CONGENITAL CARDIOLOGY TODAY
Timely News & Information for Congenital/Structural Cardiologists & Cardiothoracic Surgeons Worldwide
International Edition
Vol. 20 - Issue 3
March 2022

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Interventional Cardiac MRI – Revisited

Kanishka Ratnayaka, MD & Robert J. Lederman, MD

Editor's Note
Congenital Cardiology Today previously published this article by Drs. Ratnayaka and Lederman in August 2016. We are "revisiting" it now in tribute to Dr. Ratnayaka, who recently died. The subject matter is still highly topical, and the promise of Interventional Cardiac MRI remains largely unfulfilled.

Interventional cardiologists specializing in Congenital Heart Disease (CHD) have grown adept at using what is available, whether devices or imaging modalities, to treat their patients. Nevertheless, while procedures increase in complexity, operators continue to rely on two-dimensional imaging guidance of gray and white shadows, pattern recognition, and contrast angiography. Complex 3-dimensional spatial relationships are not addressed by current techniques, which can expose patients to significant radiation. Growing and developing children are particularly radiosensitive and carry a lifetime of oncologic risk. Chromosomal damage in the peripheral blood of children exposed to catheterization-related radiation has been detected.[1,2] Interventional cardiac MRI (ICMR) guidance offers a potential solution.[3]

Cardiac MRI is a radiation-free, robust imaging modality used to: evaluate cardiac anatomy and function, measure volume and flow, measure tissue infarction, evaluate perfusion and viability, and allow for three-dimensional reconstruction of cardiac and vascular anatomy. Real-time cardiac MRI can provide excellent soft tissue imaging at approximately 5-15 frames/second in many simultaneous planes in any orientation. Combining invasive catheter hemodynamic measurements and MRI physiologic assessment power enables us to realize the full potential of catheterization diagnosis and intervention.

State of the Art

Diagnostic (Invasive)

In patients requiring invasive diagnostic studies, particularly serial studies (single ventricle, heart transplant) the radiation-sparing argument may be most compelling; the cumulative X-ray dose may be significant.[4] MRI offers a radiation and contrast-free alternative to those patients who may benefit most from the wealth of structural, functional, and biochemical information MRI can provide. In some critical instances, such as calculating pulmonary

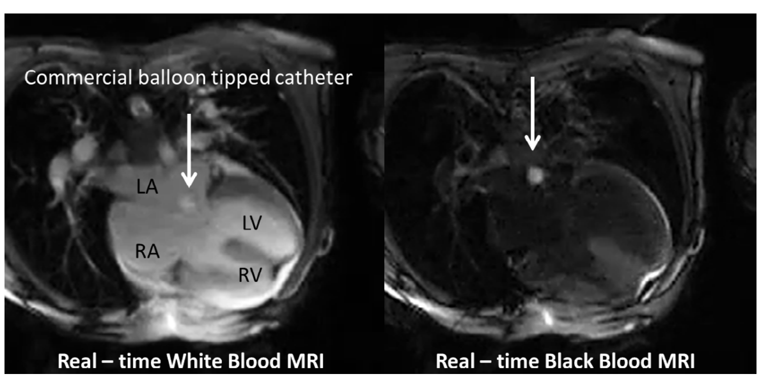

FIGURE 1
Real-time MRI Right and Left Heart Catheterization in Complete Atrioventricular Canal.

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vascular resistance in patients with pulmonary artery hypertension and undergoing staged surgical palliation, MRI catheterization evaluation can be superior to the current methods.[5] While MRI guided catheterization emerged over a decade ago,[6] it has been non-glamourous, incremental workflow and user interface enhancements that have fueled steady progress. The worldwide experience approaches one-thousand patients. An understandable critique of ICMR is the lack of compatible catheter and guidewire tools, but for invasive diagnostic studies, off-the-shelf balloon endhole wedge catheters are sufficient **(Figure 1).** A commercially available MR safe and visible guidewire would enable MRI guidance for most patients requiring diagnostic cardiac catheterization. A polymer guidewire is undergoing final stage clinical testing in Europe,[7] and safe metallic guidewires are approaching clinical testing.[8] Another typical critique is that MRI catheterization is time-consuming when compared to current standard X-ray catheterization. In our experience, simple workflow enhancements and experience have substantially decreased time to approximately 15 minutes per hemodynamic condition tested.

