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Updated Management of Pediatric Heart Failure by Use of Nebulized Furosemide and Salbutamol

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Abstract

A congenital heart disease (CHD) is a defect in the structure of the heart and great vessels which is present at birth. Many types of CHD exist, most of which either obstruct blood flow in the heart or vessels near it, or cause blood to flow through the heart in an abnormal pattern. Other diseases, such as long QT syndrome, affect the heart's rhythm. CHDs are among the most common birth defects and are the leading cause of birth defect-related deaths. Approximately 9 people in 1000 are born with CHD. Many diseases do not need treatment, but some complex CHD require medication or surgery. Heart failure in children is a clinical and pathophysiological syndrome that results from ventricular dysfunction, volume or pressure overload, either alone or in combination. Salbutamol is generally given via pressurized metered dose inhaler (pMDI) with a large volume spacer, this is a highly efficient delivery system and ensures good delivery particularly to the small-sized to moderate-sized airways. However, it can also be inhaled via a dry powder inhaler or nebuliser or given orally or intravenously Inhaled furosemide affects the respiratory system by inhibiting the movement of chlorine through the membrane of the epithelial cell , also increases the synthesis and release of the bronchodilators prostaglandin E2 (PGE2) in the airway epithelium and prostacycline (PGI2) in the vascular endothelium.

Keywords:Nebulized Furosemide, Salbutamol, Congenital Heart Diseases (CHD), Heart Failure (HF).

Pediatric Heart Failure

1-Introduction:

Heart failure (HF) is an important healthcare issue in both adults and children because of its high mortality, morbidity, and cost of care. By 2030, more than 8 million people in the Unites States (US) (1 in every 33) will have HF, and the projected cost estimates of treating patients will be 160 $ billion in direct costs as forecasted by American Heart Association (AHA) (**1**).

2- Definition:

Heart failure in children is a clinical and pathophysiological syndrome that results from ventricular dysfunction, volume or pressure overload, either alone or in combination **(2).**

As a complex clinical syndrome, HF is characterized by typical symptoms and signs associated with specific circulatory, neurohormonal, and molecular abnormalities.

The International Society for Heart and Lung Transplantation (ISHLT) stratified pediatric HF into four stages (Stages A–D) as in Table 3, which is useful to identify those at risk for HF and who are currently asymptomatic (Stage A) versus those on the other end of the spectrum (Stage D), who have advanced

HF and, thus, would require therapeutic interventions for maintenance of end-organ function **(2).**

3- Incidence and Prevalence

The true global incidence and prevalence of HF in children is difficult to estimate due to lack of standard definition used for HF. The phenotype of HF also differs in congenital heart disease (CHD) and cardiomyopathies. The reported incidence of HF in children is 0.97 to 7.4 per 100,000 **(3).**

4-Etiology:

The etiology of HF in children plays a key role in the clinical course and outcome. The two most common causes of pediatric HF are CHD and cardiomyopathies **(4).**

A- congenital heart disease:

Volume overload lesions such as ventricular septal defects (VSD), patent ductus arteriosus (PDA) and endocardial cushion defect (ECD) are the most common causes of CHF in the first 6 months of life. In infancy, the time of the onset of CHF varies with the type of the defect **(4).** All congenital heart diseases resulting in CHF are summarized in figure 3.

B- Acquired heart disease:

Acquired heart disease of various causes can lead to CHF. With acquired heart disease, the age at onset of CHF is not as predictable as with congenital heart diseases. The most common causes are endocardial fibroelastosis, viral myocarditis, acute rheumatic carditis, cardiomyopathies, either primary or secondary and patients who received surgery for some types of congenital heart diseases **(5)**

C- Miscellaneous causes:

There are several miscellaneous causes of CHF such as:

- Metabolic abnormalities as hypoxia, acidosis, hypoglycemia and hypocalcemia.
- Endocrinopathy such as hyperthyriodism.
- Arrhythemias such as supraventricular tachycardia (SVT) and complete heart block (CHB).
- Severe anemia as in hydropsfetalis.
- Acute corpulmonale can cause CHF at any age, but most commonly during early childhood.
- Acute systemic hypertension, as seen in acute post infectious glomerulonephritis **(6).**

5-Diagnostic Approach:

The diagnosis of heart failure in children is based on a historic evaluation, clinical symptoms and sings, noninvasive imaging, and biomarker profiling. **(7).**

(1) Historic evaluation:

All children with suspected heart failure should include an accurate assessment of feeding (tachypnea with feeds, gagging, diaphoresis, time to complete feeding, etc.). It should also include an assessment of nutritional status and weight gain, as this may be the first manifestation of a failing heart**(8)**.

