CONGENITAL CARDIOLOGY TODAY

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

December 2014; Volume 12; Issue 12

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Upcoming Medical Meetings
(See website for additional meetings)

PCICS 10th International Conference
Dec. 11-14, 2014; Miami, FL USA
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ICI Meeting 2014
Dec. 14-16, 2014;Tel Aviv, Israel
http://2014.icimeeting.com

Multimodality Non-invasive Imaging for Diagnosis and Management of Failing Heart and Complex Congenital Heart
Jan. 10-11, 2015; New York, NY USA
New York, NY USA
Email: debbie.takamoto@mssm.edu

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Infected Pseudoaneurysm Following a Modified Blalock-Taussig Shunt

By Papa Salmane Ba, MD; Papa Adama Dieng, MD; Amadou Gabriel Ciss, MD; Etienne Birame Sene, MD; Souleymane Diatta, MD; Magaye Gaye, MD; Mohamed Lamine Fall, MD; Assane Ndiaye, MD; Mouhamadou Ndiaye, MD

Introduction

A pseudoaneurysm due to infection after a modified Blalock-Taussig (BT) shunt is a rare, but a potentially fatal complication.[1] It is frequently fatal and presents with desaturation, fever, mediastinal compression, or massive fatal hemoptysis.[2] In this report, we describe the management of an infected pseudoaneurysm in a 4-year-old child with Tetralogy of Fallot (TOF) who had undergone a modified BT shunt placement.

Case Report

A two-year-old-male infant with TOF underwent a left-sided modified BT shunt using a 6 mm, expanded polytetrafluoroethylene (Gore-Tex) graft through a left thoracotomy to improve the increased cyanosis and small pulmonary arteries. Twenty months later, he developed pneumonia and fever of unknown origin, all of which were treated in regional hospitals. On admission, he had a temperature of 38.9°C and was cyanotic, with a peripheral oxygen saturation of 86%. A physical examination revealed a systolic ejection murmur without a diastolic component at the left sternal border. The total leukocyte count was 16,000/µl, and the C-reactive protein level was 21.38 mg/l. A blood culture was negative. The chest X-ray showed an opacity in the left upper zone (Figure 1). High-resolution computed tomography scan of the chest showed a large pseudoaneurysm that measured 75 x 58 mm in diameter in the left upper lobe causing atelectesis of the underlying lung parenchyma with a shifting of mediastinum to the right. The BT shunt was completely occluded (Figure 2).

The patient was diagnosed with a chronic pseudoaneurysm due to an infection which

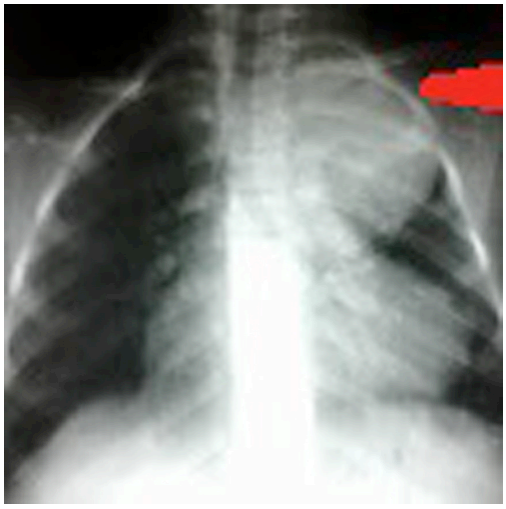

Figure 1. Chest radiogram showed left upper lobe opacity (arrow).

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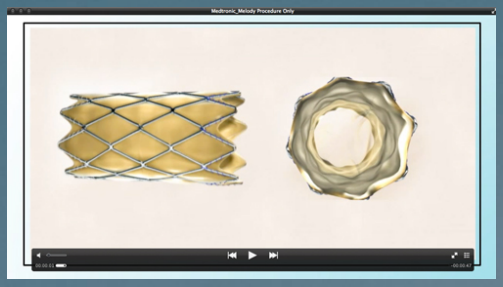

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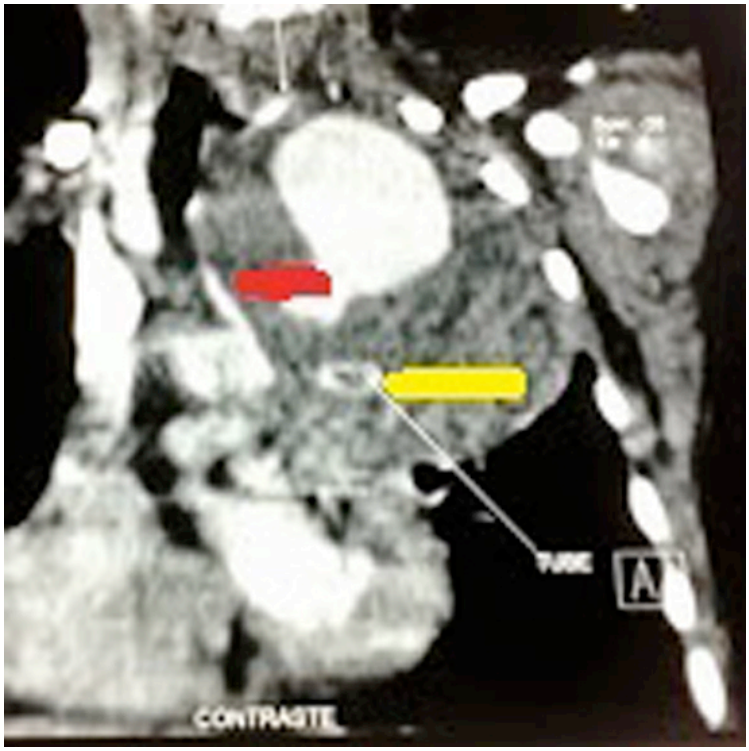

Figure 2. Contrast-enhanced chest CT demonstrating large pseudoaneurysm in the region of the right modified Blalock–Taussig shunt (yellow arrow), subclavian artery (red arrow).