The majority of worldwide experience has been performed at three centers (King College London, Great Ormond Street, and National Institutes of Health), but clinical progress has increased attention. Attendance at the Society for Cardiovascular Magnetic Resonance, www.scmr2017.org, annual scientific sessions "interventional cardiac MRI" one day pre-conference has steadily grown with over one hundred participants in each of the last three years. In the past year, the National Institutes of Health (NIH) has hosted two hands-on MRI catheterization courses for eighty guests coming from twenty centers in North America and Europe; future training courses are being scheduled for interested centers.

X-ray Fused with MRI

While MR-guided intervention remains the eventual goal, XFM (X-ray fused with MRI) is an interim step that harnesses the soft tissue information from MRI to guide anatomically and spatially complex procedures. It can be viewed as a step toward wholly MRI-guided intervention. XFM allows operators to take advantage of the superiority of MRI soft tissue visualization in the familiar working environment of the fluoroscopy suite. The goal of fusion imaging is to enhance the capabilities of X-ray interventional procedures by co-registering MRI-derived roadmaps, to depict soft-tissue features not evident on X-ray. MRI-derived cardiac regions of interest are manually segmented and presented to the operator as image overlay on live X-ray fluoroscopy. Several groups have published on XFM radiation/contrast sparing and enhanced operator confidence in clinical cases.[9,10] Other groups have shown that registration of static MRI images to live X-ray fluoroscopy takes little time[11] with minimal target registration error.[12] Nevertheless, loss of operator confidence in pre-acquired roadmaps outdated by cardiac and respiratory motion as well as stiff wires and bulky device/delivery systems, continues to be a challenge. XFM may prove most useful in guidance of unconventional interventional Congenital Heart Disease procedures[13] **(Figure 2).**

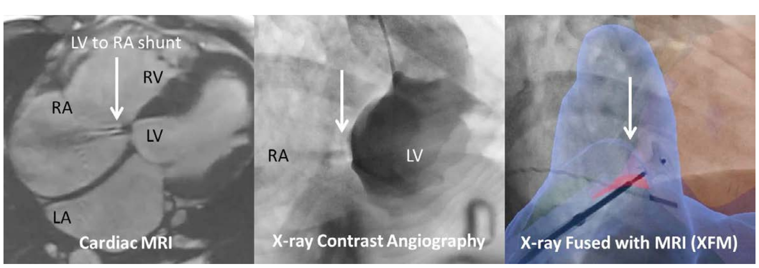

FIGURE 2 *X-ray fused with MRI (XFM) guided device closure of left ventricle to right atrium shunt.*

Intervention

Real-time MRI-guided cardiovascular intervention promises superb tissue imaging in multiple views and any orientation to guide traditional and emerging interventional procedures. Pre-clinical MRI guided cardiac intervention has ranged from aortic stenting[14] to aortic endografting to peripheral artery recanalization.[15] MRI guided catheter intervention in patients has been limited.[16,17] Progress in ICMR-guided intervention continues to encounter inadequate MR safe and visible catheter devices. Increasing numbers of small companies focused on delivery of such devices is encouraging.[17,18]

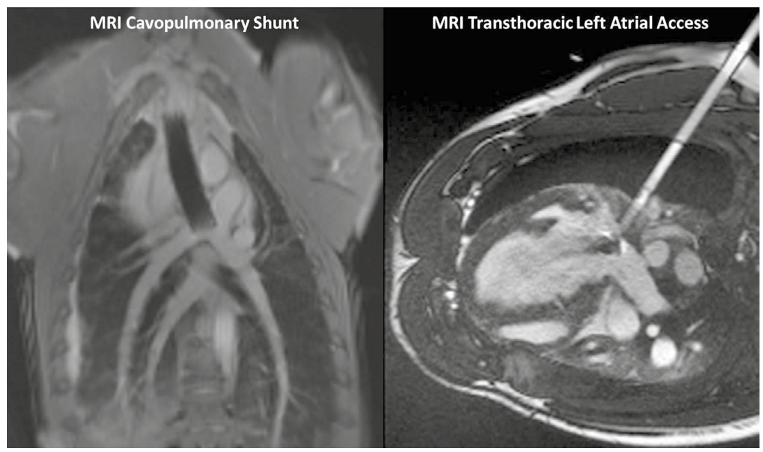

FIGURE 3 *Real time MRI guided percutaneous cavopulmonary shunt and transthoracic left atrial access.*

