Resistance breathing with PEP and CPAP

Effects on respiratory parameters

Maria Sehlin
Cover illustrations: Flow resistor CPAP device (Boussignac CPAP), PEP-mask, threshold resistor CPAP device, PEP-bottle.
I do my job like I breathe – so if I can't breathe I'm in trouble
Karl Lagerfeld
Table of contents

ABSTRACT ...................................................................................... III
SVENSK SAMMANFATTNING ......................................................... IV
ABBREVIATIONS ........................................................................ VI
ORIGINAL PAPERS ...................................................................... VIII
1 INTRODUCTION ........................................................................ 1
   1.1 RESISTANCE BREATHING .................................................... 1
   1.1.1 Resistors ......................................................................... 1
   1.1.2 Pursed-lips breathing ...................................................... 2
   1.2 PEP HISTORY ..................................................................... 2
   1.2.1 Blow bottles and the PEP-bottle ...................................... 2
   1.2.2 The PEP-mask .............................................................. 4
   1.2.3 Comparison of the PEP-bottle and IR-PEP in postoperative patients .................................................. 11
   1.3 CPAP HISTORY ................................................................. 12
   1.3.1 The Boussignac CPAP .................................................... 13
   1.4 COMPARING THE EFFECT OF PEP AND CPAP ON FRC .......... 13
   1.5 INSPIRATORY CAPACITY (IC) MEASUREMENTS ............... 14
   1.6 CPAP IN FIXED-WING AIR AMBULANCES ....................... 14
   1.7 RATIONALE ...................................................................... 14

AIMS OF THE THESIS .............................................................. 16

2 METHODS .................................................................................. 17
   2.1 STUDY DESIGN ................................................................. 17
   2.1.1 Participants ................................................................. 19
   2.1.2 Ethics .......................................................................... 19
   2.1.3 Breathing devices ......................................................... 19
   2.1.4 Hypobaric chamber ...................................................... 21
   2.2 MEASUREMENTS AND TEST PROCEDURES..................... 21
   2.2.1 Test positions ............................................................ 21
   2.2.2 Breathing instructions ................................................ 22
   2.2.3 Static produced CPAP pressure and airflow levels .......... 23
   2.2.4 IC measurements ....................................................... 23
   2.2.5 Randomization ............................................................ 23
   2.2.6 Measurements ............................................................ 23
   2.2.7 Perceived exertion ....................................................... 24
   2.3 DATA COLLECTION ........................................................ 25
   2.3.1 Airway pressure, pressure and airflow ......................... 25
   2.3.2 Pulse oximetry (SpO₂), heart rate and end-tidal CO₂ .......... 25
   2.3.3 Calibration ................................................................. 25
   2.3.4 Data processing ........................................................... 26
   2.3.5 IC analysis ................................................................. 27
   2.4 STATISTICS ...................................................................... 27
## Table of contents

### 3 RESULTS

- 3.1 PAPER I ................................................................. 29
  - 3.1.1 Expiratory phase................................................. 29
  - 3.1.2 Inspiratory phase............................................... 29
- 3.2 PAPER II ............................................................... 30
  - 3.2.1 Inspiratory phase............................................... 30
  - 3.2.2. Expiratory phase................................................ 30
- 3.3 PAPER III ................................................................ 33
  - 3.3.1 Inspiratory phase............................................... 33
  - 3.3.2 Expiratory phase............................................... 33
- 3.4 PAPER IV ............................................................... 35
  - 3.4.1 Static pressure.................................................. 35
  - 3.4.2 Static airflow................................................... 36
  - 3.4.3 Different flow selectors....................................... 37
- 3.5 ESTIMATED PERCEIVED EXERTION (PAPER I-III). .......... 38

### 4 DISCUSSION

- 4.1 THE PEP-BOTTLE AND THE PEP-MASK ......................... 39
- 4.2 THE BOUSSIGNAC CPAP ........................................... 39
- 4.3 THE EFFECT OF PEP AND CPAP ON INSPIRATORY CAPACITY .... 40
- 4.4 THE EFFECT OF CHANGES IN AMBIENT AIR PRESSURE ON CPAP DEVICE PERFORMANCE ........................................ 41
- 4.5 PERCEIVED EXERTION............................................. 42
- 4.6 METHODOLOGICAL CONSIDERATIONS............................ 43
- 4.7 CLINICAL IMPLICATIONS AND FUTURE RESEARCH .............. 44

### 5 CONCLUSIONS .......................................................... 45

ACKNOWLEDGEMENTS ..................................................... 46

REFERENCES ........................................................................ 47

DISSERTATIONS WRITTEN BY PHYSIOTHERAPISTS, UMEÅ UNIVERSITY 1989–2014 ........................................... 55
Abstract

Background: Positive expiratory pressure (PEP) and continuous positive airway pressure (CPAP) are two forms of resistance breathing used in spontaneously breathing patients. With a threshold resistor or a flow resistor, both PEP and CPAP provide a positive (elevated) pressure level during the expiratory phase. With PEP, inspiratory pressure is negative, i.e. lower than ambient air pressure, as during a normal inspiration, but with CPAP, the inspiratory pressure is positive, i.e. higher than ambient air pressure.

Methods: This thesis is based on four separate studies in which four different breathing devices, a PEP-bottle (threshold resistor device), a PEP-mask (flow resistor device), a threshold resistor CPAP and a flow resistor device were investigated. Paper I, II and III are based on studies in healthy volunteers. Paper IV is a bench study performed in a hypobaric chamber. Paper I examined differences between two PEP devices, the PEP-bottle and the PEP-mask. Paper II evaluated the performance of a flow resistor CPAP device, (Boussignac CPAP). Paper III investigated the effect of two PEP-devices, a PEP-bottle and a PEP-mask and two CPAP devices, a threshold resistor CPAP and a flow resistor CPAP, on inspiratory capacity (IC). In paper IV, the effect of changes in ambient pressure on preset CPAP levels in two different CPAP devices was compared.

Results: With the PEP bottle, both expiration and inspiration began with a zero-flow period during which airway pressure changed rapidly. With the PEP-mask, the zero-flow period was very short and the change in airway pressure almost non-existent (paper I). During normal breathing with the Boussignac CPAP, changes in airway pressure were never large enough to reduce airway pressure below zero. During forced breathing, as airflow increased, both the drop in inspiratory airway pressure and the increase in expiratory airway pressure were potentiated (paper II). IC decreased significantly with three of the breathing devices, the PEP-mask and the two CPAP devices (paper III). With the threshold resistor CPAP, measured pressure levels were close to the preset CPAP level. With the flow resistor CPAP, as the altitude increased CPAP produced pressure levels increased (paper IV).

Conclusion: The effect on airway pressure, airflow, IC and the effect of changes in ambient air pressure differ between different kinds of resistance breathing devices. These differences in device performance should be taken into consideration when choosing the optimal resistance breathing device for each patient.

Keywords: Chest physiotherapy, breathing exercises, PEP, CPAP, airway pressure, airflow, threshold resistor, flow resistor, inspiratory capacity, Borg CR10.
Svensk sammanfattning

Patienter som spontanandas men har problem med sin andning kan vara hjälpta av andningsgymnastik i form av motståndsandning. Två former av motståndssporandng är positivt exspiratoriskt tryck (PEP) och kontinuerligt positivt luftvägstryck (CPAP).


CPAP används bland annat som behandling vid akut lungödem, sömnapné och för att förebygga och behandla andningskomplikationer efter operationer. På intensivvårdsavdelningar används CPAP också för att behandla patienter med andningssvikt av andra orsaker samt vid urträngning från respirator. Till skillnad mot PEP, där luftvägstrycket under inandning är negativt, innebär CPAP spontanandning på en förhöjd trycknivå. Andning med CPAP håller luftvägstrycket positivt under hela andningscykeln och det positiva luftvägstrycket kan, på samma sätt som vid PEP, åstadkOMNAS med endera ett tryckstyrat eller ett flödesstyrat motstånd.

De fyra olika delarbetena i denna avhandling är baserade på fyra separata studier där fyra olika hjälpmazel för motståndssporandng, PEP-flaskan (tryckstyrat motstånd), PEP-masken (flödesstyrat motstånd), en tryckstyrad CPAP och en flödesstyrad CPAP har utvärderats.

I studie 2 utvärderades prestanda hos en flödesstyrad CPAP, Boussignac CPAP, i en grupp friska frivilliga försökspersoner. När försökspersonerna andades som vanligt var förändringarna i luftvägstryck aldrig så stora att luftvägstrycket blev negativt, dvs. att det kontinuerligt positiva luftvägstrycket förlorades. Allt eftersom luftflödet ökade under den forcerade andningen blev både tryckfallet under inandning och tryckökningen under utandning större.

I studie 3 undersöktes hur fyra olika andningshjälpmedel, två PEP hjälpmedel, PEP-flaskan och PEP-masken, samt två CPAP hjälpmedel, en tryckstyr CPAP och en flödesstyr CPAP påverkar inspiratorisk kapacitet (IC) i en grupp friska frivilliga försökspersoner. IC sjönk signifikant för tre av andningshjälpmedlen, PEP-masken och de två CPAP hjälpmedlen men inte för PEP-flaskan. IC såg ut att minska mest för det flödesstyrda CPAP hjälpmedlet medan minskningen i IC var lika stor för PEP-masken och det tryckstyrda CPAP hjälpmedlet.

För att simulera förhållanden i en flygplanskabin under flygning, genomfördes studie 4 som en bänkstudie i en tryckkammare. I denna studie utvärderades hur inställda CPAP nivåer hos två olika CPAP hjälpmedel, en tryckstyr CPAP och en flödesstyr CPAP, påverkades av förändringar i omgivande lufttryck. De två CPAP systemen påverkades olika av en ökad altitud. Det tryckstyrda CPAP hjälpmedlets producerade trycknivå var nära den inställda CPAP nivån oavsett simulerad altitud. För det flödesstyrda CPAP hjälpmedlet ökade den CPAP producerade trycknivån allt eftersom altituden ökade.

