Pharmacologic Approach to Heart Failure in Children

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Abstract: Heart failure may result from a wide variety of causes and present with varying degrees of severity. In large part, patients present with varying degrees of congestion and compromised cardiac output. In this review a pathophysiologic construct is provided to guide the pharmacologic management of acute heart failure that leads to decreased congestion and improved cardiac output. Pharmacologic therapies that are used to treat chronic heart failure are also highlighted and provide the framework for transitioning from acute to preventative pharmacologic strategies.

Keywords: Cardiac output, congestion, heart failure, pediatrics, pharmacologic therapies, ventricular remodeling.

INTRODUCTION

In acute heart failure pharmacologic therapies are directed at improving stroke volume and cardiac output, as well as decreasing the congested state and improving symptoms and respiratory function. In chronic heart failure, the focus shifts to agents that promote ventricular remodeling that which overtime may maintain or in some patients restore ventricular function. It is imperative to determine prior to initiating pharmacologic therapies the extent to which function and output are compromised and the overall hemodynamic profile. Accordingly, we will review circulatory physiology and discuss the pharmacologic agents that may be used in the treatment of acute and chronic failure.

CIRCULATORY PHYSIOLOGY

The ideal strategy for improving output in acute heart failure is to manipulate ventricular loading conditions. This approach is not only highly effective at improving stroke volume and cardiac output but does so without increasing myocardial or global oxygen demand. Systemic venous return is one of the most important determinants of preload. The pressure difference between the right atrium and venous reservoir is responsible for driving systemic venous return from the periphery to the right atrium [1]. The resistance to systemic venous return is unaffected by vasodilators and large adrenergic stimulation. The upstream driving pressure for systemic venous return, the pressure within the systemic venous reservoirs, is the mean systemic pressure. This pressure is a function of intravascular volume and capacitance of the circulatory system, the vast majority of which are found

within and with the venous capacitance vessels [1]. Increasing intravascular volume or decreasing venous capacitance with venoconstrictors increases the mean systemic pressure, systemic venous return and ventricular preload. The opposite occurs with diuresis and venodilators. The impact of manipulating preload on cardiac output depends on where the ventricle resides on its pressure stroke volume curve. If preload is reduced and the ventricle remains on the flat portion of its pressure stroke volume curve, filling pressures decrease, decreasing pulmonary and systemic venous congestion without effecting stroke volume and output. If the ventricle falls onto the steep portion of its pressure stroke volume curve, stroke volume and output will be adversely impacted.

As systolic function wanes the ventricle becomes increasingly more sensitive to changes in afterload. Thus efforts to decrease afterload are essential in the management of patients with systolic heart failure. Ventricular afterload may be reduced mechanically, as with positive pressure ventilation and mechanical circulatory devices, or pharmacologically. Agents that selectively vasodilate the arterial resistance vessels and lower vascular impedance improve stroke volume and cardiac output but have little if any impact on ventricular filling pressures and therefore the degree of congestion [2, 3]. Agents that increase venous capacitance and reduce ventricular afterload, significantly reduce ventricular diastolic volume and pressure and the degree of congestion while increasing stroke volume and cardiac output [2, 3].

Stroke volume is altered not only by changes in ventricular loading conditions, but also by changes in myocardial function. Inotropic agents improve stroke volume without decreasing systemic venous return and for those agent with chronotropy heart rate-dependent increases in cardiac output may occur. However, tachycardia is one of the most important determinants of myocardial oxygen demand. Thus, chronotropy may have an adverse impact on the myocardial

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oxygen supply demand relationship. Inotropy also increases myocardial oxygen consumption further challenging the relationship between myocardial oxygen supply and demand.

Optimization of ventricular loading conditions and the judicious use of inotropy provides an ideal strategy for improving cardiac output in patients with acute heart failure and inadequate cardiac output. The vasoactive regimen should be tailored to the individual's specific needs with consideration given to the underlying circulatory pathophysiology and with the goal being to improve the global and myocardial relationship between oxygen supply and demand. In chronic heart failure, the goal of pharmacologic therapy is to maintain adequate cardiac function and output and to promote ventricular remodeling.

