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Noncompaction Cardiomyopathy: A Not So Rare Cardiomyopathy in Children

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Characterized by excessive and unusual trabeculation of the mature left ventricle (LV), left ventricular noncompaction cardiomyopathy (LVNC) is thought to occur due to arrest of the final phase of cardiac development, the compaction phase, where the compact myocardium fully forms. A spongy morphologic appearance of the myocardium is typical, with abnormal trabeculations and intertrabecular recesses typically being most evident in the apical portion of the LV.[1, 2] In 2006, the American Heart Association Scientific Statement on the classification of cardiomyopathies formally classified LVNC as its own disease entity.[3] The European working group on myocardial disease, however, continues to consider LVNC as a trait rather than a specific disease, but recommends genetic analysis when a diagnosis is made. [4, 5] Multiple forms of LVNC occur, each with different features and outcomes.

Pathology of Left Ventricular Noncompaction

In the early embryo, the heart is a loose interwoven mesh of muscle fibers.[6] The developing myocardium gradually condenses, and large spaces within the trabeculation meshwork disappear, condensing and compacting the ventricular myocardium and solidifying the endocardial surfaces. Trabecular compaction is normally more complete in the LV than in the right ventricular (RV) myocardium. The situation in which this compacting pathway fails is thought to be due to an arrest in endomyocardial morphogenesis and result in postnatal LV noncompaction.[6, 7] The gross pathological appearance of LVNC is characterized by numerous, excessively prominent trabeculations and deep intertrabecular recesses resembling RV endomyocardial morphology. Histologically, the recesses and their troughs are lined with endothelium, indicating that these recesses are not sinusoids. In some cases, zones of fibrosis and elastic tissue are found scattered on the endocardial surfaces with extension into the recesses. The abnormal endocardial fibrous and elastic tissue will result in abnormal mechanics, causing the apex and bases to rotate in the same direction, without the normal twisting contraction of the heart. [8-10] The endomyocardial morphology of LVNC lends itself to the development of mural thrombi within the recesses, which can embolize and cause stroke.[11-13] The coronary arterial circulation is usually normal; however, intramural perfusion could be adversely affected by the prominent trabeculations and intertrabecular recesses, particularly in the subendocardium. While the precise mechanism for malignant ventricular arrhythmias in LVNC patients is not known, impaired flow reserve, causing intermittent ischemia, has been proposed as having a role. In addition, myocardium around the deep intertrabecular recesses may serve as zones of slow conduction and substrate for reentry.

Incidence of Left Ventricular Noncompaction Cardiomyopathy

The incidence and prevalence of LVNC is uncertain because of changing diagnostic criteria and predilection for LV hypertrabeculation in certain populations[14-20] and absence of symptoms in many patients.[21] In the 1990's, the reported prevalence of isolated LVNC was 0.05% of all adult echocardiograms in a large institution, whereas more recently the prevalence was reported as less than 0.14%. In contrast, Sandhu et al.[14] demonstrated a 3.7% prevalence of definite or probable LVNC by echocardiography in adults with LV ejection fraction (EF) ≤45% and a 0.26% prevalence for all patients referred for echocardiography. In a registry of pediatric cardiomyopathy patients, noncompaction was discovered in five.[22]

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Clinical Features and Diagnosis of Left Ventricular Noncompaction

The clinical presentation of LVNC is highly variable, ranging from asymptomatic to end-stage heart failure, lethal arrhythmias, or thromboembolic events.[2, 3, 12,13,23-25] LVNC may exist as isolated disease, but it may also be associated with hypertrophic and dilated cardiomyopathies (HCM; DCM).

In infancy, LVNC commonly develops with signs and symptoms of heart failure. Childhood LVNC can occur with heart failure, rhythm abnormalities, or sudden death.[12,13, 16,21] Concurrent systemic disease has been reported with worse outcomes.[2] When patients receiving transplants were added, the five-year survival free of death or transplantation was 75%.[2]

The same specter of arrhythmia, heart failure, and thrombosis is described in adults. However, the majority of patients are asymptomatic and identified serendipitously on echocardiography. It may be advisable to use multi-modality imaging (valid echocardiographic criteria, speckled tracking, and cardiac magnetic resonance imaging [CMR]) to confirm the diagnosis based on the ratio of compacted and non-compacted layers and on the non-trabeculated mass.[26-29]

Patients with LVNC are known to develop ventricular arrhythmias including ventricular tachycardia (VT) and ventricular fibrillation (VF), atrial fibrillation (AF), or conduction abnormalities (sinus bradycardia or complete heart block). Ventricular pre-excitation is also common.[2, 7, 26-32]