Interventional cardiac MRI's true potential is in providing surgical-type visualization to enable closed chest, off-bypass novel cardiovascular intervention. One representative example is percutaneous navigation of extra-vascular space under direct (MRI) visualization to join vessels as our surgical colleagues do today with surgical shunts.[19] ICMR provides complete thoracic context imaging that may permit new access routes to the heart for cardiac intervention such as from the patient's back[20] **(Figure 3).**

MR Invasive Electrophysiology

The rationale of MRI guidance for invasive electrophysiology is straight forward - direct observation of myocardial injury during tissue ablation would be attractive to guide procedural conduct; this premise has been explored by a number of groups in animals and most recently in clinical studies.[21] MRI safe and visible

Important Labeling Information for the United States

Indications: The Melody TPV is indicated for use in the management of pediatric and adult patients who have a clinical indication for intervention on a dysfunctional right ventricular outflow tract (RVOT) conduit or surgical bioprosthetic pulmonary valve that has ≥ moderate regurgitation, and/or a mean RVOT gradient ≥ 35 mm Hg.

Contraindications: None known.

Warnings/Precautions/Side Effects

- **DO NOT implant in the aortic or mitral position. Pre-clinical 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.

For additional information, please refer to the Instructions for Use provided with the product or available on http://manuals.medtronic.com.

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician.

Important Labeling Information for Geographies Outside of the United States

Indications: The Melody™ TPV is indicated for use in patients with the following clinical conditions:

- Patients with regurgitant prosthetic right ventricular outflow tract (RVOT) conduits or bioprostheses with a clinical indication for invasive or surgical intervention, OR
- Patients with stenotic prosthetic RVOT conduits or bioprostheses where the risk of worsening regurgitation is a relative contraindication to balloon dilatation or stenting

Contraindications

- Venous anatomy unable to accommodate a 22 Fr size introducer sheath
- Implantation of the TPV in the left heart
- RVOT unfavorable for good stent anchorage
- Severe RVOT obstruction, which cannot be dilated by balloon
- Obstruction of the central veins
- Clinical or biological signs of infection
- Active endocarditis
- Known allergy to aspirin or heparin
- Pregnancy

Potential Complications/Adverse Events: 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, 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.

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For additional information, please refer to the Instructions for Use provided with the product or available on http://manuals.medtronic.com.

The Melody Transcatheter Pulmonary Valve and Ensemble II Transcatheter Delivery System has received CE Mark approval and is available for distribution in Europe.

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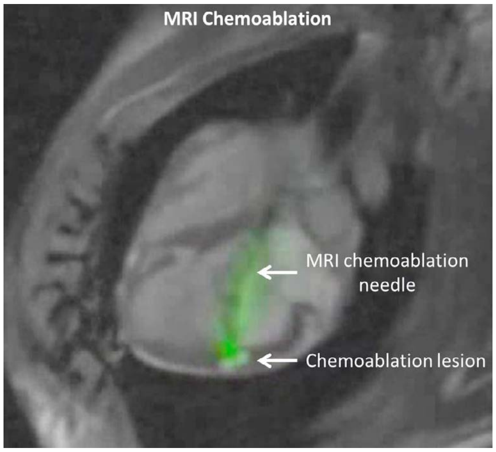

FIGURE 4 *Real time MRI guided chemoablation.*

electrophysiology device development has enjoyed tremendous recent progress. An MRI safe and visible integrated catheter mapping and ablation system has been used in clinical translation.[22] The device advancement in MRI guided electrophysiology will likely permit significant progression in the coming years. Perhaps more exciting, an alternative approach to tissue ablation using injected caustic agents (acetic acid or ethanol), instead of radiofrequency ablation, exploits the unique capabilities of MRI to map and target arrhythmia substrates and interactively visualize irreversibly necrotic ablation lesions[23] **(Figure 4).**

MRI Inspired, X-Ray Guided

Cardiac MRI provides operators with a "big picture" view of the entire thoracic context with impressive anatomic detail. Real-time imaging is presented in multiple slices and any orientation that can be manipulated quickly and easily. This ability allows an appreciation of anatomic relationships that is difficult to capture with traditional imaging. Pursuing MRI guided cardiac intervention has inspired innovative X-ray guided procedures. One novel X-ray procedure is percutaneous mitral valve repair by accessing the coronary sinus and tunneling through the myocardium to create a tensioned cerclage loop.[24] Exiting the right atrial appendage to deploy a circumferential loop in the pericardium to reduce tricuspid regurgitation is another.[25] Exiting the inferior vena cava and entering the aorta to permit vascular entry of large catheter delivery systems and devices is yet another example.[26] Clinical translation of caval-aortic access continues to grow. To date, there have been 204 patients at 27 centers **(Figure 5).**

