Acute Heart Failure in Childhood: Pathophysiology and Treatment

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Introduction

The underlying mechanisms and pathophysiology of acute heart failure in the pediatric age group differ significantly in many respects from that seen in adult patients. Therefore it is important that the differences in structure and function of the myocardium in the newborn, the transition to a more adult pattern in the older child and the different causes of acute heart failure in children compared to adults, be taken into account in considering therapy.

With the constantly changing physiology in the human newborn it is difficult to precisely follow the mechanical changes in the circulation. Consequently much of our knowledge of myocardial performance in the neonate comes from observations made in newborn animals. Although it is sometimes difficult to extrapolate from animal data to humans, it does provide us with a useful framework for studying the changes in the structure and function of the circulation after birth.

Myocardial Development in the Child

At the time of birth a major transition occurs in the neonate with a switch from right ventricular (RV) to left ventricular predominance (LV). During fetal life, the high pulmonary vascular resistance (PVR) results in the majority of the RV output passing through the ductus arteriosus into the aorta. In order to generate these systemic pressures the myocardium of the RV is more well developed than that of the LV. With the initiation of spontaneous respiration PVR rapidly falls, the ductus arteriosus closes and systemic vascular resistance (SVR) rapidly increases. This switching of ventricular dominance, with increased pressure and volume work of the LV, is largely due to the myocyte hyperplasia and hypertrophy that occurs with time, myocyte replication ceasing in the human neonate at around 3–6 months [1]. There is minimal cellular proliferation in the RV, with slower growth in early neonatal life [2, 3] and very little increase in wall thickness, at a time when LV growth is at its most rapid [4, 5]. At a cellular level, structural development of the contractile apparatus occurs with increased number, density and regularity of sarcomeres [8], and maturation of mitochondrial architecture and function. As the newborn develops, the cross sectional area of the myocyte that is contractile increases from 30% in the foetus, to the adult value of 60%, a process that evolves over a period of years.

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The structural and biochemical immaturity, as well as the ongoing maturation, have significant functional effects on the mechanical properties of newborn myocardium [7, 8]. Newborn animals demonstrate a decreased active tension (developed force) for a given change in myocardial fibre length, when compared to mature animals, together with diminished velocity of shortening and increased resting tension at any given length. It is probable that this is due in large part to the diminished contractile mass of the newborn. It has been suggested that the newborn myocardium is less compliant and therefore responds less well to preload augmentation than the adult [8–11]. However, age dependent variations in ventricular compliance and response to volume loading have been described as occurring over the first weeks of life [10, 11]. The improved LV performance is possibly a reflection of its changing post natal workload, coinciding with an increase in contractile units, altered myofibrillar organization and a change in the properties of regulatory proteins [12–14]. Although experimental evidence suggests that newborn myocardial contractility exceeds that of adult hearts [8, 12, 15], inotropic stimulation of the myocardium in normal newborns does not substantially improve functioning.

Finally, changes in afterload stress are an accompaniment of the physiological adaptations of birth. The increase in SVR, dilatation of the LV as it takes up its volume load and the high hematocrit all contribute significantly to increased afterload.

Given the relatively fixed stroke volume, the newborn will increase his cardiac output mainly by increasing heart rate, even though the autonomic system is relatively underdeveloped in the neonate. When compared to the adult, sympathetic innervation in the newborn remains incomplete, as are the stores of endogenous norepinephrine. As a consequence of this, the newborn myocardium is much more sensitive to exogenous norepinephrine than the adult, a difference which tends to become less pronounced over the first few weeks of life. The relevance of this becomes important when one examines the effect on the dopaminergic system. Driscoll [16] has shown that while there was little difference in the response of isolated neonatal myocardium to isoproterenol, dopamine resulted in an increasing contractility, which was age dependent. In the intact neonatal animal, dopamine and dobutamine produce a greater increase in cardiac output with only mild increases in heart rate when compared to isoproterenol [17]. In addition, dopamine produced an increase in renal blood flow, which confirmed that the dopaminergic effect on renal vessels also exists in the newborn animal. Since the effect of dopamine is largely mediated via release of endogenous noradrenaline, this is indirect evidence that the sympathetic nervous system is immature in the immediate newborn period, and only matures later in postnatal life.

In terms of the newborn's response to exogenous catecholamines, animal studies have shown that the newborn has diminished contractile and pressor response to both α and β-sympathomimetics as well as vasodilators. This may be due to the fact that myocardial function is at the limits of its capacity in the newborn and so the response to further stimulation is limited.

