Master Thesis

Pressure measurements during High Flow Nasal Cannula (HFNC) therapy in infants with a severe airway infection

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Abstract

High-Flow Nasal Cannula (HFNC) therapy is a relative new alternative method for non-invasive respiratory support that is increasingly used in childhood respiratory distress. Using nasal cannula it allows the delivery of heated and humidified oxygen enriched air with a high flow rate. The exact working mechanism of HFNC is largely unraveled and consequently guidelines lack evidence based support. This study aims to explore the possible mechanism of action of HFNC therapy in young children, specifically the clinical effects of HFNC induced airway pressure.

Both a clinical pilot study and a laboratory study were performed. During the clinical pilot study, flow and flow-induced pressure inside the HFNC device were recorded simultaneously with relevant physiological variables in infants receiving HFNC therapy to evaluate their relationship. In the laboratory study the difference between the pressure in the HFNC device and at the nasal cannula was measured in order to estimate the generated airway pressure in children included in the clinical pilot study.

The pressure and physiological variables data were accurately recorded of 18 patients. A positive linear relationship was found between the applied flow rate and the calculated generated pressure in the nasal cannula, dependent on the type of nasal cannula used. The pressure frequency showed no relationship with the flow rate. In some patients (responders) the heart rate showed a rapid decrease after start of HFNC therapy, while in others this parameter remained constant. In responders the time until the first reduction in flow rate was significantly shorter. In addition the responders showed a larger Q_1/kg (ratio baseline flow rate to weight) then the non-responders.

This study supports the hypothesis that airway pressure plays a key role in the clinical efficacy of HFNC therapy in infants with respiratory distress. However to further establish the efficiency and the most appropriate settings of HFNC therapy, further research is required.

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CHAPTER 1

General introduction

Bronchiolitis is a common viral lower airway infection in infants under the age of two that may require hospitalisation. [1–5] In bronchiolitis, acute inflammation results in increased mucus production and oedema of the airway wall obstructing the airways. [3, 6] Symptoms consist of rhinorrhea (runny nose), tachypnea (rapid breathing), wheezing, coughing, increased Work of Breathing (WoB), nasal flaring, feeding problems and tachycardia. [5]

In most infants, bronchiolitis resolves without complications and the mainstay of management is supportive (such as relief of nasal obstruction and adaptions to feeding regiments). However some children with more severe respiratory distress require hospitalization for additional monitoring and supportive care. In young infants severe respiratory distress can rapidly progress to respiratory failure, a well know complication of bronchiolitis. Supplemental oxygen alone may then be insufficient and additional respiratory support such as intubation and mechanical ventilation may be required. [7–9]

A relative new alternative for respiratory support increasingly being used in patients with respiratory distress is called High-Flow Nasal Cannula (HFNC) therapy. HFNC therapy is a technique that allows the delivery of heated (37 °C) and humidified (44 mg/l) oxygen enriched air with a high flow rate. Other forms of non-invasive delivery are often poorly tolerated by children, however HFNC therapy has the potential to reduce the need for intubation and be better tolerated by children. [3, 9–14] This form of non-invasive ventilation supports the infants spontaneous respiration and aims at preventing collapse of the alveoli and terminal airways during expiration, avoiding the need for tracheal intubation and related concerns about invasive ventilation. [3, 9, 11]

Figure 1.1: High Flow Nasal Cannula junior nasal cannula example.

An additional advantage is the avoidance of burdensome transport and admission to a pediatric intensive care unit.

Despite the increasing use of HFNC therapy, the exact working mechanism is largely unravelled and hampering the development of evidence based guidelines to assist pediatric physicians with regard to the use and regulation of HFNC therapy. [15]

Current literature poses five possible mechanisms of HFNC therapy:

1. HFNC induced increased inspiratoir airflow and reduction of WoB by increasing airflow. [16, 17]
2. High flow induced provision of a distending positive airway pressure for recruitement of alveoli and maintaining airway patency. [7, 16–19]
3. High flow induced washout of nasopharyngeal dead space, resulting in increased fraction of O_2 and decreased fraction of CO_2 in the alveoli. [16, 18]
4. Improvement in airway conductance and pulmonary compliance by providing heated and humidified air. [16, 20] Lubrication and conditioning of viscous mucus resulting in improvement of mobilization and evaluation of mucus.
5. Reduction in energy expenditure for gas conditioning, thus creating a reduction of the metabolic cost. [16]

1.1 Research challenges

However, there is currently little evidence and clinical experience about the possible mechanisms of action of HFNC especially in young children. [3]

Purpose of the study The primary aim of this study is to investigate mechanisms of action of HFNC, particular by studying the relation between applied flow rate and generated pressure. Subsequently the relation between these two and the clinical course will be investigated.

1.2 Research hypotheses

We hypothesize that:

- The generated pressure is the driving force reducing respiratory distress in children with respiratory distress, and that the measurement of pressure in the HFNC device can be used to monitor the pressure in the airways and is therefore a suitable method to regulate HFNC therapy.

- The provision of high flow generates an increase in airway pressure. The generated airway pressure varies between individuals (due to variations in airway geometry, cannula size and nare size) and is related to the flow rate.
- The improvement in clinical course during the HFNC therapy can be related to the generated airway pressure instead of the set flow rate.

1.3 Research questions and objectives

To determine the possible working mechanisms of HFNC therapy two research questions are formulated:

1. What is the relation between flow rate and the generated pressure?
2. What is the relation between the clinical course and 1) the flow rate and 2) the generated airway pressure?

These research questions lead to the following study objectives:

- To examine the set flow rate, generated device pressure and clinical course in a clinical pilot study in children receiving HFNC therapy.
- To determine an estimation of the airway pressure from the device pressure by means of an in-vitro measurement.
- To analyze the estimated pressure generated by the set flow rate.
- To investigate the relation between the clinical course and 1) the set flow and 2) generated airway pressure.

CHAPTER 2

Clinical Background

2.1 Respiratory distress in infants

Infants in respiratory distress often show signs that they need to exert a lot of effort to breath or that they are not getting enough oxygen. Respiratory distress is characterized by tachypnea, increased heart rate, nasal flaring, retractions, accessory muscle use, wheezing, stridor and/or hypoxemia. A common example where respiratory distress occurs is Bronchiolitis.

2.1.1 Bronchiolitis

Bronchiolitis is an acute (viral) lower airway infection with inflammation and obstruction of the small airways, that mainly occurs in children <2 years of age and is generally seen in the autumn and winter season. [21] The diagnosis can be made by increased respiratory effort (tachypnea, nasal flaring, chest retractions) and upper respiratory symptoms, such as crackles and wheezing (may not be audible if the airways are profoundly narrowed or exhaustion). [21]

Bronchiolitis is a common diagnosis in these age groups and often resolves without complications. A small percentage of these children with more severe respiratory distress require hospitalization for additional monitoring and supportive care. [1–5] These children have increased work of breathing, which can result in exhaustion and these infants often require supplemental oxygen or even endotracheal intubation and mechanical ventilation. Non-invasive respiratory support mechanisms are being used to address respiratory compromise. [22] There are various non-invasive ways in which respiratory support can be provided to infants to improve respiratory function, including head box oxygen, Low Flow Nasal Cannula (LFNC), nasal Continuous Positive Airways Pressure (nCPAP) and Nasal Intermittent Positive Pressure Ventilation (NIPPV).

Change in fysiology Bronchiolitis is characterised by an acute inflammation, edema and necrode of the epithelia cells of the lower airways and increased mucus production. [6] The increased mucus production results in an airway obstruction. [3, 6] As a consequence the lung compliance is decreased and the expiration time is increased. During inspiration a decrease in airway pressure results in intercostal and subcostal retractions. During expiration wheezing may be heard due to narrowing of the airways and turbulence of the air flow.

2.1.2 Therapy

Because there is no specific medical therapy for bronchiolitis, important pillars of treatment are the monitoring of the clinical course and providing supportive therapy. This symptomatic treatment aimes at ensuring sufficient food intake, administration of fluids and oxygen (through a nasal cannula). [1] Infants may have difficulty staying adequately hydrated due to multiple reasons: increased fluid needs (related to fever and tachypnea), decreased oral intake (related to tachypnea and respiratory distress), and/or vomiting. [23]

This symptomatic therapy focuses on ensuring food intake, administration of fluids and oxygen. [1] Saline nose drops are often provided and supplemental oxygen and respiratory support could be necessary to maintain $SpO_2 >$ 90-92%.

Respiratory support Besides the previously mentioned non-invasive ways of respiratory support (nCPAP and NIPPV), a third common method to provide additional oxygen is through nasal cannulae. Nasal cannulae consist of two small, thin tubes that sit just inside the nostrils. Low-Flow nasal cannulae (LFNC) often refers to the use of nasal cannulae with maximal flow rates of 1 L/min, were HFNC refers to flow rates larger than LFNC (>1 L/min). The use of higher flow rates in infants could provide positive end-expiratory pressure (PEEP) and is suggested as an alternative form of respiratory support for infants with respiratory distress. [24]

Children who are at risk for progression to respiratory failure often receive a trial of HFNC and/or CPAP before endotracheal intubation. HFNC and CPAP are both used to reduce the WoB, improve gas exchange and avoid the need for endotracheal intubation (including associated adverse effects) in children who are at risk for progression to respiratory failure. [3, 25]

2.2 High Flow Nasal Cannula therapy

HFNC therapy is a well-tolerated non-invasive method of ventilatory support that uses nasal cannulas to administer heated, humidified gas flows with or without increased oxygen concentration. [26]

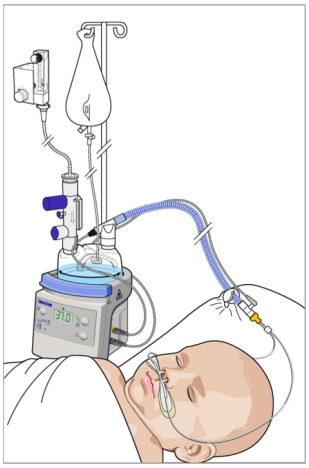


Figure 2.1: High Flow Nasal Cannula system providing respiratory support to an infant.

Clinical use of HFNC

Following protocol, the FiO_2 is adjusted according to the SaO_2 and the flow is adjusted according to clinical effect. It presents several advantages over conventional low-flow oxygen therapy in terms of humidification, oxygenation, gas exchange, and breathing pattern.

HFNC as a respiratory support modality is increasingly applied in the pediatric department because from practice it has been found to be well tolerated and to have positive effects, although the predominant mechanism of action in relieving respiratory distress is not well established.

1) Washout of nasopharyngeal dead space

The washout of nasopharyngeal dead space contributes in an enhanced oxygenation due to an improvement in the fraction of alveolar gasses (O_2 and CO_2). [16, 18, 27–30] Several studies demonstrated a higher nasopharyngeal oxygen concentration with HFNC compared to low flow nasal cannulae and even greater concentrations with higher flow rates and an open mouth. [27, 31]

2) Decreased WoB

HFNC induced increased inspiratoir airflow and reduction of WoB by providing higher flow rates. [16, 17] The distensibility of the nasopharynx provides significant resistance on inspiratory relative to expiratory efforts. [32] HFNC therapy provides flow rates to match inspiratory flow, attenuating the inspiratory resistance and thus eliminates relating work of breathing.

3) Improvement in airway conductance and pulmonary compliance

The provision of heated and humidified air to the conducting airways improves airway conductance and pulmonary compliance compared to dry, cooler gas. [16, 20, 33] Several studies even showed that the provision of

cold and dry gas could elicit a bronchoconstrictor response. [34–36] In addition, heating and humidification of the provided gas flow facilitates secretion clearance. [37]

4) Decrease in metabolic cost

The process of gas conditioning requires a significant amount of energy. [16] Energy is not only required to warm the air, but Dalton's law dictates that as gas gets warmer it holds more water vapor and energy is needed to evaporate it. By adequately warming and humidifing the povided gas, the metabolic work associated with gas conditioning is reduced. [16]

5) Provision of a mild distending positive airway pressure for recruitement of alveoli

Current evidence demonstrates that HFNC can provide positive distending airway pressure for lung recruitment in most circumstances. [7, 16–19, 38] This distending pressure to the lungs is believed to result in improved ventilatory mechanics by optimizing lung compliance and assist with gas exchange by maintaining the patency of alveoli. [39–41] The generated airway pressure is determined by: [16]

- Applied flow rate
- Leak rate
  - Nasopharyngeal anatomy.
  - Leak dependent on the relationship between nasal prong size and nares of the nose. [24, 42, 43]
  - Closed or open mouth. [38]

Nasal prong size Nasal cannula size is a critical factor in determining the pressure generation as it relates to air leak around the cannula prongs. The size of the nasal cannula is determined by fit (occluding $\pm$ 50% of the nostrils) and the size affects the maximum amount of flow. With conventional oxygen therapy, Locke et al. showed that smaller nasal prongs do not generate significant esophageal pressure, but by using larger cannulae in the same infants a clear correlation between gas flow and esophageal pressure is found. [24]

Wilkinson et al. showed that HFNC in infants can result in clinically relevant increas in pharyngeal pressure, and that the pharyngeal pressure is directly related to flow rate, but inversely related to infant size. [44]

2.3 Clinical dyspnea scoring system

To identify the respiratory status, repeated clinical assessment of the respiratory system is necessary (eg, respiratory rate, nasal flaring, retractions, grunting). Severity scores are commonly used in research and clinic to assess the severity of dyspnea. For the evaluation of bronchiolitis a number of clinical scoring systems have been used, however most of them have limited validity. [45]

Modified Tal scoring system According to McCallum et al. the Tal and Modified-Tal scoring systems for bronchiolitis can reliably be used in clinical practice and research. [45] However, they also stated that its utility for prediction of O_2 requirement is limited. Recently Golan-Tripto et al. also found that the Modified Tal score is a reliable and valid scoring system for the evaluation of infants with acute bronchiolitis. [46] The Modified Tal scoring system is displayed in table 2.1. To our knowledge this is the most validated dyspnea scoring system in children with bronchiolitis. For that reason the modified Tal score is used in this clinical pilot study to monitor the clinical course.

Table 2.1: Modified Tal scoring system. The clinical score consist of the total number of points and is considered: mild ≤ 5; moderate 6-10; severe 11-12.

Score	Respiratory rate (breaths/min)	Wheezing / crackles	SpO_2	Accessory respiratory muscle utilization
0	< 30	None	> 95	None (no chest in-drawing, i.e., absence of lower part of the chest moves in or retracts when inhalation occurs)
1	30-45	Only end expiration with stethoscope	94-95	$+$ presence of mild intercostal in-drawing (just visible), no head bobbing or tracheal tug
2	46-60	Exp & insp with stethoscope	90-93	$++$ moderate amount of intercostal in-drawing, no head bobbing or tracheal tug
3	> 60	Audible without stethoscope	< 89	$+++$ moderate or marked intercostal in-drawing with presence of head bobbing or tracheal tug

CHAPTER 3

Technical Background

During this study we are looking at the workings mechanisms of HFNC therapy and the effect it has on the respiratory dynamics. This chapter shall first describe some basic flow dynamics, followed by the normal dynamics of respiration and ventilation and subsequently the flow dynamics applicable during HFNC therapy.
We can divide the provision of air during HFNC therapy in two parts:

1. Firstly the flow of air through the device
2. Secondly the flow of air through the airways

During HFNC a flow rate (Q) is regulated through a high flow blender in the wall and first moves through the device and tubes to the nasal cannula which is inserted into the nostrils of a patient.

3.1 Respiratory physiology

The physics of breathing refers to the movement of air in and out of the lungs, producing a change in lung volume (V_L). The change in volume (volume that passes through an area) is proportional to the flow rate and the time duration:

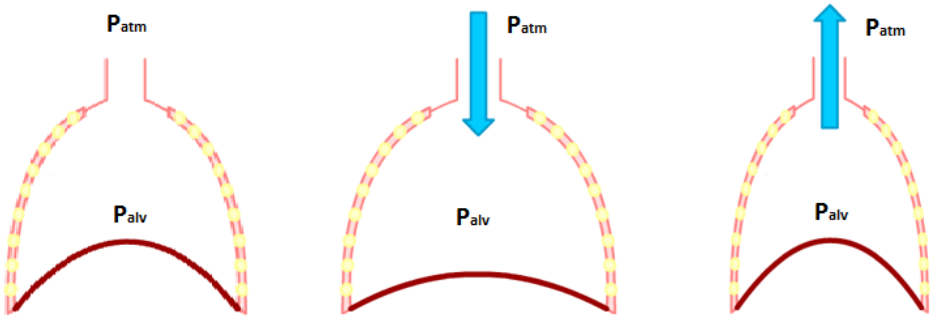
$$dV = Qdt \tag{3.1}$$

Where V is the volume, Q is the flow rate and dt is the difference in time.

During this study our study population consist of children in respiratory distress. To properly look at the effect HFNC therapy has on the respiratory dynamics, firstly the dynamics of healthy persons will be discussed followed by the effects of respiratory distress on these respiratory dynamics.

3.1.1 Healthy respiratory dynamics

Two situations can be studied, the first is a situation where no air is flowing, called **static**. The second situation is when the lungs are changing volume and air is flowing either in or out, called **dynamic**.



(a) Static (b) Dynamic inspiration (c) Dynamic expiration

Figure 3.1: A) Static situation where no air is flowing. B) Inspiration: Ribs move up and out, diafragm flattens, volume of chest increases and this increase in volume means decrease in alveolar pressure. C) Expiration: The ribs fall, diafragm moves up, volume of chest decrease and this decrease in volume means increase in alveolar pressure.

Static In a static situation, no air is flowing. During the respiratory cycle this happens between the inspiratory and expiratory phase, meaning end inspiratoir and end expiratoir. Because there is no flow ($Q = 0$), the pressure is equal throughout the respiratory tract (except gravitational effects). The alveolar pressure (P_{alv}) at end expiration is equal to atmospheric pressure ($P_{atm} = 0$ cmH_2O differential pressure), plus or minus 2 cmH_2O throughout the lung due to gravitational effects. [47, 48]

$$P_{alv} = P_{atm} \tag{3.2}$$

Dynamic In the dynamic situation, the static situation is complicated because lung volume is changing and air is flowing. P_{alv} determines whether air will flow into or out of the lungs.

Inspiration During inspiration the flow needs to go from the atmosphere to the alveoli. The lung volume (V_L) increases as a result of the contraction of the diaphragm (moving downward) and the external intercostal muscles, lifting the rib cage up and out and thereby expanding the thoracic cavity. Based on the principle of Boyle's law,

due to this increase in volume the alveolar pressure (P_{alv}) is decreased. The pressure gradient between P_{atm} and P_{alv} allows air to flow into the lungs and inhalation occurs.

$$P_{alv} < P_{atm} \tag{3.3}$$

Expiration A normal expiration is entirely passive by simply relaxing the muscles of inspiration. The thoracic volume shall decrease and due to this decrease in volume P_{alv} is increased.

$$P_{alv} > P_{atm} \tag{3.4}$$

According to Boyle's law, the absolute pressure in a closed system is inversely proportional to the volume the gas occupies.

$$P \propto \frac{1}{V}$$

3.1.2 Respiratory distress

Respiratory distress is when the body needs more oxygen and can often consists of the following physiologic measures:

- Tachypnea (rapid breathing)
- Deep breathing (each breath allows a larger oxygen intake)

When there is an obstruction in the upper or lower airways, the diaphragm is still pulled downwards, although lesser air can be inhaled and the pressure inside the lungs decrease. This is characterized by earlier mentioned measures and in addition:

- Retractions
  - Subcostal retractions (indrawing of the abdomen just below the ribs). In children also called belly breathing.
  - Substernal retractions (indrawing of the abdomen just below the sternum)
  - Intercostal retractions (Indrawing between each rib)
  - Suprasternal retractions (indrawing of the skin in the middle of the neck above the sternum. Also known as tracheal tug.
- Stridor (high pitch sound) which is caused by turbulent airflow in the respiratory tract and caused by the narrowing of air passages due to inflammation.

3.2 Dynamics of HFNC therapy

During HFNC therapy the flow rate is varied based on the clinical course.

3.2.1 Air flow inside device

The HFNC device can be seen as a serie of tubes with different diameters as illustrated in figure 3.2. During HFNC therapy the air moves through these tubes to end at the tip of the nasal cannula. Air is assumed to be incompressible, meaning that the flow rate at every cross-section of a non-branched tube remains the same (the same volume that goes into the tube, must come out at the other end).

$$Q_A = Q_B = Q_C = Q_D \tag{3.5}$$

Where respectively A,B,C and D are different cross sections of the HFNC device, displayed in figure 3.2.

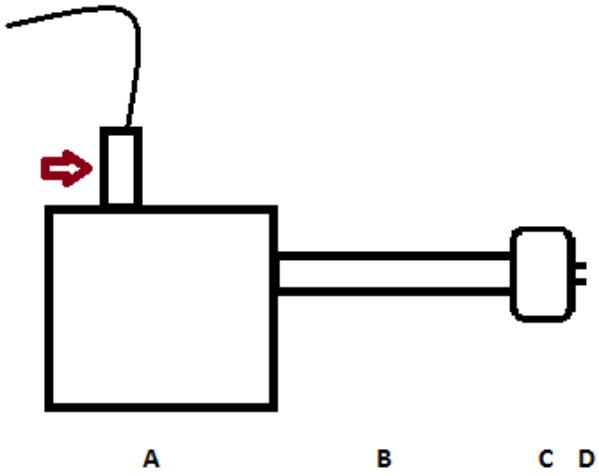


Figure 3.2: Schematic representation of the HFNC device. A is the humidifier in which the air is coming from above where the flow rate was set. *The red arrow points to the pressure port already present in the device*, B is a large heated tube, C is the connected nasal cannula and D are the nasal prongs.

