Management of Heart Failure in Children

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Advances in our understanding of the pathophysiology and molecular basis of diseases offer new, challenging, controversial, and sometimes, counterintuitive forms of therapy. This is especially true with regard to the syndrome of heart failure. Therapeutic approaches to heart failure in adults have evolved rapidly during the past decade. Unfortunately, as with many other aspects of medicine, our concepts of heart failure in the pediatric population have been reduced to a simple extrapolation of the adult model. Pediatricians know that a child is not a small adult. Consequently, heart failure is perhaps a far more complex entity in the pediatric population with regard to pathophysiology and the possible courses of action. In this review we summarize recent advances in heart failure research in adults and attempt to integrate these findings in a pediatric context.

The basic paradigm of hemodynamic derangement and the consequent symptoms have dominated our approach to congestive heart failure for most of this century (Fig 1). Despite constraint by this narrow viewpoint, the normalization of hemodynamics has an immediate positive effect on symptomatic improvement. Multiple clinical trials were conducted in the adult population with a variety of pharmacologic strategies aimed at enhancing systolic performance only. The clinical outcome of these trials was disappointing because of adverse effects on the heart in the long term, since the initial improvement in the standard measures of heart failure severity (such as exercise tolerance, symptoms, and hemodynamics) was not sustained.[1,2]

Application of information available from recent heart failure research enables us to go beyond the concept of the heart as a simple pump and formulate a more comprehensive understanding of the syndrome of heart failure (Fig 2). We are now beginning to recognize the positive and negative consequences of treatment aimed at simply improving cardiac pump performance. We now know that the development and progression of heart failure result from a complex interplay of hemodynamic and neurohormonal factors. Heart failure is now viewed as a clinical syndrome that incorporates hemodynamics and compensatory neurohumoral responses in the overall paradigm. New developments in our understanding of heart failure as a pathophysiologic syndrome are derived from the following advances.

1. Today the principal components of the major signaling pathways involved in cardiac and vascular cell function and regulation are better defined.[3-5] Furthermore, the importance of cross-communication and interplay among the various regulatory pathways is increasingly apparent.
2. The essential role of Ca^{2+} in cellular homeostasis is maintained by complex interactions among many signaling systems.
3. It has long been known that during the decompensated phase of heart failure the sympathetic nervous system (SNS) and the renin-angiotensin system (RAS) are activated. New insights into the molecular signaling pathways involved have provided a better understanding of the role of these compensatory mechanisms in cardiac and vascular remodeling.
4. New discoveries relative to the role of autocrine and paracrine factors, including angiotensin, endothelin, peptide growth factors, nitric oxide (NO), and prostacyclin, provide insights into the development of both cellular adaptive and maladaptive mechanisms in heart failure.
5. More rational pharmacologic strategies are emerging that are directed more precisely at the cellular and molecular abnormalities associated with the heart failure syndrome.

This presentation primarily focuses on the management of the patient in a compensated state of heart failure. The multifactorial causes responsible for

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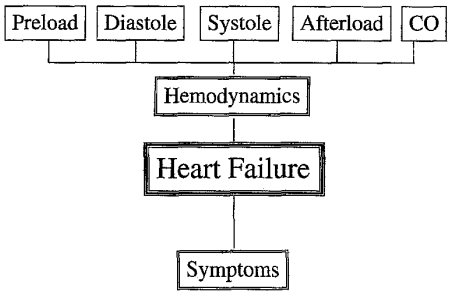

FIG 1. Traditional heart failure pathophysiology paradigm used in the past decades. The 2 basic paradigms, hemodynamic derangement and the consequent symptoms, have dominated our approach to congestive heart failure for most of this century. In the previous few decades, multiple clinical trials were conducted in the adult population with vasodilators, positive inotropes, and inodilators as strategies to enhance systolic performance. These studies mostly demonstrated worsening of the natural history of heart failure in the long term, in spite of hemodynamic improvement in the short term. *CO*, Cardiac output.