Thus the newborn animal is characterized by a high cardiac output, function near the peak of the Starling curve, limited contractile reserve and high afterload

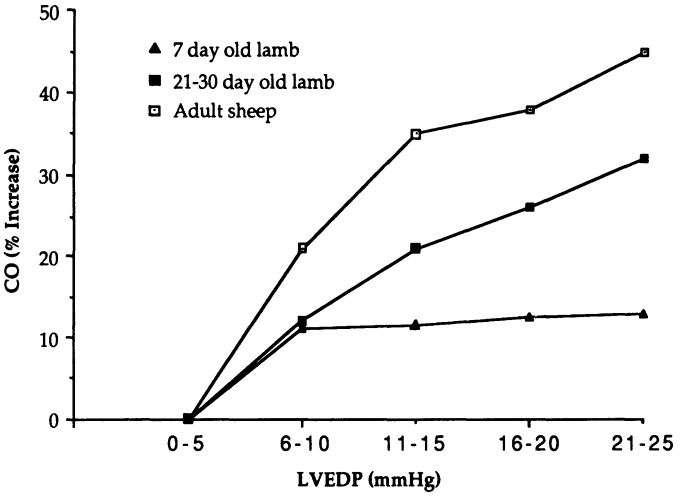

Fig. 1. Changes resulting from fluid infusion of 5 ml/kg in newborn and adult sheep. Note the marked difference in the normal ability to augment cardiac output (CO) with volume loading in the newborn animal compared to the adult. (From [11], with permission)

(Fig. 1). It is not therefore surprising that there is poor tolerance to further demands on cardiac output increases and thereby limited reserve [11]. In this situation the ability to redistribute cardiac output to preserve vital organ function is of paramount importance and again the newborn exhibits immaturity of neurogenic vascular control and local tissue autoregulation. However despite the high resting heart rate, newborns can substantially increase this, making use of the increase in contractility associated with this maneuver. There are limitations to this however, with decreased filling time leading to decreased time for coronary perfusion and increased myocardial oxygen consumption.

With increasing age the distinction between the adult and child become less pronounced. After the first few months of life the LV and RV have assumed the adult configuration and heart size increases with growth to reach adult dimensions by late adolescence. Although no clear difference exists between cardiac performance in the normal adult and child, the absence of ischemic heart disease in the latter enables them better to tolerate changes in preload, afterload or contractility. The physiological changes that occur during acute cardiac compensation such as hypotension and tachycardia, which may result in ischemic injury in the adult, can be well tolerated in the child, as can the consequences of prolonged hypoxia.

The Pathophysiology of Acute Heart Failure in Children

Acute heart failure in the pediatric age group may be caused by a variety of both cardiac and non-cardiac diseases and can be best considered according to whether they predominantly affect the left or right ventricle (Table 1).

Table 1. Causes of acute heart failure in children

Left sided lesions	Right sided lesions
Obstructive lesions	*Obstructive lesions*
Critical aortic/mitral stenosis	Critical pulmonary stenosis
Neonatal coarctation	Pulmonary atresia
Aortic atresia	
Lesions with excessive pulmonary blood flow	*Pulmonary hypertension*
Hypoplastic left heart syndrome	PPHN
Patent ductus arteriosus	Postoperative after repair of CHD
A-V Canal	Acute lung injury (ARDS)
Total anomalous pulmonary venous drainage	
Truncus arteriosus	
Ischemic/degenerative lesions	
Anomalous coronary artery	
Endomyocardial fibroelastosis	
Myocarditis/cardiomyopathy	
Kawasaki's disease	
Transient myocardial ischaemia	
Low output state	
Post C-P bypass	
Hypoxic/ischemic injury	
Gram negative septicaemia	
Meningococcemia	

Severe obstructive lesions of the left ventricle in the newborn commonly present soon after birth, as the underdeveloped myocardium in the newborn is unable to overcome outflow tract obstruction. In some of these left-sided lesions no symptoms may be evident while the ductus arteriosus remains patent, as ventricular output can bypass the obstruction. It is not uncommon for these infants to present in acute heart failure several weeks after birth, an event which is precipitated by ductal closure. The ventricle rapidly dilates and pulmonary edema results.

Congenital heart lesions associated with increased pulmonary blood flow may also present as acute heart failure in the newborn failure. The infant with total anomalous pulmonary venous drainage (TAPVD), typically has pulmonary edema with a normal heart size. In truncus arteriosus, on the other hand, the typical features are pulmonary edema with cardiomegaly. A large number of these infants will also have ischemic changes on the ECG as the truncal valve is frequently incompetent and the resulting high aortic run off and low diastolic pressure interferes with coronary perfusion.

Patent ductus arteriosus is frequently seen in the newborn infant in conjunction with severe hyaline membrane disease. The resulting high pulmonary blood flow may result in severe heart failure and has been implicated as one of the aggravating factors in the development of bronchopulmonary dysplasia.

Although ischemic/degenerative lesions are uncommon causes of acute heart failure in children, they warrant consideration when clinical findings exclude

structural heart defects. In the group with anomalous coronary arterial supply, 90% involve the origin of the left coronary from the pulmonary artery and present with acute left ventricular failure and ischemic changes on ECG. Kawasaki's disease is a microvasculitis which involves the coronary circulation, giving rise to ischemia and LV failure. Endocardial fibroelastosis is one of the variants of cardiomyopathy which present in the newborn with gross cardiomegaly. The typical appearance is of thickening of the endocardial lining of both the LV and valves and may either exist as a primary condition or be secondary to aortic and mitral valve disease. The most common alternative cause for cardiomyopathy in childhood is secondary to viral diseases, although the virus itself may be difficult to isolate. These children frequently present with acute heart failure, often improve with a combination of vasodilators and inotropes, only to be left with a severe congestive cardiomyopathy. Transient myocardial ischemia is a syndrome that presents with tachypnea and cyanosis in the newborn period, most frequently after a complicated pregnancy. The features are cardiomegaly and subendocardial ischemic on ECG, together with LV dysfunction and tricuspid valve regurgitation.

