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

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Patent Ductus Arteriosus and the Nit-Occlud PDA Device

By Gurumurthy Hiremath, MD; John L. Bass, MD

A twelve-month-old infant is followed with a continuous murmur, and echocardiographic confirmation of a Patent Ductus Arterosus (PDA). There is left atrial and left ventricular enlargement, normal right-sided pressures, runoff from the abdominal aorta, and transcatheter closure is recommended as spontaneous closure is unlikely beyond this age. The patient weighs 8.5kg. Access to the femoral artery is made with a 4F sheath, and to the femoral vein with a 5F sheath. Cardiac catheterization confirms normal pulmonary artery pressure with a large left-to-right shunt. Aortography shows a conical ductus (Figure 1)

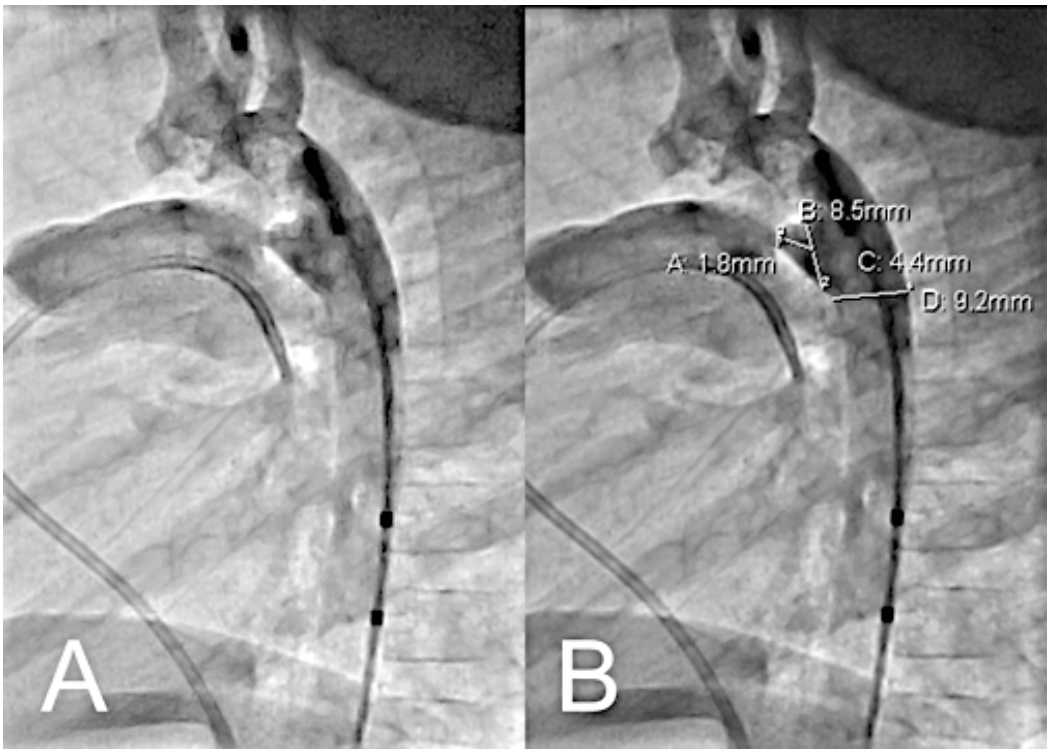

Figure 1. Lateral view of aortogram in a patient with a Type A Patent Ductus Arteriosus (A). The narrowest portion at the pulmonary end measures 1.8mm, and the ampulla at the descending aorta just under 9mm, nearly the same diameter as the descending aorta at the level of the ductus.

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Indication: The Nit-Occlud® PDA coil is a permanently implanted prosthesis indicated for percutaneous, transcatheter closure of small to moderate size patent ductus arteriosus with a minimum angiographic diameter less than 4mm. Nit-Occlud Brief Statement: Do not implant the Nit-Occlud PDA into patients who have endocarditis, endarteritis, active infection, pulmonary hypertension (calculated PVR greater than 5 Wood Units), thrombus in a blood vessel through which access to the PDA must be obtained, thrombus in the vicinity of the implantation site at the time of the implantiton or patients with a body weight < 11 lbs (5 kg). An angiogram must be performed prior to implantation for measuring length and diameter of the PDA. Only the pfm medical implantation delivery catheter should be used to implant the device. Administration of 50 units of heparin per kg body weight should be injected after femoral sheaths are placed. Antibiotics should be given before (1 dose) and after implantation (2 doses) in order to prevent infection during the implant procedure. Do not implant the Nit-Occlud PDA in an MR environment. Do not pull the Nit-Occlud coil through heart valves or ventricular chambers. Contrast media should not be injected through the implantation catheter. The catheter must not be connected to high pressure injectors. Patients may have an allergic response to this device due to small amounts of nickel that has been shown to be released from the device in very small amounts. If the patient experiences allergic symptoms, such as difficulty in breathing or swelling of the face or throat, he/she should be instructed to seek medical assistance immediately. Antibiotic prophylaxis should be performed to prevent infective endocarditis during first 6 months after coil implantation. Potential Adverse Events: Air embolism, Allergic reaction to drug/contrast, Apnea, Arrhythmia requiring medical treatment or pacing, Arteriovenous fistula, Bacterial endocarditis, Blood loss requiring transfusion, Chest pain, Damage to the tricuspid or pulmonary valves, Death, Embolization of the occluder, requiring percutaneous or surgical intervention, Endarteritis, False aneurysm of the femoral artery, Fever,Headache/migraine, Heart failure, Hemolysis after implantation of the occluder, Hypertension, Hypotension or shock, Infection, Myocardial infarction, Occluder fracture or damage, Perforation of the heart or blood vessels, Stenosis of the left pulmonary artery or descending thoracic aorta, Stroke/TIA, Thromboembolism (cerebral or pulmonary), Valvular Regurgitation, Vessel damage at the site of groin puncture (loss of pulse, hematoma etc.)

narrowed at the pulmonary end. A decision is made to implant a Nit-Occlud® PDA device to close the ductus. Measurements show a 1.8mm minimum diameter at the pulmonary artery, and 8.5mm at the aorta (Figure 1). A 9x6 Nit-Occlud® device is chosen, a 0.025in. guidewire is advanced from the pulmonary artery into the descending aorta, and the 5F delivery catheter advanced through the ductus. The 9x6 Nit-Occlud® device is flushed, is advanced through the delivery catheter, the aortic end exposed and pulled into the aortic PDA ampulla, and the pulmonary end exposed. Aortography confirms good position, the coil is detached, and the aortogram is repeated,confirming repositioning of the device after release and a moderate residual shunt (Figure 2). Catheters are removed with a good pulse distal to the arterial sheath site. Before discharge 4-hours later, the residual PDA shunt is gone.

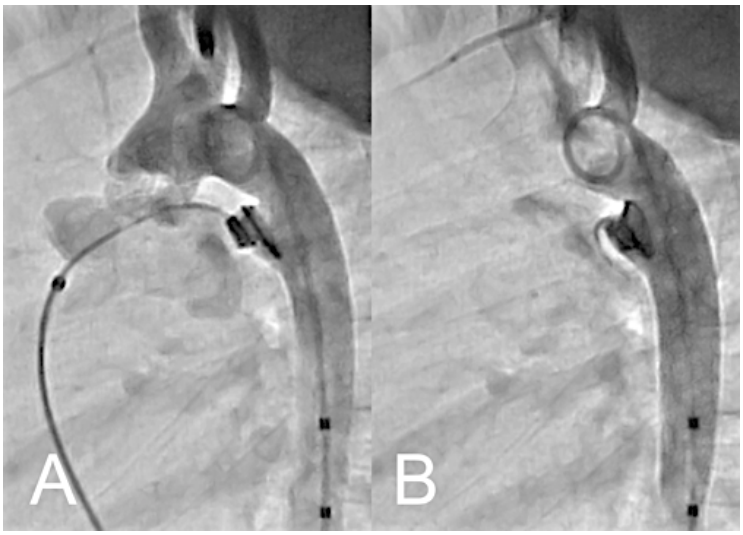


Figure 2. Lateral view of aortogram in the same patient as Figure 1. A 9x6 Nit-Occlud® ductus coil is in the aortic ampulla still attached to the retrieval cable (A). The coil lies slightly angled in the ampulla. In B the coil has been released. The coil has reoriented towards the aorta, but still is not in the true lumen. Approximately ½ turn of the coil is within the pulmonary artery. There is a modest amount of residual flow through the ductus that was completely occluded 4 hours later on echocardiography.

This relatively straightforward procedure raises a number of questions:

1. Why choose a Nit-Occlud® PDA device?
2. What is different about this device and its implantation?
3. How can you leave this residual shunt behind in the cardiac catheterization laboratory?
4. Are there any disadvantages to using this device?

Why Choose a Nit-Occlud®?

Transcatheter closure of the PDA was reported over 40 years ago.[1] Yet today, there are only three transcatheter PDA closure devices with FDA approval, most recently the Nit-Occlud® device. The first two are the Amplatzer PDA Occluders (Types 1 and 2; ADO1 and ADO2). There are minor disadvantages with these two devices. The ADO1 device aortic disc can protrude into the aorta, particularly in small infants, and it requires a relatively large delivery sheath (6F or more).