(2) Symptoms and Signs:

A- Symptoms:

Heart failure symptoms are traditionally and somewhat arbitrarily divided into "left" and "right" sided, recognizing that the left and right ventricles of the heart supply different portions of the circulation **(9).**

Left-sided failure:

Backward failure of the left ventricle causes congestion of the pulmonary vasculature, and so the symptoms are predominantly respiratory in nature. The patient will have dyspnea on exertion and in severe cases, dyspnea at rest, orthopnea , paroxysmal nocturnal dyspnea, Easy fatigue ability and exercise intolerance and Cardiac asthma may also occur **(10).**

Compromise of left ventricular forward function may result in symptoms of poor systemic circulation such as dizziness, confusion , cool extremities at rest, pallor, sweating, poor growth, altered

consciousness and syncope **(10).**

Right-sided failure:

Backward failure of the right ventricle leads to congestion of systemic capillaries. This generates excess fluid accumulation in the body. This causes peripheral edema or anasarca and usually affects the dependent parts of the body first. In progressively severe cases, ascites and hepatomegaly may develop Significant liver congestion may result in impaired liver function, and jaundice and even coagulopathy may occur **(11).**

B- Signs:

Left-sided failure:

Common respiratory signs are tachypnea and increased work of breathing. Rales or crackles, heard initially in the lung bases, and when severe, throughout the lung fields suggest the development of pulmonary edema. Cyanosis which suggests severe hypoxemia, is a late sign of extremely severe pulmonary edema **(12).**

Additional signs indicating left ventricular failure include lateral, downward displacement of the apex beat and a gallop rhythm may be heard. Heart murmurs may indicate the presence of valvular heart disease, either as a cause (e.g. aortic stenosis) or as a result (e.g., mitral regurgitation) of the heart failure **(12).**

Right-sided failure:

Physical examination can reveal pitting peripheral edema, ascites, and hepatomegaly. Jugular venous pressure is frequently assessed as a marker of fluid status, which can be accentuated by eliciting hepatojugular reflux. If the right ventricular pressure is increased, a parasternal heave may be present, signifying the compensatory increase in contraction strength **(13).**

Biventricular failure:

Dullness of the lung fields to finger percussion and reduced breath sounds at the bases of the lung may suggest the development of a pleural effusion. Though it can occur in isolated left- or right-sided heart failure, it is more common in biventricular failure because pleural veins drain both into the systemic and pulmonary venous system. When unilateral, effusions are often right sided **(12).**

(3) Non-invasive Imaging:

A- Chest Radiography:

Chest x-ray invariably provides additional information in the assessment of heart failure. An enlarged cardiac silhouette due to cardiomegaly is frequently found. A cardiothoracic ratio of >0.55 in infants and >0.5 in children is the standard for cardiomegaly. In one study, an enlarged cardiac silhouette on chest x-ray had 85% sensitivity and 95% specificity for the diagnosis of heart failure. In addition to cardiac size, the chest x-ray also allows for assessment of pulmonary congestion. In children with CHF, evidence of increased pulmonary vascular markings is usually seen **(14).**

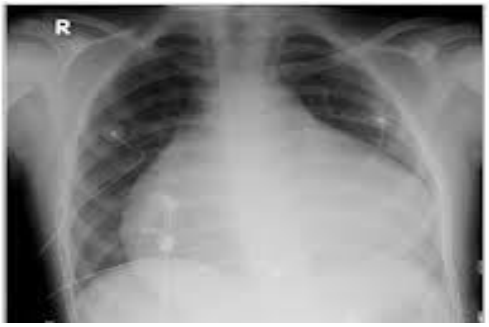

Figure (1): Chest X-ray illustrating an increased cardiothoracic ratio. There are no signs of pulmonary abnormalities **(14)**

B- Electrocardiography (ECG):