Pressure difference When looking at the pressure difference between two points of a non branched tube with different diameters: In eq 3.5 we derived that the flow rate Q at every cross-section of a non-branched tube is equal.

Assuming a stationary flow; At the surface area of a specific cross section, the velocity (v) is dependent on the surface area of the cross-section ($A = \pi r^2$).

$$Q = A * v \tag{3.6}$$

The flowrate Q is equal along the entire system. However the cross section of the tubes varies, meaning that the velocity changes in the opposite direction (decrease in diameter, means an increase in velocity.).

In-vitro measurement: Pressure gradient in device

The in-vivo pilot study measures the pressure at the pressure port of the device (P_D), however the pressure at the end of the nasal cannula (P_{NC}) can be of more clinical relevance. The pressure difference between both points can be measured and calculated.

$$\Delta P = P_D - P_{NC} = P_D - P_{atm} \tag{3.7}$$

With ΔP the difference between P_D (the pressure in the device at the pressure port) and P_{NC} (which is equal to the atmospheric pressure P_{atm}).

$$P_D - p_{NC} = f(Re) * \frac{1}{2}\rho(\frac{Q}{D})^2 \quad \text{with} \quad Re = \frac{4\rho Q}{\pi D \mu}$$

With P_D the pressure measured in the device, P_{NC} the pressure at the end of the nasal cannula, Re the Reynolds number, ρ the density, Q the flowrate and D the characteristic diameter of the prongs.

Simplified it could be said that by increasing the flow rate, the generated pressure increases quadratic (and vice verse).

3.2.2 Pressure gradient between device and infant

The nasal cannula is loosely fitted within the nose entrance, Therefore the continuous air supply can escape through the space between the cannula and the nostril wall (figure 3.3).

- At inhalation, the volume flow rate provided through the cannula (Q) is partially inhaled by the lung (Q_{in}) and partially fed back to the atmosphere:
$$Q - Q_{in} \tag{3.8}$$
- At exhalation, the volume flow rate provided through the cannula (Q) is supplemented by the air released by the lung (Q_{ex}) and completely fed back to the atmosphere:
$$Q + Q_{ex} \tag{3.9}$$

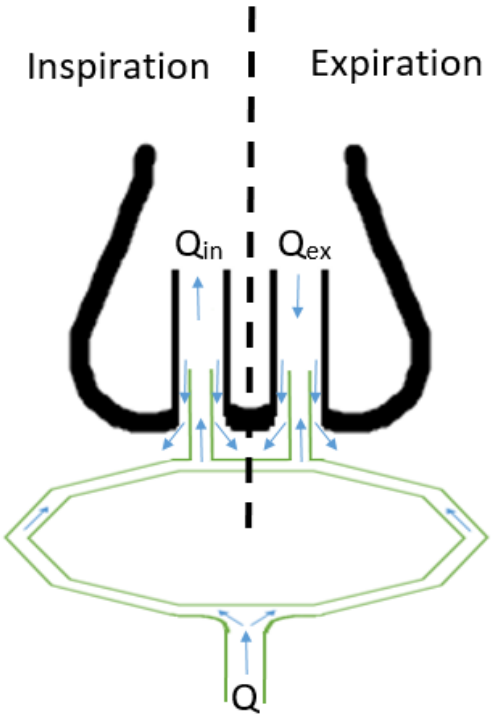


Figure 3.3: Schematic of an axial plane of the nasal cavity with the cannula (in green) inserted inside the nostrils (in black). The left side of the figure shows the flow during inspiration (Q_{in}) and the right side of the figure shows the flow during expiration (Q_{ex}).

Assuming laminar flow, the pressure difference is proportional to the flow rate:

- At inhalation $P_D - P_{atm} \sim |Q - Q_{in}|^2$
- At exhalation $P_D - P_{atm} \sim |Q + Q_{ex}|^2$

From these equations it can be deduced that by changing the flow rate of HFNC therapy, not only Q_{in} and Q_{ex} are altered, but also the average alveolar pressure (P_{alv}).
Note: In both cases the pressure inside the device (P_D) and tubes is higher than P_{atm}:

$$P_D > P_{atm} \tag{3.10}$$

3.3 Measuring airway pressure

In mechanically ventilated patients the pressure is measured. However in the case of non-invasive HFNC therapy this is not the case. In the ideal case the pressure is measured at the proximal airways. When there is no flow rate, the pressure difference is zero. End-expiratory and end-inspiratory the flow inside the airways is zero and therefor the pressure measured at the proximal airways should approximate the distal airway pressure (alveolar pressure). The shape of the pressure waveform is determined by flow, lung mechanics and any active breathing efforts of the patient.

3.3.1 Pressure transducer

A pressure transducer is a sensor that converts pressure into an analog electrical signal. For measuring the pressure on a non invasive way and suitable in a hospital environment we search for a suited pressure transducer.

The requirements of the pressure transducer:

- CE marking suitable for a hospital environment, easy to clean.
- Easily operated and the ability to connect to a computer (USB connection is a plus).
- Sample frequency: Minimal required sampling frequency according to Nyquist is two times the expected to measure frequency.

$$\begin{aligned} RR &\approx 15 - 60 \text{ bpm (beats per minute)} \\ &= 0.25 - 1 \text{ Hz.} \end{aligned}$$

- Possibility for bi-directional measurements. During normal respiration a negative alveolar pressure is created, which could mean that with lower flow rates, the possiblity exist the measured pressure inside the device becomes also negative.
- Pressure range $\geq$ 12 cmH_2O. According to literature, maximal alveolar pressure achieved in children is 12 cmH_2O.

Omega PXM409-USBH

The Omega PXM409-USBH (figure 3.4) is a high speed pressure transducer which can be directly connected to the computer due to the USB output. The micro-machined silicon exterior is suitable for pressure measurements in pharmaceutical applications and other relevant specifications are summarized in table 3.1.

Table 3.1: Pressure transducer specifications

Pressure transducer	
Transducer type	Gauge (bi-directional)
Range	25 mbar
Output	USB
Accuracy	0.08%
Weight	200g
Compensated Temperature	$-29\,^{\circ}\mathrm{C}$ to $85\,^{\circ}\mathrm{C}$

Figure 3.4: Omega (PXM409-USBH) pressure transducer

Strain-gage There are various types of pressure transducers, one of the most common, and the type this study uses, is the strain-gage base transducer. Pressure applied to the pressure transducer will produce a deflection of a diaphragm. This diaphragm is bonded to strain gages, in which the strain of the deflection of the diaphragm will cause a physical deformation of the strain gages. This strain will produce an electrical resistance change proportional to the applied pressure.

CHAPTER 4

Methods

To explore the mechanisms of HFNC therapy, specifically the generated pressure both a clinical pilot study and a laboratory study were performed. During the clinical pilot study, pressure inside the HFNC device was measured in infants receiving HFNC therapy. Simultaneously relevant physiological variables were recorded to evaluate its relationship with the applied flow rate and also the generated device pressure. Figure 4.1 shows the setup of the HFNC device with the addition of the pressure transducer inside the device.

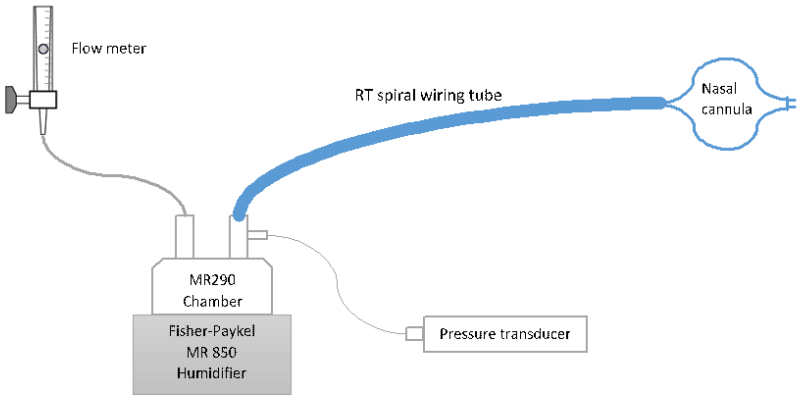


Figure 4.1: Diagram system set-up.

In parallel a laboratory study was conducted to assess the pressure inside the airways from the device pressure as a function of the flow rate and in addition to establish the friction factor $f(Re)$. The pressure at the device and at the end of the nasal cannula were simultaneously measured to calculate the pressure difference which is subsequently used to perform a nasal cannula correction in the clinical data set.

4.1 Laboratory studies

4.1.1 Study 1: Difference in pressure

During the clinical trial the pressure is measured inside the Optiflow device at the pressure port. The HFNC set-up including the pressure port with the connected pressure transducer is illustrated in figure 4.1. This laboraty study is used to measure the pressure difference between the device pressure and the pressure at the open end of the nasal cannula. This pressure difference can then be used to perform a nasal cannula correction in the clinical pilot study to assess the airway pressure. This pressure difference is independent of whether the HFNC device is connected or disconnected to a patient.

The pressure difference between the pressure port of the device (P_D) and the pressure at the end of the cannula (P_C) is a function of the flow rate(Q), the cannula diameter (D), the density (ρ) and viscosity (μ):

$$P_D - P_{NC} = f(Re)\frac{1}{2}\rho(\frac{Q^2}{D^4}) \tag{4.1}$$

As described earlier in chapter 3.2.1. Where Re is the Reynolds number which is a non-dimensional scaling of the dynamic viscosity: $Re = \frac{4}{\pi}\frac{\rho Q}{\mu D}$.

This equation tells us that if we adjust the flow rate, the pressure difference varies approximately quadratically.

Experimental set-up The set-up consisted of the Fisher and Paykel Optiflow Junior HFNC device (F&P MR290 system, Fisher&Paykel) with four different cannulae (table 4.1) and a pressure transducer. The air flow is taken from a wall source and was led through a pressure vessel (to avoid fluctuations) and connected to the HFNC device.

Table 4.1: Nasal cannula characteristics

Item code	Name	Color	Inner diameter	Max flow rate
OPT312	Premature	Red	0.13 cm	8 L/min
OPT314	Neonatal	Yellow	0.13 cm	8 L/min
OPT316	Infant	Purple	0.18 cm	20 L/min
OPT318	Paediatric	Green	0.26 cm	25 L/min

The pressure was measured as a pressure difference relative to the atmospheric pressure using a USB pressure transducer (Omega, $PXM409 - USBH$) with a frequency of 10 Hz. The pressure transducer was connected to the pressure port of the Optiflow device through a Luer-connection. Data collection was achieved by using the Digital transducer application (Omega).

Measurements The pressure was measured at the device with the cannula ending in open air. The measurements were done for flow rates up to 10 L/min (Red and yellow cannula) or 22 L/min (purple cannula) or 27 L/min (green cannula) with 1L/min increments. All measurements were performed in twofold.

Data analysis Two different fitting methods were used, a 2th order polynomial and a power law.

- A 2nd order polynomial is fitted through the measured points of each nasal cannulla type using:

$$\Delta P(Q) = a_1 Q^2 + a_2 Q + a_3 \tag{4.2}$$

With a_1, a_2 and a_3 the coefficients for a 2nd degree polynomial. Theoreticaly a_3 should be zero to satisfy the condition that $\Delta P = 0$ when $Q = 0$.

Using this equation the pressure difference as a function of the flow rate is estimated.

- A power law is calculated because this automatically satifies $\Delta P = 0$ when $Q = 0$.

$$\Delta P = a Q^b \tag{4.3}$$

It says that a change in one quantity (in our case the flow rate) results in a proportional change in the other quantity (the pressure difference).

4.2 Clinical pilot study

A pilot study was conducted at the department of Women and Child of Medisch Spectrum Twente in Enschede, the Netherlands. The study was approved by the Ethics Committee of the hospital (appendix A) and written informed consent was obtained from both parents of the participant before operation. We explored the possibility of measuring the pressure inside a HFNC device (Optiflow^{TM}) and we compared the outcomes with the applied flow rate and clinical course.

4.2.1 Study population

All infants receiving HFNC therapy at the paediatric department of the Medisch Spectrum Twente between February and July 2016 were asked to participate in this study.

Inclusion criteria

- $FiO_2 > 40\%$ and $SpO_2 < 95\%$
- Increased work of breathing

Exclusion criteria

- No signed informed consent by the parents
- Contra indications Optiflow
  - Choana-atresie (blockage of the back of the nasal passage)
  - Gastro intestinal problems in which dilation of the stomach by insuflation should be prevented
  - Recent surgical intervention in the ENT region of the upper part of the tractus digestivus
  - Reduced consiousness (GCS<8).

4.2.2 Study procedure

Measurements

All infants received respiratory support from the Optiflow^{TM}system (MR850 heated humidifier with pressure relief valve and pressure portal, RT329 heated delivery tube and an MR290 humidification chamber from Fisher and Paykel Healthcare Ltd, Auckland, New Zealand). Four Optiflow^{TM} junior nasal cannulae with different nasal interface sizes where used during this studie, namely premature, neonatal, infant, pediatric and the characteristics are described in table 4.1.
During this study different parameters were monitored to answer our research question:

Measurement of pressure The pressure inside the pressure port of the Optiflow was measured with a sample frequency of 10 Hz with the same Omega pressure transducer PXM409-USBH as used in the laboratory studies (section 4.1).

Notation of vital parameters Physiological variables, such as heart rate (HR), respiratory rate (RR) and SpO_2 were manually noted every 15 minutes from 1.5 hour prior to initiation of HFNC therapy (if possible) and continued to the end of the therapy.

Notation of set Optiflow parameters When changes, either in flow rate or in FiO_2, were made in the Optiflow settings, these changes were noted with the approximate time when these changes occurred.

Determination of clinical score Just before and half an hour after changes in flow rate were made, the subject is video recorded for 1 minute to determine the clinical dyspnea score afterwards.

Protocol Nasal cannulae were chosen to fit into the infants nostrils comfortably without occluding them. Once the system temperature was stabilized (approximately $37\,^{\circ}\mathrm{C}$ and humidified (44 mg/l)), therapy was commenced according to the local protocol. Study measurements started simultaneously and continued as long as the subject required Optiflow treatment.

4.2.3 Data analysis

All data analyses were performed using Matlab 2016a. In figure 4.2 the different steps involved in the data analysis are shown.

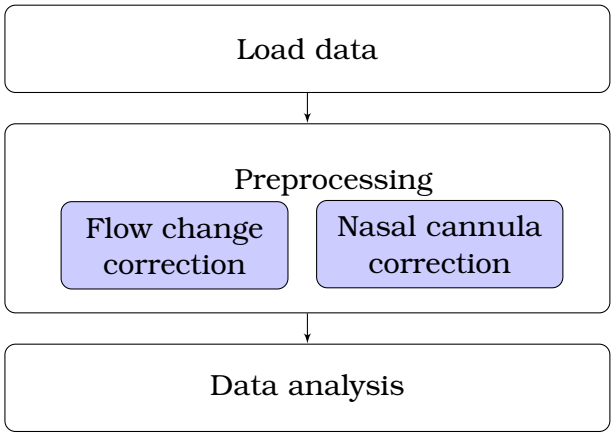


Figure 4.2: Three steps were taken to receive our results, namely first the loading of the data, secondly different preprocessing steps are done (including a flow change and location correction), followed by the data analysis resulting our results.

Load data

The first step of this study is loading the data (pressure data, vital parameters and optiflow settings) in variables (see figure 4.3) and sorting out the 'good' data from the 'bad'. Examples of 'bad' data could be missing data and/or outliers. Outliers are data values that are dramatically different from patterns in the rest of the data.

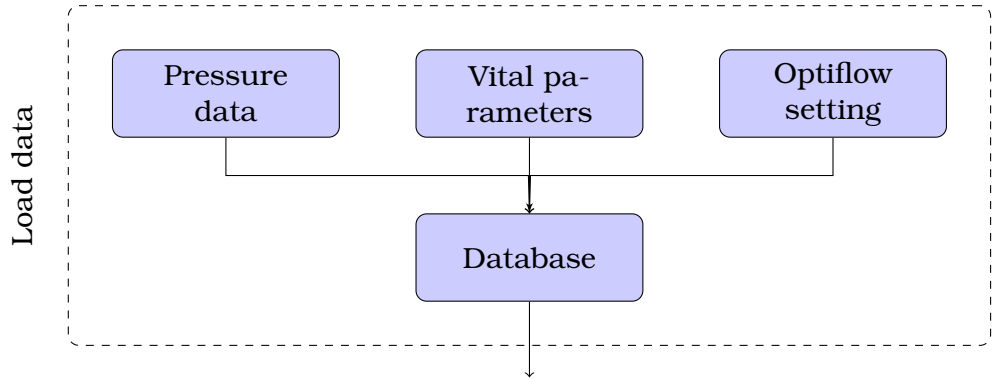


Figure 4.3: The Data collection is threefold: Firstly the measured pressure inside the device, secondly the notation of vital parameters during the therapy and thirdly the HFNC settings and changes during the therapy. All data is combined in a database.

Pre-processing

The first step of data analysis is pre-processing in which the data is filtered and smoothed to create a better estimate due to noise reduction. In order to select the windows in which the flow rate remains unchanged and to the pressure at the end of the nasal cannula, a flow change correction and nasal cannula pressure correction is performed:

- ***Flowchange correction*** Each change in flow setting is manually noted during this study. Because the data analysis will be performed in sections with a constant flow, the precise moment in time when a flow change is conducted needs to be determined. In figure 4.4, the pre-processing box shows the three steps in identifying the improved moment in time.

  Step 1 A 15 minute period before and after the manually noted time of flow change is selected.

$$T_w = \left[t_n - \frac{15 * 60}{fs} : t_n + \frac{15 * 60}{fs} \right] \tag{4.4}$$

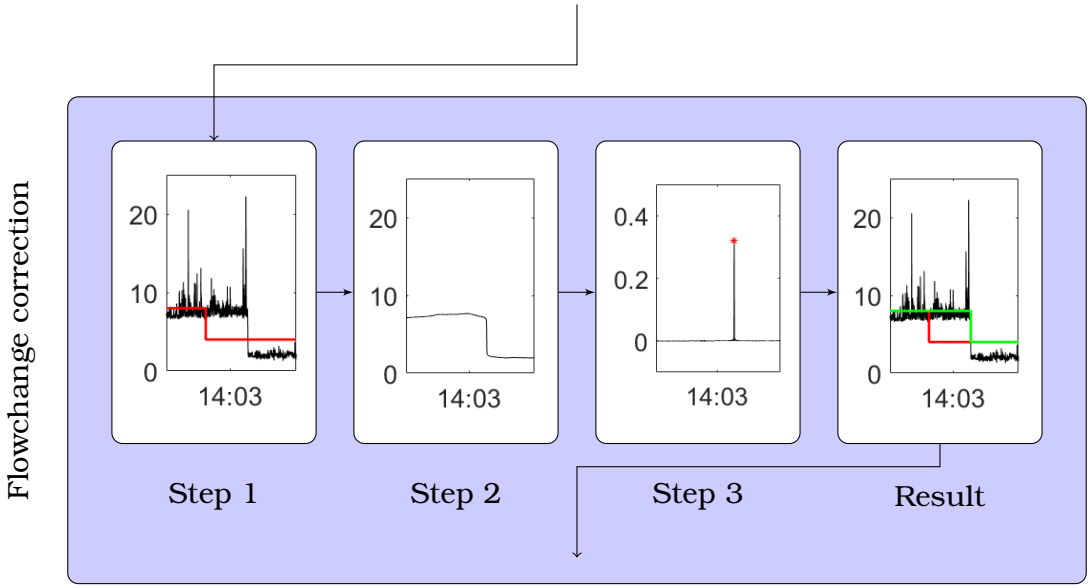


Figure 4.4: Flow change correction. Step one displays the original signal with in red the noted time of a flow change. In step 2 a median filter is applied to preserve only the step function and in step 3 the derivative of this step function.

With T_w the 30 minute period around the manually noted time t_n and fs the sampling frequency.

Step 2 Within this period a median filter can be applied for noise reduction and preserving a step function (as expected with a sudden change in flow). [49] We used a 3000th-order ($n = 3000$) one-dimensional median filter to the selected window ($f(x)$).

$$f_{median}(T_w) = median(\sum_{i=T_w(x)-1500}^{i=T_w(x)+1499} f(T_w(i))) \tag{4.5}$$

Step 3 The median filtered signal ($f_{median}(T_w)$) is differentiated to find the derivative and thus the moment an instantaneous change in signal occurs.

$$f'_{median}(T_w) = \frac{d}{dT_w}|f_{median}(T_w)| \tag{4.6}$$

Because of the median filter, the maximum value of the derivative is indicative for the moment the greatest change in signal occurs. This value and moment is calculated to select the improved moment in time a flow change is applied.

$$n_2 = \text{index of } max(f'_{median}(x)) \tag{4.7}$$

- ***Calculation of cannula pressure*** The pressure collected during this study is measured at the pressure port of the Optiflow system. The previously mentioned laboratory study will determine the correlation formulas to calculate the pressure at the nasal cannula from the measured device pressure (see section 5.1.1). This pressure difference is substracted from the pressure measured at the pressure port, resulting in the pressure at the end of the nasal cannula.

