ADITUM
Enrich your Research

Clinical Cardiology Interventions

Review Article

Pathologies of the Cardiovascular System

Elizaveta I Bon *, Maksimovich N.Ye, Kazlouski D.A
Daswani Dental College affiliated to Rajasthan University of Health Sciences, India

Article Info

Received: January 25, 2025
Accepted: February 10, 2025
Published: February 15, 2025

***Corresponding author:** Elizaveta I Bon, Daswani Dental College affiliated to Rajasthan University of Health Sciences, India.

Citation: Bon E.I, Maksimovich N.Ye, Kazlouski D.A, (2025), Pathologies of the cardiovascular system, J Clinical Cardiology Interventions, 5(1); DOI: 10.31579/2641-0419/051

Abstract

Purpose of the work: to study in detail the pathologies of the cardiovascular system in children and adults Heart failure is a syndrome of symptoms and signs caused by cardiac dysfunction, resulting in reduced life expectancy. To establish the diagnosis of heart failure, the guidelines of the European Society of Cardiology require the presence of symptoms and signs, objective evidence of cardiac dysfunction (preferably by echocardiography) and, in case of remaining doubt, a favourable response to treatment directed at heart failure. Numerous compensatory mechanisms are involved in supporting the heart in heart failure, including activation of the neurohormonal system.

Keywords: pathologies; cardiovascular system; heart failure

Introduction

Heart failure is a syndrome of symptoms and signs caused by cardiac dysfunction, resulting in reduced life expectancy. To establish the diagnosis of heart failure,the guidelines of the European Society of Cardiology require the presence of symptoms and signs, objective evidence of cardiac dysfunction (preferably by echocardiography) and, in case of remaining doubt, a favourable response to treatment directed at heart failure. Numerous compensatory mechanisms are involved in supporting the heart in heart failure, including activation of the neurohormonal system. An increase in natriuretic peptide (especially B-type natriuretic peptide) is considered the hallmark of heart failure. The diagnosis of heart failure, especially when based solely on symptoms and signs (as is often the case in primary care), is difficult. Many patients suspected of having heart failure are simply found on further investigation to be obese, have poor physical fitness, have pulmonary disease or arechaemia. There is accumulating evidence that normal natriuretic peptide levels and a normal electrocardiogram should lead to a reconsideration of the diagnosis of heart failure. Heart failure is usually a chronic condition (chronic heart failure - CHF), in which episodes of worsening symptoms and signs may occur that may require hospitalization or more frequent visits to the physician (decompensated CHF). Alternatively, heart failure may present acutely, with the onset of severe symptoms and signs within 24 hours. Acute heart failure presents clinically in several forms: acute pulmonary oedema secondary to cardiac dysfunction cardiogenic shock, usually in the context of an acute coronary syndrome, characterized by hypotension, oliguria, and peripheral vasoconstriction acute worsening (decompensation) of CHF. Genetic factors are associated with the pathogenesis and occurrence of various heart defects, and about 400 genes are involved in congenital heart disease. However, CHD is associated with various forms and multiple causes, such as external factors that can directly or indirectly affect the development of the fetus at the embryonic stage. These factors are associated with the use of thalidomide, retinoic acid, maternal alcohol consumption, hypoxia, other

During pregnancy, internal maternal factors can influence the development of CHD, such as gestational diabetes, maternal obesity, phenylketonuria, viral infection and hyperthermia. In underdeveloped countries, access to health care is unstable and reveals difficulties in various aspects such as poverty, insecurity, housing problems, education and family understanding of the disease, immigration, access to food and barriers in terms of movement and transportation. All these factors affect the clinical outcomes of people suffering from cardiovascular diseases, whether adults or children. Congenital heart disease affects not only the lives of children, but also those of their caregivers and family members. The range of repeated invasive treatments, surgeries and increased risk of death lead to stress and mental health problems. Parents of children with CHD tend to have less time for rest, have trouble maintaining a job and are overworked, which leads to social isolation and financial problems for the family. Comprehensive care for children with congenital heart disease has been organized since 2017 within the framework of a federal project of the Brazilian Ministry of Health. The project aims to expandcare of children with CHD, increasing the care of these children by 30% per year, with more than 3,400 procedures, for a total of about 12,600 procedures per year, with a direct impact on reducing neonatal mortality.

Given the evolution of the diagnosis and treatment of CHD, there is no need for a single specialist with specialized training, but rather for different specialists with different training and specialties to work together in a complementary, integrated and simultaneous way of caringfor children with this condition. These specialists must develop an active partnership with the public health system, leading to greater team training to ensure early diagnosis and appropriate treatment. Nurses are present at different stages of a child's life, including at birth, but the approach to CHD is poor in their basic training as nurses, as well as in their professional practice, and there is a lack of continuing education offerings for the care of children with CHD. Professionals caring for newborns with CHD should be preparedsystematically and continuously through their participation in training and health education with family members. However, even if the nursing approach takes into account the systematization of nursing care (SNC), specific knowledge about caring for children with CHD should be continuously improved. In addition, family members caring for children with CHD should better understand the disease and develop skills to help with home care after discharge from the hospital.

Acute heart failure

Acute heart failure (AHF) is a syndrome defined as new onset (de novo heart failure (HF)) or worsening (acute decompensated heart failure (ADHF)) of HF symptoms and signs, mostly related to systemic congestion. In the presence of underlying structural or functional cardiac dysfunction (chronic in ADHF or undiagnosed in de novo HF), one or more precipitating factors may cause AHF, although occasionally de novo HF may result directly from the onset of new cardiac dysfunction, most commonly an acute coronary syndrome. Although resulting in similar clinical manifestations, the underlying cardiac disease and precipitating factors may differ significantly, and hence the pathophysiology of AHF is highly heterogeneous. Left ventricular diastolic or systolic dysfunction results in increased preload and afterload, which in turn leads to pulmonary congestion. Fluid retention and redistribution lead to systemic congestion, ultimately causing organ dysfunction due to hypoperfusion. Current treatment of AHF is largely symptomatic, focusingon decongestant medications, at best tailoredto the initial hemodynamic statuswith little consideration of the underlying pathophysiology. As a consequence, AHF remains associated with high mortality and rehospitalization. There is an unmet need for greater individualization of in- hospital care, including treatments targeting causative factors and continuation of treatment after hospital discharge to improve long-term outcomes.

