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# Left Ventricular Myocardial Noncompaction in a Child Affected by Cri Du Chat Syndrome

*Marcello Marcì, MD & Lucrezia Lo Cascio, MD*

**Keywords:** echocardiography, Cri du chat syndrome, left ventricular noncompaction, atrial septal defect, noncompaction cardiomyopathy

## Abstract

The following is a case report of an infant born with Cri du chat syndrome that has evidence of left ventricular noncompaction.

Cri du chat syndrome is a rare association of growth retardation, severe intellectual disability, hypertelorism and typical catlike cry, often combined with congenital heart defect, the occurrence of myocardial noncompaction among the associated cardiac anomalies has not been reported so far.

## Introduction

Cri du chat syndrome is a congenital disease with a characteristic cry, psychomotor delay, growth retardation and facial dysmorphism, resulting from deletion of the short arm of chromosome 5, first described by Lejeune et al. in 1963.[1]

We report the case of a three-year-old male affected by this syndrome, who developed left ventricular noncompaction, a rare myocardial disorder that is the third most frequent cause of cardiomyopathy in childhood. Isolated left ventricular noncompaction is a congenital anomaly of myocardium characterized by prominent trabeculations consistent with myocardial meshwork with deep recesses, more evident in the lateral wall and apex of the left ventricle.

It has been hypothesized that myocardial noncompaction could be determined by failure of the process of trabecular compaction of the spongy meshwork of fibers, between gestational weeks 20 and 26, and the intertrabecular recesses become capillaries. Left ventricle noncompaction is characterized by the echocardiographic appearance of a non-compact subendocardial layer, which is two-fold thicker than the outer compact myocardial layer, in the parasternal short-axis. Moreover, there are deep inter-trabecular recesses perfused from the ventricular cavity.

This cardiomyopathy can have a wide spectrum of clinical manifestations ranging from asymptomatic cases to heart failure, thromboembolic events, malignant arrhythmias, and sudden death, especially in patients with left ventricular dilatation. In childhood, cardiac insufficiency usually manifests with failure to thrive and respiratory symptoms. To the best of our knowledge, this is the first time that association of Cri du chat syndrome with left ventricular noncompaction is reported in literature.

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## Case Presentation

The patient was the second child of non-consanguineous, healthy parents; his sister was also healthy. He was born at 39 weeks after an uncomplicated pregnancy. He showed a weight of 2,840 grams, ear malformations, bilateral single transverse palmar crease, microcephaly, systolic murmur and a cat-like cry. On the basis of dysmorphic facial appearance and atypical cry, Cri du chat syndrome was diagnosed, confirmed by karyotype 46 XX with 5p -; array CGH showed 5p15.33p14.3 deletion.

He was referred to our department for a systolic murmur. The echocardiogram showed a small secundum-type atrial septal defect and a slight prominent trabeculation that required an echographic follow-up. At the age of three-years-old, the echocardiogram was consistent with noncompaction of left ventricular apex and lateral distal wall, with a non-compacted/compacted myocardium ratio of 2:1 or more, and intertrabecular recesses filled by colour Doppler flow. Internal ventricular diameters were normal and systolic function was preserved (fractional shortening >30% and ejection fraction =55%) **(Figure 1).** At the one year follow-up, the ejection fraction is still normal, and the baby does not have symptoms of heart failure nor arrhythmias.

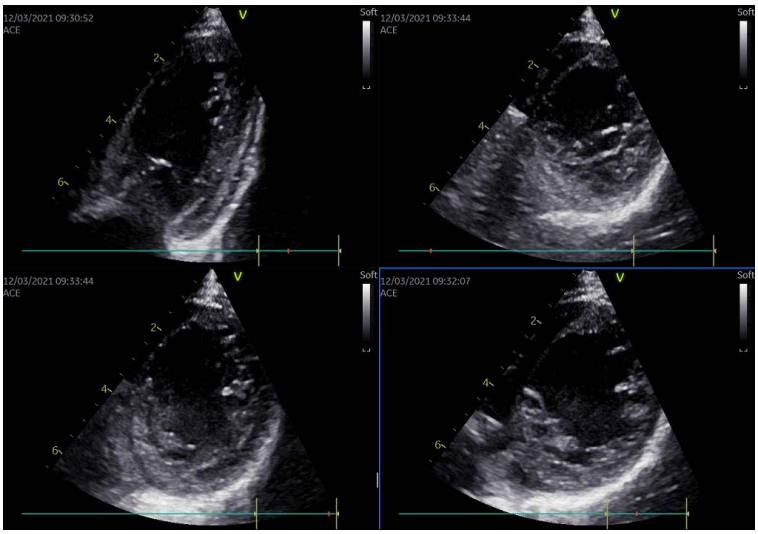


FIGURE 1 *Apical and parasternal short axis views of the left ventricle.*

## Discussion

Cri du chat (OMIM 123450) is a chromosomal syndrome, resulting from partial deletion on the short arm of chromosome 5, that is characterized by severe mental delay, cat-like cry, microcephaly, and facial abnormalities.

