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Review

The implication of coronary artery malformations and congenital heart disease on cardiomyopathy

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ABSTRACT

Coronary and congenital heart malformations contribute to and overlap with clinical cardiomyopathy. As cellular mechanisms and gene associations are better understood, overlap is becoming apparent between cardiomyopathies such as left ventricular non-compaction, hypertrophic cardiomyopathy and congenital heart disease. In current studies and registries, patients with clinical overlap are excluded limiting our understanding of the synergy of disease. We review contributing lesions and discuss genetic contributions to overlapping disease.

1. Introduction

Acquired cardiomyopathies have a wide variety of etiologies including congenital heart malformations. In most cases where the coronary arteries are the cause of cardiomyopathy, the pathophysiology is related to atherosclerosis, which results in subsequent ischemia. A small fraction, however, is attributable to congenital abnormalities of coronary artery anatomy. These malformations can cause cardiomyopathy either by ischemic or volume-overload mechanisms and should remain in the differential diagnosis when investigating a new cardiomyopathy.

Primary cardiomyopathies are diagnosed in the absence of structural cardiac lesions. The literature on primary cardiomyopathy generally excludes patients who have concomitant structural lesions and vice versa. Although this exclusion generates homogenous cohorts with fewer confounding variables for each phenotype, it obscures any overlap between them.

Here, we describe the mechanisms by which aberrant coronary artery anatomy can result in cardiomyopathy and discuss the potential genetic overlap between cardiomyopathy and congenital heart disease. These two disease groups must be considered in concert so that the full impact of their structural and functional relationships can be understood and new therapeutic approaches can be developed.

2. Anomalous coronary arteries

An anomaly is an anatomic form occurring in less than 1% of an unselected general population [1]. Angiographic and autopsy series estimate the incidence of coronary artery anomalies in the general population to be 1% [2–5]. The proportion of these anomalies that are pathogenic, however, is unknown. A pathologic anomaly is one with a mechanism capable of causing inadequate blood flow to the dependent myocardium.

The gold standard for detecting and characterizing coronary artery anomalies has been angiography. However computed tomography and magnetic resonance imaging have also demonstrated good performance characteristics in detecting anomalous coronary arteries and in delineating their course [6–10]. These newer modalities have the benefit of being non-invasive and providing omnidimensional images of the coronary arteries and their adjacent structures. Transthoracic echocardiography is limited as a screening method. Although it allows the origins of the coronary arteries to be visualized in more than 98% of children and adolescents, poor acoustic windows and aortic calcification make visualization impossible in almost 10% of adults, despite highly trained operators [11].

The clinical relevance of a coronary artery anomaly depends on the likelihood that it will cause an adverse outcome. Variant coronary anatomy has been associated with sudden death as well as with secondary cardiomyopathies. Secondary cardiomyopathies, in turn, can present throughout life and be caused by ischemia or volume overload, depending on the anatomy involved. The pathologic consequences of some abnormalities remain controversial. However surveillance and potentially interventions are warranted in a few specific anatomies, which we review here.

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2.1. Anomalous origin of a coronary artery

An anomalous origin of the left or right coronary arteries results in potentially severe pathology when the aberrantly originating artery courses between the great vessels or intramurally, within the aortic wall. In a recent analysis of sudden death in college athletes, an anomalous coronary artery origin was second only to hypertrophic cardiomyopathy as a cardiovascular cause of death (21/47 and 8/47, respectively) [12]. The mechanism is not completely understood, but is postulated to be related to decreased blood flow in the aberrant vessel resulting from a slit-like ostium and compression by the exercise-induced dilation of the sinus of Valsalva, leading to myocardial infarction.

The incidence of anomalous coronary artery origin is between 0.64% and 0.84% in screening studies [13,14] and 1% in autopsy studies of patients with congenital heart disease [15]. The presenting symptom may be sudden death. If symptoms do occur, they are most commonly syncope or chest pain. In one autopsy series of athletes succumbing to sudden death, the 10 patients who did experience pre-monitory symptoms had entirely normal cardiac investigations, including 12-lead electrocardiograms (in 9), stress testing (in 6), and echocardiography (in 2) [16]. Indeed, an adolescent male participant in a pediatric echocardiographic screening study died of an undiagnosed coronary artery malformation, highlighting the diagnostic limitations of this modality [17].

Although treatment recommendations for serendipitously diagnosed anomalous coronary artery origins in asymptomatic patients have not been standardized, surgical repair is generally recommended for any person with symptoms concerning ischemia. Surgical options include unroofing of an intramural segment, coronary reimplantation, coronary artery bypass grafting, and coronary ostioplasty. In the largest cohort of patients yet described, the Congenital Heart Surgeons Registry, 53% (104/198) of patients underwent corrective surgery at a mean age of 12.6 years old [18]. Outcome data from the registry are not yet available, but in smaller cohorts coronary arteries remained patent and symptoms had not recurred at a mean follow-up of 1–2 years [19,20].