PHARMACOLOGIC AGENTS FOR ACUTE HEART FAILURE

Catecholamines

The hemodynamic effects of catecholamines are dose dependent and mediated by adrenergic receptors. Adrenergic receptors are tightly coupled to membrane bound G proteins, which are closely associated with guanosine diphosphate and guanosine triphosphate (GTP). Activated GTP acts in either a stimulatory or inhibitory fashion, with the stimulatory pathway being the primary mechanism behind the positive inotropic and chronotropic effects of these drugs. The additional enzymes involved in further signal propagation include adenylate cyclase, phospholipase C and phosphodiesterases. The final pathway results in conversion of adenosine triphosphate to cyclic adenosine monophosphate (cAMP). Rise in intracellular cAMP leads to alterations in intracellular calcium levels and cellular function. The commonly described adrenergic receptors include α_1 , α_2 , β_1 , and β_2 .

Postsynaptic α_1 receptors within the circulation are located on vascular smooth muscle cells where their activation induces vasoconstriction. α_2 receptors are located at the pre-synaptic cleft where norepinephrine released from sympathetic nerve terminals produces feedback inhibition of further norepinephrine release. β_1 receptors are situated on cardiomyocytes and their activation leads to enhanced contractility and to some extent an increase in heart rate. Activation of β_2 receptors, which are located primarily on smooth muscle cells, induces vasodilation.

Adrenergic receptors undergo regulation with "up-regulation" occurring in response to a decrease in adrenergic activity and "down-regulation" occurring in response to an increase in exposure to adrenergic activity. Changes in receptor concentration may occur as rapidly as within a few hours. Multiple pathways are involved in receptor regulation [4]. With exposure to endogenous or exogenous catecholamines, as occurs in heart failure, mechanisms involved with down-regulation include receptor uncoupling, sequestration and internalization, and involves complete receptor degradation [4]. Catecholamines are primarily metabolized by either catechol O-methyltransferase or monoamine oxidase and have a very short half-life. Due to their linear dose-response, rapid onset of action and fast elimination, these agents can be easily titrated. Catecholamines with β_1 activity signifi-

cantly increase myocardial oxygen demand as a result of their inotropic and chronotropic effects and increase the propensity for developing tachyarrhythmias.

Dopamine is an endogenous central neurotransmitter and an immediate precursor to norepinephrine. It acts on dopaminergic and adrenergic α and β receptors resulting in its broad range of effects at various doses. Dopaminergic stimulation modulates renal blood flow as well as sodium and water excretion. The clinical significance of its effect on renal function remains controversial [5]. At low to moderate doses (<10 mcg/kg/min) dopamine provides modest inotropy and increases in heart rate. At higher doses there is little if any increase in stroke volume but further increases in heart rate and vasoconstriction ensues [6]. Dobutamine is a synthetic catecholamine with affinity for β_1 and β_2 -receptors, providing modest inotropy and vasodilation of venous capacitance and arterial resistance vessels. Dobutamine increases stroke volume and heart rate but unlike dopamine significantly reduces ventricular filling pressures as a result of its effect on venous capacitance [6]. Epinephrine is an endogenous catecholamine that functions as a hormone and has affinity for β_1 , β_2 and α_1 receptors. At low doses epinephrine provides unparalleled inotropic support as well as increases in heart rate. In addition, low dose epinephrine (<0.05 – 0.10 mcg/kg/min) reduces afterload through β_2 receptor stimulation [7, 8]. At considerably higher doses α effects predominate. Norepinephrine is a major neurotransmitter. Following its release from sympathetic nerve terminals norepinephrine crosses the synaptic cleft to act on postsynaptic adrenergic receptors. Norepinephrine preferentially acts on β_1 and α_1 receptors, inducing vasoconstriction of venous capacitance and arterial resistance vessels while providing inotropic support. Released norepinephrine also acts on presynaptic α_2 receptor, which produces feedback inhibition of additional norepinephrine release.