ECG can also be useful in the assessment of CHF. An ECG can provide information regarding atrial enlargement, ventricular hypertrophy, strain, and changes in ST-segment or T-wave morphology. ECG may reveal evidence of structural or coronary artery disease or a complete atrioventricular block or arrhythmia. In patients with myocarditis, a pattern of myocardial infarction with wide Q waves and ST-segment changes may be seen. Ventricular tachycardia, supraventricular tachycardia, atrial fibrillation, or atrioventricular block occurs in some children **(15).**

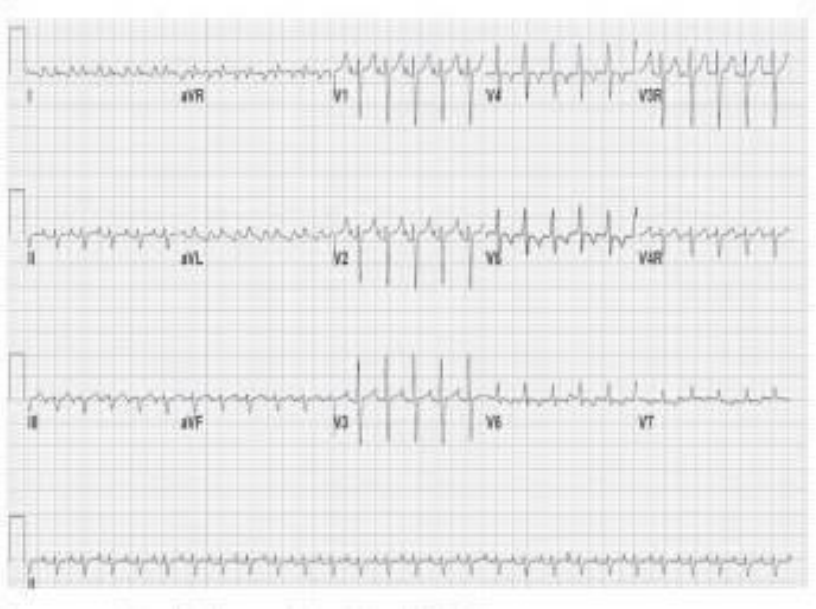

Figure (2): Electrocardiogram showing sinus tachycardia with low voltage QRS in a patient with myocarditis **(16)**

C- Echocardiography:

Echocardiography is commonly used to support a clinical diagnosis of heart failure. This modality uses ultrasound to determine the SV, the end-diastolic volume (EDV), and the SV in proportion to the EDV, a value known as EF. Normally, the EF should be between 50% and 70%; in systolic heart failure, it drops below 40%. In pediatrics, the fraction shortening (FS) is the preferred measure of systolic function. Although values vary with age, in general, normal values for FS range from 28% to 44%. Worse EF and FS at presentation have been correlated with poor outcome in children with DCM in 2 large epidemiological studies **(17).**

Echocardiography can also identify valvular heart disease and assess the state of the pericardium. Echocardiography may also aid in deciding what treatment will help the patient, such as medication, insertion of an implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy. Echocardiography can also help determine if acute myocardial ischemia is the precipitating cause and may manifest as regional wall motion abnormalities on echo **(17).**

Newer modalities such as myocardial performance index and Doppler tissue imaging are load-independent measures and allow for more global assessments of ventricular function (including diastolic function) and regional wall motion abnormalities, respectively. Assessment of right ventricular function has always been more challenging due to geometric restrictions, and myocardial performance index and Doppler tissue imaging have proved promising in this regard **(17).**

(4) Laboratory testing:

Appropriate laboratory testing includes assessment of the following: complete blood count (CBC) and

hemoglobin concentration, electrolytes, calcium level, BUN and creatinine level, renal and hepatic function **(18).**

(5) Heart Failure Biomarkers

Since early detection of remodeling is vital to preemptive management in cardiomyopathy and in heart disease arising from congenital lesions, biomarkers may offer a mean for identifying high risk patients before they develop symptoms (Table 5) **(19).**

Treatment of heart failure:

The treatment of heart failure in children depends on the underlying cause and the child's age. The aim of treatment has now shifted from symptom relief to modulation of the neuroendocrine mechanisms and normalization of the altered haemodynamics. Other goals include improving quality of life and prolonging life span. Treatment modalities include lifestyle modification, pharmacotherapy, surgical and device therapy **(20).** Eliminating the underlying cause is the most desirable approach whenever possible, for example:

