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INTRACARDIAC THROMBUS IN AN INFANT WITH DILATED CARDIOMYOPATHY: CASE REPORT

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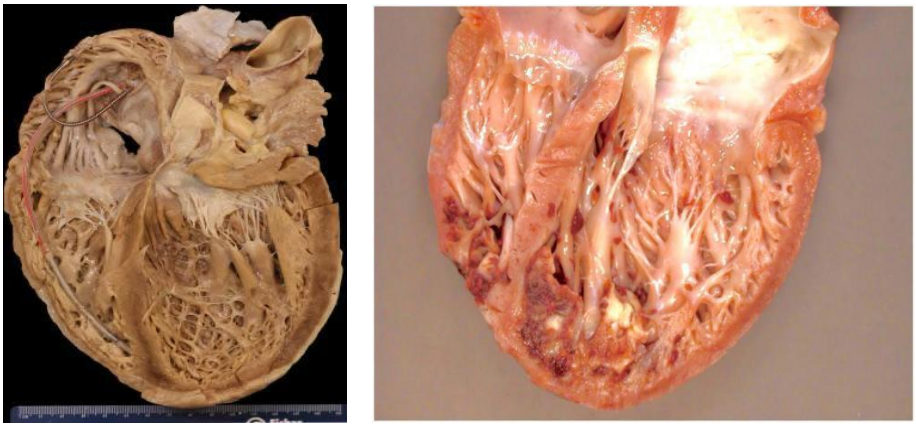
ABSTRACT

Cardiomyopathies are rare diseases of the heart muscle with wide variety of causations, that manifest with various structural and functional phenotypes but are invariably associated with cardiac dysfunction. Dilated cardiomyopathy is the commonest cardiomyopathy in children, and the majority present before one year of age. Its etiology may be acquired or genetic. Myocarditis is an important cause and is responsible for the majority of acquired cases. Inherited (familial) forms of dilated cardiomyopathy may occur in 25-50% of patients. Echocardiographic and tissue Doppler studies are the basis for diagnosis of dilated cardiomyopathy in most patients. Marked dilatation of the left ventricle with global hypokinesis is the hallmark of the disease. Dilated cardiomyopathy (DCMP) may be associated with formation or intracardiac thrombi which may embolize and result in life-threatening complications. We are presenting a 6 month old female child afflicted with DCMP and LV apical clot.

KEYWORDS: dilated cardiomyopathy, left ventricular clot, intracardiac thrombus, pediatric dilated cardiomyopathy.

INTRODUCTION

Intracardiac thrombi are a complication of dilated cardiomyopathy (DCM).[1] Factors implicated in the formation of thrombi in DCM include low-velocity swirling of blood, abnormal endocardial surfaces, atrial fibrillation, and a hypercoagulable state.[2] Thrombi complicate between 14% and 23% of DCM among children.[1, 3, 4] The most common site for thrombi in DCM is the apex where blood flow is generally reduced[5] (Figure 1-4). The major risk of the left ventricular thrombi is embolization to critical organs, particularly the brain where they may result in cerebrovascular accidents.[6]



(A) **(B)**

Figure 1: (A) Pathological specimen of dilated cardiomyopathy; (B) Pathological specimen of dilated cardiopulmonary with LV and RV apical clots.

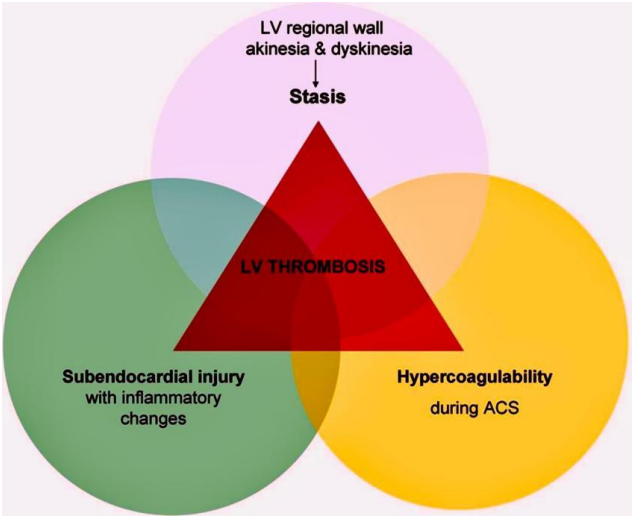


Figure 2: Diagrammatic illustration of the three components of the Virchow's triad in left ventricular thrombus formation. ACS, acute coronary syndrome; LV, left ventricular.

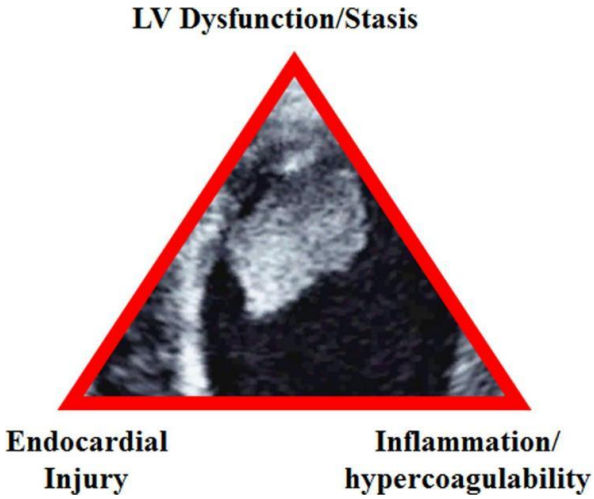


Figure 3: Echocardiographic depiction of pathophysiology of LV apical clot. LV dysfunction, endocardial injury, and inflammation/hypercoagulability (Virchow's triad) contribute to the formation of LV thrombus in different cardiac conditions. LV indicates left ventricular.

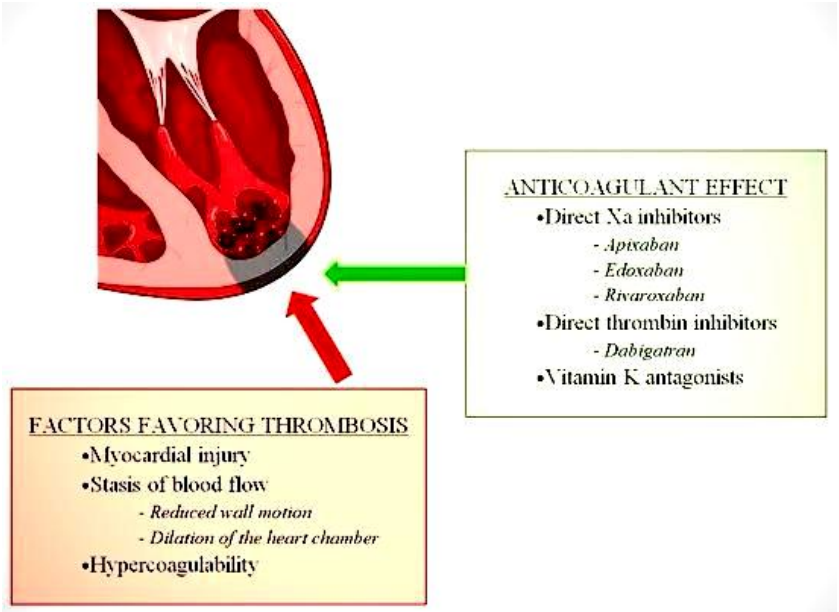


Figure 4: Anticoagulant treatment options for left intraventricular apical thrombosis.

