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# Influence of mechanical ventilation and inhalation of pulmonary vasodilators, upon pulmonary blood flow and pulmonary vascular resistance

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INFANTS AND CHILDREN WITH CONGENITAL heart disease often need respiratory support in the perioperative period. The influence of mechanical ventilation on the flow of blood to the lungs, and on pulmonary vascular resistance, is sometimes underestimated as a problem in perioperative intensive care. Here we discuss a step-by-step approach to mechanical ventilation, and the use of inhaled pulmonary vasodilators, in patients with right heart failure and passive perfusion of the lungs after a total cavo-pulmonary anastomosis, or one of the other variants of the Fontan procedure. The importance of the interaction between the cardiovascular and respiratory system in these patients will be emphasized in order to develop a better understanding of the available therapeutic options.

## The etiology of pulmonary hypertension

Right heart failure is often a result of pulmonary hypertension. The clinical spectrum may include acute or long standing pulmonary hypertension, with reversible or fixed components. The pulmonary hypertension itself may have a predominantly arterial or predominantly venous etiology. Arterial pulmonary hypertension may be due to congenital septal defects, arterio-venous shunting or arterio-venous fistulas, to vasoconstriction in consequence of hypoxia (the so-called Euler-Liljestrand mechanism) or bronchospasm, and to obliterative states such as pulmonary fibrosis, multiple pulmonary embolism, the Eisenmenger reaction, or bilharzia.[1] Venous pulmonary hypertension may be due to obstruction of the left atrium caused by constrictive pericarditis, atrial myxoma or atrial thrombus, to left heart insufficiency due to cardiomyopathy, mitral valvar stenosis or ischemic heart disease, or to pulmonary veno-occlusive disease or totally anomalous pulmonary venous connection.[2] The treatment of pulmonary hypertension is based upon the induction of pulmonary vasodilation (Table 1). Mechanical ventilation is expected to affect alveolar hypoxemia, hypercapnia and acidosis.[3] The combination of conventional ventilatory manoeuvres, and careful control of oxygenation, hypocapnia and alkalosis, are by far the most important and universally available means of preventing or treating pulmonary hypertension.

Right heart failure may result from acute myocardial dysfunction, for example due to bacterial or viral myocarditis or viral cardiomyopathy, or to congenital heart disease such as atresia of the tricuspid valve, tetralogy of Fallot, pulmonary valvar stenosis, or hypoplasia of the right heart. Alternatively, it can be the consequence of palliation of complex congenital heart disease by construction of cavo-pulmonary or atrio-pulmonary anastomoses such as the Glenn or Fontan procedures. Mechanical ventilation may be

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indicated perioperatively in children with decompensated left ventricular function, or in children with acute pulmonary failure due to infection and neurological or metabolical disorders.

Mechanical ventilation can reduce the work required for breathing. In this way, the cost of breathing in those with cardiopulmonary decompensation can be reduced from 25% of the overall consumption of oxgen down to normal values, which represent only 1–5% of the oxygen required by the whole body.[4] The supply of oxygen obtained through the coronary arteries will therefore increase due to the improvement in delivery of oxygen. Especially in those with hypertrophic myocardium, this normalisation of supply of oxygen through the coronary arteries can optimise myocardial function. But when needed, mechanical ventilation in those with right heart failure, and particularly in patients with total cavo-pulmonary anastomoses, should be provided following a stepwise regimen (Table 2).

In spontanously breathing children, the time available for expiration is approximately twice the time of inspiration. In mechanically ventilated patients with total cavo-pulmonary anastomoses, the pulmonary blood flow is increased during expiration. It may be beneficial, therefore, to increase the time of expiration in such patients, poviding a ratio of periods of inspiration to expiration between 1 to 4 and 1 to 8.

## Influences of intrathoracic pressure on preload and afterload

The elevation of intrathoracic pressure may result in an increased right atrial pressure, thus impeding venous return and decreasing right ventricular filling. This reduction in preload decreases the transmural filling pressures of the right heart, and thus decreases cardiac output.[5] Simultanously, the elevated intrathoracic pressure can collapse pulmonary capillaries and compress precapillary arterioles. In this way, it can increase pulmonary vascular resistance and right heart afterload.[6] Controversely, increased intrathoracic pressure may also reduce functional left ventricular afterload.[5]

## Using "best positive end-expiratory pressure"

"Best positive end-expiratory pressure" was defined by Suter and his colleagues in 1975. It is the titration of the positive end-expiratory pressure to an optimum level where the recruitment of collapsed alveoles, resulting in an increase in functional residual capacity, transpulmonary transport of oxygen, static compliance, and decrease of intrapulmonary shunt fraction, is balanced by the smallest possible reduction in cardiac output and the smallest possible increase in ventilation of the dead space.[7] This would be the point of intersection between optimal supply of oxygen and optimal static compliance.