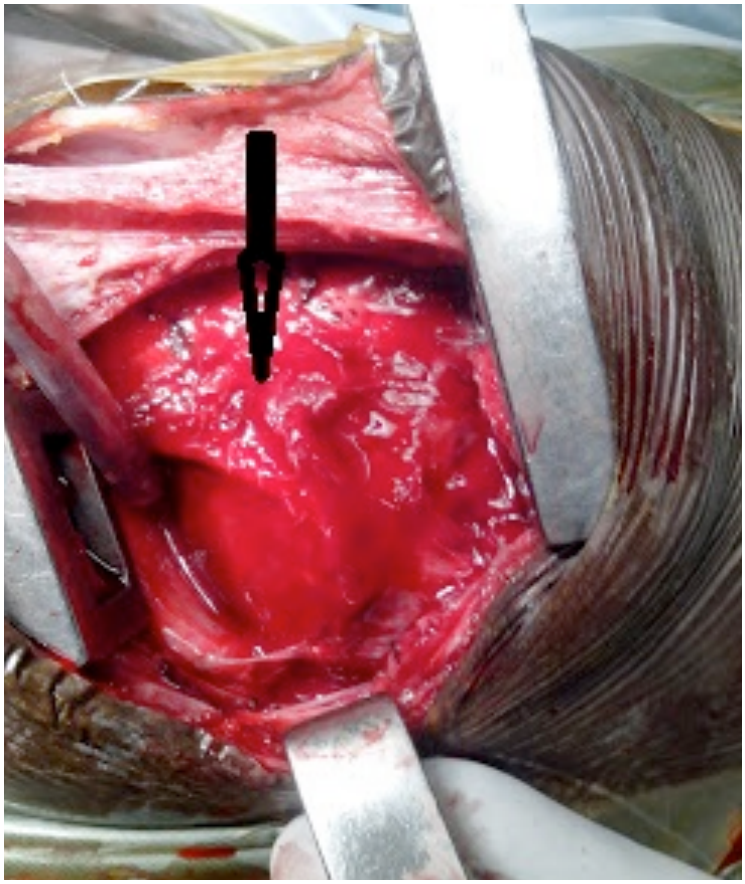

Figure 3. Intraoperative photograph of the pseudoaneurysm; large hematoma (arrow).

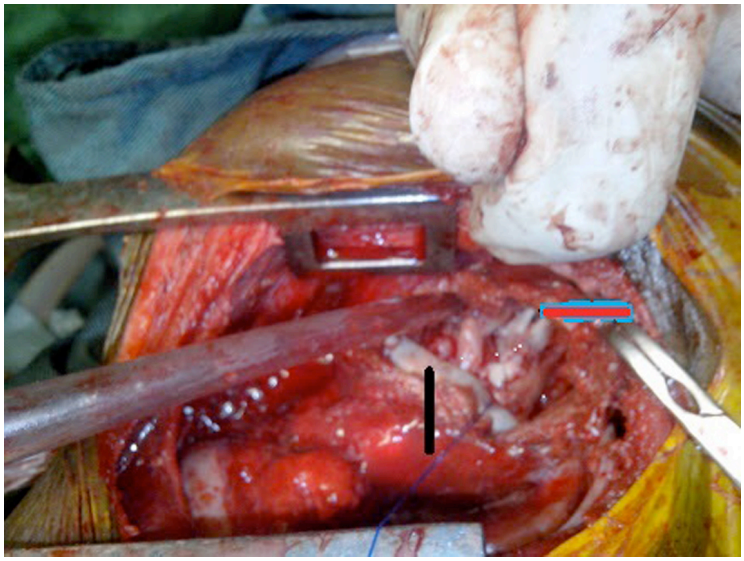

Figure 4. Intraoperative photograph of the infected pseudoaneurysm showing free floating tube (black arrow) and subclavian injury (red arrow).

occurred after a modified BT shunt. Intravenous antibiotic therapy with ceftriaxone, ampicillin and erythromicyne was continued for 20 days. During this 20-day period, repeated chest radiograms showed that the size of pseudoaneurysm had not change. Following the antibiotic therapy, the child was taken up for surgical resection of the pseudoaneurysm through a left thoracotomy approach. Intraoperatively, a pseudoaneurysm of the right subclavian artery was encountered, which was the result of an infectious dehiscence of the GORE-TEX® graft from the subclavian. The shunt was found to be completely occluded, and the distal end of the graft was totally free-floating (Figures 3, 4). However, the patient did not survive the procedure.

Discussion

The modified graft constructed from polytetrafluoroethylene effectively palliates children with Congenital Heart Disease (CHD) who have reduced pulmonary blood flow and, although it offers advantages over the classic Blalock-Taussig anastomosis, complications occasionally occur.[1] A pseudoaneurysm, after a modified BT shunt, may cause rupture or compression of mediastinal structures, collapse of underlying lung parenchyma, and shunt occlusion and bacteraemia. At first sight, our patient had classic presentations of common respiratory disease like Coren.[3] Such patients may be misdiagnosed and treated as pneumonia.[4] If the mass lesion of the chest radiogram had been detected at that time, further work-up, such as a CT-scan, would have been performed, and earlier surgery might be have been carried out.[5] Computed tomography can be a useful tool in assisting with diagnosis.[6] The infected graft and surrounding tissues were resected immediately to prevent rupture of the pseudoaneurysm and to control infection, together with construction of a new systemic-to-pulmonary artery shunt or a single-stage repair, depending on the condition of the patient.[7]

"A pseudoaneurysm, after a modified BT shunt, may cause rupture or compression of mediastinal structures, collapse of underlying lung parenchyma, and shunt occlusion and bacteraemia."

Conclusion

Placement of a modified Blalock-Taussig shunt is commonly used as palliative treatment for infants with Cyanotic Congenital Heart Disease. We present this unusual cases to alert clinicians to consider the possibility of a shunt-related pathology if such patients present with respiratory symptoms, particularly if there are ipsilateral signs clinically or on chest radiography. Computed tomography with intravenous contrast is a useful mode of investigation.