Dilated Cardiomyopathy

Definition

DCM is defined by the presence of a dilated LV with systolic dysfunction in the absence of a hemodynamic cause that can produce the existing dilation and dysfunction, including physiological (eg, sepsis) or anatomic causes with either abnormal loading conditions (eg, coarctation of the aorta) or ischemia (eg, coronary artery anomalies).[7]

Epidemiology

The prevalence of pediatric DCMP is reported to be 0.57-1.13 cases per 100,000 individuals and account for approximately 50% of all pediatric cardiomyopathies.[7, 8] In infants less than one year old, the prevalence rises to a striking 8.34 cases per 100,000. This condition exhibits variations in prevalence across demographics (per 100,000), with males (1.32) more affected than females (0.92) and black patients (1.47) showing a higher rate of disease than the white patients (1.06).[8] These figures may represent an underestimation of actual disease prevalence due to unexplained sudden deaths, emphasizing the importance of further research into this condition.[8] Pediatric DCMP predominantly affects children in the first two years of life, with a median age of diagnosis at 1.5 years, and 41% of patients being diagnosed within the first year.[8, 9] The prognosis for children diagnosed with pediatric DCMP is grim, with nearly 40% undergoing heart transplantation or dying within two years of diagnosis.[8]

Classification

A wide variety of causations and associations have been described for DCMP[7] (Table 1 & 2).

Table 1: Causes of DCM.

Primary DCM
Familial/genetic
Sarcomeric
Mitochondrial diseases
Neuromuscular disorders
Laminopathies
Secondary DCM
Inflammatory
Toxins
Iron
Lead
Cobalt
Arsenic
Anthracycline
Radiation
Metabolic disorders.
Endocrinopathies
Thyroid disorders
Catecholamine-secreting tumor
Parathyroid disease
Diabetes mellitus
Fatty acid oxidation disorders
Carnitine deficiency
Malonyl coenzyme decarboxylase deficiency
GSDs
GSD type II (Pompe disease)
GSD type IV (Andersen disease)
Lysosomal storage disorders
Gaucher disease
Mucopolysaccharidoses
Sphingolipidoses
Nutritional disorders
Thiamine deficiency
Selenium deficiency
Protein energy malnutrition
Structural heart diseases
Valvular heart disease
Ischemia: coronary artery anomalies, coronary artery injury
Single ventricle

Pulmonary diseases
DCM indicates dilated cardiomyopathy, and GSD, glycogen storage disease.

Table 2: causes of inflammatory Cardiomyopathy.

	Causal Agent or Exposure
Commonly reported	
Infectious causes	
Bacterial	
Fungal	
Viral	Adenoviruses, enteroviruses, herpes simplex virus, varicella-zoster virus, human cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, influenza A and B viruses, HIV, parvovirus B19
Rickettsial	
Spirochete	Borrelia burgdorferi
Noninfectious causes	
Autoimmune diseases	
Hypersensitive reactions	Dermatomyositis, hypereosinophilic syndrome, Kawasaki disease, lupus erythematodes, rheumatoid arthritis
Drug reactions	
Toxic reactions to drugs	Penicillin, ampicillin, cephalosporins, tetracyclines, sulfonamides, anthracyclines
Other exposures	
Rarely reported	
Infectious causes	
Bacterial	Chlamydia, Corynebacterium diphtheria, legionella, Mycobacterium tuberculosis, mycoplasma, staphylococcus, Streptococcus A, Streptococcus pneumonia
Fungal	Actinomyces, aspergillus, candida, Cryptococcus helminthic: Echinococcus granulosus, Trichinella spiralis protozoal: Toxoplasma gondii, Trypanosoma cruzi
Viral	Variola virus, vaccinia virus, mumps virus, measles virus, rubella virus, hepatitis C virus, coronavirus, respiratory syncytial virus
Rickettsial	Coxiella brunetti, Rickettsia typhi
Spirochete	Leptospira, Treponema pallidum
Noninfectious causes	
Autoimmune diseases	Celiac disease, Churg-Strauss syndrome, Crohn disease, giant-cell myocarditis, lymphofollicular myocarditis, sarcoidosis, scleroderma, ulcerative colitis
Hypersensitive reactions	Antiphlogistics, benzodiazepines, clozapine, loop and thiazide diuretics
Drug reactions	Methyldopa, smallpox vaccine, tetanus toxoid, tricyclic antidepressants
Toxic reactions to drugs	Amphetamines, catecholamines, cocaine, cyclophosphamide, 5-fluorouracil, phenytoin, trastuzumab, ethanol
Other exposures	Arsenic, copper, iron, radiotherapy, thyrotoxicosis

Imaging modalities for left ventricular intracardiac thrombus

The standard criterion for diagnosis of intracardiac thrombus is its demonstration at operation or autopsy. Two-dimensional echocardiography has been shown to be a sensitive (92%), specific (88%), practical and noninvasive bedside tool[10], to detect and delineate thrombosis in adults and children with cardiomyopathies.[10] Diagnostic features described in children[10] include location of the thrombus most frequently at the ventricular apex, the presence of distinct margins with an acoustic density different from the underlying myocardium, free motion of the intracavitary margin of the thrombus, variation in thrombus characteristics noted on serial examinations and abnormal wall motion of the associated myocardial wall segment (Figure 5). It has been found that transesophageal echocardiography is superior to transthoracic echocardiography in the detection of intracardiac thrombosis and may be indicated when no intracardiac thrombosis is detected by transthoracic echocardiography in the presence of clinical thromboembolism.[10] The main limitation of transesophageal echocardiography is the requirement of general anesthesia in children and the difficulty of examining the cardiac apex, which is a common location for thrombosis.

Several imaging techniques for detection of LV thrombus are illustrated below:

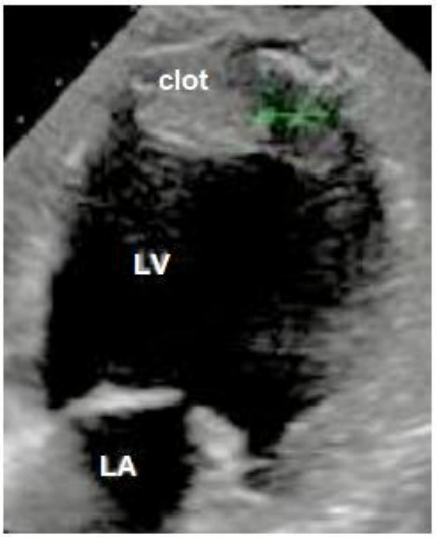


Figure 5: LV apical clot depicted by 2Dimensional echocardiography.