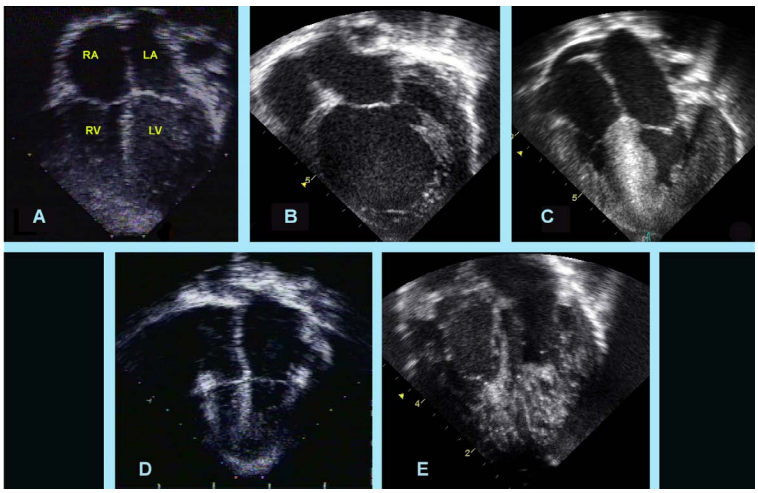

FIGURE 1
Echocardiographic Left Ventricular Noncompaction Phenotypes
The heterogeneous features that cover the spectrum of patients with the different forms of LV noncompaction. Four-chamber views demonstrate normal atrial and ventricular sizes and thickness with a hypertrabeculated LV wall and apex ***(arrow a)****; normal atrial sizes with a dilated and hypertrabeculated LV wall and apex* ***(arrow b)****; hypertrophic and hypertrabeculated ventricular walls and apex with a hypertrophic septum* ***(arrow c)****; normal to small ventricular sizes with dilated atria bilaterally* ***(arrows)*** *and a hypertrabeculated LV* ***(d)****; normal atrial sizes with severely hypertrabeculated LV and RV wall and apices* ***(arrows e)****; normal atrial sizes with tricuspid atresia (no tricuspid valve) and a hypertrabeculated LV wall and apex* ***(arrow f),*** *and Ebstein's anomaly with LVNC, which demonstrates a normal left atrial size with a large right atrium, displaced tricuspid valve towards the RV* ***(closed arrowhead)****, and a severely hypertrabeculated LV wall and apex* ***(open arrowhead)****.*

Inducibility of sustained VT during electrophysiological studies has demonstrated little value as a tool for risk stratification in LVNC.[23,33] An electrocardiographic finding suggestive of potential for reentry is the presence of QRS notches (QRS fragmentation) or J waves (early repolarization).[23, 24, 34,35] Additionally, the high proportion of patients without previously documented arrhythmias have the same amount of spontaneous arrhythmias (premature ventricular complexes [PVCS] or non-sustained VT) on Holter monitor as those who survived an arrest, suggesting that this might be a trigger for more serious events.

Subtypes of Left Ventricular Noncompaction

One of the important issues in the diagnosis and outcome of these patients, particularly in childhood, is the specific LVNC phenotype expressed, as each may have different outcomes. A special feature is that the phenotype may vary between DCM and HCM forms ("undulating phenotype") in which the heart changes from one form to the other, potentially on multiple occasions.[2] In these situations, the final "undulation" is typically an end-stage disease with severe heart failure. Subtypes of Left Ventricular Noncompaction **(Figure 1)**[36,37] include the following:

1. *Isolated LVNC, in which abnormal trabeculations are associated with normal LV size, thickness, and systolic and diastolic function in the absence of other structural heart disease and with no evidence of arrhythmias* **(Figure 1A)**.
   - Clinically, this subgroup appears to be benign during childhood and affects approximately 25%-35% of all subjects. These individuals do well unless they exhibit ventricular arrhythmias or if there is a family history of symptomatic LVNC. This subgroup, which is sometimes called the "benign form" of LVNC, usually undergoes yearly follow-ups in the outpatient clinic as infants and young children. As adolescents, they are seen every three years if there is no symptomatic change or family history of LVNC. These patients are not treated with medications or restricted from activities.[7,26,32,36]
2. *Isolated LVNC with arrhythmias (arrhythmogenic form of LVNC).*
   - These patients appear to have an elevated risk of sudden life-threatening events and require closer follow-up and therapeutic intervention. The arrhythmias noted include VT, VF, atrioventricular block, supraventricular tachycardia [SVT], and atrial fibrillation [AF].[23-25,38] This subtype is currently designated as a form of arrhythmogenic cardiomyopathy (ACM).[38]
3. *The dilated cardiomyopathy form of LVNC clinically mimics DCM, with a dilated hypertrabeculated LV with depressed systolic function and appears to have worse outcomes than isolated DCM* ***(Figure 1B).***
   - The follow-up and treatment for these patients is similar to those with pure DCM.[22,37]
4. *The HCM form of LV noncompaction mimics HCM with LV hypertrophy, commonly with asymmetric septal hypertrophy, and a small, trabeculated LV cavity* ***(Figure 1C).***
   - Hypercontractile systolic function and diastolic dysfunction also occur. This form of LVNC appears to have worse outcome than in pure HCM.[22,37]
5. *The mixed form of LVNC includes HCM with DCM, HCM or DCM with restrictive physiology* ***(Figure 1C)*** *and commonly has an "undulating phenotype" going from hypertrophic to dilated back to hypertrophic and commonly and finally ending at a DCM form of disease.*
   - This subtype may be associated with neuromuscular

disease and hypotonia. Young children, particularly infants and neonates, can succumb to heart failure or arrhythmias, especially if they have metabolic derangement.[2,11,36] Electrocardiograms (ECGs) of these patients have the same abnormalities as the other forms. In some cases, extreme QRS forces are notable.

6. *The restrictive form is a rare and clinically challenging subtype of LVNC because it mimics the clinical behavior of restrictive cardiomyopathy (RCM) with dilated atria and diastolic dysfunction associated with normal LV dimension, thickness, and systolic function* ***(Figure 1D).***[39]
   - Like children with RCM, this subgroup is typically considered a transplant candidate early after diagnosis if they have presented with syncope as they are at risk for degeneration of tachyarrhythmia and conduction disease.
7. *In the biventricular cardiomyopathy form of LVNC in which both LV and RV are hypertrabeculated, systolic dysfunction and diastolic function are common* ***(Figure 1E).***
   - Heart failure is commonly seen as well.[39]
8. *In RV noncompaction, an uncommon form, the RV is hypertrabeculated while the LV appears normal.*[40]
   - RV filling can be marginalized, and arrhythmias may occur.
9. *In the congenital heart disease (CHD) form of LVNC, any form of CHD may be associated, but right-heart obstructive forms are most typical.*[15]
   - The most common forms of CHD include atrial septal defects (ASD), ventricular septal defects (VSD), pulmonic stenosis (PS), pulmonary atresia, tricuspid atresia, Ebstein's anomaly, heterotaxy syndrome, and hypoplastic left heart syndrome (HLHS), among others.[7,26,32,41]

Outcomes depend on the specific form of CHD, but it is noted that these patients can have worse postoperative outcomes than patients with the same CHD but without LVNC.