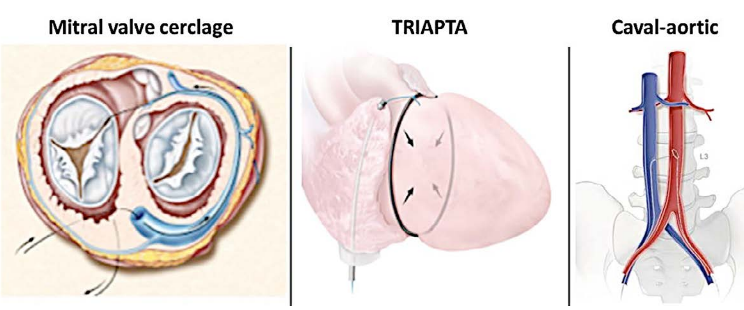

FIGURE 5 *MRI inspired novel percutaneous procedures: mitral valve cerclage, transatrial intrapericardial tricuspid annuloplasty (TRIAPTA), caval-aortic access.*

Conclusion

Minimally invasive and catheter-based therapies are targeting increasingly complex pathologies. This agenda requires better procedural image guidance. Interventional cardiac MRI provides a range of potential radiation-sparing opportunities for conventional and novel therapy.

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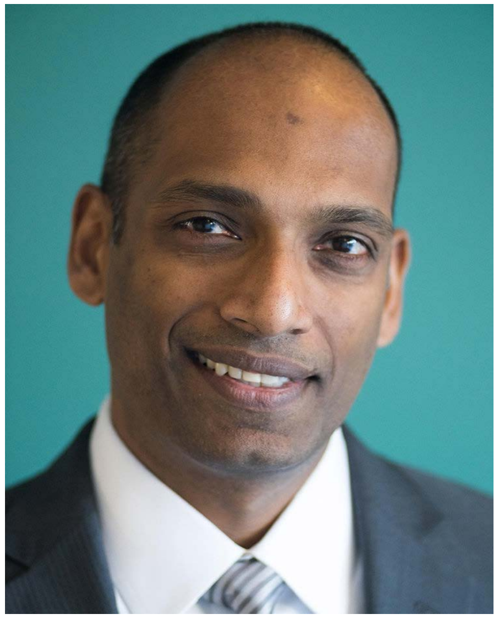
See additional references in the August 2016 issue of CCT
https://www.congenitalcardiologytoday.com/_files/ugd/616c37_bc2e14e255c84f1a95f86dfacf28086a.pdf

In Memorium: Kanishka Ratnayaka, MD (1974 – 2021)

Kanishka Ratnayaka, MD, was a pioneer who embraced the use of Magnetic Resonance Imaging to guide interventional procedures. He helped refine real-time MRI imaging to make it suitable for cardiac catheterization procedures. In 2011, he established an NIH-funded MRI Catheterization laboratory at Children's National Medical Center. In that lab, he demonstrated the feasibility and safety of performing many routine diagnostic catheterization procedures exclusively under MRI guidance. At NIH, he designed and developed new interventional procedures many of which are also exclusively MRI guided. He organized interventional MR courses and taught interventional MR in numerous educational venues. His considerable work in this field led to greater reliance on MR imaging to guide interventions. He pointed to a future when most pediatric and structural cardiac interventions will be performed under MR guidance.

At the time of his passing, he was a much-loved member of the UC San Diego faculty and of the Division of Cardiology at Rady Children's Hospital in San Diego. Shortly after arriving in San Diego in 2016, Dr. Ratnayaka began planning and fundraising for an Interventional Center combining real time MRI and traditional fluoroscopy. Ultimately, he was the principal force behind making the Dickinson Image-Guided Interventional Center at Rady Children's Hospital a reality. Tragically, the Center opened just days prior to Dr. Ratnayaka's death on Christmas Day. He was never able to perform a procedure in the Center.