Sammanfattningsvis är effekten på luftvägstryck, luftflöde och IC samt effekten av omgivande lufttryck olika för olika typer av hjälpmedel för motståndsandning. Det är signifikanta skillnader i relationen mellan luftflöde och luftvägstryck mellan PEP-flaskan och PEP-masken. Flödesstyrda hjälpmedel verkar minska IC mer än tryckstyrda hjälpmedel när PEP och CPAP hjälpmedel jämförs separat. Prestandan hos det tryckstyrda CPAP hjälpmedlet är mycket mer stabilt än det flödesstyrda CPAP hjälpmedlet när omgivande lufttryck sjunker som det gör under flygning. Dessa skillnader i hjälpmedlens prestanda bör tas i beaktande vid val av hjälpmedel för motståndsandning till en patient.
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>A-aDO₂</td>
<td>Alveolar-arterial oxygen tension difference</td>
</tr>
<tr>
<td>CF</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>cm H₂O</td>
<td>Centimeter of water</td>
</tr>
<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous Positive Airway Pressure</td>
</tr>
<tr>
<td>CR10</td>
<td>Category Ratio Scale (Borg)</td>
</tr>
<tr>
<td>EIT</td>
<td>Electric Impedance Tomography</td>
</tr>
<tr>
<td>EPAP</td>
<td>Expiratory Positive Airway Pressure</td>
</tr>
<tr>
<td>FET</td>
<td>Forced Expiratory Technique</td>
</tr>
<tr>
<td>FEV₁</td>
<td>Forced Expiratory Volume in one second</td>
</tr>
<tr>
<td>FRC</td>
<td>Functional Residual Capacity</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced Vital Capacity</td>
</tr>
<tr>
<td>IS</td>
<td>Incentive Spirometry</td>
</tr>
<tr>
<td>IC</td>
<td>Inspiratory Capacity</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IPPB</td>
<td>Intermittent Positive Pressure Breathing</td>
</tr>
<tr>
<td>IR-PEP</td>
<td>Inspiratory Resistance-Positive Expiratory Pressure</td>
</tr>
<tr>
<td>kft</td>
<td>Kilo feet</td>
</tr>
<tr>
<td>L</td>
<td>Liter</td>
</tr>
<tr>
<td>L/min</td>
<td>Liter per minute</td>
</tr>
<tr>
<td>L/s</td>
<td>Liter per second</td>
</tr>
<tr>
<td>max</td>
<td>Maximum</td>
</tr>
<tr>
<td>min</td>
<td>Minimum</td>
</tr>
<tr>
<td>mm Hg</td>
<td>Millimeter of mercury</td>
</tr>
<tr>
<td>n</td>
<td>Number</td>
</tr>
<tr>
<td>Na</td>
<td>Not available</td>
</tr>
<tr>
<td>NIV</td>
<td>Non-Invasive Ventilation</td>
</tr>
<tr>
<td>NIPPV</td>
<td>Non-Invasive Positive Pressure Ventilation</td>
</tr>
<tr>
<td>NPPV</td>
<td>Non-Invasive Positive Pressure Ventilation</td>
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</tbody>
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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Ns</td>
<td>Non-significant</td>
</tr>
<tr>
<td>PLB</td>
<td>Pursed-lips breathing</td>
</tr>
<tr>
<td>PD</td>
<td>Postural drainage</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive End Expiratory Pressure</td>
</tr>
<tr>
<td>PEP</td>
<td>Positive Expiratory Pressure</td>
</tr>
<tr>
<td>RMT</td>
<td>Respiratory Muscle Training</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>S-PEP</td>
<td>Self-administered Positive Expiratory Pressure</td>
</tr>
<tr>
<td>SpO₂</td>
<td>Oxygen saturation</td>
</tr>
<tr>
<td>tcPO₂</td>
<td>Transcutaneous partial pressure of oxygen</td>
</tr>
<tr>
<td>tcPCO₂</td>
<td>Transcutaneous partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>TLC</td>
<td>Total Lung Capacity</td>
</tr>
<tr>
<td>VC</td>
<td>Vital Capacity</td>
</tr>
<tr>
<td>WOB</td>
<td>Work of breathing</td>
</tr>
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</table>
Original papers

This thesis is based on the following papers, referred to in the text by their Roman numerals I – IV

I. Sehlin M, Öhberg F, Johansson G, Winsö O.
Physiological Responses to Positive Expiratory Pressure Breathing: A Comparison of the PEP Bottle and the PEP Mask.
Respir Care; 2007:52(8):1000-5

II. Sehlin M, Törnell SS, Öhberg F, Johansson G, Winsö O.
Pneumatic Performance of the Boussignac CPAP System in Healthy Humans. Respir Care; 2011:56(6):818-26

III. Sehlin M, Winsö O, Wadell K, Öhberg F.
Immediate effects of positive expiratory pressure and continuous positive airway pressure breathing on inspiratory capacity as an indirect measure of induced changes in functional residual capacity in healthy individuals. (In manuscript)

IV. Sehlin M, Brändström H, Winsö O, Haney M, Wadell K, Öhberg F.
Simulated flying altitude and performance of continuous positive airway pressure devices.
(Aviat Space Environ Med, in press)

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1 Introduction

1.1 Resistance breathing

Physiotherapists working in acute care settings treat patients with respiratory problems using different chest physiotherapy methods. Chest physiotherapy includes breathing exercises, such as deep breathing and resistance breathing. Positive expiratory pressure (PEP) and continuous positive airway pressure (CPAP) are two forms of resistance breathing used in spontaneously breathing patients. With a threshold resistor or a flow resistor, both PEP and CPAP provide a positive (elevated) pressure level during the expiratory phase. A threshold resistor device has a resistor that opens and closes at a specific pressure level and should keep a constant pressure as airflow varies (1, 2). Two examples of threshold resistors are the water seal (PEP-bottle) and the spring-loaded valve (threshold resistor CPAP) (2, 3). PEP with a threshold resistor is sometimes referred to as expiratory positive airway pressure (EPAP) (3, 4). Flow resistor devices use an orifice resistor that restricts airflow in combination with airflow velocity to produce a positive expiratory pressure (1, 2).

With PEP, inspiratory pressure is negative, i.e. lower than ambient air pressure, as during a normal inspiration, but with CPAP, the inspiratory pressure is positive, i.e. higher than ambient air pressure (3). For a CPAP device to keep the pressure level positive throughout the entire breathing cycle, the velocity of the air flow delivered by the CPAP device has to exceed the peak inspiratory airflow produced by the patient (3, 5).

1.1.1 Resistors

A true threshold resistor should maintain the threshold pressure regardless of velocity of airflow. However, very few threshold resistors are considered pure threshold resistors since they have additional flow-resistance properties (2). After investigating flow-resistive characteristics of expiratory positive pressure valve systems used to provide CPAP or positive end expiratory pressure (PEEP), Banner et al suggested that threshold resistors should be classified as low-resistance or high-resistance types of valves and that only low-resistance threshold resistors should be used for CPAP (1). Christensen et al (6) investigated flow-dependent properties in three PEP devices with flow resistors and three PEP devices with threshold resistors. All three flow resistors increased pressure with increased airflow. Resistors from different brands marked with the same diameter differed in produced pressure levels, especially when airflow increased. The difference could be as much as 20 cm H₂O. With the three threshold resistors, two of the resistors, the spring-loaded valve and the underwater seal showed almost ideal flow-independent characteristics but a minor degree of flow-dependency was seen, especially at higher pressure levels. The third threshold resistor had large flow dependent properties. During low airflow the spring-loaded valve...
produced lower pressure levels than the preset level. Their results showed that the pressure level should be monitored and that one device/resistor cannot be replaced with another device/resistor without examining and adjusting the pressure level.

1.1.2 Pursed-lips breathing

Pursed-lips breathing (PLB) is a predecessor to both PEP and CPAP (3, 7). During PLB, positive expiratory pressure is achieved by constriction of the mouth, as when whistling (8, 9). This breathing technique is spontaneously used by patients with chronic obstructive pulmonary disease (COPD) (10, 11). Patients undergoing abdominal surgery are instructed to use PLB (12, 13). PLB have been shown to increase tidal volume, reduce respiratory rate (8, 11) and increase oxygen saturation (SpO₂) (8, 10) in patients with COPD and myotonic muscular dystrophy (14).

1.2 PEP history

1.2.1 Blow bottles and the PEP-bottle

Bottle blowing has been evaluated in postoperative patients (15-23), in patients with respiratory insufficiency (24), COPD (25) and in patients with pneumonia (26).

1.2.1.1 Postoperative care

The blow bottles used during the 1970s and 1980s differ from the PEP-bottles used today. In 1970 Colgan et al (16) compared resistance breathing (blow bottles) with sustained hyperinflation for treatment of postoperative atelectasis. The blow bottle system consisted of two different one liter (L) plastic bottles connected with a plastic tube through the opening of the two bottles. One of the bottles was filled with water and patients were encouraged to blow water from one bottle to the other. A pressure level of 18 cm H₂O was required to blow water from one bottle to the other. As the amount of water decreased in the first bottle, an increasing pressure level was required to transport water from the first to the second bottle. When the first bottle was almost empty, a pressure level of 36 cm H₂O was required to initiate flow of water. When the connecting plastic tube was filled with water, a siphon effect was created and the required pressure level for maintaining water flow through the tube was approximately 12 cm H₂O less than the starting pressure. Because of the resistance caused by the tube, some patients generated pressure levels above 70 cm H₂O. After the use of blow bottles, functional residual capacity (FRC) increased significantly. The authors concluded that:
“the efficacy of resistance breathing as a form of therapy depends on an initial large and sustained deep breath, with prolonged gradual transfer of water from one bottle to another. Rapid transfer generates excessive and useless airway pressure and a more rapid reduction in lung volume”.

During the 1970s an additional three articles (17, 19, 20) were published using the same blow bottle system described by Colgan et al (16). The effect of blow bottles and a dead space expiratory pressure device on vital capacity (VC) was compared in 25 postoperative patients (men). The group using the dead space expiratory pressure device had significantly higher VC compared to the blow bottles group (20). Blow bottles, incentive spirometry (IS) and intermittent positive pressure breathing (IPPB) were compared in patients undergoing cardiac surgery. Postoperative lung complications occurred in 8 % of the blow bottle group, in 15 % of the IS group and in 30 % of the IPPB group (19). Conventional pulmonary physiotherapy was compared to blow bottles in patients undergoing upper abdominal surgery. There was no difference in postoperative radiological changes between the two groups (17).

In the beginning of the 80s there was a discussion whether mechanical aids had any effect on lung expansion (27, 28). It was argued that there were little or no evidence to support the use of blow bottles to reduce the incidence of postoperative pulmonary complications (28). It was also suggested that the use of blow bottles could be the cause of atelectasis (29).

In the 1980s, single bottle systems were used instead of double blow bottle systems. The effect of blow bottles and CPAP on FRC was compared in patients after abdominal surgery. The blow bottle system consisted of a two liter bottle. A teflon tube with an inner diameter of 6 mm was placed 8 cm below the water level. The teflon tube was connected to a 1 m flexible tube with an inner diameter of 8 mm. Bottle blowing or CPAP was performed four times a day for 15 minutes. Both bottle blowing and CPAP increased FRC significantly but 10 minutes after the breathing exercises were stopped FRC had returned to pre-treatment values (18).

Standard physiotherapy was compared to standard physiotherapy plus PEP in postoperative patients. The PEP device consisted of a large container fitted with a 2 cm rigid tube. The tube was connected to a flexible tube with a mouthpiece at the proximal end. Patients were instructed to breathe in through the nose and to breathe out through the mouthpiece. The patients took 10 or more consecutive breaths twice every two hours with an expiratory pressure level of 5-15 cm H$_2$O. There was no difference in pulmonary complications between the two groups. (15).
Introduction

In 2005 Westerdahl et al (22) compared the effect deep breathing during bottle blowing with no breathing exercises on atelectasis and pulmonary function in 90 patients after coronary artery bypass surgery. The PEP-bottle consisted of a bottle with 10 cm of water and a plastic tube, 50 cm long with an inner diameter of 1 cm. The patients were instructed to perform 30 breaths, three sets of 10 breaths with a 30-60 s pause between each set, one per hour during the day. A slow maximal inspiration was followed by an expiration ending approximately at FRC. Patients, who performed deep breaths with the PEP-bottle, had significantly smaller atelectatic areas and better pulmonary function than patients that did not perform any breathing exercises.

1.2.1.2 Respiratory insufficiency
In 15 patients with respiratory insufficiency the effect of thorax compression or PEP on changes in transcutaneous partial pressure of CO₂ (tcPCO₂) was compared. With PEP, patients were instructed to inhale properly and to exhale steadily without force through a plastic tube. The end of the plastic tube was positioned at the bottom of a bottle containing 10 cm of water. The patients breathed 30 breaths at a comfortable rate. The mean decrease in tcPCO₂ was the same for both therapies (24).

1.2.1.3 Chronic obstructive pulmonary disease (COPD)
With the same blow bottle system and the same breathing instructions as for the patients with respiratory insufficiency described above, the effect of PEP, CPAP and hyperventilation was investigated in 9 hypoxemic and hypercapnic patients with COPD. TcPCO₂ decreased significantly more during PEP and hyperventilation compared to CPAP (25).

1.2.1.4 Pneumonia
Björkqvist et al (26) investigated if bottle blowing (PEP-bottle) had a positive effect in patients with pneumonia. The PEP-bottle contained 10 cm of water. The patients were asked to blow bubbles through a plastic tube with an inner diameter of 10 mm at a calm speed with an effort just enough to overcome the pressure level provided by the water. Every hour between 9 in the morning till 8 in the evening, the patients performed 2 sets of 10 breaths with a short pause between the two sets. Patients who performed the PEP exercises had a significantly shorter length of hospital stay than the control group.