Imaging of Left Ventricular Noncompaction

The diagnostic criteria for LVNC are based on imaging.[18-20,22,27-29,38] Echocardiography has been the most common modality utilized to diagnose and describe LVNC **(Figure 1 & Figure 2)**. The diagnostic criteria were recently revisited by some of the original authors, and the use of multi-modality imaging (the validated echocardiographic criteria, speckled tracking, and CMR) was suggested to confirm the diagnosis.[18-20,22,27] The initial echocardiographic criteria were based on the ratio of noncompacted and compacted layers (which should be >2:1 in LVNC) and on measurement of the non-trabeculated mass versus the mass of the global LV with CMR.[38] Speckled tracking may reveal rigid body rotation, in an objective way, with the absence of the normal twist.[8-10,42-45] These findings are present in children and their family members and is associated with lower functional status.[8, 45]

Thuny et al compared two-dimensional echocardiographic images obtained at end-diastole and end-systole with the images obtained using CMR at end-diastole to validate the diagnosis of LVNC **(Figure 2).**[28] Sixteen adults (48 +/- 17 years) with LVNC underwent echocardiography and CMR within the same week and were compared to assess noncompaction in seventeen anatomical segments. All segments were analyzed using CMR, but only 87% could be analyzed using echocardiography. A two-layered structure was observed in 54% of patients by CMR and 43% by echocardiography. Therefore, CMR was thought to be superior to standard echocardiography in assessing the extent of noncompaction and providing supplemental morphological information; however, this has not been validated in children. CMR also assesses the presence of extensive fibrosis that correlates with late gadolinium enhancement (LGE).[46]

Electrocardiography in Left Ventricular Noncompaction

The ECG for patients with LVNC is typically abnormal and, in infants and young children, commonly shows excessive voltage.[2, 32] Approximately 30% of these young subjects with LVNC have extreme mid-precordial voltages and mimic the ECG seen in Pompe disease **(Figure 3)**. The childhood forms of LVNC may be associated with ventricular pre-excitation as well.

Adult patients often also have LV hypertrophy as well as atrioventricular and intraventricular conduction delay. Left bundle branch block (LBBB) is

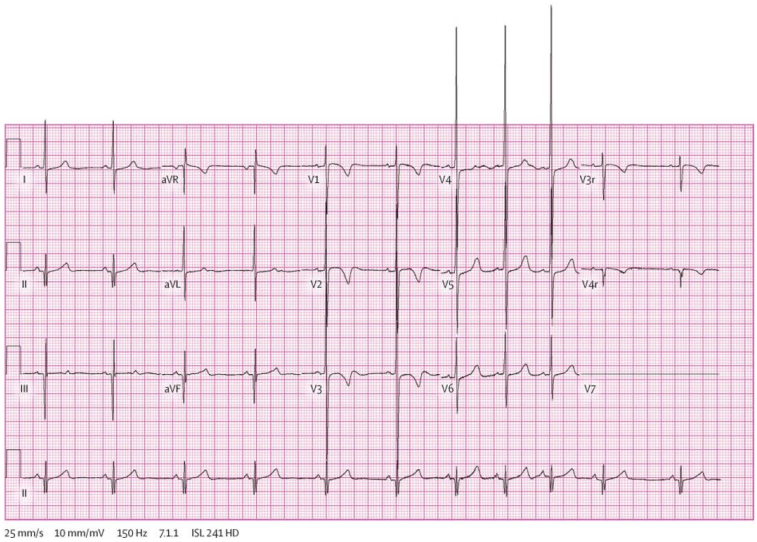

FIGURE 2
Electrocardiogram in Left Ventricular Noncompaction ECG
Note the prominent precordial voltage.

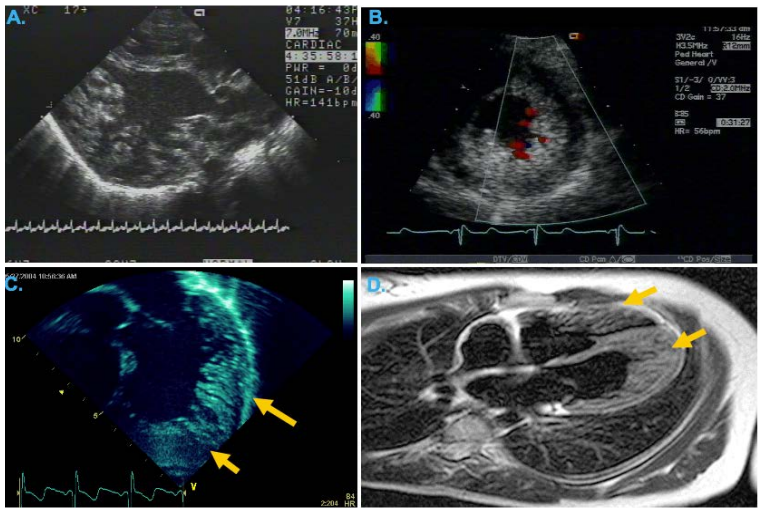

FIGURE 3
Imaging Approaches in Left Ventricular Noncompaction
A). *Parasternal long axis echocardiogram of LVNC demonstrates the appearance of the spongiform myocardium/hypertrabeculation;*
B). *Parasternal short axis echocardiogram of LVNC demonstrates the appearance of a hypertrophied hypertrabeculated myocardium with color Doppler demonstrating blood in the intratrabecular recesses;*
C). *Apical four-chamber view with severe hypertrabeculation at the apex and posterior wall LVNC seen with colorized myocardium;*
D). *Cardiac MRI demonstrating biventricular noncompaction (arrows).*

