Published online: June 30, 2019

Review

# Metabolic cardiomyopathy in pediatrics

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DOI: 10.31083/j.rcm.2019.02.5151



Currently, the percentage of non-specific myocardial lesions of non-inflammatory genesis has significantly increased in the structure of cardiovascular diseases in children and adolescents. Cardiomyopathies are a cluster of myocardial diseases that have become more of interest by cardiologists, morphologists, geneticists, and cardiac surgeons. Cardiomyopathies in children are regarded as a severe pathology characterized by a progressive course, resistance to therapy, and result in an unfavourable prognosis. The current article presents data from international publications dedicated to cardiomyopathy diagnostics in children. This article deals with terminology issues in compliance with international disease classification, primary diagnostic criteria of non-coronary myocardium pathology, and modern methods of diagnostics and pharmacotherapy.

*Keywords*

Cardiomyopathy; metabolic disorders; heart failure; pediatrics

## 1. Introduction

Cardiomyopathy (CMP) translated from the Greek (*kardia* - heart; *mys, myos* - muscle; *pathos* - disease) means "heart muscle disease" (Bridgen, 2004). This term was first proposed by W. Bridgen in 1957, and it has been used for many years to refer to myocardial diseases of unknown etiology that are characterized by cardiomegaly and electrocardiogram (ECG) changes and progress toheart failure and poor prognosis. According to the European Society of Cardiology (ESC), CMP is a group of heterogeneous diseases characterized by myocardial pathology with structural and/or functional disorders that are not caused by coronary heart disease, hypertension, valvular defects, or congenital diseases (Elliott et al., 2008). Cardiomyopathy is a serious disorder of the heart muscle and, although rare, it is potentially devastating in children (Wilkinson et al., 2008).

### *1.1 CMP classification*

In 1995, the World Health Organisation (WHO) proposed a classification of cardiomyopathies (Richardson et al., 1996). The classification is based on CMP morphological characteristics with specific features of structural changes in the myocardium (Table 1). According to WHO, CMP is a myocardial disease that is associated with myocardial dysfunction. Moreover, each CMP is a syndrome that comprises a certain complex of morphofunctional, clinical, and instrumental features that are characteristic of a heterogeneous group of myocardial diseases. This classification does not take into account CMP genetic determination, familial disease forms, and the possibility of CMP transformation from one form to another (hypertrophic cardiomyopathy transforms into dilated cardiomyopathy at later stages).

Progress in molecular biology (i.e. confirmation of the role genes play in cytoskeleton synthesis, contractile proteins (sarcomeres), and ion channel proteins) contributed to systematization of CMP causes. In 2004, a genomic or molecular classification of hereditary CMP was proposed (Table 2) (Priori et al., 2001; Priori and Napolitano, 2002; Priori et al., 2003; Thiene et al., 2004).

Afterwards, gene mutations were found not only in cytoskeleton proteins, but also in sarcomeres. Theseproteins are responsible for mitochondrial breathing, and the structure of the nuclear envelope; necessitating development of a new, more conceptual classification that was proposed by the American Heart Association

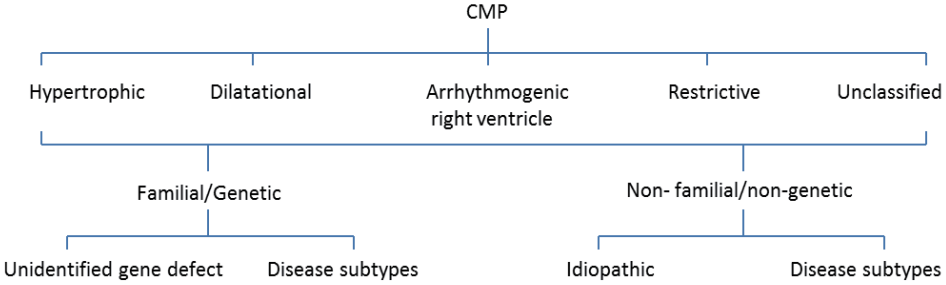


Figure 1. CMP classification (Elliott et al., 2008)