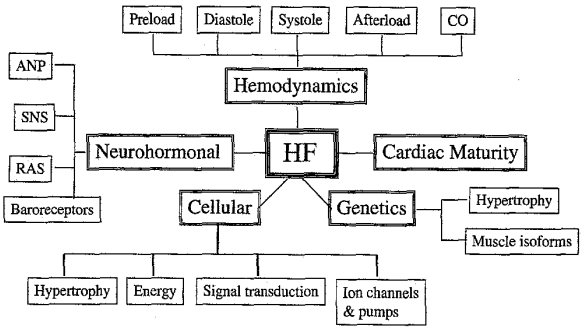

FIG 2. Current heart failure pathophysiology paradigm used. Current pathophysiologic paradigm that unifies the understanding of mechanisms that are active in the syndrome of heart failure. *ANP*, Atrial natriuretic peptide; *CO*, cardiac output; *HF*, heart failure; *RAS*, renin-angiotensin system; *SNS*, sympathetic nervous system.

development and progression of the heart failure syndrome are presented as a link to understanding controversial therapies such as the use of digoxin and β-blockers. A short section is dedicated to the care of the neonate with a congenital heart defect because this is a relatively common problem confronting pediatricians. This review departs from more traditional presentations of pediatric heart failure in that the simple enumeration of signs and symptoms for each particular disease state has been avoided. Rather, we attempt to present a more physiologically based approach that allows a grouping of different anatomic defects into similar clinical scenarios.

Definitions

There is no single definition that encompasses the syndrome of heart failure in all of its facets. As a consequence, there are several definitions, depending on how heart failure is viewed. The following is a classic definition of the disease state, congestive heart failure: *"Cardiac failure is the inability of the heart to deliver oxygen to the tissues at a rate commensurate with the metabolic demands."*[6] The clinical entity *shock* is defined in similar terms: *"Shock is an acute complex state of circulatory dysfunction that results in failure to deliver sufficient amounts of oxygen and nutrients to meet tissue metabolic demands."*[7]

At the outset, it appears as though the same clinical state is being described with 2 different terms. So how should the definitions be modified to differentiate more clearly between heart failure and shock? The following 2 very different clinical scenarios illustrate the difference: Case 1 relates to a child with an anomalous origin of the left coronary artery from the pulmonary artery, poor coronary collateral circulation, severely depressed myocardial function, and ongoing metabolic acidosis due to low cardiac output. Case 2 involves a different child, with a cyanotic heart defect with diminished pulmonary perfusion, severe hypoxemia, normal myocardial function, and ongoing metabolic acidosis due to anaerobic metabolism.

Both cases fit either of the definitions mentioned above. However, although any improvement in cardiac function may arguably favor the patient in the first case, similar maneuvers will have little if any beneficial effect in the second patient. These examples illustrate the limitations inherent in adhering to the restricted definition of heart failure on the basis of only oxygen delivery and metabolic demand of the target tissue, rather than the heart and its regulatory mechanisms. If we were to consider heart failure as simply an acute pump failure resulting in inadequate oxygen delivery, then the rationale for attempts to restore contractility toward normality would be sound in the short term. With this strategy in mind, manipulation of myocardial loading conditions and systolic function with pharmacologic agents formed the traditional basis for patient management and improved systemic oxygen delivery. Although this may be appropriate in the case of *acute, decompensated low cardiac output state* (which may be considered to be synonymous with "*cardiogenic shock*"), this approach is not satisfactory for chronic, compensated heart failure states.

Sustained inotropic stimulation of the failing heart can produce deleterious effects in the long term. At least 4 potential problems may be encountered during sustained positive inotropic therapy: (1) an increase in the rate of myocardial energy expenditure, resulting in a mismatch between oxygen availability and oxygen demands; (2) abnormalities in the processes governing contraction and relaxation; (3) an increase in intracellular calcium concentration, which may promote triggered arrhythmias; and (4) an uncoupling of the respiratory chain leading to further energy starvation.[8,9]

A better definition of heart failure is necessary to encompass all of the compensatory mechanisms of heart dysfunction. Furthermore, should we define heart failure differently in the pediatric population? The spectrum of pediatric cardiac disease does go beyond the simple anatomic abnormality in need of surgical intervention. However, irrespective of the underlying primary etiology, the heart failure syndrome has certain common characteristics.