Congenital cardiac malformations are observed in about 29% of patients with microdeletion and in 55% of individuals affected by balanced translocation. The most frequent cardiac lesions are patent ductus arteriosus and ventricular septal defects; occasionally, it is associated with ventricular outflow obstruction.[2] Several contiguous genes mapped in 5p have been associated with cardiac development, such as ADAMTS16 in the region 5p15.32, DNAh5, NDUFS6 and IRX4 in region 5p15.33.[2,3,4]

Left ventricular noncompaction has not been reported in children with Cri du chat syndrome so far. Isolated myocardial noncompaction has a heterogeneous etiology, with sporadic or familial incidence.[6] In about one third of patients with left ventricular noncompaction, a genetic cause can be detected, mostly an autosomal dominant inherited mutation of several genes, such as TAZ, Cypher/ZASP, FKBP12, CSX, mitochondrial and sarcomeric protein genes can be involved too.[6] An X-linked inheritance has been reported in 7% of the patients[6] with frequent deletion of G4.5 gene, mapped in the long arm of the X chromosome. Noncompaction of the left ventricular myocardium can occur in association with neuromuscular disorders and genetic syndromes such as deletion 22q11, monosomy X (Turner syndrome), and Trisomy 13 and 18.

Among many of the genes identified as responsible for the development of myocardial noncompaction, some authors have focused attention on Nkx2-5, a critical component of the cardiac gene regulatory network. Left ventricular noncompaction has been reported in children with a mutation of Nkx2-5 and in Nkx2-5 knockout mice.[7] Nkx2-5 transcription factor regulates many key aspects of heart development in concert with other cardiac transcription factors, particularly Irx4. In fact, mice lacking the homeobox transcription factor Nkx2-5 have markedly reduced levels of Irx4 protein in cardiomyocytes.

Recent studies have identified Irx4, belonging to the Iroquois family of transcription factor, as a possible candidate in left ventricular noncompaction development.[5] Interestingly, transgenic mice lacking Irx4 develop myocardial noncompaction and have thinner ventricular walls with excessive trabeculations.[5] In addition, Irx4-deficient mice exhibit increased expression of heart failure marker Brain Natriuretic Peptide and develop cardiomyopathy with impaired systolic function and myocardial hypertrophy.

As a matter of fact, Irx4 expressed only in the trabecular region of myocardium during all stages of cardiac development[8] is essential for the process of transformation of trabecular in compact myocardium.[5] Irx transcription factors specifically inhibit expression of Bmp10, one of the NOTCH1 associated molecules involved in myocardial hyper-trabeculation.[5-9] Notably, our patient carried a deleted region containing the Irx4 gene (5p 15.33, position1,877,413-1,877236) thus suggesting that haploinsufficiency of this transcription factor can lead to noncompaction phenotype.

## Conclusion

We described the unprecedented reported case of Cri du chat syndrome associated with left ventricle noncompaction; the child carried a deletion of 5p 15.33 containing the Irx4 gene, that plays a pivotal role in ventricular myocardium development. Myocardial noncompaction, which is an evolutionary disorder, was not detectable at the first cardiologic evaluation of our patient, and gradually manifested at annual echocardiographic follow-up. Due to the variable latency of clinical manifestations of this cardiomyopathy, a complete cardiologic evaluation is suggested at the neonatal age in every patient with Cri du chat syndrome and should be screened periodically with echocardiography and ultrasounds beyond the neonatal age to rule out any cardiomyopathy.

Since severe outcomes and major cardiac adverse events have been frequently observed in patients with left ventricular noncompaction associated with chromosomal abnormalities,[10] an early diagnosis of this cardiomyopathic condition and periodic follow-ups are essential in order to monitor cardiac complications, particularly potential malignant rhythm alterations.

## Conflict of Interest

The author has none to report. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

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**MARCELLO MARCI, MD**
Ospedali riuniti Villa Sofia Cervello
Pediatric Cardiology Department
AOOR "Villa Sofia- Cervello"
Palermo, Italy
marcellomarci60@gmail.com

**LUCREZIA LO CASCIO, MD**
Ospedali riuniti Villa Sofia Cervello
Pediatric Cardiology Department
AOOR "Villa Sofia- Cervello"
Palermo, Italy

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# Utility of 3D Printing in Neonatal Mitral Valve Repair: A Case Report

*Donald J. Mattia, MD; Jonathan D. Plasencia, PhD; Daniel A.Velez, MD; Wayne J. Franklin, MD; Christopher L. Lindblade, MD*

**Keywords:** Congenital Heart Disease, imaging, mitral regurgitation, mitral valve repair, pediatric, preoperative care

## Case

A full-term newborn female failed her Congenital Heart Disease screen and echocardiogram revealed severely dysplastic mitral valve leaflets (anterior leaflet thickened with rolled tips, P1-P2 scalloped with nearly fixed mobility, P2 thickened with cleft), resulting in mitral regurgitation (MR) and severe left atrial enlargement **(Figure 1A)**. On the second Day of Life, she developed cardiogenic shock secondary to poor cardiac output that resulted in necrotizing enterocolitis and multi-organ system failure. She was intubated, started on milrinone and epinephrine, and transferred to a tertiary center.

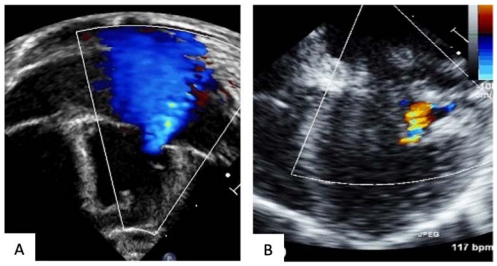


FIGURE 1
***A).*** *Transesophageal echocardiogram, mid-esophageal view demonstrating severe preoperative mitral regurgitation.*
***B).*** *Transesophageal echocardiogram showing trivial mitral regurgitation postoperatively.*

Computed-tomographic angiography (CTA) highlighted severely aneurysmal left atrium (LA) spanning over 41 cm craniocaudally, with signs of bilateral ventricular volume overload **(Figure 2A, 2B).** Echocardiogram demonstrated a dilated mitral valve annulus (2.07 cm, PHN z-score +9.6). Treatment options including medical management, transcatheter valve implantation, and surgical mitral valve repair were considered. A multidisciplinary team assessed the case and ultimately preferred surgical repair circumventing the need for a prosthetic valve and the need for anticoagulation. Echo and CT 3D reconstruction was limited in determining feasibility of surgical repair because the degree of atrial dilatation distorted typical landmarks and rotated the axis of the heart superiorly and rightward. Additionally, surgical planning required improved visualization of the pulmonary venous connection to the LA to determine the extent of left atrial wall resection.