Table 1. Pathophysiological classification of cardiomyopathies by the World Health Organisation (modified from (Richardson et al., 1996))

| Primary | Additional | Specific | Non-classified |
|---|---|---|---|
| Dilatational cardiomyopathy, Hypertrophic cardiomyopathy, Restrictive cardiomyopathy | Arrhythmogenic dysplasia of right ventricle, Postpartum cardiomyopathy | Metabolic, Inflammatory, Ischemic, Hypertensive, General system disease, Muscular dystrophies | Fibroelastosis, Syndrome of left ventricular noncompaction, Systolic myocardium dysfunction with minimal dilation, CMP with underlying mitochondriopathy |

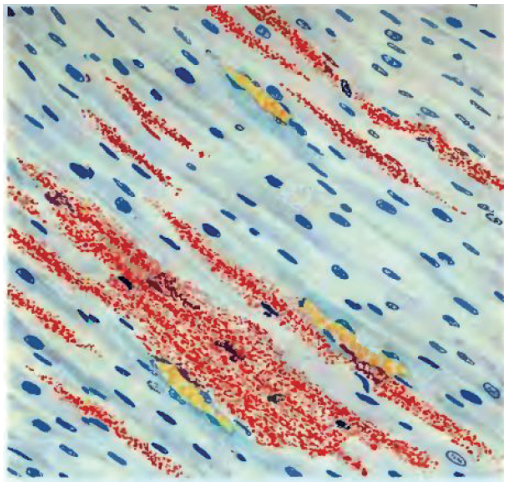

Figure 2. Fatty degeneration of the myocardium ("tiger heart"). Sudan III staining (× 200) (Paukov et al., 2015).

(AHA) in 2006 (Table 3).

CMP is now defined as a heterogeneous group of myocardial diseases associated with a mechanical and/or electrical dysfunction that are manifested by an inadequate (inappropriate) hypertrophy or dilation that are caused by varied, often genetic, factors. CMP is limited to the heart or it is a part of generalized systemic disorders that lead to cardiovascular death or progressive heart failure (Maron et al., 2006).

A new ESC classification was published in 2008 that defines CMP differently from the AHA. According to ESC, CMP is a group of heterogeneous diseases characterized by myocardial pathology with structural and/or functional disorders that are not caused by coronary heart disease, hypertension, valvular defects, and congenital diseases (Elliott et al., 2008). The basis of this classification is the change in the left ventricle structure and function, taking into account family history. This classification is focused mainly on its clinical use (Fig. 1).

## 2. Metabolic cardiomyopathy as pediatric problem

According to International Statistical Classification of Diseases and Related Health Problems, metabolic CMP has a common code I43. Metabolic CMP is a syndrome involving a non-inflammatory myocardial lesion that develops under various diseases and conditions of known etiology characterized by latent or clinically expressed myocardial dysfunction due to metabolic disorders, energy formation, and transformation in myocardium (Anichkov et al., 1981). It shall be highlighted that metabolic CMP is not an independent disease. Absence of a single approach to definition of myocardial lesion of metabolic genesis creates significant difficulties in statistical data on prevalence and clinical features of this pathology in the pediatric population.

### *2.1 Etiology*

Etiology of metabolic CMP remains understudied. According to modern concepts, the disease is considered to be a multifactorial proces (Caforio et al., 2013; Pinto et al., 2016). In pediatrics, ten etiological key factors of metabolic CMP are outlined: anemia, insufficient nutrition, obesity, vitamin deficiency, liver and kidney lesions, disorders of certain metabolism types, endocrine diseases, systemic diseases, intoxications, infections, and athletic overexertion.

### *2.2 Pathomorphological aspects of metabolic CMP*

Dystrophic changes in the myocardium can be focal or layer-by-layer. They can affect the walls of a single ventricle and morphologic manifestations may be heterogenous. Muscle fiber lesions in dystrophy is combined with changes in stroma, disorders in micro-circulation, and heart innervation (Briongos and Acena Navarro, 2015; Mancioet et al., 2013). Endothelial destruction in the form of cytoplasmic vacuolization and thinning of cytoplasmic processes can be found in capillaries of muscular stroma (Lushnikova et al., 2018). Changes in the innervation apparatus under hypoxia and acidosis play a role in the development of cardiomyocyte lesions. They are manifested by dystrophy of intermuscular nerve stipes and terminations, demyelination, decay of myelin membranes, and formation of myelin-like bodies. In nerve terminals, stratification and fragmentation of myelin plates are observed. The evolution of necrobiotic and dystrophic changes in the myocardium into microfocal fibrosis are accompanied by compensatory hypertrophy of muscle cells (Sisakian, 2014). Structural changes may occur earlier or simultaneously with functional disorders, but they never develop after them. Presently, hypertrophy and cardiosclerosis as an outcome of metabolic myocardial damage has been recognized.

