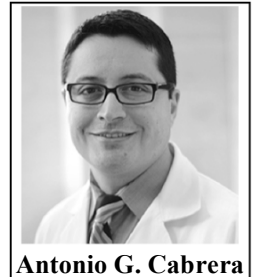


The Pathophysiology of Heart Failure in Children: The Basics

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Abstract: Few data exist on the pathophysiologic changes in pediatric heart failure. Most of the knowledge has evolved from animal models of ischemic or idiopathic dilated cardiomyopathy. This review addresses the pathophysiologic changes that occur in the failing heart from animal models and the adult experience to unique aspects of heart failure in children.

Keywords: Diastolic dysfunction, heart failure, neurohormonal activation, pediatrics, systolic dysfunction, ventricular remodeling.

INTRODUCTION

There are some 11,000-14,000 heart failure-related admissions in children annually in the United States. The proportion of admissions and the acuity of the patient's continues to increase in part due to the application of adult based technologies that have been adapted to children and the broader application of mechanical circulatory support with low associated morbidity. An understanding of the pathophysiology of heart failure is key to providing a mechanistically appropriate treatment strategy. In this review we will summarize the major pathophysiologic changes that occur in heart failure, including those aspects unique to heart failure in children.

The 2013 ACCF and AHA guidelines for the management of heart failure states that, "Heart failure is a complex clinical syndrome, which results from any structural or functional impairment of ventricular filling or ejection of blood." In adults, its primary manifestations are: dyspnea, fatigue and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema. Some patients may have exercise intolerance and little evidence of fluid retention, whereas others may complain primarily of edema, dyspnea, or fatigue.

Heart failure can have various etiologies related to pathology in one or more components of the cardiovascular system (pericardium, myocardium, endocardium or heart valves) or may be secondary to metabolic or chronic systemic conditions. Congestion may not be present in all the cases, thus the term "heart failure" is preferred over "congestive heart failure". Despite significant advancements in laboratory and diagnostic imaging modalities, heart failure

remains a clinical diagnosis based on a careful history and physical examination. Moreover, there is currently no single diagnostic test for establishing the diagnosis of heart failure [1].

Heart failure is neither synonymous with left ventricular (LV) systolic or diastolic dysfunction nor cardiomyopathy. These terms may, however, elucidate functional etiologies for the development of heart failure. Heart failure may be associated with a wide spectrum of LV functional abnormalities, ranging from patients with normal LV size and preserved ejection fraction to those with severe dilatation and/or a markedly reduced ejection fraction. In most patients, systolic and diastolic dysfunction coexist. The ejection fraction is important in the classification of adult patients with heart failure because of the variations in patient demographics, comorbid conditions, prognoses, and response to therapies [2], and because most adult clinical trials select patients based on the ejection fraction. Because other techniques may indicate abnormalities in systolic function among patients with a preserved ejection fraction, it is preferable to use the terms preserved or reduced ejection fraction over preserved or reduced systolic function. The term "restrictive" has been utilized to describe a set of echocardiographic and catheterization variables consistent with severe abnormalities in ventricular filling that may be present in a subset of patients suffering from heart failure symptoms with preserved ejection fraction. Additionally, in children the etiologies of heart failure usually differ from those in adults where structural heart lesions predominate and the coronary arteries are usually normal.

Applying the definitions described above, pediatric heart failure may result from four primary mechanisms:

- 1- Systolic dysfunction.
- 2- Diastolic dysfunction.
- 3- Pulmonary over circulation with systemic under perfusion.

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4- Inadequate mixing.

The primary focus of this review will be systolic and diastolic dysfunction as the other mechanisms, characterized by complex dissimilar physiologies, are more appropriately addressed in a separate review.