Therefore, 3D printing of the myocardium was performed to provide a more thorough anatomical assessment **(Figure 3).** This modality has been utilized for its improved pulmonary vein evaluation in other procedures involving intricate LA manipulation, including left atrial appendage closure and radiofrequency ablation planning.[1,2] The 3D print allowed the surgical team to determine a safe approach via Sondergaard's groove as well as a region for tissue excision that would maintain the integrity of the pulmonary venous insertion.

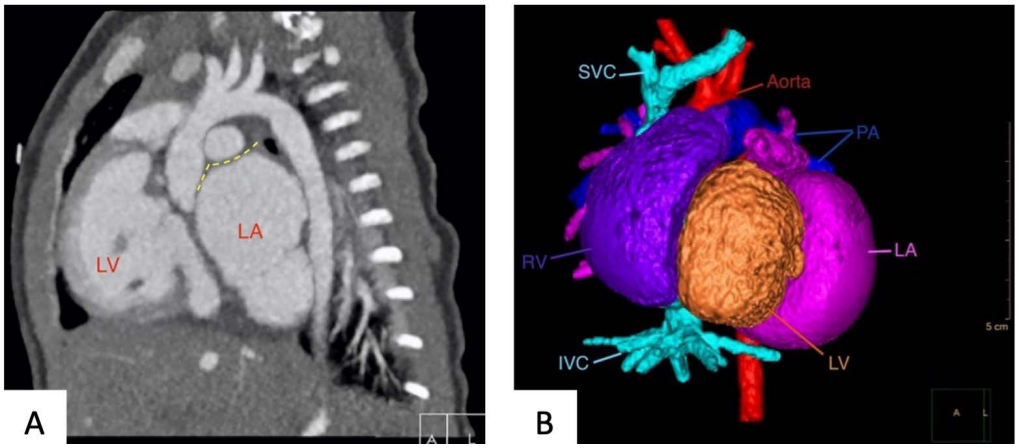


FIGURE 2
***A).*** *CTA, sagittal view. Dotted line demonstrates surgical approach via Sondergaard's groove in order to manipulate the mitral valve.*
***B).*** *Labeled CTA 3D reconstruction.*

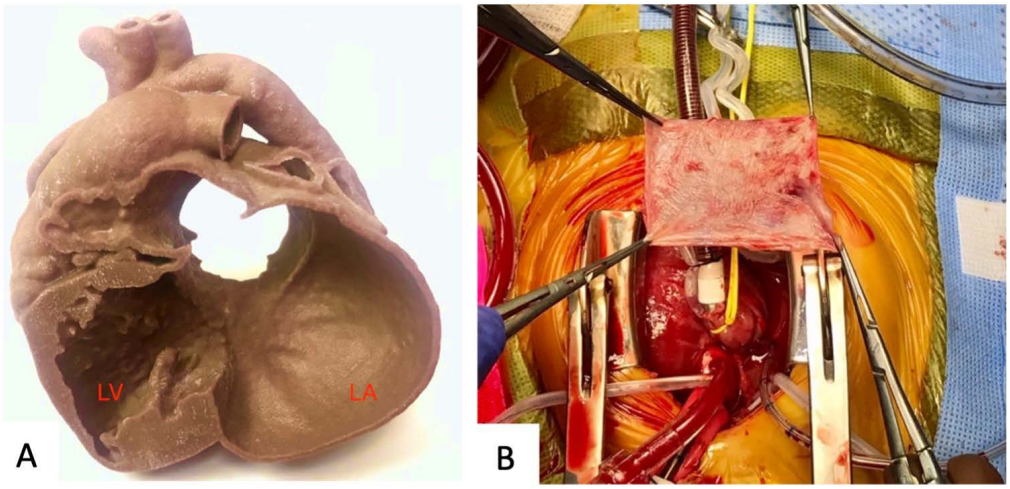


FIGURE 3
***A).*** *3D print of myocardium, sagittal view.* ***B).*** *Resected left atrium tissue.*

After extensive examination of the 3-D print, surgical mitral valve repair and commissuroplasty of both lateral and medial commissures and cleft closure on both leaflets was performed at 42 Days of Life. Utilizing the knowledge of the posterior left atrial wall anatomic landmarks obtained from examination of the 3-D print, extensive reduction atrioplasty was performed, and the LA closed in two layers. The excised LA tissue spanned an area of 4 x 5 cm. Intraoperative transesophageal echocardiogram demonstrated successful repair of the mitral valve with significant improvement of mitral regurgitation from severe to trivial **(Figure 1B).**

Mitral valve repair can be challenging because of both the unique pathologic morphology of a dysplastic mitral valve as well as the limited ability to visualize the anatomy by standard echocardiography.[3] Preoperative 3D-echocardiography is routinely performed in most congenital surgical centers to assess the entire mitral valve complex.[4] Typically, CTA is generally preferred to visualize the great vessels, coronary arteries, and extracardiac structures. However, our case demonstrates the role for CTA with 3D printing for improved evaluation of left atrial landmarks and mitral valve morphology to assist with the intricacies of surgical planning.