1.2.2 The PEP-mask.
The PEP mask was developed in Denmark in the late 1970 as a technique to mobilize secretions (30). The PEP-mask has been evaluated in patients with cystic fibrosis (31-47), in postoperative patients (12, 13, 48-52) and
in patients with chronic bronchitis (53-57). The PEP-mask has also been evaluated in patients with chronic bronchial sepsis (58), in patients with pulmonary infections (59) and in children with multiple severe disabilities (60).

1.2.2.1 Cystic fibrosis

In 1984, two articles “Improving the ketchup bottle method with positive expiratory pressure, PEP, in cystic fibrosis” by Falk et al (33) and “Positive expiratory pressure (PEP) as lung physiotherapy in cystic fibrosis: a pilot study” by Tönnesen et al (44) were published.

Falk et al (33) compared four different treatments of chest physiotherapy in 14 patients with cystic fibrosis (CF). The PEP-mask treatment consisted of diaphragmatic breathing with slightly active expiration. The patients should be able to breathe for two minutes with a steady PEP without exertion. The PEP level was 17 cm H₂O (15-30) during the middle third of the expiratory phase. 6-12 repetitions of PEP were followed by forced expiratory technique maneuvers (FET) or cough. Treatment duration was 35 minutes when PEP was used in combination with postural drainage (PD) and 20 minutes when PEP was used in the sitting position. Forced vital capacity (FVC) increased significantly after PEP treatment performed in the sitting position. Sputum expectoration was significantly higher when PEP was added to the treatment.

Tönnesen et al (44) investigated PEP in 12 patients with CF. PEP was prospectively performed during a period of 6-9 month and compared to conventional lung physiotherapy, performed one year earlier. PEP was used in the sitting position. The patients breathed normally with an active expiration against a PEP level of 10-20 cm H₂O for one minute followed by several FET maneuvers. Residual volume was significantly reduced during the PEP period (not measured during conventional lung physiotherapy) and the subjective sputum expectoration was significantly higher with PEP compared to conventional lung physiotherapy.

The flutter (an oscillating PEP device) was compared to the PEP-mask in 22 children with CF. Two treatment sessions were performed twice a day for two weeks with either breathing device in a randomized order. No significant changes in any of the investigated lung parameters occurred with either method (46). When immediate changes in transcutaneous blood-gas tension after PEP and oscillating PEP, i.e. flutter, was compared in 15 patients with CF, oscillating PEP changed transcutaneous blood-gas tension more than PEP (36). Long-term effects of the PEP-mask and the flutter were compared in 40 children with CF. Treatment was performed twice a day during one year. The authors concluded that the flutter did not maintain pulmonary function to the same degree as the PEP-mask and that the flutter was more costly due to increased number
of hospitalizations and antibiotic use (39). In another study, long-term effect of the PEP-mask and the flutter on forced expiratory volume in one second (FEV<sub>1</sub>) was examined in 42 adult patients with CF. Treatment was performed twice a day for 13 months. There was no significant difference between the two groups (47).

In two studies, PEP treatment during 20 minutes twice a day for four weeks was compared with PD in patients with cystic fibrosis. There was no difference in sputum production or lung function between the two different treatments (43, 45). In 24 patients with CF, four different treatment regimens, conventional physiotherapy (PD with percussion and FET), PEP during five minutes followed by conventional physiotherapy, PEP alone and PEP plus FET were compared, each regimen lasting four weeks. There were no significant differences in pulmonary function between the different treatment regimens. 23 patients chose PEP together with FET as their long-term treatment (42).

Short-term effects of PEP plus FET and PD plus FET on tracheobronchial clearance were investigated in 10 patients with CF and a chronic pseudomonas aeruginosa infection. The authors concluded that PEP plus FET and PD plus FET have similar effect on short term whole lung and regional tracheobronchial clearance in patients with CF and that weight of expectorated sputum as a sole evaluating factor of tracheobronchial clearance seems inadequate (40). In another study, short-term effects of PEP, PD and high-frequency chest compression physiotherapy were compared to no-treatment (control) in 16 patients with CF. Each treatment regimen was performed twice a day for two consecutive days. All three treatment regimens produced significantly more sputum than no-treatment but there was no significant difference in sputum production between the three treatments (31).

In a cross-over study, the effects of PEP plus FET, PD combined with deep breathing plus FET and physical exercise plus FET on sputum clearance were investigated in 9 patients with CF. All three treatments were performed three times for three minutes with a three minute pause in between. During each pause FET was performed. There was no statistically significant difference in sputum clearance between the three regimes (37). 18 patients with cystic fibrosis participated in a study evaluating PEP as an adjunct to chest physiotherapy, i.e. cycle of breathing technique (four deep inspirations with passive exhalation, breathing control, FET and coughing) in gravity assisted positions. Each regimen was used for 24 hours and the treatment regimen was performed four times a day and continued until the expectoration of sputum ceased. The quantity of sputum produced during chest physiotherapy was significantly higher than during PEP. PEP in the gravity assisted position produced more sputum than PEP in the sitting position (35).

Long-term effects of PEP and PD plus percussion were examined in 40 patients with CF. Treatment was performed during 20 minutes twice a
day for one year. The PEP group significantly improved FVC and FEV₁. In the PD plus percussion group pulmonary function declined (38).

The effect of no-PEP, low-PEP and high-PEP was investigated in 5 patients with CF. The results showed that both low-PEP and high-PEP improved gas mixing within the lung and that the improvements were associated with increased lung function, sputum expectoration and SpO₂ (32). The short-term effects of PEP, CPAP, non-invasive positive pressure ventilation (NPPV) and directed cough (control measurements) on sputum clearance were investigated in patients with CF and severe airway obstruction admitted to hospital for treatment of pulmonary exacerbation. There was no significant difference in sputum clearance between the different treatments (41).

In a Chochrane review from 2006, “Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis”, the authors concluded that PEP is as effective as other forms of physiotherapy, that there is some evidence that PEP is preferred over other treatments by patients with CF, but that more research is needed (61).

1.2.2.2 Postoperative care

1980s

PEP and CPAP was compared to a control group (that performed IS) in 43 patients undergoing upper abdominal surgery. In all three groups, patients performed 30 consecutive breaths with the assigned breathing device every waking hour for three days postoperatively. The CPAP level was 10-15 cm H₂O and the peak PEP level was also 10-15 cm H₂O. The authors concluded that PEP and CPAP are superior to IS in regard to gas exchange, reducing the development of atelectasis and preserving lung volumes in patients after upper abdominal surgery and that the PEP-mask is as effective as the CPAP system (52).

Self-administered PEP (S-PEP) plus conventional physiotherapy, i.e. early mobilization, diaphragmatic breathing, deep breathing and coughing exercises, was compared to conventional physiotherapy alone in 75 patients undergoing thoracotomy. The median pressure was 10 cm H₂O and the patients were instructed to use the PEP-mask for 10 minutes at least every hour when awake. The authors concluded that S-PEP did not provide any extra benefit in preventing hypoxaemia or atelectasis when compared to conventional physical therapy but when compared to no treatment S-PEP may be as effective as conventional physical therapy (49).
Introduction

1990s
The effects of conventional chest physiotherapy, chest physiotherapy plus PEP and chest physiotherapy plus respiratory muscle training (RMT) on postoperative pulmonary complications were investigated in 51 high-risk patients undergoing upper abdominal surgery. In the PEP group, patients performed 5-10 breaths with a PEP level of 5-15 cm H₂O followed by forced expirations. This cycle was repeated until expectoration ceased. In the RMT group, who performed the same breathing cycle as the PEP group, the expiratory pressure was 5-7 cm H₂O. The inspiratory pressure level was not reported. The RMT group had significantly less reduction in FVC, arterial oxygen tension and arterial saturation (12).

Three different mask regimens, CPAP, PEP and inspiratory resistance-positive expiratory pressure (IR-PEP) was investigated in 160 patients undergoing elective thoracotomy. Patients used the assigned treatment in the sitting position 5 minutes per hour during waking hours. The CPAP level was 15 cm H₂O and the PEP level was 10-15 cm H₂O. During IR-PEP the inspiratory pressure level was −20 cm H₂O. A 4.5 mm resistor was mounted on the expiratory side of the one-way valve. The expiratory pressure level was not reported. There was no statistical difference in postoperative pulmonary complications between the three mask regimens (50).

In a study with similar set up, the effect of routine chest physiotherapy, PEP and IR-PEP on postoperative pulmonary complications were compared in 66 low-risk male patients undergoing coronary artery bypass surgery. There was no statistical difference between the three groups (51).

Prophylactic chest physiotherapy was investigated in 368 patients undergoing elective open abdominal surgery. Patients were randomized to a control group or to a treatment group. Every hour during the day, the treatment group performed 30 deep breaths with huffing and coughing between every tenth breaths. Low-risk patients performed PLB and high-risk patients performed IR-PEP. Inspiratory pressure was −5 cm H₂O and expiratory pressure was +10 cm H₂O. Postoperative complications were diagnosed in 6% of the treatment group and in 27% of the control group (significant difference). Pneumonia was diagnosed in one patient in the treatment group and in 13 patients in the control group (significant difference). The patients in the treatment group had significantly higher oxygen saturation and they were mobilized significantly earlier (13).

2000
IR-PEP was compared with CPAP in 70 patients undergoing thoracoabdominal esophagus resection. During IR-PEP patients performed three sessions of 10 deep breaths with huffing and coughing between every 10 breaths, with an inspiratory pressure of −5 cm H₂O and
expiratory pressure of +10 cm H2O. The treatment session was performed every 2 hours. CPAP was performed for 30 minutes every 2 hours with a CPAP level of 5-10 cm H2O. There were significantly less re-intubations in the CPAP group (48).

1.2.2.3 Chronic bronchitis and COPD

1980s
The effect of PEP versus FET (PD + FET) on tracheobronchial clearance was compared in 8 patients with chronic bronchitis. PEP was performed in the sitting position. The patients breathed for two minutes with a PEP level of 10-15 cm H2O. They then performed a few cycles of abdominal breathing and ended the session with a few huffs. The whole procedure was repeated 5 times, which took about 20 minutes. The duration of the FET session was about 30 minutes. Control measurements were also performed. During control measurements patients had no physiotherapy but coughed spontaneously. Both PEP and FET produced significantly more sputum than control measurement but FET produced significantly more sputum than PEP (57).

1990s
The long-term prophylactic use of diaphragmatic breathing plus forced expirations and cough (control) was compared to diaphragmatic breathing during PEP plus forced expirations and cough in 43 patients with chronic bronchitis. Treatment was performed twice a day. During PEP, the patients breathed 10-15 breaths with a PEP level of 12-20 cm H2O. The treatment sequence was repeated until expectoration stopped. The authors concluded that treatment with PEP can reduce mortality and preserve lung function from a more rapid decline in patients with chronic bronchitis (54).

The effect of PEP, FET plus PD and control measurements (spontaneous coughing) on regional lung clearance was compared in 7 patients with chronic bronchitis. PEP was performed in the sitting position. The patients breathed for two minutes with a PEP level of 10-15 cm H2O. They then performed a few cycles of abdominal breathing and ended the session with a two huffs and coughing. The whole procedure was repeated 5 times, which took about 20 minutes. The duration of the FET plus PD session was about 30 minutes. There was a significant larger clearance in the inner region of the lung after FET plus PD compared with both PEP and control measurements (56).

Short term effects of FET combined with either PD or PEP on mucus clearance was investigated in 14 patients with chronic bronchitis. PEP was performed in the sitting position with a PEP level of 12-20 cm H2O. One minute of PEP breathing was followed by FET and a short period of relaxation and breathing control. PEP was used 10 times during a
treatment session and the number of forced expirations was the same in both treatment groups. Mucus clearance was significantly higher for FET plus PD compared to FET plus PEP in both the peripheral region of the lung and in the total lung field (55).