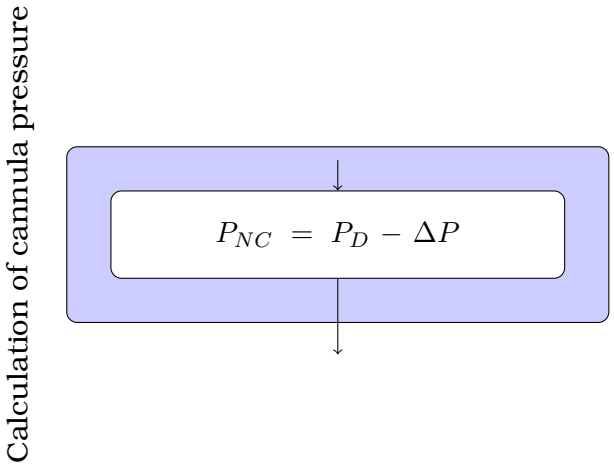


Figure 4.5: Location correction. This correction is dependent of the type of nasal cannula used, due to different size in diameter of the prongs.

Data analysis

When the different windows are selected whereby the flow rate remained constant, different variables can be compared before and after changes were made:

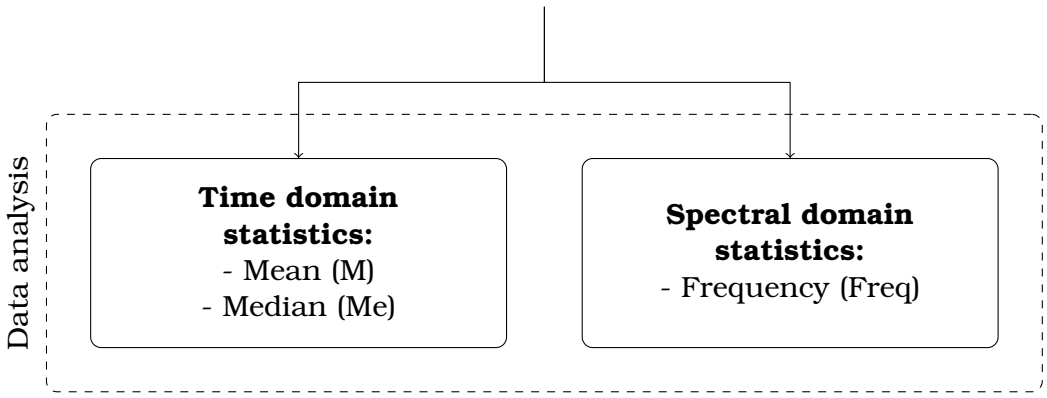


Figure 4.6: Data analysis

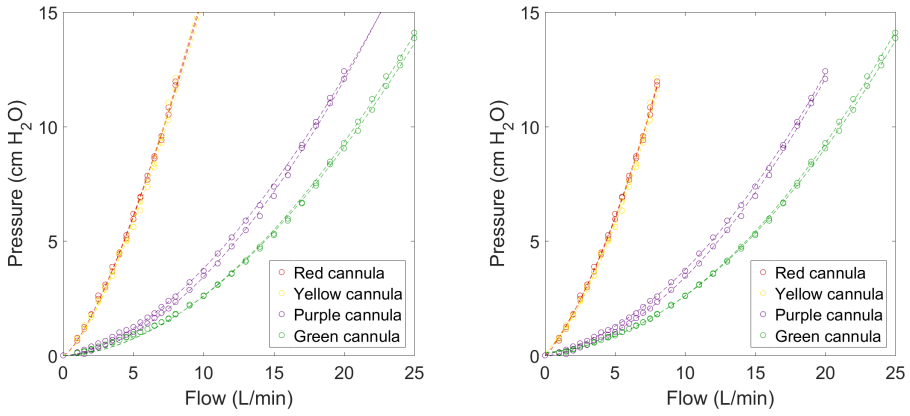
CHAPTER 5

Results

5.1 Laboratory studies

5.1.1 Study 1 - Difference in pressure

Figure 5.1 shows the difference in pressure between the pressure port of the device and the atmosphere (ΔP) at different flow rates (Q). For each nasal cannula counts that the device pressure increases with the flow rate. The smaller cannula sizes (red and yellow) on the whole have higher pressures then the larger cannulae (purple and green).



(a) Power Law (b) 2nd degree polynomial fit

Figure 5.1: Laboratory results comparing the pressure measured in the pressure port with the atmospheric pressure for all four types of nasal cannulae. Each color indicates another nasal cannula size and the dots indicate the measured pressure at a specific flow rate. The dotted line indicates a fit through these measured point in which the left figure shows a power law fit and the right figure shows a 2nd order polynomial fit.

- **2nd order polynomial fit:** The mean formula of the 2 polynomial function of each type of nasal cannula is:

$$\Delta P = a_2 Q^2 + a_1 Q + a_0 \tag{5.1}$$

With the coefficients for each cannula type:

	a_2 $(\frac{cmH_2O}{(L/min)^2})$	a_1 $(\frac{cmH_2O}{L/min})$	a_0 (cmH_2O)
Red	0.0874	0.7807	0.0740
Yellow	0.1031	0.6278	0.0669
Purple	0.0252	0.1073	0.0065
Green	0.0202	0.0467	0.1159

With ΔP in cm H_2O and Q the flow in L/min.

- **Power Law:** The mean formula of the power law function of each type of nasal cannula is:

$$\Delta P = a Q^b \tag{5.2}$$

	a $(\frac{cmH_2O}{(L/min)^b})$	b (-)
Red	0.6658	1.3759
Yellow	0.5903	1.4290
Purple	0.0667	1.7425
Green	0.0390	1.8238

With ΔP in cm H_2O and Q the flow in L/min.

Accuracy of fit The coefficient of determination (R^2) provides information about the accuracy of a fit (how well the regression line approximates the real data points). Table 5.1 shows R^2 for the two measurements of both the polynomial and power law fits.

Table 5.1: Table with the coefficients of determination (R^2) of duplicate measurements for both the polynomial and power law fits.

Cannula	Polynomial		Power Law	
	R_1^2	R_2^2	R_1^2	R_2^2
Red	0.9991	0.9994	0.9983	0.9993
Yellow	0.9982	0.9991	0.9959	0.9978
Purple	0.9998	0.9996	0.9992	0.9994
Green	0.9998	0.9998	0.9992	0.9991

5.2 Clinical pilot study

24 patients were approached to participate in the study of whom 23 patients were included. Five patients could not be used for full analysis because the date set was not complete (for example due to loss of data or due to missing connection between the pressure transducer and the HFNC device). In the remaining 18 patients the pressure data were recorded accurately and were suitable for data analysis (see table 5.2).

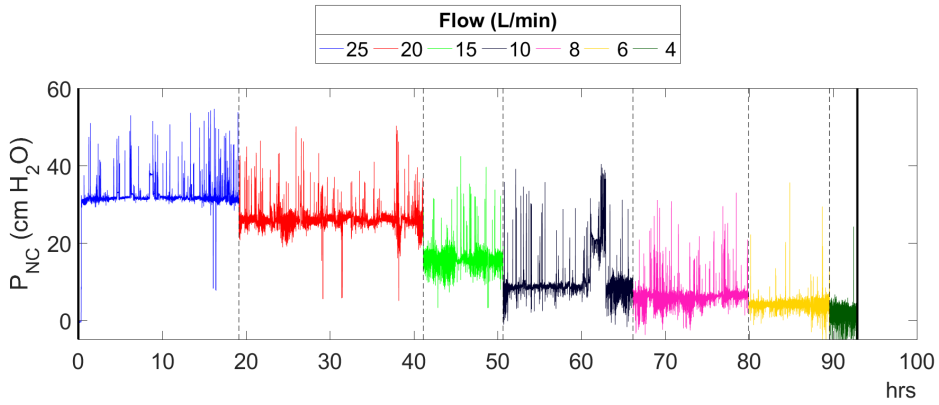
The measured device pressures are used to compute the cannula pressure by means of the pressure difference equations collected in the first laboratory test (power law equations from section 5.1.1). This pressure difference is independent of whether the HFNC device is connected to a patient, the presented pressures in this section are the cannula pressures.

Table 5.2: Patient characteristics (n = 18). LRTI = Lower respiratory tract infection, BHR = Bronchial hyperresponsiveness. Adult orange is not an infant nasal cannula, but is used is this specific case.

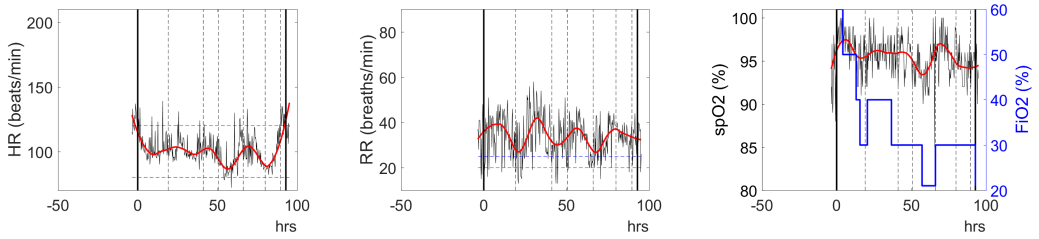
No	Age (years)	Diagnosis	Gender (m/f)	Weight (kg)	Nasal cannula type
1	0.7	Bronchiolitis	f	7	purple
2	0.2	Bronchiolitis	m	5.2	purple
3	6	LRTI/pneumonia	m	32.5	green
4	0.1	resp. insuf. (coronavirus)	m	?	yellow
5	0.3	Bronchiolitis	f	6.5	purple
6	0.5	Bronchiolitis	f	5	purple
7	1	LRTI	f	12.5	green
8	0.2	LRTI	f	3.9	yellow
9	3	LRTI, BHR, pneumonia	m	15	green
10	0.5	LRTI, BHR	m	9.0	purple
11	7	pneumonia	f	25	
12	3	pneumonia	m	15.1	green
13	5	astma exarcerbation	f	20	green
14	1.7	BHR by bilateral pneumonia	f	13	purple
15	8	Increased mucus production	m	53	green & adult orange
16	4	BHR by LRTI	m	18	green
17	1.2	Bronchiolitis	m	10.7	green
18	2.4	BHRI by LRTI	m	11	green

5.2.1 Data collection of an example subject

Figure 5.2 is an example of the data collection of one subject. The collected data and results for each individual subject can be found in appendix B.



(a) Typically recording of the measured pressure at the end of the cannula, plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and end of the HFNC therapy and the dotted vertical lines are the moments in time when the set flow rate is changed.



(b) Heart rate (c) Respiratory rate (d) Saturation

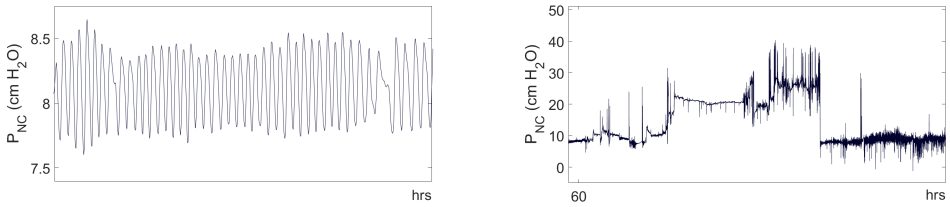
Figure 5.2: Typically recording of vital parameters during HFNC therapy. Respectively the heart rate (HR), respiratory rate (RR) and the saturation level (spO_2), with in red the trendline. In the right figure the set FiO_2 values at the device are visualized in blue.

Pressure recording In the top figure, the calculated pressure at the end of the cannula is plotted against the duration of HFNC therapy. The pressure is visualized in another color for each change in flow rate. The bold vertical lines indicate respectively the start and stop of the HFNC therapy, the dotted vertical lines indicate when there is a change in flow rate.

It is clear that with a decrease in set flow, the cannula pressure also decreases. Notable are the many high spikes in the signal, most of which are positive and evenly distributed over the signal. At the fourth set flow rate (10 L/min) a kind of plateau pressure is seen in which for a longer

period of time, the pressure is increased without notation of a change in set flow rate.

In detail When looking closer at the pressure signal, different things can be noticed. Figure 5.3a show a closer look at the pressure signal and shows a sinuisidal pattern resembling a respiratory signal. Figure 5.3b shows a longer time window with a constant applied flow rate, however there is a significant increase in pressure during from 9 cmH_2O to around 22 and even 29 cmH_2O.



(a) Pressure frequency

(b) Pressure plateau

Figure 5.3: Two typical detail of the pressure signal.

Vital parameters Figure 5.2 shows the vital parameters (respectively the heart rate, respiratory rate and saturation) in the same time period as the previously mentioned pressure recording. Again the bold vertical lines indicate the start and stop of the HFNC therapy and the dotted vertical lines indicate when there is a change in flow rate. The trendline is visualized in red.

The HR and RR appear to stay constant throughout the therapy, except sinus-shaped fluctuation reflecting day-night rhythm. In the first hours after the start of the therapy the HR decreases drastically. At the end of the therapy the HR increases drastically. Saturation levels increase, from 90-92% before start and 95-96% during HFNC. At start the FiO_2 is set at 60% oxygen, which is quickly decreased to 30%, in which the saturation levels remain relative constant. There are two moments in which the FiO_2 is decreased and shortly after again increased to the previous value, which is in both times accompanied by a decrease in SpO_2, followed by a recovery of saturation the moment the FiO_2 is again increased.

5.2.2 Mean pressure as a function of flow rate

During a window with constant flow rate, different parameters during this period can be calculated. This section described the mean pressure as a function of the flow rate. For each flow rate the mean cannula pressure has been derived during the time window whereby the flow rate remained constant.

Example subject Typical results are displayed in figure 5.4 in which each dot represents the mean of a 5 minute window. Each color again indicates another change in flow and corresponds to the recorded pressure in figure 5.2. There is a visible relationship between the flow rate and the mean pressure. When the flow increases, the mean pressure also increases which suggests a linear relation between flow rate and mean pressure. At individual flow rates (such as 10, 20 and 25 L/min) there is a large variation in mean pressures visible, and at 10 L/min it even appears to be two separate groups: a lower cluster around 7.5 cmH_2O and higher mean pressure values between 15-23 cmH_2O.

The boxplot shows the median and 25th and 75th percentile, with the interquartile range (IQR) equal to the difference between the 75th and the 25th percentile (the distance covering the middle 50% of the data). The IQR in this subject appears small, meaning small variability of the data.

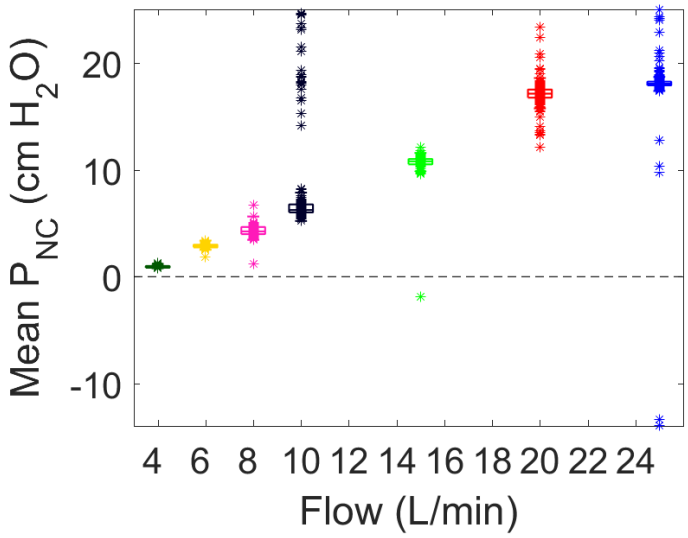


Figure 5.4: Mean pressure plotted against the different flow rates used in this therapy. Each dot is a mean pressure of a 5 minute period. The boxplot indicates the median and 25th and 75th percentile. The median is shown by the line that cuts through the box.

Mean pressure of all subjects Figure 5.5 shows a reduced version of figure 5.4 for all included subjects in which only the median value of the mean pressure is shown (center of the boxplot in figure 5.4). The subjects are divided by nasal cannula type.

The green and purple cannula have the largest number of subjects and both show a visible linear relationship (with a wide variation) between the cannula pressure and the applied flow rate (the pressure increases when flow increases). The yellow cannula is only used in two subjects of which one subject only has one flow rate. The second yellow cannula used in this study also shows a relationship between pressure and flow, however these values are situated at a higher pressure value. There is one subject who switched nasal cannula during the therapy and is considered as an unknown nasal cannula type. The unknown cannula type does not show a linear relation between the flow rate and generated cannula pressure. Notable is a visible change in direction during the measurement.

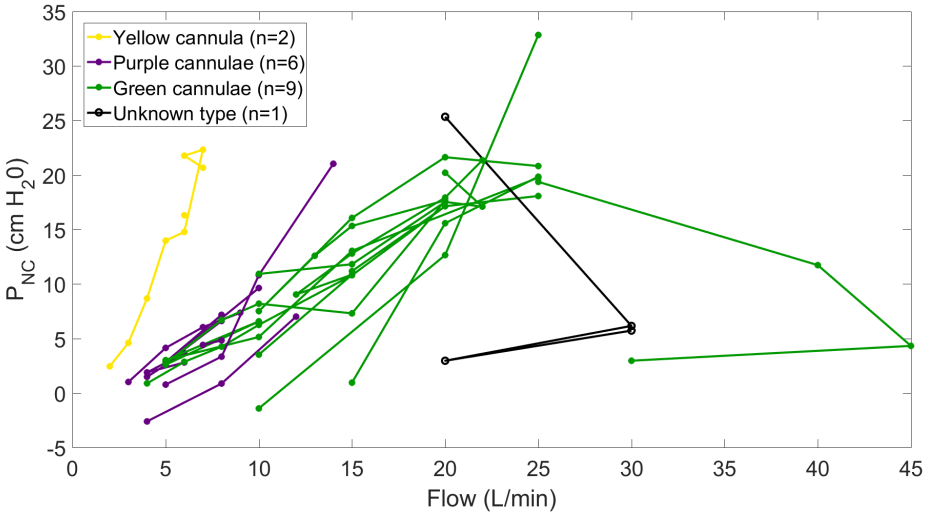


Figure 5.5: Median of the mean pressure (at the end of the nasal cannula) flow relation for all subjects divided by cannula type.

5.2.3 Pressure frequency as a function of flow rate

During a time window whereby the flow rate remains constant, different parameters during this window can be calculated. This section describes the pressure frequency as a function of the flow rate. For each flow rate the frequency from the pressure signal has been derived each 5 minutes during the time interval that particular flow rate was set. Because the cannula is inserted into the nostrils, the pressure difference generated due to breathing shows a breathing cycle and we also compare the calculated frequencies with the manually recorded RR.

Example subject Typical results of the frequency as a function of flow rate are shown in Figure 5.6. Again each dot represents the main frequency in a 5 minute window and each color indicates another flow rate corresponding tothe recorded cannula pressure in figure 5.2. At each flow rate a large scatter of frequencies are visible and thereby is the IQR in this subject large and seems to increase as the flow rate increases.

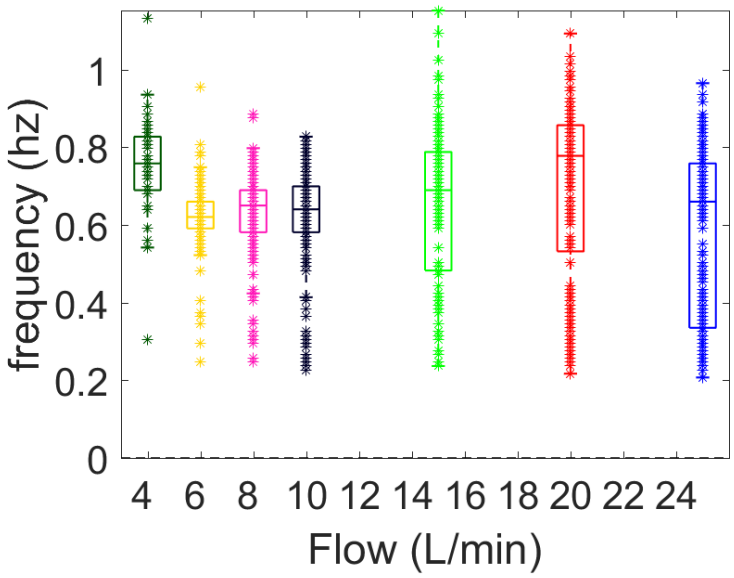


Figure 5.6: Mean frequency plotted against the different flow rates used in this therapy. Each dot is a mean pressure of a 5 minute period. The boxplot indicates the median and 25th and 75th percentile. The median is shown by the line that cuts through the box.