#### *2.2.1 Histological features*

Metabolic CMP has some peculiar features such as muscle fiber dystrophy (fibers are interrupted or become short); myocytolysis (breakdown of muscle myocardium cells), eosinophilia of cardiomyocytes, nucleus hyperchromy (nucleus chromatin becomes very dark), and increased muscle fiber diameter. Foci of various cell aggregations may be located between muscle fibers, intercellular fibrotic formation, and fatty degeneration atsites of myocaradial fiber necrosis.

### 2.2.2 *Pathomorphological features*

Dilatation and hypertrophy of cardiac chambers are observed under metabolic CMP. Flaccidness and swelling of the myocardium is formed, yellowish striation of papillary muscles and trabeculae are seen, and the organ acquires a "tiger heart" coloration (Fig. 2). Epicardial fat deposition is seen with subsequent fibrosis and cardiosclerosis.

## 2.3 *Pathogenetic aspects of metabolic CMP*

The energy supply of heart cells comes from a set of sequential and interrelated processes that invlolve ATP generation, and its transportation from synthesis to disposal sites in various energy-dependent responses (Bonora et al., 2012). The energy depot in the myocardium is from ATP accumulators and creatine phosphate; however, often times it requires a constant synthesis of macroergic compounds for cellular energy processes.

The "energy stations" of cardiomyocytes are in the mitochondria, which occupies 30-40% of the cell volume. In tissues of the conducting system, that are more adapted to anaerobic metabolism compared to myocardial contractile cells, mitochondria occupy about 10% of the volume. The primary energy substrate in the myocardium are fatty acids, glucose, lactate, pyruvate , ketone bodies, and amino acids. The total ATP amount that is used in cardiomyocyte reduction, only a small portion that is localized in myofibrils, is available. The connection between various ATP pools is via creatine phosphate.

Activity intensity of myosin ATPase determines the rate of synthesis and decay of generating bridges between actin and myosin, and consequently, the strength and rate of myocardial contraction. Under partial or complete termination of oxygen access to cardiomyocytes, oxidation of free fatty acids decreases or completely stops and anaerobic glycolysis is activated with lactate generation. This process does not provide enough energy for myocardium contraction (Antzelevitch, 2004; Paukov et al., 2014). At the initial reversible stage of cardiomyocyte lesion, contractility decreases due to energy deficiency, which occurs in parallel with a significant decreases in creatine phosphate and ATP. Accumulation of lactic acid (lactacidemia) and pyruvate in the blood leads to changes in the acid-base balance, which is an important factor to consider in metabolic disorders. In cardiomyocytes, the ATP content gradually decreases, which is followed by splitting of adenyl nucleotides to inosine and hypoxanthine. Lesions become irreversible, andit is connected with destructive changes in the sarcolemma membrane. The destruction of the sarcolemma membrane is accompanied by release into the blood of cytoplasmic enzymes, i.e. components of the damaged cytoplasm.

Destruction of myofibrils occurs when there is complete disintegration of adenyl nucleotides in myofibrils and over-saturation with calcium that lead to contracture development.

Continuous non-stop myocardium functional activity requires a constant activity of the cardiomyocyte genetic apparatus. It facil-itates DNA-based synthesis of protein structures from amino acids and hypertrophy of cellular structures.

The processes of energy formation in the cell are under adrenergic control. Increase of sympathetic influences lead to an increase in oxygen consumption by the myocardium. At the same time, catecholamines stimulate biological oxidation in myocardium and increase the delivery of substrates essential for oxidative processes to the myocardium. Myocardial adrenoreceptors were found to be more sensitive to adrenaline than to noradrenaline (Fraley et al., 2005).