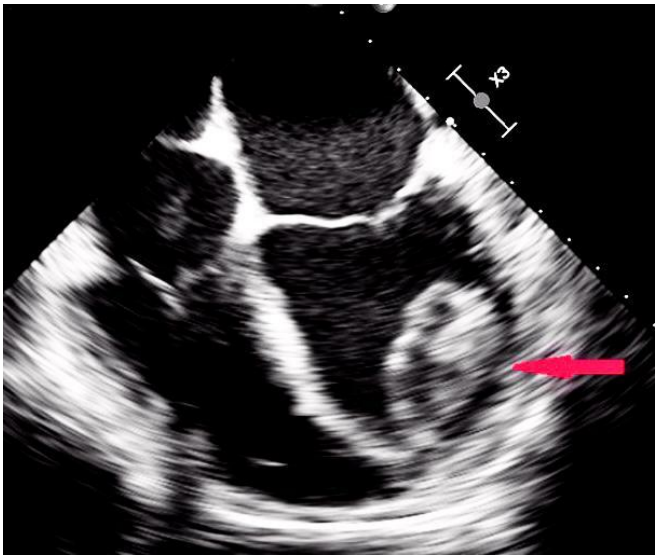


Figure 6: Transesophageal echocardiography. Apical 4-chamber view identifies LV apical thrombus.

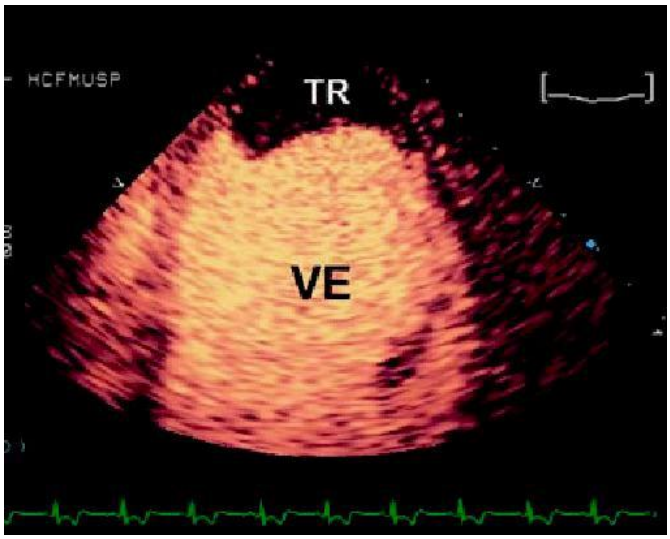
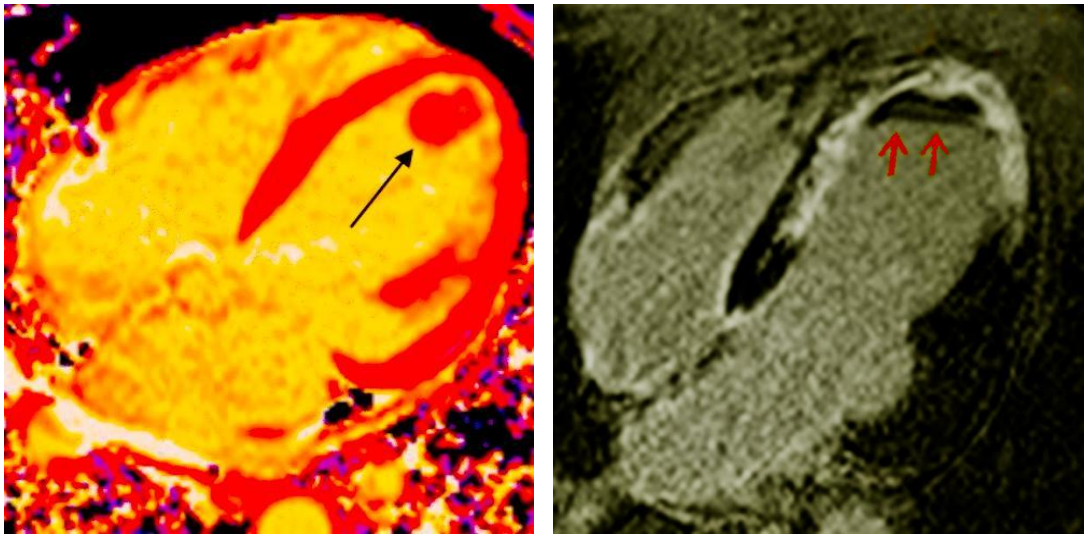


Figure 7: Contrast echocardiography. Apical four chamber view demonstrating left ventricular apical thrombus. TR-thrombus, VE-left ventricle



(A) (B)

Figure 8: Cardiac magnetic resonance (CMR) imaging. (A) Low T1 mapping of recent LV apical thrombus; (B) LV apical mural (laminar) thrombus (red arrows) seen on gadolinium-enhanced CMR.

