Chapter 6

Myocardial Infarction in Children

Meki Bilici, Mehmet Ture and Hasan Balik

Additional information is available at the end of the chapter

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Abstract

Myocardial infarction (MI) is a clinical condition that develops associated with a sudden reduction or interruption of the blood flow of the vessels supplying the heart for various reasons. The electrocardiographic, echocardiographic and enzymatic diagnostic criteria of MI have been well defined in adults, in children there are some difficulties. Although seen more often in the presence of congenital heart disease (CHD), MI may also be seen in patients without CHD. Unlike atherosclerotic coronary artery disease in adult patients, ischaemia and infarct in children are often associated with coronary artery anomalies and CHD. In addition, congenital prothrombotic diseases, vasculitis, surgical or interventional procedures may also cause ischaemia and infarct. Subendocardial ischaemia, especially aortic stenosis characterised by hypertrophy in the left ventricle is often seen in hypertrophic cardiomyopathy or hypertensive patients. The most important risk factors in neonates and infants are the presence of CHD, coronary artery anomalies and perinatal asfixia. The most frequently seen causes of pediatric myocardial infarction (PMI) are abnormal left coronary artery originating from the pulmonary artery (ALCAPA) and Kawasaki disease. Another often seen cause of PMI is patients who underwent arterial switch operations.

Keywords: children, myocardial infarction, coronary artery anomalies

1. Myocardial infarction in children

Myocardial infarction (MI) is a clinical condition that develops in association with a sudden reduction or interruption of the blood flow in coronary vessels supplying the heart for various reasons. Coronary artery spasm and myocardial ischaemia are seen in the early stage of occlusion. If the relevant coronary artery is not rapidly re-channelled or cannot be re-vascularised, then MI develops [1]. Myocardial infarction is a common event in adults, but is not common among children. Furthermore, although the electrocardiographic, echocardiographic and

enzymatic diagnostic criteria of MI have been well defined in adults, in children there are some difficulties [2, 3]. As the cardiac structure changes with age, there are sometimes difficulties in the electrocardiographic diagnostic criteria of ischaemia.

Although MI is seen more often in the presence of congenital heart disease (CHD), it may also be seen in patients without CHD. Unlike atherosclerotic coronary artery disease in adult patients, ischaemia and infarct in children are often associated with coronary artery abnormalities and CHD [4]. In addition, congenital prothrombotic diseases, vasculitis, surgical or interventional procedures may also cause ischaemia and infarction [5]. Subendocardial ischaemia, especially aortic stenosis characterised by hypertrophy in the left ventricle is often seen in hypertrophic cardiomyopathy or hypertensive patients [2].

The most important risk factors in neonates and infants are the presence of CHD, coronary artery abnormalities and perinatal asfixia [5, 6]. The most frequently seen causes of Paediatric myocardial infarction (PMI) are abnormal left coronary artery originating from the pulmonary artery (ALCAPA) and Kawasaki disease [7, 8]. Patients undergoing arterial switch operations are also at increased risk for PMI [9].

2. Anamnesis

The anamnesis in Paediatric myocardial infarction (PMI) and Paediatric myocardial ischaemia and physical examination findings show differences from adult cases. The anamnesis of infants and young children is taken from the family and carers [2]. The complaints usually reported in this period are generalised findings such as feeding problems, lack of appetite, irritability, diarrhoea, vomiting, cold extremities, pallor and tachypnea. Older children may be able to describe chest pain well and can explain the spread of pain. A compressive of chest pain spreading to the left arm and shoulder should suggest chest pain with cardiac origin [10, 11]. However, some children may not be able to describe the character of the chest pain.

In the physical examination, patients are generally anxious, pale and interactive. They may have dyspnea or tachypnea. If tachycardia, hypotension or cardiogenic shock develop, these can be determined [2]. In the cardiac examination, rhythm irregularity and gallop rhythm can be determined. Extremities may be cold and the pulse may be weak on the electrocardiography (ECG), ventricular arrhythmia or cardiac block may be determined [2, 12–14]. Patients with ventricular arrhythmias may have symptoms of palpitations, syncope and loss of conscious [12].

3. Cardiac chest pain

The anamnesis has great value in the determination of whether or not the chest pain is from cardiac origin. In the case of a child presenting with chest pain, it must be determined from the family when the pain started, how often the child has experienced chest pain, how long the pain lasts, where the pain radiates to, the relationship with exercise, factors that increase or decrease the pain, whether or not there is any relationship with feeding or respiration, whether there is any trauma anamnesis, whether or not there is any fever, or accompanying

complaints such as shortness of breath, sweating, palpitations or nausea [10, 11]. It must also be determined whether the child or any family member has any CHD and whether or not any family member has recently experienced any chest pain, or MI.

Chest pain, which is one of the most significant symptoms for adults presenting to the Emergency Dept, is generally has a benign character in children. However, it is extremely important to decide whether or not the pain frequently seen in children is of cardiac origin [15]. Chest pain with cardiac origin in childhood can be classified in 3 groups; as structural heart diseases, inflammatory causes and dysrhythmias [10]. Structural heart diseases can lead complaints associated with an increased need for oxygen or a reduction in coronary blood circulation. These include events such as hypertrophic obstructive cardiomyopathy or aortic stenosis because of an obstruction in the left ventricle outlet tractus. Coronary artery abnormalities may also cause coronary ischaemia.

Chest pain with cardiac origin generally presents in situations where an increase in cardiac output is required. It is typically in the precordial or substernal region, in a constricting form and radiates to the left arm, neck and jaw. In some cases, there may also be shortness of breath, sweating, nausea, vomiting or syncope. In infants, the findings may be seen as feeding difficulties, crying and screaming (**Table 1**), [2, 6, 15, 16].

After the anamnesis and physical examination, ECG examination must be made in all patients and X-ray imaging should be applied in order to exclude any respiratory causes [15]. In cases where the pain is thought to be of cardiac origin, troponin and creatine kinase myocardial band (CK-MB) levels must be examined and if necessary echocardiographic evaluation should be made [15, 17, 18].