HEART FAILURE DUE TO SYSTOLIC DYSFUNCTION

Most of our understanding of the mechanisms of systolic dysfunction is derived from animal models of ischemic heart disease that have demonstrated a series of myocardial adaptations to an imbalance of myocardial oxygen delivery relative to demand following an ischemic insult. These myocardial changes are known collectively as ventricular remodeling. Ventricular remodeling is the consequence of subjecting the myocardium to pathologic stress, which results in changes in ventricular size, shape and function. In adults, ventricular remodeling has been shown to correlate with cardiovascular mortality. There are two major types of remodeling:

- 1- Concentric hypertrophy: an early response to a pressure load that is characterized by an increase in LV wall thickness and mass without chamber dilatation.

- 2- Eccentric hypertrophy: a late response to a pressure or volume load where the ventricular chamber enlarges as systolic function decreases. This is the most common phenotype in advanced heart failure.

The cellular changes triggered by variable combined effects of ischemia as well as pressure and volume loads culminates in the remodeling phenotype, which includes myocyte hypertrophy, increased myocyte turnover and interstitial fibrosis. Fibrosis detected by delayed gadolinium enhancement on MRI has become an important predictor of clinical outcomes in adults with HF [3].

CELLULAR AND ORGANELLE ABNORMALITIES

At the cellular level, there are five major abnormalities in HF (Fig. 1):

- 1- Down regulation of the β_1 receptor.
- 2- Activation of neurohumoral systems.
- 3- Activation of inflammatory pathways.
- 4- Abnormalities in calcium metabolism.
- 5- Apoptosis.