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> - Michael G. Earing, MD, MS Healthcare Management
>
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often present.[23,24] Early repolarization, as described by Haissaguerre and colleagues, was more often present in those who had a history of VT or VF, but also occurred in 23% of patients without such history.[24,45] The same findings were reported by Steffel and colleagues.[23]

Arrhythmias in Left Ventricular Noncompaction

Ventricular tachyarrhythmias, including cardiac arrest owing to VF, are reported in 38%-47% and sudden death in 13%-18% of adult patients with LVNC.[24,25,33,47] Caliskan and coworkers investigated ICD therapy indications and outcomes in 77 patients with LVNC (mean age 40 +/- 14 years), 44 (57%) of whom had an ICD implanted using standard ICD guidelines for non-ischemic cardiomyopathy. Implantation for secondary prevention occurred in 12 patients (seven with VF, five with sustained VT) and for primary prevention (heart failure or severe LV dysfunction) in 32 patients.[48] During a mean follow-up of 33 +/- 24 months, the patients presented with appropriate ICD shocks owing to sustained VT after a median of 6.1 months (range 1 to 16 months), including four of 32 (13%) of patients in the primary prevention group and four of 12 (33%) in the secondary prevention group (p=0.04). During a mean follow-up of four months (range 2-23 months), an additional nine patients had received inappropriate ICD therapy: six (19%) in the primary prevention group and three (25%) in the secondary prevention group. The relatively high percentage of appropriate shocks for sustained VT in this population suggest that patients with LVNC are at high-risk for sudden cardiac death and that implanting an ICD in these adult patients is appropriate, although no patients with LVNC were included in the previous trials that were the basis of the current guidelines. These observations support the current guidelines to implant an ICD for primary prevention based on the presence of heart failure or severe LV dysfunction in combination with other (presumed) high-risk factors in patients with LVNC. (CI 14–28%) (**Figure 2A** and Suppl. **Figures 4A** and **4B**). The heart rhythm abnormalities were either reported at first presentation or occurred during the follow-up period. Interestingly, some families with distinct gene mutations showed predominantly one specific type of arrhythmia, such as sinus node disease in HCN4 gene carriers [51].[49-53]

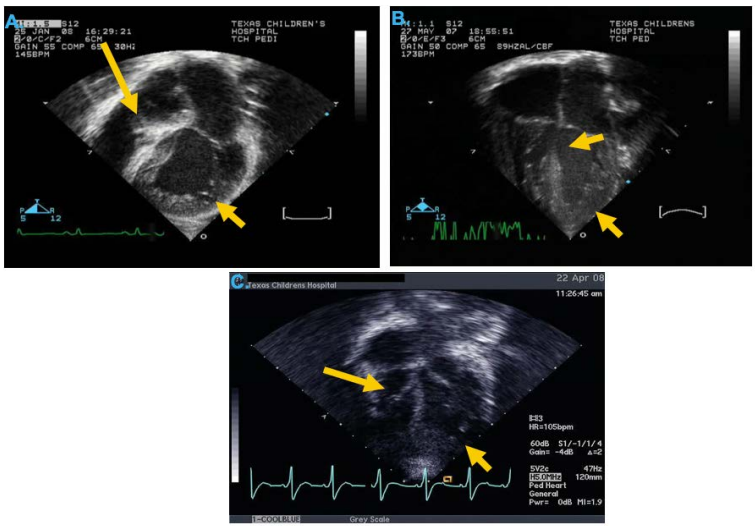

FIGURE 4
Left Ventricular Noncompaction Associated with Congenital Heart Disease
A). *LVNC with tricuspid atresia. The top arrow demonstrates the tricuspid valve abnormality and the bottom arrow points to the apical hypertrabeculation*
B). *LVNC with a large ventricular septal defect. The top arrow demonstrates the ventricular septal defect and the bottom arrow points to the apical hypertrabeculation;*
C). *LVNC with Ebstein anomaly. The top arrow demonstrates the Ebstein's tricuspid valve abnormality and the bottom arrow points to the apical hypertrabeculation.*

Brescia et al evaluated two hundred forty-two children between January 1990 and January 2009 that were diagnosed with isolated left ventricular noncompaction.54 The mean age at diagnosis was 7.2±6.9 years, although 95 patients (39%) presented within the first year of life. Thirty-one (12.8%) of the children died and 13 (5.4%) received a transplant. One hundred fifty (62%) patients presented with or developed cardiac dysfunction. The presence of cardiac dysfunction was strongly associated with mortality (hazard ratio, 11; P<0.001). ECG abnormalities were present in 87%, with ventricular hypertrophy and repolarization abnormalities occurring most commonly. Repolarization abnormalities were associated with increased mortality (hazard ratio, 2.1; P=0.02). Eighty children (33.1%) had an arrhythmia and those with arrhythmias had increased mortality (hazard ratio, 2.8; P=0.002). Forty-two (17.4%) had ventricular tachycardia, with five presenting with resuscitated sudden cardiac death. There were 15 cases of sudden cardiac death in the cohort (6.2%). Nearly all patients with sudden death (14 of 15) had abnormal cardiac dimensions or cardiac dysfunction. No patient with normal cardiac dimensions and function without preceding arrhythmias died.

Howard et al evaluated data on 348 patients with LVNC and found that thirty-eight (11%) had ventricular pre-excitation on ECG, with 84% of those with pre-excitation and LVNC having cardiac dysfunction.[55] Kaplan-Meier analysis demonstrated significantly higher risk of developing significant dysfunction in patients with WPW and LVNC versus LVNC alone (hazard ratio 4.64 [2.79, 9.90]). Twelve patients (32%) underwent an ablation procedure with an acute success rate of 83%. Four patients with cardiac dysfunction were successfully ablated, with three demonstrating an improvement in cardiac function post ablation.