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**DONALD J. MATTIA, MD**
*Pediatric Resident*
Phoenix Children's Hospital
1919 E Thomas Rd
Phoenix, Arizona, USA
602.933.3366
dmattia@phoenixchildrens.com



**JONATHAN D. PLASENCIA, PHD**
*Principle Investigator of the 4D CAVA Lab*
Phoenix Children's Hospital
Department of Cardiology
Phoenix, Arizona, USA



**DANIEL A. VELEZ, MD**
*Co-Director of Heart Center, Division Chief of Cardiothoracic Surgery*
Phoenix Children's Hospital
Department of Cardiology
Phoenix, Arizona, USA



**WAYNE J. FRANKLIN, MD**
*Co-Director of Heart Center; Director Adult Congenital Heart Disease Program*
Phoenix Children's Hospital
Department of Cardiology
University of Arizona-College of Medicine-Phoenix
Phoenix, Arizona, USA



**CHRISTOPHER L. LINDBLADE, MD**
*Medical Director of Fetal Cardiology Program*
Phoenix Children's Hospital
Department of Cardiology
Phoenix, Arizona, USA

# PICS Symposium 2022 – Welcome Back!

*Kamel Shibbani, MD*

For this month's column, we recently had a conversation with *PICS Symposium* Founder Dr. Ziyad Hijazi and current Program Director Dr. Damien Kenny about the upcoming Symposium in Chicago from September 7th – 10th, 2022.

***KS: Thank you both! Let's jump right in –what is the theme of this year's meeting?***
***D.K:*** The core sentiment of this year's meeting is all of us getting back together again and bringing back a sense of normality. Although we were together last year, many friends and colleagues were unable to attend due to the pandemic. We are very optimistic that this year we will return to business as usual and able to share our experiences together in a safe and reasonably unrestrictive way.
***KS: Last year PICS adopted a hybrid approach allowing participation both virtually and in person. What should we expect this year?***
***DK:*** We very much hope this year's meeting will be back to a full in-person meeting. The pandemic has shown us the feasibility of having speakers join virtually, especially those unable to travel. But we're hopeful that such instances will be the exception rather than the rule.
***KS: Can we expect a virtual component for participants, where cases and talks can be taped and reviewed offline for those unable to attend in person?***
***DK:*** To a very limited degree. A select number of the presentations will be recorded and made available on the members-only part of our website. This is important so that selected talks about fundamentals or major advances in our field can be disseminated to our entire community.

However, the bedrock of the annual PICS Symposium has been in-person dialogue. Consistently, the feedback we get highlights this as the most critical component of the meeting. That is the core reason our community's once-a-year "come together" is so special!

*"The bedrock of the annual PICS Symposium has been in-person dialogue. […] That is the core reason our community's once-a-year 'come together' is so special!"* – *Dr. Damien Kenny*

***KS: Live cases are always a popular component of the meeting. Can you tell us a where we'll be broadcasting from for this year for the live cases?***
***DK:*** Chicago historically has had several different centers providing congenital cardiac services and we thought it would be ideal to include all three centers. All three of them graciously accepted. That speaks to the sort of collaboration that we would like to highlight between various congenital cardiac services. So, we'll have live cases from Lurie Children's Hospital, Christ Advocate Medical Center, and Rush University Medical Center.

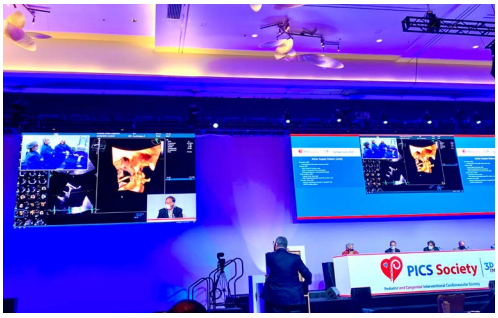
Our first day is usually our international day, and we're hoping to have teams from Cairo, Toronto, as well as teams from Sidra in Qatar.
***ZH:*** Actually, this will be the first time in 25 years that Cairo will transmit to us live! Dr. Maiy El Sayed will be joining us for live cases this year. We are honored to have Dr. El Sayed and her team playing such an important role!
***DK:*** I think that's a great reflection on how far things have come in Egypt, thanks mainly to the great work they do.
***ZH:*** We also have colleagues joining us from the US for live cases.
***DK:*** Yes! Our other live cases will be from Nationwide, Denver, and Mayo Clinic.