Of the non-cardiac causes, septic shock and hypoxic/ischemic injury represent the most common etiologies. Sepsis as a cause of acute heart failure is less common in the pediatric age group compared to the adult, except in the newborn period. The most common organisms seen in this age group are gram-negative, whereas the gram-positive organisms predominate in the older child. The other major cause of acute heart failure seen in children is that seen secondary to hypoxic ischemic multiple organ injury such as occurs in sudden infant death syndrome or near drowning with decreased cardiac output, elevated CVP and PWP [18].

Monitoring of Acute Heart Failure in Children

Invasive monitoring is as much part of the management of acute heart failure in children as in adults. Indwelling arterial lines can be used in peripheral vessels such as the radial, dorsalis pedis or posterior tibial arteries, complications rates, in terms or ischemia, being very low in children because of the absence of peripheral vascular disease. Central venous catheters are also commonly used both for CVP measurements and for the infusion of inotropic drugs. Access to the central venous circulation can be obtained through a variety of routes, the most commonly used being the internal jugular approach, which in expert hands has a minimal serious morbidity rate even in small infants [19, 20]. The subclavian approach has also been extensively used in children of all ages, including premature neonates, with complication rates comparable to the internal jugular approach. The correct siting of the catheter tip of the central venous line is particularly important in small infants as the thin walled right atrium is susceptible to perforation by misplaced catheters.

The value of pulmonary wedge pressure (PWP) measurement in children with acute heart failure is less clear, especially when one examines it in terms of a risk/benefit analysis. Although Pollack et al. [21] have shown that bedside pulmonary

artery catheterization is feasible in a pediatric ICU setting there was a significant complication rate associated both with obtaining central venous access and in maintaining catheter position in this study. In our experience, in the pediatric patient, due in large part to the absence of ischemic heart disease, there is little difference between right- and left-sided filling pressures, except in the presence of structural heart disease. Given this fact and the technical problems associated with placement of pulmonary artery catheters, little further useful information is available from wedge pressure measurements which cannot be obtained from a CVP line. Consequently we will only use a PA catheter in pulmonary hypertension and acute right heart failure, where it may be important to measure PA pressure.

Cardiac output measurements, by either thermodilution or dye dilution are also widely used in children. While the thermodilution technique has found wide acceptability in adult practice because the measurement is easy to perform and reproducible, there are problems associated with its use in infants and small children. Repeated boluses of iced saline represent a substantial fluid load to a small child. The thermodilution technique, unlike dye dilution, will not detect intracardiac shunts and the small caliber of pulmonary arteries in a child will, sometimes result in the thermistor tip impinging against the vessel wall, resulting in inaccurate readings. Although dye dilution cardiac outputs are more technically difficult and time consuming to perform, there are still some reasons to prefer this measurement over thermodilution in smaller children.

Improvements in technology in recent years have resulted in considerable advances in the accuracy and ease of application of non invasive monitoring. Nowhere is this more so than in the continuous monitoring of oxygen levels by pulse oximetry. Fanconi [22] has shown an excellent correlation between arterial saturations measured by pulse oximetry and those measured directly from samples drawn from arterial lines and superior to transcutaneous PO_2 measurements in a series of children in acute heart failure. This technique has replaced the transcutaneous PO_2 monitor as the preferred method of continuously monitoring oxygen levels in critically ill children. A new era of non invasive measurements of cardiac output using echo technology is just beginning which will hopefully further reduce our reliance on invasive monitoring techniques.

Management of Acute Heart Failure in Children

The management in acute heart failure are based on similar principles to those used in the treatment of adults, in terms of the manipulation of circulating volume and the use of vasoactive drugs, simplified to some extent because one is rarely dealing with underlying myocardial ischemia. Any differences in approach between the adult and the child are largely confined to the newborn, where the compliance of the myocardium and the underdevelopment of the autonomic nervous system may result in different responses to volume loading and inotropes.

Inotropic Therapy

Most of our knowledge on the use of inotropes in children comes from studies in adult patients. Although they are extensively used in pediatric patients, reports on their efficacy are based on non-controlled, non-randomized and at times poorly documented studies. Most of the studies that include specific hemodynamic data come from the use of inotropes in the low output state following cardiac surgery in children outside the newborn period. Studies of their effects in the human newborn are anecdotal and lack relevant hemodynamic measurements and most of our knowledge in this area therefore comes from studies in newborn animals.

Dopamine: Studies on the use of dopamine in newborn animals suggest that there is a relative insensitivity of myocardium to dopamine [16, 17] related to decreased density of synaptic terminations, decreased neurotransmitter release and number of β receptors. There is also decreased affinity for receptors and activity of adenylate cyclase [7]. Others have demonstrated improvement in cardiac output and SVR with low dose dopamine with additional benefit at progressively higher doses [23].