The genesis of metabolic CMP is split into 3 main areas: reduction of incoming energy substrates, disorder of cellular respiration and oxidative phosphorylation, and enhancement of myocardium energy needs.

## 2.4 *Reduction of incoming energy substrates (macroergic compounds, oxidation substrates, oxygen, vitamins)*

Disorders of substrate and vitamin myocardium supply is a frequent cause of cellular energetic abnormalities in the myocardium. Insufficiency or the opposite, excess of glucose and fatty acids, may lead to disorders in energy generation and myocardium dystrophy. These conditions occur in alimentary dystrophy, hypovitaminosis, syndrome of impaired intestinal absorption, liver failure, anemia, endocrinopathies, tubular kidney disease, and starvation.

## 2.5 *Disorder of cellular respiration and oxidative phosphorylation*

Disorder of cellular respiration and oxidative phosphorylation is characterized by decrease in synthesis of macroergic compounds and their inefficient use by functioning myocardial structures (dystrophy of impaired consumption or assimilation) (Rosca et al., 2008). Disorder of cellular respiration and oxidative phosphorylation can both be primary and secondary.

The primary pathology is genetically determined and facilitated by disorders of electron transfer in the mitochondrial chain of respiratory enzymes, disorders of enzyme responses in energy metabolism, and pathologies of tricarboxylic acid cycle. The causes of secondary pathology may be electrolyte imbalances, exogenous intoxications (cytotoxic poisons, cardiotoxic drugs, alcohol), and chronic infections.

## 2.6 *Tissue hypoxia*

*Tissue hypoxia* is one of the most common causes of energy imbalance. It is characterized by dissociation of cellular respiration and oxidative phosphorylation. Hypoxia is accompanied by insufficiency of biological oxidation and macroerg deficiency, which are deemed to be an important pathogenetic aspect of metabolic CMP genesis (Antzelevitch and Belardinelli, 2006). Chronic hypoxia leads to a glycolysis shift to anaerobic metabolism: the decrease of acetyl coenzyme A inflow in the Krebs cycle, lactate

Table 2. Genomic classification of congenital CMP (2004)

| **Cytoskeleton CMP** | **Sarcomere CMP** | **Ion channel CMP** |
|---|---|---|
| Dilatational cardiomyopathy, Arrhythmogenic CMP of right ventricle, Syndrome of left ventricular noncompaction | Hypertrophic cardiomyopathy, Restrictive cardiomyopathy, Syndrome of left ventricular noncompaction | Syndrome of elongated and shortened Q-T interval, Brugada syndrome, Catecholaminergic polymorphic ventricular tachycardia |

Table 3. Classification of primary CMPs by the American Heart Association (modified from (Maron et al., 2006))

| Genetic CMP | Mixed CMP | Acquired CMP |
|---|---|---|
| Hypertrophic cardiomyopathy, Arrhythmogenic CMP, Syndrome of left ventricular noncompaction, Glycogenosises, Mitochondrial myopathy, Dysfunction of ion channels | Dilatational cardiomyopathy, Primary restrictive CMP | Myocarditis (inflammatory CMP), Takotsubo CMP, Postpartum cardiomyopathy, CMP induced by tachycardia, CMP in infants of insulin-dependent mothers with diabetes |

accumulation, and decrease of macroerg synthesis. Hypoxia participates in fat metabolism disorders, decrease in fatty acid oxidation, increase in esterification, and retention of triglycerides and lipopeptides in bioplasma. There is an increase in lipid peroxidation with accumulation of hydroperoxides interacting with cellular structures. Intensifying lipid peroxidation may also have an adverse effect on microcirculation: vascular endothelium is damaged and hyalinosis is formed. Arising against the background of hypoxia, intracellular acidosis, excess of fatty acids, and lipopeptides lead to disruption of membrane ultrastructure (sarcolemma, T-system membranes, and lysosome membranes). The release of lysosomal proteases lead to autolysis of subcellular structures and mitochondria destruction. The energy resulting from oxidation is not accumulated in the form of macroergs and consumed as heat (Hazebroek et al., 2015; Song et al., 2017).