Heart failure (HF) is a chronic and progressive clinical syndrome caused by structural or functional cardiac abnormalities demonstrating either reduced (HF with reduced ejection fraction (HFrEF)) or preserved (HF with preserved ejectionfraction (HFpEF)) left ventricular ejectionfraction (LVEF)[1]. Cardiac dysfunction results in elevated cardiac filling pressures at rest and with exercise.[1] Symptoms of HF include dyspnea (shortness of breath) and fatigue, often accompanied by typical physical signs such as pulmonary crackles (abnormal crackling sounds), peripheral edema, or dilated jugular veins.[1] Significant reductions in short-term mortality in patients with several cardiac diseases (especially acute coronary syndromes and congenital heart defects) and corresponding improvements in long-term survival in patients with HFrEF (as a result of widespread use of effective oral therapies and disease-modifying devices), coupled with several demographic changes such as increased life expectancy, have dramatically increased the number of patients living with HF. In developed countries, HF has become a significant public health problem, affecting 2% of the adult population, and the number of HF-related hospitalizations has tripled since the 1990s.[2]

Acute HF (AHF) is defined as new or worsening symptoms and signs of HF and is the most common cause of unplanned hospitalization in patients aged >65 years. Clinically, we distinguish de novo HF—in which symptoms occur in patients with no previous history of HF—from acute decompensated HF (ADHF)—in which symptoms worsen in patients with previously diagnosed chronic HF. This classification provides little additional information regarding the pathophysiology of AHF but has mainly clinical implications (de novo HF requires a more extensive diagnostic workup to evaluate the underlying cardiac pathology than ADHF). Because HF is a chronic and progressive disease, most hospitalizations are due to ADHF rather than de novo ADHF[3,4]. The clinical presentation of AHF is characterized primarily by symptoms and signs related to systemic congestion (i.e. accumulation of extracellular fluid caused by elevated filling pressures of the two ventricles of the heart)[5,6]. Accordingly, initial treatment in most patients with AHF consists of noninvasive ventilation and intravenous diuretics, given alone or, particularly in Europe and Asia, in combination with short-acting vasodilators.[7] Only a small number of patients with AHF develop cardiogenic shock, a critical condition characterized by clinical evidence of peripheral tissue hypoperfusion; cardiogenic shock has a ten-fold higher in-hospital mortality than AHF without shock and requires specifictreatment.[8,9] In contrastto significant improvements in the treatment of chronic HFrEF, AHF remains associated with poor outcomes, with 90-day readmission rates and 1-year mortality rates reaching 10–30%.[10,11] Although AHF is not a specific disease but a general clinical picture of various heterogeneous cardiac anomalies, most patients still receive only

decongestant medications, at best tailored to their baseline hemodynamic status, without considering the underlying pathophysiological features. This approach may have contributed to the emergence of many neutral or negative clinical trials evaluating the effect of decongestant treatments on survival and the persistence of poor outcomes in AHF. Thus, thereis an unmet need for greater individualization and continuation of treatment after hospital discharge to improve long-term outcomes.

Epidemiology Prevalence

There are several reasons why global data on AHF are very limited. Differential coding of the syndrome, combined with subtle differences in case definitions, do not lend themselves to simple regional comparison. The International Classification of Diseases (ICD) classifies AHF and chronic HF as intermediate conditions rather than as leading causes of death. The ICD also does not distinguish between de novo HF and ADHF as causes of hospitalization. Global data on the proportion of HFrEF and HFrEF as leading causesof AHF are lacking. Nationalprevalence data on AHF or chronic HF in low- and middle-income countries are not available. All HF registries for these regions are based on hospital registries, which include only patients hospitalized with AHF, without distinguishing de novo HF from ADHF. Data from some key registries have been recently summarized [12], but the focus is on etiology, risk factors, sociodemographic profile, and mortality. The INTER-CHF study, one of the largest registries, reported on 5823 patients with CHF from 108 centers in six geographic regions.[13] Overall mortality at 1 year was 16.5%, with highest mortality in Africa (34%) and India (23%), approximately average mortality in Southeast Asia (15%), and lowest mortality in China (7%), South America (9%), and the Middle East (9%).[13]

Risk factors

A systematic review of global HF risk factors found that coronary heart disease was the major contributor to AHF hospitalization in >50% of patients in high-income regions and in Eastern and Central European regions.[14] In high-income regionsof Asia Pacificand Latin America,coronary heart disease accounted for 30–40% of hospitalizations.[14] While in sub-Saharan Africa it was<10>50% of cases) associated with significant pericardial effusion, but typically results in AHF in only 1–5 of every 10,000 infected individuals.[15] However, Chagas disease remains common in Latin America, causing HF in up to 10% of patients. In high-income regions with correspondingly high Human Development Index scores (a statistical tool that takes into account life expectancy, education, and income), patients with AHF typically have a mean age at disease onset of >75 years, whereas in other regions, such as Latin America and sub-Saharan Africa, the mean age of patients with AHF is two decades younger.[13] This difference may be due to poorly treated hypertension, coronary heart disease, and late-diagnosed rheumatic heart disease leading to the onset of HF in younger age groups. In addition, there are differences in gender distribution between regions; for example, rheumatic heart disease generally affects women more often than men.[16,17] and peripartum cardiomyopathy is particularly common in Africa.[18] Because the obesity epidemic also disproportionately affects women, hypertensive heart disease leading to HF is typically more common in women than in men.[13]

Mechanisms/pathophysiology Pathophysiological mechanisms of AHF

An underlying structuralor functional conditionof the heart is a prerequisite for AHF and includes many different acute (e.g. myocardial infarction) or chronic (e.g. dilated cardiomyopathy and ischemic heart disease) cardiac pathologies. The underlying cardiac disease leads to the activation of several pathophysiological pathways (initially adaptive responses that become maladaptive over time) that counteract the negative effects of HF on oxygen delivery to peripheral tissues, but such pathways may also ultimately cause systemic overload, ventricular remodeling, and organ dysfunction.[19] In addition, some acute diseases may act as precipitating factors and cause AHF either by directly impairing diastolic and/or systolic cardiac function or by further exacerbating systemic overload.[19] Systemic congestive response greatly influences the clinical presentation in most patients with AHF and is an important factor in the multiorgan dysfunction that occurs in AHF. The pathophysiology of AHF is heterogeneous, as it is strongly influenced by the nature of the underlying cardiac disease. It is perhaps not surprising, therefore, that responses to treatment may vary and that different patients may respond best to different treatment strategies that depend on the underlying pathophysiology.