Studies in human newborns have generally been anecdotal and somewhat contradictory [24–27]. Evidence has been presented for the need for high dose dopamine to achieve measurable clinical effect, yet others have shown demonstrable effects at low doses. Seri [24] has proposed decreased clearance of dopamine in the neonate may explain this discrepancy, however Padbury [26] demonstrated equivalent clearance rates in infants to those reported in adults. In addition they reported significant increases in mean arterial pressure (MAP) at low doses (2 μg/kg/min). On balance it would seem demonstrable clinical benefit can be achieved with dopamine using modest doses, with a titratable dose-response increase in effect and little likelihood of side effects. Dopamine can be expected to increase MAP, improve ventricular function by echo estimation, and urine output with a low incidence of side effects at doses < 10 μg/kg/min.

The most extensive body of knowledge concerning the use of dopamine in children outside the newborn period comes from its use in the low cardiac output state following open heart surgery. Williams [28] has shown a significant increase in cardiac output and heart rate at a dopamine infusion rate of 7.5 μg/kg/min in 9 children who underwent the Fontan procedure (right atrial to pulmonary artery bypass), while there was a fall in left atrial pressure (LAP). These effects are similar to those one would anticipate in an adult patient, except that the fall in LAP contrasts to adults where PWP tends to rise with dopamine. Stephenson [29] studied the effect of the drug infused at a rate of 8 μg/kg/min after corrective cardiac surgery in 28 children (mean age 7 years) and found significant increases in cardiac output and heart rate, with no change in MAP, LAP or SVR. Lang [30] used dopamine at 5–25 μg/kg/min in 5 children with low cardiac output (age 1 month to 2 years) following open heart surgery. He found that there was no significant effects on hemodynamics until a dose of 15 μg/kg/min was reached, at which cardiac output, arterial pressure and heart rate all increased. The fact that these changes did not reach significance at lower doses,

in contrast to the previous study, may be explained by the small study population. Finally Driscoll [31] studied the effect of dopamine in 10 children (mean age 10 years) with heart disease during cardiac catheterization. At doses of both 2 and 7.75 μg/kg/min there was a highly significant increase in cardiac output, stroke volume and fall in SVR, with no change in heart rate or PWP. In summary, these data would suggest that while animal studies would suggest that higher doses of dopamine are necessary to produce an inotropic response in newborns, both human neonates and older children seem to respond to dopamine in a similar way to adults. Tachycardia is less problematic at a dose of < 10 μg/kg/min and there is no change in PWP or LAP, even at high levels of dopamine.

Dobutamine: Experience of its use in pediatric age group is limited to a relatively few studies in children with heart disease. Driscoll [32] demonstrated increases in cardiac output, stroke volume and arterial pressure with doses of both 2 and 7.75 μg/kg/min in a group of children (mean age 9.5 years) with congenital heart disease undergoing cardiac catheterization. Heart rate was unchanged, while PWP fell. Bohn [33] studied the effect of dobutamine in a group of children with low cardiac output after open heart surgery (mean age 5 years) at infusion rates of 1–10 μg/kg/min. They confirmed the tendency for improvement in cardiac output and arterial pressure with increasing dosage, however significant tachycardia required discontinuation of dobutamine in 4 of the 11 patients. No change in SVR or LAP were noted. A further study of 12 children in low cardiac output, without structural heart disease, using doses from 7.5–10 μg/kg/min observed an increase in cardiac output and arterial pressure, with a slight but significant increase in heart rate and a fall in SVR [34]. PWP was not measured in this study. Perkin [35] also evaluated the effect of dobutamine on 33 patients (mean age 5 years) with acute heart failure due to either cardiogenic or septic shock, using doses from 2.5–10 μg/kg/min. Cardiac output improved, but there was no significant change in arterial pressure or heart rate. In this particular study hemodynamic responses to dobutamine varied somewhat according to age and underlying diagnosis. In those children less than one year of age there was a significant rise in PWP, which was not seen in children > 1 year, which resulted in one child developing pulmonary edema. The augmentation of cardiac output in the group of patients with cardiogenic shock was far more impressive than those with septic shock. The tendency for PWP to increase with dobutamine was confirmed in a study by Berner [36] where dobutamine was used in combination with phentolamine after cardiopulmonary bypass. Phentolamine alone resulted in a rise in cardiac output with a fall in PWP but while the addition of dobutamine resulted in a further augmentation of cardiac output, PWP returned to its previously elevated level.

Neonatal experience on the use of dobutamine is sparse and confined to animal studies. These have shown augmentation of cardiac output and decreased SVR [17]. Fiser [37] has also found an increase in cardiac output with no change in stroke volume or LAP with dobutamine in newborn animals. The augmentation of cardiac output was due to an increase in heart rate in this study. There is insufficient data to recommend its use in human newborns. The effects of dopamine and dobutamine in the pediatric patient are summarized in Table 2.

