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Myocardial Ischemia in Congenital Heart Disease: A Review

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1. Introduction

1.1. Concepts

Patients with congenital heart disease (CxHD) are surviving into adulthood, as well as living longer and growing older [1], due the major achievements in their diagnosis, medical management, surgical repair, and postoperative treatment in the last three to four decades. An increasing numbers of patients with CxHD are encountered in our everyday practice. It is therefore timely and appropriate to start addressing the somewhat-neglected issue of myocardial ischemia in this patient population [2].

CxHD is, by definition, cardiovascular disease present at birth. It refers to anatomic defects and gross cardiac abnormalities due to an embryologic malformation in the structural development of the heart and major blood vessels, which is actually of functional significance [3]. Most CxHD occur due to gross structural developmental cardiovascular anomalies such as septal defects, stenosis or atresia of valves, hypoplasia or absence of one ventricle, or abnormal connections between great vessels and the heart. A few children are also born with arrhythmias (mainly conduction defects), and hypertrophic or dilated cardiomyopathy, although these are usually present later in childhood or adulthood. CxHD are the most common of all congenital malformations, with a reported incidence of 6 to 8 cases per 1,000 live births, and in an even higher percentage of fetuses [4]. In some studies this incidence reaches 12 to 14 per 1,000 live births [5].

There is a great number of recognized heart defects occurring alone and in combination, ranging in severity from hemodynamically insignificant to extremely complex and life threatening conditions (Table 1). Although there may be genetic or environmental situations

that can affect the development of heart defects, in the majority of cases the cause is considered multifactorial, with no specific identifiable trigger. Only approximately 15% of cases of CxHD can be traced to a known cause [6]. Some types of CxHD can be related to chromosome or gene defects, environmental factors or a multifactorial aetiology [7]. Only 2% of all cases of CxHD can be attributed to known environmental factors. Risk factors, such as maternal insulin-dependent diabetes mellitus and phenylketonuria, are well known as two of the leading causes of CxHD. Other reported risk factors include maternal obesity, alcohol use in pregnancy, rubella infection, febrile illness, use of drugs such as thalidomide and retinoic acid, and exposure to organic solvents and lithium [8].

<ul style="list-style-type: none">• Patent ductus arteriosus• Atrial septal defect• Ventricular septal defect• Atrioventricular septal defect• Aortopulmonary window• Tetralogy of Fallot• Pulmonary atresia or stenosis• Aortic atresia or stenosis• Mitral atresia or stenosis• Tricuspid atresia or stenosis• Left ventricular outflow obstruction• Coarctation of the aorta	<ul style="list-style-type: none">• Interrupted aortic arch• Hypoplastic left heart syndrome• d-Transposition of the great arteries• l-Transposition of the great arteries (also known as congenitally-corrected transposition of the great arteries)• Truncus arteriosus communis• Double outlet right or left ventricle• Ebstein’s disease• Anomalies of the coronary arteries• Vascular rings and pulmonary sling• Total or partial anomalous pulmonary venous connection
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Table 1. Most common types of congenital heart defects.

Mortality occurs mainly in patients with severe forms of CxHD requiring prompt surgical intervention [9]. Interestingly, the relative contribution of the causes of death in patients with CxHD has changed over time. The CxHD causes 3% of all infant deaths and 46% of death from congenital malformations, despite advances in detection and treatment. Arrhythmia followed by congestive heart failure had been considered the main contributing cause of death. However, the mortality figures collected over the past decade showed an increase in myocardial infarction as the cause of death [10]. Until the twentieth century, the majority of newborns with CxHD died because treatment was not available. With the advances made in the field of foetal and paediatric cardiology, survival and quality of life have improved, especially in the past 10–20 years [11].

1.2. Myocardial ischemia

The advances in paediatric cardiac surgery were accompanied by refinements in extracorporeal perfusion technology that have led to significant improvements in the surgical results during the past decades. Nevertheless, perioperative myocardial damage still remains the most common cause of morbidity and death after a technically successful surgical correction.

Despite the importance of this issue, there are a few publications about this. Studies show that the younger the age of patients, the more vulnerable are their myocardium to injury caused by ischemia during definitive repair of congenital heart disease. Therefore, perioperative care for paediatric patients with congenital heart disease needs to take into consideration the dependence of the myocardial damage on age and ischemic time [12]. Others researches have shown that myocardial cell injury in infants submitted to open-heart surgery can be directly associated with varying combinations of gross, microscopic, and histochemical myocardial necrosis in up to 90% of patients who do not survive the perioperative period. The observed alterations within the myocardium can potentially be attributed to the heart defect itself, preoperative hemodynamic instability and its treatment, surgical techniques, cardiopulmonary bypass, myocardial protection strategies, and postoperative medical care.

Furthermore, patients with CxHD are at increased risk of developing myocardial ischemia or premature coronary artery disease (CAD) as the result of: (a) congenital coronary artery abnormalities (e.g., anomalous origin and course of coronary arteries, myocardial bridging, coronary artery fistulas); (b) previous surgery (e.g., arterial switch operation for d-transposition of the great arteries (d-TGA) and surgical coarctation repair); and (c) myocardial ischemia not related directly to coronary artery anomalies but presenting after the atrial switch procedure for TGA (Mustard, Senning) and also in patients with congenitally corrected transposition of the great arteries (ccTGA).

Clinical suspicion is a difficult task, especially in neonates and young infants, in whom the clinical manifestations can be unspecific and transient. In older children and adolescents, chest pain can be present, although myocardial ischemia is rarely the underlying cause [13].