Clinical Genetics of Left Ventricular Noncompaction

Ichida and colleagues reported that 44% of isolated LVNC patients had inherited LVNC, with 70% having autosomal dominant (AD) and 30% having X-linked (XL) inheritance.[32] This was confirmed by Hoedemakers and coworkers who showed by echocardiographic screening that in 194 family members from 50 LVNC probands, 2/3 of families had a familial cardiomyopathy; however, not only LVNC but HCM and DCM were also detected.[56] Pleiomorphism was confirmed by others.[22,36,37,57] Nonpenetrance of detected genetic defects was high, which means that affected family members have to be followed over time. In XL recessive LVNC, female carriers have not been found to develop frank clinical disease and are echocardiographically normal. Consistent with XL inheritance, no male-to-male transmission of the disease occurs. Autosomal dominant inheritance occurs in some familial cases of LVNC without CHD and in most, if not all, cases associated with CHD. In some families with AD LVNC associated with CHD, affected members can be identified in whom no CHD is evident at the time of evaluation because their cardiac defects include minor forms of CHD, such as small ASDs, VSDs, or patent ductus arteriosus (PDA) that have spontaneously closed, along with other individuals with severe CHD, such as HLHS. Autosomal recessive (AR) and mitochondrial inheritance is seen in cases dominated by mitochondrial and metabolic derangement.[11,37]

Molecular Genetics of Left Ventricular Noncompaction

Barth syndrome is a clinical association of myocardial dysfunction, cyclic neutropenia, cardiolipin deficiency, skeletal myopathy, abnormal mitochondria, organic aciduria (primarily 3-methylglutaconic aciduria), growth retardation, and cholesterol abnormalities.[37,58-60] It is an XL disorder and has been thought to be allelic to several phenotypically different disorders on chromosome Xq28, such as LVNC and DCM.[36,37,57,58] Pathogenic variants in the tafazzin gene (TAZ) were among the first to be identified in male patients and carrier females with isolated LVNC and with Barth syndrome, but not in the adult population with AD transmission. This gene codes a protein family called tafazzins that participate in the metabolism of cardiolipin, the signature phospholipid of mitochondria, and is also responsible for other forms of infantile cardiomyopathy. [59-61]

In AD LVNC, multiple genes have been identified. In general, genetic heterogeneity is found. Ichida et al identified pathogenic variants in α-dystrobrevin as causative in children and young adults with LVNC with or without CHD.[62] Subsequently, pathogenic variants in sarcomere protein- and Z-line-encoding genes were identified, with mutations in β-myosin heavy chain (MYH7), α-cardiac actin (ACTC), cardiac troponin T (TNNT2), and ZASP/LBD3.[63-68] Sarcomeric gene mutations in the LVNC population imply that LVNC is part of a broader spectrum of cardiomyopathies, including HCM, RCM, and DCM. In addition to sarcomere-encoding genes and cytoskeletal genes, there are pathogenic variants in ion channels, which have been shown to cause LVNC and rhythm disturbance. These include the sodium channel gene SCN5A, HCN4, transient receptor potential melastatin 4 (TRPM4) gene. This channel mediates a Ca21-activated nonselective cationic current (INSCca).468–470. In the heart, the TRPM4 channel represents the cardiac Ca2+-activated transient inward current (Iti) and plays a key role in the cardiac conduction system. [50-52, 69-71]

Dystrophin is another cytoskeletal protein that has been associated with LVNC and boys with Duchenne and Becker muscular dystrophy.[41,72,73] Skeletal muscle biopsy has, in some cases, identified mitochondrial abnormalities, suggesting a nuclear import protein is the primary abnormality.[42] Mutation analysis of the mitochondrial genome has identified mutations as well. Consideration of other potential genetic causes needs to account for the known molecular defects resulting in congenital heart anomalies, as well as those molecular abnormalities resulting in diseases of myocardium itself.

It is notable that the same gene mutation can result in different phenotypes (DCM, HCM, or RCM), even in the same family. Pedigree analysis, family evaluation, and genetic counseling are necessary, in collaboration with the cardiologist. Genetic testing is recommended when a pathogenic variant is identified in the proband. In the 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy, Towbin and colleagues made a class I recommendation with level of evidence B-NR, stating "If the proband has a disease-causing gene variant, it is recommended that first-degree relatives of individuals with LVNC undergo clinical screening for the disease along with genetic counseling and genetic testing". In addition, they made a IIa B-NR recommendation and stated, "In individuals with the clinical diagnosis of pathologic LVNC, genetic counseling and genetic testing are reasonable for diagnosis and for gene-specific targeted cascade family screening."[38]

PRDM16, a transcription factor, which has been implicated as a cause of LVNC in 1p36 syndrome patients and in dilated cardiomyopathy, promotes expression of genes required for growth of the compact myocardium, while genes involved in trabecular growth are suppressed. Cellular respiration for the generation of ATP occurs predominantly using the aerobic pathway under these conditions. When PRDM16 is deleted, genes required for compact myocardium growth demonstrate a decreased level of expression, whereas those required for trabecular growth are released from PRDM16-regulated suppression. Wu et al performed gene expression analysis and suggested a possible shift away from aerobic toward anaerobic cellular respiration.[74,75] Other studies have suggested that disturbances in the Notch pathway might be involved in LVNC development as well.

Therapy and Outcome

Heart Failure

Heart failure in LVNC reduces longevity.[76-80] The specific therapy depends on the clinical echocardiographic or CMR findings. In patients with systolic dysfunction and heart failure, anti-congestive therapies identical to those used in patients with DCM are appropriate. In particular, angiotensin converting enzyme inhibitors (ACEi) and β-adrenergic blocking agents have been useful. Consideration for the use of sacubitril/valsartan, an Angiotensin II Receptor Blocker-Neprilysin Inhibitor Combination (ARNi) treatment, instead of the ACEi, has become increasingly popular in children. Diuretics may also be needed; however, among patients exhibiting findings more consistent with an HCM or diastolic dysfunction (heart failure with preserved EF; HFpEF) physiologic phenotype (HCM, RCM), β-blocker therapy alone may be more appropriate in children. In children and adults with the HCM form of LVNC and symptomatic, myectomy may be appropriate. Cardiac resynchronization therapy can be helpful, certainly for LBBB with septal flash. Finally, in patients with heart failure associated with any form of LVNC, mechanical circulatory support and transplant may be necessary.