2000
PEP plus assisted coughing was compared with assisted coughing alone (control group) in 27 patients with acute exacerbation of COPD receiving non-invasive positive pressure ventilation (NIPPV). PEP was performed three times per day during the first three days after NIPPV was started. The patients performed tidal breathing for two minutes with a PEP level of 10-15 cm H2O followed by assisted coughing and two minutes of undisturbed breathing. The cycle was repeated 5-7 times (30-40 minutes). The PEP group produced significantly more sputum and the total time for weaning was significantly shorter in the PEP group compared to the control group (53).

1.2.2.4 Chronic bronchial sepsis
The effect of PD and PEP was compared in 12 patients with chronic bronchial sepsis. PEP was performed in the sitting position. The patients were instructed to perform 5-6 deep breaths using an active but not forced expiration with a PEP level of 10-15 cm H2O followed by FET. Six patients showed no significant difference in sputum production between the two techniques, four patients produced more secretions with PD and two patients produced more secretion with PEP (58).

1.2.2.5 Pulmonary infection
In 8 children with HIV and recurrent pulmonary infections, the effect of daily use of PEP during a 12 month period was evaluated. PEP treatment was performed twice a day for 15 minutes followed by huffing. The mean number of pulmonary infections, mean number of treatments with antibiotics and the mean number of days with antibiotics decreased significantly compared to the previous year when no PEP treatment was performed (59).

1.2.2.6 Children with multiple severe disabilities
17 children with multiple severe disabilities and one child with undefined muscle disease participated in this study. On one occasion, the children breathed with PEP for two minutes repeated three times with a five minute pause between every two minute session. The PEP level was 10-15 cm H2O and cough support was administered if needed. Transcutaneous partial pressure of oxygen (tcPO2), tcPCO2, and respiratory rate were measured before and after PEP treatment. Mean tcPO2 increased significantly (60).
1.2.2.7 The effect of PEP on FRC

PEP was examined in 12 patients with cystic fibrosis using a nitrogen washout method. During PEP treatment the patients used diaphragmatic breathing with slightly active expiration. The PEP level was 10-20 cm H₂O and the patients should be able to breathe for two minutes with a steady PEP without exertion. The treatment period was 15 minutes and every two minutes the treatment was shortly interrupted and the patients were encouraged to expectorate as much mucus as possible using FET or coughing. FRC increased significantly while washout volume, lung clear index and volume of trapped gas decreased significantly (34).

The effect of deep breathing, PEP and IR-PEP on breathing pattern (FRC) was investigated in 21 obese and 21 non-obese subjects using a body plethysmograph. PEP was performed in the sitting position with a PEP level of approximately 15 cm H₂O. During all three breathing techniques the participants were instructed to take deeper breaths than normal at a comfortable rhythm. Three sessions of 10 breaths were used. FRC was significantly lower during deep breathing than during PEP and IR-PEP (62).

In a study with similar set up, the effect of deep breathing, PEP and IR-PEP on breathing pattern (FRC) was investigated in 20 persons with tetraplegia and 20 matched able-bodied controls using a body plethysmograph. PEP was performed in the sitting position with a PEP level of approximately 10 cm H₂O. During all three breathing techniques the participants were instructed to take deep breaths at a comfortable rhythm. Three sessions of 10 breaths with a three minutes pause between every 10 breaths were used. Both PEP and IR-PEP increased FRC in the tetraplegia group (63).

1.2.3 Comparison of the PEP-bottle and IR-PEP in postoperative patients

Deep breathing, bottle blowing (PEP) and IR-PEP was compared in 98 men after coronary artery bypass graft surgery. The blow bottle (PEP-bottle) consisted of a bottle with 10 cm of water and a plastic tube, 40 cm long with an inner diameter of 1 cm. With IR-PEP inspiratory pressure was -5 cm H₂O and expiratory pressure was +10 cm H₂O. All groups were instructed to perform 30 deep breaths, three sets of 10 breaths with coughing and huffing between every set, once per hour during the day. The breathing exercises were performed in the sitting position if possible. There were no significant differences between the three groups on the 4th postoperative day except for a significantly less reduction in total lung capacity for the blow bottle group compared to the deep breathing group (21).
The immediate effect of deep breathing, bottle blowing (PEP) and IR-PEP on atelectasis and oxygenation was compared in 61 patients undergoing cardiac surgery. All three therapies were performed in the sitting position with three sets of 10 breaths with a 30-60 seconds pause between every set. The amount of water in the PEP-bottle was 10 cm. With IR-PEP inspiratory pressure was -5 cm H$_2$O and expiratory pressure was +15 cm H$_2$O. All three groups were instructed to perform a slow maximal inspiration followed by an expiration ending approximately at FRC. All three therapies significantly reduced the atelectatic area but there was no statistically significant difference between the different treatments (23).

1.3 CPAP history
The term continuous positive airway pressure (CPAP) was first used in 1971 when Gregory et al (64) described using CPAP in the treatment of idiopathic respiratory distress syndrome in 20 infants. The CPAP system had an orifice resistor and was connected to the infants through an endotracheal tube or a plastic pressure chamber which enclosed the infants head. A CPAP level up to 12 mm Hg (approximately 16 cm H$_2$O) was used. Arterial oxygen tension rose in all infants and sixteen of the infants survived.

Spontaneous breathing with CPAP was investigated in 43 infants after open intracardiac operations. The CPAP system had an orifice resistor and was connected to the infants through an endotracheal tube. The CPAP system was considered easy to use and only one of the infants was re-intubated after planned extubation (65).

In 1972 Civetta el al (66) described the use of CPAP in two adult patients with respiratory failure. The CPAP system had a 5 liter reservoir bag to ensure sufficient airflow to the patient and a water seal resistor to create the CPAP level. The patients were connected to the CPAP through a nasotracheal tube. The authors concluded that compared to using a ventilator, spontaneous breathing with CPAP produced lower peak airway pressure with the same oxygenation.

In 1975 Garg et al (67) investigated the use of CPAP for reducing intrapulmonary shunting in adults with acute respiratory failure. This CPAP system also had a 5 liter reservoir bag and a water seal resistor to create the CPAP level. The patients were connected to the CPAP through a tracheal tube or a tracheostomy. All patients significantly improved the alveolar-arterial oxygen tension difference (A-aDO$_2$) with CPAP. The authors used guidelines and objective criteria for CPAP therapy.

In 1977 Kittredge, a former editor of Respiratory Care wrote that using CPAP via face mask “is a dangerous step backward”. He argued that using CPAP via face mask could delay the use of more appropriate
ventilatory support and “if a patient is sick enough to need CPAP the patient is sick enough to need a tracheal tube” (68). This was the prevailing opinion of many practitioners at that time (69).

Treatment with CPAP has evolved since the early 1970s and is today used for treating a wide range of different pulmonary conditions (70). Since the beginning of the 1970s CPAP has been evaluated numerous times. A search in PubMed on the 1st of August 2014 using “continuous positive pressure OR CPAP” returned 9144 hits. CPAP increases FRC (71-73), reduces atelectasis (74), improve oxygenation (71, 74) and decreases work of breathing (WOB) (75, 76), and is inter alia, used for treating preterm neonates (77-79), patients with obstructive sleep apnea (80-82) and patients with cardiogenic pulmonary edema (83-85). CPAP is also used for treating patients with acute respiratory failure (86, 87), patients in postoperative care (48, 88, 89) and patients during weaning (90, 91). During the two last decades the use of non-invasive ventilation (NIV) has increased. The term NIV is sometimes used also for CPAP, but there is no consensus whether CPAP should be regarded as NIV (69).

1.3.1 The Boussignac CPAP

The Boussignac CPAP is a simple, lightweight, disposable, flow resistor CPAP device (92, 93). The Boussignac CPAP has been used in patients with acute cardiogenic pulmonary edema (92, 94-97) and in postoperative care of obese patients (98, 99). This CPAP device has also been used in the intensive care unit (ICU) in patients with a tracheostomy tube during weaning (93) and as a mean to deliver CPAP in hypoxic patients during fiberoptic bronchoscopy (100). Although the Boussignac CPAP is considered easy to use (98, 101, 102), it has been shown that with increasing CPAP levels in combination with increasing flow rates, both the drop in inspiratory pressure and the increase in expiratory pressure is enhanced (102). This indicates that the performance of the Boussignac CPAP might not be sufficient in patients with more severe respiratory distress.

1.4 Comparing the effect of PEP and CPAP on FRC

Both PEP and CPAP can be used to increase functional residual capacity (FRC) (34, 63, 73, 103, 104). When the effect of PEP and CPAP on FRC is compared the results differ. The increase in FRC was significantly higher with CPAP compared to EPAP in a study on spontaneously breathing, critically ill patients with acute respiratory failure (105). In a study on lightly anesthetized, spontaneously breathing intubated mongrel dogs, the results showed that as the pressure level increased, FRC increased progressively, but there was no significant difference between EPAP and CPAP (106). There was no significant difference in FRC when PEP
(blowing bottles) were compared to CPAP in patients undergoing abdominal surgery (18).

1.5 Inspiratory capacity (IC) measurements

It is difficult to measure immediate changes in FRC in spontaneously breathing patients in the clinical setting. FRC and IC comprise the total lung capacity (TLC) and as long as TLC is constant, a change in IC will correspond to an inverse change in FRC (107). Inspiratory capacity (IC) has been used to measure changes in hyperinflation in patients with COPD (108, 109) and measurements of changes in IC could, theoretically, be used in other groups of patients as an indirect measure of changes in FRC.

1.6 CPAP in fixed-wing air ambulances

Transporting intensive care patients from one hospital ICU to another hospital with more specialized treatment capability has become more common and are utilized on a daily bases (110). One difference between the ground environment and the environment in an air ambulance during flight is the ambient pressure level. Many patients transported by pressurized fixed-wing air ambulances are exposed to hypobaric conditions since cabin pressures at cruising altitudes normally corresponds to altitudes between 1800 m and 3000 m (111). Patients with impaired oxygenation being transported by air ambulances may benefit from positive airway pressure treatment in flight (112, 113). Fromm et al (114) demonstrated that due to differences in mechanical design in CPAP machines used for sleep apnea; the CPAP machines were affected differently when altitude increased, i.e. ambient air pressure decreased. Mask CPAP in air ambulance settings is often based on rapid application of disposable CPAP devices. Since design and mechanical principles differ between different disposable CPAP devices, these differences may, in theory, affect how CPAP devices perform at different ambient air pressures that will occur in an air ambulance during flight.

1.7 Rationale

The PEP-bottle is by tradition the first choice of a PEP device at the University Hospital of Umeå. In the clinical practice in the ICU, some patients are unable to take more than a couple of consecutive breaths when using the PEP-bottle before they get out of breath and needs to rest. Reducing the amount of water in the bottle, i.e. the PEP level does not improve these patients ability to breathe with the PEP-bottle. If the PEP-bottle is replaced with a PEP-mask, these patients are able to take 10-15 consecutive breaths with a PEP-level of 10 cm H$_2$O without getting out of breath. The PEP-bottle and the PEP-mask have different resistors and we
wanted to compare airflow and airway pressure during breathing with these two breathing devices.

The Boussignac CPAP is a new kind of CPAP device that is considered easy to use. Because of its simplicity, our postoperative ward wanted to use this CPAP device in patients needing CPAP postoperatively. In order to minimize WOB, a CPAP device should be able to maintain both inspiratory and expiratory pressure levels close to preset CPAP level. To our knowledge, only one study had previously investigated the performance of the Boussignac CPAP (102). Their results suggested that the performance of the CPAP device might be hampered during increased breathing efforts, which merited further investigation of the performance of this CPAP.