The diagnostic and treatment of paediatric CxHD has undergone remarkable progress over the last 60 years [14]. Moreover, in the past 10 years, significant advancements have been made in foetal echocardiography; in postnatal echocardiography and angiography, leading to greater accuracy in defining the cardiac defect; in interventional catheterization as a palliative or curative measure; and in surgical techniques, which have led to an estimated million adults living today with complex CxHD that required surgery in the neonatal period [15].

In the long term, as a consequence of successful cardiac surgeries in the past decades, there is an increasing number of patients with CxHD reaching adulthood and becoming old. These survivors with complex heart defects are now developing problems associated with aging. The association of CxHD, heart surgeries, and chronic coronary artery disease is not well studied yet [16]. It is possible that these patients are at an increased risk of myocardial ischemia, but epidemiological studies are needed to answer to this question.

Therefore, perioperative myocardial injury is a major determinant of cardiac dysfunction after operations for CxHD. It is very important detect and evaluate the degree of myocardial injury as soon as possible after the operative procedure. Thus in an attempt to clarify possible mechanisms involved in the development of ischemic heart disease in children with CxHD, this study aims to describe the pathological alterations observed in different types of CxHD in the heart of infants submitted to surgical correction of cardiac malformations, and to discuss potential strategies to prevent them.

2. Pathogenesis

In normal conditions, an uninterrupted flow of large quantities of oxygenated blood to the myocardium is critical to its normal function [17]. During the systole, this flow can be abolished or even reversed towards the epicardial vessels. The blood must flow from low to high intra-myocardial pressure, in order to meet the metabolic demands of each layer. Such flow must be regulated in such way that areas of high demand can immediately increase their blood supply.

The myocardium extracts about 60 to 75% of oxygen from the blood that passes through it. Because of this high level of extraction, coronary sinus blood has low oxygen tension, generally around 25–35 mm Hg. This low level of oxygen tension requires that any increase in oxygen demand be met by an increase in blood flow rather than an increase in extraction [17].

There are two main mechanisms by which myocardial ischemia can occur: (a) a reduction in myocardial supply of oxygen, and (b) an increase in myocardial oxygen demand [18]. The first situation can occur as a result of reduced coronary blood flow or reduced oxygen content despite normal coronary flow. A reduced coronary blood flow can result from congenital malformations of the coronary arteries, acquired coronary diseases, and also postoperative states, especially after surgical reimplantation of the coronary arteries. Examples of reduced oxygen content in coronary blood include cyanotic heart diseases, severe anaemia, and hemoglobinopathies. The second mechanism can occur in the presence of hypertrophic cardiomyopathy or vigorous exercises. The main diagnoses related to myocardial ischemia are summarized in Table 2.

A number of conditions can lead to myocardial ischemia, including prenatal and birth conditions, the anatomic defect, pre- and postoperative care, surgical technique, and myocardial protection during CPB. These conditions will be discussed in detail below.

2.1. Prenatal and birth conditions

Foetal hearts show a remarkable ability to develop under hypoxic conditions. The metabolic flexibility of foetal hearts allows sustained development under low oxygen conditions. In fact, hypoxia is critical for proper myocardial formation [19]. However, although “normal” hypoxia (lower oxygen tension in the foetus as compared with the adult) is essential in heart formation, further abnormal hypoxia in utero adversely affects cardiogenesis. Prenatal hypoxia alters myocardial structure and causes a decline in cardiac performance. Not only are the effects of hypoxia apparent during the perinatal period, but prolonged hypoxia in utero also causes foetal programming of abnormality in the heart’s development. The altered expression patterns of cardioprotective genes likely predispose the developing heart to increased vulnerability to ischemia and reperfusion injury later in life [19].

In addition, myocardial dysfunction is a frequent sequel of perinatal asphyxia, resulting from hypoxic-ischemic damage to the myocardium. It can lead to decreased perfusion, tachycardia, hypotension, and need for inotropic support [20,21]. As a consequence, hemodynamic

Diagnosis related to the coronary arteries
<ul style="list-style-type: none"> Anomalous coronary arteries <ul style="list-style-type: none"> Left main coronary artery from the pulmonary artery Left main coronary from the right coronary cusp Right coronary artery from the left coronary cusp Coronary artery fistula Coronary artery spasm Thromboembolic or embolic coronary artery disease Kawasaki disease Coronary artery dissection Ostial coronary artery disease status post surgical reimplantation <ul style="list-style-type: none"> d-Transposition of the great arteries (d-TGA) arterial switch Aortic root replacement Ross procedure Intramyocardial bridging
Diagnosis related to the myocardium (supply/demand mismatch)
<ul style="list-style-type: none"> Hypertrophic cardiomyopathy Severe aortic stenosis Dilated cardiomyopathy Tachycardia in the face of limited coronary blood flow
Others
<ul style="list-style-type: none"> Severe hypoxia or cyanosis

Table 2. Diagnosis related to myocardial ischemia.

impairment can develop and the myocardium may suffer additional ischemic insults. Infections, need for cardiopulmonary resuscitation, mechanical ventilation, preterm birth, among other factors may also contribute to myocardial damage during this period.

2.2. The anatomic defect

Many CxHD are associated with anomalies such that the child is prone to myocardial ischemia even after uncomplicated delivery and good hemodynamic conditions. They involve congenital anomalies of the coronary arteries and hypertrophic cardiomyopathy. Other diseases can present early in life with congestive heart failure, circulatory shock, or severe hypoxemia. All these factors can compromise coronary circulation and lead to myocardial ischemia.