Specific Conditions

In patients with LVNC and associated mitochondrial or metabolic dysfunction, some investigators add a "vitamin cocktail" to the cardiac therapy, with coenzyme Q10, carnitine, riboflavin, and thiamine commonly used alone or in combination. There is no good data to support this approach, however.

In patients having associated CHD, appropriate therapeutic approaches can include simple pharmacological therapy with diuretics for volume overload associated with left to right shunts, more complex pharmacological therapy for patients with restrictive physiology and pulmonary hypertension, or invasive therapy with catheter intervention or surgical repairs, depending on the lesions.

Antithrombotic Therapy

Anticoagulation is needed in patients with depressed LV function in the presence of AF. The CHADS2-VASC score, which is widely used by adult medicine clinicians to assess the risk of cardioembolic event among patients with AF, may be helpful. Previous studies have shown its ability to identify low-risk individuals who can be managed without antithrombotic therapy, as well as to assess the risk of stroke among others and this might be helpful in decision-making, also when AF is not present. When there is evidence of thrombi in the LV, oral anticoagulation with anti-vitamin K antagonists or heparin is warranted. To date, we have no evidence for the efficacy of the direct oral anticoagulants in patients

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with LVNC.[81,82] In children, the use of aspirin daily has been promoted by some investigators.[21] In the 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy, Towbin and colleagues made a class I recommendation with level of evidence B-NR, stating "Anticoagulation is recommended in individuals with LVNC with atrial fibrillation and in those with previous embolic events."[38] In addition, they made a IIb B-NR recommendation and stated "Anticoagulation may be reasonable in individuals with LVNC with evidence of ventricular dysfunction."

Arrhythmias

In patients with any form of LVNC who have arrhythmias or syncope, prolonged ambulatory monitoring or electrophysiological study may be warranted, and device therapy (pacing, ICD, or cardiac resynchronization) may be indicated. Catheter ablation is appropriate for WPW syndrome as well as for other arrhythmias, including atrial fibrillation. It may be challenging to address ventricular arrhythmias with catheter ablation, but this has been done as well. In adults and a small cohort of at-risk children, primary prevention with an ICD is commonly considered.

Acknowledgments

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It Takes a Team - The Pivotal Role of Allied Health Professionals

Kamel Shibbani

This month's article from The PICS Society highlights the efforts of the entire cath team - namely the highly skilled and hard-working nurses, radiologic technologists, nurse practitioners, physician assistants and all our other invaluable allied health care providers. We were fortunate enough to sit down with four who represent quintessential components of the cath team: Sharon Cheatham, PhD, ACNP-BC, FPICS (Chair of the PICS Nurses and Allied Health Professionals Committee), Emily Kish, BSN, RN (Cath Lab Assistant Nurse Manager at University Hospitals Rainbow Babies and Children's Hospital), Jason Swinning, RT(R)(CI), RCIS (Radiologic Technologist and Imaging Specialist at Nationwide Children's Hospital) and Kathleen Nolan, RT(R)(CI) (Radiologic Technologist and Imaging Specialist at Rush University).

KS: Thank you for taking time for today's discussion. We want to highlight the essential roles that allied health care providers play in the cath lab and to stress that the cath team is truly a ***team***. A team that, for it to function properly, relies on more than physicians. We're hoping you can talk about the pivotal role your professions play in the cath lab, and how the PICS Society can help bring your contributions to the forefront. ***Let's talk a bit about the roles allied health care professionals perform in the cath lab.***
SC: Thank you to everyone here! My name is Sharon Cheatham, and I have more than 20 years' experience in interventional cardiology. I actually helped with the first PICS meeting in Boston – we had about 86 attendees! Things have changed quite a bit through the years!

Regarding the role of the allied health professionals, as they say, "It takes a village!". Well, for the cath lab, it takes a team. We spend a lot of time before the patient is brought into the lab where we do intensive and detailed huddles. We make sure the entire team is informed, from patient history to previous procedures to the anesthesia plan, as well as catheters and devices that may be used. All of this is to ensure the best possible patient outcome.

Emily Kish

Dr. Sharon Cheatham

Jason Swinning

Kathleen Nolan

Dr. Kamel Shibanni

EK: Talking about a team, both Jason and I work in pediatric cath labs that greatly focus on teamwork and being comfortable playing different roles within the team. I think it's very important to have a physician who can embrace the mentality that it doesn't matter what the credentials are behind a name because very often our roles are interchangeable. We also bring to the table (as nurses, techs and NP's) diversity in training and skill sets. You can have staff with neonatal ICU experience, others with adult experience, and rad techs with CT and 3D rendering experience. This allows the team to take care of everyone from patients who are just born to 87-year-old patients with Congenital Heart Disease. It is very important to use that experience and lean in on each other's skill sets.
JS: I couldn't agree more. As a matter of fact, if we have a job opening, we post it for either a nurse or a rad tech and simply take the best candidate out of the pool of applicants.
KN: In today's lab, technologists can be brought in wherever necessary! Data collection for research, scrubbing in and assisting on cases, preparing for cases, hemodynamics monitoring, assisting nurses that are scrubbed in, really anything that's needed.