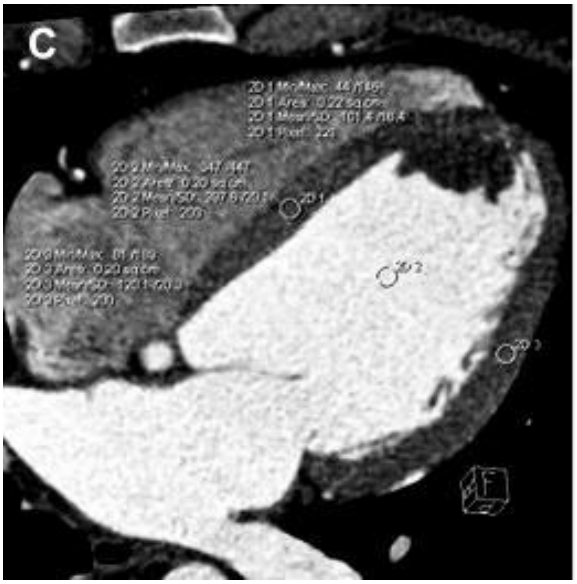


Figure 9: Cardiac CT. Cardiac CT angiography showing LV apical thrombus

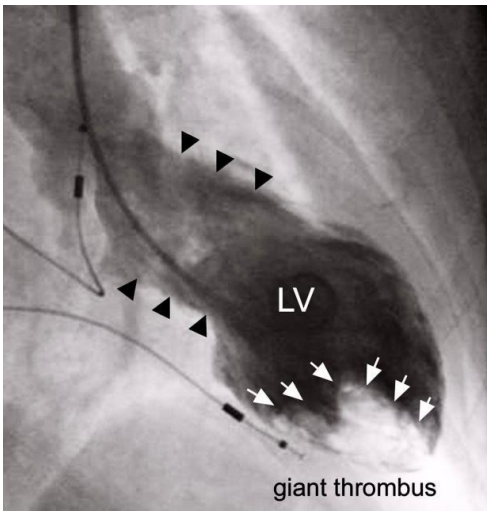
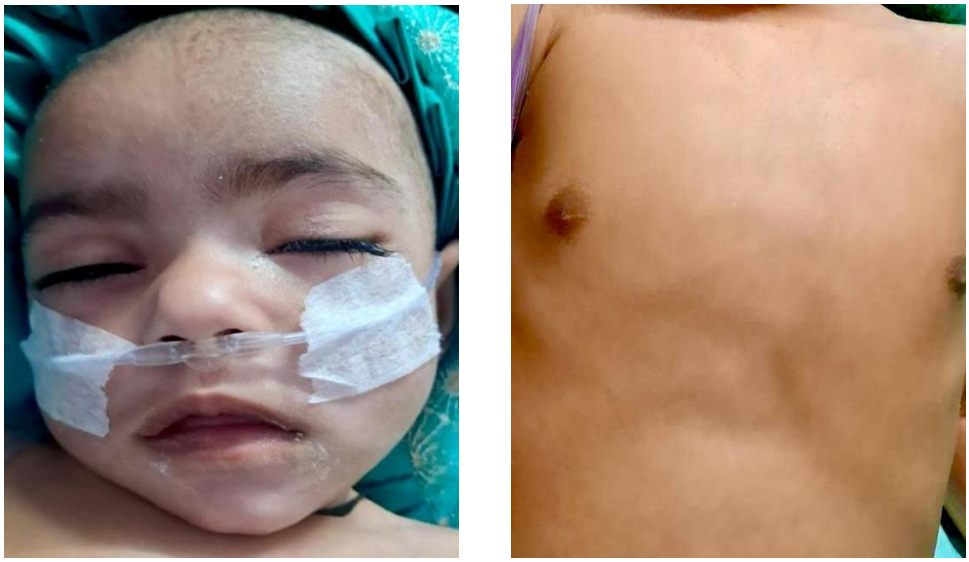


Figure 10: Left ventriculography (right anterior oblique view) showing a giant thrombus in the apex of the LV (arrows).

CASE REPORT

A six month old female infant was referred to us from a private pediatric institution for clinical cardiac evaluation, recommendations for medical management and transthoracic echocardiography (TTE). As per the history narrated by the parents the child was full term normal delivery born out of non-consanguineous marriage. There was no history of maternal risk factors of CHD (obesity, diabetes, febrile illness, smoking, alcohol intake, teratogenic drug use, or radiation exposure). They informed that the child was suffering from fever with severe breathless for last one month. The parents also reported absence of movements of right upper and lower extremity since the onset of the illness. However, they denied any history of loss of consciousness or swelling over face and lower extremities.

On clinical examination, the patient was drowsy thin built, sick looking, severely breathless and cyanosed (Figure 11A). There was presence of conspicuous protrusion of the chest wall and sternum accompanied by intercostal and epigastric retractions (Figure 11B).



(A) **(B)**

Figure 11: (A) Facial appearance. Drowsy, severely breathless, cyanosed and sick looking child (B) Chest appearance. Protruding chest wall, with intercostal and epigastric retractions.

The infant's weight was 5 kg, height was 53 cm, pulse rate was 130/min, blood pressure was 70/50 mmHg, respiratory rate was 35/min and SPO2 was 80 % at room air. All the peripheral pulses were normally palpable without any radio-femoral delay.

On cardiovascular examination, there was presence of grade 2/4 pansystolic murmur at LV apex. S3 gallop was also discerned. No clicks were heard. On neurological examination, there was presence of right sided hemiplegia. Rest of the systemic examination was normal.

Xray chest (PA) view (Figure 12) demonstrated marked cardiomegaly with pulmonary venous congestion. Pulmonary blood flow was normal.

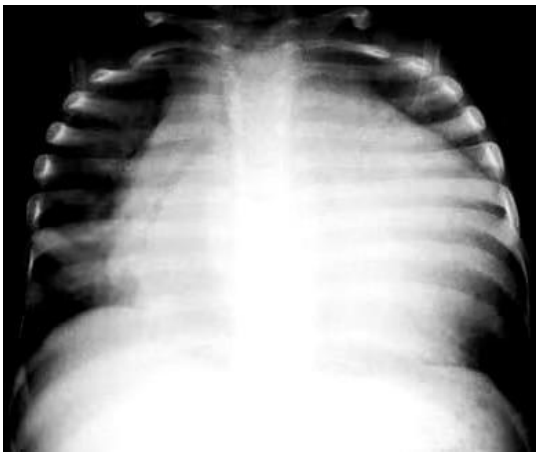


Figure 12: X-ray chest (PA) view. Massive cardiomegaly was appreciated accompanied by pulmonary venous congestion

Resting ECG (Figure 13) exhibited

- sinus tachycardia (ventricular rate 130/min)
- left ventricular hypertrophy with strain

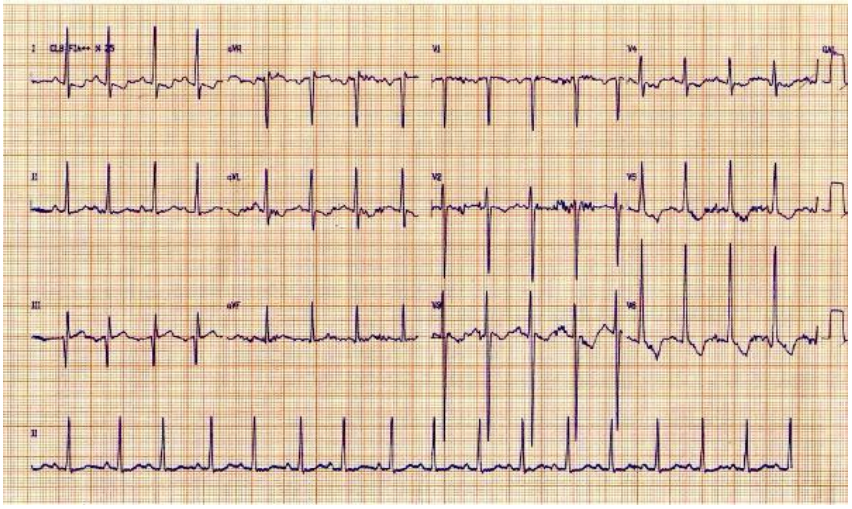


Figure 13: Resting ECG. Sinus tachycardia with a ventricle rate of 130/min. Left ventricle hypertrophy with strain was also present.

Transthoracic Echocardiography

All echocardiography evaluations were performed by the author, using My Lab X7 4D XStrain echocardiography machine, Esaote, Italy. The images were acquired using a pediatric probe equipped with harmonic variable frequency electronic single crystal array transducer while the subject was lying in supine and left lateral decubitus positions.