The impact of positive end-expiratory pressure on hemodynamics in patients after an atriopulmonary, or cavo-pulmonary arterial bypass, is much more profound than in patients with regular hemodynamics. Williams et al.[8] measured hemodynamic data, and arterial tensions of oxygen and carbon dioxide, in the early postoperative period without positive end-expiratory pressure, and with

Table 1. Factors influencing pulmonary vascular resistance

| Vasoconstriction | Vasodilation |
|---|---|
| Alveolar hypoxemia < 70 mmHg | Alveolar oxygen saturation > 90 mmHg |
| Acidosis | Alkalosis |
| Hypercapnia | Hypocapnia |
| Prostaglandins $PGF_{2\alpha}$, $PGD_2$ $TXA_2$ | Nitric oxide, Prostaglandins $PDE_1$, $PGI_2$ |
| Vasopressin | Prostacyclin |
| α-adrenergic catecholamines (norepinephrin) | β-adrenergic catecholamines (dobutamin) |
| Platelet activating factor (high concentration) | Platelet activating factor (low concentration) |
| Serotonin | Acetylcholin |
| Histamine ($H_1$ receptor) | Histamine ($H_2$ receptor) |

Table 2. Step-by-step approach to mechanical ventilation in right heart failure

1. Preset tidal volume of 10 mL/kg body weight using positive end-expiratory pressure of 2 cm $H_2O$ with physiological inspiratory/expiratory ratio
2. Titrate "best positive end-expiratory pressure"
3. Change inspiratory/expiratory time ratio to 1 : 4 or even 1 : 8
4. Administration of vasoactive drugs intravenously and/or by inhalation
5. Negative pressure ventilation, if available

a positive end-expiratory pressure level of 3, 6, 9, and 12 cm of water. The cardiac index decreased progressively, accompanied by an increase of pulmonary vascular resistance index. The fall in the cardiac index became significant at a positive end-expiratory pressure level of 9 cm of water or higher. There was a significant increase in arterial oxygen tension, however, at a positive end-expiratory pressure level of 3 cm of water or higher. The increase of the index of oxygenation, and the decrease of intrapulmonary shunting, may be due to a reduction of atelectatic posterior lung segments dependent on positive end-expiratory pressure. Atelectasis may increase the pulmonary vascular resistance by hypoxic vasoconstriction (the Euler-Liljestrand mechanism), concomitantly worsening right heart function.

## Pharmacological treatment of pulmonary hypertension

Adequate sedation and analgesia, adapted antimicrobial therapy, mucolytics, and even in some cases kinetic therapy to improve the mismatch between ventilation and perfusion, can all assist the therapeutic mechanisms mentioned above. During the last years, tremendous resources have been committed to control pharmacologically the relation between systemic and pulmonary vascular resistance.

### *Phosphodiesterase-III-Inhibitors (Enoximone=Perfan®, Amrinone=Wincoram®, Milrinone=Corotrop®)*

The inhibition of phosphodiesterase-III increases intracellular levels of cyclic adenosine-monophosphate resulting, first, in positive inotropic effects independent of the β-receptor and, second, vasodilation in the pulmonary vascular system. Systemic vasodilation, the induction of arrhythmia, and impairment of platelet function are potential side effects. There are some case reports in children and adolescents after the Fontan operation which have indicated a beneficial inotropic effect of inhibition of phosphodiesterase-III accompanied by pulmonary vascular vasodilation.[9] Recently, Bailey et al.[10] demonstrated that a loading dose of 50 μg/kg milrinone effectively increased the cardiac index in children after repair of congenital cardiac defects.

### *Prostaglandins (ProstaglandinE1=Minprog®, ProstaglandinI2=Prostacyclin=Flolan®, Iloprost=Ilomedin®)*

Prostaglandins increase intracellular levels of cyclic adenosine-monophosphate by activation of adenylate cyclase leading, first, to vasodilation of the pulmonary vascular system secondary to changes of the ratio of thromboxane $A_2$ to prostaglandin $I_2$, second, impairment of adhesion and aggregation of platelets and, third, cytoprotective effects by inhibition of chemotactic activation of polymorphonuclear neutrophils. The first case report on the beneficial effects of continuous infusion of prostacyclin in primary pulmonary hypertension was published in 1984 by Higenbotam et al.[11] They were able to lower pulmonary vascular resistance, thus producing an increased cardiac output and higher uptake of oxygen. This was accompanied by a decreased arterial pressure.