Table 2. Summary of published data on inotropic agents in children

Source	Patient population	Inotropic agent	Dose (μg/kg/min)	Effect on			
				Cardiac output	Arterial pressure	Left arterial or PA wedge pressure	Heart rate
DiSezza et al. [25]	Neonatal Asphyxia	Dopamine	2.5	↑	↑		
Padbury et al. [26]	Neonatal Asphyxia Sepsis	Dopamine	0.5–8	↑	↑		
Walther et al. [27]	Neonatal Asphyxia	Dopamine	4–10	↑	↑		↑
Williams et al. [28]	Post op cardiac	Dopamine	7.5	↑		↓	↑
Stephenson et al. [29]	Post op cardiac	Dopamine	8	↑			↑
Lang et al. [30]	Post op cardiac	Dopamine	15	↑	↑		↑
Driscoll et al. [31]	CHD	Dopamine	2&7.75	↑			
Driscoll et al. [32]	CHD	Dobutamine	2&7.75	↑	↑	↓	
Bohn et al. [33]	Post op cardiac	Dobutamine	1–10	↑	↑		↑
Schranz et al. [34]	Trauma Shock	Dobutamine	7.5–10	↑CO	↑		↑
Perkin et al. [35]	Cardiogenic/ Septic shock	Dobutamine	2.5–10	↑CO		↑	

Isoproterenol: Before the advent of the more potent inotropes, isoproterenol was the sympathomimetic drug of choice to augment cardiac output in children. It was a particularly attractive option in the newborn, with their rate dependent cardiac output which could be driven through β_1 receptors in the myocardium. In older children it was shown to be ineffective in increasing cardiac output in postoperative cardiac surgery patients in one study, yet more effective than dobutamine in another. Animal studies on neonatal use indicate that for equivalent effects on cardiac output, isoproterenol produces a greater increase in heart rate than either dopamine or dobutamine [17]. Another important consideration in its use has been the possibility of myocardial damage induced by the inevitable tachycardia, although children may be able to tolerate this better than adults.

Isoproterenol is therefore likely to prove useful in situations where low cardiac output is associated with a slow heart rate, such as A-V block after cardiac surgery when pacemaker wires are not available and its pronounced chronotropic effect via β_1 receptor stimulation may restore normal conduction. There is

a tendency to develop tachyphylaxis with prolonged usage and the chronotropic and inotropic effects are antagonised by acidemia (pH <7.2). Because of its pronounced effect on β_2 receptors there is a significant peripheral vasodilatation in the older child and arterial pressure may in fact fall slightly, due to a decrease in diastolic pressure, while at the same time cardiac output increases. A similar effect on the arteriolar vessels is also seen to some extent in the pulmonary circulation, which in the past has made isoproterenol a drug of first choice when treating low cardiac output states associated with pulmonary vascular disease.

Epinephrine: Epinephrine is a potent inotropic agent for the newborn myocardium [7], its major disadvantages can impair renal function and mesenteric vasoconstriction has been associated with bowel necrosis. Rudolph [38] infused epinephrine in doses <1.0 μg/kg/min in three infants with severe heart failure, with resultant improvement in perfusion but urine output was unchanged. Similar beneficial effects have been rarely described. Although epinephrine is rarely used nowadays as a first choice inotropic agent, except during cardiopulmonary resuscitation because of the tendency to cause tachycardia and vasoconstriction, there are still instances where it may be used when the more commonly used inotropes fail to produce an effect. This is most likely due to overwhelming disease and in this instance we find that increasing the dopamine to >30 μg/kg/min rarely produces any improvement in output. In such instances we would commence an epinephrine infusion at 0.1 μg/kg/min, increasing to 1 μg/kg/min according to response. This should always be combined with vasodilator therapy.

Vasodilator Therapy

The use of vasodilator therapy in the treatment of acute heart failure in the pediatric age group is less well documented than the adult, but a clear rationale for their use can be proposed in children. The newborn infant, functioning at a high level of performance and limited reserve capacities, an acute preload stress or afterload increase, in addition to that imposed by postnatal adaptation, may be particularly harmful. Volume loads from L-R shunts, excessive volume administration or vasoconstriction from pharmacologic therapy may all lead to cardiovascular decompensation. A number of investigators have documented success with vasodilator therapy in both newborns and older children, in conditions where inotropes have failed or have described additional benefit in function with a combination of both vasodilators and inotropes.

Nitroglycerine (TNG): There are several studies which show the beneficial effect of changing preload with intravenous TNG after open heart surgery in children. Benson [39] found that by deliberately lowering LAP by 30%, cardiac output actually increased and SVR fell and that this improvement was further augmented when the patients were volume loaded to their original filling pressure (Fig. 2). The mean dose of TNG in this study was 20 μg/kg/min, which in an adult would produce hypotension, yet there was no change in arterial pressure,

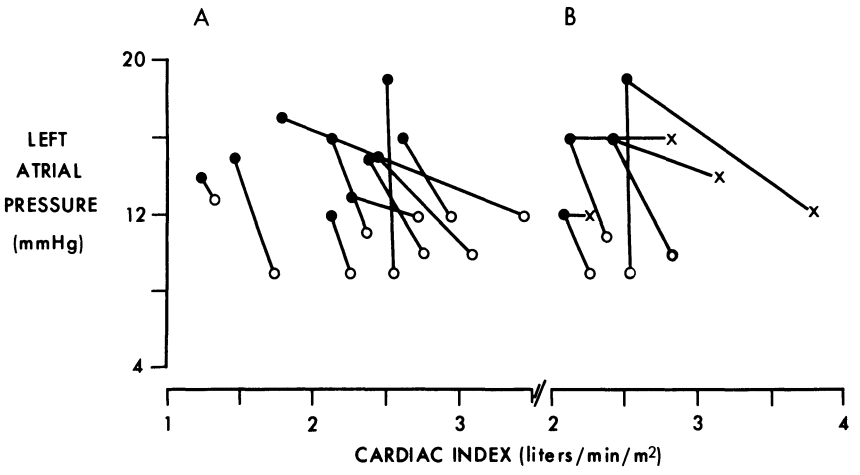

Fig. 2. Response to TNG in children with low cardiac output following open heart surgery. With a deliberate reduction in LAP of 30%, cardiac output increased from pre-infusion levels (A). Following volume loading to restore the LAP to the pre-infusion level in 4 patients there was further augmentation of cardiac output (B). (From [39], with permission)
● pre-infusion; O TNG; × volume loading