***KS: In addition to live cases from new international sites, can we expect new presenters as well?***
***DK:*** Certainly! We're constantly looking to add to our faculty. We have a "Young Leadership Award" each year, and the winner automatically joins the PICS faculty. In addition, we're having a session about new technology that will bring new faces from the FDA to share their experiences. Reflecting on feedback from last year, we have expanded faculty slots to include younger colleagues who are doing excellent work, ensuring they have an opportunity to showcase this great work.
***KS: I understand that this year's meeting will highlight the role of lymphatics in Congenital Heart Disease.***
***DK:*** We're going to have a three-hour dedicated session about lymphatics which will involve Dr. Yoav Dori as well as other international experts including Dr. Petru Liuba from Sweden. This session will include a taped case and possibly a hands-on lymphatics workshop at the beginning of the meeting! Stay tuned for confirmation of the hands-on lymphatic workshop, this would be a great opportunity to learn the techniques needed to access the lymphatic system. Exciting new direction for our field!
***KS: That sounds wonderful! Are there any other hands-on activities planned, either in the animal lab or otherwise?***
***DK:*** We're going to have a three-hour dedicated session about lymphatics which will involve Dr. Yoav Dori as well as other international experts

including Dr. Petru Liuba from Sweden. This session will include a taped case and possibly a hands-on lymphatics workshop at the beginning of the meeting! Stay tuned for confirmation of the hands-on lymphatic workshop, this would be a great opportunity to learn the techniques needed to access the lymphatic system. Exciting new direction for our field!

***KS: Can you tell us some more about the Fellows and Early Career course?***

***DK:*** We're excited to offer that course again this year! The plan is to have it over the two days prior to the meeting. It'll run on Monday, the 5th of September, and Tuesday, the 6th of September, with the full Symposium then starting on Wednesday, the 7th of September. The Fellows/Early Career Course will again be led by Dr. Vivian Dimas and Dr. Darren Berman. It was very well received last year, and we are certain that the hands-on aspect will add a very valuable dimension. The course is intended for people in their last year of fellowship and the first two years following fellowship. People interested in attending should fill out the appropriate form, which they can get on the PICS website www.picsymposium.com/fellows_registration.html, and provide a letter of interest and a letter of support from their program director.




***KS: We recently sat down with our allied health professional colleagues who talked a lot about the value of the nursing and tech breakout sessions. Can we expect such sessions again this year?***

***DK:*** Absolutely! They are an integral part of the work we do, and their sessions are always a very exciting part of the meeting. We definitely plan to have a breakout session geared towards our allied health professional colleagues.

***KS: What about our industry partners. What sort of industry involvement can we look forward to?***

***DK:*** We expect to have a number of industry sponsored symposia where industry can showcase new technology and allow attendees the opportunity to learn about innovations in our field. This was something we received great feedback on last year and will certainly bring back again this year. The exhibit hall will also be a great chance for our participants to meet our industry partners, without whom this meeting wouldn't be possible.

***KS: Since last year there was an announcement about a partnership between the PICS Society and the journal of Pediatric Cardiology, as well as other strategic partnerships. How is this going to be featured in the meeting this year?***

***DK:*** All members of the PICS Society will have free access to the journal of Pediatric Cardiology, which is now the official PICS Society journal. We'll also have our own section within the journal for interventional articles. All the abstracts from the meeting will be published in the journal as well!

I should note two additional partnerships that will be highlighted at this year's Symposium. Recently the PICS Society added a complimentary subscription to DocMatter as a free membership benefit--DocMatter is an online, global community by and for congenital heart disease interventionalists, which has become very active in sharing knowledge on a day-to-day basis.

Similarly, we are proud that *Congenital Cardiology Today (CCT)* is the official news and information source of the PICS Society. All PICS members receive a complimentary subscription to *CCT*.

Importantly, all three organizations--Pediatric Cardiology Journal, DocMatter and CCT--will have a major presence at the Symposium.

***KS: For people reading this and looking forward to attending, how should they sign up?***

***DK:*** People can register for the meeting through our website www.picsymposium.com/. We encourage people to do so as soon as possible to make use of the early bird registration!

***KS: Finally, are there any special events during the upcoming meeting that you would like to highlight?***

***DK:*** Yes, actually there is. We lost a dear friend and colleague recently, Dr. Kanishka Ratnayaka. His loss has been absolutely tragic, and we plan to honor him through a special recognition this year.

We will also have the scientific scholarship award and the travelling fellowship award; the latter being specifically created to help people from developing countries attend the meeting.

We're also planning to have a Latin session, as we do every year, to recognize our colleagues from Latin countries. That's always a very well attended and thoughtful session and we plan on having it again this year. Lastly, we will also have sessions on structural heart disease as well as sessions on adult Congenital Heart Disease.

**KS: Thank you so much for your time! We look forward to attending what promises to be another wonderful meeting.**

# 500th Heart Transplant Performed at Children's Hospital Colorado

*The Heart Institute is one of only a few centers in U.S. to reach this milestone, reinforcing its position as the leader in the Rocky Mountain Region*

The Heart Institute at Children's Hospital Colorado (Children's Colorado), https://www.childrenscolorado.org/doctors-and-departments/departments/heart, has performed its 500th pediatric heart transplant, a milestone that only a few centers across the country have reached. The new benchmark is a tribute to the many families who have entrusted Children's Colorado with their care and the multidisciplinary team of caregivers who are committed to ensuring the best possible outcomes.

"From our first transplant patient more than 30 years ago to our 500th this year and every patient in between, the entire team at the Heart Institute has been honored to help so many families," shared Melanie Everitt, MD, cardiologist and Medical Director of the Heart Transplant Program at Children's Colorado. "This milestone speaks to the breadth and depth of our team's experience, which allows us to treat the most complex cases that other hospitals may turn down, while still achieving excellent outcomes."

According to national comparison data from the Scientific Registry of Transplant Recipients, the patient survival outcomes at the Heart Institute at Children's Colorado after heart transplant are consistently better than the national average, and the hospital's average time to heart transplant is lower.