The ADO2 device was designed to overcome this with discs that rotate to lie flat against the aorta and pulmonary artery, passing through a smaller delivery system, and horizontally symmetrical so that it can be implanted from either the pulmonary artery or aortic side. The animal model for the ADO2 was a tubular PDA that was filled by the connecting waist, yet 65% of PDAs in humans are conical PDAs. The aortic disc of the ADO2 can lie horizontally in the PDA ampulla with residual shunting, or with a shorter PDA, the waist and aortic disc may remain floating in the aorta despite successful occlusion. For decades the primary method of transcatheter occlusion of the PDA was the Gianturco stainless steel coil,[2] and this worked well for smaller PDAs. But this is off-label use; the coil is not designed to occlude a PDA. Tubular PDAs can also be closed with implantation of the Amplatzer Vascular Plug 2, usually quite effectively, but still an off-label use of the device. It is into this milieu of off-label use for transcatheter PDA occlusion, occasional obstruction of the aorta, and some hemodynamic instability with a large delivery sheath, that the Nit-Occlud® PDA device was introduced and reached FDA approval in August 2013. The advantages of this device are the smaller delivery catheter (4-5F), less chance of protrusion into the aorta or pulmonary artery especially in conical PDAs, FDA approval (on-label use of a device designed specifically to close the PDA), and a high degree of effectiveness. The cost of the Nit-Occlud® PDA device is competitive with, or cheaper than, the alternative FDA-approved PDA closure devices. PDAs with minimum diameters up to 4mm can be effectively closed with this device.

What Is Different about the Nit-Occlud®?

Unlike other coils placed in the PDA, the Nit-Occlud® device has no fibers attached. The Nitinol surface of the coil leads to rapid thrombosis and occlusion. It is designed to be deployed from the venous side, and the delivery catheter must be placed from the femoral or internal jugular vein. The attachment mechanism uses friction between coils of the proximal end of the device and a mandrel (Figure 3) to maintain the connection, allowing easy retrieval once deployed. The Amplatzer device family and the Flipper coils use a screw attachment. In the unlikely event of embolization of the Nit-Occlud® PDA device, it is easily snared and retrieved through a 6F sheath (through the PDA if embolized to the aorta).

Sizing the device may be a little uncertain for beginning users. Device sizes are given as two numbers, e.g. 6x5. The second number is the diameter of the proximal-pulmonary end of the conformed coil, and the first the diameter of the distal-aortic end of the conformed coil (Figure 4). A sizing table is supplied by the manufacturing company (PFM) (Figure 4) with the distal/aortic end designed to be at least 3-4mm larger than the narrow pulmonary end of the PDA, and no more than 2mm larger than the aortic ampulla. This guide is a starting point. In general we have chosen a proximal/pulmonary diameter 2-4mm larger than the minimum PDA diameter to maximize the occlusion rate, and a distal/aortic diameter that will fit into the PDA ampulla keeping it out of the aortic lumen. In the case presented here, with a nearly 9mm distal aortic diameter and a 1.8mm pulmonary diameter, an 11x6 device could have been chosen. But an 11mm distal coil would have protruded into the aorta, even if it configured when exposed with a descending aortic diameter of 9mm. A 7x6 device would have worked as well, and perhaps even a 6x5. So why not choose a minimum distal coil diameter? A smaller distal diameter may leave the coil "rattling around" in the PDA ampulla, and changing position could influence occlusion.

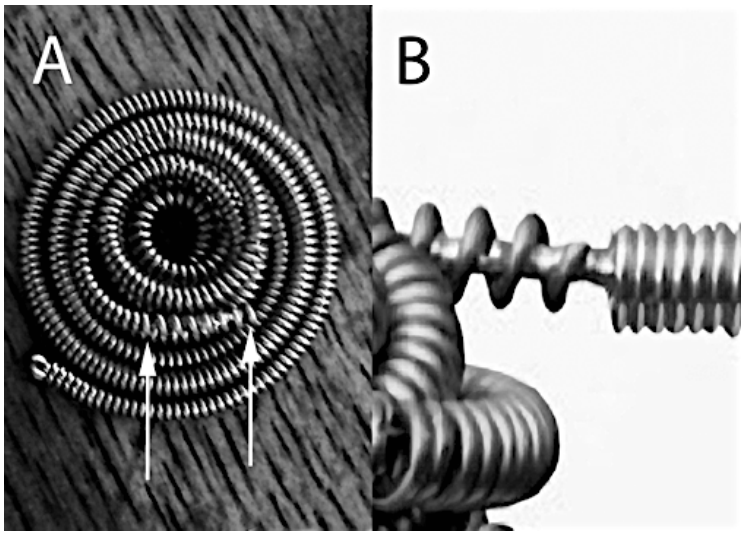
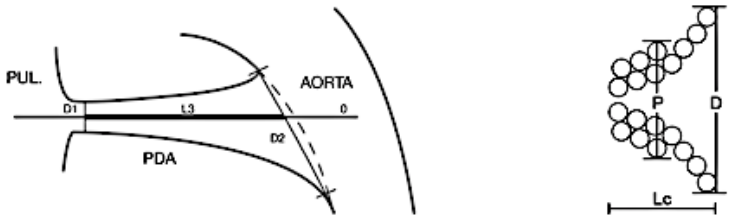


Figure 3. A Nit-Occlud® coil is seen with arrows pointing to the terminal portion of the coil that has no core (A) allowing the outer winding to wrap around the inner mandrel of the delivery cable (B). This attachment mechanism relies on the friction between the winding and the mandrel.



D1	D2	Device
1mm	≤ 3mm	4x4
1mm	4mm	5x4
1mm	≥ 5mm	6x5
1mm	≤ 5mm	6x5
2mm	6-7mm	7x6
2mm	≥8mm	9x6

D1	D2	Device
3mm	≤7mm	7x6
3mm	8-9mm	9x6
3mm	≥ 9mm	9x6 or 11x6
< 4mm	9mm	11x6
< 4mm	10-11mm	11x6
< 4mm	≥ 12mm	11x6

Table: Selection of Nit-Occuld PDA coil (according to angiographic PDA dimensions).

Figure 4. Sizing table supplied by PFM Medical for selecting the appropriate sized Nit-Occlud® coil for occlusion of a Patent Ductus Arteriosus. D2 in the left upper panel is the measure of the diameter of the aortic ductal ampulla matches to largest diameter D of the Nit-Occlud ® ductal coil in the upper right. D1 is the narrowest portion of the ductus and matches to the smallest coil diameter of the rewound portion (P). The device size-designation (e.g. 9x6) indicates the larger coil diameter as the first number by the smaller rewound coil diameter as the second number. Recommendations are that the larger coil diameter be no more than 1-2mm larger than the aortic ampulla, and at least 3-4mm larger than the minimum ductal diameter. PDA = Patent Ductus Arteriosus.

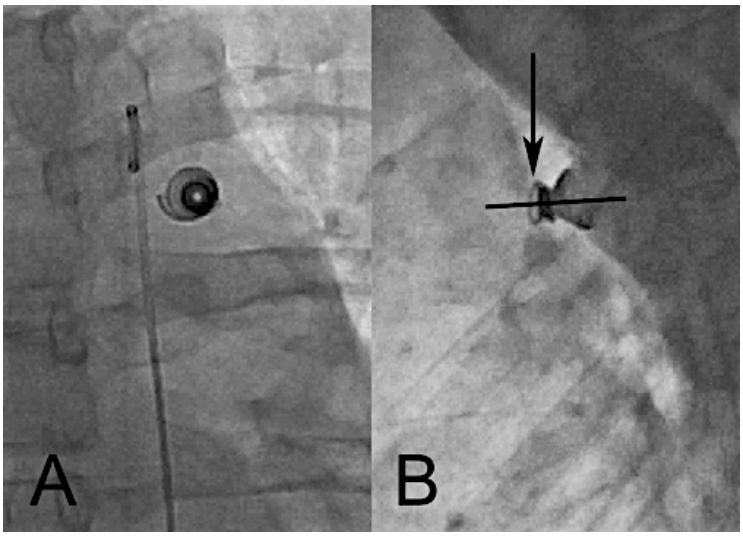


Figure 5. Cineradiography in a patient with a Type A ductus. In A the camera is positioned RAO 30° and there in an apparent hole through the device in the long axis of the ductus. In B, however, the long axis of the device (solid line) does not point to the communication through the ductus (arrow) where the proximal Nit-Occlud® coil passes into the pulmonary artery.