confirming its predominant preload effect in children. Ilbawi [40] used doses between 1 and 5 μg/kg/min in a group of 20 children after repair of congenital heart defects and found an increase in cardiac output and a fall in SVR only when the dose exceeded 3 μg/kg/min. This study has illustrated a dose related effect on the peripheral vascular bed with doses <2 μg/kg/min resulting in venodilation. Dosage increases from 3–5 μg/kg/min were characterized by progressive arteriolar dilatation, decreases in SVR and a rise in cardiac output. In addition a fall in PVR in patients with pulmonary hypertension was noted.

There is little information available in neonates. In an animal model of group B streptococcal sepsis induced pulmonary hypertension, Rudinsky [41] could demonstrate no selective reduction pulmonary artery pressure and noted a fall in cardiac output. These animals were likely volume depleted with low-normal filling pressures. Butt [42] used TNG in 10 newborn infants with low cardiac output secondary to congenital heart disease, asphyxia or sepsis. Doses used were from 1–12 μg/kg/min, and all infants were on concurrent inotropic therapy (dopamine/isoproterenol/epinephrine). Arterial pressure, urine output and arterial pH improved.

Sodium Nitroprusside (SNP): Experience on the use of SNP in the treatment of acute heart failure in children mirrors that in adults, both in terms of effect and dosage. Appelbaum [43] used SNP in 16 infants <18 months of age after cardiovascular surgery. All had documented low cardiac output, increased SVR and arterial pressure. Doses used were from 2.5–12 μg/kg/min with the aim to reduce arterial pressure to the age appropriate level. They documented a fall in filling pressures, a rise in cardiac output and no change in heart rate. In addition volume loading to achieve pretreatment filling pressures resulted in additional

improvement in cardiac output. In their study on SNP in children after open heart surgery, Stephenson [29] in fact showed that SNP in a dose of 3 μg/kg/min resulted in a fall in arterial pressure and SVR but no improvement in cardiac output. This adverse effect can be explained by the fact that both left- and right-sided filling pressures fell in this study. The importance of maintaining adequate filling pressures in order to achieve maximum benefit from vasodilator therapy is underlined by this and studies using TNG.

Williams [28] found that cardiac output increased while SVR and MAP fell, in a group of patients with low cardiac output after the Fontan procedure. Benzing [44] has also shown that SNP produced a fall in arterial pressure and SVR and an 80% rise in cardiac output in children after corrective cardiac surgery.

There is little well documented hemodynamic data on the use of SNP in newborns and most of the published literature consists of reports on the empirical use of the drug in a variety of low cardiac output states which include sepsis, PPHN and RDS. The trend is for an improvement in peripheral perfusion, urine output and pH status, which tends to confirm the findings regarding the efficacy and safety of the drug in older children.

Probably the most clear-cut indication for the use of vasodilator therapy in the pediatric age group is in the treatment of congestive cardiomyopathy. These patients present in a low cardiac output state with high filling pressures and a low arterial pressure. The conduction disturbances frequently seen in this disease makes the use of inotropes hazardous, particularly digoxin. Beekman [45] has demonstrated significant hemodynamic and symptomatic improvement in 13 children (5 of whom were less than 1 year of age) with the use of vasodilator therapy. In this instance they used either SNP or hydralazine. We on the other hand favor the use of intravenous TNG (1–5 μg/kg/min) because of its beneficial effect in reducing preload and improving coronary blood flow, without any fall in arterial pressure. There is little doubt that most children with congestive cardiomyopathy will improve with the use of vasodilator therapy alone, without necessarily having to resort to inotropes.

Amrinone: Although there is a considerable experience of its use in low cardiac output states in adults, information its use in the pediatric age group is limited. Neal [46] has shown an improvement of 93% and 143% in cardiac output in two children with congestive cardiomyopathy, at an infusion rate of 5–10 μg/kg/min. Recently age-dependent differences in performance have been described in various animal species with a pronounced negative inotropic effect in newborn [47, 48]. Vasodilatation has consistently been observed, seeming to occur in a dose-dependent fashion with increasing dosage. Despite its demonstrated benefit in adults and the fact that the described neonatal effects may represent species differences, the indications for the use of amrinone in children are, as yet, unclear.