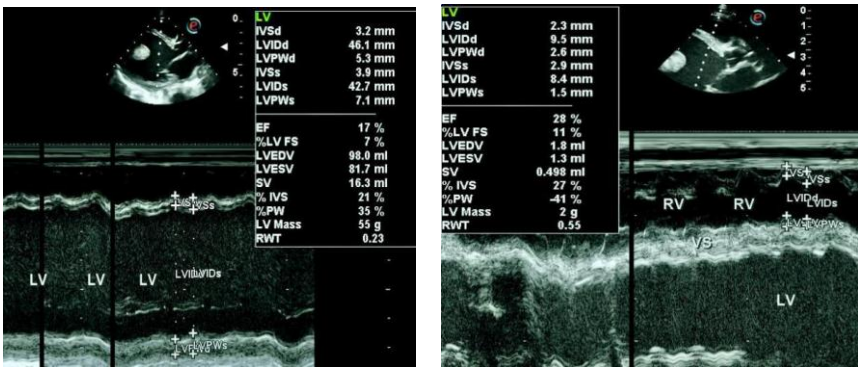
Conventional M-mode, two-dimensional and pulse wave doppler (PWD) and continuous wave doppler (CWD) echocardiography was performed in the classical subcostal, parasternal long axis (LX), parasternal short axis (SX), 4-Chamber (4CH), 5-Chamber (5CH) and suprasternal views. Contemporary sequential segmental approach for echocardiographic analysis of our index patient was accomplished and the characteristic features were outlined (Figures 15-19).

M-mode Echocardiography

M-mode echocardiography of right and left ventricle was performed and the estimated measurements are outlined (Table 3, Figure 14).

Table 3: Calculations of M-mode echocardiography

Measurements	LV	RV
IVS d	3.2 mm	2.3 mm
LVID d	46.1 mm	9.5 mm
LVPW d	5.3 mm	2.6 mm
IVS s	3.9 mm	2.9 mm
LVID s	42.7 mm	8.4 mm
LVPW s	7.1 mm	1.5 mm
EF	17 %	28 %
%LVFS	7 %	11 %
LVEDV	98.0 ml	1.8 ml
LVESV	81.7 ml	1.3 ml
SV	16.3 ml	0.498 ml
LV Mass	55 g	2 g



(A) **(B)**

Figure 14: (A) M-mode measurements of left ventricle; (B) M-mode measurements of right ventricle

Summary of M-mode echocardiography

1. LV was dilated with small RV cavity
2. LV and RV mass were 55 g and 2 g, respectively
3. There was severely reduced biventricular systolic functions; LVEF and RVEF were 17 % and 28 %, respectively.

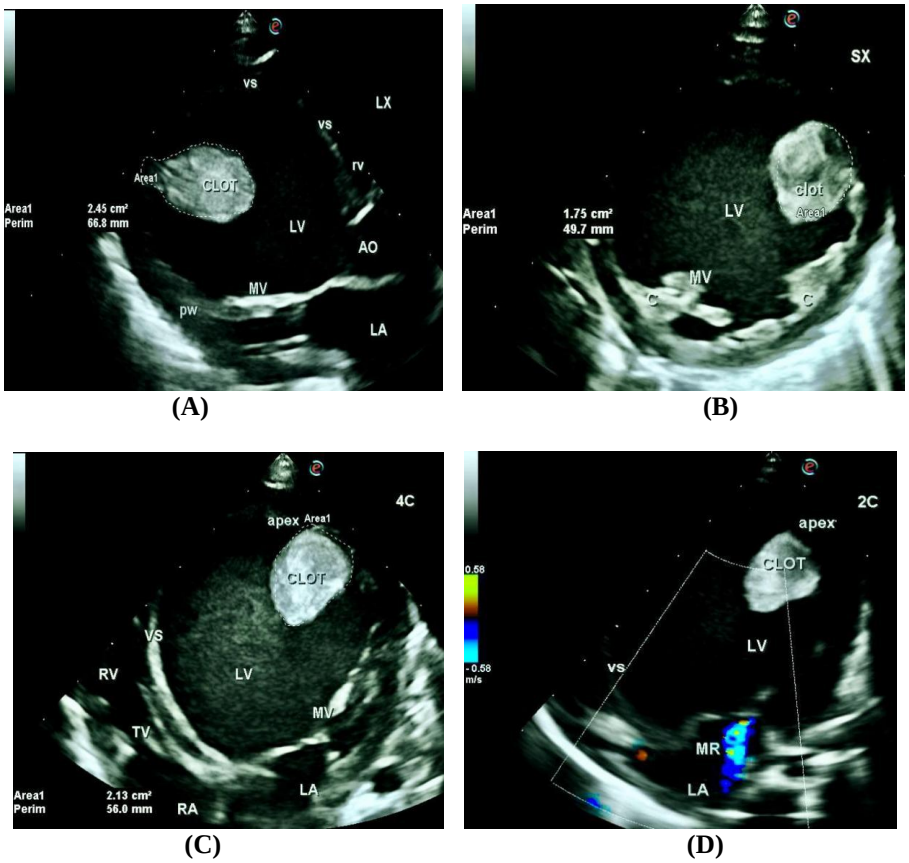
2Dimensional color echocardiography

Transthoracic color echocardiography exhibited multiple features as outlined below:

- Levocardia
- Situs solitus
- A-V concordance
- V-A concordance
- Concordant D-bulboventricular loop
- Normally related great arteries (NRGA)
- Left aortic arch
- Normal pulmonary and systolic venous drainage

LV thrombus portrayal

2-Dimensional TTE demonstrated a massively dilated LV with oval moderate sized thrombus (size 2.45 sqcm) attached to the LV apex with a wide base (Figure 15). The thrombus was immobile, non calcified and non pedunculated. We documented the thrombus in LX, SX, apical 4C and 2C views. The largest size measured was 2.45 sqcm in the LX view.

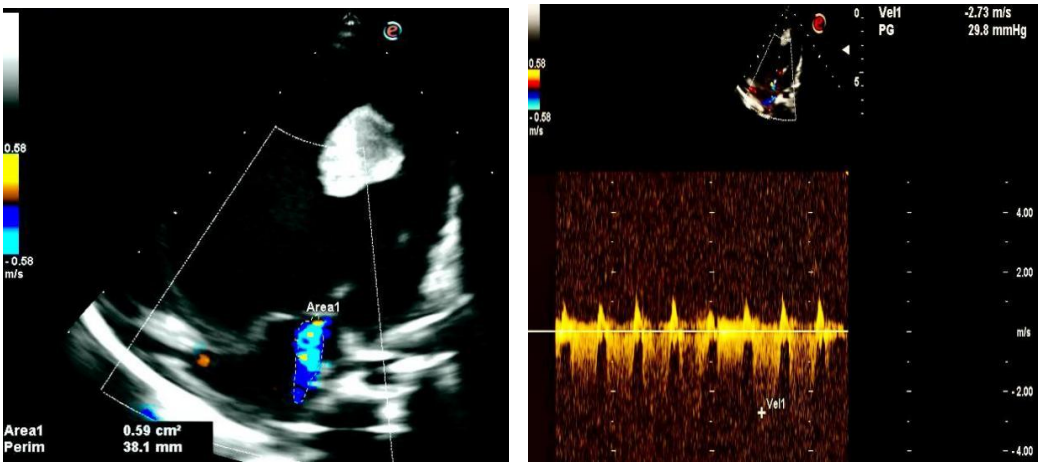


(A) **(B)**

(C) **(D)**

Figure 15: Dilated cardiomyopathy with LV apical thrombus. (A) LX view depicting oval, moderate sized (2.45 sqcm), non calcified, immobile thrombus; (B) SX view; (C) apical 4C view and (D) apical 2C view illustrating the same LV thrombus

Mild mitral regurgitation (MR) was present, due to the presence of papillary muscle dysfunction, caused by gross dilatation of LV (Figure 16). MR velocity was 2.71 m/sec and the MR JET area was 0.59 sqcm.

