Introduction

Heart lung interaction, that is the interaction between ventilation and perfusion, already starts in the beginning of fetal development. Angiogenesis develops together with pulmonary growth and the segmentation of the bronchi by permanent interaction of the growth factors of the two systems (Fig.1). Thus, the cardiovascular and respiratory systems create a true functional unit.

The principal circulatory parameter is cardiac output (CO) that guarantees tissular perfusion, defined as:

$$\text{CO} = \text{SV} \times \text{HR} \ (\text{l/min}) \ (1)$$

With CO = cardiac output, SV = stroke volume, HR = heart rate.

CO depends on preload that is ventricular filling, and afterload (the forces against the ventricle must contract). These parameters are exposed to respiratory influences as intra-thoracic pressure changes, pulmonary vascular resistances and myocardial oxygenation.

The cardio-pulmonary interaction

It is based on the following pathophysiological concepts:

- the trans-myocardial pressure of the left ventricle (LV) which is the pressure gradient between the LV that equals the aortic pressure ($P_{ao}$) and the thorax that equals pleural pressure ($P_{pl}$) calculated by the formula:

$$P_{\text{trans-myocardial}} = P_{ao} - P_{pl} \ (2)$$

Trans-myocardial pressure represents afterload and the stress of the myocardial tissue, therefore called « wall stress » (T) (Fig.2). The wall stress is a parameter
particularly important in a failing ventricle because it depends on the intra-
ventricular pressure, the thickness of the myocardium and the end-diastolic 
diameter of the ventricle.

![Diagram of Ventricular components of the myocardial « wall stress »](image)

Therefore afterload of the contracting ventricle will rise in the presence of 
negative intra-thoracic pressure (spontaneous inspiration) because of a decrease 
of pleural pressure, whereas an augmentation of pleural pressure (ventilation 
with positive pressure) will lead to a decrease of LV afterload as a 
counterbalance to the wall stress.

- The right ventricular (RV) function is directly exposed to respiration in a way 
that intrathoracic pressure influences blood return of the caval veins into the 
right atrium (RA) and therefore RV filling. At the same time, it directly 
influences the pulmonary vessels modifying their resistance and therefore their 
after-load and their ejection volume. Other respiratory parameters like PaCO$_2$, 
PaO$_2$ and blood pH also influence the pulmonary vascular tonus and thus right 
ventricular after-load.

- The third important concept is that of the intra- and extra-thoracic 
compartments. Indeed, the major part of the systemic vessels and the inferior V. 
cave are located in an extra-thoracic compartment, the abdomen, and thus 
exposed to variations of the atmosphere pressure instead of pleural pressure. 
This is the driving force for systemic venous return during spontaneous 
inspiration with a decrease of pleural pressure.

- Finally, there is the phenomenon of ventricular interdependence. The two 
ventricles share the same non extensible envelope, the pericardium, with a 
common contractile element, the inter-ventricular septum. Thus, any 
modification of a ventricle’s end-diastolic filling or its contractility modifies the 
volume and the contractility of the other.

Mechanical ventilation with positive pressure notably modifies these interactions.

- First, mechanical ventilation positively affects left heart function by optimizing 
the conditions of pulmonary filling. Indeed, as mechanical ventilation influences 
lung volume it also modifies its blood capacitance in a cyclic manner and 
therefore the amount of blood that the lungs may store in their vessels. Thus, 
ventilation influences pulmonary venous return.
- Also, it modifies LV after-load. Arterial systemic pressure rises, but also the gradient between the intra- and extra-thoracic vessels, thus creating an effect of blood expulsion from the intra- to the extra-thoracic aorta.

- And, by changing pleural pressure to positive values it reduces the trans-myocardial gradient, therefore the LV afterload.

- On the other hand, positive pressure ventilation augments the alveolar pressure thus rising pulmonary vascular resistances and therefore RV afterload.

- Moreover, by augmenting pleural pressures through mechanical ventilation, RA pressure rises thus impeding systemic venous return, therewith reducing RV preload.

In conclusion, mechanical ventilation has a beneficial effect on left heart circulation but rather a negative one on right heart function.