Mean pressure frequency of all subjects Figure 5.7 shows a reduced version of figure 5.6 in which the frequency from the pressure signal as a function of the flow rate for all included subjects is shown. The yellow only has data in the lower flow rates (<8 L/min) and the purple cannula doesn't included flow rates higher then 15 L/min. Both yellow and purple cannulae show no frequencies above 0.65 Hz and no clear relationship is visible between flow rate and pressure frequency. The green cannula reaches higher flow rates and frequencies, but also shows no clear relationship between frequency and flow rate. The one unknown cannula type shows frequency of approximately 0.4 Hz showing a decrease in pressure frequency over time because this subject received flow rates of 30→20→30→20 L/min.

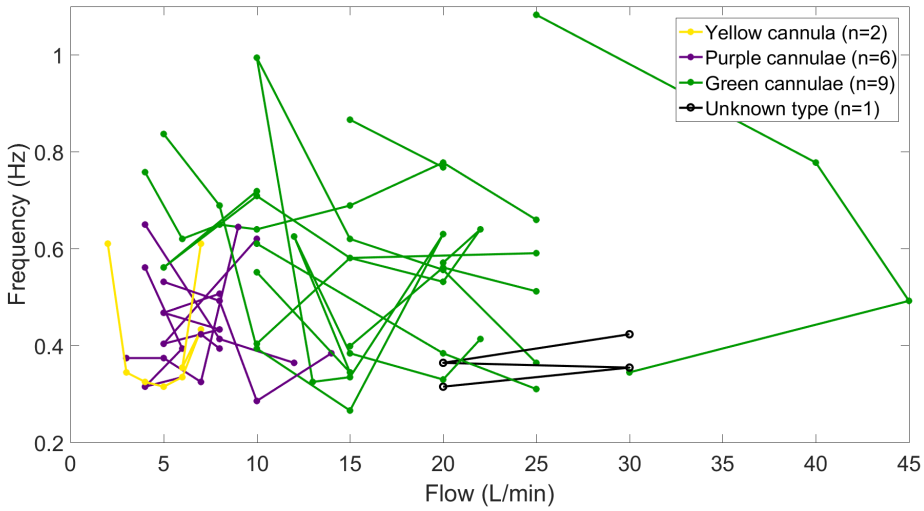


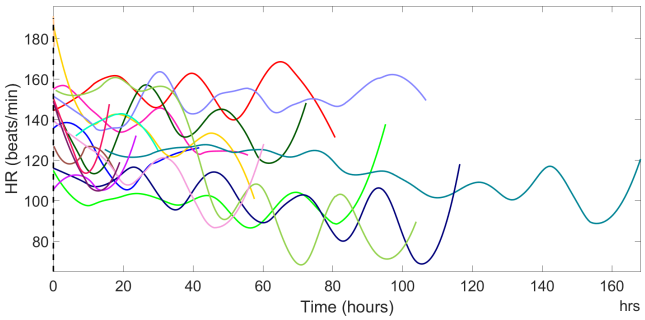
Figure 5.7: Median of the frequency (at the end of the nasal cannula) flow relation for all subjects.

5.2.4 Vital parameters

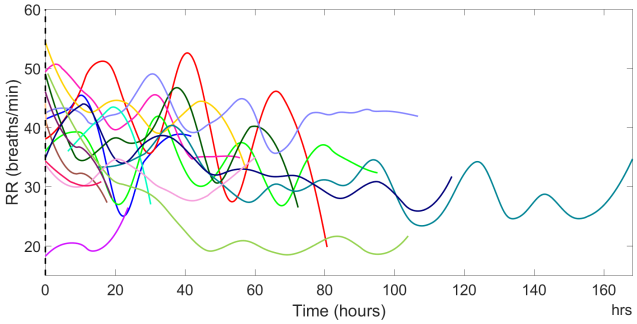
In figure 5.8 the heart and respiratory rate throughout the entire HFNC therapy are shown for each subject individually (if available).

Heart rate At the start of HFNC therapy (at time = 0) there is a wide range in heart rate, ranging between 100-190 beats/min. All subjects show a sinusoidal rhythm accounted for by a day/night rhythm. There is also a wide variety in HFNC therapy duration visible. Notable is that some heart rate decrease throughout the therapy, while others remain at the same level (with exception of the day/night rythm).

Respiratory rate The respiratory rate in figure 5.8b show some same observations. The variability in therapy duration and the day/night rhythm is also observable in the RR. Most RR start between 35 and 50 breaths/min, while some discernible decrease throughout therapy.



(a) Heart rate



(b) Respiratory rate

Figure 5.8: Heart and respiratory rate throughout the entire HFNC therapy for all subjects with available data.

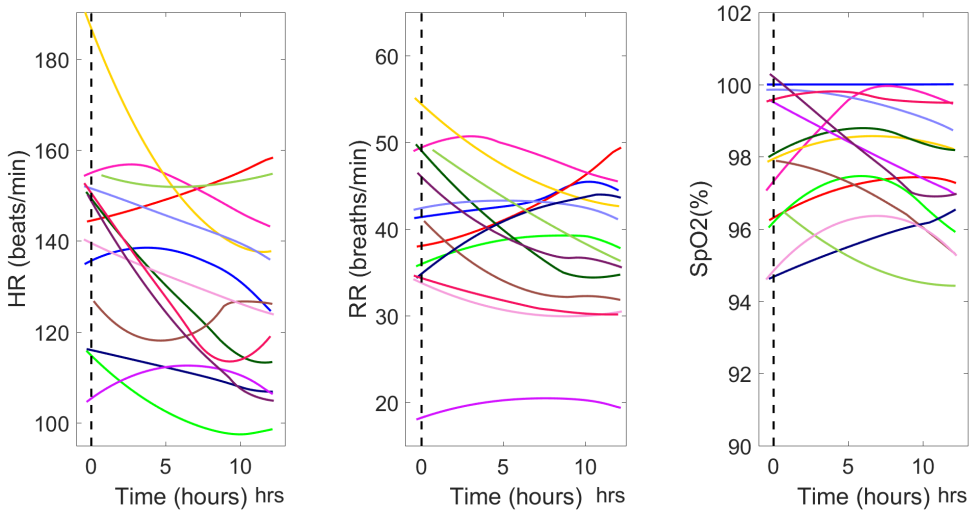
First 12 hours after start HFNC

We expect to see the most changes in clinical evaluation and vital parameters in the few hours after the start of HFNC therapy. Figure 5.9 shows the vital parameters per subject in a short period before until 12 hours after start HFNC therapy.

Heart rate Figure 5.9a shows the heart rate for the begin period. Notable are five subject with drastically decreasing heart rates after start, however other subjects show no clear changes in heart rate. Two subjects (002 and 010) appear to have an small increase in heart rate (+10 beats/min).

Respiratory rate Figure 5.9b shows the respiratory frequency for the begin period. In which halve of the patients show no changes in respiratory rate, and the other halve shows a decrease. No subjects show an increases in respiratory rate.

Saturation Figure 5.9c shows the saturation values in the begin period of HFNC therapy. Most subjects increase 1% during the first few hours, four subjects have decreasing saturation values and the remaining subjects show no change.



(a) Heart rate (b) Respiratory rate (c) Saturation

Figure 5.9: Vital parameters in the period before and few hours after the start of HFNC therapy for all subjects with available data.

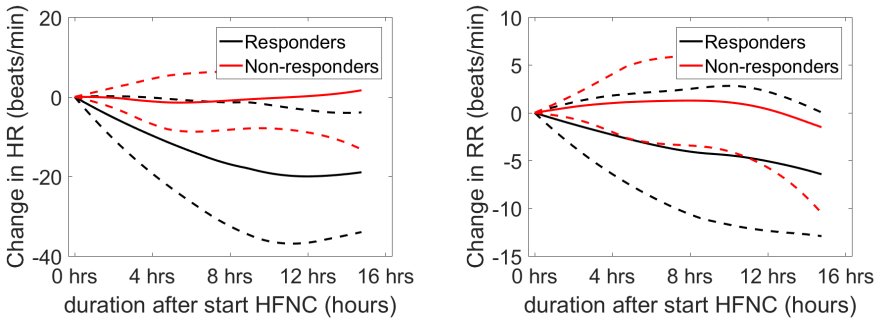
Responders vs non-responders

As just described, some subjects show a direct decrease of heart rate after the start the HFNC therapy, while others show a relatively small to no change in heart rate. When dividing the total subjects by a decreasing heart rate after start therapy versus no decrease in heart rate, we can compare these two groups. Patient characteristics of these two groups are described in table 5.3.

Table 5.3: Patient characteristics of the group subjects with a decrease in HR after start HFNC therapy (responders) and without change or increase in HR (non-responders).

	Responders (n=8) mean (SD)	Non-responders (n=10) mean (SD)
Male (%)	4 (50%)	6 (60%)
Age	1.6 (1.8)	3.2 (2.6)
Weight	12.0 (8.5)	18.5 (13.5)

The mean and standard deviation of both heart and respiratory rate in the first couple of hours for each group are shown in figure 5.10. The HR and RR are normalized from the start of HFNC therapy, meaning that the HR and RR at the start of therapy is set to zero and the change in HR or RR after this start is visualized. With in black the responders group and the red lines the non-responders. The groups are divided by effect in HR after start HFNC.



(a) Heart rate

(b) Respiratory rate

Figure 5.10: The mean and standard deviation of both heart and respiratory rate in the first couple of hours for each group. The means are visualized with a continuous line, while the dashed line represents the standard deviation. The responders group are in black and the non-responders in red.

In figure 5.10a the mean and standard deviation of the HR of both groups are visible and as expected we see a decrease of the mean HR in the responders group, while the mean HR of the non-responders remain around

constant. Figure 5.10b shows the mean and standard deviation of the RR of both groups. Again there is a decrease in RR visible in the responders group, however the non-responders show a small increase and start decreasing after 12 hours.
In table 5.4 the patient outcomes of both groups are shown.

Table 5.4: Patient outcomes of both groups responders versus non-responders. Because the patient characteristics show no normal distribution, the median and range are taken. With LOT = Length of therapy.

	Responders median (range)	Non-responders median (range)
Q_1/kg	1.7 ($\pm$0.5)	1 ($\pm$0.4)
time to Q_1	14.8 ($\pm$4.5)	67 ($\pm$33)
Additional O_2 req.	1 (13%)	5 (50%)
Intubations	0 (0%)	2 (20%)
LOT	50 (32)	73 (60)

5.2.5 Clinical evaluation

Video recording were taken every time there was a chance in flow rate. The clinical evaluation was not possible due to several reason which will be discussed in the discussion section. However individual ratings of the available video recordings are displayed for each subject in the appendix were only is looked whether there was an increase, decrease or no change in respiratory distress over time during the HFNC therapy.

CHAPTER 6

Discussion

The primary aim of this study was to investigate mechanisms of action of HFNC therapy, particular by studying the relation between applied flow rate and generated pressure. Subsequently the relation between these two and the clinical course was investigated. This study measures the device pressure generated at different flow rates in infants receiving HFNC therapy and describes the nasal cannula pressures delivered during the entire respiratory cycle. As with any observational analysis, it is always difficult to demonstrate a cause and effect relationship, but there are some important findings in our analysis that may have been related to the generated pressure.

Laboratory study

In the laboratory study we determined two different fits to calculate the pressure difference between the measured device pressure and the required cannula pressure: a 2nd order polynomial fit ($\Delta P = a_1 Q^2 + a_2 Q + a_3$) and a power law ($\Delta P = a Q^b$). Both have excellent coefficient of determination (R^2) values for all cannulae, all larger then 0.99. When choosing the 2nd order polynomial fit, a_3 theoretically should be zero to satisfy the condition that $\Delta P = 0$ when $Q = 0$. However in our first laboratory study we found a_3 values for all four cannulae of 0.07, 0.07, 0.01 and 0.12. Although the power law has minimally poorer R^2 values, the power law automatically satisfies that there is no pressure difference if the flow rate is zero and is therefore preferred and used to calculate the nasal cannula pressure from the device pressure in the clinical pilot study.

Clinical study

This study was limited to a single institution without a control group which would normally provide the researchers with reliable baseline data to compare the results. Control groups are an important part of any experiment,

because it is practically impossible to eliminate all of the confounding variables and bias. We used this pilot study to determine the possibility of assessing the airway pressure in a non-invasive way and determining the possibility of a future randomized control trial.

Device pressure The cannula pressure is calculated from the device pressure to assess the airway pressure. The relation between cannula pressure and the airway pressure, however, is not yet known. The HFNC device, nasal cannula and airways are connected to each other and in the case of no flow, the pressures are equal to each other. However when measuring an increased pressure inside the device, four situations could explain this increase:

- Two reasons can be easily verified:
  - A silent increase in flow rate without notation.
  - A closed mouth
- The remaining two situations are harder to verify:
  - The pressure in the airways is also increased
  - There is a large resistance somewhere along the device or at the nasal cannula (for example due to mucus blocking a prong).

Without monitoring the airway pressure the reason of the increased device pressure cannot be determined with certainty. A follow-up study comparing the device pressure with the airway pressure could possible provide some insight of the aspects responsible for the increased device pressure.

Frequency Patients in respiratory distress often show signs of trying to decrease the feeling of dyspnea. To increase the oxygen intake, two compensatory mechanisms are visible: increase in tidal volume and/or increase in respiratory rate. However not all subjects showed a decrease in respiratory rate during the HFNC therapy. The measurements of amplitude size in the pressure signal could provide some more information about tidal volume as a compensatory mechanisms.

Saturation Prior to the start of the HFNC therapy not all subjects had insufficient saturation levels. According to the local protocol FiO_2 is started at 60% and decreased in response to the saturation level. It can then be expected that the SpO_2 always increases in the few hours after start (or at least until FiO_2 is reduced). However some subject have shown a decrease in SpO_2 after the start of HFNC therapy. A possible explanations could be the use of other respiratory support prior to the start of HFNC, such as low flow which provides 100% oxygen. Another possibility is an insufficient effect of the by HFNC generated pressure.

Clinical course To determine the clinical course of children with HFNC therapy, right before and half a hour after a change in flow rate a video recording was taken of the patient to determine degree of respiratory distress using the modified Tal score afterwards. However we could not collect all videos for all children due to several reasons: in some cases video recordings were forgotten by the nurses, sometimes a picture was taken instead of a video and some videos were not usable because it was to dark. Determining the entire clinical course during HFNC therapy was therefore difficult to quantify. For this study we only determined whether there was an increase, decrease or no visible change in respiratory distress over time during the HFNC therapy. Another parallel study will later on investigate the possibility of using the modified Tal scoring system to monitor the clinical course using our video recordings.

Nasal cannula type Subject 15 changed nasal cannula type during the HFNC therapy, the junior green cannula was exchanged for an adult orange cannula. As visible in the appendix, this exchange results in a decrease in pressure. This change is made simultaneously with an increase in flow rate, suggesting the therapy is inadequate until that moment. However by exchanging the nasal cannula for a larger size cannula, the opposite effect is achieved namely a decrease in cannula pressure.

Strengths and limitations

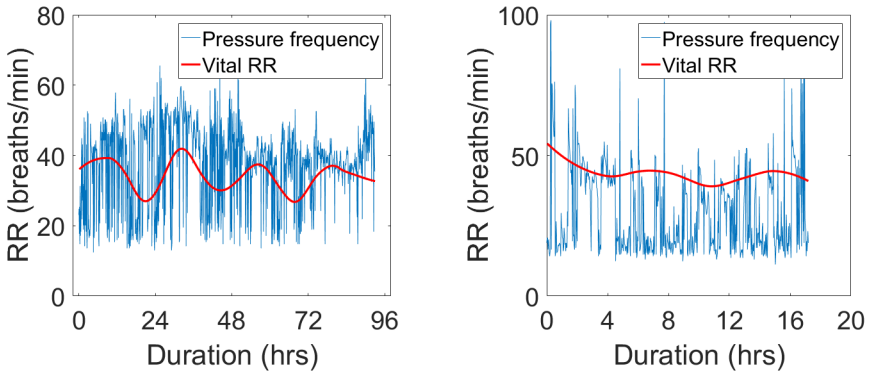
Despite the fact we started including at the end of the winter season a surprisingly large number of patients were included. During the HFNC therapy in these patients, the pressure could be measured on a non-invasive method without any additional discomfort for the patients. However the late inclusion start did result in a wide variety of work diagnoses besides bronchiolitis. This makes dividing the subjects in groups to compare data hard and no normal distribution could be found. In addition it means that to little data is collected to show trends and that future research is needed to confirm the relationship we found between flow rate and generated pressure.

In the ideal case there is a possibility to adjust the flow rate several time during the therapy, such that during different moments in therapy the same flow rates and the generated pressure could be evaluated for a short period of time. This could provide some insights in the repeatability and possible changes occurring the clinical course and the effect on the measured pressure signal.

In addition the diameter of the nostrils were not measured during this study, with the result that we could not determine the air leak available in each subject. When looking at the relationship between flow rate and generated pressure, a wide variability is visible in each nasal cannula, a

possible explanation could be the variability in air leak around the nasal prongs.

Determining pressure frequency In determining the main frequency of the pressure signal, several methods were tried such as periodograms (which becomes more eratic as the number of data samples grows) and Welch method for noise reduction. However the best results were given by using a selection of 5 minute time windows, multiplying these windows by a hamming window and deciding the largest frequency present in that window. Because logically the sinusoidal shape present in the pressure data represent the breathing cycle, we decided to compare our frequency analysis with the manually noted respiratory rate. Figure 6.1 shows two examples of this comparison. Most subjects show some similar results as in figure 6.1a, however in two subjects the pressure frequency is consistently lower than the manually noted RR as shown in figure 6.1b. Surprisingly the calculated pressure frequency remains consistently around 20 cmH_2O. Wrong selection of the highest frequency often show low frequencies around 0 Hz, however this provides no good explanations in this subject and no other explanation could be found.



(a) Subject 3 (b) Subject 6

Figure 6.1: Comparison of our calculated pressure frequency with the manually noted respiratory rate.

Future research

In spite of these limitations, it is evident that a positive cannula pressure is generated in infants with respiratory distress using HFNC therapy which may have relevant clinical implications. To assess the extent in which these clinical implications are associated with HFNC, future research is required.

An addition to this research could be the comparison of the cannula pressure with the airway pressure, to assess and provide the correct flow rate to

generate the most effective pressure and thereby the fastest recovery. although this makes the study more invasive than the current study. Most infants with bronchiolitis already require a feeding tube and a tube in combination with a pressure sensor could provide minimal additional burden for the patient. The addition of an extra tube for measuring the airway pressure also changes the airleak around the nasal prongs and this effect should then be taken into account. After that, a randomized controlled trial comparing flow controlled and pressure controlled therapy can be performed to show evidence which therapy provides the better care.

CHAPTER 7

Conclusion

During this study we hypothesized that the generated pressure is the driving force reducing respiratory distress in children with respiratory distress and that the measurement of pressure in the HFNC device can be used to monitor the pressure in the airways, providing a suitable method to regulate HFNC therapy. Several conclusion can be made regarding this hypothesis.

Laboratory study During the laboratory study we found the relationship between the pressure measured in the device and the pressure at the end of the nasal cannula, this relationship is a function of the flow rate and differs between sizes of nasal cannulae. Using this relationship we were able to calculate the pressure at the end of the nasal cannula instead of the device pressure during a clinical pilot study.

Clinical pilot study During the clinical pilot study we hypothesize that the provision of high flow generates an increase in airway pressure. We indeed found a positive linear relationship between the applied flow rate and the generated cannula pressure. This relationship is however cannula dependent, meaning that when providing a certain flow rate the generated pressure is dependent of the chosen nasal cannula size. Were a smaller nasal cannulae results in an increased measured cannula pressure. There is also a small variation visible between individuals (possibly due to variations in airway geometry and prong size, wherefore determination of the air leak is required to provide a possible explanation).

When providing higher flow rates and generating airway pressure, it could be expected that the breathing pattern changes. When investigating the effect of flow rate on the breathing frequency, no clear relationship can be found.

We also hypothesize that the improvement in clinical course during the HFNC therapy can be related to the generated airway pressure instead of the set flow rate. Indeed some patients show an instant decrease in HR

and RR after start of HFNC therapy and continue decreasing throughout the therapy, while others show no change in vital parameters. When dividing the group in responders (with a decrease in HR after start HFNC) versus the non-responders several outcomes stand out. There is a great increase in the duration before the first decrease in flow rate is made in the non-responders group and the responders group starts with a significantly higher first flow rate. The recorded videos for the evaluation of the clinical course were unfortunately insufficient for this study, but will be evaluated in a later study.

These measurements of the generated pressure provide the evidence that a positive cannula pressure is generated in infants using HFNC therapy. However to investigate whether flow or pressure controlled HFNC accelerate the clinical course and to definitively establish the safety and efficiency of HFNC further research is required.

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METC: Letter of approval

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Ons kenmerk
RvB/jvdp/2011-16/73.0

Betreft: Goedkeuring onderzoeksproject niet-WMO-plichtige studie, K16-08, Drukmeting bij HFNC therapie

Geachte heer Thio,

De Raad van Bestuur gaat akkoord met het starten van de studie Drukmeting tijdens High Flow Nasal Cannula (HFNC) therapie bij kinderen met een ernstige luchtweginfectie, bekend onder nummer K16-08.
De lokale adviescommissie uitvoerbaarheid heeft vastgesteld, dat een Medisch Ethische Toetsingscommissie uw projectvoorstel niet-WMO-plichtig heeft verklaard en dat ook verder aan gestelde voorwaarden is voldaan.