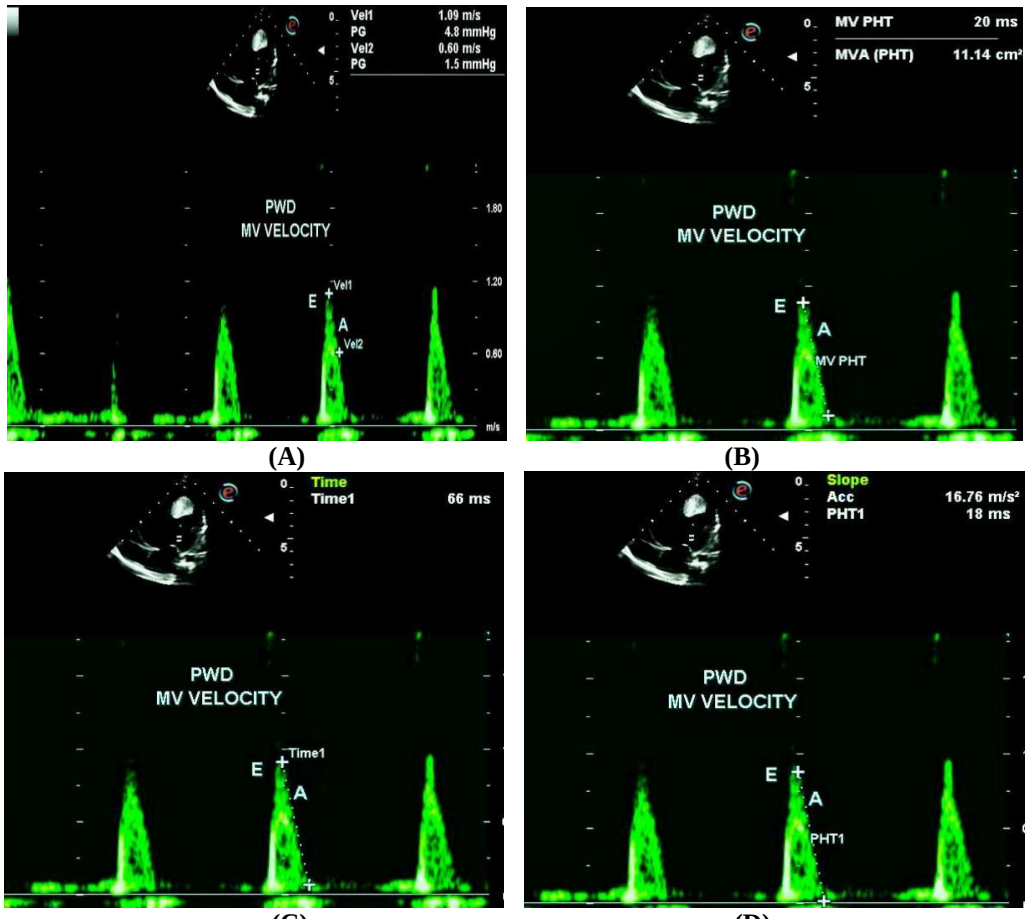


(A) **(B)**

Figure 16. Mitral regurgitation. (A) There was mild MR with a MR jet area of 0.59 sqcm; (B) MR velocity was 2.71 m/sec

Diastolic dysfunction assessment

On pulse wave doppler (PWD) analysis of MV signals, the E wave velocity was 1.09 m/sec and A wave velocity was 0.6 m/sec. The E/A ratio was 1.81:1, suggesting a restrictive diastolic dysfunction (Figure 17). The pressure half time and the deceleration time were 20 ms and 66 ms, respectively.



(A) **(B)**

(C) **(D)**

Figure 17: Pulse wave doppler (PWD) analysis of MV signals. (A) E velocity was 1.09 m/sec, A velocity was 0.6 m/sec; (B) MV pressure half time (PHT) was 20 m/sec; (C) MV deceleration time was 66 ms; (D) MV deceleration was 16.76 m/s^2

Tissue doppler imaging and E/E' estimation

- Mitral inflow velocity and LV lateral E' velocity were 1.06 m/s and 0.02 m/sec respectively
- E/E' ratio was 53:1, consistent with severe LV diastolic dysfunction of grade ≥ 3 (Figure 18)

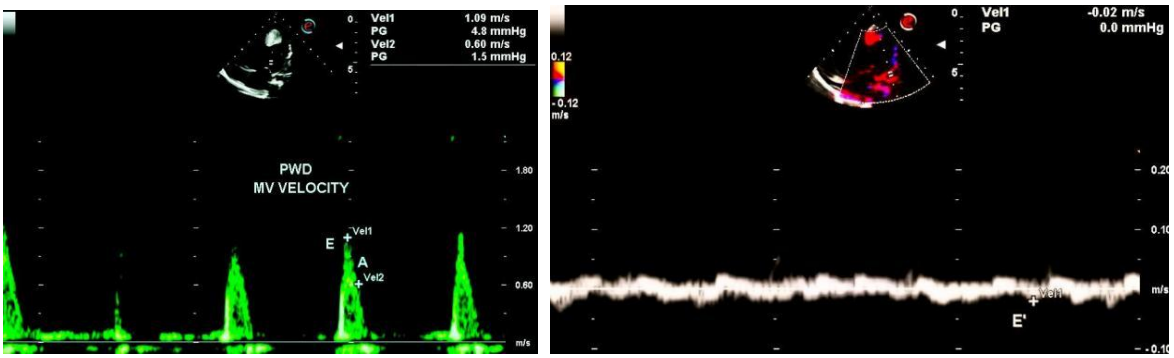


Figure 18: Tissue Doppler Imaging (TDI) and E/E' estimation. (A) Mitral inflow velocity by PWD shows E velocity of 1.06 m/s; (B) E' velocity on TDI shows a velocity of 0.02m/s. E/E' ratio was 53:1, consistent with grade ≥ 3 restrictive diastolic dysfunction

Summary of 2Dimensional color echocardiography

Our index patient, a female infant of 6 months of age was suffering from dilated cardiomyopathy with massively dilated LV and severely reduced biventricular systolic function.

Additionally, the infant was severely breathless and cyanotic with SPO2 of 80 % at room air without overt signs of congestive heart failure. However, there was severe diastolic dysfunction which explains the presence of severe breathless and cyanosis by the ongoing pulmonary venous congestion.

Furthermore, the demonstration of moderate sized LV apical thrombus suggested a grim prognosis in the backdrop of right sided hemiplegia. Perhaps the cause of hemiplegia was due to cardiovascular embolism to the left cerebral artery.

Future course of action

For effective longterm management we recommended oxygen inhalation to maintain an SPO2 of ≥ 98 %, digoxin, diuretics including mineralocorticoid receptor antagonists, beta-blockers, ACE inhibitors for dilated cardiomyopathy and vitamin K antagonists and intravenous heparin for resolution of LV thrombus. Moreover, we suggested a clinical review and repeat 2D TTE after 1 week. On repeating the echocardiography, there was significant improvement in LVEF, LV dimensions, LV mass and the size of LV apical thrombus (Table 4, Figure 19).