1-year patient survival rate
- Children's Colorado: 96%
- National: 91.37%

3-year patient survival rate
- Children's Colorado: 95.83%
- National: 88.61%

Median time to heart transplant
- Children's Colorado: 2.7 months
- Region: 5.0 months
- National: 5.5 months

"When pediatric hospitals began performing heart transplants in the 1980's, the focus was solely on survival," said Dr. Everitt. "But now, thanks to multidisciplinary teams such as the one at Children's Hospital Colorado, the focus includes getting children back home and returning to normal childhood life as soon as possible."

The Heart Institute's multidisciplinary team focuses on more than a patient's physical needs. The team--which includes not only pediatric and adult congenital cardiologists, cardiothoracic surgeons and interventionists, pulmonologists, pharmacists, transplant coordinators and cardiac care nurses, but also psychologists, dieticians, physical and occupational therapists, social workers, child life specialists and chaplains, attends to every aspect of their patient's wellbeing, including their mental, emotional and spiritual needs.

"It is important to keep in mind that none of this would be possible without families who are willing to make this precious gift," said Matt Stone, MD, cardiothoracic surgeon and surgical director of the pediatric heart transplant program at Children's Colorado. "There is a very special donor at the center of every heart transplant, and we are thankful for each and every one."

Children's Hospital Colorado coordinates all of its heart transplant procedures with the help of Donor Alliance.

"Every patient we've served has meant the world to us, and we're grateful for the opportunity to provide care to the children and families in our program," said Dave Campbell, MD, cardiothoracic surgeon and former director of the pediatric heart transplant program.

Children's Colorado is home to the only pediatric transplant center in the state and one of just a few in the entire Rocky Mountain region. When the hospital's pediatric patients reach adulthood, they transition to Children's Hospital Colorado's Adult Congenital Heart Disease Program, a joint program with UCHealth University of Colorado Hospital, also located on the Anschutz Medical Campus.

Children's Hospital Colorado
**Press Release**
childrenscolorado.org

BEST CHILDREN'S HOSPITALS U.S.News HONOR ROLL 2021-22

## About Children's Hospital Colorado

Children's Hospital Colorado is one of the nation's leading and most expansive nonprofit pediatric healthcare systems with a mission to improve the health of children through patient care, education, research and advocacy. Founded in 1908 and recognized as a top 10 children's hospital by U.S. News & World Report, Children's Colorado has established itself as a pioneer in the discovery of innovative and groundbreaking treatments that are shaping the future of pediatric healthcare worldwide. Children's Colorado offers a full spectrum of family-centered care at its urgent, emergency and specialty care locations throughout Colorado, including an academic medical center on the Anschutz Medical Campus in Aurora, hospitals in Colorado Springs, Highlands Ranch and Broomfield, and outreach clinics across the region. For more information, visit www.childrenscolorado.org or connect with us on Facebook, Twitter, Instagram and YouTube.

# Coverage of ACC.22

## Tricuspid Valve Repair with Edwards Pascal Transcatheter Repair System at One Year: CLASP TR

*Kalkidan Bishu, MD, MS, FSCAI*

**Why is this study important?**

Severe symptomatic tricuspid regurgitation (TR) is prevalent and causes significant morbidity. Surgical intervention is less commonly utilized, compared to left sided valve disease and there are questions regarding outcomes with surgical intervention in advanced stages. Thus, there is a need for a percutaneous intervention for native valve TR.

**Should I change my practice because of these findings?**

Ewards Pascal Transcatheter Repair System in the treatment of TR is investigational at this time.

**What question was this study supposed to answer?**

This prospective, single-arm multicenter early feasibility study was designed to evaluate the safety and performance of the PASCAL transcatheter valve repair system in symptomatic severe TR.

**What did the study show?**

Sixty-five patients (mean age 77; 55% women) with severe symptomatic TR despite medical therapy underwent treatment using Ewards Pascal Transcatheter Repair System. Primary endpoint was the composite of major adverse events at 30 days with follow up at six months and then annually. One-year follow-up results were reported for 46 out of 65 patients in whom follow-up data was available (loss of follow-up attributed to Covid-19 pandemic). Mortality was 10.8%. Eighteen percent were hospitalized for heart failure and 16.9% experienced a major adverse event, the most common adverse event was bleeding at 9.2%. Eighty-six percent had TR that was moderate or less. Seventy-five percent had a two-grade reduction in TR severity. There was improvement in tricuspid annulus diameter, RV end diastolic diameter, RA volume, inferior vena cava diameter and TR jet area. Heart failure severity, six-minute walk test and quality of life were improved.

**How good was the approach/methodology?**

The one-year report of CLASP-TR extends the findings at 30 days regarding safety. It is limited due to the lack of follow-up in 19 out of 65 participants (29%). CLASP II TR is a prospective, multicenter, randomized controlled pivotal trial that is enrolling 825 participants and will provide more definitive answers regarding efficacy compared to medical therapy.

## Clinical Impact of Residual Leaks Following Left Atrial Appendage Occlusion: Insights from the NCDR LAAO Registry

*Andrew M. Goldsweig, MD, MSc, RPVI, FSCAI*

**Why is this study important?**

This analysis of the National Cardiovascular Data Registry (NCDR) Left Atrial Appendage Occlusion (LAAO) Registry was the first study to show that peri-device leak is associated with increased stroke risk.

**Should I change my practice because of these findings?**

Because peri-device leak is associated with increased stroke risk, LAAO operators should assess devices carefully for leakage and strive to leave no leak.

**What question was this study supposed to answer?**

The study examined rates of a primary endpoint composite of stroke, transient ischemic attack, and systemic embolism among LAAO patients stratified by no leak, small leak (<5 mm), and large leak (>5 mm).