Wij wensen u veel succes met de uitvoering van dit onderzoek en worden te zijner tijd graag geïnformeerd over de uitkomsten.

Met vriendelijke groet,

Bas Leerink,
Voorzitter Raad van Bestuur

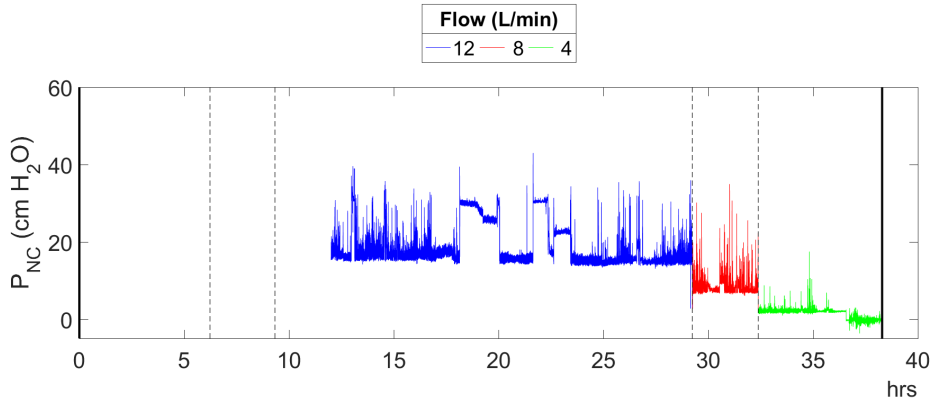
I.a.a.:
RVE-management, R.J. Zijlstra
De heer P. Dalhuisen, ziekenhuisjurist
Mevrouw K. Dam, bestuurssecretariaat
METC
ITWO

Data collection of all subjects

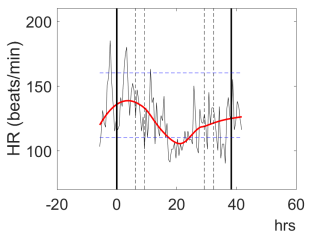
Table B.1: Normal values for heart and respiratory rate for different ages taken from the Advanced Paediatric Life support book. [50]

Age	RR	HR
<1	30-40	110-160
1-2	25-35	100-150
2-5	25-30	95-140
5-12	20-25	80-120
>12	15-20	60-100

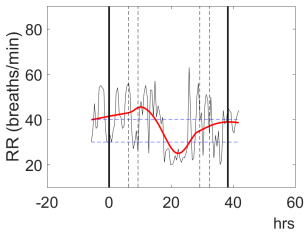
Data collection of subject 1



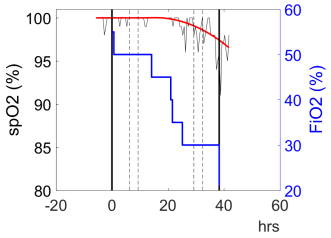
(a) Recorded and pre-processed pressure data



(b) Heart rate



(c) Respiratory rate



(d) Saturation

Figure B.1: Recorded & pre-processed pressure data and vital parameters of subject 1 (8 months old infant with a weight of 7 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

Data description - *Interaction recorded pressure and vital parameters*

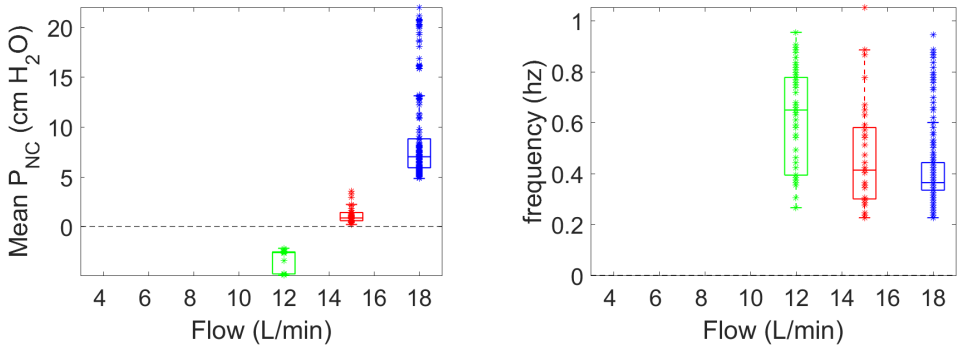
The pressure data is collected during almost the entire HFNC therapy, however unfortunately the first twelve hours are absent. Table B.2 shows the changes in vital parameters and the work of breathing clinical evaluation. Because we expect to see the most effect right after the start of Optiflow, we first specifically looked at the first 3 hours after start. During the first 3 hours we don't see much changes in all the vital parameter, even a small increase during the first three hours. The FiO2 is step-by-step decreased to 30% and the saturation reamins costant until 30% FiO_2 is reached, however

SPO_2 remains above 95%.. The first change in flow is after 6 hours. In which the heart rate decreases where the respiratory rate increases. The biggest change appears when the flow is changes from 15 to 12 L/min. Both heart and respiratory rate decrease significantly.

Table B.2: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment					
		First 3 hours	1	2	3	4	5
Flow		18	18	15	12	8	4
HR	123	±	±	↓	↓	±	↑
RR	32	±	±	±	↓	±	↑
SpO2	100	±	±	±	±	↓	↓
Dysnea score			-	-	-	-	-

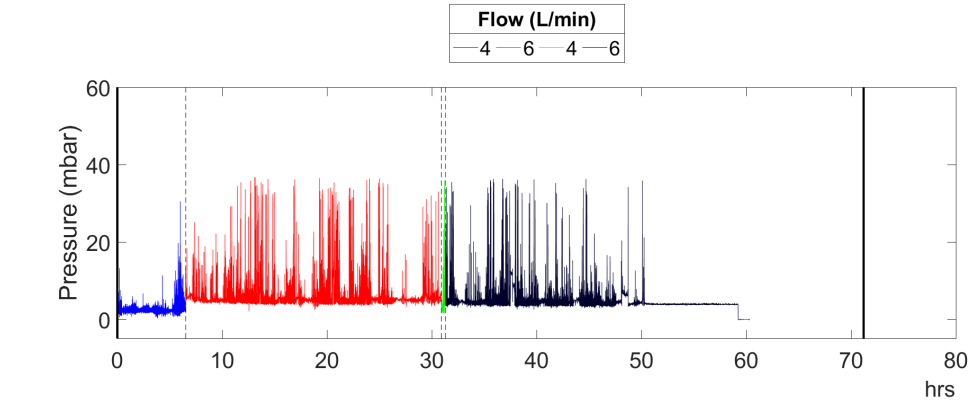
Data analysis - *Analysis parameters as a function of flow rate*



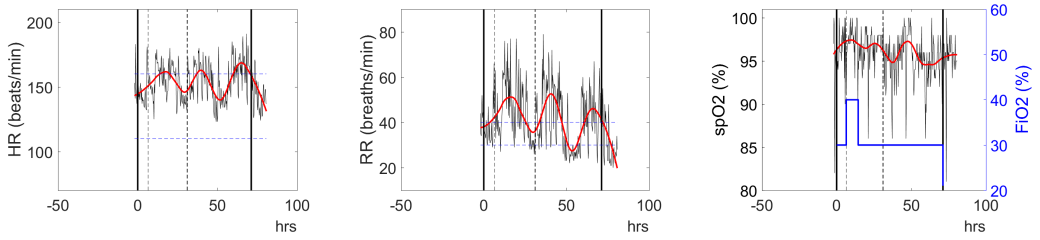
(a) Mean (b) Frequency

Figure B.2: Data Analysis of parameters as a function of flow rate.

Data collection of subject 2



(a) Recorded and pre-processed pressure data



(b) Heart rate (c) Respiratory rate (d) Saturation

Figure B.3: Recorded & pre-processed pressure data and vital parameters of subject 2 (2 months old with a weight of 5.2 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

Data description - *Interaction recorded pressure and vital parameters*

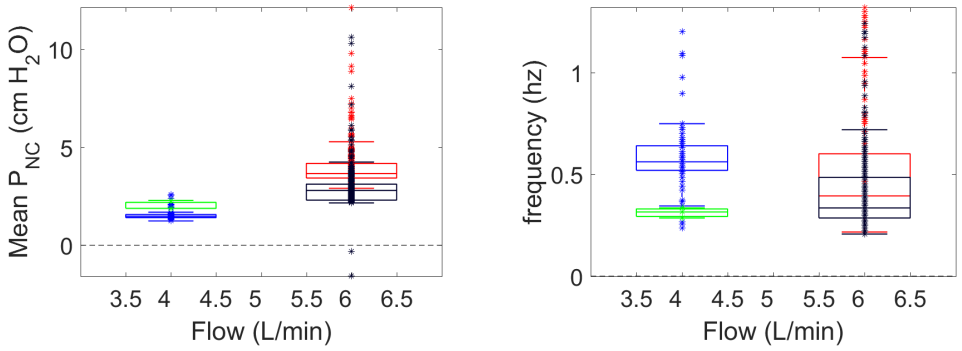
The pressure data is collected during almost the entire HFNC therapy with exception of the last hours. Table B.3 shows the changes in vital parameters and the work of breathing clinical evaluation. Because we expect to see the most effect right after the start of Optiflow, we first specifically looked at the first 3 hours after start. During the first 3 hours we see an increase in HR, RR and SpO_2, possibly coinciding with the day/night rhythm. Both the flow rate and FiO_2 are increased after 8 hours, however in the vital parameters no clear change is thereby visible. Approximately 32 hours after the start

of HFNC they tried to reduce the flow rate, however this is of short duration before the flow rate is again increased. The trendline of the vital parameters show no change, however this could also be due to the short duration of the decreased flow rate. When looking at the black manuaaly noted HR and RR, an increase is visible in both parameters. The therapy is discontinued after 70 hours and no additional O_2 was required.

Table B.3: Vital parameters and work of breathing clinical evaluation per flow rate window. With: $\pm$ = unchanged, $\downarrow$ = decreased, $\uparrow$ = increased, * = not usable, - = no available data.

	Before start	Flow moment				
		First 3 hours	1	2	3	4
Flow		4	4	6	4	6
HR	160	$\uparrow$	$\uparrow$	$\pm$	$\pm$	$\pm$
RR	37	$\uparrow$	$\uparrow$	$\downarrow$	$\pm$	$\downarrow$
SpO2	100	$\uparrow$	$\uparrow$	$\pm$	$\downarrow$	$\pm$
Dysnea score			-	-	-	-

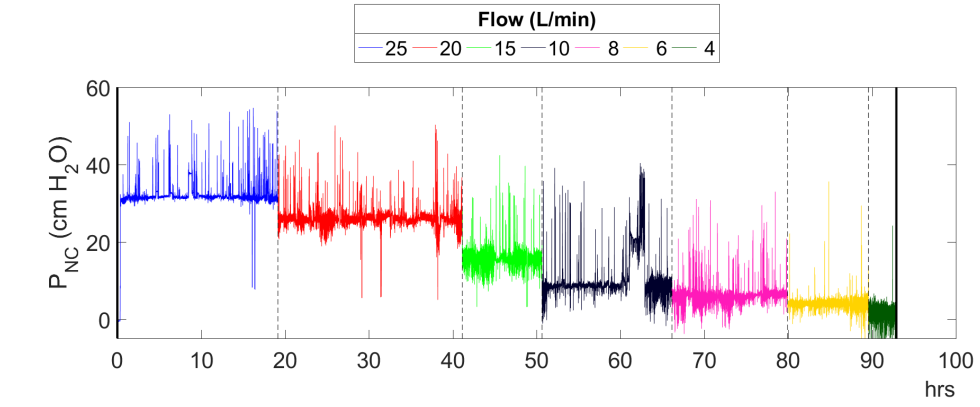
Data analysis - *Analysis parameters as a function of flow rate*



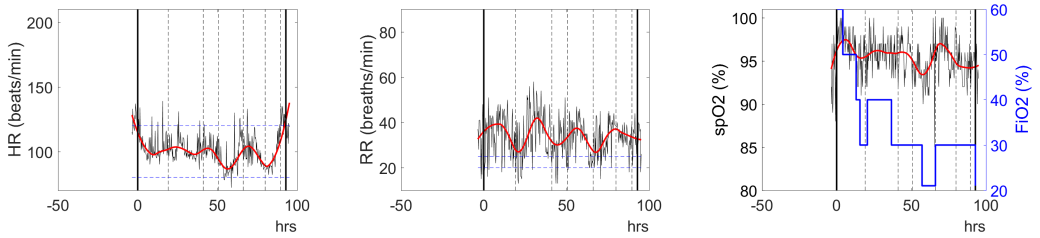
(a) Mean (b) Frequency

Figure B.4: Data Analysis of parameters as a function of flow rate.

Data collection of subject 3



(a) Recorded and pre-processed pressure data



(b) Heart rate (c) Respiratory rate (d) Saturation

Figure B.5: Recorded & pre-processed pressure data and vital parameters of subject 3 (6 years old with a weight of 32.5 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

Data description - *Interaction recorded pressure and vital parameters*

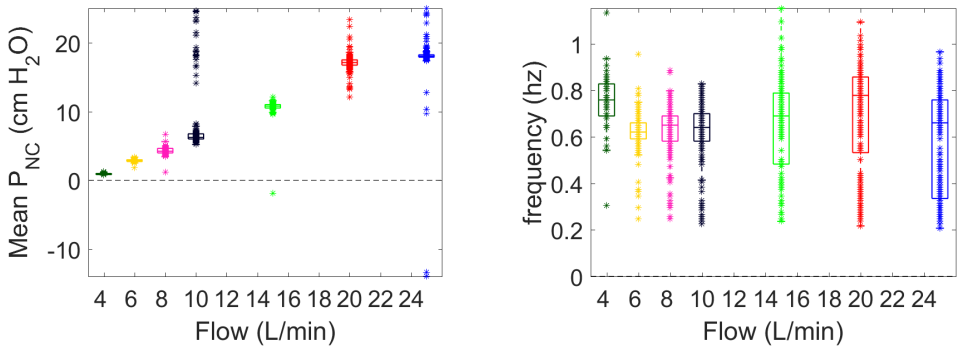
Before the start of HFNC this subject received low flow (100%, 2.5 L/min). The pressure data is collected during the entire HFNC therapy. Table B.4 shows the changes in vital parameters and the work of breathing clinical evaluation. Because we expect to see the most effect right after the start of Optiflow, we first specifically looked at the first 3 hours after start. During the first 3 hours we see an decrease in HR, RR show no clear change and the SpO_2 vastly increases. The first decrease in flow rate is after 18 hours after which the HR remains constant, however because the day/night rhythm

should increase the HR, this can also be construed as a decrease. The FiO_2 was decreased quickly after start therapy in several steps of 10% per time. All show no clear decrease in SpO_2. However when the SpO_2 decreased to 95% the FiO_2 is temporarily increased back to 40%. The same happens again after 60 hours in which the FiO_2 is reduced to 20% but after a couple of hours is increased to 30% again. The flow rate is decreased in evenly distributed periods and rates and after 96 hours the therapy was discontinued. However this subject received additional low flow oxygen (100%, 2.5 L/min) after the stop of HFNC.

Table B.4: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment							
		First 3 hours	1	2	3	4	5	6	7
Flow		25	25	20	15	10	8	6	4
HR	115	↓	↓	±	↓	±	↓	↑	↑
RR	17	↑	↓	↑	↓	↓	↑	↓	↓
SpO2	99	↑	↑	±	±	↓↑	±	±	↑
Dysnea score			±	↓	±	±	*	*	±

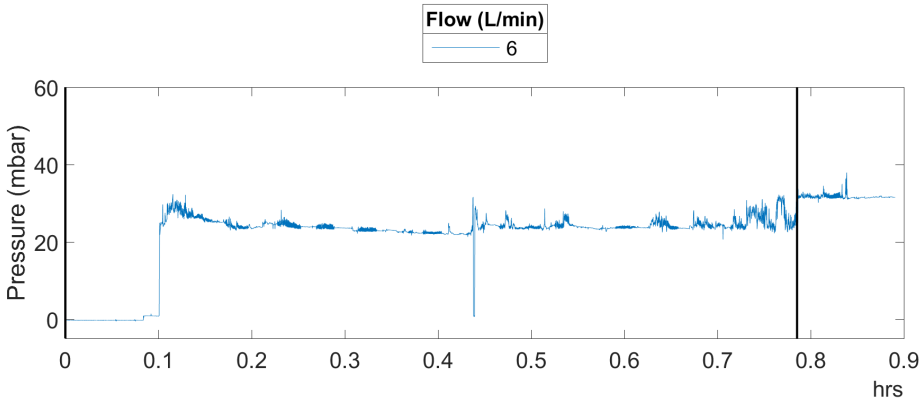
Data analysis - *Analysis parameters as a function of flow rate*



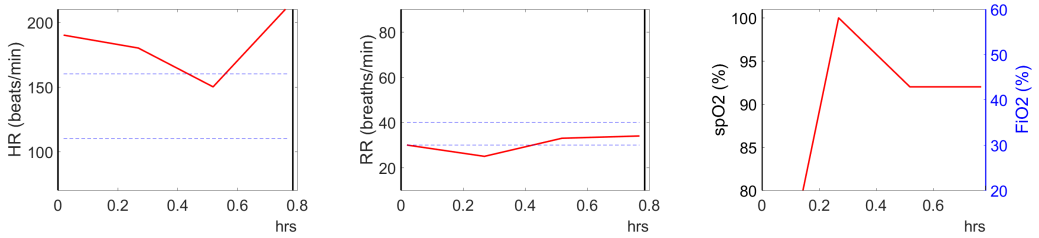
(a) Mean (b) Frequency

Figure B.6: Data Analysis of parameters as a function of flow rate.

Data collection of subject 4



(a) Recorded and pre-processed pressure data



(b) Heart rate (c) Respiratory rate (d) Saturation

Figure B.7: Recorded & pre-processed pressure data and vital parameters of subject 4 (1 month old infant with a unknown weight). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

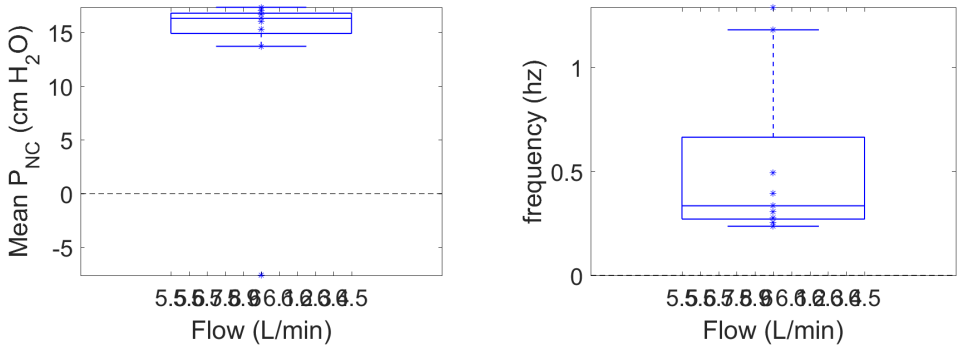
Data description - *Interaction recorded pressure and vital parameters*

The pressure data is collected during the entire HFNC therapy which only lasted 45 minutes before intubation was required. Table B.5 shows the changes in vital parameters and the work of breathing clinical evaluation. Initially the HR decreases slowly with the RR remaining constant. However the SpO_2 increases significant with an FiO_2 of 100%. However as visible in the pressure data, apneas (cessations in breathing) were continuously present, which eventually required intubation.

Table B.5: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment
		First 3 hours
Flow		6
HR	190	↓
RR	30	±
SpO2	60	↑
Dysnea score		-

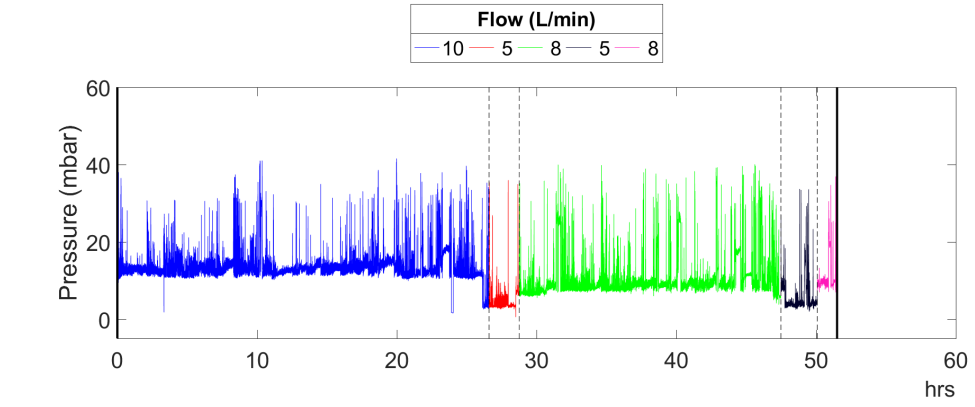
Data analysis - *Analysis parameters as a function of flow rate*



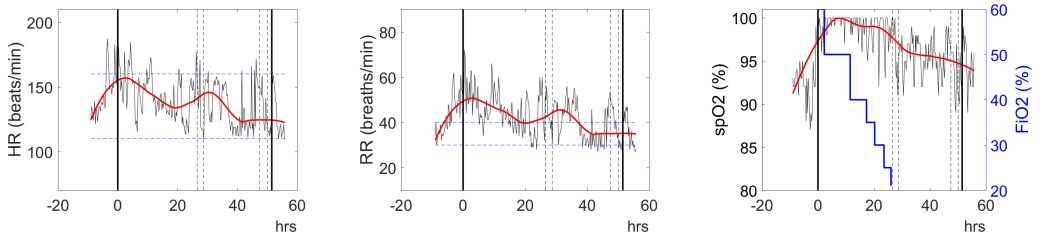
(a) Mean (b) Frequency

Figure B.8: Data Analysis of parameters as a function of flow rate.