Conditions accompanied by electrolyte metabolism disorders can also cause energy deficiency and myocardial dystrophy. These conditions develop under hypo- or hyperkalemia, hyper- and hypocalcemia, thyroid gland functions, adrenal glands, and hypothalamus. Electrolyte disorders are also based on hypoxia: it limits functioning of the transmembrane electrolyte pump, forms the electrolyte imbalance by losing intracellular potassium and its aggregation in extracellular space. Electrolyte imbalance in intra- and extracellular space leads to hyperosmia-cell edema. Hypokaligistia is one of the main causes in formation of myocardium necrosis and heart rhythm disorders. Accumulation of calcium ions is related to either increased $Ca^{2+}$ ions in cardiomyocytes or calcium binding disorders and its reaccumulation in the sarcoplasmic reticulum and mitochondria. The excess concentration of $Ca^{2+}$ ions in bioplasma contributes to the dissociation of cell respiration and oxidative phosphorylation (Fuchs and Martyn, 2005; Ivanov et al., 2013).

### *2.7 Enhancement of myocardium energy needs*

Enhancement of myocardium energy needs is a discrepancy between the energy synthesis and its consumption by functioning myocardium structures (hyperfunction metabolic CMP). The increased myocardium energy needs contributing to CMP development due to hyperfunction, can occur against the background of conditions requiring an excessive myocardium energy consumption. A significant role is played by diastole shortening (in tachycardia) during the recovery processes in the myocardium (Bresnahan and Eastwood, 2007). Most often this problem occurs in children and adolescents who are intensely engaged in sports.

### *2.8 Hypersympathicotonia*

Hypersympathicotonia leads to increased myocardial energy needs combined with a weakening of biological oxidation and a breach in its effectiveness. Excessive adrenergic impact on the myocardium is accompanied by wasteful intracellular oxygen spending with a simultaneous decrease of ATP release. It leads to disruption of the process of oxidative phosphorylation and development of myocardial hypoxia (Arbustini et al., 2014; Poskrebysheva et al., 2003).

Pathological effects of catecholamines are glycolysis shifting to anaerobic with macroergic deficiency, toxic impact on myocardium, excessive $Ca^{2+}$ release from sarcoplasmic reticulum, inhibition of protein synthesis in the myocardium, and disruption of electrolyte cell balance.

Any stressful condition (physical overexertion, hypo- and hyperthermia, injury, starvation, pain, or emotional stress) may lead to excessive activation of sympaticoadrenal system, hypoxia, and energy deficiency. It activates the peroxidation process, interferes with architectonics of cellular structures of the sarcoplasmic reticulum, and the chain of respiratory enzymes.

Manifestation of clinically significant metabolic CMP depends on reserves of mitochondria functional activity. It gradually decreases with pathology progression or hyperfunction, and it coincides with clinical manifestations of heart failure.

## 3. Metabolic CMP classification

In clinical practice, the classification proposed by Ostropolets S. S. used metabolic CMPs combined into seven groups that are dependent on the main etiological factors (Ostropolets and Zolotova, 1986) (Table 4).

## 4. Anamnestic and clinical manifestations of metabolic CMP in children

For metabolic CMP diagnosis, patient history is of much importance. It is important for a pediatrician to be concerned about the availability of aggravated familial history in cardiovascular diseases, the age of cardiovascular disease manifestations in relatives, the course of pregnancy and childbirth in view of identifying possible perinatal pathology, presence of diseases and pathological conditions with a chronic hypoxic tissue syndrome (anemia, endocrinopathy, chronic tonsillitis, significant physical exertion and sports overload, suffered myocarditis, poisoning, etc.), occurrence of conflict situations in family and at school, daily routine disturbances (lack of sleep), and family eating habits (irregular meals, unbalanced diet).