Vasodilator/Inotrope Combination Therapy: Perhaps the most logical pharmacological approach to the child with acute heart failure is to use a combination of vasodilators and inotropes. Both Williams et al. [28] and Stephenson et al. [29] have adopted this approach by the addition of SNP in children receiving do-

pamine infusions for low cardiac output states following cardiac surgery. In both studies there was a further improvement in hemodynamics with the addition of the vasodilator. Berner [36] used the combination of phentolamine (10 μg/kg/min) and dobutamine (5 μg/kg/min), this time using the vasodilator first and then adding the inotrope. They found that the combination of the two drugs produced a greater improvement in cardiac output than the vasodilator alone. It is also our practice to use the vasodilator/inotrope combination; we favor the combination of dopamine and nitroglycerine together, especially when one has to use rates of dopamine > 10 μg/kg/min, where the vasoconstricting effects will be attenuated by vasodilator therapy.

Pulmonary Hypertension and Acute Right Ventricular Failure

Diseases which result in pulmonary hypertension and acute right heart failure are commonly encountered in the pediatric age group. Right-sided obstructive lesions of the RV outflow tract usually present with cyanosis in the immediate newborn period, due to poor pulmonary blood flow. The immediate treatment of these lesions is directed to maintaining ductal patency with prostaglandins, and thereby providing adequate pulmonary blood flow, prior to a surgical shunt procedure. With severe obstructive lesions in the newborn period there is frequently an abnormality in myocardial development and pulmonary stenosis and atresia are commonly associated with right ventricular hypoplasia.

The most common cause of RV failure in the newborn period is persistent pulmonary hypertension of the newborn (PPHN). This occurs secondary to a variety of pre-or postnatal insults to the lung. Failure of the normal mechanisms whereby the pulmonary vessels dilate and become less muscular in the first 48 hours of life, results in persistent elevation in PVR, pulmonary hypertension and R-to-L shunting at ductal level. These infants will go on to die of RV failure unless this cycle is reversed.

The other situation where acute right heart failure is seen is congenital heart defects associated with L-to-R shunts. The increased pulmonary blood flow in these lesions results in changes in pulmonary vessels with intimal hyperplasia and increased smooth muscle proliferation. These patients demonstrate increased reactivity in the pulmonary vascular bed which are responsible for acute life-threatening rises in pulmonary artery pressure and right ventricular failure in the immediate postoperative period [49, 50]. This occurs after repair of lesions such as VSD or A-V canal. The management of this pulmonary hypertension in both the newborn and older child is by ventilatory and pharmacological manipulation of pulmonary vascular resistance.

Acute Right Heart Failure: Ventilatory Management

The abnormal pulmonary vascular bed is highly susceptible to changes in both blood gases and lung mechanics. The former has been used to advantage in infants with PPHN. Drummond [51] has shown that hyperventilation to a $PaCO_2$ less than 25 mm Hg and a pH greater than 7.6 results in marked increases in

PaO_2 secondary to a reduction in the pulmonary artery to systemic artery pressure ratio (PAP/SAP). Although hyperventilation is widely accepted as a method of treating increases in PAP in infants, until recently little information was available on the response of the pulmonary vascular bed outside the newborn period. Salmonpara [52] has recently shown that the pulmonary vascular bed in the adult may respond in a similar fashion. They examined the effect of hypo- and hypercarbia on PVR in a group of patients undergoing coronary artery bypass surgery and showed that PAP increased significantly with a rise in $PaCO_2$ and decreased during hypocarbia. This effect of CO occurred independent of any change in tidal volume or FRC. It is certainly our experience that the pulmonary vascular bed responds very readily to hyperventilation in the postoperative period and that this change in PVR is predominantly pH - rather than CO_2 mediated.

As well as the actual changes in blood gases there is additional evidence that there is a beneficial effect of positive pressure on lung mechanics which helps in controlling PAP. Mechanical ventilation by stretching the lung releases prostaglandins, which cause pulmonary vasodilation and help explain the rapid reductions in PAP seen immediately after the onset of hyperventilation, before there has been any time for a change in $PaCO_2$.

Changes in lung volume may also account for the abrupt rises in PAP when weaning from mechanical ventilation to CPAP. Jenkins [53] has shown that when weaning from low IMV to CPAP in a group of children following cardiac surgery there is a fall in FRC and a rise in PAP and PVR, especially in children with underlying pulmonary hypertension. For these reasons we believe that manipulation of PAP and PVR through changes in blood gases and lung mechanics is of primary importance in the management of patients with reactive pulmonary vasculature.

With these principles in mind, we have adopted the following strategy for the management of patients at risk for the development of postoperative pulmonary hypertension and acute RV failure [54]. These children are identified on the basis of preoperative hemodynamics. A PA line is placed at the completion of bypass and the object of postoperative management is to maintain PAP $< 50\%$ of SAP. The patients are paralyzed and electively hyperventilated to a $PaCO_2$ of 30–35 mm Hg for the first 12 hours. If at the end of this period PAP remains $< 50\%$ of SAP, the muscle relaxant is discontinued and the patient is weaned gradually to CPAP using the IMV mode of ventilation, as long as PaO_2 and $PaCO_2$ are normal. If there is persistent elevation in PAP during this period, as distinct from the normal brief rises that occur with coughing, suctioning etc., muscle paralysis and hyperventilation are reintroduced for a further 24 hours, before weaning is attempted again. If this mild degree of hyperventilation fails to control PAP, the $PaCO_2$ is reduced further to 25–30 mm Hg for the next 12 hours. We adopt this approach since manipulation of $PaCO_2$ and changes in hydrogen ion concentration are the simplest and most consistent method of reducing PAP while at the same time causing the least change in systemic hemodynamics. If this strategy proves successful in controlling PAP, the patient is weaned from mechanical ventilation in steps, first by allowing the $PaCO_2$ to rise to 30–35 mm Hg and then stopping muscle relaxants before weaning to CPAP.