2.2.1. Congenital anomalies of the coronary arteries

The entire blood flow to the myocardium comes from two main coronary arteries that arise from the right and left aortic sinuses of Valsalva. In 69% of the population, the right coronary

artery is dominant [18]. Although there are normal variations for the coronary anatomy, a comprehensive discussion of this topic is beyond the scope of this chapter, which will focus only on the clinically significant anomalies.

The most common anomaly, accounting for about one third of all major coronary arterial anomalies, is origin of the left circumflex coronary artery from the right main coronary artery. However, this anomaly is rarely of clinical significance. Less common, the origin of the left coronary artery from the right sinus of Valsalva, is of greater significance, and was associated with sudden death in children during or just after vigorous exercise when the vessel passes between the two great arteries [18].

A single coronary artery may be observed in 5–20% of major coronary anomalies. About 40% of these anomalies are associated with other cardiac malformations, including d-TGA, tetralogy of Fallot, ccTGA, double-inlet left ventricle, double-outlet right ventricle, truncus arteriosus, coronary-cameral fistulas, and bicuspid aortic valve [18]. Only a small number of premature deaths have been reported with this anomaly.

When the coronary arteries (either right or left) have their origins in inappropriate sinus, the mechanism of ischemia and death involves an increase in myocardial oxygen demand during exercise that, in turn, causes increases in systolic blood pressure and aortic root distension. If part of the anomalous artery runs within or adjacent to the aortic wall, it may be stretched, compressed, or both, leading to insufficient coronary blood flow.

Other rare coronary anomalies include coronary atresia, stenosis or atresia of a coronary ostium, all coronary arteries from pulmonary artery, left anterior descending coronary artery from pulmonary artery, left circumflex coronary artery from the pulmonary artery or branches, right coronary artery from pulmonary artery, myocardial bridges, etc.

2.2.2. Anomalous origin of left coronary artery from the pulmonary artery (ALCAPA)

In this anomaly the left coronary artery arises from the pulmonary artery. Therefore, after birth, the left ventricle is perfused with desaturated blood in a regimen of low pressures. The left ventricle becomes then hypoxic, and collaterals start to develop. The left ventricle vessels then dilate to reduce their resistance and increase flow, but this is often not enough to prevent ischemia with compromise of the left ventricular function. This leads to congestive heart failure that can be worsened by mitral regurgitation. With time, the collaterals between right and left coronary artery enlarge until the collateral flow tends to reverse in the left coronary and ultimately into the pulmonary artery. The left-to-right shunt is usually not significant [18,22].

This anomaly is usually isolated but can be associated with patent ductus arteriosus, ventricular septal defect, tetralogy of Fallot, or coarctation of the aorta [18].

2.2.3. Tetralogy of fallot

In this disease, a hypertrophied right ventricle is always present, with a high oxygen demand to overcome the outflow tract obstruction and provide pulmonary blood flow. In face of severe

cyanosis, hemodynamic impairment, the oxygen supply may not balance the high requirements of the right ventricle, leading to myocardial ischemia.

2.2.4. Pulmonary atresia with intact ventricular septum

In this disease, the absence of anterograde blood flow across the pulmonary valve associated with the absence of a ventricular septal defect precludes the development of the right ventricle, which becomes hypoplastic. A network of vascular channels, called sinusoids, then develops, communicating the right ventricular cavity with one or both of the coronary arteries.

With systemic or supra-systemic systolic pressure within the right ventricular cavity, blood flow in these fistulous connections may compete with the normal coronary blood flow originating in the ascending aorta. Sometimes, these competing blood coronary streams may cause tortuosity, severe intimal proliferation with obstruction, such that portions of the myocardium may be dependent on the right ventricle-originated coronary flow (so-called right ventricle-dependent coronary circulation) [23]. This portion of the myocardium would then be perfused with unsaturated blood. If these sinusoids are not diagnosed properly, a pulmonary valvotomy can be catastrophic, since the sudden fall in right ventricle pressure will reflect in a dramatic fall in coronary pressure, leading to acute myocardial ischemia and, potentially, death.

2.2.5. Other heart defects

Children with a large patent ductus arteriosus with left-to-right shunt, those with severe aortic regurgitation, and those with hypoplastic left heart syndrome, among others, are at great risk for myocardial ischemia, especially in the presence of severe hypoxemia or hypotension. A large patent ductus arteriosus with significant left-to-right shunt can decrease the diastolic pressure in the aorta, significantly diminishing coronary blood flow. A severe aortic regurgitation can lead the same deleterious consequences in diastolic pressure. In patients with hypoplastic left heart syndrome, the ascending aorta receives a retrograde poorly oxygenated blood flow originated from a patent ductus arteriosus. Therefore, these patients are particularly sensitive to hypotension, severe hypoxemia, imbalances between pulmonary and systemic blood flows, and a claudicating ductus arteriosus.

In patients with ccTGA, the right ventricle supports the systemic circulation and can become dilated and hypertrophied with time. Once ventricular dilation and hypertrophy settle in, the blood supply through a normal right coronary artery can become insufficient to meet the increased metabolic demands of the systemic right ventricle [24,25], leading to further ventricular dysfunction. The latter may also have a deleterious effect on left ventricular perfusion, ultimately leading to left ventricular dysfunction [24]. Hypertrophy can also develop in many other situations, especially aortic stenosis and chronic systemic hypertension.