Data collection of subject 5



(a) Recorded and pre-processed pressure data



(b) Heart rate (c) Respiratory rate (d) Saturation

Figure B.9: Recorded & pre-processed pressure data and vital parameters of subject 5 (4 months old with a weight of 6.5 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

Data description - *Interaction recorded pressure and vital parameters*

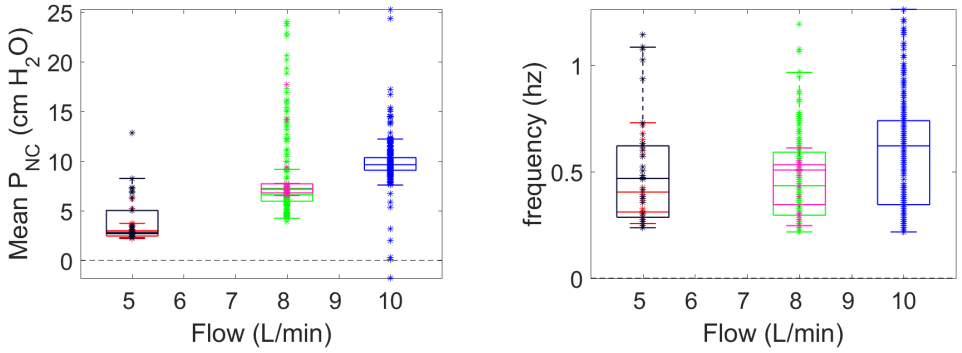
The pressure data is collected during the entire HFNC therapy. Table B.6 shows the changes in vital parameters and the work of breathing clinical evaluation. Because we expect to see the most effect right after the start of Optiflow, we first specifically looked at the first 3 hours after start. During the first flow rate of 10 L/min we see a slow decrease in HR and RR. Simultaniously the SpO_2 increases while the FiO_2 can be quickly reduced and before the first flow rate reduction, the FiO_2 is decreased to 21%. After 27 hours the first flow rate reduction from 10 to 5 L/min is taken place. In

that period the HR and RR increases and the flow rate is again increased to 8 L/min for 18 hours before attempting another decrease to 5 L/min. The second time the HR and RR remain constant. However for a short period of 2 hours the flow rate is finally increased to 8 L/min again. After the stop of HFNC therapy, this subject received additional oxygen (100%, 1 L/min) through a nasal cannula.

Table B.6: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment					
		First 3 hours	1	2	3	4	5
Flow		10	10	5	8	5	8
HR	180	↑	↓	↑	↓	±	±
RR	47	±	↓	↑	↓	±	±
SpO2	96	↑	↑	↓	↓	↓	↓
Dysnea score			↓	±	±	±	↓

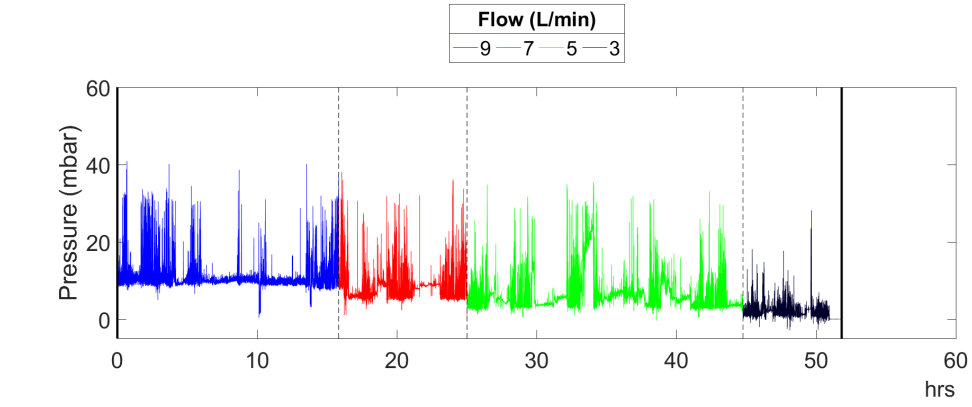
Data analysis - *Analysis parameters as a function of flow rate*



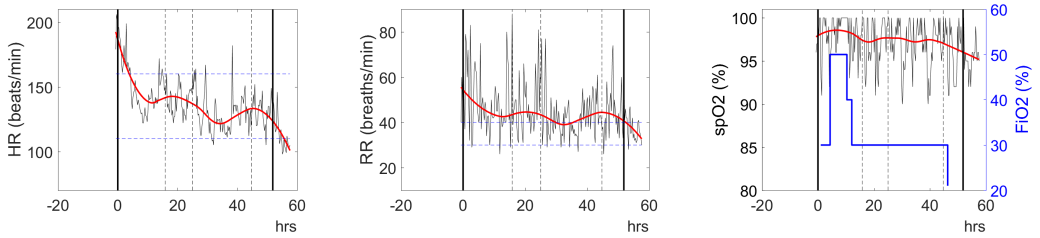
(a) Mean (b) Frequency

Figure B.10: Data Analysis of parameters as a function of flow rate.

Data collection of subject 6



(a) Recorded and pre-processed pressure data



(b) Heart rate (c) Respiratory rate (d) Saturation

Figure B.11: Recorded & pre-processed pressure data and vital parameters of subject 6 (6 month old with a weight of 5 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

Data description - *Interaction recorded pressure and vital parameters*

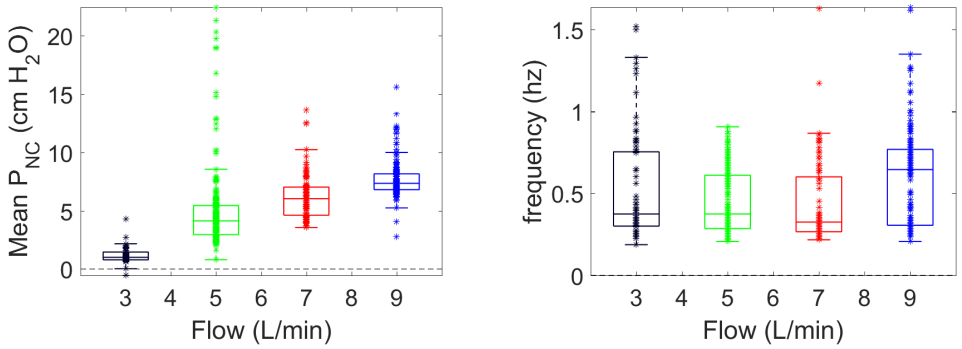
The pressure data is collected during the entire HFNC therapy. Table B.7 shows the changes in vital parameters and the work of breathing clinical evaluation. Because we expect to see the most effect right after the start of Optiflow, we first specifically looked at the first 3 hours after start. During the first 3 hours we see a clear decrease in both HR and RR. The saturation remains constant while the FiO_2 is increased from 30% to 50%. The first flow rate reduction occurs after 16 hours after which the HR and RR remain constant and the flow rate is again decreased to 5 L/min. During the entire

therapy the HR and RR decreases, especially the HR. The SpO_2 values remain constant and during the entire therapy above 95%.

Table B.7: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment				
		First 3 hours	1	2	3	4
Flow		9	9	7	5	3
HR	196	↓	↓	↓	↓	↓
RR	75	↓	↓	±	±	↓
SpO2	100	↑	±	±	±	↓
Dysnea score			↓	±	↓	±

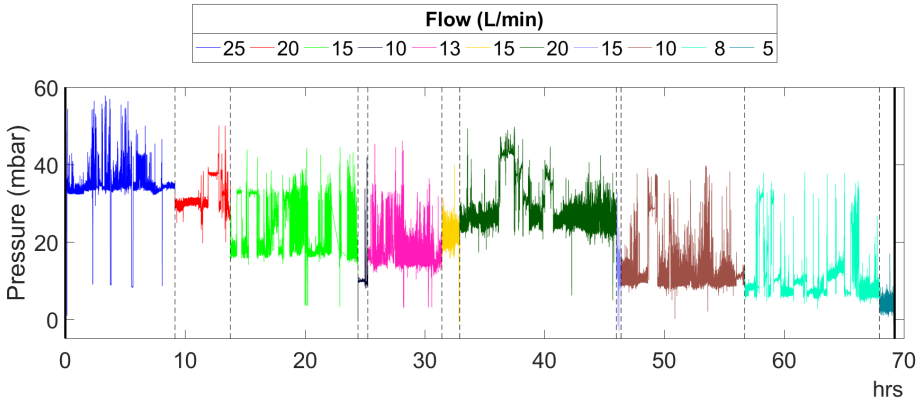
Data analysis - *Analysis parameters as a function of flow rate*



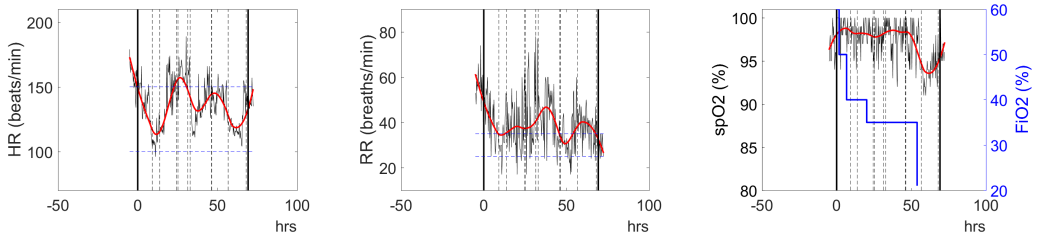
(a) Mean (b) Frequency

Figure B.12: Data Analysis of parameters as a function of flow rate.

Data collection of subject 7



(a) Recorded and pre-processed pressure data



(b) Heart rate (c) Respiratory rate (d) Saturation

Figure B.13: Recorded & pre-processed pressure data and vital parameters of subject 7 (1 years old with a weight of 12.5 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

Data description - *Interaction recorded pressure and vital parameters*

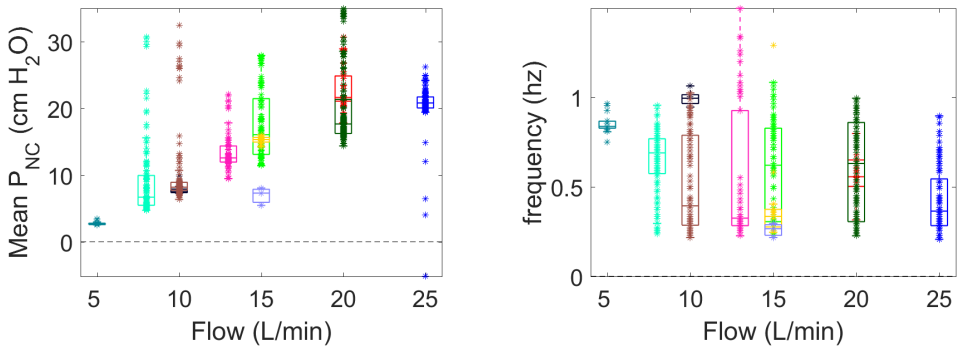
The pressure data is collected during the entire HFNC therapy. Table B.8 shows the changes in vital parameters and the work of breathing clinical evaluation. Because we expect to see the most effect right after the start of Optiflow, we first specifically looked at the first 3 hours after start. During the first 3 hours we see a significant decrease in HR both RR while SpO_2 remains constant and the $FiO2$ could be quickly reduced. The first flow rate decrease occurs after 10 hours in which the HR and RR remain constant and after 5 hours the flow rate is again decreased. This continues a couple

of times until after 25 hours after the start, when the flow rate is increased several times after the HR was increased. During the increasing flow rates, the HR decreases again while the RR increases. After 46 hours the flow rate is again reduced in several steps, with both the HR and RR decreasing. During the beginning of the therapy the FiO_2 is decreased to 35% and the saturation remains >97%. Only in the last couple of hours of HFNC the FiO_2 is reduced to 21% when the saturation decreases to 95%.

Table B.8: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment											
		First 3 hours	1	2	3	4	5	6	7	8	9	10	11
Flow		25	25	20	15	10	13	15	20	15	10	8	5
HR	170	↓	↓	↓	↑	↑	↓	↓	↓	±	↓	±	
RR	36	↓	↓	↓	±	±	↑	↑	↓	↓	±	↓	
SpO2	99	↑	↑	↓	±	±	↑	±	±	±	↓	↑	↑
Dysnea score			↓	±	±	±	↑	↓	±	↓	-	±	-

Data analysis - *Analysis parameters as a function of flow rate*

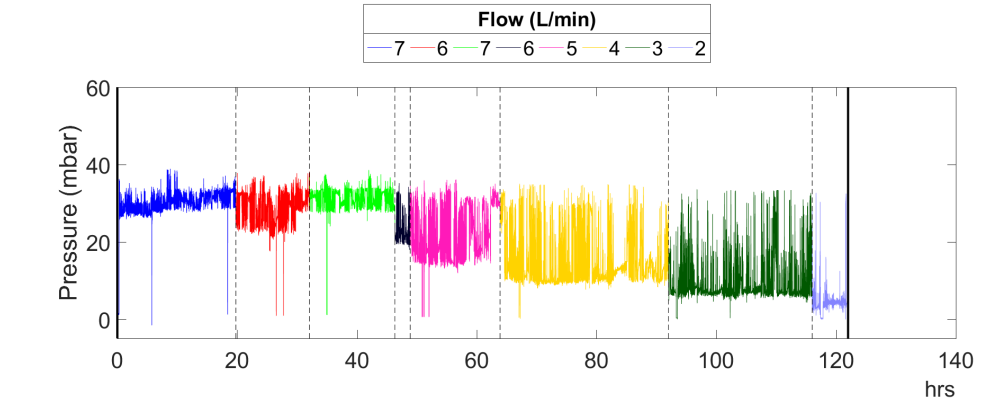


(a) Mean (b) Frequency

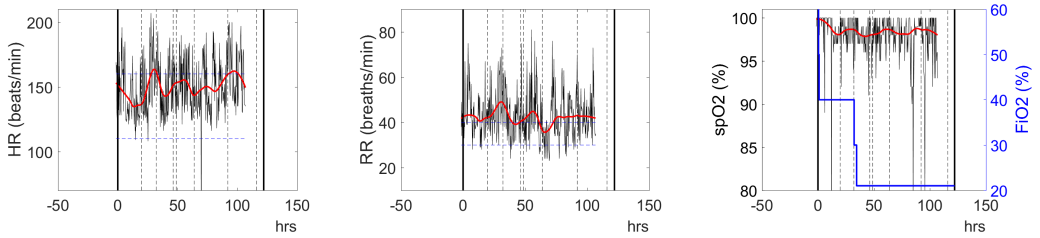
[

]Data Analysis of parameters as a function of flow rate.

Data collection of subject 8



(a) Recorded and pre-processed pressure data



(b) Heart rate (c) Respiratory rate (d) Saturation

Figure B.15: Recorded & pre-processed pressure data and vital parameters of subject 8 (3 months old with a weight of 3.9 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

Data description - *Interaction recorded pressure and vital parameters*

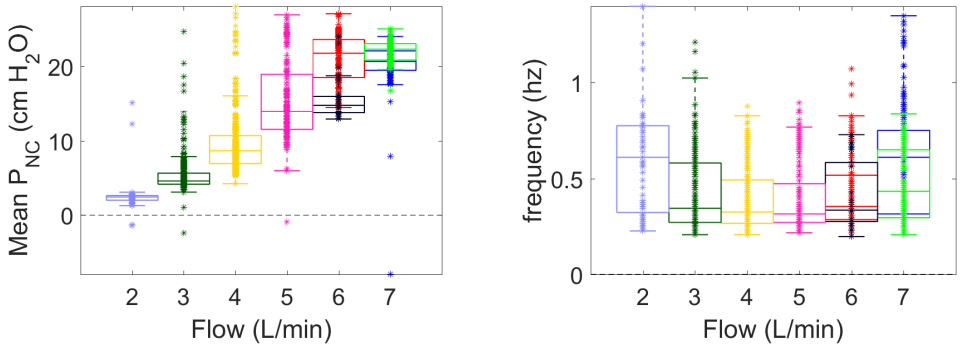
The pressure data is collected during the entire HFNC therapy. Table B.9 shows the changes in vital parameters and the work of breathing clinical evaluation. Because we expect to see the most effect right after the start of Optiflow, we first specifically looked at the first 3 hours after start. During the first 3 hours we see a decrease in heart rate and a small decrease in respiratory rate. The FiO2 is quickly decreased to 40% and the saturation decreases minimaly. The first change in flow is after 20 hours. In which especially the heart rate is reduced, however after this first change the heart

rate remains the same. Th respiratory rate remains the same in the beginning of the therapy, but slowely decreses. The saturation remains high and the FiO_2 can be quickly decreased to 21%.

Table B.9: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment							
		First 3 hours	1	2	3	4	5	6	7
Flow		7	7	6	7	6	5	3	2
HR	131	↓	↓	↑	↑	±	↓	↓	-
RR	38	±	±	↑	↓	±	↓	±	-
SpO2	100	±	↓	±	↓	↑	↑	±	-
Dysnea score			±	-	±	↓	↓	±	-

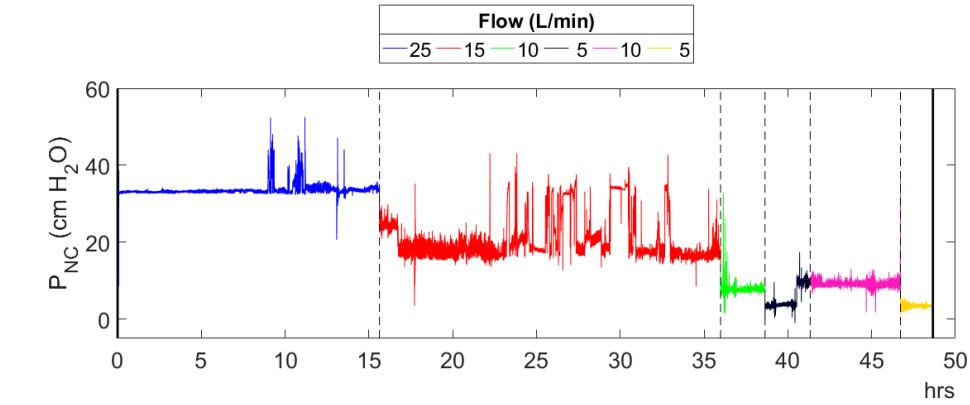
Data analysis - *Analysis parameters as a function of flow rate*



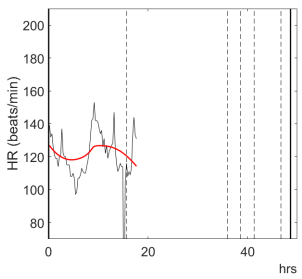
(a) Mean (b) Frequency

Figure B.16: Data Analysis of parameters as a function of flow rate.

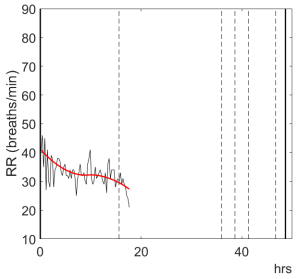
Data collection of subject 9



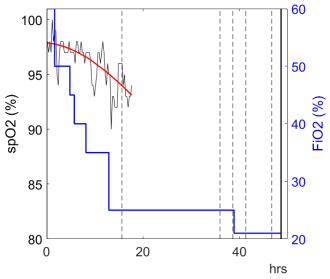
(a) Recorded and pre-processed pressure data



(b) Heart rate



(c) Respiratory rate



(d) Saturation

Figure B.17: Recorded & pre-processed pressure data and vital parameters of subject 9 (3 years of age with a weight of 15 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

Data description - *Interaction recorded pressure and vital parameters*

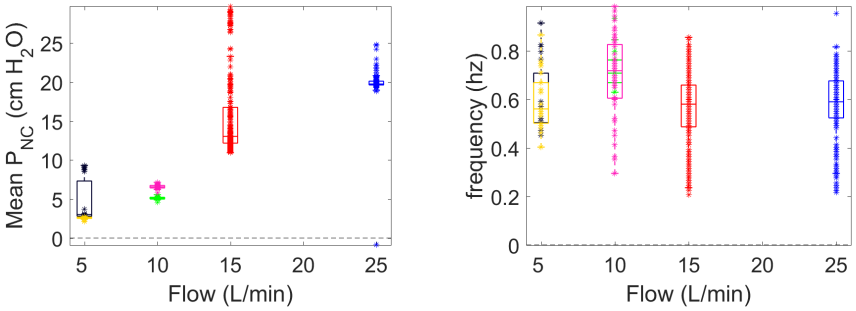
The pressure data is collected during the entire HFNC therapy. Table B.10 shows the changes in vital parameters and the work of breathing clinical evaluation. Because we expect to see the most effect right after the start of Optiflow, we first specifically looked at the first 3 hours after start. During the first 3 hours we see a clear decrease in both heart rate and respiratory rate and the saturation remains approximately the same with an $FiO2$ of

60/50%. The first change in flow is after 15 hours and 33 minutes. In which especially the respiratory rate is greatly reduced. Unfortunately the rest of the vital parameters aren't available.