Acute changes in cardiac function, mainly deterioration of left ventricular (LV) diastolic function, which in turn leads to increased LV filling pressures and pulmonary congestion, can lead to AHF[20]; an example of such sudden changes is acute myocardial ischemia. Several pathophysiological mechanisms underlie the relationship between ischemia, LV systolic and diastolic dysfunction, and pulmonary congestion. LV contraction relies heavily on oxidative energy generation, and ischemiatherefore causes systolicimpairment, leading to increases in LV residual end-diastolic volume and filling pressures. LV filling typically occurs in two phases: an early rapid phase that relies heavily on rapid myocardial relaxation, and a later phase that relies on left atrial contraction and the atrial-to-ventricular pressure gradient, which in turn is influenced by LV physical properties (e.g., stiffness). Myocardial relaxation is also an active, energy-consuming process that involves the removal of cytoplasmic calcium, mainly by reuptake into the sarcoplasmic reticulum by the sarcoplasmic reticulum Ca2+ ATPase (SERCA) pump and partly by extrusion across the cardiomyocyte plasma membrane. LV end-diastolic properties depend on residual LV end-diastolic volume, structural changes (eg, fibrosis), and extremely slow relaxation. Decreased oxidative ATP generation in cardiomyocytes with the onset of severe acute ischemia rapidly impairs myocardial relaxation, thereby affecting early LV filling and further increasing filling pressures. The presence of any concomitant conditions in which relaxation is already impaired or LV end-diastolic stiffness is increased will increase the likelihood of AHF. Conditions in which LV end-diastolic stiffness may be increased (and hence also conditions with an increased risk of ischemia-induced AHF) include chronic LV systolic dysfunction with increased LV end-diastolic volume and structural fibrosisand/or hypertrophy, both of whichmay result from diabetes mellitus, chronic hypertension, chronic kidney disease, chronic aortic stenosis, and aging.[21] LV filling may also be impaired by the sudden onset of atrial fibrillation with concomitant loss of atrial contraction, which can substantially increase filling pressures in the presence of pre-existing diastolic dysfunction. For example, severe mitral stenosis (which is a common manifestation of rheumatic heart disease) is a

type of diastolic dysfunction due to a valve abnormality rather than LV structural disease, and it can also cause atrial fibrillation, thereby increasing the risk of triggering AHF.

Clinical presentation.

Symptoms and signs related to systemic congestion characterize the clinical presentation of patients with AHF. The most common symptoms include dyspnea during exercise or at rest, orthopnea, fatigue, and decreased exercise tolerance; symptoms are often accompanied by clinical features such as peripheral edema, jugular venous distension, the presence of a third heart sound (known as an S3 gallop, an early diastoliclow-pitched sound that may be present in various hemodynamic states and may represent cessation of rapid left ventricular filling), and pulmonary crackles.[22] In patients with chest discomfort, differentiation between AHF and acute coronary syndrome may be difficult. Symptoms and signs related to peripheral hypoperfusion, such as cold and clammy skin, altered mental status, and oliguria, characterize cardiogenic shock. Cardiogenic shock, as well as respiratory failure, myocardial infarction, and arrhythmia, should be rapidly excluded during the initial triage of patients admitted with suspected AHF, as these conditions require an appropriate level of monitoring and specific treatment.[23,24] Conventional criteria for admission to the intensive care unit or cardiac surgery unit include instability (heart rate <40>130 bpm, systolic blood pressure <90>25 breaths per minute, peripheral oxygen saturation <90>

Diagnostic testing.

The clinical presentation of AHF is not sensitive and specific enough to confirm or exclude the diagnosis; therefore, additionaltesting is required.[26] Cardiovascular biomarkers play a critical role in the diagnostic process of AHF. Patients with suspected AHF should undergo measurement of plasma natriuretic peptides (eg, brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), or mid-regional pro-atrial natriuretic peptide (MR-proANP)). Although no diagnostic test alone can reliably differentiate AHF from chronic HF, since all cardiovascular biomarkers are abnormal in both patient groups, natriuretic peptides demonstrate high sensitivity for identifying underlying cardiac disease in patients with acute dyspnea. In patients with AHF, circulating natriuretic peptide levels are elevated compared with levels in patients with dyspnea of non-cardiac origin[27–29]; Thus, measurement of natriuretic peptides provides higher diagnostic accuracy than clinical assessment alone.[30] In contrast, dyspnea in patients with normal (or unchanged) circulating natriuretic peptide is more likely to be of non-cardiac origin. Measurement of natriuretic peptides is recommended in patients with suspected AHF on admission.[1,24] In patients with chronically elevated natriuretic peptide levels due to chronic HF, a corresponding increase in circulating natriuretic peptides may indicate AHF. Additional tests, such as echocardiography or other imaging procedures, are required to confirm the diagnosis of AHF in patients with elevated natriuretic peptides.

Quality of life

Patients with AHF and chronic HF experience numerous physical and psychological symptoms that negatively impact their quality of life. Dyspnea, fatigue, dry mouth, orthopnea, sleep disturbance, and difficulty concentrating are common, distressing, and burdensome, and predict decreased quality of life in this population.[31] Depression is more common among patients with HF than in the general population, with at least 20% of patients with HF meeting criteria for major depression.[32] Estimates of the prevalence of depression in the HF population vary widely, from 9% to 60%, and such differences are thought to be largely due to differences in outcome ascertainment methods (i.e., interviews versus self-report questionnaires) and HF severity at the time of assessment.[32,33] HF patients with more severe depression have higher rates of healthcare utilization, hospital readmissions, and mortality.[32,34–36] It can be challenging for clinicians to differentiate symptoms associated with heart failure from those associated with depression, highlighting the urgent need for a pragmatic and standardised approach to assessing quality of life as part of everyday clinical care.