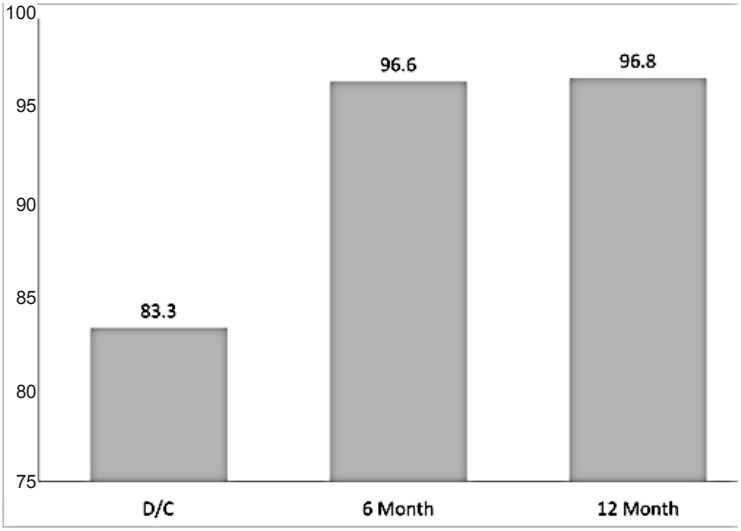


Figure 6. Echocardiographic closure rates over time from the combined pivotal and continued access trials (3). Only 83% of patients had closure at discharge (D/C). By 6 months follow-up there was almost 97% closure (Personal Communication, Dave Mittl, B. Braun Interventional Systems Inc. Bethlehem PA). Of the residual shunts at discharge, 77% had closed by 6 months. There was no further change by 12 months.

What about the apparent "hole" in the device (Figure 5)? Doesn't this work against occlusion? The actual hole in the coil is never pointed into the PDA communication on the pulmonary end, as the coil passing through the PDA is "above" it. When the device lies sideways in the ampulla, occlusion is just as certain, and the device does not need to be reimplanted. The rewound proximal coils of the device are the most important to occlusion of the PDA, and only need to be in the pulmonary end of the PDA regardless of orientation.

The Angiographic Residual Shunt?

Only the tiniest of PDAs (≤1mm minimum diameter) will leave the cardiac catheterization laboratory with complete occlusion of the PDA after deployment of a Nit-Occlud® PDA device. In our 30 patients who

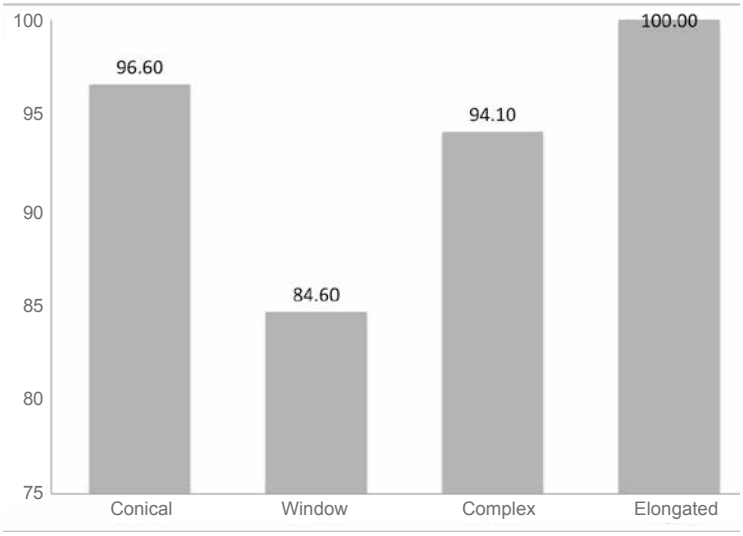


Figure 7. Final closure rates by type of Patent Ductus Arteriosus. There were no statistical differences of closure rates for conical, complex or elongated ductuses (96.6-100%). However, just under 85% of window/short ductuses were closed with one device. There were too few tubular ductuses to allow analysis.

underwent closure with Nit-Occlud® PDA device in the last 2 years, all but 3 had complete occlusion before same day discharge. The other three were occluded at follow-up two months later. Fourteen have returned for 6-month follow-up, and all were occluded including the three discharged with a residual shunt. This parallels the experience reported from the pivotal study where there was 83% occlusion at discharge, and over 96% at both 6-month (Personal Communication, Dave Mittl, B. Braun Interventional Systems Inc. Bethlehem PA) and 1-year follow-up on echocardiogram (Figure 6).[3] Over ¾ of residual shunts at discharge closed after 6 months. This is in contrast to the experience with Gianturco coils, where no patient is left with a residual shunt as additional coils would usually be required later. The Amplatzer devices may have flow through the device after deployment, but no discrete jets. Residual shunts are the rule with the Nit-Occlud® PDA device at the end of the procedure, but these will close, usually within 24 hours.

The pivotal study showed a definitive difference in effectiveness by type of PDA.[4] There were too few tubular PDAs closed to draw a conclusion (though all were closed), but only 85% of 'window-type' PDAs were effectively closed (Figure 7). And the device is not recommended for transcatheter occlusion of this type of PDA.

Disadvantages

There are few disadvantages to the Nit-Occlud® PDA device. In using the device, it is important to remember that friction between the device coils and mandrel are responsible for retrievability. The mechanism of release is pushing the coils off the end of the mandrel. Prior to retrieval or once the device has been retrieved before release, a separation or "gap" may develop between the coils and the pusher winding (Figure 8) to allow a smooth retrieval into the catheter. The gap at the proximal device coil leaves a step that could catch on retrieval into the delivery catheter, stripping the coil off the mandrel and leading to premature detachment. The manufacturer recommends looking for this gap prior to and during deployment (especially prior to retrieval) of the device into the delivery catheter, and pushing the outer winding up to the device when it is observed (Figure 8). It is also recommended that testing the attachment of the device to the mandrel be confined to pulling the device back within the delivery catheter, rather than exposing the coils from the loader, which could loosen the attachment.

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Important Labeling Information for United States

Indications: The Melody TPV is indicated for use as an adjunct to surgery in the management of pediatric and adult patients with the following clinical conditions:

- Existence of a full (circumferential) RVOT conduit that was equal to or greater than 16 mm in diameter when originally implanted AND
- Dysfunctional RVOT conduits with a clinical indication for intervention, AND:
  - regurgitation: ≥ moderate regurgitation, AND/OR
  - stenosis: mean RVOT gradient ≥ 35 mm Hg

Contraindications: None known.

Warnings/Precautions/Side Effects

- DO NOT implant in the aortic or mitral position. Preclinical bench testing of the Melody valve suggests that valve function and durability will be extremely limited when used in these locations.
- DO NOT use if patient's anatomy precludes introduction of the valve, if the venous anatomy cannot accommodate a 22-Fr size introducer, or if there is significant obstruction of the central veins.
- DO NOT use if there are clinical or biological signs of infection including active endocarditis. Standard medical and surgical care should be strongly considered in these circumstances.
- Assessment of the coronary artery anatomy for the risk of coronary artery compression should be performed in all patients prior to deployment of the TPV.
- To minimize the risk of conduit rupture, do not use a balloon with a diameter greater than 110% of the nominal diameter (original implant size) of the conduit for pre-dilation of the intended site of deployment, or for deployment of the TPV.
- The potential for stent fracture should be considered in all patients who undergo TPV placement. Radiographic assessment of the stent with chest radiography or fluoroscopy should be included in the routine postoperative evaluation of patients who receive a TPV.
- If a stent fracture is detected, continued monitoring of the stent should be performed in conjunction with clinically appropriate hemodynamic assessment. In patients with stent fracture and significant associated RVOT obstruction or regurgitation, reintervention should be considered in accordance with usual clinical practice.

Potential procedural complications that may result from implantation of the Melody device include the following: rupture of the RVOT conduit, compression of a coronary artery, perforation of a major blood vessel, embolization or migration of the device, perforation of a heart chamber, arrhythmias, allergic reaction to contrast media, cerebrovascular events (TIA, CVA), infection/sepsis, fever, hematoma, radiation-induced erythema, blistering, or peeling of skin, pain, swelling, or bruising at the catheterization site.

Potential device-related adverse events that may occur following device implantation include the following: stent fracture,* stent fracture resulting in recurrent obstruction, endocarditis, embolization or migration of the device, valvular dysfunction (stenosis or regurgitation), paravalvular leak, valvular thrombosis, pulmonary thromboembolism, hemolysis.