**Extubation**

Extubation is a critical period in the post-surgical intensive care of patients with congenital heart disease. Respiratory complications may be possible and, in their majority, occur rapidly, 22% during the first minutes after extubation. They are predominantly obstructive due to the anatomy of the infant. Its airways are finer, especially in the sub-glottis region. Also frequently, when passing the intubation’s tube, laryngospasm may occur as a reflex that protects the infant from secret aspiration. Other complications or even a failure of extubation might be due to physical weakness or fatigue of the infant.

Besides its respiratory complications, extubation may also have hemodynamic consequences. First, there is a rise of arterial blood pressure and heart rate reflecting the excretion of catecholamines under stress that may lead to a reduction of stroke volume through an augmentation of LV after-load in patients with heart failure. To this systolic dysfunction, a diastolic dysfunction may add, through a reduction of the coronary perfusion due to a more important trans-myocardial gradient of the LV.

**The pathophysiology of heart failure**

Heart failure or heart insufficiency is defined as the inability of the heart to guarantee an adequate perfusion of the tissues and organs. It is modified by load changes of the ventricles and particularly aggravated in the presence of a higher afterload. Afterload represents all the forces against which the ventricle must contract and exerts an effect of stress on the myocardial tissue: the “wall stress” (Fig. 2). This may lead to a decrease of myocardial contractility with, subsequently, a reduction of stroke volume and thus cardiac output. The decrease of CO activates the rennin-angiotensin-aldosteron (RAAS) system and, as a counter-reaction, the secretion of brain natriuretic peptide (BNP).

BNP is a hormone synthesized in the ventricles as a response to the stretch of the myocardial fibers in the presence of wall stress. To resume, its functions result in a decrease of the systemic vascular resistances and the plasmatic volume (Fig. 3) thus the ventricular afterload.
The aim of our studies was to observe the modifications of the heart lung interaction in infants after pediatric cardiac surgery under conditions of extubation after mechanical ventilation, under non invasive ventilation after extubation and under chest physiotherapy in an intubated and ventilated patient.

1\textsuperscript{st} study: respiratory and hemodynamic parameters before and after extubation, is there a cut-off for BNP as a pre-extubational diagnostic parameter indicating a certain risk for compromised hemodynamics after extubation?

2\textsuperscript{nd} study: respiratory and hemodynamic parameters before and after extubation with and without non invasive ventilation immediately after extubation.

3\textsuperscript{rd} study: respiratory and hemodynamic effects of respiratory physiotherapy in an intubated and ventilated patient with congenital heart disease.

Materials and Methods

1) Ventilators

The infants enrolled in the studies were ventilated in a conventional manner (IPPV, SIMV, CPAP before extubation) by one of the following respirators: Evita XL\textsuperscript{®} (Dräger), Servo\textsuperscript{i} (Maquet), and Engström\textsuperscript{®} (General Electrics), the latter equipped with a module for FRC measurement.

For NIV, we used the Infantflow\textsuperscript{®} respirator (SEBAC) which limited the maximum weight of the patients enrolled in the NIV study at 5 kg.

2) Electrical velocimetry (EV)

Cardiac output was measured in the infants non invasively by the AESCULON\textsuperscript{®} or ICON\textsuperscript{®} bioimpedance monitor (Osypka Medical Inc. Berlin, San Diego) that, on the basis of electrical velocimetry, allow the measurement of SV and CO by measuring changes in thoracic impedance that are due to the ejection of blood from the left ventricle into the aorta. They also allow to measure an index of contractility of the left ventricle (ICON). The principle of electrical velocimetry is based on the concept of changes in thoracic impedance related to the red blood cells alignment in the ascending aorta during systole (Fig. 4).
3) Patients

The patients included in the studies were newborns or infants with stable respiratory and hemodynamic conditions, without shunt in order not to falsify the CO measurements. During the measurement period there were no changes of therapy (analgesia, sedation, vaso-active treatment, ventilation). The infants of every study were distinct cohorts. The patients in the 1st and 2nd study that were extubated received all the same pre-extubational weaning: PEEP +4 cm H₂O, Inspiratory aid (IA) +12 cm H₂O and FiO₂ 40% during 30 minutes.