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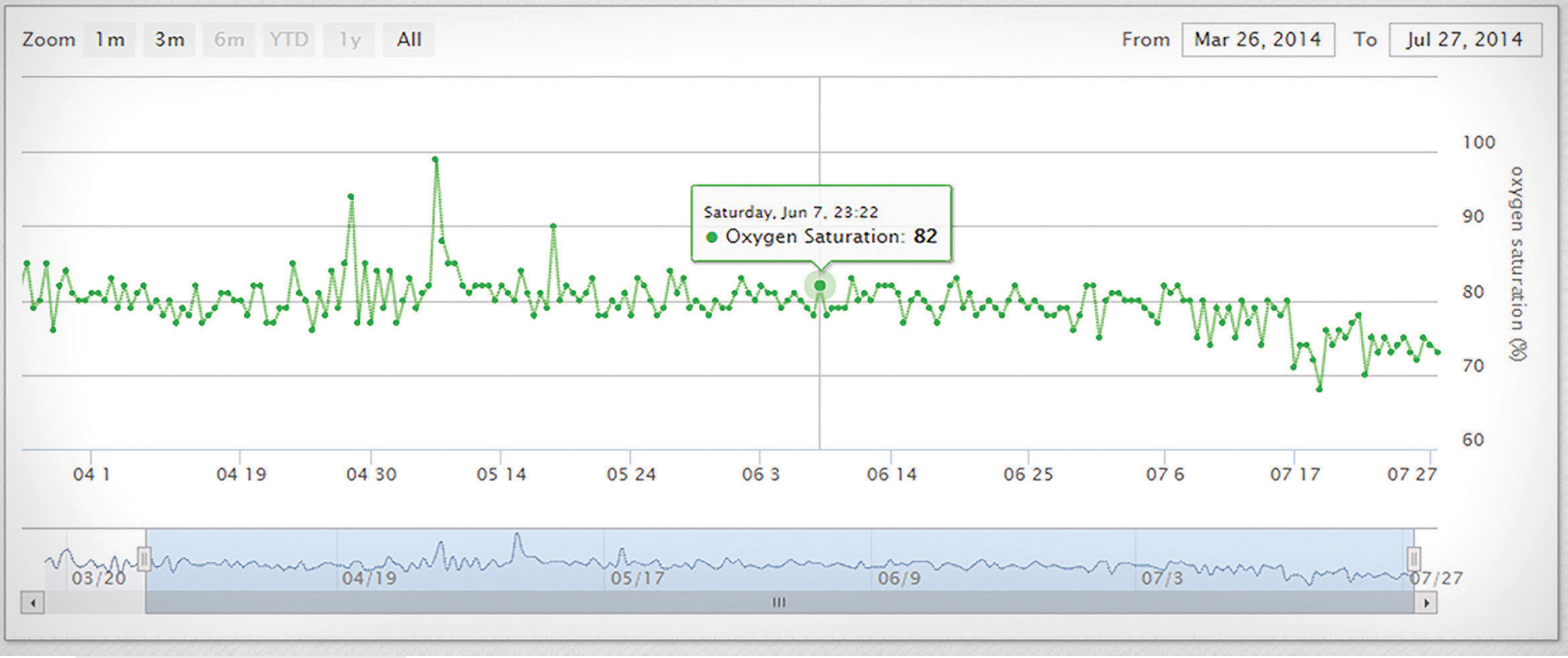

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China California Heart Watch Yunnan Province Pediatric Heart Training Program

By Tao Guo MD; Jia Hua Pan, MD; Fangqi Guo, MS; Shan Shan Chen; Song Yuan Tang, PhD; Yang Juan Bai, RN; Cheng Loh, MD; Robert Detrano, MD, PhD

Summary

Undiagnosed congenital cardiac shunt lesions with Pulmonary Hypertension and critical duct-dependent Congenital Heart Disease kill 3 to 4 of every thousand children born in developing countries. Most of these heart defects are curable if discovered early. We are conducting a training program for doctors responsible for the care of neonates and small infants in rural Yunnan Province, China. We are teaching the doctors proper cardiac examination of neonates and small infants. Though rural Yunnan is one of the poorest regions of China, both medical insurance options and financial assistance mechanisms are growing, and the level of medical care is continuously improving. The conditions for increased awareness and discovery of undiagnosed congenital heart cases are, therefore, ideal for addressing this problem in Yunnan Province. We plan to train all county hospital and most town hospital doctors who are responsible for the care of newborns and small infants to do proper cardiac examinations including pulse oximetry in the newborn, and stethoscope examination in newborns and infants less than one year of age. The present application addresses the problem of objective evaluation of our training project using the Kirkpatrick four-step model.

Project Aims

The aims of this project are to:

- Improve knowledge regarding the significance and detection of large shunt lesions and Critical Congenital Heart Disease (CCHD) in the newborn.
- Beneficially change behavior on the part of the trainee physicians and nurses.
- Increase case findings compared to a period immediately prior to the execution of the program.

Introduction

Mission of the China California Heart Watch

The mission of our organization is to teach, research and provide clinical care regarding Cardiovascular Disease in rural Yunnan province. Our major focus has turned toward pediatric congenital heart disease prevention, detection and treatment. During the past five years, we have screened over 90,000 school children for Congenital Heart Disease (CHD), and discovered approximately 500 cases. Of these, about 200 were amenable to interventional or surgical correction, and all have undergone or will soon undergo correction. Unfortunately, we have discovered approximately 50 cases (10%) with large shunt lesions and pulmonary hypertension, for whom surgical correction cannot be done because diagnoses were not made sufficiently early for effective life saving treatment.

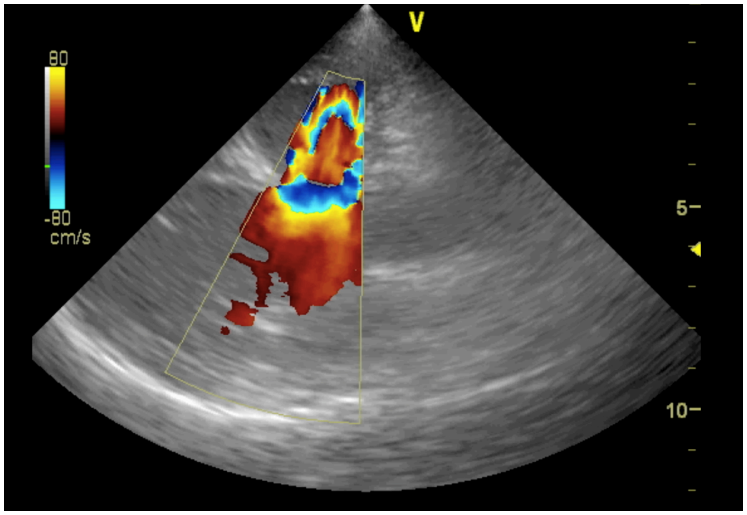
The Problems

Despite rapid advances in the level of rural Chinese pediatric cardiac care, two distinct problems remain to be solved.