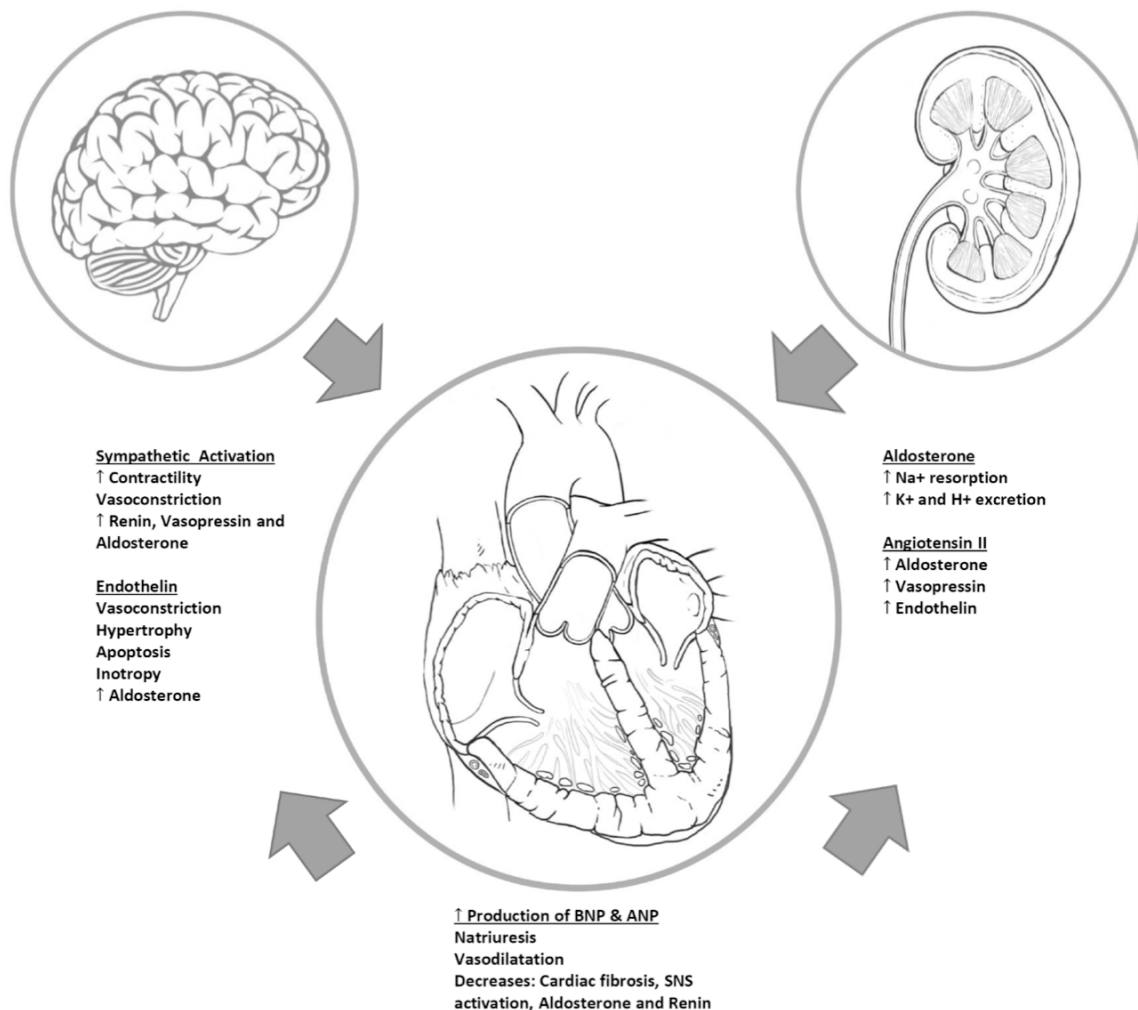


Fig. (1). Neurohormonal activation in Heart Failure.

SNS: Sympathetic Nervous System, Na⁺: Sodium, K⁺: Potassium, BNP: B-type natriuretic peptide, ANP: atrial natriuretic peptide.

The β_1 receptor is critical for the cardiac response to physiologic stressors and plays an integral role in the pathogenesis of heart failure. If β_1 receptors remain activated in heart failure, overstimulation results in increased myocardial oxygen consumption; decreased myocardial performance; perpetuation of myocyte remodeling; and a loss of cardiomyocytes due to apoptosis [4]. The process by which adaptive deactivation is accomplished is through receptor desensitization, which occurs when the β -arrestin molecule binds to the receptor preventing interactions with downstream mediators. In addition to deactivation, receptor density is down regulated. As a result of these changes, despite a rise in endogenous catecholamine levels β_1 signaling is reduced due to diminished receptor density and responsiveness.

Activation of the renin angiotensin aldosterone system (RAAS) has been the focus of intense research [5]. The renal juxtaglomerular apparatus releases renin into the circulation in response to sympathetic activation, as well as in response to decreased glomerular hydrostatic pressure (renal hypoperfusion) and a tubuloglomerular feedback mechanism (decreased sodium delivery to the distal nephron). Renin then catalyzes the conversion of angiotensinogen to angiotensin I, which is cleaved by the angiotensin converting enzyme into its active form, angiotensin II. In addition to angiotensin II being a potent vasoconstrictor it also contributes to ventricular remodeling through direct pro-apoptotic and pro-hypertrophic signaling pathways in cardiomyocytes. The systemic vasoconstrictor effect (after-load increase) coupled with direct effects on cardiomyocytes leads to ventricular hypertrophy. Ultimately, fibroblast migration and endocardial fibrosis [6] results, which correlates with impaired diastolic function and mortality. Angiotensin II also stimulates the release of aldosterone from the adrenal glands resulting in renal sodium and water retention, which contributes to ventricular volume overload and a worsening of the congested state. The importance of the RAAS in the evolution of heart failure was demonstrated in the RALES trial, which substitute demonstrated by showed that spironolactone (aldosterone antagonist) results in an attenuation of cardiac remodeling and a survival benefit [7]. In addition to the RAAS, chronic activation of the sympathetic nervous system and elevated catecholamine levels contribute to the pathophysiology of ventricular remodeling. Counter regulatory hormones are released to offset the affect of neurohormonal activation, and include the release of natriuretic peptides. The β -type natriuretic peptide has been the most intensely studied of the natriuretic peptides. It is secreted by ventricular cardiomyocytes in response to a volume or pressure load and promotes vasodilatation and natriuresis, and inhibits ventricular remodeling. Finally, activation of inflammatory pathways, particularly the release of cytokines, contributes to ventricular remodeling.