In addition, to his contributions related to use of MRI guidance for cardiac catheterization procedures, Dr. Ratnayaka also designed novel cardiac devices and developed new interventional techniques. His designs include a covered stent, purpose-built for creation of percutaneous cavo-pulmonary anastomosis, and a biodegradable stent for use in pediatric



patients. Among other things, he also developed methodologies for the trans-caval access procedure (used in percutaneous aortic valve replacement), for a percutaneous Glenn procedure, and for use of coronary stents to maintain ductal patency in all cyanotic infants requiring "shunt" type palliation. Dr. Ratnayaka's legacy includes many fundamental, practice-changing contributions.

Kanishka Ratnayaka was born in Sri Lanka and grew up in Athens, Georgia. He attended Brown University and earned his medical degree at Emory University School of Medicine. He completed pediatrics training at Children's National Medical Center in Washington DC. His sub-specialty training in pediatric/congenital interventional cardiac catheterization and interventional cardiac MRI was at Children's National Medical Center and at the National Institutes of Health in Bethesda, Maryland. He remained in Washington DC on the cardiology staff at Children's National and as a researcher at the National Heart Lung and Blood Institute until he was recruited to San Diego. In San Diego, he continued as a part time NHLBI researcher making regular trips to Bethesda.

Beyond his direct professional activities and contributions, Dr. Ratnayaka found many additional avenues to serve his fellow man. In 2011, he and two of his college friends founded The World Children's Initiative, a non-profit organization dedicated to improving and rebuilding the healthcare and educational infrastructure for children in developing countries. WCI has completed several major projects: In Sri Lanka, WCI helped rebuild the Children's Hospital after it was devastated by a tsunami and established a scholarship fund for promising students. In Madagascar, WCI equipped modern operating rooms and trained staff in modern surgical techniques. Most recently in Uganda, WCI built a modern catheterization laboratory and trained hospital staff in pediatric interventional techniques.

Kanishka Ratnayaka was a visionary cardiologist who worked to transform his field. He was a true pioneer and a rising thought leader. He also made major contributions to advance healthcare for less fortunate children around the world. Notwithstanding these accomplishments, he was a very humble man.

On a personal level, my colleagues and I loved his optimistic perspective and his playful sense of humor. He was truly a team player who was always available and supportive of others. Perhaps most importantly, he was a loving husband and father. He will be greatly missed by all who knew him.

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The PICS Society and the CCISC Launch New Digital Global Medical Community for Physician-to-Physician Collaboration

This New Membership Benefit will Dramatically Advance Peer-to-Peer Interactions to Improve Pediatric and Congenital Patient Care Internationally

Damien Kenny, MD, FPICS

Thomas Forbes, MD, FPICS

Jacqueline Kreutzer, MD, FPICS

Lee Benson, MD, FPICS

*To ensure the relevancy and utility of the PICS/CCISC DocMatter Community platform, both PICS and CCISC have appointed a **Senior Steering Committee** comprised of physicians in leadership roles from both organizations. The Senior Steering Committee is comprised of Damien Kenny, MD, FPICS; Thomas Forbes, MD, FPICS; Jacqueline Kreutzer, MD, FPICS; and Lee Benson, MD, FPICS. The Senior Steering Committee is supported by a group of physician Advisors, also experts from PICS and/or CCISC, that will help DocMatter identify relevant content and hold the community to a high academic standard.*

The Pediatric and Congenital Interventional Cardiovascular Society (PICS), in conjunction with the Congenital Cardiovascular Interventional Study Consortium (CCISC), announced their joint venture to launch the PICS/CCISC DocMatter Community during February's Congenital Heart Disease Awareness Week. DocMatter is an established digital community platform for healthcare professionals, which will be tailored to transform peer-to-peer collaboration within the pediatric and congenital interventional cardiovascular community. The new benefit of society membership will be open to all active physician members of PICS and CCISC this month.

The annual PICS Symposium has a twenty-five-year legacy as the leading global event for stimulating peer-to-peer debate, discussion and collaboration. The Symposium has advanced interventional care for patients of all ages with Congenital Heart Disease (CHD). In 2020 the Symposium's leaders formed the PICS Society as the professional home for physicians and other health providers in this field. The PICS Society will continue the annual PICS Symposium while additionally launching the DocMatter Community to connect these professionals year-round.

Similarly, for nearly two decades the CCISC has managed an active community of more than 250 physicians that collaborate daily via an email platform. The CCISC has a long, proud history of connecting CHD interventionalists involved with research studies, through centralized patient registries that advance scientific knowledge.