2.3. Preoperative care and drugs

Preoperative care is of special interest in neonates and young infants because usually the CxHD manifests as a critical illness. The neonatal myocardium is less compliant than that

of the older child, is less tolerant to increases in afterload, and is less responsive to increases in preload. In the other hand, despite being more labile, this age group is more resilient to metabolic or ischemic injuries, which can play a relative protective role [17]. After birth, neonates with CxHD can deteriorate their hemodynamic status requiring prompt interventions. The higher metabolic rate and oxygen consumption of the neonate account for the rapid appearance of hypoxemia in this age group. In addition, undiagnosed infants and older children may present in shock, congestive heart failure, severe hypoxemia, severe arrhythmia with hemodynamic impairment, or a combination of them, also requiring immediate intensive care. This highly specialized care requires careful evaluation of the structure and function of the heart, the transitional neonatal circulation, and the secondary effects of the defect on other organ systems. All efforts need to be put on making a definitive, precise diagnosis, so appropriate therapeutic measures can be started [17]. The treatment of the newborn or infant with severe hemodynamic compromise often involves the use of catecholamines that, despite improving myocardial contractility, can further increase the myocardial metabolic rate and oxygen consumption. Therefore, the attending clinician shall be aware that these drugs need to be used only at the minimum effective dose to obtain the desired effect. Alternatively, when the renal function is preserved, milrinone and levosimendan are very good options, since they can increase myocardial contractility without increasing metabolic rate and oxygen consumption.

Special attention shall be put also on coronary blood flow. Careful monitoring with continuous electrocardiography, as well as serially measuring CK-MB and cardiac troponins, is mandatory for the child with severe hemodynamic impairment, and prompt interventions need to be done quickly in face of a suspected or confirmed coronary insufficiency.

In older patients, the CxHD usually present as congestive heart failure or arrhythmias, not requiring critical care before surgery. There are, obviously, exceptions that shall be properly managed.

2.4. Surgical technique

2.4.1. d-Transposition of the great arteries

In this malformation, a number of different patterns of coronary anatomy have been described. Since the arterial switch operation includes the transfer of the coronary arteries along with the aortic root, it is important that the surgeon knows exactly what the anatomy is. There are at least nine anatomic variations in the way the two coronary arteries arise from the native aorta. Some coronary patterns are more difficult to transfer than others. In 60% of cases, the coronary arteries come from their appropriate sinuses and branch normally. However, the presence of a ventricular septal defect or side-by-side great vessels should alert the cardiologist to an increased likelihood of coronary anomalies, like left circumflex coronary artery arising from the right coronary artery, or inversion of the coronary arteries origin [18,23].

2.4.2. *Tetralogy of Fallot*

In this disease, the surgical repair includes patch-closure of the ventricular septal defect and widening of the right ventricular outflow tract by infundibular muscle resection combined with either a patch placement across the pulmonary valve annulus or use of a prosthetic conduit from the right ventricle to the pulmonary artery. There are some aberrant coronary patterns associated with tetralogy of Fallot. In some cases, there may be a large conus branch or an accessory left anterior descending artery running across the face of the right ventricular outflow tract that may be inadvertently damaged during surgery, leading to myocardial ischemia [23].

2.5. Cardiopulmonary bypass and myocardial protection

Recent advances in surgical techniques, myocardial preservation and postoperative care have resulted in complete repair of many CxHD in the neonatal period or early infancy. On the other hand, several investigators have reported that immature myocardium in the paediatric heart is more vulnerable to surgically-induced injury than mature myocardium in the adult heart, due to different structural and functional characteristics [26].

It is widely accepted that the immature heart has a greater tolerance to ischemia than the adult or mature heart. However, most of this laboratory data has been obtained with normal hearts. It is unclear what the ischemic tolerance is when there are pre-existing conditions such as cyanosis, hypertrophy, or acidosis. Many of these conditions may be present in neonates and infants who require surgical correction of their heart defect and may compromise myocardial protection [26].

Newer surgical techniques are being developed to allow for total correction of many CxHD, while limiting the time spent on continuous CPB or in deep hypothermia with circulatory arrest [27]. Therefore, surgeries have been the choice of management in these patients. However, there is a significant procedural- and anaesthesia-related morbidity and mortality in patients with CxHD who undergo repeated surgical interventions [28,29].

Despite the potentially detrimental side effects of CPB, this technique is still an essential assisting method for open-heart surgery [30]. CPB is a primary circulatory support technique to cardiac surgery in neonates and infants and remains one of the most important factors associated with postoperative mortality and morbidity in open-heart surgery. With improvements in equipment and techniques, CPB has become safer and more reliable. However, it causes profound alterations in physiological fluid homeostasis [31]. The age and size of the patient, the underlying cardiac pathology, and the type of surgical techniques influence what perfusion methods are chosen and the construction of the CPB circuit [32]. Despite significant improvements, CPB remains a non-physiological procedure. The effects of hypothermia, altered perfusion, hemodilution, acid-base management, embolization, and the systemic inflammatory response have been challenging, particularly for neonates and infants. These challenges are primarily related to the smaller circulatory volume, the immaturity of most organ systems, and the increased capillary membrane permeability of neonates and infants [32,33]. Moreover, cardiomyocytes can be affected by hypoxic conditions, and the ischemic

effects can induce rapid or gradual changes in the membrane systems that cause reversible or irreversible injury [34]. Experimental studies of myocardial ischemia and reperfusion have established that reperfusion also has negative consequences during circulatory interruption [35,36]. Due to the necessary interruption in coronary circulation required by nearly all cardiac surgeries, the potential for reperfusion damage is significant. If a reperfusion injury does occur, the initial damage may contribute to the impaired cardiac performance that develops immediately after surgery that may then lead to myocardial fibrosis [37,38].