Phosphodiesterase Inhibitors

Milrinone is the only phosphodiesterase inhibitor currently in use for the acute treatment of low cardiac output. It functions by inhibiting phosphodiesterase III, an enzyme responsible for the metabolism of cyclic adenosine monophosphate (cAMP). cAMP-dependent protein kinases control the phosphorylation of specific substrate proteins at the sarcoplasmic reticulum, triggering a faster release of stored calcium from the sarcoplasmic reticulum while increasing the availability of calcium at the myofilaments. Milrinone also induces vasodilation of venous capacitance as well as pulmonary and systemic arterial vessels. Milrinone reduces ventricular filling pressures while increasing cardiac output as a result of its modest inotropic and vasodilatory properties [9]. Relative to other agents, milrinone has a long half-life of 1-2 hours, and because its elimination is primarily renal (80%), dosing should be adjusted in patients with renal insufficiency. Milrinone is the only vasoactive agent that has been studied in a prospective randomized placebo controlled manner in children at risk for developing the low cardiac output syndrome. Hoffman and colleagues demonstrated that high-dose milrinone (versus placebo, low and moderate doses) was associated with a significantly reduced incidence of the low cardiac output syndrome following pediatric cardiac surgery [10].

Nitric Oxide Donors: Nitroprusside and Nitroglycerin

Nitroprusside is comprised of sodium salt with Fe^{2+} bound to nitric oxide and cyanide anions. After interaction with erythrocytes and other proteins nitric oxide is released, stimulating guanyl cyclase to produce cyclic GMP and inhibition of smooth muscle contraction [11]. Nitroprusside exerts a dose-dependent vasodilatory effect on venous capacitance and arterial resistance vessels [11]. A well-known side effect of nitroprusside is the generation of cyanide. Excessive doses or prolonged use of nitroprusside carries the highest risk for developing cyanide poisoning [12]. Nitroglycerin also functions as a nitric oxide donor and exerts a dose-dependent effect on vascular function. At low doses (<3 mcg/kg/min) it increases venous capacitance decreasing pulmonary congestion. At higher doses it also induces vasodilation of systemic arterial resistance vessels, increasing stroke volume and cardiac output [13].

Calcium Sensitizers

Calcium sensitizers exert positive inotropic effects by enhancing myofilament sensitivity to the prevailing calcium transient [14, 15]. Levosimendan is the calcium sensitizer in use in Europe, Australia and South America. It is not approved for use in the US or Canada. Levosimendan also induces vasodilation of venous capacitance and arterial resistance vessels as a result of activation of ATP-sensitive K^+ channels. Because of its impact on calcium cycling, levosimendan does not increase myocardial oxygen demand. Metabolism of levosimendan produces active metabolites with long half-lives, significantly extending levosimendan's duration of action.

PHARMACOLOGIC AGENTS FOR CHRONIC HEART FAILURE

Angiotensin Converting Enzyme Inhibitors (ACEIs)

Neurohormonal activation plays a pivot role in the pathophysiology of chronic heart failure and includes stimulation of the renin angiotensin aldosterone system (RAAS). Renin is secreted by the kidney and catalyzes the conversion of angiotensin I from angiotensinogen. The angiotensin-converting enzyme (ACE) then converts angiotensin I to angiotensin II, which is a potent vasoconstrictor that also induces the release of aldosterone from the adrenal gland, resulting in sodium and water reabsorption within the nephron. In addition, the generation of angiotensin II decreases the production of the potent vasodilator bradykinin. The net effect of RAAS stimulation is a significant increase in ventricular preload and afterload. ACEIs have been shown to induce a significant improvement in symptoms and survival in adult patients with heart failure [16]. Studies demonstrating an improvement in outcomes in children have not been published. Captopril and enalapril are commonly used ACEIs in the management of chronic heart failure. ACEIs favorably alter ventricular loading conditions by reducing ventricular reload, as a result of venodilation and a decrease in the reabsorption of sodium and water, and by vasodilating arterial resistance vessels. ACEIs have also been shown to induce ventricular remodeling and improve ventricular function [17]. ACEIs should be initiated as acute vasoactive sup-

port is weaned in the acute care setting. ACEIs should be continued indefinitely, even after normalization of cardiac function, although the duration of therapy remains uncertain.