There are few studies comparing effects of PEP and CPAP on FRC. This may be because FRC is difficult to measure in the clinical setting and requires advanced equipment, e.g. body plethysmograph. IC can be used for measuring changes in lung hyperinflation in patients with COPD. In this thesis, we wanted to investigate if PEP and CPAP induced changes in IC could be used as an indirect measure of changes in FRC. Secondly, we wanted to estimate the magnitude of immediate effects of PEP and CPAP devices, with different kinds of resistors, on IC.

Intensive care patients might need CPAP when being transported by air ambulance. Fixed-wing air ambulances often cruise with a pressure level inside the cabin corresponding to an altitude between 1800 m and 3000 m. There are to our knowledge no studies examining the effect of altitude on different disposable CPAP devices with different kinds of resistors.

The observation that some patients get out of breath when using the PEP-bottle, together with the knowledge that a CPAP device should keep airway pressure close to preset CPAP level to minimize WOB made us wonder how exerting breathing with different resistance breathing devices are perceived.
Aims of the thesis

The overall aim of this thesis was to, from an intensive care physiotherapy perspective, gain a wider understanding on how different forms of resistance breathing and different forms of resistors physiologically effects breathing and how strenuous different forms of resistance breathing is perceived.

Specific aims:

- To, in healthy volunteers, elucidate and compare the relationship between airway pressure and airflow when breathing with a threshold resistor PEP device (PEP-bottle) and a flow resistor PEP device (PEP-mask).

- To, in healthy volunteers, evaluate the stability of a flow resistor CPAP device (Boussignac CPAP) in terms of maintaining adequate inspiratory and expiratory pressure levels during the entire breathing cycle.

- To, in healthy volunteers, investigate and compare how breathing with two PEP devices, one threshold resistor device and one flow resistor device, and two CPAP devices, one threshold resistor device and one flow resistor device affects inspiratory capacity as an indirect measure of functional residual capacity.

- To, in a bench study, elucidate and compare the effect of changes in ambient air pressures on preset CPAP levels and CPAP produced airflow in two different kinds of CPAP devices, a threshold resistor CPAP device and a flow resistor CPAP device.

- To evaluate and compare the participants perceived exertion when breathing with the different breathing devices.
2 Methods

2.1 Study design

The four papers in this thesis are based on four separate studies. Paper I is a randomized crossover study examining two PEP devices, the PEP-bottle (threshold resistor) and the PEP-mask (flow resistor). Paper II is a randomized study evaluating the performance of a flow resistor CPAP, the Boussignac CPAP. Paper III is a randomized crossover study investigating the effect of four different breathing devices, two PEP-devices, a PEP-bottle and a PEP-mask and two CPAP devices, a threshold resistor CPAP and a flow resistor CPAP, on IC. Paper IV is a bench study performed in a hypobaric chamber. This study evaluates the effect of changes in ambient pressure on preset CPAP levels in two different CPAP devices, a threshold resistor device and a flow resistor device. Outcome measures are presented in table 1. Investigated breathing devices and equipment used during measurements are presented in table 2.

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
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<tbody>
<tr>
<td>Breathing</td>
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<tr>
<td>Airway pressure (cm H₂O)</td>
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<td>Air flow (L/s)</td>
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<td>Time (s)</td>
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<tr>
<td>Inspiratory capacity (L)</td>
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<tr>
<td>Respiratory rate (breaths/min)</td>
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<td>SpO₂ (%)</td>
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<tr>
<td>Heart rate (beats/min)</td>
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</table>

|                  |          |          | ●         |          |
| Static pressure (cm H₂O)                 |         |          |           | ●        |
| Static airflow (L/s)                     |         |          |           | ●        |
| Dynamic pressure (cm H₂O)                |         |          |           | ●        |

Estimated perceived exertion

Borg CR10

SpO₂ = Oxygen saturation, Borg CR10 = Borg Category Ratio Scale
Table 2. Investigated devices and equipment used during measurements.

<table>
<thead>
<tr>
<th>Breathing devices</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
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<tr>
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<td>PEP-mask - (flow resistor PEP)</td>
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<table>
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<th>Equipment</th>
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<td></td>
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</tr>
<tr>
<td>Ventilator</td>
<td>Oxylog</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vent aid Training test lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Methods

2.1.1 Participants
Three separate groups of healthy volunteers participated in paper I-III, one group of volunteers in each study. All participants were non-smokers and they could not have an ongoing cold. To ensure that all participants had normal lung function, vital capacity (VC) and forced expiratory volume in one second (FEV₁) were measured. Characteristics of the participants are presented in table 3.

Table 3. Characteristics of participants.

<table>
<thead>
<tr>
<th></th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>n=20</td>
<td>n=18</td>
<td>n=20</td>
</tr>
<tr>
<td>Women/Men</td>
<td>13/7</td>
<td>13/5</td>
<td>14/6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37±9</td>
<td>44±8</td>
<td>44±11</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>171±9</td>
<td>171±8</td>
<td>171±9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75±18</td>
<td>77±12</td>
<td>75±14</td>
</tr>
<tr>
<td><strong>Pulmonary function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VC (L)</td>
<td>4.33±0.92</td>
<td>4.22±0.97</td>
<td>4.48±0.95</td>
</tr>
<tr>
<td>VC (% of predicted)</td>
<td>105±13</td>
<td>107±11</td>
<td>119±16</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>3.57±0.76</td>
<td>3.40±0.72</td>
<td>3.44±0.75</td>
</tr>
<tr>
<td>FEV₁ (% of predicted)</td>
<td>104±14</td>
<td>106±11</td>
<td>109±12</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. VC = vital capacity, FEV₁ = forced expiratory volume in one second.

2.1.2 Ethics
All participants in paper I-III received both oral and written information and written consent was obtained from all participants (paper I-III). Paper I was approved by the Research Ethics Committee of the medical faculty of Umeå University, Sweden (Um dnr 01-281). Paper II (Dnr 06-095M) and Paper III (Dnr 2012-251-31M) was approved by the Regional Ethical Review Board in Umeå, Sweden. No ethical approval was necessary for the bench study (paper IV).

2.1.3 Breathing devices

2.1.3.1 PEP devices
The PEP-bottle (paper I and III) is a threshold resistor device. It consists of a bottle filled with water and a tube with an inner diameter of at least 8 mm (115). The height of the water in the bottle determines the PEP level. The expiration is done through the tube into the water and an airway pressure higher than the water seal is acquired before airflow begins.
Methods

The PEP-mask (Wellspect Healthcare, Möndal, Sweden) (paper I and III) is a flow resistor device. It consists of a face mask or a mouthpiece, a t-valve that separates inspiratory and expiratory airflow and 8 different orificial resistors with inner diameters ranging from 1.5 – 6.0 mm. The speed of the expiratory airflow together with the inner diameter of the orificial resistor determines the PEP level. With a flow resistor device there is no threshold level to overcome before airflow occurs.

2.1.3.4 CPAP devices

The two CPAP devices used in this thesis are considered to be simple, disposable, single-patient systems.

The threshold resistor CPAP device (O2-RESQ™ System, IM-Medico, Saltsjö-Boo, Sweden) (paper III and IV) consists of a face mask, a preset spring-loaded valve, an anti-asphyxia circuit and a fixed flow generator. The spring loaded valve can be adjusted to deliver three different CPAP levels, 5, 7.5 and 10 cm H2O. The fixed flow generator, which is a venturi device, is connected to a gas source. The generator uses the gas supply from the gas source in combination with entrained air to generate output flow to the patient.

The flow resistor CPAP device (Boussignac CPAP, Vygon, Skellefteå, Sweden) (paper II-IV) consists of a face mask and a 5.5 cm long plastic tube. The plastic tube, which is open to the atmosphere, has four micro channels in the wall. The CPAP level is produced by injecting air or oxygen through the micro channels. As gas flow accelerates through the micro channels a virtual valve is created on the patient side of the plastic tube. The velocity of gas flow through the micro channels determines the size of the virtual valve and thereby the CPAP level, making this CPAP device flow dependent.

2.1.3.5 Connecting CPAP devices to a gas source

The supply gas pressure was 4.5 bar in paper II and III and 3.5 bar in paper IV. 4.5 bar is the standard supply pressure level in Swedish hospitals and 3.5 bar is used as supply pressure level in fixed wing air ambulances in Sweden. The 3.5 bar pressure regulator used in paper IV was placed both outside and inside the hypobaric chamber (see below).

In paper II-IV the flow resistor CPAP device was connected to a gas source through a rotameter. Airflow from the rotameter was titrated to the desired CPAP level using a manometer. In paper IV, the flow resistor CPAP device was also connected to a gas source through four different flow selectors. Since these flow selectors deliver airflow at fixed flow levels, airflow cannot be titrated to a desired CPAP level when connected to the flow resistor CPAP device. Except for flow selector n (see table 2),
the highest possible flow produced by each flow selector was selected. With flow selector n, the flow closest to the flow delivered by the other flow selectors was chosen. The delivered gas flow was 25 L/min (flow selector m), 26 L/min (flow selector n), 25 L/min (flow selector o) and 15 L/min (flow selector p).

The threshold resistor CPAP was connected to a gas source through a rotameter (paper III) and through a Quick-Connect™ included in the threshold resistor CPAP device package (paper IV).

2.1.3.6 Expiratory pressure levels during PEP and CPAP
The PEP level used in paper I and III was 10 cm H₂O. The PEP-bottle was filled with water and a tube with an inner diameter of 1 cm (paper I) and 1.1 cm (paper III) was submerged 10 cm below the water surface. The length of the tube was 42 cm in paper I and 21.1 cm in paper III. With the PEP-mask, the orifice resistor resulting in a PEP level of approximately 10 cm H₂O was used (paper I and III). The pressure level was measured with a manometer.

In paper II preset CPAP levels were 0 cm H₂O (control breathing), 5, 7.5 and 10 cm H₂O. In paper III the preset CPAP level was 10 cm H₂O. In paper IV preset CPAP levels were 5 and 10 cm H₂O when a rotameter or a Quick-Connect™ was used to produce CPAP levels. When each of the four flow selectors was used, the pressure level could not be determined but was a result of the airflow produced by the respective flow selector.

2.1.4 Hypobaric chamber
In paper IV, measurements were done in a hypobaric chamber (SAAB, Linköping) at four different altitudes; ground level (52 m above sea level) and three different simulated altitudes (2 400 m (8 kft), 3 000 m (10 kft) and 10 700 m (35 kft)). During the first measurement the time frame at each altitude was 10 minutes but an analysis of the first recording showed that the altitude effect on the recording stabilized within one minute. The time frame at each altitude was therefore decreased to 3 minutes for all subsequent measurements.

2.2 Measurements and test procedures.
Test procedures for paper I-IV are presented in figure 1.

2.2.1 Test positions.
The participants’ position during the measurements was standardized (paper I-III). The participants sat on an adjustable chair in front of a table (in paper II and III the table was adjustable). They sat with 90 degree
Methods

flexion in their knees and hips with the feet firmly placed on the floor (paper I-III) or if needed on a foot stool (paper I). In paper I and III, the participants had their elbows on the table. Fingers were placed on the mouthpiece or the mask (paper I) and they held the mask to the face using their hands in paper III. In paper II, the participants had their elbows on the chair armrests and hands on the armrest or in the lap except during the first measurement period (0 cm H₂O) where the hands were placed on the mask.

In paper I-III, all participants practiced breathing with the breathing devices included in the respective study and they practiced how to perform the IC maneuvers (paper III). They were also instructed in how to use the Borg Category Ratio scale (CR10) (116).