Chronic heartfailure

Healthcare systems worldwide are faced with an ever-increasing need to understand the mechanisms underlying the pathogenesis of chronic heart failure (CHF). There is a wealth of information on the role of inflammatory cells and pathways during acute injury and the reparative processes that are subsequently activated. The various causes that lead to the development of chronic CHF are discussed, and how the sum of the initial inflammatory and reparative responses only sets the trajectory of disease progression. Unfortunately, relatively little is known about the contribution of the immune system once the trajectory is established and chronic CHF is established, which is what most patients clinically present with. Chronic CHF is known to be associated with circulating inflammatory cytokines that can predictclinical outcomes, however, the causal role of inflammation in disease progression has not been well defined, and most clinical trials targeting aspects of inflammation in patients with chronic CHF have been largely negative.

Heart failure (HF) is primarily a clinical diagnosis that develops secondary to systolic and diastolic dysfunction of the left ventricle (LV). Despite significant advances in medical therapy aimed at both preventing the development of HF and treating HF once it has occurred, the prognosis for patients following their first hospitalization is poor. Worldwide, 2% to 17% of patients die during their first hospitalization, with 17% to 45% of deaths occurringwithin 1 year of hospitalization and>50% of deaths within 5 years.[37] Given the staggering burden that chronic HF places on society in terms of not only mortality but also morbidity associated with repeated and prolonged hospitalizations, a better understanding of the pathophysiological mechanisms involved deserves accelerated study.For decades, activation of the neurohormonal and sympathetic systems has dominated research in established HF, both in experimental animals and in clinical patients. Blockade of these pathways has demonstrated significant beneficial effects in various patient groups, particularly in patients with reduced LV systolic function.[38] However, ≈50% of all HF hospitalizations occur in patients with HF with preserved ejection fraction (HFpEF), and unfortunately, none of the demonstrably effective therapies that focus on neurohormonal blockade (eg, angiotensin- converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers) have a beneficial effect in HFpEF.[39,40] Importantly, a common feature of HF with reduced EF (from both ischemic and nonischemic causes) and HFpEF patients is a correlation between elevated serum proinflammatory cytokines and adverse clinical outcomes.[41-44] The magnitude of proinflammatory cytokineelevation in chronicHF is significantly

less than that seen in autoimmune diseases or acute infections, suggesting that low-grade chronic inflammation may be an important factor in the maintenance or clinical deterioration of patients with established chronic HF.[45-47]

Causes of Chronic HF

Important to the discussion of HF is the underlying cause, which defines the mechanisms that drive the development of HF. These can be divided into 4 broad categories. The first is based on traditional risk factors such as ischemic injury, hypertension, and metabolic syndrome (diabetes mellitus, central obesity, and hyperlipidemia), which include the majority of patients with HF.[48,49] The second is genetic cardiomyopathies. The greatest understanding comes from autosomal dominant mutations/familial clusters with rare allele frequencies but major pathophysiological effects (eg, hypertrophic cardiomyopathy), many of which have been modeled in mice.[50-52] The third cause is mechanical, due to valve dysfunction, most commonly aortic stenosis in the elderly, resulting in LV pressure overload that initially leads to cardiac hypertrophy but may eventually progress to LV dysfunction, which has also been modeled in mice.[48,49] Common to these first three causes is that the initial injury was not immune, and immune activation was a secondary response. The final category is immune, which includes autoimmune and infectious (viral and bacterial) triggers, where the innate and adaptive immune systems are activated to coordinate the primary response.[53,54] Each of these causes contributes to the development of both HF with reduced EF and HFpEF.

Myocarditis: A Viral Perspective

Defending the host against invading pathogens is a major responsibility of the immune system during the acute stages of infection. Viral infection is an importantdriver of NICM, and the immune response (innate and adaptive) is activated during acute infection. Importantly, there is compelling clinical evidence that we are underestimating the clinical impact of viral myocarditis and virus-induced cardiomyopathy. Coxsackie B virus is the most prominent primary infectious agent associated with viral myocarditis; however, parvovirus and adenovirus have become more common over the past decade. Viral genomes can be detected in the myocardium of approximately 64% of patients with dilated cardiomyopathy, indicating a high prevalence of infection. T cells are required to clear virus-infected host cells, and nearly half of patients with dilated cardiomyopathy have cardiac T cell infiltrates, indicating a chronic inflammatory process. Interestingly, patients who resolve myocardial viral infection spontaneously improve LV function, whereas those with persistent virus in the myocardium gradually deteriorate LV function. Antiviral therapy may improve LV function; however, this is likely to depend on the specific viral genome. Clinical trials have yielded mixed results but suggest that there may be some clinical improvement in patients with persistent viral genome detection. Interestingly, although there are clear associations between the presence of viral genomes in the myocardium and cardiac dysfunction, the presence of the virus does not predict whether an individual will develop chronic HF. It is unclear why a subset of patients with severe viral myocarditis and LV dysfunction develop chronic HF, while others recover completely. However, it has been hypothesized that host susceptibility plays a role. Unfortunately, trials using immunosuppressive therapy have been ineffective in patients with features of chronic myocarditis, and few have used reliable genotyping to separate chronically infected from uninfected subjects.

Myocarditis: Circulating Autoantibodies and an Autoimmune Perspective

The clinical association between autoantibodies and chronic HF has been known for decades, suggesting that host antigen recognition and antibody deposition in a subset of patients may induce and/or maintain inflammation and thus contribute to HF. Autoantibodies targeting intracellular cardiomyocyte antigens such as cardiac troponin I, cardiac actin, Na/K ATPase, β1 receptor, and muscarinic M2 receptor are elevated in patients with ischemic or NICM, as well as during viral myocarditis. It is conceivable that corticosteroids used to treat conditions in which autoantibodies are causative, such as traditional autoimmune diseases (e.g., lupus), would have a similarly dramatic effect in these cases of HF. However, as mentioned above, trials using corticosteroids in chronic HF have had little success and autoantibodies have been detected in patients without heart disease, suggesting that an additional level of specificity may be needed to demonstrate whether autoantibodies are causative factors in chronic HF. Next-generation detection systems, such as for the β1 receptor, may help facilitate the detection of true autoantibodies and reduce the rate of false positives.