Calcium is essential for excitation-contraction coupling. As the cardiomyocyte depolarizes, Ca^{++} enters through voltage-dependent Ca^{++} channels. This so called "trigger calcium" activates the ryanodine receptor (RyR2), the gateway for Ca^{++} release from the sarcoplasmic reticulum into the cytosol. The majority of cytosolic Ca^{++} required for sarcomere shortening is intracellular and released from the sar-

coplasmic reticulum. Myocyte relaxation occurs as sarcoplasmic reticulum Ca^{++} adenosine triphosphatase (SERCA2a) sequesters Ca^{++} from the cytosol back into the sarcoplasmic reticulum. The concentration of SERCA2a is reduced in heart failure, leading to impaired reuptake of Ca^{++} and thus impaired. Due to increased β_1 stimulation in heart failure, there is a reduction of the inhibitory factor of the ryanodine receptor (RyR2). This leads to an increased diastolic leak of Ca^{++} , which when combined with SERCA2a dysfunction produces delayed after-repolarizations, increasing the propensity for ventricular arrhythmias.

Apoptosis is a process of programmed cell death that is characterized by cell shrinkage, activation of caspases and subsequent DNA fragmentation, and may be triggered by two processes:

- 1- Extrinsic: by binding through death ligands to tumor necrosis factors (TNF) receptor-like substances on the cell surface. This recruits procaspase-8 into a death-inducing signaling pathway.
- 2- Intrinsic: Triggered by different cellular stressors including: hypoxia, radiation, energy or nutrient deprivation, DNA damage or reactive oxygen species. Oxidative stress and a subsequent decrease in activity of anti-oxidant enzymes activate cell death through the mitochondria.

These mechanisms of accelerated cell death have been implicated in necrosis and autophagia and overall myocyte loss in ischemic heart failure models.

HEART FAILURE DUE TO DIASTOLIC DYSFUNCTION

It is generally agreed upon that most patients with heart failure have some degree of both systolic and diastolic dysfunction. There are two major clinical categories of diastolic dysfunction:

- 1- Congenital: genetic hypertrophic, restrictive cardiomyopathies and genetic diseases result in deposition or infiltration of the myocardium with a metabolic precursor (e.g. Pompe disease).
- 2- Acquired: relaxation abnormalities secondary to cardiac dilation (reduced compliance reserve) or myocardial stiffening secondary to ischemia-induced fibrosis. Other acquired conditions include deposition diseases that reduce ventricular compliance (e.g.: iron infiltration).

This review will focus on acquired LV diastolic dysfunction secondary to dilation and fibrosis. Dilation of the left ventricle, regardless of mechanism (egs., volume load due to pulmonary overcirculation or depressed contractility due to ischemic heart disease), results in some degree of relaxation impairment. According to LaPlace's law, as the ventricular radius increases, myocardial wall tension increases [8-10]. Thus, relaxation is progressively impaired as the ventricle dilates.

As discussed earlier, the RAAS plays an integral role in the pathogenesis of heart failure. LV remodeling results in myocardial fibrosis and reduced ventricular compliance

(stiffness). A vicious cycle ensues where the neurohumoral effects converge, that is to say dilation and depressed contractility secondary to RAAS-mediated exacerbated hypertrophy and cell death, and RAAS-mediated cell death and fibroblast migration and activation. With ventricular dilation and fibrosis and resultant diastolic dysfunction, wall stress and tension increase leading to increased myocardial oxygen consumption and an imbalance between myocardial oxygen supply and demand.

RIGHT VENTRICULAR FAILURE

In general, the right ventricle (RV) has better adaptive mechanisms to volume than to pressure loads and to chronic rather than to acute insults. This is well demonstrated in patients with a flail tricuspid valve where the presence of severe tricuspid regurgitation is associated with a high incidence of heart failure symptoms, atrial fibrillation and mortality [11].