**What did the study show?**

Among 51,333 patients undergoing LAAO with the Watchman 2.5 device (Boston Scientific, Marlborough, MA) from 2016 through 2019, 37,696 (73.4%) had no leak, 13,258 (25.8%) had small leaks (<5 mm), and 379 (0.7%) had large leaks (>5 mm). The presence of a small leak was associated with a slightly higher rate of the primary endpoint (adjusted HR 1.152, 95% confidence interval [CI] 1.025-1.294), major bleeding (HR 1.11, 95% CI 1.029-1.120), and any major adverse events (HR 1.102, 95% CI 1.048-1.160). Large leaks were not statistically associated with adverse events, although more patients with large leaks continued anticoagulation.

**How good was the approach/methodology?**

The NCDR LAAO Registry is the largest LAAO dataset in the world, including every commercial LAAO procedure performed in the US. However, the study was subject to the usual cadre of biases inherent when performing a retrospective analysis of a large data registry, particularly information bias.

# The Cardiac Safety Research Consortium Announces Prospective Collection of Pediatric Cardiac Screening Data for the National Pediatric Cardiac Screening Data Warehouse to Inform Prevention of Sudden Cardiac Death in the Young and Pediatric Product Development

*Multi-Stakeholder Project Aims to Improve Pediatric Cardiac Safety*

The Cardiac Safety Research Consortium (CSRC) announced that the Prevention of Sudden Cardiac Death in the Young (SCDY) National Cardiac Screening Warehouse Pilot Study continues to advance with prospective screening data collection having started in 2021. The first-of-kind national pediatric cardiac screening data warehouse is being created through a collaboration with the U.S. Food and Drug Administration (FDA), Duke University and multiple public screening groups from across the country. Over 40,000 high quality digital electrocardiograms (ECGs) recorded during community screenings dating from 2015 to 2021 have been added to the warehouse. However, starting in May 2021, prospective data are being acquired which, in addition to the ECG, include screened individual's demographics (race, ethnicity, and other variables) as well cardiac screening history and physical information. The national data warehouse may offer significant public health benefits not only in assessing SCDY risk in children, but also in establishing better guidelines for pre- and post-market cardiac safety evaluation, as well as the development of biomarkers for use in pediatric clinical trials. Currently the FDA uses an ECG data warehouse to support cardiac safety review in adults, but until now, there has been no equivalent for children.

"This warehouse has the potential to address two major unmet public health needs – identification of children at risk for SCDY and enhanced cardiac safety in pediatric drug development," said the project's principal investigator, Salim F. Idriss, MD, PhD, Executive Co-Director of the Duke Pediatric and Congenital Heart Center and Director of Pediatric Electrophysiology at Duke University Medical Center. "Thanks to the support of our industry and academic partners and especially our collaborating public screening groups, many of whom are parent-led foundations with limited funding, we have improved the efficiency and quality of ECG data collection, leading to an unprecedented volume of reliable real-world data," he added. "We now have the ability to begin establishing pediatric ECG interpretation normal values based on sex, race, and ethnicity, in addition to the current values used for age, based on these data alone."

Data collection and data warehouse refinement is ongoing, and the next major step is the addition of collecting long-term data on individuals who had a cardiac screening. The CSRC pilot program will be rolling-out a feasibility study in early 2022 which enables recurrent electronic follow-up months after a screening to determine if a screened individual has a change in cardiac health status. Follow-up data are essential in determination of screening efficacy and establishment of screening best practices.

"The potential impact of this project demonstrates the power of multi-stakeholder teams working together to solve a problem facing the medical community," said Jonathan Seltzer, MD, MBA, FACC, executive director of the CSRC. "We're proud to be able to bring these groups together as part of our mission to improve cardiac safety and look forward to the possibility of future collaborations that will come out of this project."

The identification of children at risk for SCDY may allow for early initiation of medical interventions to reduce the risk. SCDY can occur in healthy-appearing children without symptoms. Since many of the diseases known to cause SCDY are genetic, the identification of children at risk may help in determining if other members of the family are also at risk.

Dedicated to protecting youth from SCDY, over ten community screening organizations from across the country are working as partners to help establish the national data warehouse. The organizations were recruited through national project partner, Parent Heart Watch, whose prevention-driven initiatives include cultivating local champions who create community programs focused on the prevention of SCDY.

In addition to Parent Heart Watch, current partners include:

- Community screening organizations including: Championship Hearts Foundation (Texas), Cody Stephens Go Big or Go Home Memorial Foundation (Texas), Saving Hearts Foundation (California), Eric Paredes Save A Life Foundation (California), Screening America (South Dakota), Heart Screen New York (New York), Peyton Walker Foundation (Pennsylvania), Hearts for Athletes (Alabama), Thomas Smith Memorial Foundation (Michigan), Play for Jake Foundation (Indiana), Zac Mago Foundation (Indiana), Kyle J. Taylor Foundation (California)
- Academic leaders from Children's Hospital of Philadelphia, Lurie Children's Hospital, Baylor College of Medicine, St. Luke's Health System (Idaho and Oregon), and The Pediatric and Congenital Electrophysiology Society
- Industry partners including: AMPS LLC (Analyzing Medical Parameters for Solutions), AstraZeneca, Cardiac Insight Inc., Eli Lilly, and Clario (formerly ERT).

The study is ongoing, and anyone interested in supporting the initiative is encouraged to contact CSRC about how to get involved. "This project is a success because of the collaborative nature of the CSRC and could not have happened without our partnerships with the public groups. We would love to have others join in supporting to establish this important national public health resource," Dr. Idriss added.