- **Early Diagnosis of Shunt Lesions with Pulmonary Hypertension.** Failure to make sufficiently early diagnosis of significant shunt lesions that lead to pulmonary hypertension and deterioration of pulmonary vasculature.
- **Failure to Recognize and Treat the Critical Duct-Dependent Disease in the Newborn.**

1. Early Diagnosis of Shunt Lesions with Pulmonary Hypertension. Congenital Heart Diseases are the most common congenital anomalies and a leading cause of death in newborns and young children.[1] A high percentage of CHD lesions involve moderately restrictive or non-restrictive ventricular septal defects, patent ducti arteriosus and double outlet right ventricles, which result in gradual deterioration of the pulmonary arterial walls leading eventually to irreversible pulmonary vasculature disease and Eisenmenger's Syndrome.[2,3]

During five years of work in rural Yunnan province, we have found that medical personnel are not sufficiently trained to detect CHD in newborns. The result is that children with large ventricular septal or other defects go undetected and exhibit first symptoms between 5 and 15 years of age, when pulmonary artery pressure approaches systemic levels and symptoms of right-to-left shunting develop.[4] By this time, catheterization shows increased, irreversible pulmonary vascular resistance, indicating that it is too late for corrective surgery. These



Large peri-membranous ventricular septal defect with bi-directional shunting of blood in a cyanotic 14-year-old girl with high hematocrit and high pulmonary vascular resistance that was not reversible on 100% oxygen.

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BC/BE Pediatric Cardiac Electrophysiologist

The Carman and Ann Adams Department of Pediatrics at the Children's Hospital of Michigan, Wayne State University School of Medicine is recruiting a Board Certified/Board Eligible Pediatric Cardiac Electrophysiologist at the Assistant or Associate Professor level to join an established Electrophysiology program. IBHRE certification is strongly recommended but not required. The position will be available early 2015. Please circulate this to interested staff.

The successful applicant must be licensed/licensable to practice in the state of Michigan and will join the current senior Pediatric Electrophysiologist and dedicated EP nurse practitioner as well as 15 other cardiologists, 2 surgeons and 7 other mid-level providers in Detroit's largest cardiology and only Pediatric EP and cardiovascular surgical programs. The position includes providing invasive and non-invasive electrophysiology services, including inpatient and outpatient consultations, EP studies with 3D mapping and catheter ablations as well device implant and explant to both pediatric and adult congenital heart patients. Expertise in pacing/ICD lead extraction is strongly recommended. Some general cardiology duties as well as Resident/Fellow teaching are to be expected.

In addition to EP, the Division of Cardiology has established echocardiography, interventional, adult congenital, heart failure/transplant, pulmonary hypertension, as well as Cardiology Fellowship training programs. Drawing from a population of approximately 5 million people in Southeast Michigan, the division provides about 7500 outpatient visits, 700 cardiac catheterizations, and 110-130 EP/pacemaker procedures annually and is in the process of a major physical expansion. We currently actively follow 200 patients after pacemaker implantation and 55 patients with ICD's. Two congenital heart surgeons perform over 300 operations annually including heart transplant. Inpatient work is performed in Children's Hospital of Michigan, the only free-standing children's hospital in Michigan and the teaching hospital for Wayne State University. In addition, there are numerous opportunities for clinical, translational and basic science research. Salary will be commensurate with training and experience.

BC/BE Pediatric Cardiologist

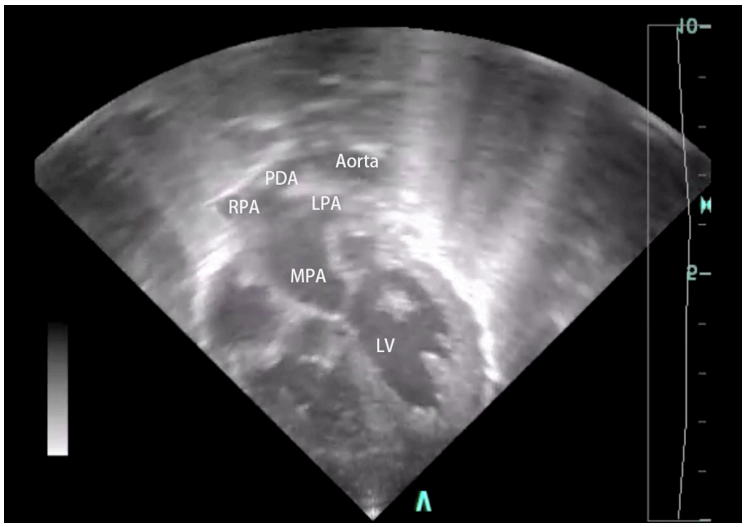
The Carman and Ann Adams Department of Pediatrics at the Children's Hospital of Michigan, Wayne State University School of Medicine is recruiting a Board Certified/Board Eligible Pediatric Cardiologist with expertise in cardiac non-invasive imaging at the Assistant or Associate Professor level to join an established non-invasive imaging program. The position will be available early 2015. Please circulate this to interested staff.

The successful applicant must be licensed/licensable to practice in the state of Michigan and will join 15 other pediatric cardiologists. Drawing from a population of approximately 5 million people in Southeast Michigan, the division provides about 7500 outpatient visits, 9000+ echocardiograms, 700 cardiac catheterizations, and 200+ cardiac MRI procedures annually. There is an active telemedicine program interpreting 1300+ echocardiograms at outside institutions. Two congenital heart surgeons perform over 300 operations annually including heart transplant. Inpatient work is performed in Children's Hospital of Michigan, the only free-standing children's hospital in Michigan and the teaching hospital for Wayne State University. In addition, there are numerous opportunities for clinical, translational and basic science research. Salary will be commensurate with training and experience.

The primary assignment will involve inpatient and outpatient consultations, performing/interpreting echocardiograms, TEE and fetal echocardiograms. Participation in the CMR service is dependent upon experience and interest. Some general cardiology duties as well as Resident/Fellow teaching are to be expected.

Interested candidates for either position should send a curriculum vitae with a cover letter of introduction to:

Dr. Richard A. Humes, MD,
Chief, Division of Cardiology
Children's Hospital of Michigan
3901 Beaubien Blvd.
Detroit, MI 48201-2119
Tel: 313-745-5956
email: rhumes@dmc.org



21-day-old male infant with transposition of the great vessels. Baby underwent successful arterial switch operation.

Trainee doctor contemplates infant with abnormal pulse oximetry reading.

patients die in young adulthood. Newborn and infant screening can prevent this tragic scenario. Screening would require adequate examination with a standard stethoscope and pulse oximetry at birth, followed by a thorough stethoscope examination at one to six months of age. Our purpose is to develop a method for local doctors to make educated decisions regarding further examination. This method can be applied in other developing countries, which do not have sufficiently trained local personnel to accurately diagnose infantile CHD.