Neonates	Older children
Feeding problems	Fatigue
Lack of interest in surroundings	Lack of appetite
Irritability	Paleness
Diarrhoea	Dyspnoea
Sweating	Tachypnea
Vomiting	Tachycardia
Pallor	Hypotension
Tachypnea	Weak pulse
Dyspnea	Rhythm irregularity
Sudden paroxysmal abdominal pain	Gallop rhythm
	Cold extremities
	Shock
	Ventricular arrhythmia
	Heart block

Table 1. Symptoms and physical examination findings in Paediatric myocardial infarction.

4. Electrocardiography in Paediatric myocardial infarction

The 12-lead ECG is an integral part of the evaluation of coronary artery disease [16]. Elevation of the J point which joins the QRS and the ST segment is the first finding of myocardial ischaemia [7]. Compared to baseline, an elevation of 1–2 mm is seen in the J point and the ST segment in myocardial ischaemia. An elevation of >2 mm should rouse suspicion of MI (**Figures 1** and **2**). When ST elevation is determined, there should be a progression through differential diagnosis of benign early repolarisation, pericarditis, MI, bundle branch block and left ventricle aneurism [18]. While pathological ST elevation does not show variability, J point and ST elevation seen in early repolarisation in healthy adults is generally corrected with isoproteronol infusion or exercise [19].

The presence of PR segment depression is an ECG finding which is valuable in the differentiation of myopericarditis from MI in favour of myopericarditis [18]. The positive predictive value of PR depression seen in chest and extremity derivations has been determined to be 96.7% [19].

T-wave alterations generally accompany ST segment alterations in AMI. Initially, T-waves may be long and sharp (hyperacute T-wave). These changes determined on ECG show myocardial injury (**Figure 3**). ST depression may reflect the reciprocal effect of the region in the derivation corresponding to approximately 180° [7]. The standard leads does not show ST segment elevation in patients with true posterior wall MI. Instead ST elevation, ST segment depression may be seen as a reciprocal change in V4R-V2 on the ECG [20, 21].

Electrocardiographic findings that show recent MI are pathological Q-waves. A long Q-wave from 3 small squares (0.12 secs) in whichever derivation should be evaluated as pathological Q. In addition, broad Q-wave in V1 and V2 may be seen in patients with left ventricle hypertrophy. In short, the evaluation of anamnesis, physical examination and laboratory findings together with the ECG findings is important for every patient.

Generally pathological Q-waves are seen to emerge within the first 12–48 hours on at least 2 adjacent leads, and when they are present at inferior, lateral or anterior derivations, they have

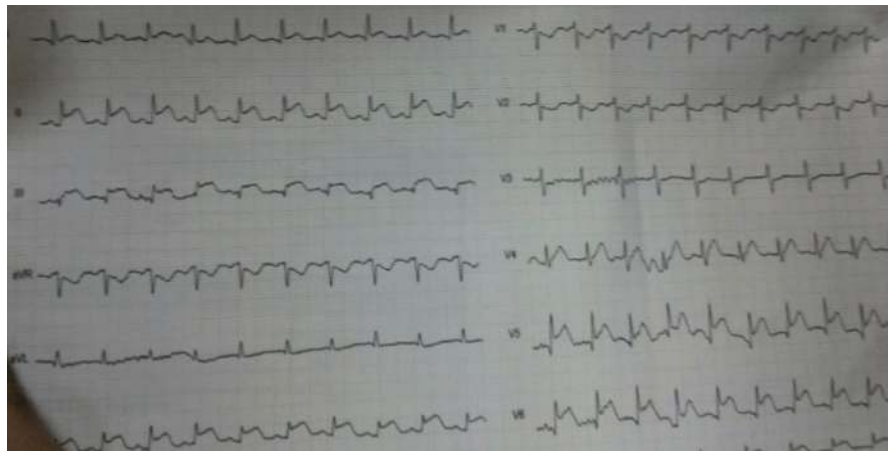

Figure 1. 2–3 mm ST elevations in DII, DIII, aVF, V5, and V6 leads of electrocardiography show that myocardial infarction.

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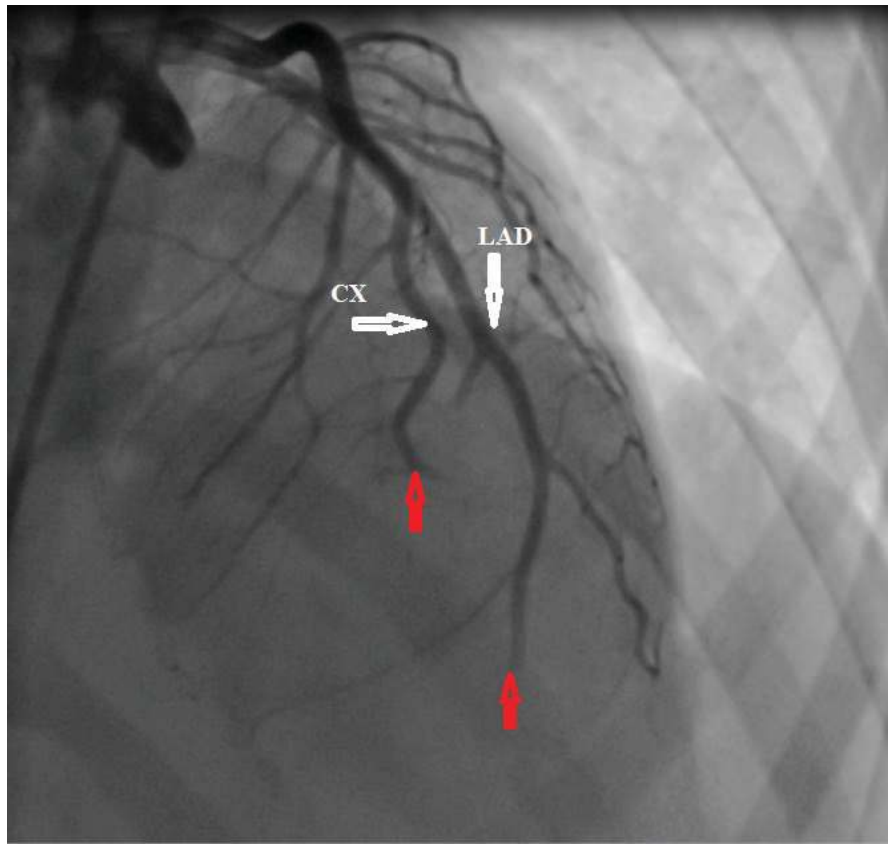

Figure 2. Coronary angiography revealed total occlusion of the left anterior descending [LAD] and distal circumflex (CX) coronary arteries (red arrows).