**The term "stent fracture" refers to the fracturing of the Melody TPV. However, in subjects with multiple stents in the RVOT it is difficult to definitively attribute stent fractures to the Melody frame versus another stent.*

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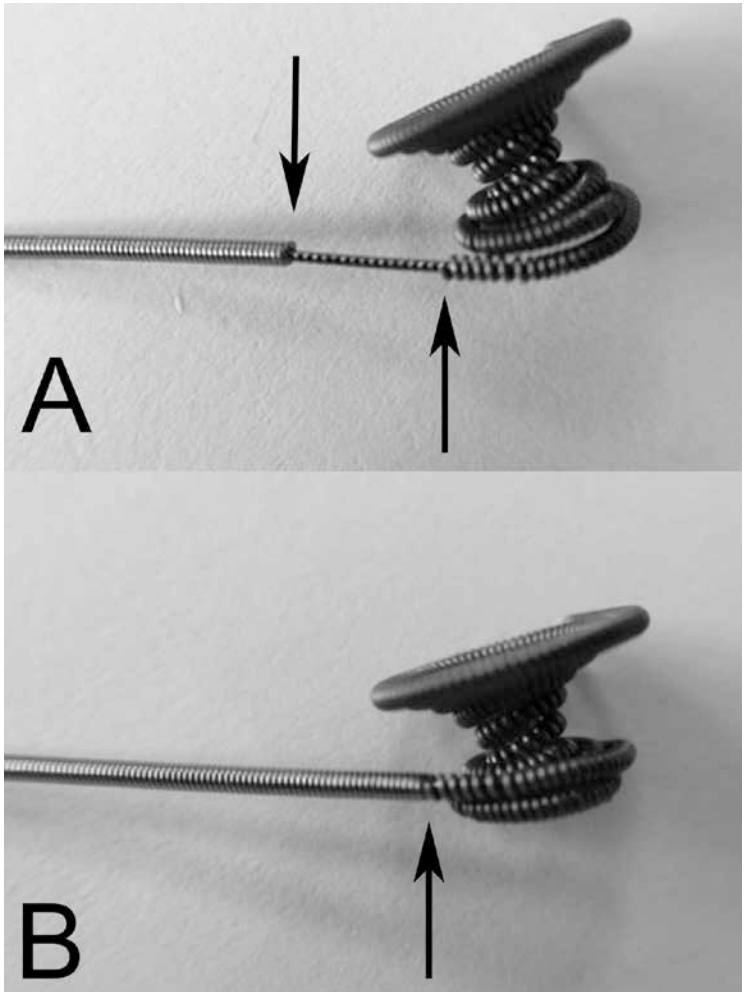

Figure 8. Photographs of the Nit-Occlud® device attached to the mandrel of the delivery system after full deployment, but prior to device release. In panel A, there is a "gap" shown between the arrows. The "gap" is a length of mandrel between the pusher winding and the end of the device, attached to the end of the mandrel. Prior to release or recapture of the device, as shown at the arrow in Panel B, the "gap" should be eliminated by advancing the pusher winding to the end of the device.

Advantages

The Nit-Occlud® device enters a space (transcatheter PDA closure devices) that is already occupied by several devices specifically designed for PDA closure, as well as some off-label devices that are, nevertheless effective. It's ease of use and effective closure rates outweigh unfamiliarity with the device, anxiety over residual shunting in the cardiac catheterization laboratory, and the remote possibility of premature release. The delivery system is smaller than for the ADO1 device for transvenous approach. It can be used with a 3.3F arterial sheath. The cost is competitive. In our hands the device has been easy to use and effective. Not all PDAs can be addressed with the Nit-Occlud® PDA device. However, it significantly expands the options for treating children with a persistentl Patent Ductus Arteriosus.

"Not all PDAs can be addressed with the Nit-Occlud® PDA device. However, it significantly expands the options for treating children with a persistently Patent Ductus Arteriosus."

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3. Summary of safety and effectiveness data (SSED), Device Generic Name: Transcatheter Patent Ductus Arteriosus (PDA) Occlusion Device, Device Trade Name: Nit-Occlud® PDA, http://www.accessdata.fda.gov/cdrh_docs/pdf12/P120009b.pdfww.
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Dr. Gurumurthy Hiremath is an Assistant Professor of Pediatrics at the University of Minnesota Masonic Children's Hospital. He did his Pediatric Residency at Wayne State University in Detroit MI, and Pediatric Cardiology Fellowship at USCF in San Francisco CA. Dr. Hiremath completed a 4th year of Interventional training at UCSF, where he pursued a study of the effects of relief of unilateral pulmonary artery stenosis on exercise capacity, and late outcomes after Atrial Septal Defect (ASD) device closure in infants under 15kg. His early efforts in Minnesota center around Interventional Catheterization with stent placement and treatment of paravalvar leaks. He continues a multicenter study on the effects of relieving unilateral branch pulmonary artery stenosis.

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Highlights from the Second Fetal Cardiac Symposium at Rush University in Chicago - September 10th-12th, 2015

By Karim Diab, MD

The Second Fetal Cardiac Symposium took place in the amazing summertime that the windy city offers. The meeting was held at Rush University Medical Center in Chicago and was expanded from last year to two-and-a-half days, and included a total of 15 faculty members from various institutions. With the persistence of the low national prenatal detection rate of congenital cardiac defects, despite universal screening during pregnancy, the main goal of the conference was to boost the education in the field in order help improve the status of prenatal diagnosis of Congenital Heart Disease. This was done through a series of didactic lectures, as well as by focusing on improving the technical skills in scanning the fetal heart through hands-on sessions.

As was the case with the first year of launching the meeting, the symposium continued to be a tremendous success and was nearly sold-out with an audience of 140 registrants who came from 10 different countries and more than 19 states within the U.S. Fifteen percent of the registrants came from overseas, including countries such as: Canada, Japan, Brazil, Mexico, China, Columbia, The Netherlands, Iran, Qatar and Saudi Arabia.

Most of the attendees (~65%), however, came from the Midwest states, highlighting the need for such a conference focusing on the fetal heart in this region. Although more than 50% of the attendees were physicians, there were about 30% sonographers attending the meeting, likely reflecting the attractiveness of hands-on workshops included in the meeting and that provide the attendees with practical scanning opportunities rather than only didactic lectures. The attendees came from various specialties including: Pediatric Cardiology, OB and MFM as well as other specialties such as Neonatology and Radiology.

The conference featured a two-and-a-half day meeting that offered thorough and updated presentations on scanning the fetal heart and diagnosing and managing various common fetal congenital heart disease malformations. The activity was designated for a maximum of 19.25 AMA PRA Category 1 continuing medical education credit, 19.25 continuing Nursing Education credits and 19.25 CME credits in medical sonography (SDMS). Lectures, given by an internationally acclaimed faculty in Pediatric Cardiology and Maternal-Fetal Medicine specialists, emphasized the basics of fetal cardiac scanning coupled with live case demonstrations and tips for diagnosing various anomalies. There was intensive focus on anomalies of the four-chamber and outflow-tracts views, reflecting the recently published guidelines for screening for fetal heart disease. In addition, there was specific focus on the 3-vessel and tracheal view that Dr. Alfred Abuhamad lectured on very extensively with ample video clips and examples to the point that he almost called it the most important view, and likely the only view needed for screening for Critical Congenital Heart Disease (CCHD)! The symposium featured a unique two-hour workshop on both days of the meeting, which gave the attendees a unique opportunity to scan pregnant volunteers with both normal hearts and cardiac pathology. The pathologies included: right-sided and left-sided critical lesions that helped attendees practice scanning fetuses with anomalies. This provided an excellent opportunity for becoming more familiar with the required cardiac views, including the four-chamber, the outflow tracts and the three-vessel views. It also allowed participants to experiment scanning using

various technological instruments and machines that are currently on the market. All this was done under the supervision of expert faculty in the field of Fetal Cardiology and Maternal Fetal Medicine.

The first day of the meeting started with an overview of the basics of fetal cardiovascular physiology and the current guidelines and indications for performing fetal echocardiography by Drs. Abdulla and Young. Then, Dr. Mark Sklansky from UCLA went over the impact of prenatal diagnosis of CHD on the outcome for these patients. This was followed by a live scanning demonstration of a complete fetal echocardiographic study. It then sequentially focused on the essential screening views of the fetal heart, including the four-chamber and the outflow tract views, as well as the three-vessel view. This demonstrated the normal findings, as well as typical cardiac lesions diagnosed with the particular view which helped give the audience practical tips for scanning and diagnosing various cardiac malformations. Additional lectures focused on specific lesions. Dr. E. Alboliras went over Ventricular Septal Defect (VSD) and AVC lesions, and Dr. W. Tworetzky talked about Ebstein's Anomaly and some of the newly suggested in-utero treatment modalities in some cases using NSAIDs to close the ductus. He also talked about HLHS with the skinny LV vs. the fat and globular LV. Dr. E. Jaeggi went over Total Anomalous Pulmonary Venous Return (TAPVR), which continues to be tricky to diagnose and is missed on prenatal screens, as well as DILV and MV anomalies. Other lesions that were discussed included: D-TGA and cc-TGA (Dr. Sklansky), ductal anomalies and conotruncal anomalies, as well as coarctation and arch anomalies. The first day ended with the first hands-on session of the symposium with 6 stations for hands-on scanning on fetuses with normal hearts as well as cardiac pathologies.

The second day of the symposium started with a session focusing on the national guidelines for screening for CHD by Dr. Abuhamad. Additional lectures went over various cases and tips in imaging (Dr. Awad), 3-D and 4-D imaging by Dr. Sklansky, cardiomegaly and CM (Dr. Young), fetal cardiac tumors (Dr. Jaeggi) and hydrops and its management (Dr. Hornberger).

Dr. Abuhamad lectured extensively on the three-vessel and tracheal view and Dr. Tworetzky talked about the various heterotaxy lesions.

Midday on the second day of the meeting there was another hands-on session with an additional 6 stations for scanning and practice.

There was also a session on the "Most Interesting Case I've Seen," where the audience presented interesting, and unusual fetal cases with cardiac pathology that included cases such as

"Given the recent updates and revisions to the North American guidelines, as well as the International Society of Ultrasound in Obstetrics and Gynecology (IUSOG) practice guidelines on sonographic screening examination of the fetal heart, the need for such annual fetal symposia in different regions is a must, without any doubt, in order to improve the skills of various practitioners in the field and ultimately improve the prenatal detection of CHD!"

fetal aortic-LV tunnel, critical PS, aneurysm of the intervalvular fibrosa and AVC, Ebstein's Anomaly, fetal AF, and a case of a giant LA pseudoaneurysm.