# Baby Receives World's First Combination Heart Transplant-Thymus Procedure

## *Using Processed Thymus Tissue from the Heart Donor Could Lower the Risk of Organ Rejection*

*Sarah Avery, Duke Health*

A baby believed to be the first person to receive a combination heart transplant and allogeneic processed thymus tissue implantation appears to be gaining the immune cells necessary to reduce or eliminate the need for prolonged use of toxic anti-rejection drugs.

The two procedures -- performed at Duke University Hospital last summer under an expanded access application that was cleared by the FDA -- represent a milestone in heart transplantation.

"This has the potential to change the face of solid organ transplantation in the future," said Joseph W. Turek, MD, PhD, Duke's Chief of Pediatric Cardiac Surgery, and a member of the surgical team that performed the landmark procedure.

"If this approach proves successful – and further validation is contemplated – it would mean transplant recipients would not reject the donated organ and they would also not need to undergo treatment with long-term immune-suppression medications, which can be highly toxic, particularly to the kidneys," Turek said. "This concept of tolerance has always been the holy grail in transplantation, and we are now on the doorstep."

Currently, transplanted hearts have an average lifespan of about 10 to 15 years. With durability limited by the toxicity of immune-suppression drugs, other options have long been sought.

The idea of using donated and processed thymus tissue during heart transplantation has been under study at Duke and other sites for several years. Because the thymus gland stimulates the development of T-cells, which fight foreign substances in the body, implanting the processed tissue is hoped to establish the donor's immune system as the recipient's, so the donated heart is recognized as "self."

The approach has shown promise in animal experiments, including in Turek's lab at Duke, but it had previously not been tried in a living organ recipient.

Duke researchers received permission from the FDA for the investigational procedures after two important factors lined up serendipitously – the youngster, Easton Sinnamon, needed both a heart transplant and processed thymus tissue implantation independent of one another, and he was a patient at Duke, where the processed thymus tissue implantation is solely available.

The processed thymus tissue implantation method, pioneered at Duke by Louise Markert, MD, uses a proprietary technique to culture and administer processed thymus tissue; the process has been licensed to Enzyvant Therapeutics GmbH. The company received FDA approval last fall for allogeneic processed thymus tissue-agdc, indicated for immune reconstitution in pediatric patients with congenital athymia, a rare condition in which children are born without a thymus. Enzyvant provided financial support for processing of the thymus tissue that was used in this research.

"We see tremendous promise in this technology for patients and we are working with urgency to advance research and development for all children in need of cardiac transplants," said Rachelle Jacques, Chief Executive Officer of Enzyvant.

For Easton, the first-in-human combination of procedures appears to be working. Tests taken 172 days post-transplant/implantation indicate the processed thymus tissue is functioning, building the critical T-cells that are integral to a well-functioning immune system. Easton's care team at Duke continues to monitor progress; another milestone is possible in several months when he could be tapered off anti-rejection drugs.

"Cases like this underscore how important new insights emerge when surgery and science are expertly practiced together," said Allan D. Kirk, MD, PhD, Chair of the Department of Surgery at Duke University School of Medicine. "This case has implications for more than just heart transplantation – it could change the way that many solid organ transplants are done in the future."

*Baby Easton is held by grandmother Julie O'Neal alongside mother Kaitlyn. This was Julie's first meeting with Easton.*

"The team performed the transplant and implant in a patient who lacked significant thymus function, providing an excellent opportunity to examine how allogeneic processed thymus tissue can shape a person's immune system to be more receptive to a donor organ," Kirk said. "If this can be extrapolated to patients who already have a functioning thymus, it could potentially allow them to restructure their immune systems to accept transplanted organs with substantially less dependence on anti-rejection medication. The processing method used for the thymus tissue seems to be critical and is of great interest."

Born with severe heart defects as well as thymic deficiency from an unknown cause, which severely impaired his immune system, Easton received his transplant on August 6th, 2021, when he was 6-months-old, followed two weeks later with the implantation of the cultured thymus tissue from his heart donor. Easton recently celebrated his first birthday and continues to do well.

"It was one of those things where it could help him, and if it works, it not only helps him, but it could help thousands of other people as well with their children who need transplants," said Easton's mom, Kaitlyn. "When we talked about it, it was like 'Why would we not do it when we can make a difference for all these other people?'"

# AUGUST

## 03-06

**NeoHeart: Cardiovascular Management of the Neonate**
Anaheim, California, USA
https://web.cvent.com/event/f5efadb3-8886-4c5b-9944-c41980940049/summary

## 05-06

**International PDA Symposium 2022**
Anaheim, California, USA
https://pdasymposium.com/

## 21-26

**Pediatric & Adult Congenital Cardiology Review**
Huntington Beach, California, USA
https://ce.mayo.edu/cardiovascular-diseases/content/2022-pediatric-and-adult-congenital-cardiology-review-course

## 26-29

**ESC Congress 2022**
Barcelona, Spain
https://www.escardio.org/Congresses-&-Events/ESC-Congress?utm_medium=Email&utm_source=&utm_campaign=ESC+-+Congress+-+Lauch+of+the+game+ladies+and+gentlemen

## 30-03

**Cardiology 2022: 25th Annual Update on Pediatric and Congenital Cardiovascular Disease**
Huntington Beach, California, USA
https://chop.cloud-cme.com/course/courseoverview?P=5&EID=2646

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