Angiotensin Receptor-Blocking Agents (ARBs)

ARBs inhibit sodium reabsorption and fluid retention by acting at the level of the angiotensin receptor in the adrenal gland. Given that there are enzymes other than ACE which can convert Angiotensin I to Angiotensin II, ARBs theoretically provide a more comprehensive inhibition of the RAAS [18]. The efficacy of ARBs is similar to that of ACEIs [18, 19]. ARBs have become part of the armamentarium in the treatment of adults with heart failure where they are used as an alternative to ACEIs due to side-effects or in addition to in patients with persistent symptoms despite receiving optimal dosing of an ACEI and beta-blocker. ARBs remain an unproven therapy for pediatric heart failure. Also, just as inhibition of neurohormonal activation with ACEIs has been shown to induce ventricular remodeling so too has ARBs [17-19].

Diuretics

Diuretics such as furosemide have been studied in adults and demonstrated to be effective at relieving symptoms of congestion however their impact on outcomes is less clear [20]. Electrolyte disturbance are exceedingly common and include progressive hyponatremia, hypokalemia, hypomagnesemia and hypocalcemia. Loop diuretics act within the nephron by inhibiting the Na/K/2Cl cotransporter in the thick ascending loop of Henle. The net effect is a reduction in the absorption of sodium and water. As discussed above, diuretics decrease systemic venous return and congestion but have no impact on output unless the ventricle falls onto the steep portion of its pressure stroke volume curve. Thiazide diuretics are often used in conjunction with loop diuretics, as they have been shown to significantly enhance the effect of loop diuretics [21]. Their mechanism of action within the nephron involves inhibition of the Na/Cl cotransporter in the distal convoluted tubule.

Aldosterone Antagonists

Aldosterone antagonists such as spironolactone work both by inhibiting the aldosterone receptor in the distal nephron. Large, randomized, placebo-controlled trials in adults have demonstrated that aldosterone antagonists in addition to diuretics and ACEIs significantly improve symptoms and reduce mortality in adults with severe systolic heart failure [22]. Another theoretical indication for adding an aldosterone antagonist to a diuretic regimen consisting of a loop and thiazide diuretic is to provide complete sequential nephron blockade in attempt to overcome diuretic resistance [21]. Despite the favorable impact of these agents in adult heart failure, their benefits are yet unproven in children. Nonetheless, these agents are commonly used in children with unrelenting, severe heart failure.

β Adrenergic Antagonists

As described above, sympathetic activation plays a pivotal role in the progression of heart failure. Large random-

ized controlled trials in adult heart failure have demonstrated a significant improvement in mortality initially with metoprolol and subsequently with carvedilol, a non-selective β -blocker and α -1 receptor blocker [23, 24]. β -blockers are essential first-line therapy in patients with heart failure and left ventricular systolic dysfunction, regardless of the etiology. Shaddy and colleagues conducted the first randomized, double blind study of β -blockers in pediatric heart failure (n=161) [25]. The trial failed to demonstrate a significant improvement in regards to function, symptoms or outcomes. However, there were significant limitations to the study including sub-optimal dosing and limited enrollment. Though largely used in the adult population for the treatment of heart failure of diverse etiology (examples include ischemic, hypertensive and idiopathic), it remains to be determined whether these agents improve outcomes in pediatric heart failure.

CONCLUSION

The ultimate goals of pharmacologic support of heart failure are to improve symptoms and cardiac output in acute heart failure and to maintain and restore heart function in the chronic setting. Ensuring that oxygen delivery is sufficient to meet metabolic demand is essential and requires a clear understanding of circulatory physiology and hemodynamic disturbances that are present in the setting of acute and chronic. Once the hemodynamic profile is defined, a determination of the ideal pharmacologic strategy for improving cardiac and circulatory function can be made.

CONFLICT OF INTEREST

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

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