Table 4: Impact of medical management on dilated cardiomyopathy and LV thrombus - evaluation by 2-Dimensional TTE

Variables	First day of clinical presentation	One week after medical management	Remarks
LVIDd			
LVEF	46.1 mm	42.5 mm	Regressed
LV mass	17 %	24 %	Improved
LV thrombus	55 g	53 g	Regressed
Size (area)	2.49 sqcm	1.79 sqcm	Regressed
LX view	2.13 sqcm	2.03 sqcm	Regressed
4C view			
LVIDd, left ventricular internal dimension-diastole; LVEF, left ventricular ejection fraction; LX, parasternal long axis; 4C, apical four chamber.			

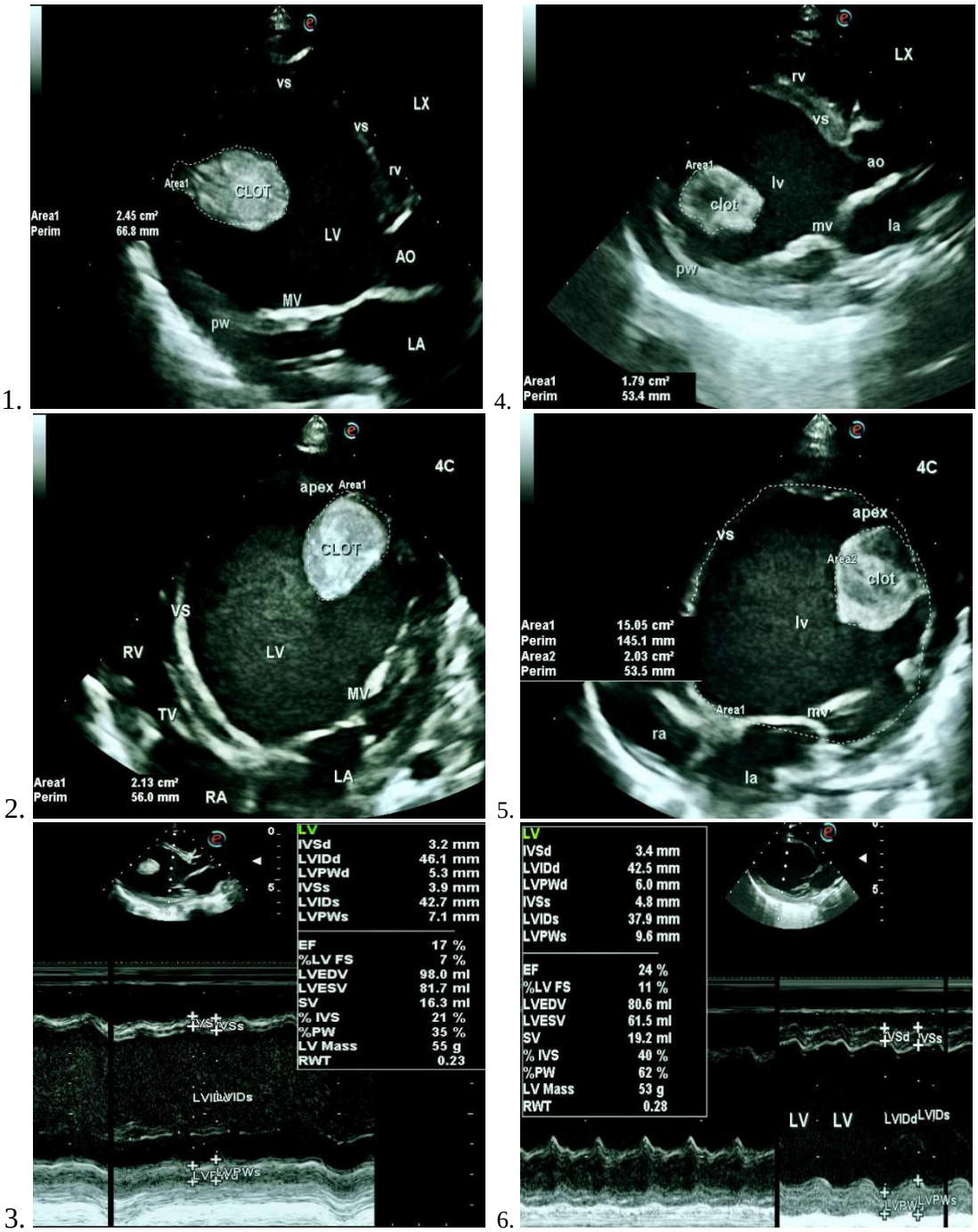


Figure 19: 2-Dimensional TTE at the time of presentation and after after one week of intensive medical management. (A) 1, 2, 3 depicts dilated LV, severely reduced LVEF with moderate sized LV apical thrombus, at the time of first presentation; (B) 4, 5, 6 subsequently demonstrates the impact of medical management

DISCUSSION

Intracardiac thrombus is the most common type of cardiac mass. Thrombus in the left ventricle (LV) or left atrium is of particular clinical concern due to significant risk of embolic events in the brain or other organs resulting in significant morbidity and mortality.[11] Left atrium and atrial appendage (LA/LAA) thrombus is prevalent in patients with atrial fibrillation (AF) and also may be associated with valvular disease.[11] LV thrombus is associated with severe myocardial dysfunction, which may occur in both ischemic and non-ischemic etiologies.[11] The presence of LA/ LAA or LV thrombus typically requires adjustment in clinical management, and therefore, detection and assessment of left chamber intracardiac thrombus are highly clinically relevant.[11]

There are multiple factors that have been proposed that may predispose patients with cardiomyopathy to thrombosis.[10] These may include:

1) impaired LV systolic function[10]
2) stasis of blood flow[10]

3) the presence of an abnormal and procoagulant endocardial surface[10]
4) dysrhythmias (atrial fibrillation)[10]
5) hypercoagulable state[10]
6) fractional shortening of $\leq$ 10 %[10]
7) elevated levels of fibrinogen[12]
8) elevated levels of C-reactive protein[12]
9) elevated levels of tissue factor[12]
10) elevated levels of D-Dimer[12]
11) elevated levels of anti-cardiolipin antibodies (IgM and IgG)[12]
12) low-velocity swirling of blood[2]
13) abnormal endocardial surfaces[2]

Dilated cardiomyopathy

Pathophysiology

Injury to the myocardial cell is the initiating factor that leads to cell death. If considerable cell loss occurs, the myocardium fails to generate enough contractile force to produce adequate cardiac output. This results in the activation of the following compensatory mechanisms[13-17]:

- The renin-angiotensin-aldosterone system
- Sympathetic stimulations
- Antidiuretic hormone production
- Release of atrial natriuretic peptide

These compensatory mechanisms help to maintain cardiac output in the initial phase; however, as myocardial damage progresses, persistent and excessive activation can be detrimental to cardiac function, leading to overt congestive heart failure (Figure 20).