2. Critical Duct-Dependent Disease of the Newborn. About one to two per 1000 newborn babies have CCHD, which is defined as disease that causes death or needs invasive intervention in the neonatal period. Neonates with this disease benefit most from early detection.[5] During the past few years, several studies have supported the addition of pulse oximetry to routine clinical assessment as a

Professor Jia Hua Pan lectures to rural doctors on the importance of detecting large cardia shunt lesions and Critical Congenital Heart Disease in newborns.

complementary method for detection of CCHD.[6–11] It is important to note that one of the largest and perhaps the best evaluation of this technology was done in China.[2] These investigators screened 6,785 consecutive newborn babies using pulse oximetry and clinical assessment at birth. They found that pulse oximetry plus clinical assessment is feasible and reliable for the detection of major congenital heart disease in newborn babies in China. They recommended that this simple and accurate combined method should be used in maternity hospitals throughout China to screen for CHD.

Preliminary Work

We executed a pilot program in Hong He Prefecture, Yunnan Province, to train local physicians, who attend at births, on the proper use of a common stethoscope for screening neonates. We chose Hong He because 80% of all babies there are born in county hospitals, which is a trend in rural Yunnan.

During this preliminary pilot program in Hong He Prefecture, we first assessed 73 county obstetricians who attend at births in their cardiac examination of neonates using a checklist completed by a cardiac nurse at the bedside. The results of this assessment are in Table 1. Note that most of the county doctors attempted some kind of cardiac examination, though only 20 of the 73 performed a four-point cardiac exam and measured heart rate. None of the hospitals had pulse oximetry available.

At the end of the assessment we trained the doctors to:

- Properly use of a standard stethoscope;
- Do complete full physical examination on all neonates.
- Refer all babies with suspected heart murmurs for echocardiograph.

The Hong He prefecture health department supported this work. This preliminary evaluation proves the feasibility of this type of training.

Table 1. Pre Training Cardiac Exams in Hong He Prefecture

No Cardiac	1 auscul	2 auscul	3 auscul	4 auscul	Heart Rate	Blood Pressure	Pulse Ox
exam	point	points	points	points			
2	25	20	6	20	36	0	0

Knowledge Assessment Before and After Training

A second preliminary training trip was made to De Hong Prefecture in the southwest corner of Yunnan Province. Four Kunming doctors travelled to Dehong for a period of one week. One hundred ninety-five local doctors were assembled in three locations. Both practical training and didactic lectures were given in each place. Student doctors were tested before and after didactic lecture, using 38 questions (multiple choice and true/false). Questions covered topics ranging from proper stethoscope placement to proper presentation of abnormal results to families.

Scores before and after listening to lectures are presented in Table 2.

Table 2. Before and After Training Scores on 38 Question Exam Administered to Trainees in De Hong Prefecture

	N	Lowest Score	Highest Score	Mean Score	SD Score	Passed Exam	T	P
Before	195	6	38	21.8	6.54484	33.7%	-11.311	<0.001
After	169	14	45	29.8	6.83372	66.3%		

Work Plan

We have established a training school centered in Yunnan Province capital Kunming city with a five person Directors' Committee consisting of a School Director, a public health expert, a cardiologist, a nurse, and an administrator. We have trained rural doctors in two prefectures, and in the coming months plan to train in a third prefecture.

This committee has the following responsibilities:

1. Arrange with the Yunnan Department of Health and the prefecture departments of health for the training sessions and supervision of rural doctors regarding the proper cardiac examination of newborns and infants, including stethoscope exam, heart rate measurement and pulse oximetry in neonates and stethoscope examination in both neonates and infants at 3 to 6 months of age.
2. Train 6 to 12 Kunming cardiologists and pediatricians regarding who will, in turn, train local rural doctors responsible for the care of neonates and infants how to properly examine their patients at birth and again before the sixth month of life.
3. Assess effectiveness of training with repeat visits to county and town hospitals to assess case findings assuming that incidence of CHD is at least 4 per thousand.

Learning Objectives

The objectives of this training program are:

1. Trainees (physicians responsible for care of newborns and young infants) should understand the pathophysiology of large cardiac shunt lesions and pulmonary hypertension.
2. Trainees should understand the pathophysiology of Critical Duct-Dependent Congenital Heart Disease.
3. Trainees should have simple stethoscopes.
4. Trainees should be able to distinguish neonates and infants with and without heart murmurs.
5. Trainees, working in county hospitals, should have access to high quality pulse-oximetry, available near or in delivery rooms and neonatal ward units.
6. Trainees working in county hospitals, should demonstrate proficiency in the use of high quality pulse-oximeters.
7. Trainees working in county hospitals, should recommend immediate echocardiography examination within 24 hours before discharge for neonates / young infants who have failed the pulse oximetry and clinical examination screening.
8. Trainees, working in county hospitals, should be able to explain to parents the purpose of screening, the meaning of a pass / fail result, and provide parents information regarding referral centers in Kunming.

Evaluation and Assessment

Evaluation of the training program will utilize the Donald Kirkpatrick Four Step Evaluation Model.[13,14]

The four-steps of evaluation consist of:

- **Step 1: Reaction** - How well did the learners like the learning process?
- **Step 2: Learning** - What did they learn?
- **Step 3: Behavior Modification** - What changes in job performance resulted from the learning process?
- **Step 4: Results** - What are the tangible results of the learning process in terms of case findings and treatments?

Step 1. Reaction

Immediately after each training session, a five-question questionnaire will be administered to all trainees.

The questionnaire will consist of the following questions:

- Was the training worth your time?
- Was the training successful?
- What were the greatest strengths of the training and the greatest weaknesses?
- Did you like the presentation style?

Step 2. Learning

Learning will be assessed using structured quizzes administered at the end of each training session and with assessment of behavior modification by a graduate student led team of research personnel between three and six months following the training sessions.

Quizzes are administered before and after the training and will cover the following subjects:

1. Pathophysiology and clinical prognosis of untreated shunt lesions with pulmonary hypertension.
2. Potential treatment options for patients with untreated shunt lesions with pulmonary hypertensions.
3. Pathophysiology and clinical prognosis of untreated critical duct dependent lesions.
4. Potential treatment options for patients with untreated critical duct dependent lesions.
5. Assessment of proficiency in distinguishing normal from abnormal heart sounds.
6. Assessment of proficiency in the performance of pulse oximetry examinations.
7. Proficiency in explaining to families the reasons for screening.
8. Proficiency in explaining to families the nature of CHD and the possibility for treatment.

Step 3. Behavior Modification

Behavior modification will be assessed by a team consisting of a graduate student and a team of research personnel on the county hospital level.

The team will use a checklist method to assess the behavior of the trainees before and three to six months after the training.