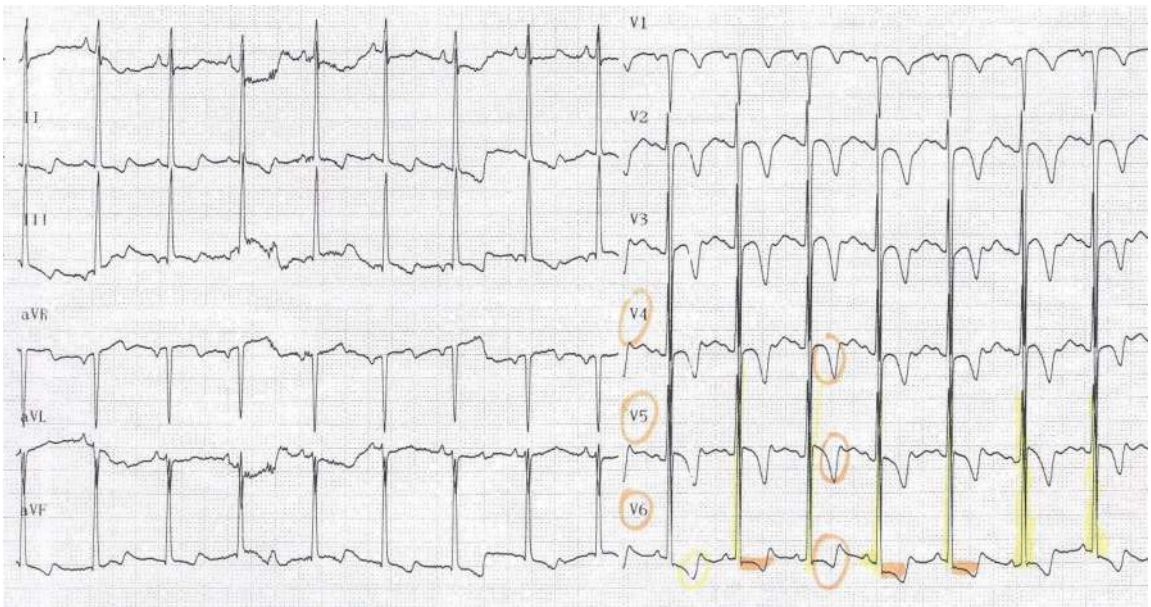

Figure 3. In this patient with aortic stenosis, ST depression on V4–6 and negative T wave show that coronary ischemia.

got extremely high value for the diagnosis of MI [1, 21]. However, in Paediatric patients, the determination of Q-wave in just one derivation could even be sufficient to determine MI [21]. While these Q-waves show infarct of the myocardial wall, high R waves in V1 and/or V2 (negative Q-waves) may represent true posterior wall MI. On the ECG of approximately half of cases, pathological Q-waves have a tendency to regress with time. In newborn infants, the presence of Q-waves in derivations DII, DIII and AVF may be normal. Furthermore, if ECG leads are placed on the upper part of the chest, Q-waves can be incorrectly shown in V5–6 that can cause misinterpretation of an integral part of the evaluation of coronary artery disease [16]. Elevation of the J point that joins the QRS and the ST segment is the first finding of myocardial ischaemia [7]. Compared to baseline, an elevation of 1–2 mm of the J point and the ST segment can be determined in myocardial ischaemia. An elevation of >2 mm should rouse suspicion of MI [7].

When the clinician has suspicions on the resence of pathological Q-wave, ECG in deep inspirium can be helpful. There is a change in the voltage of the Q-waves in physiological cases while there is no change of voltage at deep inspirium in pathological Q waves [7]. Towbin et al. reported that the presence of Q-waves wider than 35 msn on ECG was the most valuable finding for MI and a diagnosis of transmural MI diagnosis should not be made in patients with no Q-wave abnormalities [2].

Towbin et al. evaluated the ECG and clinical findings in the pre-MI records of 37 patients who died because of MI. In this retrospective study, it was reported that findings of MI were determined on the pre-mortem ECG records of 28 children who suffered fatal acute MI, while it was reported in 9 cases who died because of chronic MI [3]. It was also reported by the same authors that when MI was determined in a hypertrophic heart, the infarction was determined at the hypertrophic ventricle. This showed that in PMI, the presence of hypertrophy was a risk factor for MI. At least one of the criteria shown in the **Table 2** was determined to be present in 30 patients included into the study by Towbin et al [2]. Furthermore, no finding was determined on ECG in approximately 19% of the cases in that study, ECG was not sufficient to make a diagnosis of PMI alone. The evaluation of the patient should be made together with the anamnesis, physical examination, ECG and laboratory data.

Furthermore, Nakanishi et al. showed that deep Q-waves were a good marker for MI in Kawasaki patients. It was also determined in the same study that T-wave inversion in derivations II, III and AVF showed MI in the inferior wall [22].

1. New appearance of wide Q waves >35 ms in duration
2. Increased amplitude or duration [>35 ms] of pre-existing Q waves
3. New onset Q waves in serial tracings
4. Q waves notching
5. ST segment elevation [≥2 mm] and prolonged QT interval corrected for heart rate [>440 ms] with any other criteria.

Table 2. Electrocardiographic findings significant for MI in children, as reported by Towbin et al.

In the adult guidelines of MI criteria, it is stated that there should be ECG changes in more than one lead [23]. However, in Paediatric cases, when there are ECG changes in one derivation, there should be suspicion of MI [3]. Moreover, the observation on ECG of more than one of these changes, such as ST elevation, Q-wave changes, ST depression or T-wave inversion should more strongly suggest MI diagnosis.

5. Cardiac enzymes

An increase in the level of enzymes released into circulation from cells exposed to injury is important in the diagnosis of MI. These enzymes are creatine kinase myocardial band (CK-MB) and troponin [7, 10]. In all Paediatric cases thought to have myocardial damage, the troponin level should be examined. Values more than 2 ng/ml value are especially more valuable for cardiac origin [17]. Even in cases of mild damage in myocardial cells, an increase in enzyme levels may be seen [19]. In addition, the events causing an increase in troponin levels must be known (**Table 3**) [6].