Complete transposition of the great arteries

Patients with d-TGA continue to present significant treatment challenges for physicians despite advances over the past several decades. Early attempts at great artery switch repair were essentially limited by the difficulties of coronary artery reimplantation. It was not until the conceptof coronary "buttons" was developed that the arterialswitch procedure becamea viable alternative to the atrial switch procedures developed by Mustard and Senning and the intracardiac repair developed by Rastelli. Although interest in the variations in coronary anatomy in patients with d-TGA has long existed, the development of arterial switch repair prompted a large body of literature in the 1970s and 1980s on the topics of nomenclature, anatomy, risk stratification of variants, imaging for preoperative variant recognition, and surgical maneuvers to manage specific variants. Most commonly, patients with d-TGA have a right anterior aorta relative to the pulmonary artery. This position, the aorta directly to the right ('side by side') or directly in front of the pulmonary artery,accounts for the vast majorityof patients; a right posterioror left anterior aorta is rare. They usually originate at the midpoints of the inverted sinuses, but may be ectopic within or above the sinus and may rarely arise from the non-inverted sinus. Commissure displacement or bicuspid valve may contribute to a variant origin (for a detailed discussion of commissure displacement and displacement and its surgical implications. With an ectopic or commissural origin, there is a risk of a slit-like origin and an oblique proximal course that may be in the vessel wall. These intramural segments are seen in about 3% of patients and are usually (but not always) associated with interarterial courses. In cases of right anterior aorta, about two-thirds of patients will have 2 coronary arteries from the reversed sinuses with typical branching and distribution patterns (the so-called "regular" coronaryarteries. In the next most common variant,the RCA from the right posterior reversed sinus gives off a circumflex that runs along the retropulmonary course. Beyond this, the variations are almost endless, although as noted, 9 types account for 95% of cases. It should be noted that in patients with

side-by-side main arteries arteries, there is an increased incidence of unusual patterns, including "inverted" coronary arteries.

"Inverted" coronary arteries, single (or mixed common trunk) coronary artery, and intramural coronary artery (oblique segment in the aortic wall) have been identified as significant risk factors for the procedure. Less well-defined risk factors may include a course between great arteries (called "interarterial" course), short distance to 1st branch, ectopic origin in sinus, origin from nonfacing sinus, and malposition of facing commissures. As experience increases and the procedures are concentrated in fewer centers, these risk factors may decrease. The recent recognition of a 10-15% incidence of late coronary complications after arterial switch procedures has further stimulated interest in coronary arteries. The concepts of ingrowth of epicardial cellular cords into the adjacent great artery and their subsequent development into the lumen [38,39] have been discussed in earlier presentations. The postulate that epicardial vessels contact the aortic sinus to which they are closest would explain the usual coronary anatomy observed in patients with d-TGA who have a typical right anterior aorta: morphologically, the right coronary artery communicates with the right posterior sinus, which is closest to the right atrioventricular groove, and the left coronary artery communicates with the left posterior sinus, which is closest to the anterior interventricular groove and the left atrioventricular groove.

Tetralogy of Fallot

In angiographic, surgical, and autopsy series, coronary artery anomalies have been reported in 2% to 9% of patients with tetralogy of Fallot. The anomalies cover a spectrum of origin, course, and distribution, but 2 are of particular importance: those in which a vessel crosses the RV outflow tract and those in which a coronary artery contributes to the pulmonary blood flow, particularly in patients with pulmonary atresia of the tetralogy. In the vast majority of tetralogy patients with coronary anomalies, some component of their LAD territory bloodsupply comes from the RCA via a vessel that crosses the RV free wall at variable distances below the pulmonary annulus, or they have a single right or left coronary artery (mixed common trunk) and therefore have the potential to have a crossing vessel. All such crossing vessels (but especially those buried in muscle or epicardial fat) are vulnerable during surgical reconstruction of the outflow tract, the location of which sometimes requires placement of a conduit rather than a transannular patch.

The postulate that the epicardial vessels contact the aortic sinus to which they are closest provides a clear explanation for how these crossing vessels develop: clockwise rotation of the aortic root when viewed from the apex, or side-by-side arrangement of the great arteries, places the right anterior sinus in a higher, more leftward, and anterior position, closer to the developing LAD. 44 This postulate may also explain the connection of the RCA with the right anterior sinus (with its proximal course crossing the RV outflow tract) in those rare patients with a tetrad with a left anterior aorta relative to the pulmonary artery. However, as discussed in relation to patients with d-TGA, this postulate does not easily explain the anatomy in those patients who, despite the right posterior aorta, still have a vessel crossing the RV outflow tract, nor does it easily explain the presence of separate coronary arteries (mixed common trunk). In patients with tetrad pulmonary atresia, various systemic sources contribute to the pulmonary blood flow, most commonly the patent ductus arteriosus. In those who receive some or all of their pulmonary blood supply via the aorta or other splanchnic arteries, the coronary arteries contribute to the flow in about 10% of cases. Very rarely, a coronary artery may be connected to a pulmonary artery, thereby serving as the main or sole source of blood flow.