The Masimo Corporation of Irvine, California has donated 125 Rad-5 SET pulse oximeters to this research. These devices are being distributed to each of the 125 rural county hospitals in Yunnan Province. We will be using a protocol similar to that of Granelli et al and Zhao et al to assess foot and hand blood oxygen saturation.[12,16]

These devices have an internal memory that retains the pulse oximetry results. Local county hospital personnel will be given instruction in the use these devices and how to download measurement results to a local computer and send these results to personnel at Kunming Medical University and to the University of California, Irvine. The graduate students will analyze completeness of measurement by comparing the number of properly recorded pulse oximetry results with the number of newborns at the respective hospitals.

Step 4. Results

Concrete results of the training will be newly discovered cases of CHD, shunt lesions and CCHD.

Additional results of the training will be the increase in provincial rural children undergoing surgery for CHD as assessed by the Yunnan Department of Health.

Statistics on the known cases of CHD and the number of surgeries will be obtained from the local county health department records in the year 2013 before training began. These will be compared with the cases found in 2016 after the completion of training.

Power Calculation for Case Finding

If the 2013 incidence of heart disease is 5 cases per thousand live births and if there are 200,000 live births in a province, and we require that our training program increases case finding by 2% to an incidence of 7%, our training program would have a power of 99% to find such a 2% increase.

If we evaluate only 10,000 of the babies born in counties where we train, then the power to find a 2% increase in incidence would 77%.

Here we are using the one-sample binomial test with the typical normal approximation.[16]

Conclusion

As treatment facilities increase in number in developing areas of China and the world, such a training model will become more relevant. Our program can thus, serve as a model for other underdeveloped areas in China and other developing nations. The China Cal board of directors contains members who are consultants to the Chinese Ministry of Health. They will ensure that the results of our training program are utilized to give thousands of infants a chance for healthy and productive lives.

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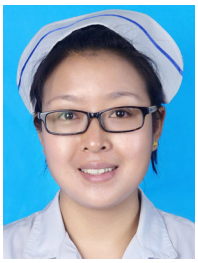

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Letters to the Editor

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Medical News, Products & Information

By Tony Carlson, Senior Editor, CCT

Novel Protein in Heart Muscle Linked to Cardiac Short-Circuiting and Sudden Cardiac Deaths

Cardiovascular scientists at NYU Langone Medical Center have identified in mouse models a protein known as Pcp4 as a regulator of the heart's rhythm. Additionally, when the Pcp4 gene is disrupted, it can cause ventricular arrhythmias.

Results from this animal study were released online Oct. 8th in the peer-reviewed publication, *The Journal of Clinical Investigation.*

"This study demonstrates that Purkinje cell protein-4 (Pcp4) is not only important in maintaining the heart's normal rhythmic behavior, but that when Pcp4 expression is reduced, it short-circuits electrical activity in a small but critical population of cells in the heart muscle, leading to cardiac arrhythmias," said Glenn I. Fishman, MD, William Goldring, Professor of Medicine and Director of the Leon H. Charney, Division of Cardiology at NYU Langone, and the study's senior author. "We see increased morbidity and mortality when Pcp4 expression is abnormal in our animal models, including ventricular arrhythmias and sudden cardiac death."

Using mouse models of cardiomyopathy and fluorescent tags, the research team was able to isolate cardiac Purkinje cells and show that Pcp4 expression was down-regulated in the diseased hearts, producing electrical abnormalities that increased their susceptibility to arrhythmias. Investigators also found Pcp4 in cardiac ganglia, where it also influences the heart's rhythm and modulates heart rate control. "Now that we know that Pcp4 is an important regulator of the heart's rhythm, it could serve as an important drug target for treating arrhythmias," added Dr. Fishman. "Although much work remains to be done, our data suggest that drugs that mimic Pcp4's action in the heart could potentially stabilize the heart's rhythm."

According to the American Heart Association, an estimated 2.7 million Americans are living with arrhythmias. People with arrhythmias can be treated with a surgical procedure, such as getting a pacemaker, implantable defibrillator or a cardiac ablation, or by delivering a shock with external defibrillators. Ablations are effective but limited to specific types of rhythm abnormalities. Drug therapies have fallen out of favor because of side effects. The NYU Langone research team believes that with better understanding of the molecular behavior underpinning arrhythmias, more targeted drugs are on the horizon.

A Heartbeat Away? Hybrid 'Patch' Could Replace Transplants

Because heart cells cannot multiply and cardiac muscles contain few stem cells, heart tissue is unable to repair itself after a heart attack. Now Tel Aviv University researchers are literally setting a new gold standard in cardiac tissue engineering.

Dr. Tal Dvir and his graduate student Michal Shevach of TAU's Department of Biotechnology, Department of Materials Science and Engineering, and Center for Nanoscience and Nanotechnology, have been developing sophisticated micro- and nanotechnological tools — ranging in size from one millionth to one billionth of a meter — to develop functional substitutes for damaged heart tissues. Searching for innovative methods to restore heart function, especially cardiac "patches" that could be transplanted into the body to replace damaged heart tissue, Dr. Dvir literally struck gold. He and his team discovered that gold particles are able to increase the conductivity of biomaterials.
In a study published by Nano Letters, Dr. Dvir's team presented their model for a superior hybrid cardiac patch, which incorporates biomaterial harvested from patients and gold nanoparticles. "Our goal was twofold," said Dr. Dvir. "To engineer tissue that would not trigger an immune response in the patient, and to fabricate a functional patch not beset by signalling or conductivity problems."

A scaffold for heart cells

Cardiac tissue is engineered by allowing cells, taken from the patient or other sources, to grow on a three-dimensional scaffold, similar to the collagen grid that naturally supports the cells in the heart. Over time, the cells come together to form a tissue that generates its own electrical impulses and expands and contracts spontaneously. The tissue can then be surgically implanted as a patch to replace damaged tissue and improve heart function in patients.

According to Dr. Dvir, recent efforts in the scientific world focus on the use of scaffolds from pig hearts to supply the collagen grid, called the extracellular matrix, with the goal of implanting them in human patients. However, due to residual remnants of antigens such as sugar or other molecules, the human patients' immune cells are likely to attack the animal matrix.

In order to address this immunogenic response, Dr. Dvir's group suggested a new approach: fatty tissue from a patient's own stomach could be easily and quickly harvested, its cells efficiently removed, and the remaining matrix preserved. This scaffold does not provoke an immune response.

Using gold to create a cardiac network

The second dilemma, to establish functional network signals, was complicated by the use of the human extracellular matrix. "Engineered patches do not establish connections immediately," said Dr. Dvir. "Biomaterial harvested for a matrix tends to be insulating and thus disruptive to network signals."