### *Nitric oxide*

Inhaled nitric oxide has a great diffusion capacity, reaching the pulmonary vessels via bronchiolar membranes. It is then inactivated by hemoglobin, giving it a very short elimination half-life. Potential side effects are immunosupression, inhibition of platelets, and the toxic effects of its oxidative products peroxyte nitrite and nitric dioxide. The improvement of cardiac function in right heart failure was first demonstrated in adults with respiratory distress syndrome[12] due to reduced pulmonary vascular resistance. Until now, however, nitric oxide has not been shown in a randomized trial to improve outcome of patients with adult respiratory distress syndrome. In contrast, its use in the treatment of pulmonary hypertension after operations for congenital heart defects has been well established.[13,14]

Inhalation of nitric oxide offers the opportunity of gradual therapy, and the availability of monitoring continuously the inspiratory content of nitric oxide and its oxidative products nitrite and nitrate. Devices for its administration, however, need special interfaces with the ventilator. Furthermore, measurements have to be frequently calibrated, which makes them expensive and difficult to run. These devices, therefore, are not available in every institution.

### *Inhaled prostacyclin*

Inhaled prostacyclin offers the advantage of selective pulmonary vasodilation without the generation of toxic products of oxidation, and without expensive mechanical devices for delivery. The inhalation of iloprost, which is a stable analogue of prostacyclin, reduced pulmonary vascular resistance in adults with severe pulmonary hypertension. It also improved cardiac output and arterial oxygenation without affecting heart rate or

Table 3. Influence of different vasodilators on primary pulmonary hypertension in an 8-year old child undergoing heart catheterization. During spontanuous breathing different vasodilators (oxygen, prostacyclin intravenously in different dose ranges and aerosolized iloprost) were given. Pressure and saturation were measured in the aorta and the pulmonary arteries. (i.v. = intravenously)

| | Aortic pressure [mmHg] | Pulmonary arterial pressure [mmHg] | Aortic Saturation [%] | Pulmonary arterial saturation [%] |
|---|---|---|---|---|
| 21 % oxygen | 120/90 (101) | 158/58 (98) | 92.5 | 71.9 |
| 40 % oxygen | 115/78 (93) | 149/57 (95) | 95.1 | 73.1 |
| Prostacyclin i.v. | | | | |
| 5 ng/kg/min | 105/77 (94) | 140/60 (92) | 95.9 | 73.3 |
| Prostacyclin i.v. 10 ng/kg/min | 116/80 (97) | 140/60 (92) | 95.6 | 70.5 |
| Prostacyclin i.v. 15 ng/kg/min | 110/76 (93) | 150/80 (93) | 93.8 | 71.2 |
| Inhaled Iloprost 1μ/kg | 110/74 (93) | 134/57 (84) | 98.7 | 76 |

systemic vascular resistance.[15] For example, in an 8 year old child with primary pulmonary hypertension undergoing cardiac catheterization, aerosolized iloprost given at a dose of 1 microgram per kilogram reduced the pulmonary arterial pressure markedly without influencing arterial pressure (Table 3). The concomitant increase in pulmonary arterial saturation, and the decrease in pulmonary arterial pressure, could not be observed when prostacyclin was given intravenously in various doses. The aerosolized administration of prostacyclin analogues can be continued after discharge from the hospital.

## Negative pressure ventilation

If low cardiac output persists after the Fontan procedure secondary to reduced pulmonary blood flow, external negative pressure ventilation may be used as a last resort for these patients. Shekerdemian and her colleagues[16] were able to demonstrate that conversion from conventional intermittent positive pressure ventilation to external negative pressure ventilation improved stroke volume significantly by a mean of 48.5%, and cardiac output by a mean of 46%, without changing heart rate. These results were confirmed in a study of anesthetized patients undergoing cardiac catheterization in the convalescent phase after Fontan operations. Pulmonary blood flow increased by a mean of 42% to 54 5% in a time dependent manner.[17] It has to be remembered, however, that the technique requires an adequate size of the cuirass for the different age groups, and suitable medical as well as nursing experience.

## Insufflation of carbon dioxide after Norwood palliation in hypoplastic left heart syndrome

In the hypoplastic left heart syndrome, systemic flow equals pulmonary flow. After palliation by means of the Norwood procedure, this balance may change. If systemic flow then exceeds pulmonary flow, hypoxemia and metabolic imbalances will require new measures to reduce pulmonary vascular resistance. If flow through the lungs exceeds systemic flow, systemic hypoperfusion and metabolic acidosis may develop. Pulmonary vascular resistance should be increased in this circumstance. This can easily be done without changing the ventilatory regimen simply by adding inspired carbon dioxide to the ventilatory circuit. Weldner et al.[18] were able to demonstrate a marked reduction in mortality after institution of a protocol adding carbon dioxide to the inspired gas during and after the Norwood operation.

## Conclusion

Mechanical ventilation in those with right heart failure, and in patients with total cavo-pulmonary or atrio-pulmonary anastomoses, remains one of the most vexing problems in pediatric intensive care. Its use requires a stepwise approach that takes into consideration the physiological interactions between the cardiovascular and respiratory systems. Mechanical ventilation in these patients offers the opportunity of controlled inhalational administration of vasoactive drugs, enabling the intensivist favourably to influence the relationship between systemic and pulmonary vascular resistance.

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