2.2. Anomalous origin of the left coronary artery from the pulmonary artery

The youngest presentation of cardiomyopathy secondary to anomalous coronary anatomy occurs when the left coronary artery originates from the pulmonary artery. In fetal life and immediately after birth, pulmonary artery pressures are systemic and the anomalous coronary artery is well perfused from the pulmonary artery. As pulmonary pressures rapidly drop in the first 7 to 10 days of life and subsequently continue to decline over the next four months, perfusion is compromised and ischemia occurs [21]. In most cases, there is flow reversal and the anomalous left coronary artery fills from right coronary artery collaterals and drains into the pulmonary artery. Additionally, the decreased pressure in the coronary arteries on the epicardial surface reduces the transmural gradient. The resulting ischemia leads to dilation and hypertrophy and thus to an even greater demand–supply mismatch.

The incidence of this anomaly is estimated to be 1 in 300,000 live births, although this estimate came from a single center in 1959 [22]. An autopsy series of patients with congenital heart disease placed the incidence at 0.42% [15]. Most cases present at about eight weeks of life; however, two factors have been proposed to explain how the degree of left ventricular ischemia is mitigated and potentially delays presentation until adulthood. The first factor is extensive interarterial collateral circulation with favorable hemodynamics, such that collateral flow to the anomalous left coronary artery empties into the distal circulation and not into the low-resistance pulmonary artery. The second factor is a right coronary artery that supplies a larger-than-normal area of myocardium, thus reducing the proportion of the myocardium that depends on the anomalous left coronary artery.

In infancy, the presentation of heart failure manifests with tachypnea, failure to thrive, pallor and distress with feeding. However, older children and adults may present with symptoms of chest pain or shortness of breath. On clinical exam, most patients have a continuous murmur and some may have ventricular arrhythmia, mitral insufficiency from papillary muscle scarring or mitral valve ring dilatation.

Treatment is focused on surgical repair by creating two-coronary ostia from the aorta. In most cases concomitant mitral valve repair is not required unless mitral valve regurgitation is severe. Mortality in children is less than 10% in the literature [23,24]. Post-operatively, survivors have improved ejection fraction, reduced ventricular dilation and rates of arrhythmia, and less mitral regurgitation.

2.3. Coronary fistulae

Most commonly symptomatic in adulthood, coronary fistulae are coronary artery branches that terminate into a cardiac chamber (coronary-cameral fistulae), low-pressure vein (coronary-vascular fistulae), or other structure without passing through the myocardial capillary network, usually creating a left-to-right shunt. Overt heart failure can occur when the shunt is large enough to cause chronic volume overload. Less commonly, ischemic cardiomyopathy can occur when coronary blood flow distal to the fistula is markedly reduced. This steal physiology is believed to be responsible for infarction in patients without concomitant atherosclerosis [25].

The incidence of angiographically diagnosed coronary fistula is estimated to be 0.2% of the population [26]. The most common presenting symptoms are in the heart failure spectrum: dyspnea, chest pain, and angina [27,28]. Symptoms are more common and more severe with age and occur more frequently in fistulae that originate in the right coronary system [27]. About 80% of patients have a murmur with both systolic and diastolic components, heard best in the left mid-sternal region.

Treatment with surgery or catheter embolization is indicated when patients are symptomatic [29]. Treatment for asymptomatic patients is controversial. Early closure has been advocated because of the increased likelihood of symptoms with age and more frequent adverse events associated with older age at closure [28,30]. Other studies have advocated expectant management with routine Doppler echocardiography because of the proportion of patients who remain asymptomatic and the possibility of spontaneous closure [29,31].

3. Congenital heart disease

Congenital heart disease encompasses a variety of functionally important structural abnormalities of the heart or thoracic great vessels. The incidence of congenital heart disease ranges from 6000 to 10,500 per million live births, with cyanotic lesions occurring in 1000 to 1500 per million live births [32].

Traditionally, congenital arrhythmias and cardiomyopathies have not been included in these figures and have been considered separate conditions because of their distinct clinical presentations. However, shared genetic mutations (Table 1), molecular pathways, and hemodynamic structure–function relationships imply some degree of overlap in etiology between these disease categories.

3.1. Transcription factors common to structural and functional disease

A transcription factor is a protein that binds to a specific DNA sequence and promotes or inhibits its transcription into RNA; thereby regulating gene expression. Genes that encode transcription factors have been associated with abnormalities in cardiac structure. For example TBX1 contributes to the cardiac abnormalities of DiGeorge syndrome and TBX5 results in the septation defects of Holt–Oram syndrome. The downstream effects of cardiac transcription factors have implications for both structural defects as well as myocardial function.