6. Echocardiographic evaluation of Paediatric acute myocardial infarction

Acute heart failure
Cardiac contusion
Myopericarditis
Pulmonary embolism
Sepsis
Strenuous exercise
Sympatomimetic drugs
Tachyarrhythmia

Table 3. Non-coronary events which increase troponin.

The increasing experience with echocardiography [echo] in recent decades has greatly facilitated the diagnosis of acute myocardial infarction [AMI], as echo is an inexpensive, readily available, ambulatory, non-invasive method [24]. **Echo is useful, not only in the diagnosis of AMI but also in prognosis, the monitoring of complications and in follow-up.** In Paediatric AMI patients, echo provides very valuable information in the determination of segmentary wall movement abnormalities and in the diagnosis of CHD, pericarditis, myocarditis, Kawasaki disease, cardiomyopathy, aortic stenosis and ALCAPA which often accompanies chest pain. In adult studies, abnormal wall movement findings have been determined in 91% of patients applied with echo in the early stage in

the emergency departments [25]. It has also been shown in studies of adults that a decrease in left ventricular ejection fraction [LVEF] and left ventricle volume loading are significant risk factors for morbidity and mortality [24].

Segmentary wall movement abnormalities are seen in the necrotic region in AMI. If left ventricle function is looked at globally, this finding can be overlooked [24]. The American Society of Cardiology recommends examination of the heart in 16 segments and scoring from 1 to 5 as follows:

1. Normal.
2. Hypokinesis.
3. Akinesis.
4. Dyskinesis.
5. Aneurismal.

A higher score indicates a greater wall abnormality [26]. The score increases in cases with more widespread MI. It has been shown in studies of adults that in addition to segmentary wall movement abnormalities, complications which are rarely seen in children including post-infarct ventricular septal defect, left ventricle free wall rupture, right ventricle failure, and papillary muscle rupture have both value in diagnosis and follow-up of MI [24].

6.1. Aetiology

Paediatric myocardial infarction may be associated with many different diseases (**Table 4**) [2, 3, 5–9, 15]. It has been proposed that the reasons that coronary ischaemia and MI are frequently seen in CHD are multifactorial [27]. Abnormalities in the coronary artery anatomy have been reported to increase the risk of MI. It has been suggested that the stenosis risk after cutting and transfer of coronary arteries could have a potential role in early atherosclerosis and premature coronary artery disease [9]. In addition, congenital heart diseases with right to left shunts may cause paradoxal embolism. A sedentary lifestyle, diabetes mellitus and hypertension are other risk factors for ischaemic heart disease.

In autopsies performed between 1996 and 2010, Bamber et al. determined myocardial necrosis in 1637 patients, and in a group of 187 infant patients with perinatal asphyxia, sepsis, pulmonary disease, cardiomyopathy, tumour, coagulopathy and left ventricle aneurism. The myocardial necrosis was reported to be focal in patients with coronary artery abnormality, while it was diffuse among patients; who died in intensive care unit, with metabolic disease, or myocarditis, the idiopathic group, with mechanical asphyxia and who died during a surgical intervention [6]. In that study, the necrosis in 50% of the cases was determined at the subendocardial region, the papillary muscle and trabeculae. In the same study, CHD, asphyxia and coronary artery abnormalities were reported to be the most common causes of MI seen in this period. It was also strange that there was most frequently ASD, VSD and

- Neonatal Causes
  - Coronary artery abnormalities
  - Congenital heart disease
  - Severe neonatal asphyxia
  - Sepsis
  - Admission to Intensive Care Unit
  - Lung pathologies
  - Pulmonary atresia with intact ventricular septum
  - Metabolic causes
  - Myocarditis
  - Cardiomyopathy
  - Tumours
  - Endocardial fibroelastosis
  - Mediocalsinosis of the coronary arteries
  - Disseminated intravascular coagulation
  - Renal artery thrombosis
  - Idiopathic
  - Coagulopathies
  - Left ventricular aneurisms
- Causes of MI in childhood and adolescence
  - Kawasaki disease
  - Congenital heart disease
  - Coronary artery abnormalities
  - Hypertrophic cardiomyopathy
  - Dilated cardiomyopathy
  - Myocarditis
    - Viral
    - Idiopathic
    - Rheumatic
    - Collagen vascular diseases' induced
  - Substance Use
    - Cocaine
    - Marijuana
    - Bonzai (synthetic cannabis)
  - Previous surgery to the Truncus Arteriosus

Arterial switch operation
Post-transplantation
Post-coronary surgery
Drugs
Epinephrine
Amphetamine
Benzodiazepines
Hyperlipidemia
Blunt Chest trauma
Nephrotic syndrome
Vasculitis
Polyarteritis nodosa
Systemic lupus erythematosus
Behcet's disease
Takayasu arteritis
Atherosclerotic coronary artery disease
Disseminated intravascular coagulation
Genetic diseases
ALKaptonuria
Fabry's disease
Familial hypercholesterolemia (homozygotes or heterozygotes)]
Homocysteinuria
Hurler's syndrome
Hyperbetalipoproteinemia, familial combined hyperlipidaemia, and hypoalphalipoproteinemia
Mucopolysaccharidoses
Pompe's Disease
Progeria
Pseudoxanthoma elasticum
Sepsis
Occult Malignancy
Myocardial bridging
Pulmonary atresia with intact ventricular septum

Table 4. Causes of Paediatric myocardial infarction.

PDA accompanying the CHD. Of 105 cases with acquired or inherited CHD, 63 [60%] were determined to be severe, multiple and complex [6].

In another study conducted in Sweden between 1970 and 1993, the presence of CHD was seen to be a reason for hospitalisation because of ischaemic heart disease (IHD). The risk was reported 16.5 fold increased compared to the control group [27]. These data support that the presence of CHD as an additional risk factor for MI in children. Fedchenko et al. reported the possible mechanisms as; a] a physiological response to a previous surgical procedure could contribute to the development of IHD, b] a predisposition to IHD because of an increased need for oxygen with reduced maximal oxygen re-uptake due to volume and pressure loading in CHD patients, and c] exposure of CHD patients at an early age to radiological procedures and radiation could accelerate atherosclerosis [27].