- Surgical treatment of the congenital heart defects and valvularheart diseases.
- If hypertension is the cause of CHF, antihypertensive treatment should be given.
- If arrhythmias or advanced heart block is the cause of CHF, antiarrhythmic agents should be given.
- For anemia, packed cell transfusion is given to raise the hematocrit to 35% or more. **(7)**

I-General measures:

1. **Diet:** Dietary requirements are high because of the catabolic state, recurrent infections, increased muscle activity, and need for rapid growth. Dietary intake may be inadequate consequent to the anorexia, dietary restrictions, malabsorption, diarrhea, and frequent exacerbations of heart failure. Temporary nasogastric tube feedings may be required for sick and severely anorectic children **(21)**

2. **Activity:** Enforced bed rest is impractical and unnecessary, restriction of physical activity is self-enforced. There is evidence that regular physical activity can result in sustained improvements in physical functioning even in children with complex congenital heart disease **(22).**

3. Medical Therapy:

A- Preload Reducing Agents (Diuretics):

There are three main classes of diuretics that are commercially available:

1- Thiazide diuretics (e.g., chlorothiazide, hydrochlorothiazide) which act at the proximal and distal convoluted tubules, are no longer popular.

2- Loop diuretics, such as furosemide and ethacrynic acid, are the drugs of choice. They act primarily at the loop of henle.

3- Aldosterone antagonists, such as spironolactone, which act on the distal tubule to inhibit sodium-potassium exchange. These drugs have the value in preventing hypokalemia produced by other diuretics and thus are used in conjunction with loop diuretics. (**23)**

Side effects of diuretics therapy must be monitored closely. Hypokalemia can be treated with spironolactone. Hyponatremia should be aggressively treated with restriction of free-water intake because the diuretics are less effective when serum sodium is low. Similarly, metabolic alkalosis secondary to chloride depletion is seen occasionally with the potent loop diuretics and, along with volume contraction, stimulates aldosterone production, which should be avoided. Oral potassium chloride supplements may be effective, but if the alkalosis persists, ammonium chloride may be used for replacement **(24).**

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B- Inotropic Agents:

(1) Cardiac glycosides:

The principal myocardial effect of the digitalis glycosides is to increase the force and the velocity of cardiac muscle contraction. This "inotropic" effect which is present in cardiac but not skeletal muscle, is dependent on the concentration of a number of ions including potassium, sodium, calcium, and magnesium, and is entirely independent of the adrenergic system **(25).**

For children with myocardial failure, this inotropic effect appears to increase CO, resulting in a reduction or elimination of symptoms. Much of the proven utility of digoxin relates to its electrophysiologic effects, the most important of which is an increase in the effective refractory period of the conduction system, which tends to slow the ventricular response to atrial fibrillation or atrial flutter. In addition, digitalis increases the sensitivity of the arterial baroreceptor reflex, resulting in an increase in vagal and a decrease in sympathetic efferent activity, thereby reducing the resting heart rate **(25).**

(2) Beta-adrenergic agonist:

These drugs are used in resistant cases as intravenous infusions and are stimulators of beta-adrenergic receptors in the myocardium. They are also useful for periodic home inotropic therapy in end stage of disease, when cardiac transplant is not feasible, to improve the quality of life. However, studies have shown increased mortality related to arrhythmogenic potential, they include dopamine, dobutamine and isoptoterenol **(25).**

- **Dopamine:**

Dopamine is currently the most widely used inotrope for acute support in pediatric practice. At low doses (2-5 mcg/kg/min), dopamine receptors in the renal, cerebral, coronary, mesenteric and pulmonary vasculature are stimulated leading to increased renal blood flow and urine output. Medium doses of dopamine (5-15 mcg/kg/min) stimulate β-adrenergic receptors, increasing contractility and heart rate. At higher doses (≥ 20 mcg/kg/min), significant α-adrenergic stimulation occurs, resulting in vasoconstriction and increased systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) **(26).**

- **Dobutamine:**

Dobutamine is a synthetic sympathomimetic agent and causes increase in contractility with relatively less tachycardia or rise in blood pressure if enhance contractility by direct stimulation of B_1 receptors **(27).**