At his Laboratory for Tissue Engineering and Regenerative Medicine, Dr. Dvir explored the integration of gold nanoparticles into cardiac tissue to optimize electrical signaling between cells. "To address our electrical signaling problem, we deposited gold nanoparticles on the surface of our patient-harvested matrix, 'decorating' the biomaterial with conductors," said Dr. Dvir. "The result was that the nonimmunogenic hybrid patch contracted nicely due to the nanoparticles, transferring electrical signals much faster and more efficiently than non-modified scaffolds."

Preliminary test results of the hybrid patch in animals have been positive. "We now have to prove that these autologous hybrid cardiac patches improve heart function after heart attacks with minimal immune response," said Dr. Dvir. "Then we plan to move it to large animals and after that, to clinical trials."

Dr. Dvir has been awarded a fellowship from the American Heart Association, the Marie Curie Award for Young Investigators, the Alon Fellowship for Young Investigators from the Israeli Ministry of Education, and the Slezak Super Center Award for Cardiac Research.

Discovery of a Novel Heart and Gut Disease

Physicians and researchers at CHU Sainte-Justine, Université de Montréal, CHU de Québec, Université Laval, and Hubrecht Institute have discovered a rare disease affecting both heart rate and intestinal movements. The disease, which has been named "Chronic Atrial Intestinal Dysrhythmia Syndrome" (CAID), is a serious condition caused by a rare genetic mutation. This finding

demonstrates that heart and guts rhythmic contractions are closely linked by a single gene in the human body, as shown in a study published on October 5th, 2014 in *Nature Genetics*.

The research teams in Canada have also developed a diagnostic test for the CAID Syndrome. "This test will identify with certainty the syndrome, which is characterized by the combined presence of various cardiac and intestinal symptoms," said Dr. Gregor Andelfinger, a pediatric cardiologist and researcher at CHU Sainte-Justine. "The symptoms are severe, and treatments are very aggressive and invasive," added Dr. Philippe Chetaille, a pediatric cardiologist and researcher at the university hospital CHU de Québec. At the cardiac level, patients suffer primarily from a slow heart rate, a condition which will require the implantation of a pacemaker for half of them, often as early as in their childhood. At the digestive level, a chronic intestinal pseudo-obstruction will often force patients to feed exclusively intravenously. Furthermore, many of them will also have to undergo bowel surgery.

Discovery of the CAID Syndrome

By analysing the DNA of patients of French-Canadian origin and a patient of Scandinavian origin showing both the cardiac and the gastrointestinal condition, the researchers were able to identify a mutation in the gene SGOL1 that is common to all the patients showing both profiles. "To lift any doubts concerning the role of the identified mutation, we also made sure it was ruled out in people showing only one of the profiles," said Dr. Andelfinger. Similarly, Dr. Jeroen Bakkers, at Hubrecht Institute, in The Netherlands, who also collaborated on the project, studied zebrafish with the same gene mutation. "The mutated fish showed the same cardiac symptoms as humans, which confirms the causal role played by SGOL1," he continued.

A Transatlantic Founder Eeffect T

The research team traced back the genealogy of eight patients of French-Canadian origin using the Quebec population BALSAC historical database. They were able to identify a common ancestry dating back to the 17th century, more precisely, a founder couple married in France in 1620. Molecular genetic tests also proved that the identified French-Canadian and the Swedish mutations share the same origin, suggesting the existence of a founder effect, and the major role played by migration of populations. According to the investigators' calculations, the genetic legacy would date back to the 12th century, then following the migration route of the Vikings from Scandinavia to Normandy, then that of the settlers who migrated to New France in the 17th century.

An Unsuspected Role for SGOL1

The researchers believe that the mutation of SGOL1 acts mechanistically to reduce the protection of specific nerve and muscle cells in the gut and the heart, causing them to age prematurely due to an accelerated replication cycle. Their findings suggest an unsuspected role for SGOL1 in the heart's ability to maintain its rhythm throughout life. The specific role played by the gene and the impact of its mutation will take center stage in future investigations of the research group. Along with physicians and patients, the group hopes their understanding of the disease will help them identify new avenues for treatments specifically targeting the underlying genetic and molecular causes.

The study "Mutations in a novel because SGOL1 cohesinopathy affecting heart and gut rhythm" was published in *Nature Genetics* on October 5th, 2014. Funding for this project provided by the FORGE Canada Consortium, the Canadian Institutes of Health Research, the Ontario Genomics Institute, Genome Quebec, Genome British Columbia, and André Foundation Nussia Aisenstadt, GO Foundation, Leducq Foundation and Association des pseudo-obstructions intestinales chroniques, France.

About the Researchers

Dr. Gregor Andelfinger, MD is a pediatric cardiologist at CHU Sainte-Justine, a researcher at Sainte-Justine University Hospital Research Center in the Fetomaternal and Neonatal Pathologies axis, and Associate Research Professor in the Department of Pediatrics at Université de Montréal. He also holds a Research Chair in cardiovascular genetics.

Dr. Philippe Chetaille, MD, MSc, is a pediatric cardiologist at CHU de Québec, an Associate Researcher at CHU de Québec Research

Centre and a Full Associate Professor in the Department of Pediatrics at the Université Laval.

Dr. Jeroen Bakkers, PhD, is a senior principle investigator of the Cardiac Development and Genetics group at the Hubrecht Institute in Utrecht, the Netherlands.

Mayo Clinic and Invenshure™ Launch Oneome™

Mayo Clinic and venture catalyst Invenshure announce the launch of Oneome, a genomics interpretation company that exports Mayo's extensive pharmacogenomics knowledge in the form of concise, actionable reports to help providers anywhere deliver the right medication at the right time. Oneome reports will focus on providing pharmacogenomically-driven guidance for medications with high levels of evidence in medical literature. Financial terms of the agreement were not disclosed. Mayo's financial investment in Oneome comes from the Mayo Clinic Center for Individualized Medicine.

"Our own genetic makeup can have a significant impact on how our bodies process and use prescription medication, which in turn affects whether or not a drug works the way our doctor intended," says Oneome co-founder John Logan Black, MD, a Mayo Clinic physician and Co-Director of the Personalized Genomics Laboratory in Mayo's Department of Laboratory Medicine and Pathology. "We have developed sophisticated decision algorithms that can help providers use genomic testing to get their prescriptions right the first time."