Analysis of metabolic CMP manifestations revealed the absence of specific clinical CMP markers. The complaints that parents and children typically presented and consulted a physician are characterized by extreme polymorphism. The most common complaint is cardial syndrome. Cardialgia is revealed in children, and commonly presents with paroxysmal, jabbing pain that rarely radiates towards the left scapula area. It is frequently related to

Table 4. Metabolic CMP classification (Ostropolets and Zolotova, 1986)

| Metabolic CMP form | | Chronic heart failure stages |
|---|---|---|
| **By etiological factor** | **By progressing** | |
| **Intoxicational** (acute infectious disease, chronic infection sites, intoxications), **Dysmetabolic** (dystrophy, hypo-, hypervitaminosis, anemias, enzymopathies), **Neurovegetative, Hormonal** (endocrine diseases, puberty age dishormonosis), **Allergic, Hyperfunctional, Mixed genesis** | **Transient** (up to 1 month) **Persistent** (up to 1 year) **Chronic** (more than 1 year) | **Stage I**. The initial stage of heart diseases. Hemodynamics is not disturbed. Latent heart failure. **Stage II-A**. Clinically expressed disease stage. Hemodynamic disorders in a blood circulation circle, moderately expressed. **Stage II-B**. Severe stage of heart disease. Expressed hemodynamic changes in both blood circulation circles, moderately expressed. **Stage III**. The final stage of heart lesion. Expressed hemodynamic changes and severe (irreversible) structural changes of target organs (heart, lungs, vessels, brain, kidneys). |

emotional stress. Some children complain of a feeling of incomplete inhalation or shortness of breath during exercise (fast walking, climbing the stairs). Arrhythmic syndrome is also very frequent and characterized by irregular rhythm, tachycardia, bradycardia, and extrasystole. Asthenovegetative syndrome is characterized by fatigue, weakness, headaches, dizziness, presyncopal conditions, irritability, and mood instability that complies with the neurovegetative form of metabolic CMP. Clinical markers often comprise joint syndrome. As a rule, it is peculiar for children who are often ill or suffer chronic diseases of ENT organs (toxic metabolic CMP). Abdominal syndrome is manifested by a decreased appetite, nausea, and abdominal pain. These children have verified diseases of gastrointestinal and biliary tracts.

At the same time, some children do not complain at all and maintain satisfactory physical activity. Heart changes were discovered accidentally. There is no strict correlation between cardiovascular disorders and clinical manifestations of the underlying disease. In some cases, subjective disorders prevail over objective signs of heart pathology.

During heart auscultation, most children have dullness of Tone I detected above the apex. During the pre-and pubertal period, the accent of Tone II can be recorded (auscultative signs of functional narrowness of pulmonary artery) in the left second intercostal space midclavicular line. Systolic murmur is heard in Point V and has varied intensity, duration, and timbre, but it is not conducted beyond the heart. The noise is better heard in a horizontal position, and it weakens or disappears during afterload. Cardiomegaly is not characteristic of most children with metabolic CMP. In cases of acutely developing myocardiodystrophy, as well as under the progressive course of the disease, hemodynamic disorders are detected.

### *4.1 Diagnostic programme for metabolic CMP*

#### *4.1.1 Paraclinical examination*

Biochemical blood test (aspartate aminotransferase, creatine kinase-MB, and lactate dehydrogenase); lipid spectrum of blood serum is done to exclude dyslipidemia; hemostasis (fibrinogen, international normalized ratio (INR), activated partial thromboplastin time are analyzed in presence of factors predisposing to thrombosis: arrhythmias, artificial valves, significant dilation of heart chambers, reduced contractility); glycemic level (with overweight and obesity-oral glucose tolerance test); blood electrolytes (potassium, sodium, calcium, magnesium); lactate and pyruvate levels in blood against the background of a standard glucose tolerance test (enables estimating glycolysis shift to the anaerobic side); examination of mitochondrial enzymes in peripheral blood lymphocytes (succinate and alpha-glycerophosphate dehydrogenase) in view of evaluating the oxidative phosphorylation processes; thyrostate (TSH, T3, T4); catecholamines (adrenaline, noradrenaline); troponins I and T - as markers of myocardial damage; and brain natriuretic peptide (BNP).

#### *4.1.2 Instrumental examination*

The main method of diagnosing dystrophic changes in myocardium is electrocardiography (ECG). The key marker in ECG are changes in the "exchange area" - ST. The key ECG criteria of metabolic CMP are T-wave reduction, flattening, and inversion; displacement of ST segment by more than 1.5 mm above or 0.5 mm below the contour; reduction of R-peak voltage; change in the duration of PQ and QT; polymorphism of P wave/serrations, two-phase, widening, amplitude reduction; and conductivity dysfunction. For confirmation of metabolic CMP diagnosis drug sensitivity testing is done.