Milton Packer[10] defines congestive heart failure as the following: *"Heart failure is now thought as a disorder of the circulation, not merely a disease of the heart. Heart failure develops not when the heart is injured, but when compensatory hemodynamic and neurohormonal mechanisms are overwhelmed or exhausted."* To this we add that heart failure develops not only when the compensatory mechanisms are overwhelmed and exhausted but also *as a consequence of the actions of these same compensatory mechanisms*. Signs and symptoms of heart failure result from interactions of a malfunctioning pump and the physiologic responses in attempting to sustain vital functions. The development of signs and symptoms represents an acute decompensation in the setting of a long-term attempt to maintain vital function by the body's own compensatory mechanisms. This understanding of the coexistence of acuity and chronicity is important to us in pediatrics, where surgical palliation prevails over complete repair of structural defects. With these concepts in mind, we offer the following definitions as a framework for understanding and addressing the pediatric heart failure syndrome.

Chronic Heart Failure Syndrome (Compensated State)

Chronic heart failure syndrome is a cardiac pump dysfunction with activation of compensatory responses that ultimately contribute to silent and progressive deterioration of myocardial function. Patients with this syndrome may exhibit few, if any, symptoms of "congestive" heart failure because systemic compensatory mechanisms, mainly activation of the SNS and the RAS, maintain homeostasis. However, sustained SNS and RAS activation promotes progression of disease mediated by paracrine and autocrine factors.[11] These points are further expanded in the section about the pathophysiology of heart failure.

Acute Heart Failure Syndrome (Decompensated State)

Acute heart failure syndrome is an acute functional uncoupling between compensatory mechanisms and depressed myocardial pump function leading to homeostatic imbalance and overt symptoms. The development of symptoms or the worsening of a previous clinical state marks the beginning of decompensation and acute heart failure. Additional myocardial injury, increased metabolic demands, or changes in loading conditions may bring about this new clinical state. Symptoms of fluid retention develop or progress primarily as a consequence of peripheral vasoconstriction and sodium retention. Congestion, a word closely identified with heart failure, is only 1 manifestation and is a minimal part of the overall heart failure syndrome. According to our conceptual framework for pediatric heart failure syndrome, a congested circulatory state represents a decompensated state.

Shock

Shock is a state of acute circulatory dysfunction with completely overwhelmed physiologic compensatory mechanisms. Shock can result from a variety of causes with cardiogenic shock occurring infrequently in the pediatric population. Because the normal physiologic responses are completely inadequate to maintain circulatory homeostasis, shock must be corrected promptly to prevent death. The pathophysiology and treatment of shock are beyond the scope of this review and are not fully discussed.

Etiology of Heart Failure in Children

Numerous primary causes of the heart failure syndrome exist in the pediatric population. In many cases, precise determination of the underlying cause is crucial for defining optimal therapy, especially for anatomic, metabolic, toxic, and infectious etiologies. Table 1 provides an etiologic classification of heart

TABLE 1. Etiologic classification of heart failure in children

Anatomic (congenital and acquired)	L-R shunts
	Valvar obstruction
	Valvar regurgitation
	Hypertension
	Cardiomyopathy
	Loss of myocardium
Arrhythmias	
Infections	Viruses, HIV, mycobacteria, bacteria, fungus, and parasites
Metabolic errors	Inborn errors of metabolism, storage disorders, hyperthyroidism, adrenal insufficiency, carnitine deficiency
Tumors	
Drugs	β-Blockers, calcium channel blockers, antiarrhythmics, chemotherapeutic agents, antiviral agents
Toxins	Ethanol, cocaine, hypoxia, metals

CHF, Chronic heart failure.