Individual patients may have minor but significant variations in hundreds of genes. Some of these can result in potentially life-threatening reactions to a medication that may be perfectly safe for most of the population, while others make prescriptions less effective. Some people, for instance, cannot process the common pain relievers codeine and tramadol, rendering the drugs ineffective against pain. Other people process the drugs too quickly, giving the patient a rapid and dangerous pulse of relief, which may result in accidental overdose. In many cases, a patient's genomic information offers insight into how that person is likely to respond to a particular medication.

"Even some of our most widely prescribed medications don't work the same way in every patient," says Dr. Black. "The same dosage of warfarin can have markedly different effects in different individuals — this is why patients taking anticoagulants need routine clotting tests."

Invenshur™ co-founder and Oneome CEO Troy Kopischke says combining his company's data processing platform with Mayo's pharmacogenomics knowledge base positions Oneome to meet a critical and untapped need in clinical care.

"We are delighted to partner with Mayo on this initiative," says Kopischke. "Together, we expect the unique combination of our respective technologies to rapidly enable health care IT solutions that will save lives and reduce costs."

Research and development of the algorithms come from the Mayo Clinic Department of Laboratory Medicine and Pathology and the Mayo Clinic Center for Individualized Medicine.

Dr. Black has a financial interest in Oneome and the technology described in this release. Revenue Mayo receives is used to support the clinic's nonprofit mission in patient care, education and research.

For more information, www.mayoclinic.org.

Salk Scientists Discover a Key to Mending Broken Hearts

Newswise - Researchers at the Salk Institute have healed injured hearts of living mice by reactivating long dormant molecular machinery found in the animals' cells, a finding that could help pave the way to new therapies for heart disorders in humans.

The new results, published November 6th in the journal *Cell Stem Cell*, suggest that although adult mammals don't normally regenerate damaged tissue, they may retain a latent ability as a holdover from development like their distant ancestors on the evolutionary tree. When the Salk researchers blocked four molecules thought to suppress these programs for regenerating organs, they saw a drastic improvement in heart regeneration and healing in the mice.

The findings provide proof-of-concept for a new type of clinical treatment in the fight against heart disease, which kills about 600,000 people each year in the United States —more than AIDS and all cancer types

combined, according to the U.S. Centers for Disease Control and Prevention.

"Organ regeneration is a fascinating phenomenon that seemingly recapitulates the processes observed during development. However, despite our current understanding of how embryogenesis and development proceeds, the mechanisms preventing regeneration in adult mammals have remained elusive," says the study's senior author Juan Carlos Izpisua Belmonte, a professor in the Gene Expression Laboratory at Salk.

Within the genomes of every cell in our bodies, we have what information we need to generate an organ. Izpisua Belmonte's group has for many years focused on elucidating the key molecules involved in embryonic development as well as those potentially underlying healing responses in regenerative organisms such as the zebrafish.

Indeed, back in 2003, Izpisua Belmonte's laboratory first identified the signals preceding zebrafish heart regeneration. And in a 2010 *Nature* paper, the researchers described how regeneration occurred in the zebrafish. Rather than stem cells invading injured heart tissue, the cardiac cells themselves were reverting to a precursor-like state (a process called 'dedifferentiation'), which, in turn, allowed them to proliferate in tissue.

Although in theory it might have seemed like the next logical step to ask whether mammals had evolutionarily conserved any of the right molecular players for this kind of regenerative reprogramming, in practice it was a scientific risk, recalls Ignacio Sancho-Martinez, a postdoctoral researcher in Izpisua Belmonte's lab.

"When you speak about these things, the first thing that comes to peoples' minds is that you're crazy," he says. "It's a strange sounding idea, since we associate regeneration with salamanders and fish, but not mammals."

Most other studies have looked to the hearts of neonatal mammals for molecular clues about proliferation, to no avail. "Instead, we thought, 'If fish know how to do it, there must be something they can teach us about it,'" says the study's first author Aitor Aguirre, a postdoctoral researcher in Izpisua Belmonte's group.

The team decided to focus on microRNAs, in part because these short strings of RNA control the expression of many genes. They performed a comprehensive screen for microRNAs that were changing in their expression levels during the healing of the zebrafish heart and that were also conserved in the mammalian genome.

Their studies uncovered four molecules in particular—MiR-99, MiR-100, Let-7a and Let-7c—that fit their criteria. All were heavily repressed during heart injury in zebrafish and they were also present in rats, mice and humans.

However, in studies of mammalian cells in a culture dish and studies of living mice with heart damage, the group saw that the levels of these molecules were high in adults and did not decline with injury. So the team used adeno-associated viruses specific for the heart to target each of those four microRNAs, suppressing their levels experimentally.

Injecting the inhibitors into the hearts of mice that had suffered a heart attack triggered the regeneration of cardiac cells, improving numerous physical and functional aspects of the heart, such as the thickness of its walls and its ability to pump blood. The scarring caused by the heart attack was much reduced with treatment compared to controls, the researchers found.

The improvements were still obvious three and six months after treatment—a long time in a mouse's life. "The good thing is that the

success was not limited to the short term, which is quite common in cardiac regenerative biology," Sancho-Martinez says.

The new study focused only on a handful of 70 some microRNA candidates that turned up in the group's initial screen. These other molecules will likely also play a part in heart cell proliferation, healing scars and promoting the formation of new blood vessels—all processes critical for heart repair, Sancho-Martinez says. The data are available so that other research groups can focus on molecules that interest them.

The next step for Izpisua Belmonte's team is to move into larger animals and see whether "regenerative reprogramming" can work in larger hearts, and for extended periods after treatment, says Sancho-Martinez. And, although the virus packaging disappeared from the animals' bodies by 2 weeks after treatment, the scientists are working on a new way to deliver the inhibitors to avoid the need for viruses altogether.

Other authors of the study include: Nuria Montserrat of the Center of Regenerative Medicine of Barcelona (CMRB), Barcelona, Spain; Josep Maria Campistol of the Hospital Clinic, Barcelona, Spain; Serena Zachiggna and Mauro Giacca of the International Center for Genetic Engineering and Biotechnology in Trieste, Italy; Emmanuel Nivet, Tomoaki Hishida, Marie Nicole Krause, Leo Kurian, Alejandro Ocampo, Eric Vazquez-Ferrer, Concepcion Rodriguez-Esteban, and Sachin Kumar of the Salk Institute for Biological Studies; and James Moresco and John Yates III of the Scripps Research Institute in La Jolla, California.

The work was supported by: the Ipsen Foundation, the California Institute for Regenerative Medicine, a Nomis Foundation postdoctoral fellowship; the National Heart, Lung, and Blood Institute, the G. Harold and Leila Y. Mathers Charitable Foundation, and The Leona M. and Harry B. Helmsley Charitable Trust.

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