ECG under artificial hyperkalemia conditions a non-toxic hyperkalemia from 5.0 to 5.5 mmol/l is achieved by taking fasting potassium chloride at the rate of 0.1 mg/kg, no more than 3 grams. The maximum potassium concentration is observed after 1.5 hours. Hyperkalemia results in a raising T wave where it becomes similar to an equilateral triangle. It also leads to ST segment normalization in shape and position and recovery of the repolarization processes, which confirms the functional genesis of ECG changes. Absence of dynamics on ECG under hyperkalemia conditions demonstrates the existence of an organic myocardium lesion.

ECG test with beta-adrenergic antagonists (Obzidan, Anaprilin (Propranolol) at a dose of 0.5 - 1 mg/kg) shows recovery of the positive T wave polarity, its amplitude increase, as well as dynamics of ST-T segment vago-dependent changes. Insensitivity to beta-adrenergic antagonists is related to deep dystrophic changes in the myocardium.

During exercise, the submaximal heart rate is between 150 to 170 beats per minute using bicycle ergometry. Exercise ECG detects tolerance to physical exercise, which is 2-2.5 W per kg/body weight. T-wave amplitude and dynamics of ST-T segment are evaluated. T-wave flattening and inversion shows presence of struc-

tural changes in the myocardium. At different stages, exercise ECG can verify disorders of cardiac rhythm and conductivity and reveal signs of myocardial ischemia.

Echocardiographic test (Echo-CG) values are non-specific and can occur under various cardiovascular pathologies such as signs of a moderate decrease in myocardial contractility, a minor increase in size of the left ventricle up to the $99^{th}$ percentile, a slight hypertrophy of the interventricular septum and posterior wall of the left ventricle, diastolic dysfunction (early diagnostic criterion), and prolapse of mitral valve flaps at localization of degenerative changes in papillary muscles.

Nuclear magnetic resonance imaging verifies focal or diffuse myocardial lesions, uneven heart walls thickening (at early stages) or their thinning, and enlargement of heart chambers.

Myocardial scintigraphy allows evaluating of perfusion and metabolic processes in myocardium, extension and localization of dystrophic process, as well as to determine the main mechanism (perfusion or metabolic disorders) in metabolic CMP genesis.

Myocardial biopsy is the most reliable invasive diagnostic method, but it is rarely used and often accompanied by complications.

## 5. The principles of metabolic CMP therapy

The therapy comprises rational hypochloride nutrition (adding to the diet of foods highest in potassium, magnesium, vitamins, microelements, and foods containing Omega 3 polyunsaturated fatty acids), etiotropic therapy by indications, and anti-hypoxia ac-tivities. Heart failure correction is aimed to impact the etiological factor, reduce cardiac output requirements (restriction of physical activity, creation of temperature comfort, and reduction of peripheral vascular resistance), impact the myocardium (increasing myocardial contractility, reduction of resistance to ejection, regulation of circulating blood volume), correction of homeostasis disorders and prevention/treatment of complications (correction of electrolyte balance and acid-base balance, elimination of neurohormonal shifts, prevention and treatment of thromboembolic syndrome), and regulation of heart rate and treatment of cardiac arrhythmias and conductivity.

### *5.1 Principles of medication treatment*

In view of pharmacological correction of heart failure under metabolic CMP, the following major medication groups are used:

*Angiotensin-converting enzyme inhibitors (ACE inhibitors (I,A* are first-line drugs in congestive heart failure (CHF) treatment. They contribute to the reverse development of myocardial hypertrophy, myocardiofibrosis, and reduction of heart chamber volume. ACE-inhibitors ensure load reduction on the heart and enhance cardiac ejection due to dilatation of arterial and venous vessels reduce the heart rate, have an antiarrhythmic effect, and produce a diuretic effect.