2.2.2 Breathing instructions

2.2.2.1 PEP breathing

When breathing with the two PEP devices, the participants were instructed to take a deep breath, to exhale slightly actively and to try finding a comfortable rhythm (paper I and III). In paper I the participants were instructed to breath in and out through the mouth since the measurements on the PEP-bottle were done with a mouthpiece and a nose-clip.
2.2.2.2 CPAP breathing
With the CPAP devices, the participants were asked to breathe normally, i.e. to think as little as possible about how they were breathing (paper II and III). During the forced breaths (paper II) the participants were instructed to breathe as if running. In paper IV, a ventilator connected to a lung model (see table 2) was used to simulate CPAP breathing. Simulated breathing was performed with a preset tidal volume of 700 ml and a ventilator frequency of 12 breaths per minute.

2.2.3 Static produced CPAP pressure and airflow levels.
In paper IV, static pressure and static airflow, i.e. the pressure and airflow generated by the CPAP device, were measured.

2.2.4 IC measurements
For the IC measurements, (paper III), the participants were instructed to hold a face mask firmly against their face. They were asked to take three normal, quiet breaths and then, without hesitation, breathe in as much as they possibly could, to breathe out as a sigh followed by four normal, quiet breaths (117).

2.2.5 Randomization
The order the participants breathed with the different breathing devices was randomized (paper I and III). In paper II, the participants started by breathing one minute through the CPAP device with the CPAP turned off (control breathing – 0 cm H₂O). After the control breathing, a randomization procedure determined which CPAP level the participants started breathing with.

2.2.6 Measurements
In paper I the participants breathed three sessions of 10 breaths with the PEP-bottle or the PEP-mask. To avoid carryover effects, the participants waited 15 minutes before breathing with the second PEP device.
In paper II, the participants breathed with CPAP for 10 minutes and after 10 minutes of normal breathing with CPAP, while still on CPAP, they took 10 big forced breaths to simulate respiratory distress. To avoid carryover effects, the participants waited 15 minutes before breathing at the next CPAP level.
In paper III, the participants performed the initial IC maneuver. The participants then performed 30 breaths with one of the four breathing devices (PEP-bottle, PEP-mask, threshold resistor CPAP or flow resistor CPAP). As breath 31, the participants, while still connected to the
Methods

breathing device, performed the second IC maneuver. To avoid carryover effects the participants waited 10 minutes before breathing with each of the four breathing devices.

In paper IV static measurements and simulated breathing were performed. Static measurements were divided into three categories, a) static pressure, b) static airflow and c) static pressure and airflow using four different flow selectors. Pressure and airflow were also measured during simulated breathing (figure 2). During the static measurements (category a and b) two threshold resistor CPAP devices and two flow resistor CPAP devices were tested simultaneously. Concerning static measurements with four different flow selectors (category c), each flow selector was connected to one flow resistor CPAP and tested simultaneously. During simulated breathing, one threshold resistor CPAP device or one flow resistor CPAP device was tested separately. During the static measurements, pressure and airflow measurements were done separately but during simulated breathing measurements, pressure and airflow were tested in parallel.

Figure 2. Experimental protocol. During static measurements, two threshold resistor CPAP devices and two flow resistor CPAP devices were tested simultaneously. For the 10 cm H2O static measurement with the 3.5 bar regulator inside the hypobaric chamber, eight additional CPAP devices, four threshold resistor CPAP devices and four flow resistor CPAP devices were tested. During the simulated breathing measurements, one threshold resistor CPAP device and one flow resistor CPAP device were tested separately. During the test of the four different flow selectors, each flow selector was connected to one flow resistor CPAP device and tested simultaneously.

2.2.7 Perceived exertion

In paper I-III, the participants estimated their perceived exertion using the Borg CR10 scale (116). In paper I, the participants scored their perceived exertion after the third session with each breathing device. In paper II, the scoring of perceived exertion was done by the participants after 10 minutes of normal breathing at each CPAP level, just before the forced breaths. In paper III, the participants estimated their perceived
exertion directly after the second IC maneuver with each breathing device. However, they were instructed to score the 30 breaths prior to the second IC maneuver and not the IC maneuver itself.

2.3 Data collection

2.3.1 Airway pressure, pressure and airflow
In paper I-III the PEP or CPAP devices were connected to a flow transducer (SS11LA, Biopac Systems, Goleta, California) and a pressure transducer (PMST 1 TNF-R, Beckton Dickinson, Singapore). In paper IV the CPAP devices were connected to a flow sensor (Novametrix medical systems Inc., Wallingford, Connecticut) and a pressure sensor (Freescale semiconductor, Inc., Austin, Texas). The configuration of the pressure sensor differed between pressure and airflow measurements. In all four papers, airway pressure (paper I-III) or pressure (paper IV) and airflow were recorded continuously at 200 Hz using a MP30 system (Biopac Student Lab Pro version 3.0.3 (paper I), 3.7.1 (paper II), 3.7.7 (paper III and IV), Biopac Systems, Goleta, California).

2.3.2 Pulse oximetry (SpO₂), heart rate and end-tidal CO₂
In paper I, pulse oximetry (SpO₂) was measured with a pulse oximeter (Omeda Biox 3740, Ohmeda, Louisville, Kentucky) connected to the MP30 system. In paper II, measurements of SpO₂, heart rate (pulse oximeter) and end-tidal CO₂ were recorded continuously at 0.5 Hz with custom made data acquisition software (MRDView 2.4.2.6).

2.3.3 Calibration
Before the measurements, pressure and airflow transducers/sensors were calibrated using a two-point calibration procedure. The pressure transducer (paper I-III) or the pressure sensor (paper IV) was calibrated at 0 and 10 cm H₂O using a water column (paper I and II) and a manometer (paper III and IV). The pressure transducer was tested during a longer period of time, to evaluate offset drift and sensitivity drift. The sensitivity drift was small compared to the offset drift and the offset drift was therefore compensated for before each test series (paper I and II). In paper I and II, the airflow transducer was calibrated at 0 and 0.6 L using a 0.6 L calibration syringe. The airflow transducer (paper III) and the airflow sensor (paper IV) were calibrated at 0 and 1 L with a 1 L calibration syringe. Since the flow transducer and the flow sensor have a slight non-linear property they were further calibrated using a VT plus Gas flow analyzer BIO-TEK® (Biotech Instruments INC., Winooski, Vermont). Airflow was stepwise increased by 0.2 L/s in the interval between 0 and 3 L/s (paper III) and 0 and 3.2 L/s (paper IV). The values from these calibrations were used in the data processing.
2.3.4 Data processing

There was a constant offset in the airflow baseline throughout the registration period (paper I-IV). In paper I and II, airflow baseline was measured during a period with no airflow and the difference between the measured baseline and zero was calculated. The calculated difference, i.e. the offset, was then subtracted from the recorded baseline. Further, any existing drift in the recording was removed.

The pressure baseline was adjusted in a similar manner. During a period of no airflow, mean pressure was measured and any offset in the baseline was subtracted from the recorded signal. In paper II, the recorded airflow and pressure signals were filtered with a numerical finite-impulse-response low-pass filter with a cutoff frequency of 10 Hz, implemented with a Hanning window with 39 coefficients to eliminate high-frequency noise.

The analysis of airflow and airway pressure recordings in paper I and II were done manually for each individual breath. In paper I, 60 breaths per participant, (30 breaths from each PEP device), were analyzed. In paper II, 10 breaths of the one minute recording at 0 cm H2O were analyzed for each participant. For the 10 min recordings, 30 breaths per participant were analyzed (10 at the beginning, 10 in the middle and 10 breaths at the end of a recording period). Of the ten forced breaths, the first 9 breaths were analyzed. Since the participants were instructed to end the 10th breath by holding their breath, the 10th breath was much longer than the other 9 breaths. The 10th breath was therefore not analyzed. The shift between inspiration and expiration was defined as the point where the airflow signal passed zero L/s, i.e. the airflow signal changed from a positive (inspiration) to a negative (expiration) value, or vice versa. For the SpO2, heart rate and end-tidal CO2 measurements, the last five sampled values from each of the one minute, 10 minute and forced breathing period were analyzed. In paper II, inspiratory and expiratory volumes were obtained by integrating the airflow signal.

In paper III and IV, pressure and airflow recordings were analyzed in Matlab (2013b – paper III, R2007b – paper IV) Mathworks, Inc., Natick, MA). Baseline pressure and airflow levels were measured during a period with no airflow. The difference between the measured baseline and zero, i.e. the offset, was subtracted from the recorded baseline before subsequent analyses were performed. The recalculated airflow signal was interpolated with a cubic spline algorithm using data from the calibration of non-linear effects described above.

In paper III, volumes were obtained through integration of the airflow signal and any drift in the resulting volumes were removed (detrend function). Airflow, pressure and volume were filtered using a 4th order Butterworth 10 Hz low pass filter. Local maximum and minimum volume values were identified (findpeaks) and inspiratory and expiratory volumes were calculated. For every breath, inspiratory and expiratory
median pressure and inspiratory and expiratory time were calculated and exported together with inspiratory and expiratory volumes to Excel. Pressure, airflow and volume (original data after adjustment for offset and drift, as described above) were down sampled to 10 Hz and exported to Excel.

In paper IV, the pressure and airflow signals were also down sampled to 10 Hz and exported to Excel. At each ambient air pressure level (ground level and the three different simulated altitudes), data from three different 15-30 seconds periods were analyzed.

2.3.5 IC analysis
A baseline, based on the three breaths preceding the first IC-maneuver, was identified. Similarly, a baseline was defined based on the five breaths preceding the second IC-maneuver. For these selected breaths, end-expiratory volumes within a 99% confidence interval were used to calculate the baseline. Primarily, all baselines were mathematically calculated and assessed by the authors. When in doubt, two blinded independent experts were asked to define the baseline, by “eye-balling”. For analysis, a mean value of their assessment for each of the 27 baselines that were manually determined was used. As previously described, each baseline was used to adjust the corresponding IC values (107).

2.4 Statistics
All statistical analyses were performed with SPSS statistics software (IBM SPSS Statistics 12.0 – paper I, 18.0 – paper II, 22.0 – paper III and IV, IBM, Armonk, New York). A p-value < 0.05 was considered statistically significant. Data are presented as mean ± SD (paper I-IV). In paper IV, data are also presented as estimate ± standard error of estimate and confidence intervals. Descriptive data on perceived exertion (Borg CR10) are reported as median (max-min) (paper I-III).

A paired t-test was used to compare data between the PEP-bottle and the PEP-mask (paper I) and normal breathing and forced breathing for each CPAP level (paper II). Repeated measures analysis of variance was used to compare data between the CPAP levels. If Mauchly test indicated a violation in the assumption of sphericity the Greenhous-Geisser correction was used. Bonferroni correction was used as an adjustment for multiple comparisons (paper II).

Linear mixed effects models were used for statistical analysis in paper III and IV. In paper III, all data except data on perceived exertion (Borg CR10), were tested for normality with Shapiro-Wilk normality test. One parameter, inspiratory time, was not normally distributed and therefore log transformed, after which the parameter was normally distributed. To
compare data between the different breathing devices and to compare
data within breathing devices a linear mixed effects model was used.
Breathing device was used as a repeated variable and as a fixed factor and
repeated covariance type was set to diagonal. To adjust for multiple
comparisons a Bonferroni correction was used. In paper IV, two different
linear effects models were used to compare the threshold resistor CPAP
device and the flow resistor CPAP device. In the first model, CPAP device,
CPAP level and the interaction between CPAP device, 3.5 bar regulator
(being inside or outside the hypobaric chamber) and simulated altitude
(0, 8, 10, 35 kft) were used as fixed factors and simulated altitude was set
as a covariate. A random effect for baseline variations between different
unique CPAP-units was included in the model. The covariance matrix was
set to diagonal with separate estimates for random effects for the two
CPAP types. Noise-level in the static pressure measurements was the
outcome variable in the second model. CPAP type and CPAP level was
used as fixed factors and a random effect for baseline variations between
unique CPAP units was included in the model. The covariance matrix was
set to diagonal with separate estimates for random effects for the two
CPAP types.
3 Results

3.1 Paper I

3.1.1 Expiratory phase.

3.1.1.1 Airway pressure
With the PEP-bottle, the expiratory phase started with a 0.39 ± 0.1 s period during which no detectable airflow occurred (zero-flow period). During this period airway pressure increased 11.9 ± 1.0 cm H₂O. With the PEP-mask, the corresponding period with no airflow was 0.04 ± 0.03 s and the increase in airway pressure was 0.4 ± 0.1 cm H₂O. At the end of the expiratory phase, airway pressure was 9.5 ± 0.3 cm H₂O with the PEP-bottle and almost zero (-0.06 ± 0.06 cm H₂O) with the PEP-mask (table 4).