There were two winners of a special prize and a free registration to next year's symposium which was awarded to two of the presenters. This gave the audience ample opportunity to present challenging fetal cardiac cases and discuss them with the faculty.

The third day of the meeting focused on fetal rhythm abnormalities, with lectures on the techniques to evaluate the fetal rhythm by echo and by fetal magnetocardiography, as well as diagnosing and managing fetal tachy and brady-arrhythmias and heart block. The last session of the meeting focused on fetal cardiac imaging in early gestation, genetic evaluation of the fetus with CHD and neurologic development of the fetus with CHD.

In addition to an extensive series of didactic presentations and live-scanning sessions, the symposium offered a variety of exhibitors that showcased the latest in ultrasound technology. The symposium also offered an exceptional opportunity for fellows and attendees to network and meet with pioneers in the field, as well as an opportunity to catch up with colleagues and meet new friends.

Given the recent updates and revisions to the North American guidelines, as well as the International Society of Ultrasound in Obstetrics and Gynecology (IUSOG) practice guidelines on sonographic screening examination of the fetal heart, the need for such annual fetal symposia in different regions is a must, without any doubt, in order to improve the skills of various practitioners in the field and ultimately improve the prenatal detection of CHD!

Keep an eye out for next year's meeting information as the registration sold out this year!! Dates for next year's symposium will be announced in the near future; for more information, you can reach Dr. Diab at Karim_Diab@rush.edu or visit the meeting website at www.FetalCardiacSymposium.com.

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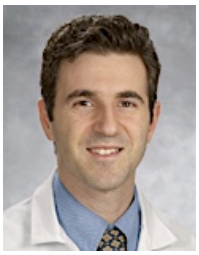

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Atrioventricular Septal Defect: Case Report

By Felipe Guimarães Machado, MD; Éric Guimarães Machado, MD; Maria Clara Menezes de Jesus Lisboa, MD; Léo Guimarães Soares, DDS, PhD; Paulo Sérgio Lopes Soares, MD; Gabriel Porto Soares, MD, PhD

Introduction

The Atrioventricular Septal Defect (AVSD) occurs in 2: 10.000 live births, accounting for 3% of Congenital Heart Disease (CHD), AVSD is more frequent in females and usually associated with carriers of the Down Syndrome (DS).[1,2]

The AVSD is characterized by the absence of the atrioventricular septum, and five or more atrioventricular valve leaflets of varying sizes are usually present.[1,2]

This clinical case is characterized by increased pulmonary blood flow in the first weeks of life. The natural history of this defect is survival of 54% at six months and 15% at two years.[1] If significant regurgitation of the common atrioventricular valve is present, a systolic cardiac murmur and gallop rhythm are frequently heard. Over time, pulmonary hypertension and congestive heart failure (CHF) are observed.[2]

The main cause of death in infants is CHF; after the first year of life, occlusive pulmonary vascular disease predominates,[1]

The diagnosis should be suspected in patients with CHF symptoms in the first months of life. Chest radiographs show cardiomegaly. The electrocardiogram may show left-axis deviation and bi-atrial and bi-ventricular enlargement, in addition to pressure and volume overload. Echocardiography is the main tool for both the diagnosis and anatomical classification of this malformation, according to Rastelli classification (Type A, B or C). The electrocardiogram also demonstrated the Atrial Septal Defect, which is commonly associated with AVSD. Echocardiography can still observe anatomical defects, such as atrial septal defect with the underlying common atrioventricular valve and Ventricular Septal Defect (VSD).

Medical treatment is aimed at improving the signs and symptoms of CHF. Medications used may be digoxin, diuretics (such as furosemide and spironolactone), and vasodilators (often angiotensin-converting enzyme inhibitors). Administration of these medications, pre-operatively, may result in an improved post-operative course and prognosis.

The surgery to repair AVSD involves the use of two patches (an atrial and a ventricular patch), which maintains the integrity of the valvular leaflets.[1]

Case Report

A 24-year-old woman was admitted to the cardiology clinic from the Hospital Universitário Sul Fluminense (HUSF), reporting effort dyspnea on exertion and chest pain.

The patient reported strong chest pain, which did not radiate, but was effort-related and was relieved by rest. The patient also presented with cyanosis of fingers and lips, numbness in left hemibody, more pronounced in the upper limb. Physical examination of the cardiovascular system showed a Grade 3/6 murmur at the left-midsternal border. The patient had no cognitive impairment, nor Down Syndrome stigmata.

An electrocardiogram was conducted, which showed sinus rhythm, 1st degree atrioventricular blockage, left-anterior hemiblock and change in lower and anteroseptal repolarization. Structural and functional study of the heart was requested through Doppler echocardiography.

On Color Dopper...(Figure 1), right ventricular and right atrial enlargement were noted, as was the presence of large Atrial Septal Defects with left-to-right shunt, mild tricuspid insufficiency and mild pulmonary arterial hypertension. Other parameters were normal. Transesophageal echocardiography or cardiac MRI was recommended.

Transesophageal echocardiography revealed a partial form of AVSD (interatrial communication ostium primum), enlargement of the right ventricle and right atrium , valve regurgitation, moderate right-sided valve regurgitation, mild pulmonary hypertension, (pulmonary artery systolic pressure (PASP) estimated to be 39 mm Hg by Doppler). Bi-ventricular systolic function was preserved. There were no thrombi observed, and flow was normal in the left atrial appendage.

It was concluded that there was an AVSD with single atrioventricular valve, classified as Type A in the Rastelli classification. Consequently, the patient was referred for cardiac surgery, where Inteventricular Communication Closure (IVC), Interatrial Communication Closure (IAC), and mitral and tricuspid valvuloplasty were performed.

When she returned to the clinic, the patient reported improvement in signs and symptoms of heart failure, with mild pain in the surgical wound. Physical examination of the cardiovascular system showed a regular heart rate, accentuated P2 and no murmurs.

Two-dimensional echocardiography with Color Doppler was conducted and showed cardiac chambers of normal morphology and dimensions. Global Left Ventricular (LV) and Right Ventricular (RV) systolic function were normal. LV wall thickness was normal. Segmental contractility normal. Left atrial diameter was normal. The mitral valve had thickened leaflets. The aortic, tricuspid and pulmonary valves were normal. The inferior vena cava and pericardium were normal. There was mild mitral regurgitation. There was normal flow in the outflow tract of the left ventricle and aorta. Tricuspid and pulmonary flow were unchanged.

The patient was discharged eight days after being admitted to the hospital and is currently under follow-up at HUSF cardiology clinic.