Congenitals correstedtransposition of the great arteris

In clinical practice, patients with CC-TGA (atrioventricular and ventriculoarterial discordance) are a rather heterogeneous group, frequently having ventricular septal defects, AV valve abnormalities, semilunar valve abnormalities, tetralogy-type malformations including pulmonary atresia, and twisted or hypoplastic ventricles. At first glance, these patients may appear to have odd coronary anatomy, not only because the ventricular-to-trunk relationships (left anterior aorta) are different from those to which most angiographers are accustomed, but also because patients with atrial situs solitus often have dextrocardia, and a small number have inverted atria. Coronary artery anatomy has proven to be clinically relevant in a numerically significant subset of patients with tetralogy malformations requiring RVOT reconstruction. Recent interest in the double switch procedure has added further relevance to coronary anatomy. Typically, 2 vessels arise from facing sinuses, and the postulate that epicardial vesselscontact the aortic sinus to which they are closest also explains this. Anomalies of coronary origin and proximal course, such as a common mixed trunk (single coronary artery) and vessels crossing the RVOT, are observed. In addition to its origin and proximal course, it has been observed for many years that coronary artery morphology "follows" ventricular morphology. Thus, when there is a left anterior aorta, the coronaryartery connecting to the rightanterior sinus has an epicardial distribution morphologically of a left coronary artery, while the coronary artery connecting to the left posterior sinus courses in the left AV groove and supplies the RV and posterior interventricular septum, as the RCA would. This principle has proven useful not only for determining ventricular morphology but also for determining ventricular size or the plane of the interventricular septum in patients with hypoplastic or twisted ventricles. The development of epicardial and myocardial coronary arteries involves a predictable migration of developing vessels along the planes of the atrioventricular and interventricular grooves. If this predictable migration persists regardless of the orientation of these planes or the size of the ventricles, then this migration largely explains the anatomical observation that coronary artery morphology "follows" the ventricle and represents another example of the interaction between congenital heart disease and coronary artery morphology.

Coronary arteryanomalies

Coronary artery anomalies are a well-recognized feature of many cardiac malformations and have been catalogued in a number of reviews. This review focuses on 1) the interaction between congenital heart disease and coronary morphogenesis, examining how part of embryology corresponds to nature's experiments encountered in clinical practice; and 2) the impact of coronary anatomy on patient management. This section uses as examples pulmonary atresia with an intact ventricular septum, complete and congenitally corrected transposition of the great arteries, and tetralogy of Fallot.

Imaging and reporting coronary anatomy

While angiography has been the mainstay of detailed coronary imaging in patients with congenital heart disease. [55], sonography

has played an important role, especially in children with d-TGA4,5. Cross-sectional imaging with both gated computed tomography (CT) and magnetic resonance imaging (MRI) is increasingly being studied.[56-58] Whichever imaging technique is chosen—the decision is usually made depending on the treatment problem being addressed— imaging can provide information such as the interrelationships of the great arteries, the number of coronary ostia and their location in the sinuses, proximal courses of the vessels, branching patterns, and areas of blood supply. Whether the physician uses AP views during angiography [59,60] or cross-sectional imaging, he or she needs a good understanding of the norm to recognize some subtle abnormalities, such as whether a vessel courses intramuscularly rather than more typically epicardially; this cannot be overemphasized.

Once the coronary arteries have been visualized, communication becomes an important issue. Many systems have been proposed to denote the coronary anatomy in patients with valvular heart disease, which is discussed elsewhere, [55,61-64] but ours prefers a brief description supplemented by a simple diagram. A brief description might be: "right anterior aorta with normal coronary arteries from the midpoint of the inverted sinuses and without significant commissure displacement." When more detail is needed about the coronary course and distribution, a diagram is used that allows the course and distribution of the myocardiumof each vessel to be represented [65,66].

As an aside, let me note that in everyday clinical practice, the commonly used brief terminology is well understood, although it may be descriptively imprecise. For example, a patient with d-TGA might be described as having "lateral great arteries with inverted coronary arteries." In this case, the coronary arteries themselves are not “inverted” (morphologically, they are designated as left or right depending on their distal course and distribution); rather, their origin and proximal course are the opposite of those typically seen in d-TGA, with the right coronary artery communicating with the left anterior sinus and running along the free wall of the right ventricle (RV) to reach the right atrioventricular (AV) groove, and the left coronary artery communicating with the right posterior sinus and running via the retropulmonary course to reach the left atrioventricular groove.

Pulmonary atresiawith intact interventricular septum.

A striking example of the relationship between malformation and coronary morphogenesis is PA- IVS. This malformation is characterized by complete muscular or membranous obstruction of the RV outflow tract, an intact interventricular septum, an obligatory shunt at the atrial level, and pulmonary blood flow mediated by a patent ductus arteriosus. However, as Freed formulated, this characterization does not do justice to the disorder and is akin to characterizing Da Vinci as "just an artist", since there is enormous morphological and functional heterogeneity, not least in the coronary arteries. These may be normal or grossly abnormal and are a major determinant of outcome, since myocardial perfusion may be partially or entirely dependent on communications between the RV and the coronary arteries ("RV-dependent circulation"). Anomalies of coronary origin, course, and distribution—such as common, mixed trunk, and pulmonary connections— exhibit the same spectrum as that seen in normal hearts.[67,68] In addition, there is an interaction between cardiac malformation and coronary morphogenesis (or vice versa), in which the development of ventriculocoronary arterial communications (VCACs) is accompanied by secondary vascular changes. The development of VCACs in these patients has been discussed elsewhere in these presentations. The incidence of such communications varies in reported autopsy and angiographic series.[67,69,70] The incidence of such communications was approximately 45% in patients for whom data were available in the Congenital Heart Surgeons Study. [70] These communications typically lead to the right coronary artery (RCA) or left anterior descending coronary artery (LAD) (Fig. 2) and are often multiple,[67–69] although they may be to distant coronary branches such as the circumflex or may be single. In addition, the vessels that communicate with VCAC may be dilated.

The coronary arteries involved in VCAC exhibit characteristic histopathological changes of myointimal hyperplasia,[71] which is thought to result from repeated intimal injury by turbulent, high-pressure RV systolic flow mediated through the communications. Indeed, in the vast majority of patients, this process results in profound distortion of the angiographic appearance of the coronary arteries,[68,69] ranging from irregularity to luminal narrowing and frank interruption in half to two-thirds of those with VCAC. Interruptions may be seen anywhere along the length of the affected coronary artery.[67–69] Such proliferative lesions have been found even in the fetus[72] and neonates, as well as in older children, and are thought to progress as long as the coronary arteries are subjected to systemic and suprasystemic pressures generated by the hypertensive RV.[68] It remains unclear whether the absence of the proximal lumen is due to defective ingrowth or lucency of the coronary vessels, occlusion due to late-stage intimal hyperplasia, or all of these.