Table B.10: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment						
		First 3 hours	1	2	3	4	5	6
Flow		20	20	15	10	5	10	5
HR	139	↓	↓	-	-	-	-	-
RR	41	↓	↓	-	-	-	-	-
SpO2	98	↓	±	-	-	-	-	-
Work of breathing			*	±	↓	±	±	±

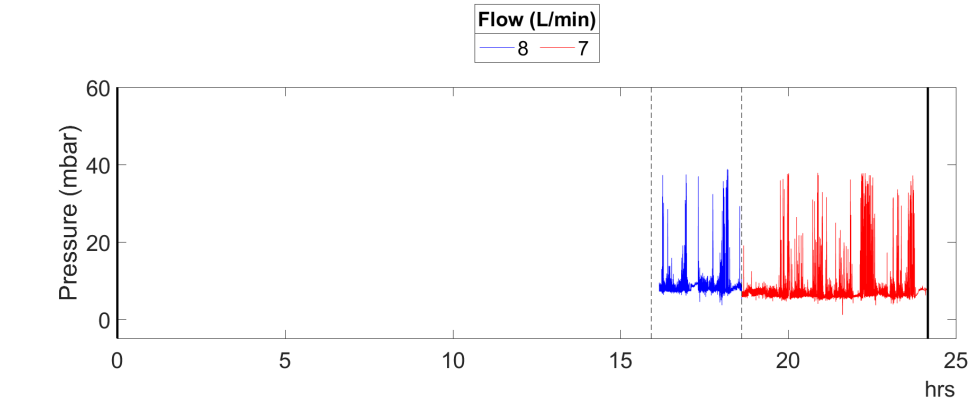
Data analysis - *Analysis parameters as a function of flow rate*



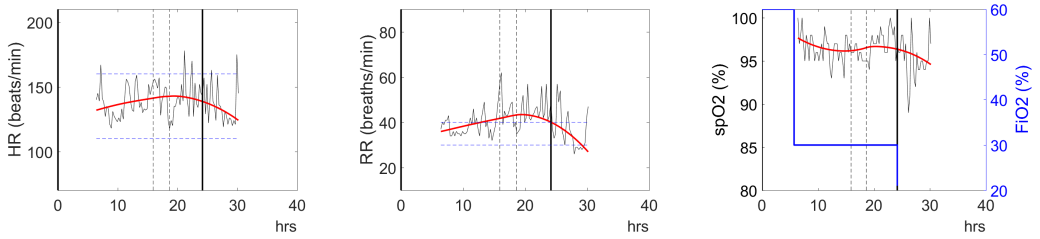
(a) Mean pressure (b) Frequency

Figure B.18: Data Analysis of parameters as a function of flow rate.

Data collection of subject 10



(a) Recorded and pre-processed pressure data



(b) Heart rate (c) Respiratory rate (d) Saturation

Figure B.19: Recorded & pre-processed pressure data and vital parameters of subject 10 (6 months old male with a weight of 9 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

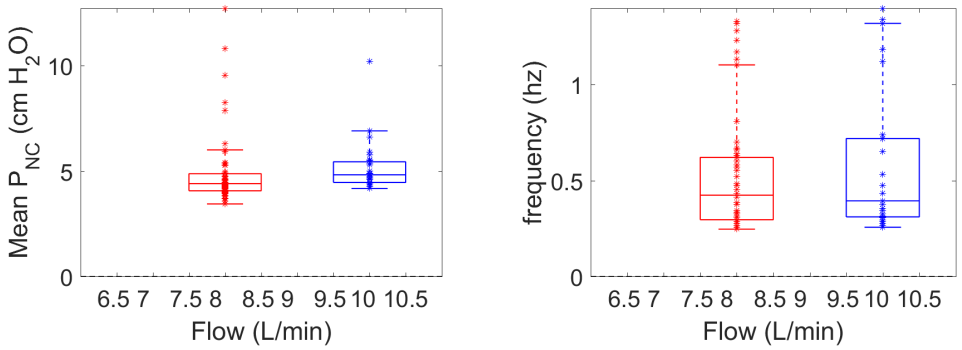
Data description - *Interaction recorded pressure and vital parameters*

The pressure data is collected during the last hours of HFNC therapy. Table B.11 shows the changes in vital parameters and the work of breathing clinical evaluation. We expect to see the most effect right after the start of Optiflow, unfortuanetely these data is missing. During the period we did acquire data, the HR, RR and SpO_2 remain relative constant.

Table B.11: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment			
		First 3 hours	1	2	3
Flow		10	10	8	7
HR	-		-	±	±
RR	-		-	±	±
SpO2	-	-	-	±	±
Dysnea score		-	±	±	↓

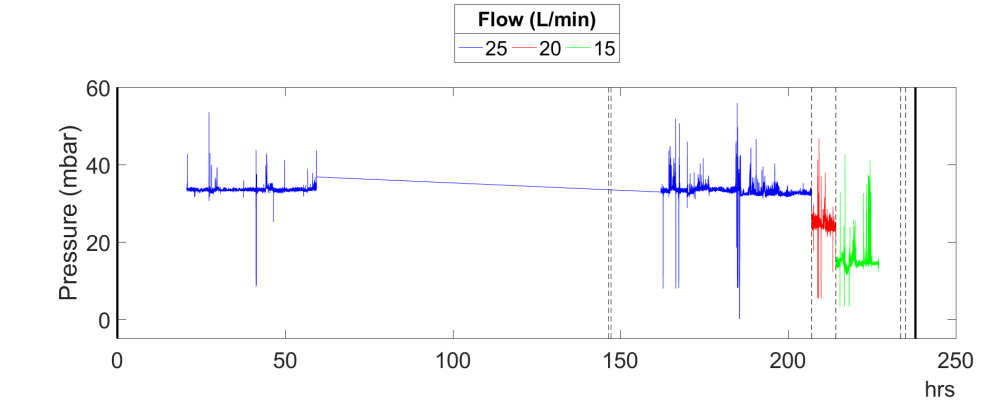
Data analysis - *Analysis parameters as a function of flow rate*



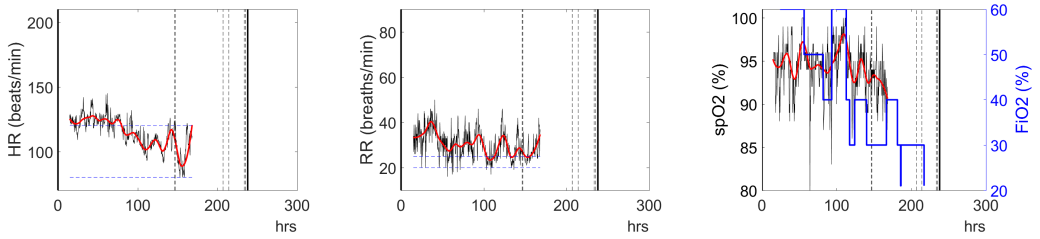
(a) Mean (b) Frequency

Figure B.20: Data Analysis of parameters as a function of flow rate.

Data collection of subject 11



(a) Recorded and pre-processed pressure data



(b) Heart rate (c) Respiratory rate (d) Saturation

Figure B.21: Recorded & pre-processed pressure data and vital parameters of subject 11 (7 years old female with a weight of 25 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

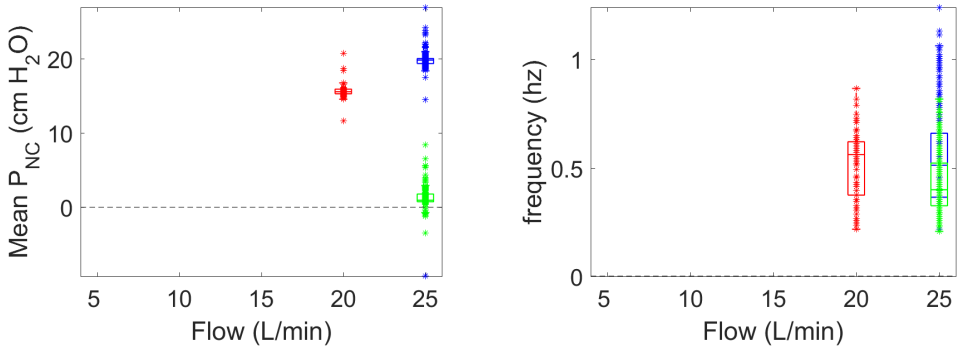
Data description - *Interaction recorded pressure and vital parameters*

The pressure data is collected from 2 small windows during the HFNC therapy. Table B.12 shows the changes in vital parameters and the work of breathing clinical evaluation. We expect to see the most effect right after the start of Optiflow, however this data is unfortunately missing. During the entire therapy the HR and RR are decreasing, more significantly the HR.

Table B.12: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment			
		First 3 hours	1	2	3
Flow		25	25	20	15
HR	-	-	↓	-	-
RR	-	-	↓	-	-
SpO2	-	-	±	-	-
Dysnea score					

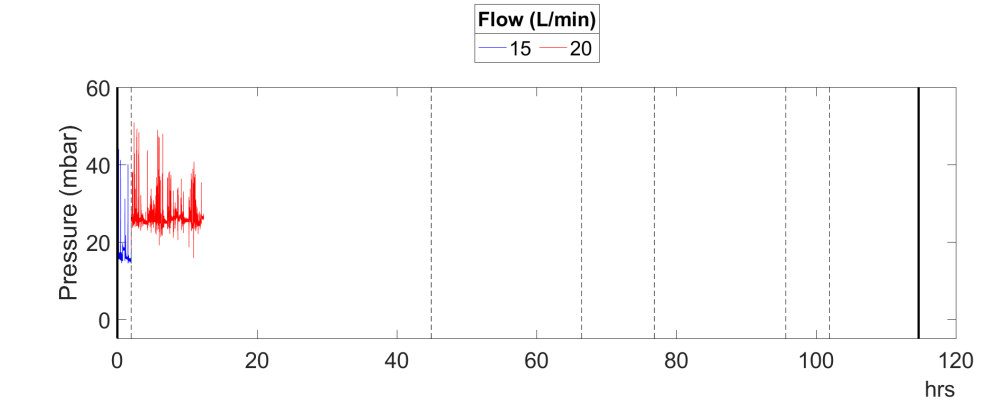
Data analysis - *Analysis parameters as a function of flow rate*



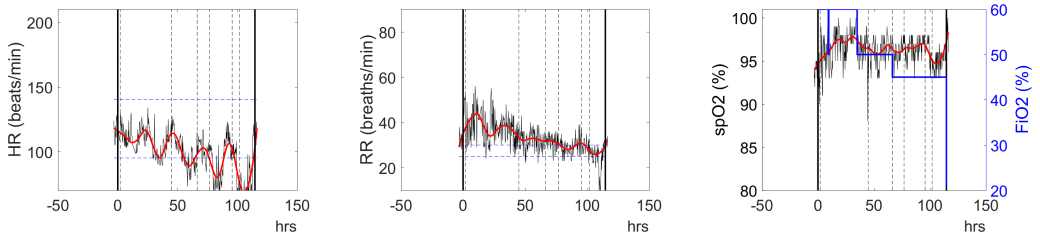
(a) Mean (b) Frequency

Figure B.22: Data Analysis of parameters as a function of flow rate.

Data collection of subject 12



(a) Recorded and pre-processed pressure data



(b) Heart rate (c) Respiratory rate (d) Saturation

Figure B.23: Recorded & pre-processed pressure data and vital parameters of subject 12 (3 year old male with a weight of 15.1 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

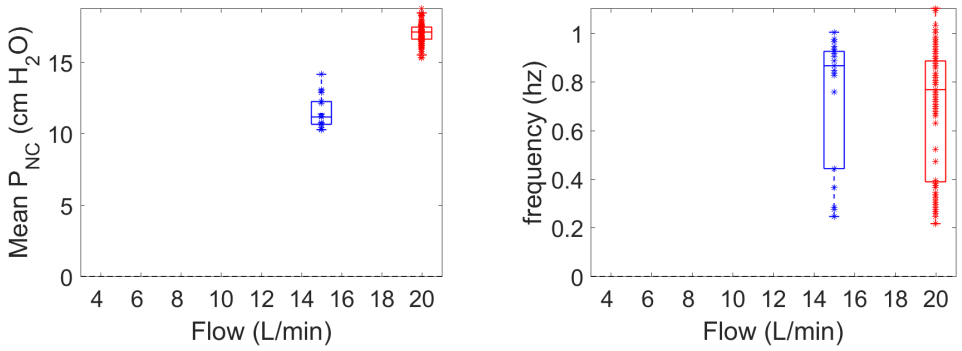
Data description - *Interaction recorded pressure and vital parameters*

The pressure data is only successfully collected during the first 12 hours of the HFNC therapy. Table B.13 shows the changes in vital parameters and the work of breathing clinical evaluation. Because we expect to see the most effect right after the start of Optiflow, we first specifically looked at the first 3 hours after start. During the first 3 hours we see a decrease in HR, however the RR increases. The SpO_2 increases after start therapy and continues constant while the FiO_2 is slowly reduced.

Table B.13: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment							
		First 3 hours	1	2	3	4	5	6	7
Flow		15	15	20	15	10	8	6	4
HR	125	↓	±	↓	↓	↓	↑	↓	↓
RR	32	↑	±	↓	↓	↓	↓	±	±
SpO2	95	↑	↑	↑	±	±	±	↓	↑
Dysnea score			-	±	±	↓	±	-	±

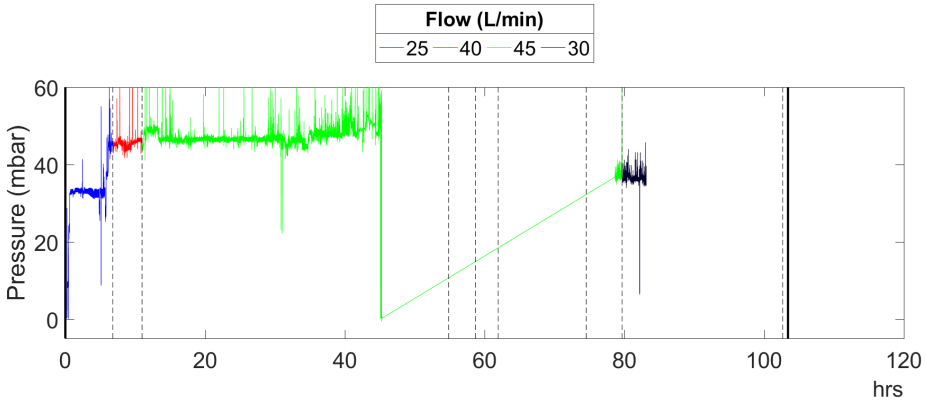
Data analysis - *Analysis parameters as a function of flow rate*



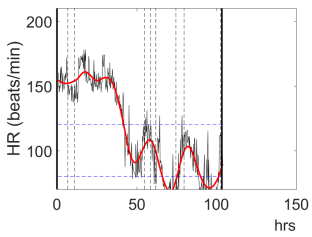
(a) Mean (b) Frequency

Figure B.24: Data Analysis of parameters as a function of flow rate.

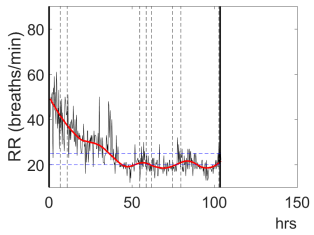
Data collection of subject 13



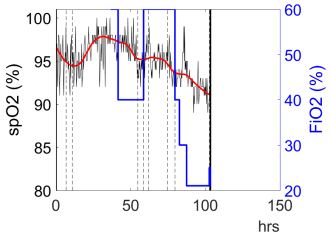
(a) Recorded and pre-processed pressure data



(b) Heart rate



(c) Respiratory rate



(d) Saturation

Figure B.25: Recorded & pre-processed pressure data and vital parameters of subject 13 (5 year old female with a weight of 20 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

Data description - *Interaction recorded pressure and vital parameters*

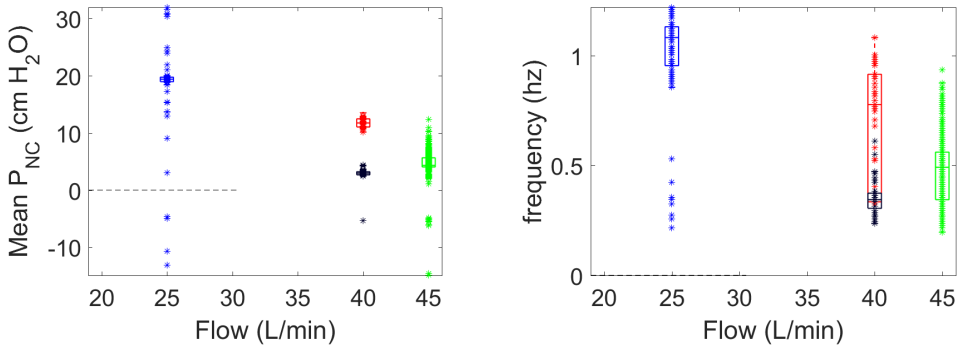
The pressure data is collected during the beginning of the HFNC therapy and during a couple hours after 80 hours of the start. Table B.14 shows the changes in vital parameters and the work of breathing clinical evaluation. Because we expect to see the most effect right after the start of Optiflow, we first specifically looked at the first 3 hours after start. During the first 3 hours we see that the HR remains constant and that the RR decreases significantly. The SpO_2 decreases to 95%, however this again increases after the flow rate is increased after 8 hours. Throughout the entire HFNC therapy

both the HR and RR decreases. Notable is that the HR show a large decrease halfway during the 45 L/min flow rate while nothing else is changed in the therapy.

Table B.14: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment									
		First 3 hours	1	2	3	4	5	6	7	8	9
Flow		25	25	40	45	40	35	30	45	30	20
HR	-	↓	±	±	↓	↑	↓	↓	↑	↓	↑
RR	-	↓	↓	↓	↑	±	±	±	↑	±	↑
SpO2	-	↓	↓	↓	↑	±	±	↓	↓	↓	↓
Dysnea score											

Data analysis - *Analysis parameters as a function of flow rate*

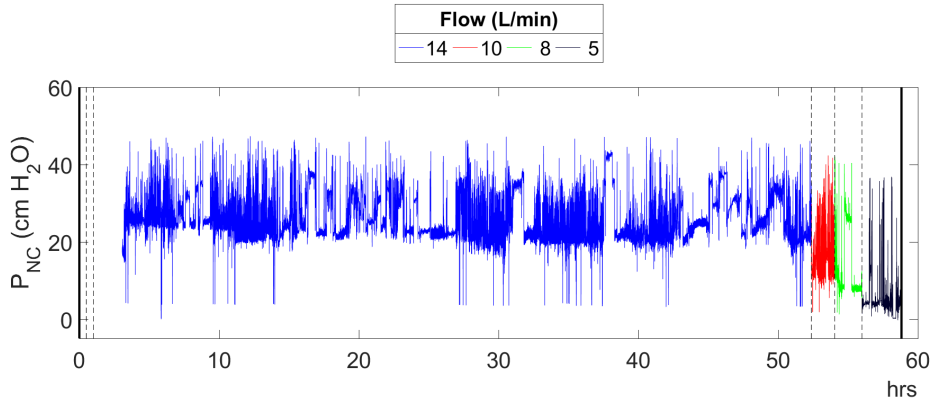


(a) Mean

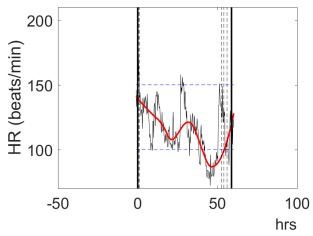
(b) Frequency

Figure B.26: Data Analysis of parameters as a function of flow rate.