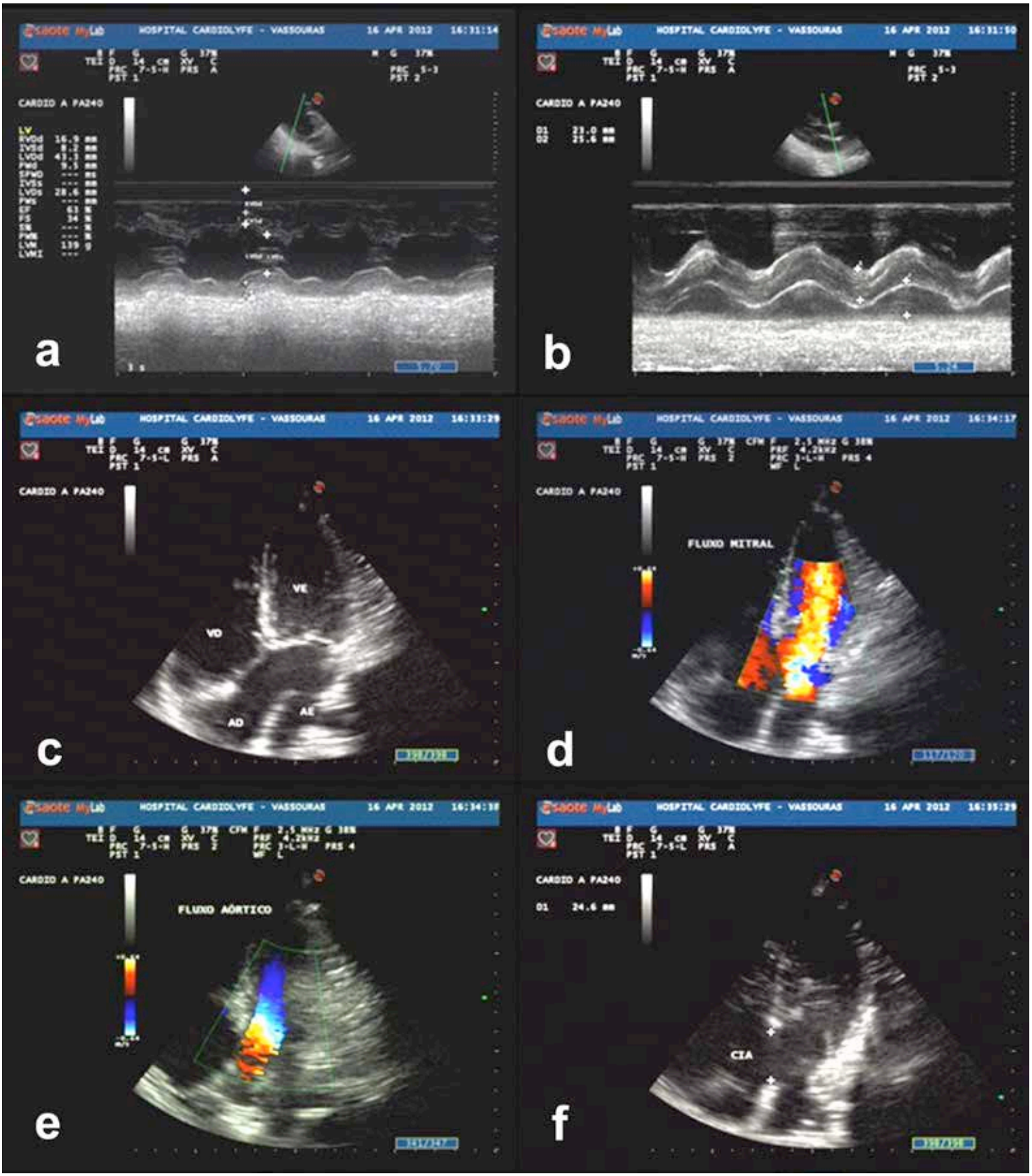

Figure 1. Echocardiogram with Color Doppler. A: M mode or unidimensional left ventricle longitudinal section. B: M mode or one-dimensional aorta and left atrium longitudinal section. C: Apical 4-chamber view. D: Mitral flow demonstrated by Color Doppler. E: Aortic flow demonstratedby Color Doppler. F: Interatrial communication visualization.

Discussion

The case reported is about a female patient, without a genetic syndrome, who became symptomatic in the third decade of life. According to literature,[1,3,4] the incidence in women is slightly higher than in men, ranging between 52% and 62%.

Typically, the clinical manifestation and surgical correction occur in early age. The scientific literature shows average ages of the correction ranging from 3.7 to 18.7 months of age.[1, 3-6] However, in this case, the patient showed signs and symptoms in the third decade of life, with the surgical correction performed at that time.

Atrialventricular Septal Defect is usually associated with Down Syndrome in 64% to 89% of patients, according to previous reports. [1, 3-6] However, this is a report of a patient without Down Syndrome.

The definitive diagnosis and Rastelli classification of this case was achieved through echocardiography. Other authors also used echocardiography for diagnosis and classification. The patient has a Rastelli Type A defect, which is the most common type in the earlier studies, ranging from 58% to 80%.

Regarding medical therapy, beta-blockers were used; for surgery, the technique of two patches was used. Both were similar to other reports.[2] Other authors [1, 4-6] reported use of the double-patch surgical technique in 72% of patients.[1,3,4,5] Studies[6] comparing the surgical techniques have concluded that the single- and double-patch technique present similar final results.

Thus, it can be concluded that this case was similar to the literature because the patient was female, and because of the methods of diagnosis and treatment. However, the age and lack of Down Syndrome are different from most reported cases. Finally, this case report demonstrates the importance of diagnosing and treating this disease.

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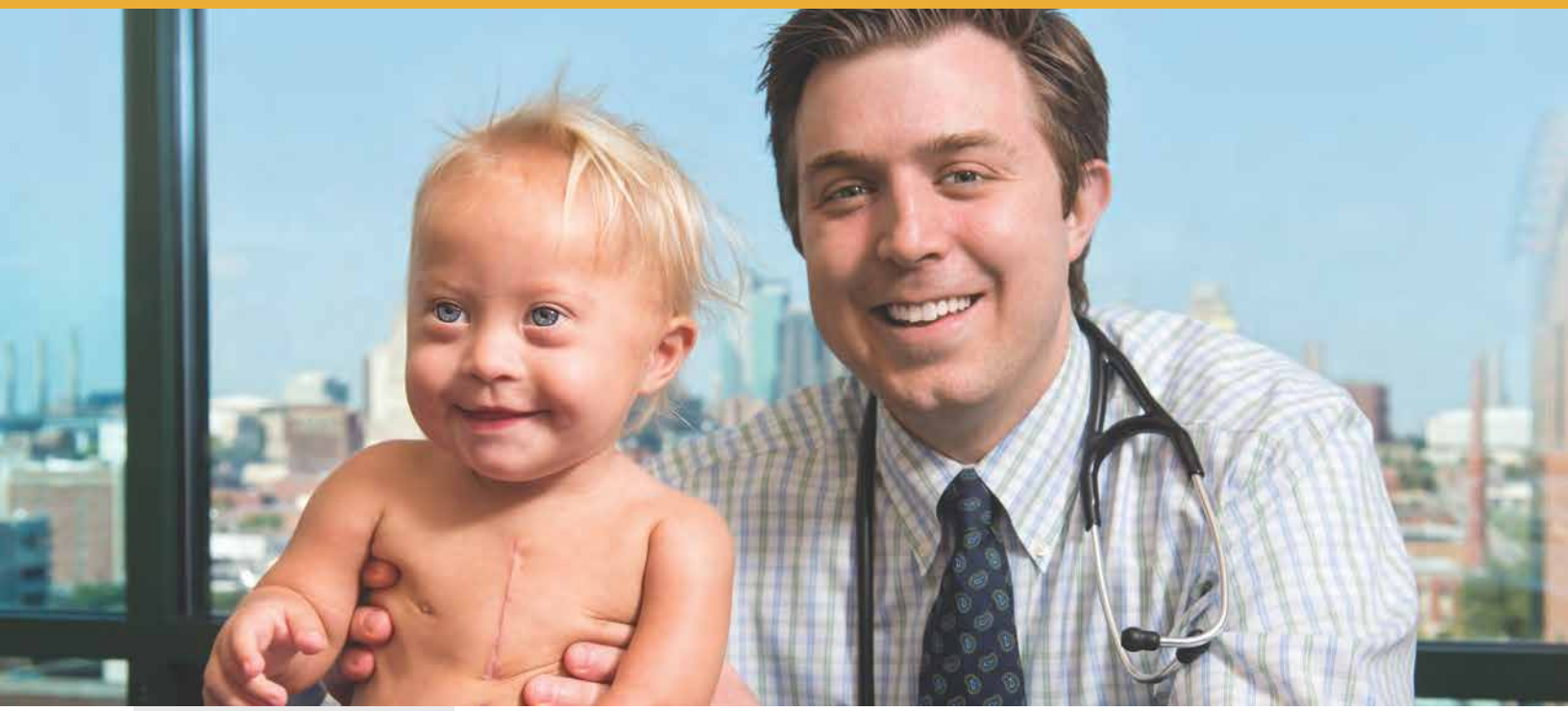

BEST CHILDREN'S HOSPITALS
U.S.News & WORLD REPORT
CARDIOLOGY & HEART SURGERY
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The 48th Annual Southeast Pediatric Cardiology Society Conference Meeting Review

By F. Bennett Pearce, MD

The 48th Annual Southeastern Pediatric Cardiology Society (SPCS) Meeting was held in Birmingham, AL at Renaissance Birmingham Ross Bridge Golf Resort and Spa, September 25th-26th, 2015 The Society, which was founded by Dr. Arno Hohn and other Pediatric Cardiologists from the Southeast, has met yearly in various locations in the Southeastern US. The meeting occurs in the fall of each year. Generous support from industry sponsors and local institutions have helped defray the costs of the meeting.

On the evening of September 24th, a Welcome Reception was held on the Ross Bridge Patio. *SPCS* attendees, including team members and trainees from pediatric cardiac programs throughout the Southeast, as well as attendees from as far away as Minnesota and Seattle, were able to get reacquainted and network.

On Friday, September 25th, the scientific session began featuring prestigious guest speakers. Dr. Michael Ackerman from Mayo Clinic gave state-of-the-art presentations on "Molecular Autopsy" and "Long QT Diagnosis and Treatment." Dr. Prince Kannakeril from Vanderbilt University presented "Personalized Treatment of Arrhythmias."

The attendees were then provided lunch at Children's of Alabama, where two outstanding abstracts were presented by Dr. Srikant Das of Arkansas Children's Hospital and Dr. Aamisha Gupta of Georgia Regent's University. There was also a tour of the new Joseph A. Bruno Heart Center at Children's of Alabama.

Additional presentations on September 25th included guest speakers: Dr. Heather T Henderson from Duke University who

presented "Mechanical Circulatory Support Options in Children," and Dr. Iki Adachi from Texas Children's Hospital who presented "Evolution of the Mechanical Circulatory Support Program at Texas Children's Hospital." Further presentations that afternoon from local faculty included: talks on "Outpatient Treatment of Children on VAD Support," presentations on database research, new information on registry participation, and findings from some of the largest Pediatric Cardiac Registries including: PHTS (The Pediatric Heart Transplant Study), INTERMACs (The Interagency Registry for Mechanically-Assisted Circulatory Support), PediMacs, STS (Society of Thoracic Surgeons) and CHSS (Congenital Heart Surgeons' Society) databases. Panel discussions with interactive audience participation followed each of the sessions.