7. Congenital coronary artery abnormalities

Coronary artery abnormalities generally do not cause clinical findings or the findings are subclinical. However, some coronary artery abnormalities cause serious haemodynamic outcomes [16]. The left coronary artery emerging from the right coronary sinus and the right coronary artery emerging from the left coronary sinus can cause coronary artery circulation problems. The section of the coronary artery that passes between the aorta and the pulmonary artery exposed to pressure at a critical level causes clinical findings [28].

Congenital cardiac abnormalities are a significant cause of MI-related sudden death, most often in the neonatal period (**Table 5**) [28]. Sudden death is often related to exercise especially in patients where the coronary arteries originate from the pulmonary artery and pass between the aorta and the pulmonary artery [28]. Although some cases may show clinical findings with MI in the neonatal period, some cases can remain asymptomatic [29]. In infancy, there may be noticeable findings of heart failure, such as rapid fatigue, sweating, tachypnea and retarded growth and development [2].

Exercise-related death is most often encountered when the left coronary artery emerges from the right coronary sinus, in ALCAPA, and when the right coronary artery emerges from the left coronary sinus [28]. In patients with coronary artery abnormality, the symptoms include chest pain, syncope and findings of heart failure. In infants with ALCAPA, Q-wave seen at DI, AVL or V5–6 on ECG is a good marker for diagnosis [7].

In a Paediatric autopsy study, cardiomegaly was seen in all the cases of children with coronary artery abnormality [30]. The cause of MI seen during exercise in children with coronary artery abnormality has been suggested to originate from an increase in acute angulation of the coronary artery during exercise [29].

Sudden death in the asymptomatic period is a frightening complication of the disease in a significant proportion of cases with coronary artery abnormality [28].

I.	Anomalous origin of ≥1 CA from pulmonary trunk
a.	LMCA or LAD from pulmonary trunk
b.	Both CAS from pulmonary trunk
c.	RCA from pulmonary trunk
II.	Anomalous origin of ≥1 CA from Aortic Sinus
a.	LMCA and RCA from right Aortic Sinus
b.	RCA and LMCA from left Aortic Sinus
c.	LCx and RCA from right Aortic Sinus
d.	RCA and/or LMCA from posterior Aortic Sinus
e.	RCA and LAD from right Aortic Sinus
III.	Single CA ostium from Aorta
IV.	Congenital hypoplastic CAs
V.	CA fistula

LCx: left circumflex, CA: Coronary artery, CAs: Coronary arteryies, LMCA: left main coronary artery, left anterior descending, RCA: right coronary artery.

Table 5. Taylor classification of congenital coronary artery abnormalities.

8. Kawasaki disease

Kawasaki disease is a self-limiting acute vasculitis. Children aged between 5 months and 5 years are especially sensitive to Kawasaki disease. It is one of the most common causes of vasculitis and MI in children [41, 42]. Destruction in the coronary arteries, ectasia and coronary artery aneurisms are frightening complications of the disease [43]. Diagnosis is made from the presence of four of the five diagnostic criteria together with unexplained fever ongoing for at least 5 days. The diagnostic criteria are bilateral non-purulent conjunctivitis, oropharynx changes, cervical lymphadenopathy, persistent oedema in the hands and feet and erythematous rash.

9. Takotsuba cardiomyopathy

Takotsuba cardiomyopathy is a benign clinical condition characterised by chest pain, elevated ST segment on ECG and elevated cardiac enzymes [31]. It is thought to be stress-related. It develops more often with emotional stress and sometimes related to physical stress. Due to chest pain and shortness of breath, it mimics acute myocardial infarction. There is ballooning and/or systolic dysfunction on echo or left ventriculography [32]. Coronary angiography is normal and there is no coronary artery disease. Cardiac enzymes are normal or may be slightly elevated.

10. Myocarditis

As myocarditis is generally seen together with pericarditis, it is known as myopericarditis. Myopericarditis may show differences according to whether the effects of the clinical findings are focal or generalised [19]. Typically, diagnosis is made from the determination of chest pain, the sound of pericardial friction, ST elevation on ECG, high levels of troponin I, cardiomegaly on telecardiography and pericardial effusion on echo (**Table 6**).

Pericardial effusion is observed in 60% of pericarditis patients. Wall movement abnormalities on echo or systolic dysfunction are a warning sign of myocarditis and/or MI. As the ECG findings in myopericarditis are focal in 50% of cases, differential diagnosis from AMI can be difficult. The presence of PR segment depression on II is a valuable finding of myopericarditis [19]. It has been suggested that coronary thrombus, coronary spasm, coronary artery embolism, large vessel and microvascular vasculitis could be reasons for MI seen in myopericarditis [33, 34]. In follow-up,

	Anamnesis	**Physical examination**	**ECG**	**Echocardiography**	**Cardiac angiography**	**Magnetic resonance**	**Telecardiography**	**Biopsy**	**Laboratory**
Myocardial infarction	Sudden onset	Gallop rhythm, ventricular arrhythmia may be seen	ST elevation T-wave changes, pathological Q wave, Ventricular arrhythmia, extended QT distance	Segmentary wall movement abnormalities, reduction in EF, papillary muscle rupture, left ventricle free wall rupture	Coronary artery thrombosis	Increased focal involvement	Normal	Necrosis in the involved area	Elevated levels of Troponin, CKMB
Myocarditis	First there may be findings of viral infection	The sound of pericardial friction, Gallop rhythm, and arrhythmias may be seen	Sinus tachycardia, low voltage, PR segment depression, ST elevation, T-wave changes	Pericardial effusion, reduction in EF, segmentary wall movement abnormalities	Normal	Increased signal in the myocardium and increased contrast involvement in the myocardium and myocardial thickening	Cardiomegaly	Necrosis and inflammatory cells in the involved area	Elevation of troponin, and CKMB levels

Table 6. Differential diagnosis of myocardial infarction and myocarditis.

thinning and fibrosis in the MI area may be seen in echocardiographic examination and in unaffected parts, compensatory hypertrophy may be present. Although it is difficult to apply in infants, endomyocardial biopsy is the gold standard in myocarditis. The death of myocites and inflammatory cells may be seen in biopsy material [36]. Another diagnostic method is cardiac MRI, which requires general anaesthesia. An increase in cardiac signal and increased myocardial contrast involvement is seen on cardiac magnetic resonance imaging [37].

11. Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is characterised by a global thickening of the heart muscle. It should be kept in mind especially in children with exercise-related chest pain [36]. The incidence in the general population is 1 per 500 births and genetic transfer is autosomal dominant. Hypertrophy seen in the ventricular septum together with movement of the mitral valve anteriorally causes a narrowing of the left ventricle outlet [36]. Especially during exercise, this narrowness may cause a decrease in cardiac output and sudden death [38]. Shortness of breath and chest pain are frequent complaints. Situations such as exercise which reduces the pre-load and increases the after-load, tachycardia or dehydration, exacerbate the narrowing of the left ventricle outlet [38].

12. Sudden cardiac death

Sudden cardiac death is defined as death occurring within 1 hour without the emergence of any prodromal finding [39]. A significant cause of sudden cardiac death in children is MI. Previous studies have reported that chest pain is seen in few cases of MI-related sudden cardiac death. More frightening is that a large proportion of these cases suffer sudden cardiac death at rest [40]. Cigarette smoking and dyslipidaemia have been determined as significant risk factors for sudden cardiac death related to coronary artery disease in children and young adults [40].

13. Vasculitis

In patients with vasculitis, especially those with coronary artery involvement, anginal complaints may be seen at an early age. Myocardial infarction and unexpected sudden cardiac death can be determined [44–47]. In some cases the clinical findings are non-specific such as abdominal pain, myalgia and muscle pain, and the diagnosis can only be made by postmortem study [46].

Polyarteritis Nodosa (PAN) is a rarely seen severe vasculitis that affects small and medium diameter arteries in particular. Diagnosis of the disease is made according to the criteria defined in 1990 by the American College of Rheumatology (**Table 7**). The disease can cause infarction in the organs by creating transmural necrotising vasculitis mostly in medium diameter arteries [46]. In addition to the heart, the kidneys, the gastrointestinal system, the skin, the nervous system, the joints and the muscles may be affected. The cardiac effect is less compared to the other systems. A coronary involvement alone has been reported in few cases [41].

1.	Arteriographic abnormality
2.	Diastolic blood pressure > 90 mmHg
3.	Elevated blood nitrogen or serum creatinine
4.	Livedo reticularis
5.	Mononeuropathy or polyneuropathy
6.	Myalgias
7.	Presence of hepatitis B reactants in serum
8.	Testicular pain or tenderness
9.	Weight loss
10.	Biopsy-confirmed granulocytic or mixed leukocytic infiltrate in an arterial wall

Table 7. Diagnostic criteria for PAN.

Coronary artery involvement can occasionally be seen in Takayasu arteritis, which tends to involve larger vessels than PAN [48–50]. It has also been reported that Paediatric MI can be seen in Behçet's disease [45].

14. Slow coronary flow phenomenon

Slow coronary flow phenomenon is a microvascular disease characterised by slow progress of the contrast dye within the vessel, which is not obstructive coronary artery flow [51]. Despite evaluation as a benign clinical setting, it is concerning for families and physicians because of the relationship with MI and anginal symptoms. In addition, the mechanism and clinical outcomes of the disease are not yet fully understood.

Occasionally, clinical findings can be seen in children with ST-segment elevation myocardial infarction (STEMI) [51]. On coronary angiography, there is no vessel obstruction or it is close to normal, but the peripheral blood flow is noticeably slow. Studies of these patients have shown cellular oedema, thickening in the capillary endothelium, fibromuscular hyperplasia, myofibril disorganisation and microvascular thickening, causing endothelial dysfunction [52, 53].

15. Atherosclerosis

As atherosclerotic coronary artery disease seen in adults originates in childhood, it is necessary to start taking preventative measures against atherosclerosis in that period. However, as there are few cases related to atherosclerosis within the PMI cases reported in literature it is thought that MI cases developing on an atherosclerotic basis are rare in children [3, 7, 54].

In an autopsy study of 760 murder or accident cases aged 15–34 years, atheroma was determined in males at 2% and was not determined in females [54]. Other risk factors increasing

atherosclerotic changes are known to be familial hypercholesterolemia in particular, and elevated LDL level, substance abuse, smoking, hypertension, obesity and cardiovascular events experienced by a family member at an early age [54].

16. Epinephrine use

Racemic adrenaline is a sympathomimetic drug used in Paediatric bronchiolitis and severe upper respiratory tract obstructions. Although this treatment has been used safely for many years, there is a need for heart rate and ECG monitorisation in cases administered epinephrine consecutively [55]. It has been reported that MI has developed associated with epinephrine not only in cases with racemic epinephrine but also in cases where epinephrine has been used when applying cardiopulmonary resuscitation [56]. The coronary vasospasm of epinephrine is made over alpha 1 and alpha 2 receptors. While low-dose adrenaline shows a beta mimetic effect, at high doses the effect is seen by vasoconstriction, primarily over the alpha 1 and alpha 2 receptors. As there is a relationship between epinephrine used intravenously and a higher complication rate, the selection of intramuscular or subcutaneous routes could contribute greatly to reducing the cardiovascular risks [56] Vasodilators such as nitrate and calcium channel blockers are selected in MI cases related to epinephrine [57, 58].

17. Sickle cell anaemia

In sickle cell anaemia (SCA), because of the sickle cells that develop during the disease, infarcts affect the lungs, heart, spleen, central nervous system, retina, bones and kidneys [59]. SCA is known to create a widening in the left ventricle, hypertrophy, pulmonary hypertension and heart failure. The reason for MI seen in children with SCA is not fully known. However, it has been reported that vasospasm caused by thromboxane expressed from sequestered thrombocytes could play an important role in coronary ischaemia and necrosis [60]. Varying membrane flexibility and varying viscosity in SCA patients have also been reported to be possible causes of ischaemia and infarction.

More detailed examinations should be made of SCA patients especially in conditions of acidosis, deep anaemia, kidney failure and infection. During a vaso-occlusive crisis in SCA children, when there are non-specific ST-T changes on ECG together with chest pain, cardiac enzymes should be examined and the patient should be closely monitored. In patients with suspected myocardial ischaemia, hydration and oxygenation must be provided. It is thought that nitrates could be useful [59]. Although the role of anti-thrombotic treatment is not known, it should be considered in treatment.

18. Substance abuse

The use of marijuana and cocaine should be investigated in adolescents seen with MI. Tramadol, amphetamines, benzodiazepines and opiates are also substances that can cause PMI [61].