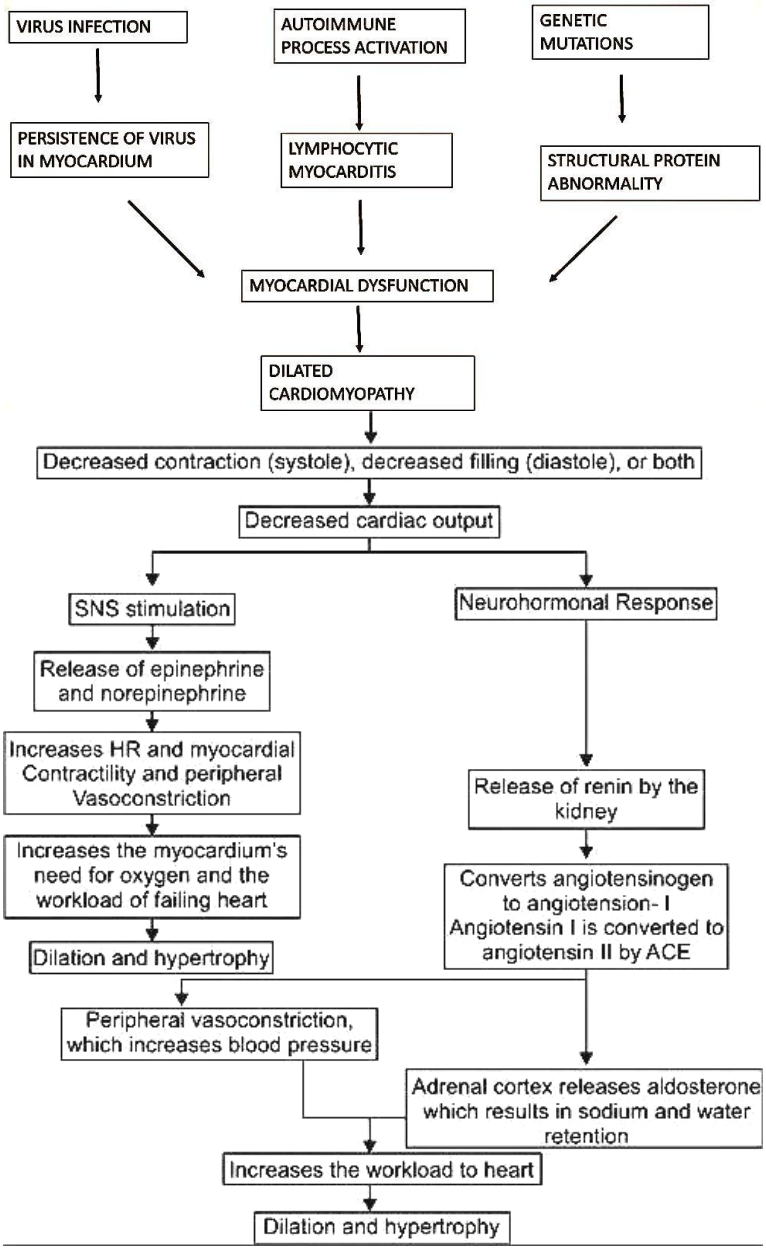


Figure 20: Pathophysiology of acute - decompensated heart failure

Dilated cardiomyopathy with LV thrombus
Pharmacologic Therapy
It is well known that diuretics including mineralocorticoid receptor antagonists, ACE inhibitors, and beta-blockers form the pharmacologic regimen for heart failure in DCM. Diuretics may provide an improvement in symptoms, whereas, ACE inhibitors appear to prolong survival.[18]

Beta-blocker therapy in children with chronic heart failure due to DCM has been shown to improve symptoms and left ventricular ejection fraction. Carvedilol is a beta-adrenergic blocker with additional vasodilating action. Carvedilol, in addition to standard therapy for dilated cardiomyopathy in children, is believed to improve cardiac function and symptoms; it is well tolerated, with minimal adverse effects, but close monitoring is necessary because it might worsen congestive heart failure and precipitate asthma.[19]

Anticoagulants and antiarrhythmic agents, particularly amiodarone, are often used in patients with low myocardial contractility and symptomatic arrhythmias, respectively. Results are encouraging. Presence of intracardiac thrombi, is an indication for anticoagulant therapy.[20]

Heart rate reduction by ivabradine in children with DCM was attempted which showed improvement of left ventricular function and quality of life parameters[21] and such therapy is worth investigating in future studies.

Palliative, Bridge, and Experimental Surgery
Palliative surgical measures are associated with significant mortality and morbidity rates despite advances. Resection of a large segment of the hypertrophied ventricular muscle (Batista procedure) and repair or replacement of mitral valve to minimize volume overload of left ventricle have been used as palliative measures. Cardiomyoplasty is the transposition of electrically transformed skeletal muscle to provide systolic and diastolic augmentation to the native heart.

Mitral valve repair and partial left ventriculectomy have been found to be feasible in selected patients and help reduce symptoms in most patients and help[22] reduce left ventricular dimensions in some patients; however, whether it can modify the natural history, especially the need for cardiac transplantation, is unclear.[23]

Implantable mechanical support devices, modified for use in infants and children, have been introduced to support the failing heart until a suitable donor is available for transplantation (bridge to transplant). The Berlin Heart EXOR pediatric has also been successfully used in several centers.[24] Major limitations include infection, thromboembolism, disturbance from noise, and the need to frequently recharge batteries.

Cardiac resynchronization therapy using a biventricular pacemaker has been shown to be effective in adults with DCM. In addition, these devices are available with defibrillator backup for patients at risk for ventricular arrhythmias. They are used in children with DCM with early favorable results.[25]

Stem cells, particularly cardiac stem cells, and cardiac progenitor cells may represent promising types of cellular therapy to replace dead myocardial cells, but the technology is presently a research topic rather than a clinical option.[26, 27]

Plasma exchange by producing immunoadsorption in order to eliminate autoantibodies in children with DCM resulted in improvement in cardiac function[28], similar to that reported in adult subjects and may considered as a bridge transplant or ventricular assist devices.

CONCLUSIONS
Pediatric dilated cardiomyopathies are a group of myocardial diseases with myriads of etiologies. They may be associated with variable complications, most often heart failure, LV thrombus, arrhythmias, cardiovascular embolism and sudden death.

Children with DCM accompanied by progressive dilatation of the heart and worsening heart failure have a worse prognosis. In DCM with no obvious detectable etiology, outcome depends on severity of myocardial dysfunction, and compliance with therapy. The degree of depression of fractional shortening or LVEF on initial echocardiography, cardiothoracic ratio and elevation of LV end-diastolic pressure, have all been applied as predictors of outcome, although they are often not predictive. Other possible prognostic factors include age at onset (better for infants), presence of symptomatic arrhythmias, and thromboembolic episodes.

We recommend that children with massively dilated LV with decreased LV systolic function and LV thrombus should receive aggressive anticongestive heart failure pharmacological treatment and anticoagulant therapy to improve their morbidity and mortality.

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