Dobutamine is used in patient with heart failure refractory to conventional oral medications. Intravenous infusion of dobutamine up to several days is usually well tolerated. The dose of dobutamine is typically initiated at low dose 2-3 mcg/kg/min and may be titrated according to symptoms and diuretic responsiveness or towards a hemodynamic target but not to exceed 40 mcg/kg/min **(27). Isoproterenol:**

Isoproterenol (isoprenaline) is an intravenous preparation used for treating low CO in a dose of 0.1-0.5 mcg/kg/minute. It has both central and peripheral β-adrenergic effects, hence improve myocardial contractility and reduce cardiac overload. It is administrated in the ICU where continuous determination of arterial blood pressure and heart rate are mandatory **(27).**

(2) Phosphodiestrase inhibitors:

Amrinone and milrinone inhibit phosphodiestrase type III in cardiac and smooth vascular muscle, preventing degradation of C-AMP resulting in reduced afterload, reduced preload and increase inotrope so, both acts to reduce systemic vascular resistance and to increase cardiac contractility **(25).**

- **Amrinone:**

This phosphdiestrase inhibitor inotropic agent has pulmonary vasodilating properties also a loading dose of 3mg/kg over one hour followed by 3-10 mcg/kg/min is used in children, mainly in postoperative or refractory failure **(27).**

- **Milrinone:**

It is also a phosphodiestrase inhibitor that enhance contractility and is useful for patients with low CO heart failure and pulmonary hypertension because it is a more potent pulmonary vasodilator than dobutamine, it used in a dose of 0.25-1.0 mcg/kg/min in decompensated hospitalized patient who have developed tolerance to dobutamine or used with it **(25).**

The toxicity of these agents is dose related and depends also on route of administration and include (gastrointestinal intolerance, hepatotoxicity, fever and thrombocytopenia) **(25).**

C- Afterload Reducing Agents

This group of drugs reduces ventricular afterload by decreasing peripheral vascular resistance and thereby improving myocardial performance. It also decreases myocardial remodeling that worsens chronic heart failure. Some of these agents also decrease systemic venous tone, which significantly reduces preload. Afterload reducers are especially useful in children with heart failure secondary to cardiomyopathy **(28).**

(1) Angiotensin-Converting Enzyme Inhibitors (ACEIs):

As discussed previously, the chronic activation of the SNS and RAAS, although acutely beneficial, contributes to the progression of heart failure over time. The well-documented efficacy of ACEI therapy in heart failure is related to disruption of the activation of the renin-angiotensin axis and to decreased cardiac adrenergic drive. ACEIs are popular in children with chronic severe CHF **(27).**

The main side effect from ACE inhibitors is a dry hacking cough (5-20% of children) which can necessitate change to an Angiotensin II Receptor Blocker (ARB). Most patients who cough on ACEIs have this symptom because of heart failure rather than ACEI intolerance and might improve with further diuretics**(27).**

ACE inhibitors should be given cautiously in renal impairment, valvular stenosis, or severe CHF with hypotension; tachycardia; renal failure. The hypotensive effects of ACEIs may be enhanced when given concurrently with diuretics **(27).**

(2) Angiotensin Receptor Blockers (ARBs):

In contrast to the ACEIs, which act by blocking the formation of angiotensin, ARBs are competitive antagonists for the angiotensin II receptor. The angiotensin II receptors mediate vasoconstriction, aldosterone secretion, sodium resorption, and cell proliferation. The potential advantages to the ARBs include (1) absence of bradykinin breakdown inhibition, which has been implicated in causing the troublesome cough and angioedema that are seen with ACEIs; (2) potential for synergism when used in combination with ACEIs; and (3) the theoretical advantage to unopposed angiotensin II agonism, which is believed to counter the angiotensin I response through vasodilation and antiproliferative effects **(28).**

However, effective doses of ARBs represent as much of a risk for hypotension and renal dysfunction as with an ACEI. No safety or efficacy data regarding the use of ARBs in children with heart failure are available **(30).**

(3) Intravenous vasodilators:

- **Nitroglycerine:**

Nitroglycerine is a nitric oxide donor that causes vasodilation. It is a venodilator at low doses and

arterial dilator at higher doses, lowering intracardiac pressure and alleviating pulmonary congestion also dilates coronary arteries, making it useful for patients with heart failure and myocardial ischemia. Intravenous nitroglycerine is safe and very effective, therapy of pulmonary edema **(27).**