The use of a vasoconstrictor substance, especially by those who smoke, increases the risk of ischaemic cardiac complications, even in a healthy heart. [62]. Marijuana stimulates the sympathetic nervous system by expressing epinephrine and the effect is seen with an increase in vasoconstriction, tachycardia, hypertension and cardiac output [63]. Furthermore, by increasing the carboxyhaemoglobin level, the oxygen carrying capacity is reduced [62]. The coronary ischaemia and MI which occur as a result of increased heart rate, vasoconstriction and the increased need for oxygen can be life-threatening for the patient [63–65]. As most substances causing Paediatric MI are illegal, the users may deny having used them. In cases suspected of substance abuse, a toxicology examination must be made. Cardiac ischaemia can also be seen related to the use of bonzai, which is a synthetic cannabinoid [63].

Cocaine with sympathomimetic effect on coronary arteries can cause MI by vasoconstriction. As a result of increasing blood pressure and heart rate, the myocardium has an increased need for oxygen and with the tendency for thrombosis resulting from endothelial dysfunction, MI can develop in patients [4].

In an autopsy examination of 477 cases of sudden cardiac death aged 1–49 years, Bjune et al. determined positive results in the toxicology scan of 57% of the cases [61]. The toxicological substances determined in the blood in that study were benzodiazepines, opioids, antidepressants, anticonvulsants, antipsychotics, ethanol, cannabis, cocaine, amphetamines and gamma hydroxybutyrate. In 39% of the cases with substances determined in the blood, multiple substances were present. Despite the subpharmacological basis of the substances determined and the pharmacological dose, that death occurred was concluded to be due to the interaction of multiple drugs and/or substances.

19. Myocardial bridge

In normal individuals, the coronary arteries have a course over the myocardium. Myocardial bridge [MB] is a clinical event characterised by the course of a section of the coronary arteries within the myocardium [4, 66, 67]. On angiography, the loss in diastole of the narrowing in the vessel lumen that is observed during systole [milking effect] is valuable for diagnosis. The degree of coronary obstruction created by the MB depends on the localisation of the MB, the thickness, length and degree of cardiac contractility [68]. It has been reported to be seen more often in patients with left ventricle hypertrophy such as HCM and aortic stenosis in particular [38]. Other coronary arteries can be affected, but the most commonly affected is the LAD [38, 67, 69].

It has been shown that there is a relationship between the clinical results of MB and ischaemic heart disease, MI, arrhythmia and sudden death and that MB can cause MI even in Paediatric cases [66]. It has not yet been understood how important the haemodynamic effects are of the coronary artery in the intramural region remaining under pressure during systole when >75% of the coronary is in diastole.

Despite the use of beta-blockers at appropriate doses, it has been reported that in symptomatic patients with >75% systolic narrowing, good results can be obtained with supra-arterial myotomy and the risk of MI and sudden death can be prevented [70].

20. Nephrotic syndrome

Nephrotic syndrome is a known condition which increases the tendency to thrombosis [71, 72]. Although the mechanism of the tendency to thrombosis is not completely known, it is thought that lipid abnormalities increase the tendency to thrombosis by increasing haemoconcentration and hypervolemia and the viscosity of full blood and plasma and that hypoalbuminemia stimulates the synthesis of fibronectin, fibrinogen and factors II, V, X, XI, from the liver [73].

21. Antiphospholipid antibody syndrome

Antiphospholipid antibody syndrome is a syndrome characterised by low antiphospholipid antibodies in the blood during pregnancy and arterial and venous thromboses [74, 75]. Just as antiphospholipid antibody syndrome can be seen isolated as primary antiphospholipid antibody syndrome, it may also be seen together with diseases such as systemic lupus erythematosus [4].

22. Diagnosis

When diagnosing MI in children it can be useful to request consultation from adult cardiologists experienced with MI. The anamnesis, laboratory tests and imaging methods should be used to full benefit in diagnosis. Even if the anamnesis does not have such a satisfactory role in Paediatric diagnosis as it does for adults, information must be obtained about the character and radiation of the pain, especially from school-age children and adolescents. The determination of CHD, previous surgical interventions because of the CHD in the anamnesis aortic stenosis, hypertrophic cardiomyopathy, patients underwent operation for transposition of great artery particularly have additional risks for MI [76].

In the physical examination, the determination of weak pulse, dyspnoea, rhythm irregularity, sudden paroxysmal abdominal pain, gallop rhythm, cold extremities and shock should suggest MI [2]. The determination of PR segment depression on ECG, ST segment elevation together with the J point in at least two adjacent derivations, deep and/or wide Q-wave in at least one derivation, T-wave changes, ventricular arrhythmia and cardiac block should suggest a diagnosis of MI [14].

On echocardiography, segmentary wall movement abnormalities, a reduction in left ventricle functions, papillary muscle rupture and left ventricle free wall rupture are valuable for diagnosis [24, 77]. In the laboratory examination, elevation in troponin levels and increased CKMB levels are important for diagnosis.

Coronary angiography is the standard diagnostic method for MI [35]. The application of coronary angiography should be considered in patients with high troponin levels and findings in the anamnesis suggestive of MI. It must also not be forgotten that coronary angiography in MI cases related to vasoconstrictor substance intake, could be normal [63].

23. Treatment

As there are no comprehensive studies related to PMI treatment, the treatment principles of adult MI treatments have been adapted for children and have been formed from experience focussed on cases. Treatment must be organised according to the aetiology and clinical status of the patient. To determine arrhythmia or for early intervention when it has been determined, ECG monitorisation should be applied as soon as possible to all patients with suspected MI [10, 23].