3.1.1.2 Airflow and breathing pattern
Results for airflow and time/breath are presented in table 4.

Table 4. PEP produced respiratory parameters during the expiratory phase of the breathing cycle.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PEP-bottle</th>
<th>PEP-mask</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expiratory phase</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zero-flow period (s)</td>
<td>0.39 ± 0.1</td>
<td>0.04 ± 0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>*Increase airway pressure (cm H₂O)</td>
<td>11.9 ± 1.0</td>
<td>0.4 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum airway pressure (cm H₂O)</td>
<td>14.9 ± 1.5</td>
<td>12.3 ± 3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean airway pressure (cm H₂O)</td>
<td>11.7 ± 0.8</td>
<td>8.6 ± 2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End-expiratory airway pressure (cm H₂O)</td>
<td>9.5 ± 0.3</td>
<td>-0.06 ± 0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum airflow (L/s)</td>
<td>0.98 ± 0.19</td>
<td>0.36 ± 0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean airflow (L/s)</td>
<td>0.33 ± 0.11</td>
<td>0.29 ± 0.12</td>
<td>0.026</td>
</tr>
<tr>
<td>Time (s)</td>
<td>5.14 ± 1.54</td>
<td>5.80 ± 2.0</td>
<td>0.068</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. *During zero-flow period.

3.1.2 Inspiratory phase.

3.1.2.1 Airway pressure
With the PEP-bottle, the inspiratory phase started with a 0.43 ± 0.14 s period during which no detectable airflow occurred (zero-flow period). From the end-expiratory airway pressure level, airway pressure decreased with 9.6 ± 0.3 cm H₂O during the zero-flow period. With the PEP-mask, the corresponding period with no airflow was 0.01 ± 0.02 s with no change in airway pressure observed (0.0 ± 0.1) (table 5).
3.1.2.2 Breathing pattern
Results for inspiratory time/breath are presented in table 5.

Table 5. PEP produced respiratory parameters during the inspiratory phase of the breathing cycle.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PEP-bottle</th>
<th>PEP-mask</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspiratory phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time inspiratory zero-flow period (s)</td>
<td>0.43 ± 0.14</td>
<td>0.01 ± 0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>*Decrease in airway pressure (cm H\textsubscript{2}O)</td>
<td>9.6 ± 0.3</td>
<td>0.0 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time (s)</td>
<td>2.56 ± 0.83</td>
<td>2.25 ± 0.74</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. *During zero-flow period.

3.2 Paper II
During normal breathing with CPAP, the participants breathed at 20 % of their VC and 14 % of their FEV\textsubscript{1} and during forced breathing with CPAP, they breathed at 38-42 % of VC and 49-56 % of FEV\textsubscript{1}.

3.2.1 Inspiratory phase

3.2.1.1 Airway pressure
The decrease in airway pressure during control breathing (0 cm H\textsubscript{2}O) was smaller than during both normal and forced breathing at all three preset CPAP levels. Forced breathing decreased airway pressure more than normal breathing at each preset CPAP level and during forced breathing airway pressure became negative, i.e. lower than air pressure in the surrounding atmosphere (figure 3, panel A).

3.2.1.2 Airflow and breathing pattern
Results for airflow, volume and time/breath are presented in table 6.

3.2.2. Expiratory phase

3.2.2.1 Airway pressure
The increase in airway pressure during control breathing (0 cm H\textsubscript{2}O) was smaller than for both normal and forced breathing at all three CPAP levels. Airway pressure increased more during forced breathing than during normal breathing at each preset CPAP level (figure 3, panel B).

3.2.2.2 Airflow and breathing pattern
Results for airflow, volume and time/breath are presented in table 6.
### Results

Figure 3 Inspiratory pressure levels (panel A) and expiratory pressure levels (panel B) during normal and forced breathing.

Minimum inspiratory pressure - normal breathing (open diamond), forced breathing (filled diamond), mean inspiratory pressure – normal breathing (open circle), forced breathing (filled circle), maximum expiratory pressure – normal breathing (open square), maximum breathing (filled square), mean expiratory pressure – normal breathing (open triangle), forced breathing (filled triangle).

Data are presented as mean ± SD.

Minimum inspiratory pressure:
- \( P < 0.001 \) control vs normal breathing and forced breathing at all CPAP levels,
- \( p = 0.006 \) normal breathing at CPAP level 5 cm H\(_2\)O vs 7.5 cm H\(_2\)O,
- \( p = 0.006 \) forced breathing at CPAP level 7.5 vs 10 cm H\(_2\)O,
- \( p < 0.001 \) normal breathing vs forced breathing at each CPAP level (panel A).

Mean inspiratory pressure:
- \( P < 0.001 \) control vs normal breathing and forced breathing at all CPAP levels,
- \( p = 0.01 \) normal breathing at CPAP level 5 cm H\(_2\)O vs 7.5 cm H\(_2\)O,
- \( p = 0.02 \) forced breathing at CPAP level 7.5 cm H\(_2\)O vs 10 cm H\(_2\)O,
- \( p < 0.001 \) normal breathing vs forced breathing at each CPAP level (panel A).

Maximum expiratory pressure:
- \( P < 0.001 \) control vs normal breathing and forced breathing at all CPAP levels,
- \( p = 0.026 \) normal breathing at CPAP level 7.5 vs 10 cm H\(_2\)O,
- \( p < 0.001 \) normal breathing vs forced breathing at each CPAP level (panel B).

Mean expiratory pressure:
- \( P < 0.001 \) control vs normal breathing and forced breathing at all CPAP levels,
- \( p < 0.001 \) normal breathing at CPAP level 5 cm H\(_2\)O vs 7.5 cm H\(_2\)O,
- \( p < 0.001 \) normal breathing vs forced breathing at each CPAP level (panel B).
Table 6. CPAP produced respiratory parameters during the inspiratory and expiratory phase of the breathing cycle

<table>
<thead>
<tr>
<th>CPAP (cm H₂O)</th>
<th>Normal breathing</th>
<th>Forced breathing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Airflow (L/s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak</td>
<td>0.52 ± 0.11</td>
<td>0.61 ± 0.11</td>
</tr>
<tr>
<td>P vs control*</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>P nb vs fb†</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>Mean</td>
<td>0.37 ± 0.08</td>
<td>0.44 ± 0.10</td>
</tr>
<tr>
<td>P vs control*</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>P nb vs fb†</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>Volume (L)</td>
<td>0.72 ± 0.17</td>
<td>0.80 ± 0.11</td>
</tr>
<tr>
<td>P vs control*</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>P nb vs fb†</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>Time (S)</td>
<td>2.0 ± 0.5</td>
<td>1.9 ± 0.4</td>
</tr>
<tr>
<td>P vs control*</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>P nb vs fb†</td>
<td>Na</td>
<td>Na</td>
</tr>
</tbody>
</table>

Expiratory phase

| Airflow (L/s) |                  |                  |                 |    |
|---------------|------------------|------------------|                 |    |
| Peak          | 0.45 ± 0.15      | 0.47 ± 0.09      | 0.45 ± 0.07     | 0.44 ± 0.07 | 1.87 ± 0.97 | 1.68 ± 0.87 | 1.80 ± 0.91 |
| P vs control* | Na               | 0.02             | 0.003           | 0.001      | <0.001     | <0.001     | <0.001     |
| P nb vs fb†   | Na               | Na               | Na              | Na          | <0.001     | <0.001     | <0.001     |
| Mean          | 0.26 ± 0.07      | 0.30 ± 0.07      | 0.29 ± 0.06     | 0.27 ± 0.04 | 1.32 ± 0.67 | 1.18 ± 0.53 | 1.28 ± 0.65 |
| P vs control* | Na               | 0.045            | 0.03            | 0.04       | <0.001     | <0.001     | <0.001     |
| P nb vs fb†   | Na               | Na               | Na              | Na          | <0.001     | <0.001     | <0.001     |
| Volume (L)    | 0.72 ± 0.19      | 0.78 ± 0.12      | 0.81 ± 0.12     | 0.80 ± 0.13 | 1.57 ± 0.48 | 1.54 ± 0.63 | 1.72 ± 0.62 |
| P vs control* | Na               | Na               | Na              | Na          | <0.001     | <0.001     | <0.001     |
| P nb vs fb†   | Na               | Na               | Na              | Na          | <0.001     | <0.001     | <0.001     |
| Time (S)      | 2.8 ± 0.5        | 2.7 ± 0.7        | 2.9 ± 0.6       | 3.0 ± 0.8   | 1.5 ± 0.7   | 1.5 ± 0.7   | 1.7 ± 1.0   |
| P vs control* | Na               | Na               | Na              | Na          | <0.001     | <0.001     | <0.001     |
| P nb vs fb†   | Na               | Na               | Na              | Na          | <0.001     | <0.001     | <0.001     |

Data are presented as mean ± SD. P < 0.05 was considered significant. * Each CPAP level vs 0 cm H₂O (control). † Normal breathing vs forced breathing at each preset CPAP level. Na = not applicable, Ns = not significant.
Results

3.3 Paper III

3.3.1 Inspiratory phase

3.3.1.1 Inspiratory capacity

The initial IC maneuver, performed prior to breathing with each of the four breathing devices, showed no statistical difference between the different breathing devices. The second IC maneuver, performed directly after breathing with each of the four breathing devices, showed that IC decreased for all four breathing devices. The decrease was significant for the PEP-mask, the flow resistor CPAP and the threshold resistor CPAP but not the PEP-bottle (figure 4).

Figure 4. Decrease in IC between the initial and second IC maneuver. Data are presented as mean ± SD. *p < 0.001 IC1 vs IC2.

3.3.1.2 Airway pressure

Airway pressure decreased for all four breathing devices, reaching negative values for the two PEP devices. With the two CPAP devices, airway pressure decreased significantly more with the flow resistor CPAP compared with the threshold resistor CPAP (table 7).

3.3.1.3 Breathing pattern

Results for time/breath and volume are presented in table 7.

3.3.2 Expiratory phase

3.3.2.1 Airway pressure

Airway pressure increased with all four breathing devices. Airway pressure was significantly higher for the PEP-bottle compared to the PEP-mask. Airway pressure was also significantly higher for the flow resistor CPAP compared to the threshold resistor CPAP (table 8).
3.3.2.2 Breathing pattern
Results for time/breath and volume are presented in table 8.

Table 7. PEP and CPAP produced respiratory parameters during the inspiratory phase

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PEP-bottle</th>
<th>PEP-mask</th>
<th>Flow resistor CPAP</th>
<th>Threshold resistor CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspiratory phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Airway pressure (cm H₂O)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean median</td>
<td>-2.21 ± 0.55</td>
<td>-2.26 ± 0.59</td>
<td>8.35 ± 0.61</td>
<td>9.05 ± 0.68*</td>
</tr>
<tr>
<td>Time (s)</td>
<td>1.91 ± 0.56</td>
<td>1.74 ± 0.56</td>
<td>1.61 ± 0.48</td>
<td>1.79 ± 0.56</td>
</tr>
<tr>
<td>Volume (L)</td>
<td>1.22 ± 0.40</td>
<td>0.95 ± 0.30</td>
<td>0.84 ± 0.27**</td>
<td>0.99 ± 0.37</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. * p = 0.008 Flow resistor CPAP vs Threshold resistor CPAP, **p = 0.008 PEP-bottle vs Flow resistor CPAP.