Myocardial preservation during surgically induced myocardial ischemia has been the subject of hundreds of publications in recent years. The most used technique is hypothermic cardioplegia. The consequences of incomplete myocardial protection during surgically induced myocardial ischemia can have a dominant effect on the postoperative course, including low cardiac output, elevated atrial filling pressures, and requirements for increased inotropic support [39]. Cardioplegic solutions are used by most surgeons, and their basic components are potassium (to achieve diastolic arrest) and cold temperature (to reduce the metabolic demands of the heart during ischemia) [39]. There is a variety of different cardioplegic solutions, and there is no consensus on which one is the best. In fact, there is wide variation between institutions regarding cardioplegia and myocardial protection.

Aortic cross clamping during CPB allows the surgeon to intervene on the aortic root, the aortic valve, and the left ventricle outflow tract. However, since during CPB myocardial perfusion is retrograde, during cross clamping the heart is stopped and is not perfused [26,31,39]. Therefore, long cross clamping times are more likely to cause more ischemic injury to the heart.

2.6. Postoperative care and drugs

After surgery, the first 9–12 hours are crucial because during this time the patient will experience a transient decrease in myocardial performance and cardiac output, with increasing need of inotropic support as a consequence of CPB and ischemia-reperfusion injury in the heart and lungs [40]. Besides, the child may deteriorate as a result of residual lesions, pulmonary hypertension, and bleeding. All these factors may lead to poor organ perfusion and hypotension, with consequent reduced coronary blood flow.

In some cases, when the surgical technique involves coronary reimplantation, like the arterial switch for d-TGA, there is a considerable risk of myocardial ischemia. The implantation of the coronary arteries on the neo-aorta may be technically challenging, and the coronary insertion may be stenotic or distorted, resulting in insufficient coronary flow. Other causes of insufficient coronary blood flow include spasms of the coronary arteries, air embolism, and thrombosis. Arrhythmias, especially on weaning from CPB, frequently indicate coronary insufficiency; the coronary anastomoses should be promptly investigated before leaving the operating room, as well as transesophageal assessment of left ventricle wall motion. Left ventricular dysfunction may also indicate coronary insufficiency [17].

Many drugs used to improve myocardial contractility and cardiac output can substantially increase myocardial oxygen requirements. In face of hypotension, low cardiac output, or marginally sufficient coronary blood flow, these drugs may actually lead to or aggravate

myocardial ischemia. These drugs include dopamine, dobutamine, epinephrine, and norepinephrine.

Arrhythmias, particularly tachyarrhythmias, can also significantly augment the oxygen demand within the myocardium, while compromising the cardiac output, ultimately leading to myocardial ischemia.

Severe blood loss can cause hypotension and a reduction on the arterial oxygen content, substantially affecting oxygen transport to the myocardium.

3. Diagnostic evaluation

3.1. Acute ischemia

Chest pain is the hallmark of myocardial ischemia in adults and the elderly. In children and adolescents, however, the great majority of chest pain episodes are of non-cardiac origin [23]. When myocardial ischemia is present in a critically ill patient admitted to an intensive care unit, there may be no specific sign or symptom, and the diagnosis usually need to be made based on ECG findings and biomarkers alone.

3.1.1. Electrocardiogram

The electrocardiogram (ECG) remains the most important diagnostic test in the evaluation for myocardial ischemia. Many factors are involved in the interpretation of the ECG: age, autonomic tone, heart rate, race, gender, and body habitus. Interestingly, pseudo-abnormal ECGs were found in up to 40% of Olympic athletes with structurally normal hearts [13]. It is important to notice that the ECG should be obtained during the episode or shortly after the event whenever possible; otherwise, the alterations in ECG may disappear. The main ECG findings of myocardial ischemia are ST changes, namely elevation or depression of the ST segment. Although repolarization changes, pericardial diseases, drugs, and electrolyte abnormalities can also cause ST changes, a negative ECG is extremely predictive of non-ischemic events [13].

3.1.2. Biomarkers

When myocardial ischemia occurs, some enzymes from the myocardium are released and can be detected in peripheral blood approximately 2 hours later. The main biomarkers available are cardiac troponins (both I and T) and creatine kinase MB isoenzyme (CK-MB). When elevated, they can diagnose myocardial ischemia with good sensitivity and specificity [13].

3.1.3. Echocardiogram

Echocardiography is the predominant imaging modality used for the diagnosis and management of CxHD because of its widespread availability, ease of use, real-time imaging and cost effectiveness. The role of echocardiography specifically for the detection of myocardial

ischemia in the CxHD population is less well established. Furthermore, the indications and clinical applications of other newer echo techniques such as tissue Doppler imaging, strain and strain rate imaging, contrast and real-time three-dimensional (3D) echocardiography to detect myocardial ischemia will need to be determined in these patients [2]. It can be helpful to detect the following: hypertrophic cardiomyopathy, severe aortic stenosis, and dilated cardiomyopathy, all of them potentially associated with coronary flow abnormalities and myocardial ischemia. In some cases, it can show clues to the suspicion of ALCAPA and other coronary abnormalities [13].

3.2. Chronic ischemia

The diagnosis of chronic ischemia in patients with CxHD may be challenging for the physician because this population, often adults operated on early in life, may have pre-existing anatomic, functional, or electrocardiographic abnormalities. They may also have pre-existing coronary disease that, in association with other environmental, metabolic and genetic factors, may increase the risk of coronary insufficiency. However, discussing the diagnosis of these abnormalities is beyond the scope of this chapter.