> *"I think the more involved staff can be, that will only lead to better patient outcomes because everyone is working together as one cohesive team."*
>
> *Jason Swinning, RT(R)(CI)*

KS: **Are there any changes that you can think of that can promote your roles and help with patient care?**
JS: One of the things we do well, and can build on, is involving all of our staff and making sure that all team members are engaged in the procedure. For example, staff interested and trained in 3D reconstruction can do that while the physician scrubbed in is getting ready for the next step. We've moved away from the traditional roles of a circulating nurse only opens packages or a scrub tech that only wipes wires. I think the more involved staff is in the procedures, the better patient outcomes we will see because everyone is working together as one cohesive team.
EK: I completely agree with that! I would also emphasize the need to cross-train staff to different roles because that really helps you appreciate the other roles and allows you to anticipate what your teammates need next. No one can do their role and succeed without the person next to them, including the physician.
SC: As a nurse practitioner, I had something similar to an interventional cardiology fellowship because my mentor took the time and effort to train me in how he wanted the cardiac catheterization to be. That training and education served me throughout my career. And I, in turn, taught the nurses that were scrubbed at the table. I think that by training others you're only going to make your life easier and improve your outcomes. So, if I could do one thing, it would be to train more people in a way similar to how I was trained. I would encourage interventional cardiologists to find someone they can invest in and train, because in the long run, outcomes will improve, and it will be well worth the effort.

KS: **I would love to hear your thoughts on the role you see yourselves playing beyond the cath lab - things like patient advocacy, safety, quality standards…etc.**
EK: I think our role as nurses and techs definitely expands beyond the four walls of the cath lab. One of the things I can do as a lab manager is to foster a "speak-up" culture. This not only improves the safety and quality of the lab, but also allows me and the team to be patient advocates. We also try to engage the team in quality initiatives and make sure they are always asking "Why?". I think every team member needs to find their

passion outside of circulating or scrubbing, and they should be encouraged to pursue that. Research is another example! I'll let Jason chime in there because that is an area he is very passionate about.

JS: I think it's very important to have staff involved in research because it allows you to understand why we're making the decisions we make in the cath lab. It also gives you a chance to be involved in cutting-edge technology and gives you the chance to see something go from the bench to clinical practice! And to echo what Emily said, the ability to speak up in a procedure is tremendously important. Being able to speak up ensures that everyone is on the same page and that we are all doing what's best for the patient.

KS: **Jason, you brought up non-physician staff involvement in research. What role do you all think the PICS Society can play in promoting that?**

JS: Well, one of the ways that PICS Society can do that is through the Nurse/Tech break out sessions at PICS. These can be opportunities to focus on nurse and rad tech-driven research. I think there's a role for PICS Society to support nurses and techs that would like to do their own research, beyond just data mining or involvement in animal studies.

EK: I think it's also important for physicians to think of nurses and rad techs as team members that can play an important role in research. Physicians tend to default to fellows to help with research, but I think it would be great to have physicians involve both the fellows and the nurses/rad techs! As far as what PICS Society can do to help with research, the most exciting aspect for me is the networking opportunities. If you're thinking of doing a purely nursing / tech driven research project, I think you'll get more out of that if you can use your networks from the PICS Society to make it a multi-center study.

"No one can do their role and succeed without the person next to them, including the physician."

Emily Kish, RN

KS: **Outside of research, how can the PICS Society promote the roles that you all are playing? And how can we also promote more participation from our allied healthcare members within PICS Society?**

SC: Marketing and education! Making sure that allied health care professionals know that the Society exists and understand the benefits of being a member. Knowing that they can reach out to other members to ask about availability of various devices or techniques being used at other centers. I think we need to be marketing to the allied health professionals to join and to make sure we have educational material immediately available to them.

EK: That's exactly where I would start – with marketing. There are nurses and techs that don't even know that PICS or PICS Society exists! That can start with the physicians – encouraging the physicians to bring in more of their team. I think it's also important to keep it affordable to staff. Not a lot of hospitals can afford to send their staff. As for the meeting itself, the nursing breakout sessions are amazing! We could also have a round-table discussion for nurses where we discuss new topics or share experience from different centers.

JS: If PICS Society can help to spread the word that the PICS can be virtual for those who aren't able to participate due to funding, I think that would be huge. Also, some of the hands-on vendor sponsored activities like heart dissection or ICE-catheter simulation are very helpful for staff! It really helps us understand the procedure and be more engaged.

KN: Even though the PICS meeting provides a lot of continuing education credits for radiation technologists, not a lot of technologists attend the meeting. If the PICS Society can give a scholarship or a grant for techs to attend the meeting, that would be great. Also, continuing education for technologists does not focus on congenital cardiac interventions, whereas these meetings are specifically focused on what we do every day. So, there's a lot of value for technologists to attend. Oddly, one of the benefits of this terrible pandemic has been that PICS was accessible to a lot more people! A virtual component of the meeting would definitely help attendance for technologists, even if it's just to attend the live cases. Another option could be to provide the opportunity for folks to watch taped cases after the fact.

SC: I agree, if we can figure out how to make the meeting virtual and more accessible to people that couldn't attend in person, that would be very important. For example, making that a perk for being a member of the PICS Society to encourage people to join.

EK: Another place that PICS Society can help with: physicians have always had the opportunity to bounce ideas off each other in different platforms, and I think that's something we can help allied health professionals do!

JS: I agree! A list-serve would be hugely helpful! It could be for both research projects and to ask others how they handle day to day issues in the lab.

KS: **Thank you all for this fantastic opportunity and this great conversation! I appreciate everyone's time and I look forward to continuing this conversation, in person, in Chicago!**

atHeart Medical Receives FDA Approval for the Second Phase of the ASCENT ASD US IDE Trial

Company's reSept™ ASD Occluder Aims to Evolve Septal Closure with its Novel Metal-Free Frame Design

atHeart Medical, a medical device company dedicated to establishing the new standard of care for closure of atrial septal defects (ASD), today announced it has received approval for the start of the second phase of its ASCENT ASD U.S. Investigational Device Exemption (IDE) pivotal trial.