*β -adrenoblockers (BAB)(I,A)*Mechanisms of BAB effect under CHF include decrease heart rate, improved synchronization of myocardial contractility, prevention of toxic effects of catecholamines on myocytes, antiarrhythmic effect, improvement of myocardial energy conservation. Besides cardiomyocyte overload, calcium is reduced and diastolic heart function is improved. Due to the negative chronotropic and inotropic BAB effect, the myocardial demand for oxygen is reduced.

*Diuretics (I,A).* Besides the decrease in pre- and post-loading, a decrease of extracellular fluid amount leads to improvement in functional condition of the internal organs and elimination of peripheral edema.

*Calcium antagonists (I,A).* These drugs improve coronary blood flow, reduce the heart demand for oxygen, reduce diastolic dysfunction of the left ventricle, exhibit antiarrhythmic activity, and inhibit platelet aggregation.

Correction of cellular energy disorders is conducted to normalize the metabolic processes in myocardium, improve transmembrane transport, and activate aerobic glycolysis and oxidative phosphorylation L-carnitine (A16AA, Carnitine). Drugs targeting the electron transport chain Ubiquinone 10 (V03AX, Ubichinonum 10) and Cytochrome C (C01CX, Cytochrome C). Cofactors of enzyme reactions (B vitamins). Lipoic acid (A16AX01, Thioctic acid) as a structural element of coenzymes. Limontar (A13A, Limontar) activates the Krebs cycle. Biotin (A11HA05, Biotinum) is a coenzyme that reduces the level of lactate in blood. Cocarboxylase hydrochloride (A11DA, Cocarboxylase hydrochloride) normalizes the processes of oxidative phosphorylation.

Symptomatic therapy assumes prescribing potassium and magnesium drugs Panangin (A12CX, Panangin), Asparcam (A12CX, Asparcam), Magnerot (A12CC09, Magnerot), coformulated drugs: Magne B6 (A11JB, Magne B6), vascular therapy: Cinnarizine (N07CA02, Cinnarizine), Vinpocetine (N06BX18, Vinpocetine), antioxidants: A Vitamin (A11CA01, Retinol), E Vitamin (A11HA03, Tocopherol), C Vitamin (A11GA01, Acidum ascorbinicum).

Balneological therapy (pearl, coniferous, sea baths, circular shower), electrosleep; massage, and therapeutic exercises.

## 6. Prognosis

Peculiarities of metabolism in cardiomyocytes, such as high-rate energy processes, a minimum reserve of macroergic compounds, and adrenergic control of energy formation processes create prerequisites for the frequent development of dystrophic processes in the myocardium. At the same time, oxidative phosphorylation is the main way of energy formation, and it is associated with a high oxygen consumption. The heart is most sensitive to cellular energy deficiency. With an increase of energy deficit, the plastic processes and myocardium structure are disturbed. The risk factors for metabolic CMP development are intense exercise, aggravated family history in cardiovascular diseases, chronic infection sites, frequent intercurrent diseases, and neurovegetative dysfunction with excessive sympathetic effects. It should be mentioned that the degree of heart lesion and the clinical picture depend on the nature and duration of etiological factor impact and on the severity of the dystrophic process, its localization, the ratio of restorative (compensatory), and damaging processes in the myocardium. In case of timely diagnosis of myocardiodystrophy and its adequate therapy, the prognosis of the disease is favorable due to high regenerative ability of cardiomyocyte. Correction of the adverse factors mentioned above and contributing to progression of dystrophic processes in the myocardium should be regarded as a priority in pediatric practice.

## 7. Conclusion

Metabolic disorders in the myocardium contributes to a more profound understanding of functional heart disorders. Nowadays, the problem of perfect metabolic CMP diagnosing has not been completely, and its complexity is explained by the absence of specific clinical markers and a long asymptomatic course. Metabolic CMP holds a unique position between myocardial diseases of various genesis and requires the development of a unified and distinct diagnostic algorithm that is preventive, therapeutic, and rehabilitative in clinical pediatric practice.


## Acknowledgment

Authors express the gratitude to all the peer reviewers and editors for their opinions and constructive suggestions.


## Conflict of Interest

The author confirms that the data provided do not comprise a conflict of interests.


Submitted: May 15, 2019
Accepted: June 28, 2019
Published: June 30, 2019


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