failure in children. Anatomic congenital heart defects display an age dependency in the development of signs and symptoms of congestive heart failure. Pulmonary vascular resistance is the single most important factor determining the degree of severity and time of onset of heart failure in patients with excessive pulmonary blood flow *(left-to-right [L-R] shunt lesions)* or duct-dependent lesions. The severity of flow *obstruction*, either arterial (aortic and pulmonary stenosis, coarctation of the aorta) or venous (total anomalous pulmonary venous connection [TAPVC]), is also an important determinant not only of time of presentation but also of the clinical picture. Although shock is a common presentation of obstructive lesions in the neonatal period, heart failure predominates in infants (see later in "Clinical Manifestations" section). Patients with coarctation of the aorta have systemic *hypertension* in infancy and childhood. While correction of the anatomic defect may normalize blood pressure, the substrate exists for the development of hypertension later on in life, although the mechanism of hypertension is still unclear in such patients. Patients with anomalous origin of the left coronary artery from the pulmonary artery display a bimodal clinical picture. Patients with poorly developed collateral coronary circulation are seen early in life with signs and symptoms of cardiogenic shock resulting from myocardial infarction *(muscle loss, mitral regurgitation)*. Patients with adequate collateral circulation are seen later on in life with signs of heart failure and *dilated cardiomyopathy*.

Acquired factors are the result of therapeutic interventions designed to treat anatomic defects that lead to congestive heart failure. Persistent *arrhythmias* can worsen heart function in patients who have undergone multiple surgical interventions. This is an unfortunate, long-term complication of procedures such as the atrial switch operation (Mustard or Senning procedures) for transposition of the great arteries, tetralogy of Fallot repair, and the Fontan procedure for single ventricle defects (single ventricle bypass surgery in which the systemic vena cavae are directly connected to the pulmonary arteries).[12] Right *ventricular dilatation* with *poor systolic* and *diastolic function* is a recognized late complication after repeated operations for the reconstruction of the right ventricular outflow tract.[13,14] Ventricular injury is linked to valvar *obstruction-regurgitation* physiology and the consequent development of myocardial hypertrophy and fibrosis. The need for several operative procedures exposes the myocardium to repeated *ischemic* and *reperfusion* injury. Inborn errors of metabolism such as Pompe's disease or carnitine deficiency may display a certain relationship to time in terms of age of onset of symptoms. However, there are other etiologic factors that show a more or less similar incidence across the pediatric age span, such as infection, inflammation, tumors, and toxins.

Pathophysiology of Heart Failure

The pathophysiology of heart failure is now a multifaceted entity that encompasses several systems that were not previously thought significant with respect to heart failure (Fig 2). The compensatory mechanisms that control cardiac function have been studied and are targeted in the treatment of heart failure syndrome, especially in the chronic compensated states. Furthermore, developmental changes in the heart and its control mechanisms at different levels have to be taken into account while treating a child in heart failure with medications that were tested mostly in adults.

Developmental Stage and Age of the Patient

The pediatric age is perhaps unique in its intimate relationship to surgical intervention. Today, surgery is timed not only according to the presence of anatomic disease and failure of medical therapy, but also according to consideration of myocardial cell adaptation and chamber remodeling. The latter is well illustrated in the timely fashion with which the multiple surgical steps to the single ventricle heart are planned. In pediatric heart failure, surgery can end decompensation (acute heart failure), which is clearly demonstrated in patients with large L-R shunts (eg, patent

ductus arteriosus [PDA], ventricular septal defect [VSD]). Surgical intervention can also slow the progression of the compensated state (chronic heart failure) through palliative procedures.

The child's age is an important factor not only in the planning of surgery but also in the mode of presentation of the disease. As much as it is true that a child is not a small adult, a neonate is not a small child. Significant differences exist in the neonatal myocardium, which together with ongoing maturation processes in other organs, make the pharmacologic approach to the newborn child unique (see the "Immature Heart" section). The relaxation of the pulmonary vasculature determines the time of symptomatic manifestation of a disease existent at birth (eg, VSD, PDA, and atrioventricular [AV] septal defect). The issues related to age and onset of symptoms are further addressed later in the section on clinical presentations.