4. Alterations observed within the myocardium

Myocardial infarction is defined by pathology as myocardial cell death due to prolonged ischemia. Cell death is categorized pathologically by coagulation necrosis and/or contraction band necrosis, which usually evolves through oncosis, but can result to a lesser degree from apoptosis. Mallory, et al, 1939, and Lodge-Patch, 1951 described myocardial infarction as a form of coagulation necrosis in which cells transform into eosinophilic hyaline masses [41,42]. Other types of necrosis are also quite common in myocardial infarction. The term contraction band necrosis [43] have been used to describe degenerative changes of myocardial fibers characterized by a hypercontraction or spasm of the fibers, with the formation of irregular abnormal transverse bands due to compression of adjacent sarcomeres. These changes have been observed in association with electric shock, deficiency of potassium, administration of catecholamines, coronary arterial reperfusion, and death after cardiac surgery [44,45]. Although the primary event leading to the formation of “contraction bands” is unknown, most often they probably develop in areas of reflow [46] or “twilight blood flow” after ischemia [47].

Colliquative myocytolysis, have been used to describe focal lesions, mainly in the subendocardium and in perivascular regions, which were characterized by progressive vacuolization of fibers with lysis of contractile elements until only empty sarcolemmal tubes remain [48]. Schlesinger and Reiner, 1955 have proposed that focal myocytolysis is a result of metabolic imbalances secondary to a large variety of disorders. In contraction band necrosis and colliquative myocytolysis, healing is thought to occur by fibroblastic proliferation, without the usual sequence of changes that occurs with coagulation necrosis. Careful analysis of histologic sections by an experienced observer is necessary to distinguish these entities [49] (Fig. 1).

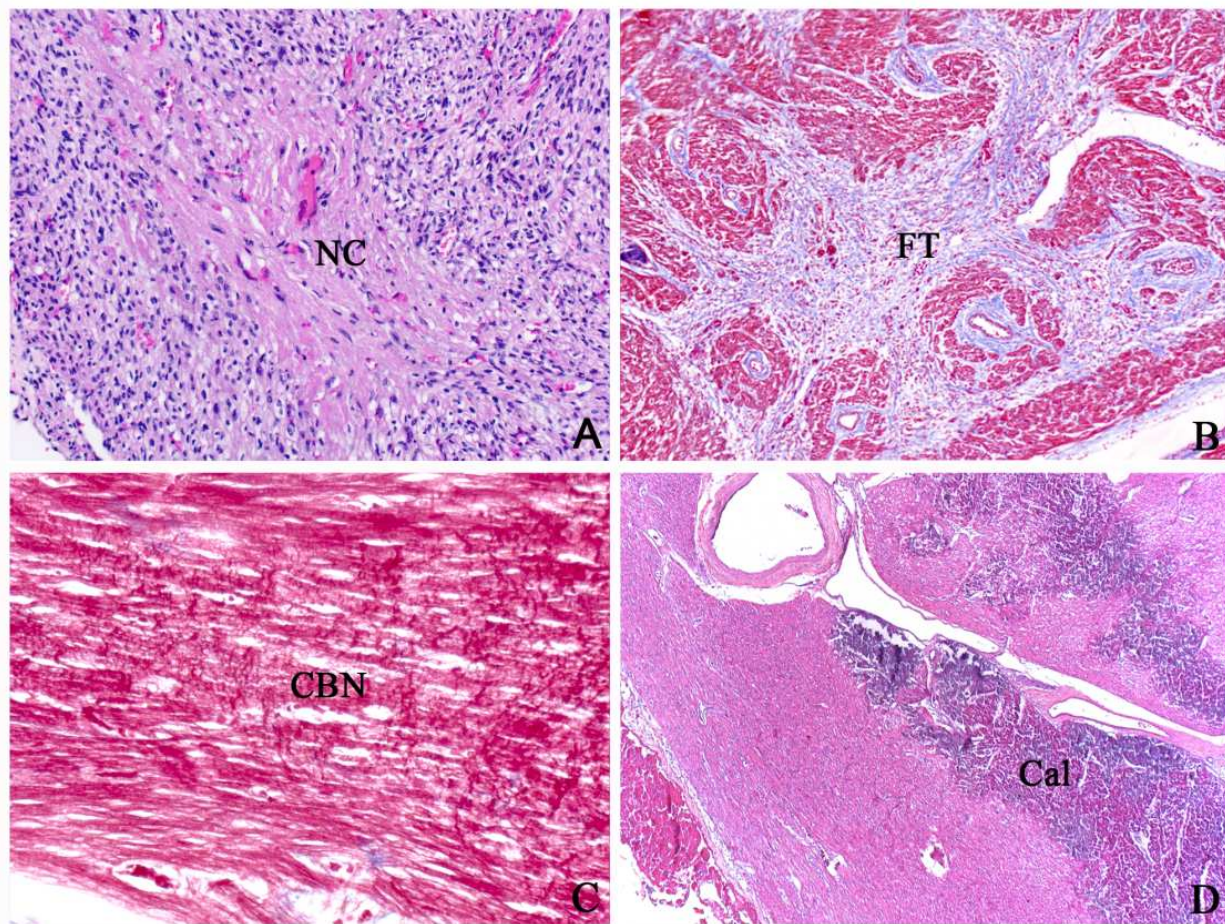


Figure 1. Myocardial injuries observed in infants submitted to cardiac surgery with cardiopulmonary bypass. The histopathology of myocardial injuries observed in infants with congenital cardiac heart disease submitted to surgery with cardiopulmonary bypass (CPB). **(A)** Area of coagulation necrosis (CN) characterized by cells with a cytoplasm that exhibits an increased eosinophilia, loss of cross-striations, granularity, and nuclear karyolysis or pyknosis, H&E; 200x. **(B)** Extensive area of fibrous tissue, Azan; 100x. **(C)** Contraction band necrosis (CBN), Azan; 400x. **(D)** Large calcified intramural band in the myocardium, H&E; 50x.