The molecular mechanisms involved in RV remodeling have been derived from ventricular pressure overload models. The RV has limited capacity to perform when exposed to an acute pressure load but with a more chronic increase in afterload a compensatory hypertrophy occurs, enabling the RV to maintain stroke volume. However, if the increase in afterload occurs too quickly or is too great, the RV will fail. The overall ability of the RV to adapt to a pressure and or volume load is significantly less than that of the LV. The reasons for this “increased vulnerability” have not been completely elucidated. It has been hypothesized that the RV loses its protective structural fetal phenotype. The fetal RV that never transitions to the “adult type”, as is the case in patients with congenital structural lesions, appear to adapt better to pressure loading. A multitude of molecular mechanisms and signaling pathways have been implicated in this:

1. Increase in α (myosin heavy chain) MHC and β -MHC is a feature of stressed myocardium.
2. Metabolic switch from glycolysis (cytosol) to fatty acid oxidation (mitochondria). This produces mitochondrial hyperpolarization, a state in which mitochondrial-dependent apoptosis is suppressed. As compensatory RV hypertrophy increases, the mitochondria become more hyperpolarized [12]. This avails the RV with more ATP from the mitochondria than from the cytosol.
3. Other factors involved are:
 - a. Changes in extracellular matrix and increase fibrosis.
 - b. Microvascular ischemia.
 - c. Neurohumoral activation.

Although, these maladaptive mechanisms accelerate remodeling similar to the LV, the RV has the capacity to reverse remodel once the volume or pressure load has been removed. For instance, RV volumes and function return to normal after lung transplantation in patients with pulmonary hypertension or after thrombectomy in patients with pulmonary embolism [13].

CONNECTING PATHOPHYSIOLOGY WITH CLINICAL FINDINGS

There is controversy as to the value of the physical exam in the assessment of patients with heart failure. In a classic study by Forrester and colleagues, patients sustaining an acute myocardial infarction had four distinct hemodynamic profiles that were based on the presence or absence of congestion (pulmonary capillary wedge pressure $>$ or \leq 18 mm Hg) and adequacy of perfusion (cardiac index greater than 2.2 L/m/m²) [14]. The following profiles were assigned:

- Profile I: no congestion or hypoperfusion.
- Profile II: congestion without hypoperfusion.
- Profile III. hypoperfusion without congestion.
- Profile IV: both congestion and hypoperfusion.

Clinical and invasive hemodynamic profiles predicted short-term survival and showed an increased mortality when congestion was present. Worse outcomes were found when congestion and hypoperfusion were present in combination. Orthopnea and proportional pulse pressure correlated well with hemodynamics in chronic heart failure as opposed to rales and peripheral edema. In a subsequent study, Nohria and colleagues investigated if congestion and adequacy of perfusion on clinical examination were able to define prognostic categories in adult patients admitted with a history of heart failure [15]. They defined four states: Warm and dry, warm and wet, cold and dry and cold and wet. Their analysis showed that the presence of congestion was associated with an increased risk of urgent transplantation or death. In addition, even when applied to patients' with New York Heart Association class III and IV symptoms, clinical profiles provided further prognostic information. Patients who were dry and warm may do well in spite of the severity of symptoms [15]. Singh and collaborators explored the application of these hemodynamic profiles to a cohort of 476 children with dilated cardiomyopathy from the OPTN (Organ Procurement and Transplant Network) database from 2000 to 2010. In adjusted analysis, cold-dry (hazard ratio [HR] 3.5, 95% confidence interval [CI] 1.1, 11.5) and cold-wet (HR 3.2, 95% CI 1.2, 8.6) children were at higher risk of wait-list death versus warm-dry children, whereas warm-wet children were not (HR 2.3, 95% CI 0.8, 6.6). Showing that children with low cardiac output (not warm) fare worse while awaiting for cardiac transplantation [16].

CONCLUSION

HF is a complex clinical syndrome, which results from any structural or functional impairment of ventricular filling or ejection of blood. Initial adaptive mechanisms to ventricular dysfunction trigger a series of changes that leads to compensatory hypertrophy, which over time if left unchecked leads to fibrosis and ventricular failure. A mechanistic understanding of the pathophysiology of heart failure is essential for guiding optimal therapeutic strategies both in the acute and chronic phase of heart failure.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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AUTHOR CONTRIBUTIONS

Authors Jarrod Knudson and Antonio Cabrera contributed equally to the manuscript's research, preparation, editing, revisions and completion.

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