There were over 40 abstracts submitted and accepted by the *SPCS* Scientific Committee, who also selected the outstanding abstracts for oral presentation. All abstracts were displayed as posters and generated a great deal of interest.

The day's session was followed by a fellow's networking reception and dinner with live music on the Ross Bridge Patio.

On the morning of the second day, there were physician and nursing breakout sessions. For the physician section, local faculty provided presentations on current topics in imaging, quality improvement, diagnosis and management of aortopathies, and interventional cardiology.

The nursing breakout sessions featured presentations from local nursing faculty, as well as invited speakers including: Emily Moore, ARNP, BSN, Seattle Children's Hospital who presented, "Pain Management Following Cardiac Catheterization," Bronwyn Bartle, DNP, MSN, of Duke University presented a talk entitled, "Care Transitions–Easy as Child's Play–Right?" Misty Ellis, MSN, APRN, of Kosair Children's Hospital presented, "Gas Prices on the Rise." JoAnn Nieves, MSN, APRN of Miami Children's Hospital presented "Interstage Monitoring: Who, Why and How."

At the conclusion of the meeting, the location for next year's meeting was announced. *The 49th Annual Southeastern Pediatric Cardiology Society Conference* will be hosted by Joe DiMaggio Children's Hospital in sunny south Florida. The meeting will be held on September 15th-17th, 2016 at the Hyatt Regency Pier Sixty-Six in Ft. Lauderdale, FL. Dr. Maryanne Chrisant will serve as Program Director.

Information concerning the 48th annual meeting, meeting presentations described above and information for other upcoming meetings of interest can be found on the 48th annual meeting website - https://www.childrensal.org/spcs2015.

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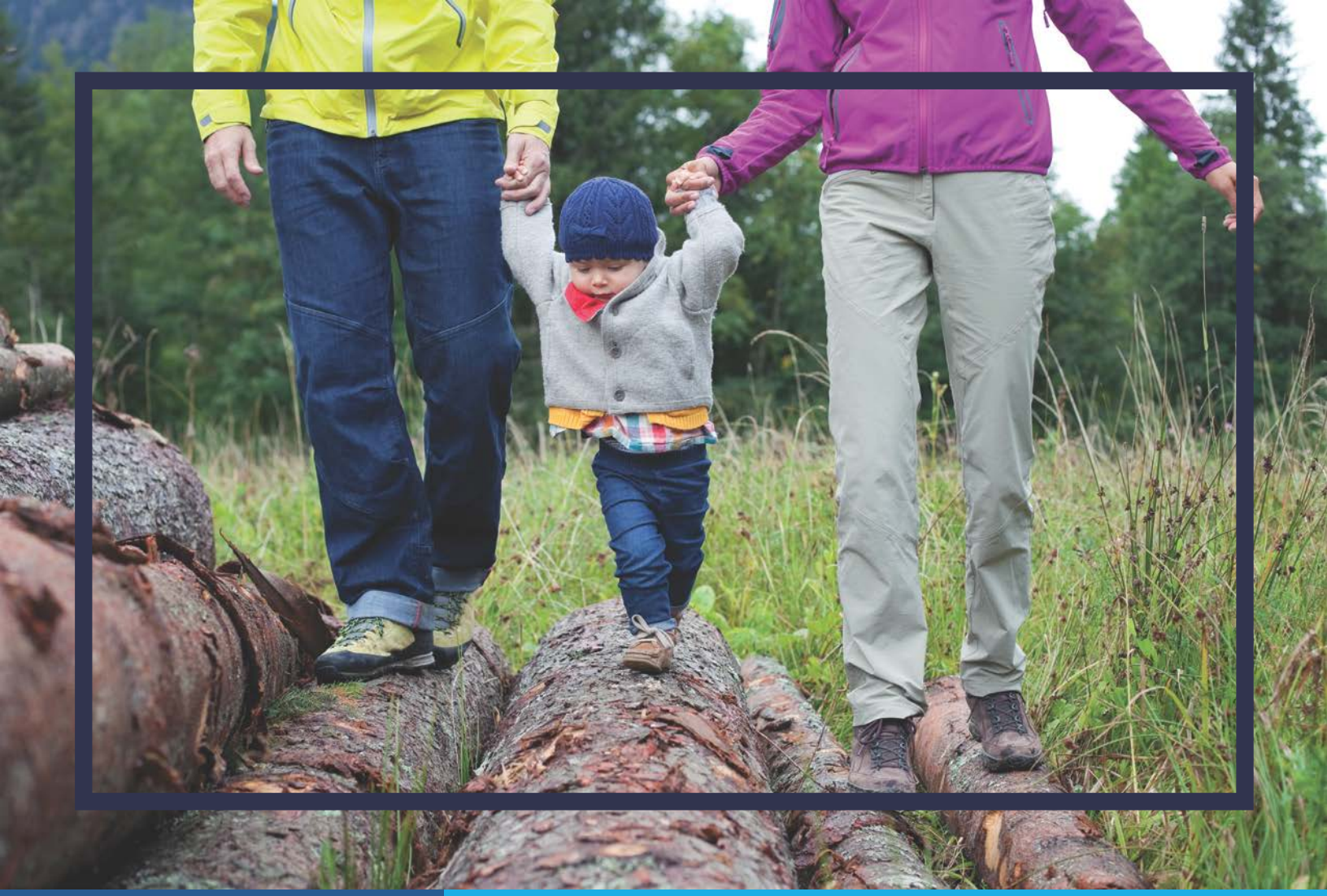

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Hearts Build New Muscle with this Simple Protein Patch

An international team of researchers has identified a protein that helps heart muscle cells regenerate after a heart attack. Researchers also showed that a patch loaded with the protein and placed inside the heart improved cardiac function and survival rates after a heart attack in mice and pigs.

Animal hearts regained close to normal function within four to eight weeks after treatment with the protein patch. It might be possible to test the patch in human clinical trials as early as 2017. The team, led by Professor Pilar Ruiz-Lozano at Stanford University and involving researchers from the University of California, San Diego and Sanford Burnham Prebys Medical Discovery Institute (SBP) published their findings in the Sept. 16 online issue of *Nature*.

"We are really excited about the prospect of bringing this technology to the clinic," said Mark Mercola, Professor of Bioengineering at UC San Diego and a professor in the Development, Aging and Regeneration Program at SBP. "It's commercially viable, clinically attractive and you don't need immunosuppressive drugs."

High throughput technology in Mercola's lab was critical in identifying a natural protein, called Follistatin-like 1 (FSTL1), and showing that it can stimulate cultured heart muscle cells to divide. Researchers led by Ruiz-Lozano at Stanford embedded the protein in a patch and applied it to the surface of mouse and pig hearts that had undergone an experimental form of myocardial infarction or "heart attack." Remarkably, FSTL1 caused heart muscle cells already present within the heart to multiply and re-build the damaged heart and reduce scarring.

Heart muscle regeneration and scarring are two major issues that current treatments for heart attacks do not address, said Ruiz-Lozano. "Treatments don't deal with this fundamental problem--and consequently

many patients progressively lose heart function, leading to long-term disability and eventually death," she said.

Today, most patients survive a heart attack immediately after it happens. However, the organ is damaged and scarred, making it harder to pump blood. Sustained pressure causes scarring to spread and ultimately leads to heart failure. Heart failure is a major source of mortality worldwide, and roughly half of heart failure patients die within five to six years. Treatments available today focus primarily on making it easier for the heart to pump blood, and advances have extended patients' lives. But they can't help regenerate heart tissue.

The team initially looked to other species for inspiration. Lower vertebrates, such as fish, can regenerate heart muscle, and prior studies in fish suggested that the epicardium, the heart's outside layer, might produce regenerative compounds. The researchers joined forces to find a solution.

The team started with the epicardial cells themselves, and showed that they stimulated existing heart muscle cells, or cardiomyocytes, to replicate. To find whether a single compound might be responsible, the Mercola lab used mass spectrometry, a sophisticated technology, to find over 300 proteins produced by the cells that could fit the bill. They then screened a number of these candidates using high throughput assays to look for the ones that had the same activity as the cells, and found that only one did the job: Follistatin-like 1 (FSTL1).

The group at Stanford--including teams led by Ruiz-Lozano, Dan Bernstein, Manish Butte and Phil Yang-- led the development effort for a therapeutic patch made out of collagen, which was cast with FSTL1 at its core. The patch has the elasticity of fetal heart tissue and slowly releases the protein. "It could act like a cell nursery," Ruiz-Lozano said. "It's a hospitable environment. Over time, it gets remodeled and becomes vascularized as new muscle cells come in."

Testing the patch loaded with FSTL1 in a heart attack model in mice and pigs showed that it stimulated tissue regeneration even if implanted after the injury. For example, in pigs that had suffered a heart attack, the fraction of blood pumped out of the left ventricle dropped from the normal 50% to 30%. But function was restored to 40% after the patch was surgically placed onto the heart a week after injury and remained stable. The pigs' heart tissue also scarred considerably less.

Ruiz-Lozano is the co-founder of EpikaBio, a startup that aims to bring the patches to human clinical trials as soon as possible.