The prospective, single-arm study is evaluating the safety and efficacy of the reSept™ ASD Occluder, the first occluder with a metal-free, bioresorbable frame, for the treatment of patients with clinically significant, isolated ASDs. Primary endpoints will be compared with established performance goals for previously FDA-approved transcatheter ASD occluders.

"I am pleased the first phase of enrollment in our pivotal trial progressed smoothly and according to plan. This is an exciting milestone for the company," said Laurent Grandidier, CEO of atHeart Medical. "As we initiate the second phase, our team is focused on adding clinical sites across the U.S. and expanding internationally to include several enrolling sites in France. I commend the team's diligence to further validating the safety and efficacy of the reSept ASD Occluder, a critical step in our journey to evolve septal closure and provide a better solution for patients."

The reSept ASD Occluder aims to address the limitations of current occluders which have metallic frames that can place patients at risk of complications associated with long-term presence of metal in the heart and may limit future transseptal interventions, such as mitral valve interventions. Initial clinical experience demonstrates positive safety and performance in the closure of the ASDs treated with the company's device.[1]

"The low-profile reSept Occluder is a dynamic system that allows for versatile physician control during the intervention, potentially adapting to the different patient anatomies to address ASDs," commented Dr. Scott Lim, Professor of Medicine & Pediatrics at the University of Virginia in Charlottesville, VA, and a leading enrolling site in the trial. "Over time, reSept's metal-free frame resorbs, leaving a minimal implant behind. This is an exciting advancement that provides the potential to preserve future treatment options and potentially do better for our patients."

About ASCENT-ASD Investigational Device Exemption (IDE) Trial

ASCENT-ASD is a prospective, single-arm, global multi-site clinical investigation study that will enroll a total of up to 250 patients. The study aims to demonstrate the safety and efficacy of the reSept™ ASD Occluder for treating clinically significant secundum ASD with a transcatheter approach as compared to pre-defined performance goals from other commercially available occluder devices. For more information, please visit www.clinicaltrials.gov – Trial Identifier: NCT04591392.

About atHeart Medical

atHeart Medical is a medical device company with offices in Switzerland and the United States committed to establish a new standard of care for treatment of atrial septal defects (ASD).

For more information, please visit: www.atheartmedical.com.

About ASD

Commonly described as a "hole in the heart", an ASD is an opening in the septum between the left and right atria. Most ASDs are congenital defects, affecting six in 10,000 births.[2] They can also be the result of a procedure that requires transseptal crossing. A large atrial septal defect can cause extra blood to overfill the lungs and overwork the right side of the heart. If not treated, the right side of the heart eventually enlarges and weakens. The blood pressure in the lungs can also increase, leading to pulmonary hypertension. When ASDs require closure, the current standard of care is to implant a septal occluder with a metallic frame through a minimally invasive procedure.

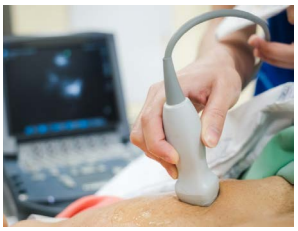
A Non-Invasive Way to Predict Heart Attack and Stroke

Pitt's Kang Kim Receives Nearly $3 Million in NIH Funding to Detect Dangerous Atherosclerotic Plaques Using Super-Resolution Ultrasound

Acute coronary syndromes (such as heart attacks) and strokes are a leading cause of morbidity and mortality in the U.S. and Europe. About 80 percent of those events occur because a build-up of plaque in the arteries—or atherosclerotic plaque (AP)—ruptures.

Research led by Kang Kim, PhD, Associate Professor at the University of Pittsburgh, recently received $2,996,514 over four years from the National Institutes of Health for work that will use super-resolution ultrasound (SRU) imaging to noninvasively detect APs that have a high chance of rupturing so that doctors can intervene.

"Over the past decade, researchers have been pushing for a way to identify rupture-prone APs," said Kim, who holds appointments in both the Swanson School of Engineering's Department of Bioengineering and the School of Medicine's Department of Medicine. "One thing that plays a critical role in AP rupture is when a new, dense network of blood vessels begins growing into the AP from the vasa vasorum (VV), or the smaller vessels that supply larger arteries and veins. However, we don't yet have the noninvasive tools to assess abnormal microvascular expansion in vivo, or inside the living body. That's the problem this project is meant to solve."



The technology developed through this project seeks to shift the current imaging approach in identifying microvessels of AP from "intravascular," or an ultrasound that uses a catheter to view the inside of the artery, to a "fully noninvasive transcutaneous" imaging approach, which instead can noninvasively see microvasculature.

If successful, the technology could be incorporated into current ultrasound scanners already in use to identify plaques at high risk of rupturing, allowing doctors to prescribe life-saving interventions and treatments to prevent a stroke.

"In addition to further evaluating our super resolution ultrasound imaging technology, I'm excited about determining if characteristics of the VV can be a predictive biomarker of AP rupture," said Kim.

Kim's team includes:

- Flordaliza Villanueva, MD, Associate Chief of Cardiology Translational Research and professor of medicine and bioengineering
- Edith Tzeng, MD, Chief of VA Vascular Surgery and Professor of Surgery and Bioengineering
- Julie Phillippi, PhD, UPMC Pellegrini Chair in Cardiothoracic Surgery and Associate Professor of Cardiothoracic Surgery and Bioengineering

For this research, the Pitt team is also partnering with Dr. Alkystis Phinikaridou from King's College in London, and Dr. Renu Virmani, President and Medical Director at CVPath Institute.

The four-year project is titled "Super Resolution Ultrasound Imaging of Vasa Vasorum to Characterize the Progression of Atherosclerotic Plaques and Predict Rupture Vulnerability" and began Feb. 1, 2022. The work was funded through the competitive funding opportunity titled NIH Research Project Grant (Parent R01). Read more about the project here: https://reporter.nih.gov/search/RIHs6jejJECD9RW3IKjTRg/project-details/10374343

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10-13

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AUGUST

03-06

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21-26

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