screening process. Making sure that all Michigan schools, public and private, use the new forms and that the screenings are performed by physicians familiar with the guidelines is an important next step.

"Simply improving pre-participation screening forms and conducting electrocardiograms on properly selected children and adults may help reduce cardiac deaths," says Sharlene M. Day, MD, Director of the Hypertrophic Cardiomyopathy Clinic at the U-M Cardiovascular Center. "It is also very important for athletes, their families, and their coaches to recognize potential warning signs, like a seizure, passing out, or shortness of breath."

Yet there is still more that can be done to try to reduce the incidence of sudden cardiac death. U-M experts support having automated external defibrillators available in schools and training coaches and other school personnel on use and maintenance of the devices. Yearly training in basic life support or CPR for coaches and trainers will help them respond as quickly as possible in an emergency.

Emergency response training programs will have the added benefit of not only improving a school's ability to respond to an emergency that occurs on the sports field, but to any emergencies that occur on school property. It will also prepare individuals who will take their emergency response skills to their home and to their community.

Electronic Medical Records Improve Quality of Care in Resource-limited Countries

A new study, conducted by researchers from the Regenstrief Institute and the schools of medicine at Indiana University and Moi University, is one of the first to explore and demonstrate the impact of electronic record systems on quality of medical care in a developing country.

In a paper published in the March 2011 issue of the *Journal of the American Medical Informatics Association*, Martin Chieng Were, MD, MS, Assistant Professor of Medicine at the IU School of Medicine and a Regenstrief Institute investigator, and colleagues report that computer-generated reminders about overdue tests yielded nearly a 50% increase in the appropriate ordering of CD4 blood tests. CD4

counts are critical to monitoring the health of patients with HIV and guide treatment decisions. The research evaluating impact of just-in-time clinician support (implemented within electronic medical records) on health care provider behavior and quality of care was conducted in clinics in Eldoret, Kenya. The comparative study, which is one of the first to use computer-generated clinical reminders in sub-Saharan Africa, found that clinical summaries with computer-generated reminders significantly improved clinician adherence to CD4 testing guidelines.

This work is particularly significant because of the many medical errors that occur in settings where too few skilled healthcare providers deal with a large patient population with critical illnesses. In developed countries, patients with HIV are often seen by infectious disease specialists for their HIV care. In contrast, a large number of HIV-positive patients in resource-limited countries like Kenya are taken care of by clinical officers whose level of training is similar to that of nurse practitioners. The combination of overworked staff with limited training, increasingly busy clinics, the challenges of providing chronic disease management, and the difficulty of keeping up-to-date often results in suboptimal patient care.

"We need to improve quality of care in the developing world at a time when funding for HIV and other diseases is stagnating or decreasing - which means we will have to do it with fewer personnel as the number of patients increases. Finding innovative ways to improve care within these constraints is critical. This study shows how electronic medical record systems with clinical decision support capabilities can help fill this need," said Dr. Were. In a previous study, Dr. Were and colleagues reported on approaches that can be used to successfully implement computerized clinical decision support systems in resource-limited environments.

The Academic Model Providing Access to Healthcare (AMPATH) clinics in the study employ OpenMRS, an open source electronic medical record system widely used in the developing world. AMPATH, which cares for more than 120,000 HIV-infected adults and children at 25 main clinical sites in Western Kenya, is one of Africa's largest, most comprehensive and effective HIV/AIDS control systems.

This study was primarily supported by a grant from the Abbott Fund. The US Agency for

International Development, as part of the President's Emergency Plan for AIDS Relief (PEPFAR), provided partial support.

In addition to Dr. Were, co-authors of "The Evaluation of Computer-generated Reminders to Improve CD4 Laboratory Monitoring" are Changyu Shen, PhD, William M. Tierney, MD, Paul G. Biondich, MD, Xiaochun Li, PhD, and Burke W Mamlin, MD, all of the Regenstrief Institute and IU School of Medicine; Sylvester Kimaiyo, MB.ChB, M.Med. of Moi University School of Medicine and AMPATH; and Joseph J. Mamlin, MD of IU School of Medicine and AMPATH.

Drug Could Help Preserve Brain Function After Cardiac Arrest

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.

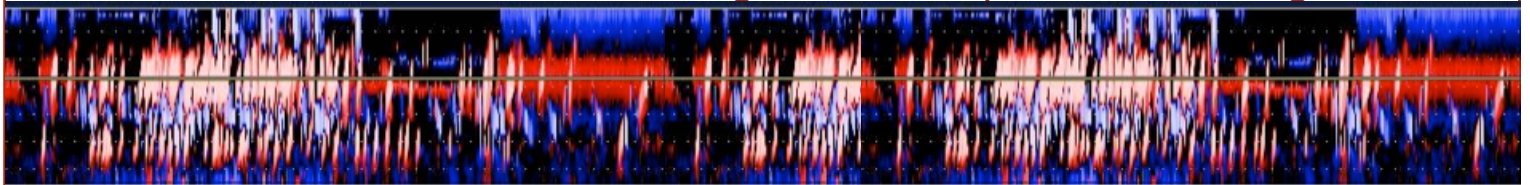
The researchers, led by a team at Ohio State University, believe these neurological problems might relate to inflammation and brain-cell death. The study revealed how the brain is damaged during cardiac arrest, as well as how a drug might counter those effects.

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

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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."

The research was published in the March 2nd issue of *The Journal of Neuroscience*.

In sudden cardiac arrest, the heart's electrical system malfunctions and blood flow stops altogether. The American Heart Association estimates that fewer than 8 percent 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.

"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.

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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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