The PICS/CCISC DocMatter Community resource marks an evolution point for both professional networks, which will dramatically expand collaboration in this highly specialized medical discipline. Notably, this new partnership will allow the frequency of this collaboration to increase in an archivable, secure, internet-enabled and human-supported format. The DocMatter platform and its dedicated team will improve the quality and significance of "best practice" sharing among physician society members through sharing of case images and knowledge generally in an easily accessible format.

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"The PICS Society, as the professional global home for our specialty, will be better positioned to live our vision and mission of fostering research, education and advocacy through the formation of this digital sharing platform with CCISC," said PICS Society Vice President, Damien Kenny, MD, FPICS, on behalf of PICS President Ziyad M. Hijazi, MD, MPH, FPICS. "We are excited to launch the community…and anticipate immediate benefits to the patients we are privileged to treat."

The opportunity to create the PICS/CCISC DocMatter Community was identified and fully funded by B. Braun Interventional Systems and NuMED for Children, two long-term medical device industry sponsors of the PICS and CCISC missions. The intent is that the industry sponsors bear the full cost of the platform, and are committed to doing so for multiple years, so that this membership benefit can be made available at no cost to all members-in-good-standing.

"Both PICS and CCISC recognize the significance of industry, provider and society collaboration and its impact on the advancement of our specialty," said CCISC Founder Thomas Forbes, MD, FPICS. "Our industry sponsors have experience with DocMatter specifically and believe the DocMatter Community will spark innovative ideas moving us all forward together as a collective team. We agree that open industry communication and partnership is vital in improving how we can best treat children and adults with Congenital Heart Disease."

The DocMatter team began adding PICS and CCISC members to the PICS/CCISC DocMatter Community in late February. If you are a Society member and need help activating your DocMatter account, contact the Community's Clinical Engagement Specialist, Inês Silva at ISilva@docmatter.com.

About the Pediatric and Congenital Interventional Cardiovascular Society (PICS)

The vision of the PICS Society is a world where anyone who can benefit from minimally invasive techniques to treat CHD can access safe, effective care. PICS promotes the highest quality care globally for infants, children and adults with CHD through minimally invasive techniques. The Society partners with dedicated national societies and other stakeholders to further knowledge and skills, fostering research, education and advocacy on behalf of health professionals and the patients our members are privileged to treat. For more information about PICS, including how to become a member, visit www.chdinterventions.org.

About the Congenital Cardiovascular Interventional Study Consortium (CCISC)

The CCISC is a not-for-profit organization dedicated to advancement of the science and treatment of infants, children and adults requiring surgical or interventional procedures for treatment of Congenital Heart Disease. The CCISC mission is to design, conduct and report findings of scientific studies in interventional cardiovascular care for individuals with congenital heart disease. To learn more about the CCISC visit https://ccisc.med.wayne.edu.

About DocMatter

DocMatter was founded on the simple premise that individual physicians should be empowered with online, real-time access to discover and then collaborate with experts on any medical topic. Today, DocMatter's artificial intelligence-driven software platform supports physicians at 60,000+ institutions across 160+ countries. The broad awareness of best practices advocated by experts and shared across specialist networks on DocMatter translates every day to better patient outcomes. To learn more visit https://www.docmatter.com.

How a Pig Heart Was Transplanted into a Human for the First Time

The First Transplant of a Pig Heart Genetically Modified for Acceptance into Human Bodies Raises Hopes for a New Solution to Donor Organ Shortages

For the first time, a human has been given a transplant of a pig's heart. David Bennett, 57, had the operation in Baltimore, Maryland, on January 7th using a heart that had been genetically modified to boost the chances of acceptance in a human body.

The donated heart came from a pig developed by US firm Revivicor, https://pipeline.unither.com/. In total, the animal had 10 genes modified. Four of those were inactivated, including one that causes an aggressive immune response and one that would otherwise cause the pig's heart to continue growing after transplant into a human body.

To further increase the chances of acceptance, the donor pig had six human genes inserted into its genome and Bennett is taking immune-suppressing medications. As this story went to press, Bennett was coping well with the new heart, but had not yet been taken off a heart-lung bypass machine supporting its function. His medical team told *The New York Times* that the animal heart was doing most of the work and that, so far, the heart "looks normal".