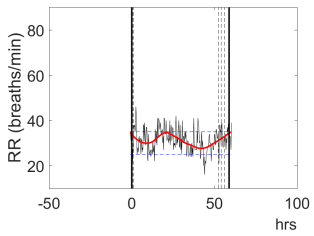
Data collection of subject 14



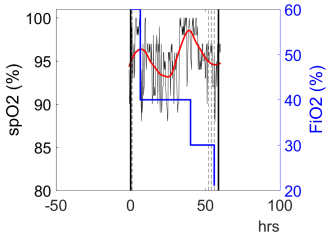
(a) Recorded and pre-processed pressure data



(b) Heart rate



(c) Respiratory rate



(d) Saturation

Figure B.27: Recorded & pre-processed pressure data and vital parameters of subject 14 (1 year and 8 months old female with a weight of 13 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

Data description - *Interaction recorded pressure and vital parameters*

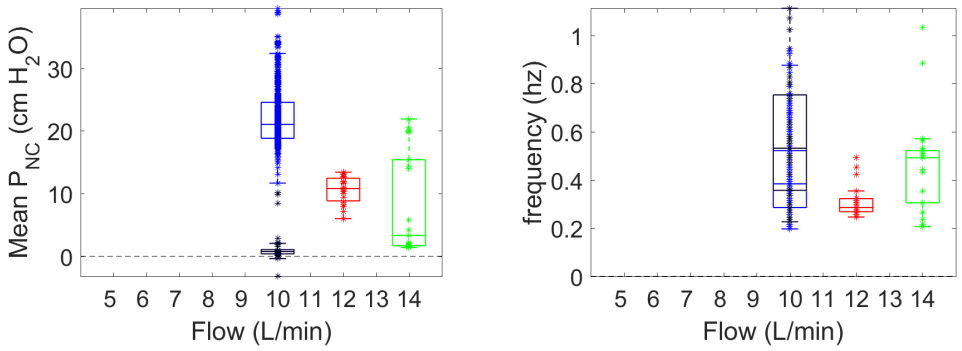
The pressure data is collected during almost the entire HFNC therapy with exception of the first 4 hours. Table B.15 shows the changes in vital parameters and the work of breathing clinical evaluation. Because we expect to see the most effect right after the start of Optiflow, we first specifically looked at the first 3 hours after start. During the first 3 hours we see a decrease in HR and RR. The flow rate is twice increased in the hour after start Optiflow from

10 L/min to 12 till 14 L/min, which remains for 52 hours the same. During this period the HR decreases drastically and the RR remains constant around 35 breaths/min. The last 8 hours the flow is reduced to 5 L/min after which the therapy is stopped. The FiO_2 is reduced in the first period of the therapy from 60 to 40% during which the SpO_2 remained constant 96%, however decreases to 94% after the reduction. After a couple of hours the SpO_2 again increases until the FiO_2 is reduced to 30% and just before the stop of therapy again reduced to 21%. Throughout the therapy and changes in FiO_2 the SpO_2 stays above 94%.

Table B.15: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment						
		First 3 hours	1	2	3	4	5	6
Flow		10	10	12	14	10	8	5
HR	142	↓	↓	↓	↓	↑	↑	↑
RR	39	↓	↓	↓	±	↑	↑	↑
SpO2	93	↑	↑	↑	±	±	±	±
Dysnea score								

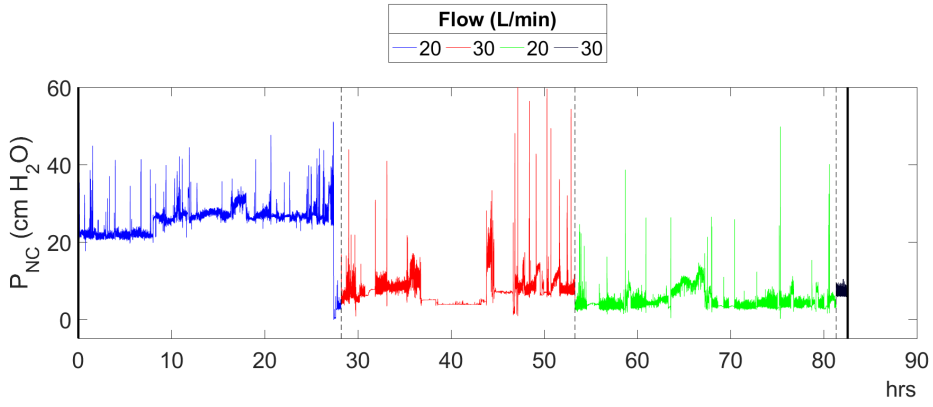
Data analysis - *Analysis parameters as a function of flow rate*



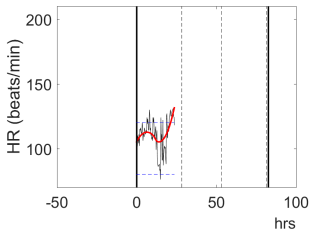
(a) Mean (b) Frequency

Figure B.28: Data Analysis of parameters as a function of flow rate.

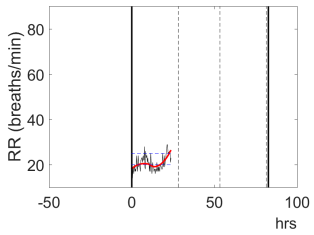
Data collection of subject 15



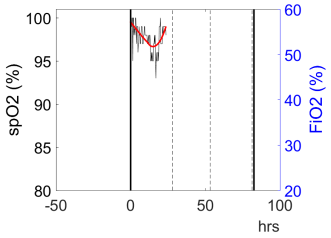
(a) Recorded and pre-processed pressure data



(b) Heart rate



(c) Respiratory rate



(d) Saturation

Figure B.29: Recorded & pre-processed pressure data and vital parameters of subject 15 (8 year old male with a weight of 53 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

Data description - *Interaction recorded pressure and vital parameters*

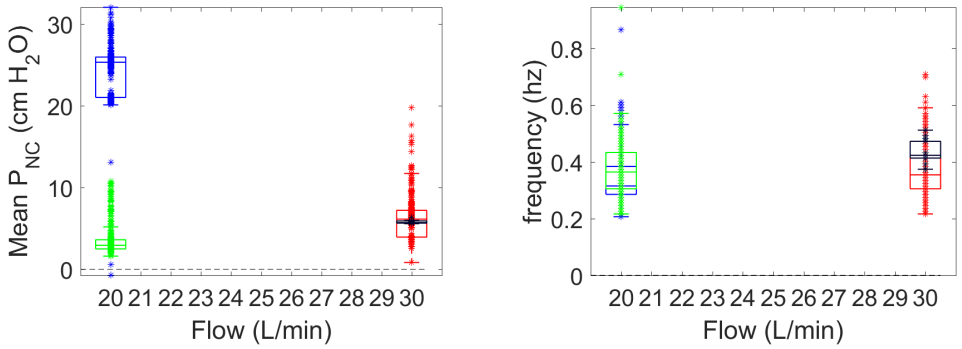
The pressure data is collected during the entire HFNC therapy. Table B.16 shows the changes in vital parameters and the work of breathing clinical evaluation. Because we expect to see the most effect right after the start of Optiflow, we first specifically looked at the first 3 hours after start. During the first 3 hours we see an increase in HR and RR with a decrease in SpO_2, possibly coinciding with the day/night rhythm. Although the vital parameters aren't collected after the first 24 hours, we noticed increasing values in HR and RR throughout the start of the therapy. After 28 hours the flow rate

is reduced, however the **nasal cannula is also changed from junior green to adult orange**. This explains the suggestion that an increase in flow rate results in a decrease in cannula pressure.

Table B.16: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment				
		First 3 hours	1	2	3	4
Flow		20	20	30	20	30
HR	97	↑	↑	-	-	-
RR	22	↑	↑	-	-	-
SpO2	99	↓	±	-	-	-
Dysnea score						

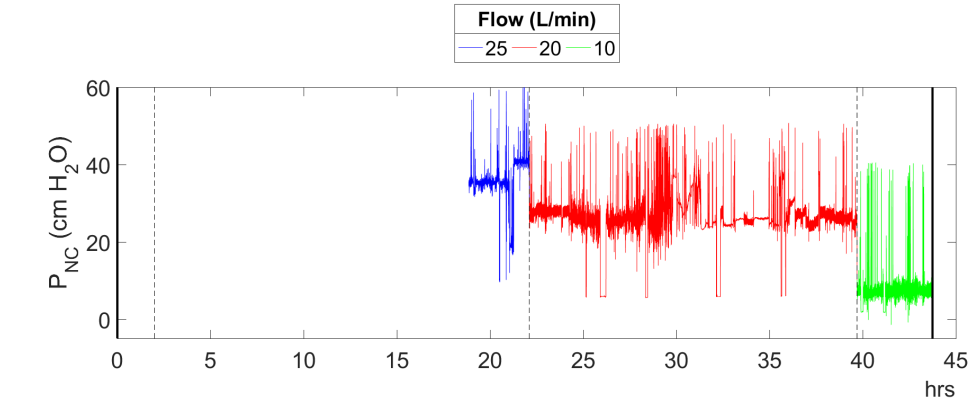
Data analysis - *Analysis parameters as a function of flow rate*



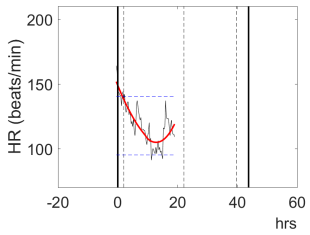
(a) Mean (b) Frequency

Figure B.30: Data Analysis of parameters as a function of flow rate.

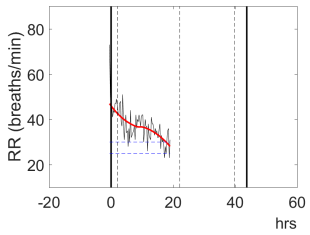
Data collection of subject 16



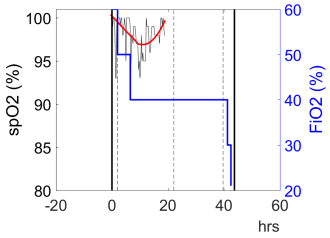
(a) Recorded and pre-processed pressure data



(b) Heart rate



(c) Respiratory rate



(d) Saturation

Figure B.31: Recorded & pre-processed pressure data and vital parameters of subject 16 (4 year old male with a weight of 18 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

Data description - *Interaction recorded pressure and vital parameters*

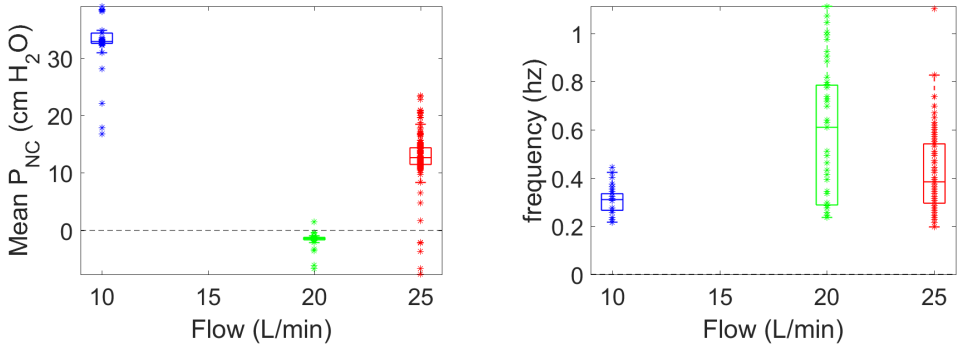
The pressure data is collected during last part of the HFNC therapy. Table B.17 shows the changes in vital parameters and the work of breathing clinical evaluation. Because we expect to see the most effect right after the start of Optiflow, we first specifically looked at the first 3 hours after start. During the first 3 hours we see a decrease in HR, RR and SpO_2, possibly also coinciding with the day/night rhythm. Unfortunately no vital parameters are known after the first 18 hours after start HFNC. Remarkable the pressure data is only measured after the first 18 hours of HFNC. The flow rate was

started at 10 L/min but was increased to 25 L/min after 2 hours. This flow rate remained for 20 hours after which the therapy was slowly reduced to 20 L/min and even 10 L/min until the therapy was discontinued.

Table B.17: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment				
		First 3 hours	1	2	3	4
Flow		10	10	25	20	10
HR	148	↓	↓	-	-	-
RR	39	↓	↓	-	-	-
SpO2	97	↓	↓	-	-	-
Dysnea score						

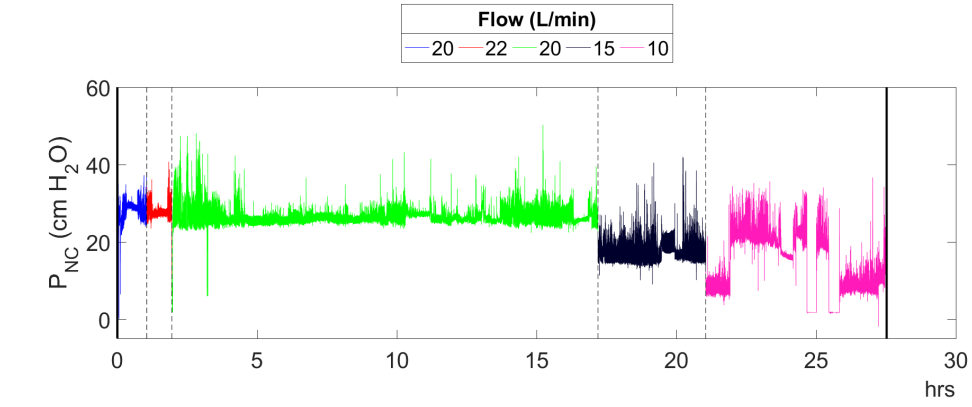
Data analysis - *Analysis parameters as a function of flow rate*



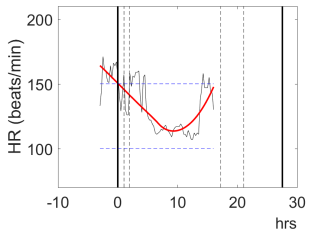
(a) Mean (b) Frequency

Figure B.32: Data Analysis of parameters as a function of flow rate.

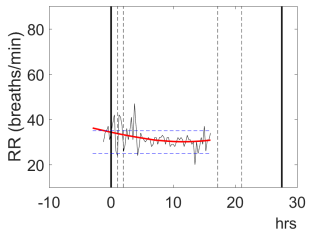
Data collection of subject 17



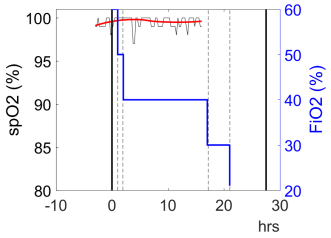
(a) Recorded and pre-processed pressure data



(b) Heart rate



(c) Respiratory rate



(d) Saturation

Figure B.33: Recorded & pre-processed pressure data and vital parameters of subject 17 (1 year and 3 month old male with a weight of 10.7 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

Data description - *Interaction recorded pressure and vital parameters*

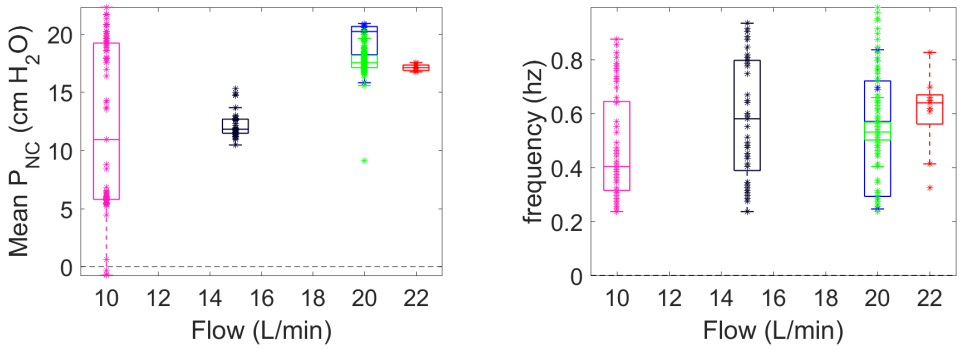
The pressure data is collected during the entire HFNC therapy. Table B.18 shows the changes in vital parameters and the work of breathing clinical evaluation. Because we expect to see the most effect right after the start of Optiflow, we first specifically looked at the first 3 hours after start. During the first 3 hours we see a clear decrease in HR with a smaller decrease in RR, while SpO_2 remains constant. During the first few hours of therapy the HR and RR keeps decreasing while the fLow rate is shortly increased to 22

L/min before decreasing to 20 L/min again. 17 hours after the start of the therapy the flow rate is officially reduced for the first time, unfortunately no vital parameters are available during this period. The SpO_2 remains a constant 98% while the FiO_2 is decreased.

Table B.18: Vital parameters and work of breathing clinical evaluation per flow rate window. With: $\pm$ = unchanged, $\downarrow$ = decreased, $\uparrow$ = increased, * = not usable, - = no available data.

	Before start	Flow moment					
		First 3 hours	1	2	3	4	5
Flow							
HR	167	$\downarrow$	$\downarrow$	$\downarrow$	$\downarrow$	-	-
RR	31	$\downarrow$	$\downarrow$	$\downarrow$	$\downarrow$	-	-
SpO2	98	$\pm$	$\pm$	$\pm$	$\pm$	-	-
Dysnea score							

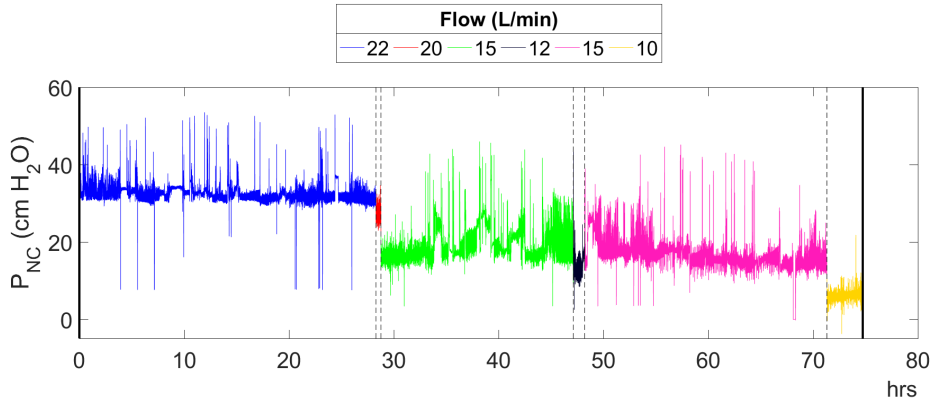
Data analysis - *Analysis parameters as a function of flow rate*



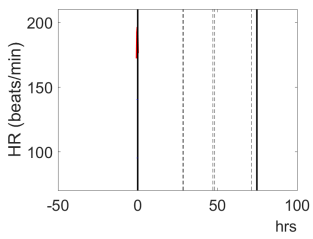
(a) Mean (b) Frequency

Figure B.34: Data Analysis of parameters as a function of flow rate.

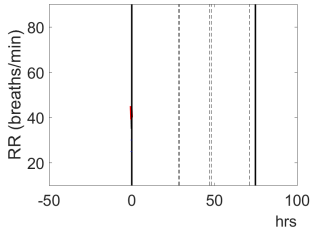
Data collection of subject 18



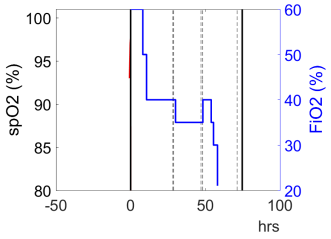
(a) Recorded and pre-processed pressure data



(b) Heart rate



(c) Respiratory rate



(d) Saturation

Figure B.35: Recorded & pre-processed pressure data and vital parameters of subject 18 (2 year old male with a weight of 11 kg). Figure a) the measured pressure at the end of the cannula if plotted against the duration of HFNC therapy. The bold vertical lines show respectively the start and the end of the HFNC therapy and the dotted vertical lines are the moments in time the the set flow rate is changed; figure b,c,d) vital parameters with in red the trendline of the raw data: figure b) Heart rate; figure c) respiratory rate; figure d) saturation level and in blue the $FiO2$ values set at the device.

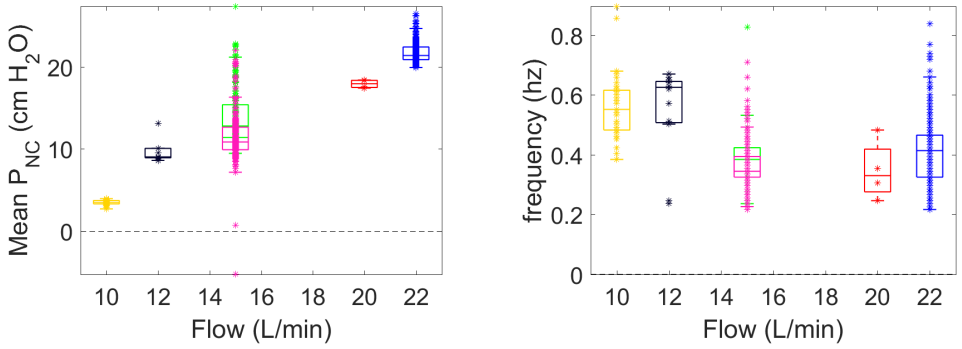
Data description - *Interaction recorded pressure and vital parameters*

The pressure data is collected during the entire HFNC therapy. Table B.19 shows the changes in vital parameters and the work of breathing clinical evaluation. Unfortunately no vital parameters are noted throughout the entire therapy.

Table B.19: Vital parameters and work of breathing clinical evaluation per flow rate window. With: ± = unchanged, ↓ = decreased, ↑ = increased, * = not usable, - = no available data.

	Before start	Flow moment						
		First 3 hours	1	2	3	4	5	6
Flow		22	22	20	15	12	15	10
HR	196	-	-	-	-	-	-	-
RR	39	-	-	-	-	-	-	-
SpO2	97	-	-	-	-	-	-	-
Dysnea score								

Data analysis - *Analysis parameters as a function of flow rate*



(a) Mean (b) Frequency

Figure B.36: Data Analysis of parameters as a function of flow rate.

Acknowledgments

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