This coronary arterial anatomy has a profound impact on patient management and outcomes.[70] In those with no communication between the proximal coronary artery and the aorta, or who have severe luminal stenosis or interruption, part or all of the coronary circulation is dependent on perfusion from the RV cavity, the "RV-dependent circulation." In normal hearts, the left coronary arterial flow is predominantly a diastolic event, whereas the right coronaryflow is both systolic and diastolic due to lower transmural pressure. In those with RV-dependent circulation, the diastolic component is reduced because retrograde flow must be under sufficient pressure to overcome both the stenoses and the prolonged isometric ventricular contraction, which produces relatively high wall stress [73]. Worse, blood from the RV cavity must meet the nutritional demands of the hypertrophied and disordered myocardium, which generates systemic or suprasystemic pressure. These patients thus have a substrate for myocardial ischemia, particularly RV subendocardial ischemia. Maneuvers that obliterate the cavity, such as thromboecclusion or tricuspid valve suturing, or that decompress the cavity, such as RV outflow tract reconstruction or valve excision, reduce or eliminate the driving pressure for coronary flow and worsen the ischemia. In patients who have continuity between the aorta, coronary arteries, and RV cavity, there is bidirectional flow in the coronary vessels. A small number of these patients have diastolic outflow into the RV cavity, with ischemia resulting from a steal phenomenon. Maneuvers that decrease RV cavity pressure may worsen the shunt, whereas those that decrease aortic pressure, such as the use of prostaglandins or the creation of a systemic shunt to the pulmonary arteries, may decrease driving pressure. Both options worsen ischemia.

Assessment and guidance for physical activity as part of routine clinical care in patients with congenital heart disease

Advances in surgical, percutaneous, and medical treatments have resulted in an increasing number of patients with congenital heart disease (CHD) surviving into adulthood. Although mortality is declining, these patients often face a number of morbidities that may be related to the presence of residual cardiac lesions and the accumulation of acquired cardiovascular risk factors. Inappropriate lifestyle choices further exacerbate the risk of life-threatening comorbidities, which can be reducedby adopting a healthy lifestyle. Physical activity is important for patients with CHD, and most of its health benefits are achieved not through participation in competitive sports, but through moderate-intensity exercise. For example, frequent and consistent physical activity is associated with improvedskeletal muscle function, immunity, and cognitive and psychosocial well-being. A direct correlation between aerobic exercise and perceived quality of life has also been reported in young patients with CHD. Physical activity is important even from an early age; The lack of effective perception and experience of movement, even from preschool age, may be related to the motor development deficits observed in children with repaired CHD. However, despite these findings, very few patients with CHD receive formal physical activity guidance, and this deficit has implications in clinical practice. Children with CHD are more likely to be overweight compared to their healthy peers, and due to the lack of guidance, some patients may engage in unsafe sports, which may impact their health. A stronger belief or confidence that a person can successfully perform a task using their skills under certain circumstances, in other words, higher so-called "self-efficacy", may be motivating and increase the likelihood of engaging in a particular task. Self-efficacy may also have a significant impact on the approach to physical activity,and this is discussed by Moshovi et al. An examination of the relationship between exercise self-efficacy and self-reported physical activity also found a direct relationship between the two; lower self-efficacy, in other words, lower confidence in being able to perform physical activity under different circumstances, was associated with lower physical activity, but no difference in self-efficacy levels was noted between patients and healthy controls. It is possible that the inclusion of patients with mild CHD lesions, who are often unaware of their lesions and can lead normal lives after successful recovery, plays a role in this lack of difference in self-efficacy levels between CHD and controls. Furthermore, the authors documented that none of the included CHD patients had any significant residual lesions; however, this cannot exclude the presence of arrhythmias, impaired ventricular function, or changes in oxygen saturation at rest and during exercise, which may affect both self-efficacy and physical activity and confound the results of the current study. Current European and US guidelines focus on participation requirements in competitive sports, which apply to a minority of patients with CHD, and few recommendations can be found for participation in recreational sports without specific mention of children. If lifestyle recommendations are to be incorporated into routine clinicalpractice, structured protocolsand programs are needed to help clinicians guide and counsel patients on lifestyle choices and physical activity engagement according to their needs. Professionals in exercise prescription and physiology should be an integral part of the care package for patients with CHD and provide individualized information on the type and intensity of physical activity recommended, as well as potential limitations . Previous studies have shown that remote lifestyle interventions in children with congenital heart disease may be effective in reducing overweight or obesity. Other authors have demonstrated that home-based interval training improves endurance and peak physical performance in adults with complex congenital heart disease, thus potentially influencing the timing of re-intervention. However, it should be noted that ineffective exercise interventions may not have the intended effect, and the design of such programs is critical for optimal outcomesin terms of physical performance, quality of life, and even hormonal response. Diet and nutrition are other equally important milestones for human health and cannot be separated from physical activity. Despite the amount of research conducted in the field of clinical nutrition, patients are often unaware of dietary optimization, including the optimal timing and composition of meals. With appropriate guidance, obesity and various acquired comorbidities such as diabetes, dyslipidemia, hypertension can be reduced and well-being can be improved. Lifestyle intervention programs in adults do not provide long-term benefits because they require significant changes in the individual's daily routine and, even if maintained for some time, patients tend to return to their "old" unhealthy lifestyle. These results highlight the significance of the study by Moshovi et al. and suggest that physical activitytraining in patientswith CHD should be started in early childhood. Physicians and families should remember that it is easier to maintain a healthy lifestyle than to try to change established "bad" habits later in life.