4.1. Cardiac surgery and myocardial injury

Myocardial injury in association with cardiac surgery can be caused by different mechanisms, including direct trauma by sewing needles, focal trauma from surgical manipulation of the heart, global ischemia from inadequate perfusion, myocardial cell protection or anoxia, and other complications of the procedure [49]. Cardiac surgery with CPB is frequently associated with postoperative organ dysfunction [50]. Paediatric patients are particularly prone to these complications, and oxidative stress seems to contribute to CPB related postoperative complications. Early systemic oxidative stress could also have been a consequence of ischemia-reperfusion injury to the myocardium [51]. It is recognized that acute stress episodes can induce heart injury that results in the release of cytosolic enzymes and catecholamines to the blood [52,53]. Although catecholamines play an important role in normal cardiac function [54], the use of CPB in cardiac surgery leads to a significant increase in circulating catecholamine

levels [55,56] and this excessive release is responsible for the development of various cardiac dysfunctions, e.g. in cardiac remodelling following acute myocardial infarction [54], myocyte death in heart failure [57,58], and myocardial infarction [59]. In a recent study, Oliveira, et al, 2011 described that multifocal areas of myocardial injury seem to be the cause of heart failure for infants who do not survive beyond the perioperative period [60]. They were described in patients submitted to surgery for CxHD with and without CPB, and in patients who died from CxHD prior to surgical intervention. Most of the infants who had undergone surgery with CPB showed important areas of contraction band necrosis and dystrophic calcification. Whereas infants who had undergone surgery without CPB showed coagulation necrosis and healing, suggesting ischemia as the main cause. Importantly, 4-hydroxynonenal (4-HNE), a marker of lipid peroxidation, was strongly expressed, especially in irreversible myocardial lesions. This finding suggests that 4-HNE may be the predominant oxidative stress mechanism that occurs in these patients.

4.2. Adrenergic receptors and cardiopulmonary bypass

CPB and cardioplegic arrest remain the most popular techniques in clinical intervention during open-heart surgery. However, both can directly or indirectly result in cardiac morbidity following surgery [61]. Cardioplegic arrest renders the heart globally ischemic and, upon reperfusion, triggers myocardial injury [62]. The use of CPB and cardioplegic arrest during cardiac surgery also leads to desensitization of myocardial β -adrenergic receptors (β -ARs) and impaired signalling through this pathway, which is critical in the regulation of cardiac function [63,64]. Previous studies have demonstrated that cardiac β -AR signalling is impaired after CPB with cardioplegic arrest in children with acyanotic heart disease who underwent cardiac surgery [56]. Adrenergic receptors (ARs), first described by Ahlquist, 1948, belong to the superfamily of membrane proteins that activate heterotrimeric guanine nucleotide (G) binding proteins [65]. The heart expresses both β and α_1 adrenergic receptors [66]. The effect of β -adrenergic receptor activation is well established: the increase of both heart rate and force of contraction. The effect of α_1 -receptor activation is more complex. It is usually described as a biphasic or a triphasic effect: initial positive inotropy, followed by a transient negative and finally a more sustained positive inotropy without effect on chronotropy [67]. In the heart, agonist occupancy of β -ARs leads to the primary activation of the adenylyl cyclase (AC) stimulatory G protein (Gs), which leads to increases in intracellular cAMP and protein kinase A (PKA) activity [68]. Alterations in adrenergic signalling are important in a number of cardiac diseases. Undoubtedly, the alterations that take place in the β -AR system during the progression of heart failure (HF) are the most well characterized [68].

A primary mechanism of β -AR desensitization following prolonged stimulation is phosphorylation of agonist-occupied receptors by G protein-coupled receptor kinase-2 (GRK2), a member of the family of serine-threonine kinases known as G protein-coupled receptor kinases [69]. GRK2 has been shown to be important in the modulation of cardiac function in vivo [70, 71] and enhanced activity leads to uncoupling of β -ARs and impaired ventricular systolic and diastolic function.

Bulcao, et al, 2008 also found significant uncoupling of β -ARs from adenylyl cyclase under basal conditions and following β -agonist stimulation in a patient population following CPB and arrest [72].

In animal studies, inhibition of GRK2 has led to improved myocardial function after ischemic injury [73]. Myocardial GRK2 activity is known to be elevated in patients with chronic heart failure by approximately 2-3-fold compared to normal controls leading to impaired signalling through β -ARs and blunted inotropic reserve [74]. This is thought to be an important mechanism in the pathogenesis of chronic heart failure resulting from an increase in circulating catecholamines [75]. During myocardial ischemia, there is a decrease in the supply of oxygen and nutrients to the heart [62]. This, in turn, provokes a fall in energy production by the mitochondria, which is quickly followed by abnormal accumulation and depletion of several intracellular metabolites (e.g. a fall in adenosine triphosphate (ATP) and a rise in lactate). These metabolic changes lead to a decrease in intracellular pH and an increase in the intracellular concentrations of sodium and Ca^{2+} , which further consumes ATP [76], moreover, a local metabolic release of large amounts of noradrenaline occurs [77,78] together with an increased density of β -adrenergic receptors [79-81]. Consecutively, the capacity of β -adrenergic agonists to stimulate adenylyl cyclase activity is enhanced during the first 15 minutes of ischemia [79].