- **Sodium nitroprusside:**

Na nitroprusside is an intravenous vasodilator with a more potent arterial dilator requires carefully monitoring of intra-arterial pressure. So should be administrated only in the ICU in a dose range of 0.5-8 mcg/kg/min and for short period as it is rapid acting and severe hypotension occur within minutes. Peripheral arterial vasodilatation and afterload reduction are the major effects but venodilatation causing a decrease in venous return to the heart may be beneficial.The infusion fluid needs to be protected from sunlight and Na nitroprusside should be infused for a short duration in patient with severe renal disease to prevent the accumulation of thiocyanate **(31).**

- **Nesiritide**

Nesiritide is a synthetic form of B-type natriuretic peptide that was approved by the Food and Drug Administration for Treatment of acute decompensated heart failure (ADHF). Administration of nesiritide results in venous, arterial, and coronary vasodilatation, reducing the cardiac pre- and afterload, which increases CO without direct inotropic effects. Nesiritide is currently used in the treatment of ADHF, where it has been shown to decrease pulmonary capillary wedge pressure, pulmonary artery pressure, right atrial pressure, and systemic vascular resistance, as well as increasing cardiac and stroke volume indexes. In addition, nesiritide has long been known to attenuate neurohormonal activity, and no surprisingly, it increases GFR and filtration fraction, suppresses the RAAS, and enhances diuresis and natriuresis **(32).**

- **Hydralazine and Nitrate**

Hydralazine is an arterial vasodilator, the combination of hydralazine and nitrate used for cases who have current or prior symptoms of heart failure and reduced LVEF and who cannot be given an ACEIs or ARBs because of drug intolerance, hyperkalemia, or renal insufficiency. Hydralazine and nitrate also may be added to ACEIs and beta blockers when additional afterload reduction is needed, or pulmonary hypertension is present **(33).**

Salbutamol:

Introduction:

For over 5000 years, the herb Ma Huang was used in Chinese medicine to treat asthma, hay fever and bronchitis. In 1885, Yamanashi isolated its active principle, which was subsequently obtained in a pure form and named ephedrine. Ephedrine is a non-selective α-adrenoceptor (AR) and β-AR agonist that sparked a new age of sympathomimetic drug discovery and ultimately the development of salbutamol, short-acting β2-AR agonist (SABA) **(34).**

When salbutamol is nebulized, a large range of particle sizes are produced. Larger particles created by nebulization will be filtered by the nose and are likely to be absorbed and 'recirculated' via the blood into the lungs. Thus, nebulization may result in slightly different effects than those seen with inhaled salbutamol and nebulizers are still recommended for severe asthma attacks where oxygen is required, that is, those with hypoxia are likely to have the biggest ventilation/perfusion mismatch and therefore might benefit most from increased blood salbutamol levels. However, salbutamol will transiently increase ventilation/perfusion mismatch and thus lead to worsening hypoxia. Home nebulizers which are driven by air are discouraged for this reason **(35).**

Salbutamol being a partial agonist reaches its maximal bronchodilating effects at relatively low doses.

It binds to β2-ARs which are present on airway smooth muscle (ASM) that is found throughout the airways , this binding induces a postsynaptic action on adenyl cyclase resulting in the generation of intracellular cyclic AMP (cAMP) from ATP which in turn activates other effector molecules: cAMP-dependent protein kinase A (PKA) and nucleotide exchange factor Epac, which combine to cause sequestration of intracellular Ca^{2+}, leading to relaxation of the ASM as shown in figure 10 **(36).**

Although its main action is by direct bronchodilator, salbutamol also inhibits mast cell mediator release and tumour necrosis factor alpha (TNFα) release from monocytes. It also increases mucus secretion and mucociliary clearance. **(37)**