Results

1st study : Extubation

Patients enrolled in the study : 60 newborns (mean age 10 days at surgery, mean weight 3.3 kg) after uncomplicated switch procedure for transposition of the great vessels (TGV).

<table>
<thead>
<tr>
<th>Paramètres</th>
<th>Avant extubation</th>
<th>6h après extubation</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7,41 (7,34 – 7,56)</td>
<td>7,38 (7,30 – 7,48)</td>
<td>&lt; 0,001</td>
</tr>
<tr>
<td>Base excess (BE) (mval/l)</td>
<td>1,5 (-2,3 – 9,8)</td>
<td>-0,05 (-3,6 – 6,3)</td>
<td>= 0,005</td>
</tr>
<tr>
<td>Volume ejection (VE)</td>
<td>5,157 ± 0,2</td>
<td>4,681 ± 0,25</td>
<td>=0,006</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>554,5 (172 – 6522)</td>
<td>1165 (288 – 10354)</td>
<td>&lt; 0,001</td>
</tr>
</tbody>
</table>

Table 1 : Per definition (BNP > 400 pg/ml), the patients suffer already from heart insufficiency before extubation. Extubation doubles BNP indicating an important augmentation of ventricular after-load that is associated with a decrease of SV, pH and BE. The metabolic changes are, in the absence of respiratory interferences (paCO₂, respiratory rate) rather due to a compromised cardiac output.
In order define a pre-extubational BNP cut-off for the patients that are likely to suffer from an alteration of their metabolism, we calculated ROCs for the target parameters BE and SV. (Fig 5):

We then wanted divided the patients into subgroups: first those with a pre-extubational BNP under the cut-off point of 379 pg/ml (group 1 = “low secretors”). Then the patients with BNP above the cut-off (group 2). In group 2 we defined a group of “high secreters” (> 75% level of BNP of all patients = 1137 pg/ml) in the following text called group 2B (group 2 A would then be the patients with BNP from 379 to 1137 pg = “medium secretors”). We then compared relative and absolute post-extubational BNP secretion between the different subgroups. The groups behaved differently: Highest relative BNP secretion was found in group 1 with, highest absolute secretion in group 2B whereas the most important decrease of BE was found in group 2A. This leads to the conclusion that the “low” and “high” BNP “secretors” are probably better protected against metabolic alterations after extubation than the “medium secretors” (Fig 6).
Conclusion:

1. Extubation induces an afterload augmentation demonstrated by an increase of BNP and, at the same time, a decrease of SV.

2. The afterload increase together with SV decrease is responsible for the metabolism turning to acidosis.

3. BNP can serve as a marker for better detection of those heart-insufficient patients who might suffer from low cardiac output with metabolic impact after extubation.

2nd study: Non invasive ventilation

The questions for this study were: Is there an impact of extubation on a heterogeneous cohort of infants with heart insufficiency? Can this impact be modified using NVI immediately after extubation? Can BNP help to identify the need for and the efficacy of NVI?

The population of this study was: n = 48 infants (25 with spontaneous breathing after extubation, 23 under NIV) with different congenital heart diseases, < 5 kg, BNP before extubation > 400 ng/ml. Design of the study: group comparison: spontaneous breathing versus NII (CPAP + 4 cmH2O, FiO2 0.4) immediately after extubation. No significant respiratory, hemodynamic and metabolic differences before extubation.

Results (Fig 7). Only significant results are shown.

Fig 7: Spontaneous breathing: Significant decrease of BE and SV, at the same time increase of BNP indicating a more important afterload. Under NIV these effects are not visible any more.
Conclusion:

1. Extubation has a hemodynamic and metabolic impact in a heterogeneous group of patients with heart insufficiency (as documented by an elevated BNP) after cardiac surgery.

2. NIV installed immediately after extubation is able to ameliorate the hemodynamic conditions as can be seen by the stability of BNP. BNP thus serves as a marker of ventricular load or insufficiency and the efficacy of NVI.

3. NVI in the infant is well tolerated (besides a slight increase of respiratory rate). It should be introduced rapidly after extubation in a patient with imminent risks for heart failure whereas – from a hemodynamic point of view - it is useless in patients without compromised cardiac function.