Inotropic Therapy

Certain misconceptions exist about the use of inotropic drugs in diseases of the right heart and pulmonary circulation, the principal of which is that these drugs may cause increases in PAP and PVR. The source of this confusion arises from considering the pulmonary circulation in isolation to the systemic. Changes in the systemic circulation have a great influence on both PAP and PVR. A fall in LV output results in a decrease in pulmonary blood flow and a rise in both PVR and the PAP/SAP ratio, whereas an improvement in LV performance will result in an increase in pulmonary blood flow and a fall in PVR and the PAP/SAP ratio. When assessing the effects of inotropic drugs on the pulmonary circulation these changes in hemodynamics must be taken into account and attention focused on the beneficial effects on LV and RV function. Of the inotropes currently in use isoproterenol is known to have exclusively β-sympathomimetic properties which will cause a drop in PVR as well as SVR, at the same time as augmenting cardiac output.

The situation with dopamine is less clear. When the inotropic effect is isolated from the effect on vessels themselves, there is evidence that dopamine causes a mild degree of pulmonary vasoconstriction, if one examines its effect independent of changes in cardiac output [29, 55]. However, when its inotropic effects on ventricular performance are examined in patients with pulmonary vascular disease, there is no evidence that it increases PVR, rather the contrary. Holloway [55] studied the effect of dopamine (2–16 μg/kg/min) in 10 adult patients with pulmonary hypertension and found that while PAP increased it did SAP, so that the ratio PAP/SAP was unchanged. Furthermore, cardiac output increased, PVR decreased and RV pressure actually fell, so there was on overall hemodynamic improvement. Williams [28] found no change in PVR with dopamine 7.5 μg/kg/min in postoperative Fontan patients. Neither Stephenson [29] nor Driscoll [31] showed any adverse effect of dopamine on PAP or PVR in a group of children after corrective cardiac surgery, while cardiac output increased. The results of these studies would indicate that there is no evidence that dopamine, in doses that primarily produce β-adrenergic stimulation (5–10 μg/kg/min), has any adverse effect on the pulmonary circulation, but on the contrary may lead to a decrease in PVR and PAP/SAP ratio by its beneficial effect on ventricular performance and cardiac output. When combined with a systemic vasodilator, (SNP) this beneficial effect has been shown to be further enhanced [29].

Vasodilator Therapy

The value of "pulmonary" vasodilators in the treatment of pulmonary hypertension is debatable. Most of our information about these drugs comes from the treatment of adults with primary pulmonary hypertension and infants with PPHN. The adult studies consist of small series with limited hemodynamic data and little information regarding potential long-term benefit. Vasodilators that have been used include hydralazine, isoproterenol, nifedipine, SNP and TNG. The number of vasodilators that have been tried attests to the fact that there is

no genuine pulmonary vasodilator (i.e. a drug that consistently dilates the pulmonary vascular bed in preference to the systemic circulation). Of the drugs most commonly used to treat pulmonary hypertension in children, tolazoline is perhaps best known. Although claims have been advanced for its selective action on the pulmonary vascular bed, particularly in infants with PPHN, it also has a pronounced systemic effect. As well as being a vasodilator, tolazoline has sympathomimetic properties, which will change systemic output. For these reasons, its effect as a pulmonary vasodilator is often variable. Reports of its use in infants with PPHN consist of small series with unpredictable responses. Both Drummond [51] and Peckham [56] have reported small numbers of favorable responders in their series, as well as infants whose condition deteriorated with the use of the drug. Although both Wheller [49] and Jones [50] have used the drug successfully to ablate acute pulmonary hypertensive crises during and after cardiac surgery, the drug does have a serious side effect, namely gastrointestinal hemorrhage, which cautions against its overenthusiastic use.

Summary

The principles of pharmacological support for the failing heart in children is based on a similar approach to the adult. There is no evidence that the young infant responds less predictably to inotropes than the older child, except that part of the response in the infant may be more rate dependent. The greatest body of experience has been accumulated with dopamine, which produces an effective inotropic response, without the unwanted rise in PWP seen in adults. There is no data which would suggest that dobutamine is a more effective inotrope in children. Given the added benefit of dopamine's effect on the kidney, there is no reason to believe that dobutamine offers advantage in terms of either efficacy or side effects over the former. The use of intravenous vasodilator therapy, either alone or in addition to sympathomimetic drugs, has proven to be very effective in acute heart failure in children, particularly in the treatment of cardiomyopathies.

Acute right heart failure secondary to abnormalities of the pulmonary vascular bed in children responds very readily to changes in ventilation through alterations in pH and lung volume. In addition to RV preload, afterload may be manipulated with the use of vasodilators and contractility may be augmented with inotropes even in situations of increased pulmonary artery pressure.

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