24. Fibrinolytic treatment

24.1. Alteplase

In recent years, alteplase has become the most widely used fibrinolytic drug in children. The most important reasons for selection are that the half-life is short (approximately 5 mins), it is not antigenic and the effect is fibrin-specific [78]. It is a recombinant tissue plasminogen activator. In literature, there is no standard application related to r-tPA dosage in Paediatric patients. There are different applications in different centres. Nakagawa et al. applied intracoronary tPA at the dose of 200,000 unit/kg (0.34 mg/kg) to a patient with Kawasaki disease who suffered MI, but the patient died [79]. Subsequently, doses of 400,000 unit/kg (0.69 mg/kg) and 800,000 unit/kg (1.38 mg/kg) intra-coronary tPA were applied to 2 other patients with Kawasaki disease who suffered MI, and the thrombi and cliinical findings of the patients were determined to have recovered without any complications. In addition to the tPA, Nakagawa et al. also administered urokinase infusion to the first and third of these three patients. Tsubata et al. applied a dose of 300,000 unit/kg tPA to an MI patient with Kawasaki disease as 10% of the total dose in bolus form and the remainder with a 1-hour infusion [80]. After 2 days, a dose of 50,000 unit/kg tPA was administered intra -coronary, but only a partial response was obtained in the thrombus. Krendal et al. treated a 7-year old Kawasaki patient with MI with intravenous 700,000 unit/kg tPA and a response was obtained clinically on echo. The success in that case compared to Tsubata et al. was associated with the administration of high-dose tPA [81].

In cases of intracardiac thrombus and intravascular thrombose**s,** while some centres have used 0.05–0.5 mg/kg/hr. infusion after 0.3–0.6 mg/kg bolus, other centres have administered infusion of 0.01–0.5 mg/kg/hr. without any loading dose, until the thrombus is resolved (max 96 hrs). This has been used and successful results have been obtained in Paediatric cases, especially in the opening of a central venous catheter and in intracardiac or intra-arterial and intravenous thrombus cases [83–86].

After a loading dose of 0.1 mg/kg/10 mins in neonatal infants, some centres have administered maintenance at 0.3 mg/kg/hr. while others have given a loading dose of 0.7 mg/kg in 30—60 mins followed by 0.2 mg/kg/hr. As the infusion time extends, so the possibility of complications developing increases [82, 83]. Major complications that can develop are intracranial bleeding, epistaxis, melena and hematuria and minor complications may be seen as mucosal bleeding or bleeding from the needle entry site. Therefore, patients must be closely

monitored. In patients who develop complications, plasminogen or fibrinogen levels in the blood are examined, and if necessary the treatment must be stopped.

In adult cases, following a 15 mg iv bolus dose, 0.75 mg/kg/hr. is administered in 30 mins. The success of fibrinolytic treatment is evaluated with the correction of ST elevation and the patient symptoms [23].

As Paediatric MI cases are emergencies and the condition is urgent and life-threatening, it may be more appropriate to administer intra-coronary or iv high-dose bolus treatment followed by 0.1–0.5 mg/kg /hr. infusion.

24.2. Reteplase

Unlike alteplase, there is no need for an infusion following the administration of IV bolus. To open blocked catheters in Paediatric patients, 0.1 units was administered and in cases where no response could be obtained, increases were applied of 0.1 units up to a maximum of 0.4 units. Successful results have been obtained with this treatment [85]. In adult coronary thrombo-embolic cases, it is recommended that 10 units are given in the form of 2 doses at a 30-min interval [23].

24.3. Tenecteplase

This is a drug given in bolus form to myocardial infarction patients after diagnosis [23]. Unlike other tissue plasminogen activators, it is a time-saving application as there is no requirement for repeated bolus doses. The recommended doses for adults are 30 mg (6000 unit) for patients <60 kg in weight, 35 mg for those weighing 60–70 kg, and 40 mg for those of 70–80 kg [23].

24.4. Streptokinase

Streptokinase has been used for many years in adult MI patients. Experience related to the efficacy of streptokinase in PMI has been acquired from Kawasaki patients in particular. Studies have shown that in Kawasaki patients with MI, the use of intravenous or intra-coronary streptokinase followed by heparinisation and warfarin or dipyridamol in maintenance, is effective [87, 88]. If Percutaneous Coronary Intervention (PCI) is not applied within the first 2 hours after diagnosis in cases with MI, immediate thrombolytic treatment should be applied with a half-hour infusion. Fibrinolytic treatment can be administered to patients diagnosed with MI within the first 12 hours of diagnosis [23].

25. Percutaneous coronary intervention

In adult patients, it is recommended that PCI is applied within 2 hours of MI diagnosis. In patients where it is predicted that the time from diagnosis to PCI will exceed 2 hours, it is recommended that fibrinolytic treatment is given first in bolus form, after that fibrinolytic treatment catheter unit intake for PCI [23].

26. Anticoagulant treatment

Anticoagulation is recommended for all patients in addition to antiplatelet therapy during primary PCI [23]. The most commonly used drug for this is unfractioned heparin. The initial dose is given in bolus form as 70–100 units/kg and in maintenance, it can be given according to the active clotting time or as 10–15 units/kg/hr. After admission to hospital, it can be terminated within 8 hours of clearance of the coronary occlusion or it can be continued intra venously for 24–48 hrs to heparinisation. The goal is an aPTT value of 50–70 seconds or 1.5–2-fold the control value. It is recommended that the test is repeated at 3, 6, 12 and 24 hours [23].

27. Anti-aggregant treatment

As aspirin is given at the classic anti-aggregant dose (75-100 mg) following classic anti-aggregant dose loading (150-300 mg) in adult MI cases, in Paediatric cases loading is given of 5 mg/kg/day followed by 3-5 mg/kg/day aspirin. Adolescents can benefit from doses similar to those of adults.

The administration of clopidogrel together with aspirin increases the chance of success. The recommended Paediatric dose for clopidogrel is 0.2 mg/kg/day [89]. In adult patients diagnosed with MI, after 300 mg loading, maintenance treatment is given of 75 mg/day clopidogrel. It is recommended that clopidogrel and aspirin treatment is continued for 12 months in adult patients after MI [23].

27.1. Beta blockers

When arrythmia has been determined in MI patients, electrolyte levels must be examined and if the electrolyte levels are normal, beta blockers are preferred in treatment. Metoprolol can be given for this at a single dose of 1-2 mg/kg/day [23]. In addition to the anti-arrhythmic effects of beta blockers, patients who have undergone MI also beenfit from the anti-ischaemic effect because of the vasodilatory properties.

Conflict of interest

Authors declare that they have no conflict of interest to declare.

Author details

Meki Bilici*, Mehmet Ture and Hasan Balik

*Address all correspondence to: drmekibilici@hotmail.com

Department of Pediatric Cardiology, Dicle University Medical Faculty, Diyarbakir, Turkey

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