As a sympathomimetic, it has widespread effects across several organ systems and administration leads to dose-dependent tachycardia, hyperglycaemia, hypokalaemia and tremor. The systemic metabolic effects inducing glucogenolysis and concomitant insulin release (possibly stimulated by pancreatic β2 cells) combine with stimulation of the β-AR Na–K ATPase pump to induce hyperglycaemia and serum hypokalaemia, the latter occurring as a result of cellular sodium excretion and potassium influx. This 'side effect' is very helpful in the emergency treatment of hyperkalaemia where continuous salbutamol administration can lead to a reduction in serum potassium between 1 and 1.5 mmol/L, but can also have adverse effects such as do`se-related tremor (the 'salbutamol shakes'), and when combined with cardiac receptor, stimulation can lead to tachyarrhythmias **(38).**

At very high doses, it is important to remember that cardiac arrhythmias and myocardial ischemia can occur. Therefore, cardiac monitoring and admission to HDU or PICU is required for children receiving continuous intravenous salbutamol **(39).**

Furosemide

Introduction

Furosemide increases the delivery of solutes out of the loop of Henle, is a sulphonamide derivative, and is the most commonly used diuretic in the newborn period and when given in excessive amounts can lead to dehydration and electrolytic depletion (**40**).

Mechanism of action of inhaled furosemide:

Despite extensive research into the mechanism of action using in vitro models, the precise mechanism of action of nebulized furosemide is still unknown, leading to speculation that more then one mechanism of action is involved. It is hypothesized that the mechanism of action of inhaled furosemide is local and not renal. This hypothesis is based on the observed pulmonary effects of inhaled furosemide in the absence of diuresis and on the observation that changes in the pulmonary bed occur before diuresis is caused by parenteral furosemide **(41).**

Inhaled furosemide affects the respiratory system by inhibiting the movement of chlorine through the membrane of the epithelial cell, also increases the synthesis and release of the bronchodilators prostaglandin E2 (PGE2) in the airway epithelium and prostacycline (PGI2) in the vascular endothelium. It also inhibits the conversion of the PGE2 into PGF2a which has a constrictor effect . Indirectly, furosemide inhibits the degranulation of mast cells and other inflammatory cells, blocking the dehydration of the epithelial cells and decreasing the membrane potential which decreases the calcium and sodium uptake, inhibiting the sodium ± calcium pump which finally causes the relaxation of smooth muscle **(42**).

Furosemide also has a protective effect against bronchoconstriction induced by several indirect stimuli in asthma, which could be due to inhibition of airway nerve activity, owing to decreased airway responsiveness to neurokinin A (NKA) after administration of inhaled furosemide. Moreover furosemide has been shown to improve pulmonary gas exchange and intrapulmonary shunt in animal models of ARDS by preferential perfusion of non-edematous lung, also furosemide improves LIS, PO_2/FIO_2, and Q_s/Q_t and decreases PEEP requirements in this model of ARDS**(43).**

Inhaled furosemide in cases after cardiac surgery:

Postoperative lung mechanics are often compromised after cardiac surgery for the repair of congenital heart disease. Decreased compliance and increased airway resistance of the respiratory system, due to increased lung water content, are considered to be responsible for the difficulty of weaning these patients from the respirator postoperatively. Consequently, current therapeutic interventions are directed towards, amongst others, a negative total body water balance and diuretics are administered to reduce total body, including lung, water content **(44).**

A selective reduction of pulmonary water by drugs which act directly at the lung, as target organ, would be a major therapeutic achievement. In recent studies intratracheal administration of furosemide has been shown to attenuate bronchospasm in adult and pediatric asthmatics, effects which were specific for inhaled furosemide and not seen with intravenous and oral administration **(45).**

Furosemide was also found to relax the airway and vascular smooth muscles independent of cyclooxygenase blockade or endothelial removal, these topical effects appear to be more pronounced in the less mature guinea pig (**46).**

Recently, inhaled furosemide increased compliance in infants with bronchopulmonary dysplasia (BPD) up to 50 % without causing significant systemic effects, however, the theory of topical action has already been challenged by the demonstration of rapid absorption of intratracheal furosemide from the lung into the blood in guinea pigs **(47).**

Because some investigators failed to confirm the effect with inhaled furosemide in intubated infants instillation of furosemide into the trachea (i.e. intratracheally) in a manner similar to surfactant introduction, was chosen as the mode of administration, we therefore tested the hypothesis that intratracheally administered furosemide would also increase respiratory compliance after cardiac surgery in children with compromised lung mechanics, presumably due to increased pulmonary water accumulation **(48).**

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