Research Team Identifies New Genetic Cause for Heart Arrhythmia

Newswise – Scientists at The Ohio State University Dorothy M. Davis Heart and Lung Research Institute have identified a new genetic cause for congenital heart arrhythmia. The results of their research are published online by the Proceedings of the National Academy of Sciences (PNAS).

The mechanism is due to defects in the regulation of the primary sodium channel, which controls the flow of sodium ions across the heart cell membrane. When these channels don't work properly, it promotes abnormal heart rate (arrhythmia) and symptoms of heart failure.

"The mechanism of disease was unexpected," said Hassan Musa, a research scientist in Ohio State's Department of Physiology and Cell Biology and first author of the publication. "As a field, we are beginning to identify genetic variants that alter the sodium channel's association with essential regulatory proteins. However, in this case, we were surprised by the impact of this gene variant on the regulation of the sodium channel by a protein called FGF12."

Musa and the team examined genes from a 27-year-old man who had suffered sudden cardiac arrest while moving boxes at work. In addition to the cardiac arrest, tests showed the man also has atrial fibrillation. Doctors implanted a defibrillator, which has appropriately fired several times to save the man's life.

"Because of this man's cardiac arrest at a young age, as well as his family history of sudden cardiac death, our team in the Inherited Arrhythmia Clinic had a high suspicion for an inherited arrhythmia disease, so we conducted genetic testing for known arrhythmia genes," said Amy Sturm, licensed genetic counselor and a co-author on the research. "This identified a novel mutation previously undescribed in the sodium channel SCN5A gene. Mutations in SCN5A are associated with several hereditary cardiovascular diseases, so we knew it was a strong candidate for his and his family's arrhythmia condition."

Further screening of the man's family showed his mother, sister and young niece also have the SCN5A gene variant.

The team tested the impact the mutation had on signaling proteins (fibroblast growth factor homologous factors – FHFs) that regulate sodium channels and found it blocked the proteins from binding and caused abnormal function consistent with human arrhythmia.

"It's the first evidence of human arrhythmia based on gene variants that block FHFs," said Peter Mohler, Director of the Davis Heart and Lung Research Institute, and corresponding author of the study. "This will need to be tested further as more regulatory proteins are associated with cardiac cell function."

Other members of the Ohio State research team include: Crystal Kline, Nathaniel Murphy, Sara Adelman, Benjamin Johnson, Thomas Csepe, Dr. Ahmet Kilic, Paul Janssen, Vadim Fedorov, Dr. Raul Weiss and Thomas Hund, as well as Geoffrey Pitt and colleagues at Duke University Medical Center.

This research was supported by grants from the National Institutes of Health, the American Heart Association and the William D. and Jacquelyn L. Wells Fund for Cardiovascular Research.

Personalized Heart Models for Surgical Planning - System Can Convert MRI Scans into 3D-Printed, Physical Models in Hours

Researchers at MIT and Boston Children's Hospital have developed a system that can take MRI scans of a patient's heart and, in a matter of hours, convert them into a tangible, physical model that surgeons can use to plan surgery.

The models could provide a more intuitive way for surgeons to assess and prepare for the anatomical idiosyncrasies of individual

patients. “Our collaborators are convinced that this will make a difference,” says Polina Golland, a professor of Electrical Engineering and Computer Science at MIT, who led the project. “The phrase I heard is that ‘surgeons see with their hands,’ that the perception is in the touch.”

This fall, seven cardiac surgeons at Boston Children’s Hospital will participate in a study intended to evaluate the models’ usefulness.

Golland and her colleagues described their new system at the *International Conference on Medical Image Computing and Computer Assisted Intervention* in October. Danielle Pace, an MIT graduate student in Electrical Engineering and Computer Science, is first author on the paper and spearheaded the development of the software that analyzes the MRI scans. Mehdi Moghari, a physicist at Boston Children’s Hospital, developed new procedures that increase the precision of MRI scans tenfold, and Andrew Powell, a cardiologist at the hospital, leads the project’s clinical work.

The work was funded by both Boston Children’s Hospital and by Harvard Catalyst, a consortium aimed at rapidly moving scientific innovation into the clinic.

MRI data consist of a series of cross sections of a three-dimensional object. Like a black-and-white photograph, each cross section has regions of dark and light, and the boundaries between those regions may indicate the edges of anatomical structures. Then again, they may not.

Determining the boundaries between distinct objects in an image is one of the central problems in computer vision, known as “image segmentation.” But general-purpose image-segmentation algorithms aren’t reliable enough to produce the very precise models that surgical planning requires.

Human Factors

Typically, the way to make an image-segmentation algorithm more precise is to augment it with a generic model of the object to be segmented. Human hearts, for instance, have chambers and blood vessels that are usually in roughly the same places relative to each other. That anatomical consistency could give a segmentation algorithm a way to weed out improbable conclusions about object boundaries.

The problem with that approach is that many of the cardiac patients at Boston Children’s Hospital require surgery precisely because the anatomy of their hearts is irregular. Inferences from a generic model could obscure the very features that matter most to the surgeon.

In the past, researchers have produced printable models of the heart by manually indicating boundaries in MRI scans. But with the 200 or so cross-sections in one of Moghari’s high-precision scans, that process can take eight to 10 hours.

“They want to bring the kids in for scanning and spend probably a day or two doing planning of how exactly they’re going to operate,” Golland says. “If it takes another day just to process the images, it becomes unwieldy.”

Pace and Golland’s solution was to ask a human expert to identify boundaries in a few of the cross sections and allow algorithms to take over from there. Their strongest results came when they asked the expert to segment only a small patch —one-ninth of the total area — of each cross-section.

In that case, segmenting just 14 patches and letting the algorithm infer the rest yielded 90% agreement with expert segmentation of the entire collection of 200 cross-sections. Human segmentation of just three patches yielded 80% agreement.

“I think that if somebody told me that I could segment the whole heart from eight slices out of 200, I would not have believed them,” Golland says. “It was a surprise to us.”

Together, human segmentation of sample patches and the algorithmic generation of a digital, 3-D heart model takes about an hour. The 3-D-printing process takes a couple of hours more.

Prognosis

Currently, the algorithm examines patches of unsegmented cross-sections and looks for similar features in the nearest segmented cross-sections. But Golland believes that its performance might be improved if it also examined patches that

ran obliquely across several cross-sections. This and other variations on the algorithm are the subject of ongoing research.

The clinical study in the fall will involve MRIs from 10 patients who have already received treatment at Boston Children's Hospital. Each of seven surgeons will be given data on all 10 patients — some, probably, more than once. That data will include the raw MRI scans and, on a randomized basis, either a physical model or a computerized 3-D model, based, again at random, on either human segmentations or algorithmic segmentations.

Using that data, the surgeons will draw up surgical plans, which will be compared with documentation of the interventions that were performed on each of the patients. The hope is that the study will shed light on whether 3-D-printed physical models can actually improve surgical outcomes.

What Powers the Pumping Heart?

Researchers at the Ted Rogers Centre for Heart Research have uncovered a treasure trove of proteins, which holds answers about how our heart pumps -- a phenomenon known as contractility.

Led by University of Toronto Physiology Professor Anthony Gramolini and his collaborator, Professor Thomas Kislinger in the Department of Medical Biophysics, the team used high-throughput methods to identify more than 500 membrane proteins on the surfaces of cardiac contractile cells, which are likely to have a critical role in normal heart function. The proteins may also play a part in heart failure and abnormal heartbeat patterns known as arrhythmias.

"In addition to providing a new understanding of what makes our hearts pump, these findings could also help researchers uncover new information about how heart disease affects the signal pathways in our hearts. That might pave the way to find ways to prevent or reverse those changes," says Gramolini.

During the study, the researchers found about 500 novel molecules that have been conserved throughout evolution. These molecules haven't been studied in the heart and little is known about what they do in other tissues.

The group's research focused on a protein called transmembrane protein 65 (Tmem65). By studying human stem cells and zebrafish using cell imaging and biochemical techniques, the researchers discovered that Tmem65 is involved in communication and electrical processes known as electrical coupling and calcium signaling. The team showed that Tmem65 regulates the connection point between adjacent cardiac contractile cells where it contributes to making the heart contract normally. Removing the protein had fatal consequences. The team also identified Tmem65 as the first critical tool for stem-cell researchers to monitor the maturation of cells in the heart's two main chambers, known as ventricles.

"These proteins are theoretically targetable for intervention as well as basic study. In this study, our focus was on Tmem65, but there are 555 proteins that we identified and showed that they are present throughout many species and are conserved throughout evolution-- at least in the mouse and the human -- in the heart's membrane-enriched contractile cells. Tmem65 was only the number-one candidate in our study, but theoretically, we have 554 other proteins to work through," says Gramolini.

The study, published in *Nature Communications*, also provides the first resource of healthy human and mouse heart-cell proteins that will help scientists develop a better understanding of the mechanisms involved in cardiac disease.

Gramolini says the findings are essential for understanding cardiac biology, and hopes they open the door for further study into health and disease in his lab and others.

"We need to figure out what all of these molecules are doing. My team and I hope our research sets the stage for other people to begin to pick up some of this work," says Gramolini. "These are molecules that haven't been studied, but must play some role in heart function. If a protein is conserved in evolution, generally it must have a critical function. We are very excited to look at the role of a number of these new proteins."

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