References:

1. Serota H, Barth CW 3rd, Seuc CA, Vandormael M, Aguirre F, Kern MJ. Rapid identification of the course of anomalous coronary arteries in adults: the "dot and eye" method. Am J Cardiol 1990;65:891–898.
2. Anderson RH. Description of the origins and epicardial course of the coronary arteries in complete transposition [editorial]. Cardiol Young 1991;1:11–12.
3. Angelini P, de la Cruz MV, Valencia AM, Sanchez-Gomez C, Kearney DL, Sadowinski S, Real GR. Coronary arteries in transposition of the great arteries. Am J Cardiol 1994;74:1037–1041.
4. Anderson RH, Becker AE. Coronary arterial patterns: a guide to identification of congenital heart disease. In: Becker AE, Losekoot G, Marcelletti C, Anderson RH, editors. Paediatr cardiol. Edinburgh: Churchill Livingstone: 1981;251–262.
5. Vrancken Peeters MP, Gittenberger-de Groot AC, Mentink MM, Poelmann RE. Smooth muscle cells and fibroblasts of the coronary arteries derive from epithelial-mesenchymal transformation of the epicardium. Anat Embryol (Berl) 1999;199:367–178.
6. Pasquini L, Parness IA, Colan SD, Wernovsky G, Mayer JE, Sanders SP. Diagnosis of intramural coronary artery in transposition of the great arteries using two-

dimensional echocardiography. Circulation 1993;88:1136–1141.
7. Pasquini L, Sanders SP, Parness IA, Wernovsky G, Mayer JE Jr, Van der Velde ME, et al. Coronary echocardiography in 406 patients with d-loop transposition of the great arteries. J Am Coll Cardiol 1994;24:763–768.
8. Saxena A. Congenital heart disease in India: a status report. Indian Pediatr. 2018;55:1075–1082.
9. Saxena A, Mehta A, Sharma M, et al. Birth prevalence of congenital heart disease: a cross- sectional observational study from North India. Ann Pediatr Cardiol. 2016;9:205–209.
10. Ekure EN, Sokunbi O, Kalu N, Olusegun-Joseph A, Kushimo O, Amadi C, et al. Congenital heart disease in school children in Lagos, Nigeria: prevalence and the diagnostic gap. Am J Med Genet C Semin Med Genet. 2020;184:47–52.
11. Zhuang J. The continuing challenge of congenital heart disease in china. J Thorac Cardiovasc Surg. 2015;150:738.
12. Ho TC, Ouyang H, Lu Y, Young AH, Chintala K, Detrano RC. Postprocedural outcomes of rural children undergoing correction of congenital heart lesions in Yunnan Province, China. Pediatr Cardiol. 2011;32:811–814.
13. Zhao QM, Liu F, Wu L, Ma XJ, Niu C, Huang GY. Prevalence of congenital heart disease at live birth in China. J Pediatr. 2019;204:53–58.
14. Liu X, Xu W, Yu J, Shu Q. Screening for congenital heart defects: Diversified strategies in current china. World J Pediatr Surg. 2019;2:e000051.
15. ossano JW. Congenital heart disease: a global public health concern. Lancet Child Adolesc Health. 2020;4:168–169.
16. Collaborators GBDCHD Global, regional, and national burden of congenital heart disease, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet Child Adolesc Health. 2020;4:185–200.
17. He Y, Xu W, Su Z, Liu K, Zhang H. Addressing the rising burden of congenital heart disease in china. Lancet Child Adolesc Health. 2020;4:e7.
18. Liu Y, Chen S, Zuhlke L, Black GC, Choy MK, Li N, et al. Global birth prevalence of congenital heart defects 1970–2017: updated systematic review and meta-analysis of 260 studies. Int J Epidemiol. 2019;48:455–463.
19. Steinberger J, Moller JH, Berry JM, Sinaiko AR. Echocardiographic diagnosis of heart disease in apparently healthy adolescents. Pediatrics. 2000;105:815–818.
20. Zhao Q, Chen H, Zhang G, Chen W, Jia B, Liu F, et al. High prevalence of unrecognized congenital heart disease in school-age children in rural China: a population-based echocardiographic screening study. Circulation. 2021;144:1896–1898.
21. Zhao QM, Ma XJ, Ge XL, Liu F, Yan WL, Wu L, et al. Pulse oximetry with clinical assessment to screen for congenital heart disease in neonates in china: a prospective study. Lancet.
22. Virani SS, Alonso A, Aparicio HJ, et al. ; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. Circulation.
23. Martin GR, Ewer AK, Gaviglio A, et al. Updated strategies for pulse oximetry screening for critical congenital heart disease. Pediatrics. 2020;146(1):e20191650
24. Abouk R, Grosse SD, Ailes EC, Oster ME. Association of US state implementation of newborn screening policies for critical congenital heart disease with early infant cardiac deaths. JAMA. 2017
25. hu PY, Li JS, Kosinski AS, Hornik CP, Hill KD. Congenital heart disease in premature infants 25–32 weeks' gestational age. J Pediatr. 2017
26. Costello JM, Pasquali SK, Jacobs JP, et al. Gestational age at birth and outcomes after neonatal cardiac surgery: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. Circulation 2014;129(24):2511–2517.
27. Best KE, Tennant PWG, Rankin J. Survival, by birth weight and gestational age, in individuals with congenital heart disease: a population-based study. J Am Heart Assoc. 2017;6(7):e005213.
28. Archer JM, Yeager SB, Kenny MJ, Soll RF, Horbar JD. Distribution of and mortality from serious congenital heart disease in very low birth weight infants. Pediatrics. 2011;127(2):293–299\
29. Higgins RD, Shankaran S. The Neonatal Research Network: history since 2003, future directions and challenges. Semin Perinatol. 2016; 40(6):337–340
30. NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development. Best Pharmaceuticals for Children Act.
31. Laventhal N, Tarini BA, Lantos J. Ethical issues in neonatal and pediatric clinical trials. Pediatr Clin North Am. 2012;59(5):1205–1220
32. Pearson GD, Burns KM, Pemberton VL. Clinical trials in

children. In: Piantadosi S, Meinert CL, eds. Principles and Practice of Clinical Trials. New York, NY: Springer; 2022:2379–2395

33. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129–2200.
34. National Institute of Clinical Excellence. Chronic heart failure in adults: management 2010. Clinical guideline
35. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. Int J Cardiol. 2014;171(3):368–376.
36. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007;93(9):1137–1146.
37. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail. 2016;
38. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure: the Rotterdam Study. Eur Heart J. 2004;25(18):1614–1619.
39. Donkor A, Cleland J, McDonagh T, Hardman S. National Heart Failure Audit 2016 11.07.2016. 40.Gheorghiade M, Zannad F, Sopko G, Klein L, Pina IL, Konstam MA, et al. Acute heart failure syndromes: current state and framework for future research. Circulation. 2005;112(25):3958–3968.