3rd study: Respiratory physiotherapy

Patients enrolled in the study: n = 42, 51 measurements, mean age 73 days, infants with congenital heart disease after cardiac surgery, no intra- or extra-cardiac shunt, respiratory and hemodynamic stability under mechanical ventilation. Respiratory physiotherapy with acceleration of the expiratory flow (FET), aspiration, mask ventilation.

The study was designed to find answers to the following questions:

- What are the respiratory effects of the respiratory physiotherapy in these patients?
- What are its hemodynamic effects?

Results (Tab2, p<0.05)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before physiotherapy</th>
<th>After physiotherapy</th>
<th>1h after physiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume TV (ml)</td>
<td>33.6</td>
<td>38.9</td>
<td>35</td>
</tr>
<tr>
<td>Positive inspiratory pressure PIP (cmH2O)</td>
<td>22.3</td>
<td>19</td>
<td>19.3</td>
</tr>
<tr>
<td>Compliance C (l/cmH2O)</td>
<td>2</td>
<td>2.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Resistance R (dyn x sec/cm²)</td>
<td>89.5</td>
<td>68.3</td>
<td>74</td>
</tr>
<tr>
<td>Function residual capacity - alveolar recruitment FRC (ml)</td>
<td>33</td>
<td>49</td>
<td>47.5</td>
</tr>
<tr>
<td>Mitral Velocity Time Integral MVTI (cm)</td>
<td>8.9</td>
<td>10.1</td>
<td>10.4</td>
</tr>
<tr>
<td>Stroke volume SV (ml)</td>
<td>5.6</td>
<td>6.3</td>
<td>6</td>
</tr>
<tr>
<td>Index of Contractility ICON</td>
<td>49</td>
<td>63.4</td>
<td>60.2</td>
</tr>
<tr>
<td>Heart rate HR (min) – Mean arterial blood pressure MAP (mmHg)</td>
<td>149.4/63.4</td>
<td>153.4/68.1</td>
<td>NS</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>391</td>
<td></td>
<td>358</td>
</tr>
</tbody>
</table>
Tab 2: The short term respiratory effects of respiratory physiotherapy (immediately/1h after therapy) are: TV plus 16%/4%, PIP minus 16%/13%, C plus 35%/20%, R minus 24%/17%, FRC plus 48%/44%. These respiratory changes are corresponding to hemodynamic changes as: MVTI plus 13%/17%, SV plus 11%/7%, ICON plus 29%/23%, BNP minus 8% (1h) suggesting a decrease of after-load due to a respiration-related increase of CO and ventricular contractility.

There were good and even strong correlations between the respiratory and hemodynamic parameters creating evidence for lung heart interaction (not shown).

**Conclusion:**

1. Respiratory physiotherapy in patients with congenital heart disease under conditions of ventilation with positive pressure has positive respiratory effects: increase of tidal volume, compliance, FRC, decrease of inspiratory pressure and airway resistance.

2. There are positive circulatory effects, too: better LV filling (MVTI) with increase of SV and LV contractility (Frank-Starling) conditioning an after-load reduction.

3. The respiratory positive effects seem to lead to positive hemodynamic effects in the sense of lung heart interaction. Thus, there is a positive short time effect of respiratory physiotherapy in these patients.

**General conclusion:**

1. The lungs, the pulmonary vessels and the heart are an anatomic and physiological unit.

2. In the patient with heart disease, this functional unit is at stake. It is therefore necessary to maintain a good pulmonary function (mechanical ventilation, NIV, respiratory physiotherapy) and a correct oxygenation in order to guarantee a correct ventricular function.

3. In patients with congenital heart disease, BNP may serve as a marker of cardiac function as well as of cardiorespiratory interaction and therapy effects on it.

4. Respiratory physiotherapy seems to have beneficial (at least) short time respiratory and therefore circulatory effects. It stays open whether there are also long term indications and conditions for this treatment. In any case, respiratory physiotherapy and NIV must be adapted to the needs and evolutions of the individual patient.

5. These studies demand further investigations on larger and more different populations.