Organ Dysfunction

The hemodynamic abnormalities in patients with heart failure are relatively simple. Systemic cardiac output may be insufficient because of either reduced ejection of blood into the great arteries (systolic dysfunction) or inadequacy of the heart to receive venous return (diastolic dysfunction). In heart failure, the interaction between the contractile (*inotropic*) and relaxation *(lusitropic)* properties of the heart is altered. At end diastole, intraventricular pressure and volume are determined by *preload* (venous return) and the *lusitropic* state of the ventricular myocardium. On the other hand, peripheral impedance, afterload, and the inotropic state of the ventricular myocardium determine end-systolic ventricular pressure and volume.

Systolic Dysfunction. The fundamental problem in systolic dysfunction is impaired ventricular contractility. The ability to increase stroke volume with an increase in preload is therefore diminished when systolic performance is impaired.[15] The normal ventricle, assuming preload (venous return) is adequate, is relatively insensitive to small changes in afterload. In contrast, in a ventricle with systolic dysfunction, a very small increase in afterload may lead to a marked decline in cardiac output. Conversely, a small decrease in afterload may significantly improve left ventricular function. Afterload encompasses a variety of factors relating to the vasculature and its coupling with the ventricle. Systemic vascular resistance (SVR) and arterial pressure are important components of afterload, but large-artery impedance and left ventricular volume may also contribute significantly. The Laplace relationship implies that the end-systolic wall stress (afterload) is proportional to both end-systolic pressure and end-systolic volume. When ventricular systolic function is reduced, end-systolic volume increases, which when coupled with an increase in preload, leads to an increase in afterload.[16]

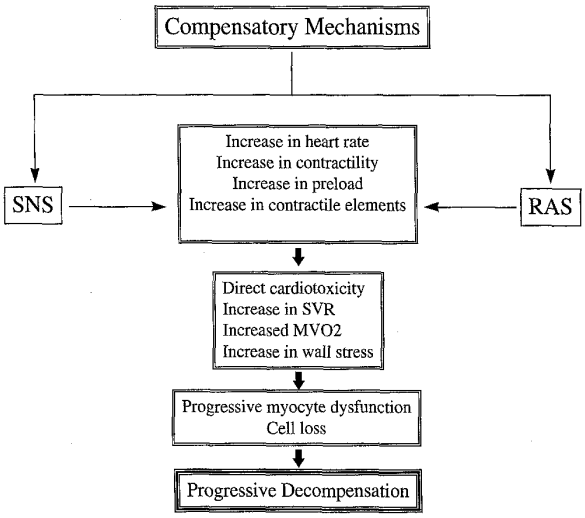

FIG 3. Path to decompensation. During the decompensated phase of heart failure, the SNS and the RAS are activated as compensatory mechanisms. Yet, a relentless progression of cardiac and vascular remodeling can be observed. Continued activation of compensatory mechanisms plays an important role in the development of the initially adaptive and eventually maladaptive mechanisms that lead to decompensation. *MVO2,* Myocardial oxygen consumption; *RAS,* renin-angiotensin system; *SNS,* sympathetic nervous system; *SVR,* systemic vascular resistance.

Diastolic Dysfunction. Diastolic cardiac dysfunction is characterized by decreased ventricular compliance, necessitating an elevated venous pressure to sustain adequate ventricular filling. Abnormal diastolic function may cause symptoms of inadequate cardiac output despite normal systolic function.[15,17] The causes of diastolic dysfunction in children are listed in Table 2.

Neurohormonal Factors

The Path to Decompensation. Compromise in cardiac output and perfusion pressure activates acute stress mechanisms (Fig 3). The maintenance of blood flow and pressure to vital organs becomes a priority. To this end, the activity of the SNS and RAS is enhanced. This compensatory increase in neurohumoral activity initially results in an increase in myocardial contractility, selective peripheral vasocon-

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