"This is a great step forward – you can compare it with the first landing on the moon," says Joachim Denner at the Free University of Berlin.

Transplants from other animals, known as xenotransplantation, have long been seen as a way to save the lives of the thousands of people who die each year while waiting for an organ transplant. The chief concern is whether our immune systems will accept such transplants, as organ rejection can happen even between carefully, immunologically-matched human donors and recipients.

Many research groups have been trying for years to modify animals, so their organs provoke less of an immune reaction, and have had success transplanting them into primates such as baboons.

These first days are a critical test, although immune rejection could take weeks or longer to develop, says Denner, who has been involved in primate research using Revivicor's pig organs, but has no financial connection to the firm. "We have to be cautious. We have to wait and see," he says.

Bennett was approved to have the risky procedure as he was too sick to go on the waiting list to get a human heart. If he is successfully taken off the bypass machine and continues to stay well, it could open the door to such transplants for a growing pool of other people. It could also lead to pig-to-human transplants of kidneys, livers and lungs in future.

There have been fears that virus genes naturally found in pig DNA could cross to humans, but these have faded after successful transplants of pig pancreas cells into people with diabetes. No such problems have arisen with transplants of whole pig organs into primates either. Still, it is likely that Bennett's doctors are closely monitoring him to check for this possibility, says Anthony Warrens at Queen Mary University of London, who was not involved in the work.

"This is a very early experiment and will not translate into clinical practice within a short period of time," he says. "If it works, it could be a small number of years away."

If this procedure succeeds, providing the organs to offer it more widely in future should not be a major obstacle. Pigs have about eight piglets in each litter and can start breeding before they are a year old, although they would need to be farmed in special hygienic conditions.

A spokesperson for NHS Blood and Transplant in the UK said in a statement: "We have been watching this particular field of research for many years. However, there is still some way to go before transplants of this kind become an everyday reality."

View the video here: https://www.newscientist.com/article/2304167-how-a-pig-heart-was-transplanted-into-a-human-for-the-first-time/?jwsource=cl

Australian Researchers Develop New Technique to Uncover Genes Involved in Congenital Heart Disease

One in every 100 babies is born with a Congenital Heart Disease (CHD), and CHD is the major cause of death in newborns – however, the genetic cause of these developmental disorders is not fully understood, hindering the development of accurate pre-natal genetic testing.

Now researchers from Monash University in Melbourne, Australia, have developed a way to determine which genes are "in play" in causing these cardiac abnormalities. The technique not only confirmed well-known CHD genes, but also discovered 35 new genes not previously suspected in the disease. The research opens the way, in the future, for more accurate pre-natal genetic testing for congenital heart disease.

The collaborative study, published in *Genome Biology*, and co-led by Associate Professor Mirana Ramialison from Monash University's Australian Regenerative Medicine Institute and the Murdoch Children's Research Institute, and Dr Travis Johnson from Monash University's School of Biological Sciences, aimed to improve on the current conventional approach to identifying disease-causing genes "which focuses on screening genes that are present in heart only– an approach that often overlooks genes that are present in other tissues as well, despite still playing important roles in heart development," Dr. Hieu Nim from Australian Regenerative Medicine Institute, the first author of the study said.

The resulting computational pipeline to identify not only genes specific for the heart, but genes that may also be associated with other organs such as the liver or kidney "These could comprise many of the missing congenital heart disease genes, but have been, to date, discounted because they are not unique to the heart," Associate Professor Ramialison, said.

The researchers then used the vinegar fly, *Drosophila melanogaster*, as a testing model to determine some of the functional impacts of these novel genes. Researchers use *Drosophila* because it is a well-established model organism to understand the genetic mechanisms of many human diseases. This is because: about 75% of human disease-causing genes are found in the fly in a similar form, it is easy to work with and breeds quickly, and many tools are available to manipulate any genes in it.

According to Dr Johnson, the vinegar-fly studies revealed "a long list of high-quality candidate genes for causing heart abnormalities in humans, giving real insight into just how susceptible this organ is to genetic mutations."

Dr Johnson cautioned that the identification of dozens of new CHD candidate genes is some time from providing more accurate pre-natal genetic testing for CHD. "We now need to conduct functional studies on all of these genes in animal experiments to determine what they actually do, so its early days, but we now have an excellent starting point."

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ISSN 1554-7787 print. ISSN 1554-0499 electronic.
Published monthly.