With progressive ischemia, however, isoproterenol-stimulated activity of adenylyl cyclase decreases to below the control value, although the density of β -receptors remains elevated [80]. This dissociation of receptor number and functional activity has been found in different models of cardiac ischemia [81], including the isolated perfused rat heart [79], and in human myocardium subjected to hypoxia during cardiopulmonary bypass surgery [56].

Similarly, heart failure in humans has also been characterized by specific alterations in the AR signalling system [82]. The enhanced desensitization of myocardial ARs is likely due, at least in part, to the elevated expression of GRK-2 present in human failing heart [74,83]. Mouse models of severe heart failure have been used to demonstrate that inhibition of GRK-2 with a peptide inhibitor can prevent agonist-stimulated desensitization of cardiac β -ARs. This is sufficient to increase mean survival, reduce dilation, and improve cardiac function. This may represent a novel strategy to improve myocardial function in the setting of compromised heart function [70].

5. Strategies for prevention

Prevention of myocardial ischemia in the setting of CxHD is an enormous task. Given the complex pathophysiology, it is very unlikely that a single intervention will show significant reductions on the incidence of myocardial ischemia in patients with CxHD. We can, though, comment on a few of issues that have been matter of investigation recently.

5.1. Before birth

The rate of CxHD that are diagnosed before birth is still low, especially in developing countries, where foetal echocardiography is not widely available. Babies with a prenatal diagnostic of

CxHD may benefit from catheter-based interventions such as balloon valve dilations or device-closure of abnormal communications. These interventions may lead to better intra-uterus myocardial perfusion and development.

5.2. After birth

Babies with CxHD should ideally be delivered in a tertiary-care hospital with a dedicated cardiac paediatric intensive care unit. However, this can only be accomplished by increasing prenatal diagnostic of CxHD, which is known to be limited. Babies with a prenatal diagnostic of CxHD that are delivered in an adequate setting are more likely to receive high quality care and less likely to develop hemodynamic instability and myocardial ischemia.

In addition, a precise anatomic diagnosis is mandatory for an adequate preoperative management, and can help clinical decision making on drugs and dosing, oxygen supplementation, and need for mechanical ventilation.

5.3. During surgery

Only a few episodes of myocardial ischemia occurring during surgical procedures can be attributed to the procedure itself. When the procedures involve repositioning of the coronary arteries, special attention should be put on the technique, but other factors may be equally important. Minimizing the duration of CPB and aortic cross clamping can also help reducing periods of myocardial ischemia. In particular, the type of cardioplegia and myocardial protection may substantially affect the likelihood of ischemia both during and after surgery. Some authors defend that blood cardioplegia may be superior to crystalloid cardioplegia especially for longer (> 1 hour) myocardial ischemic time [26]. However, the superiority of one type of cardioplegic solution over the others is still matter of debate.

5.4. Postoperatively

Immediately after surgery and within the first 24–48 hours, some strategies may significantly reduce the risk of myocardial ischemia following heart surgery, such as: (a) use of coronary vasodilators, like nitroglycerin, especially when the coronary arteries were surgically repositioned; (b) avoiding hypotension; (c) avoiding hyperthermia; (d) minimizing the use of drugs that increase myocardial oxygen demand; (e) keeping the haemoglobin content in blood of at least 10 g/dL; and (f) avoiding tachycardia and aggressively treating tachyarrhythmias. In the setting of hyperthermia, tachyarrhythmias, or low cardiac output syndrome, a mild hypothermia may result in lower oxygen requirements and lower heart rates with better diastolic filling and improved cardiac output.

5.5. Long-term follow-up

Preventive measures for coronary disease in the long term in patients with CxHD are not different from the general population. Dyslipidaemias, chronic arterial hypertension, diet, exercise, are diabetes, among others, shall be managed accordingly. Screening for coronary disease and myocardial ischemia should probably be more frequent and comprehensive in

people with CxHD but, to date, there is no additional recommendation for these people in order to prevent coronary disease in the adulthood.

6. Future research

Results of paediatric heart surgery have improved through evolution of surgical techniques, CPB, and paediatric cardiac intensive care over the last several years. These efforts are the result of the collaboration of all subspecialties involved in the care of paediatric patients with CxHD. Despite these advances, the field of paediatric cardiac intensive care is still an exciting, demanding, and evolving discipline, necessitating the ongoing commitment of various disciplines to pursue a greater understanding of disease processes and how to best go about treating them [84].

However, it is very important detect and evaluate the degree of myocardial injury as soon as possible after the operative procedure, in an attempt to clarify possible mechanisms involved in the development of ischemic heart disease in children with CxHD, aiming to discuss potential strategies of the prevent this disease [85].

Future research should focus on molecular mechanisms of myocardial injury, including ischemia-reperfusion injury and the systemic inflammatory response. Clinical trials comparing different myocardial protection strategies and anti-inflammatory drugs are strongly needed. In addition, individualized care based on genetic profiles and the presence of polymorphisms may also contribute to better outcomes.

7. Conclusions

In conclusion, myocardial ischemia following paediatric heart surgery for CxHD is an important issue, probably under diagnosed by physicians, which can lead to catastrophic consequences shortly after surgery or in the long term. The number of people with CxHD reaching adulthood is increasing, and knowing the number of patients with CxHD who were born, who are still alive, and who are reaching adulthood at any given time is required for the adequate allocation of care. These patients are at an increased risk of chronic coronary artery disease and myocardial ischemia. A better understanding of the underlying pathophysiology and the development of screening tests and prophylactic and therapeutic interventions deserve special attention from physicians and researchers.

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