Table 8. PEP and CPAP produced respiratory parameters during the expiratory phase

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PEP-bottle</th>
<th>PEP-mask</th>
<th>Flow resistor CPAP</th>
<th>Threshold resistor CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expiratory phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Airway pressure (cm H₂O)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean median</td>
<td>11.17 ± 0.29</td>
<td>8.33 ± 2.86*</td>
<td>10.55 ± 0.26</td>
<td>10.24 ± 0.06**</td>
</tr>
<tr>
<td>Time (s)</td>
<td>4.46 ± 1.42</td>
<td>4.66 ± 1.65</td>
<td>2.65 ± 0.88†</td>
<td>2.71 ± 0.85†</td>
</tr>
<tr>
<td>Volume (L)</td>
<td>1.23 ± 0.41</td>
<td>0.93 ± 0.30</td>
<td>0.83 ± 0.27†</td>
<td>0.98 ± 0.38</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. * p = 0.002 PEP-bottle vs PEP-mask, **p = p < 0.001 Flow resistor CPAP vs Threshold resistor CPAP, †p < 0.001 PEP devices vs CPAP devices, ‡p = 0.006 PEP-bottle vs Flow resistor CPAP.
3.4 Paper IV

3.4.1 Static pressure

With the threshold resistor CPAP, static measured pressure level was close to preset CPAP level (5 or 10 cm H2O) irrespective of simulated altitude. With the flow resistor CPAP, static measured pressure level increased as the simulated altitude increased (figure 5, panel A and B).

A statistical analysis of the interaction between CPAP device (threshold resistor CPAP, flow resistor CPAP), 3.5 bar regulator (outside or inside the hypobaric chamber) and simulated altitude showed that for every kft increase in simulated altitude, the estimated pressure level decreased 0.0024 ± 0.0039 cm H2O (p = 0.539) for the threshold resistor CPAP when the 3.5 bar regulator was outside the hypobaric chamber. Estimated pressure level decreased 0.0140 ± 0.0030 cm H2O (p ≤ 0.001) with the 3.5 bar regulator inside the hypobaric chamber. With the flow resistor CPAP, for every kft increase in altitude, the estimated pressure level increased 0.2475 ± 0.0038 H2O (p ≤ 0.001) when the 3.5 bar regulator was outside the hypobaric chamber. Estimated pressure level increased 0.1368 ± 0.0030 cm H2O (p ≤ 0.001) with the 3.5 bar regulator inside the hypobaric chamber.

![Figure 5, panel A-B. Static pressure at CPAP levels 5 cm H2O (panel A) and 10 cm H2O (panel B). Threshold resistor CPAP – regulator outside (filled bar), Threshold resistor CPAP – regulator inside (striped bar), Flow resistor CPAP – regulator outside (grey bar), Flow resistor CPAP – regulator inside (open bar). Data are presented as mean ± SD. Variable estimate: Threshold resistor CPAP × regulator outside × altitude, p = 0.539. Variable estimate: Threshold resistor CPAP × regulator inside × altitude, p < 0.001. Variable estimate: Flow resistor CPAP × regulator outside × altitude, p < 0.001. Variable estimate: Flow resistor CPAP × regulator inside × altitude, p < 0.001.](image-url)
3.4.2 Static airflow

The performance of the two CPAP devices differed when the simulated altitude increased (figure 6, panel A and panel B). A statistical analysis of the interaction between CPAP device (threshold resistor CPAP, flow resistor CPAP), 3.5 bar regulator (outside or inside the hypobaric chamber) and simulated altitude showed that, for every kft increase in altitude, the estimated airflow level decreased 0.0033 ± 0.0016 L/s (p = 0.034) for the threshold resistor CPAP when the 3.5 bar regulator was outside the hypobaric chamber. The estimated airflow level decreased 0.0023 ± 0.0018 L/s (p = 0.203) with the 3.5 bar regulator inside the hypobaric chamber. For the flow resistor CPAP, for every kft increase in altitude, the estimated airflow increased 0.0273 ± 0.0016 L/s (p ≤ 0.001) when the 3.5 bar regulator was outside the hypobaric chamber. The estimated airflow level increased 0.0142 ± 0.0018 L/s (p ≤ 0.001) with the 3.5 bar regulator inside the hypobaric chamber.

Figure 6, panel A-B. Static airflow at CPAP levels 5 cm H2O (panel A) and 10 cm H2O (panel B).

Threshold resistor CPAP – regulator outside (filled bar), Threshold resistor CPAP – regulator inside (striped bar), Flow resistor CPAP – regulator outside (grey bar), Flow resistor CPAP – regulator inside (open bar).

Data are presented as mean ± SD.

Variable estimate: Threshold resistor CPAP × regulator outside × altitude p = 0.034.

Variable estimate: Threshold resistor CPAP × regulator inside × altitude p = 0.203.

Variable estimate: Flow resistor CPAP × regulator outside × altitude p < 0.001.

Variable estimate: Flow resistor CPAP × regulator inside × altitude p < 0.001.
3.4.3 Different flow selectors

With the four different flow selectors separately connected to a flow resistor CPAP device, as seen during the static measurements of pressure and airflow, when simulated altitude increased the measured pressure (figure 7, panel A) and airflow levels (figure 7, panel B) increased.

Figure 7, panel A-B. Static pressure (panel A) and static airflow (panel B) with different flow selectors.

Flow selector \( m \) – filled bar, flow selector \( n \) – striped bar, flow selector \( o \) – grey bar, flow selector \( p \) – open bar.

Single measurements (no statistical tests performed).
3.5 Estimated perceived exertion (paper I-III).

As illustrated in figure 8, the participants’ estimations of perceived exertion differed within the different breathing devices and different pressure levels.

Figure 8, panel A-C. Estimated perceived exertion when breathing with different breathing devices, paper I (panel A), paper II (panel B) and paper III (panel C).

Data are presented as median (max – min).

Median values – PEP-bottle (black square), PEP-mask (grey square), Flow resistor CPAP (open square), Threshold resistor device (striped square). Max values - PEP-bottle (black diamond), PEP-mask (grey diamond), Flow resistor CPAP (open diamond), Threshold resistor device (striped diamond). Min values – PEP-bottle (black triangle), PEP-mask (grey triangle), Flow resistor CPAP (open triangle), Threshold resistor device (striped triangle).
4 Discussion

This thesis shows that different resistance breathing devices affect airway pressure, airflow and IC differently. The effect of changes in ambient air pressure differ between different kinds of resistance breathing devices and the range in estimated perceived exertion within different breathing devices are quite large.

4.1 The PEP-bottle and the PEP-mask

There were major differences between the PEP-bottle and the PEP-mask in the relationship between airflow and airway pressure during both the expiratory and the inspiratory phase. With the PEP-bottle both the expiratory and the inspiratory phase began with a zero-flow period. The length of the zero-flow period denotes the time it took for the airway pressure to rise above the threshold level of the water seal. When airway pressure was higher than the threshold level, i.e. the PEP level, air started to flow into the water in the PEP-bottle. At the end of the expiratory phase, airway pressure was 9.5 cm H2O. The length of the inspiratory zero-flow period denotes the time it took for airway pressure to decrease, from the end expiratory pressure level, to just below 0 cm H2O. When airway pressure became negative, inspiratory airflow began. With the PEP-mask both expiratory and inspiratory zero-flow periods were very short and the changes in airway pressures were almost non-existent. This can be explained by the fact that the resistor in the PEP-mask does not have a threshold level that needs to be overcome before expiratory airflow starts. At the end of the expiratory phase airway pressure was 0 cm H2O which explains why inspiratory airflow started almost immediately.

The two zero-flow periods seen, especially with the PEP-bottle, causes a patient to briefly hold their breath at the beginning of every expiration and inspiration. It is possible that the longer zero-flow period causes some patients to become dyspneic when breathing with the PEP-bottle.

4.2 The Boussignac CPAP

During normal breathing, inspiratory pressure decreased slightly. The decrease in inspiratory pressure was more pronounced as CPAP levels increased, but was never large enough for CPAP to be lost, i.e. for the inspiratory pressure to become negative. However, during forced breathing, airway pressure became negative during the inspiratory phase. During both normal and forced breathing, expiratory airway pressure increased. The increase in airway pressure was higher during forced breathing when expiratory airflow was higher than during normal breathing, which shows that the resistor in the Boussignac system is flow dependent.
These findings are in concordance with the findings of Bellani et al (102). In a bench study investigating the Boussignac CPAP, they found that the decrease in airway pressure during the inspiratory phase correlated with increased airflow. During the expiratory phase, as airflow increased, which led to larger tidal volumes, the increase in airway pressure became larger. Higher CPAP levels have also been shown to produce larger differences between inspiratory and expiratory pressure levels in patients with acute pulmonary edema (95). The Boussignac CPAP seems to be functioning well during normal breathing, but when airflow increases as it does in patients with respiratory distress, caution is necessary, since large changes in airway pressure may increase breathing efforts.

4.3 The effect of PEP and CPAP on inspiratory capacity

IC decreased significantly with the PEP-mask, the flow resistor CPAP device and the threshold resistor CPAP device but not with the PEP-bottle. The PEP-mask and the threshold resistor CPAP produced a similar decrease in IC. We are not aware of any other study that has compared these two devices. Studies comparing the effect of CPAP and PEP with threshold resistors have shown both a higher increase in FRC with CPAP compared to PEP (EPAP) (105) and that CPAP and PEP (EPAP and blow bottles) produced a similar increase in FRC (18, 106). Our results show that the PEP-mask with its flow resistor can be as effective as a CPAP device in decreasing IC and thereby increasing FRC.

The flow resistor CPAP device seems to induce a larger decrease in IC compared to the threshold resistor CPAP device. This observation is in agreement with a study examining the effect of the WhisperFlow CPAP (threshold resistor), the Boussignac CPAP (flow resistor) and the Siemens Servo 300 (ventilator) on end expiratory lung volume (EELV), i.e. FRC, in 14 healthy volunteers, using a nitrogen dilution technique and electric impedance tomography (EIT). The increase in EELV was significantly higher with the Boussignac CPAP device compared to the other two devices (72).

PEP-mask induced changes in FRC have previously been investigated. When the second FRC measurement was performed in direct continuation of PEP breathing, FRC increased significantly in a study in 12 patients with cystic fibrosis (34). There were no significant changes in FRC when deep breathing without aid, during PEP and during IR-PEP was compared in obese and non-obese subjects. The second FRC measurement was performed within two minutes after each breathing exercise had ended (62). In a study investigating deep breathing without aid, during PEP and during IR-PEP in people with tetraplegia (SCL group) and able-body controls, the second FRC measurement was also performed within two minutes after each breathing exercise had ended. Deep breathing during both PEP and IR-PEP produced a significant
Discussion

increase in FRC in the SCL-group. In the control group deep breathing during IR-PEP significantly increased FRC while deep breathing without aid significantly decreased FRC (63).

The effect of threshold resistor PEP devices on FRC has also previously been investigated. FRC was measured in seven healthy males during breathing with an EPAP device (Emmerson water column) at ambient airway pressure and at 5, 10 and 15 cm H$_2$O. For every 5 cm H$_2$O increase in the expiratory pressure level, FRC increased 6.3% which was statistically significant (103). In a study by van der Schans et al (118) FRC was investigated in eight patients with cystic fibrosis during breathing at ambient pressure and at 5 and 15 cm H$_2$O (spring loaded valve). Both PEP levels increased FRC significantly but the increase in FRC during breathing at a PEP level of 15 cm H$_2$O was significantly higher than during breathing at 5 cm H$_2$O. After discontinuation of PEP, FRC rapidly returned to baseline values.

Both flow resistor and threshold resistor PEP devices can be used to increase FRC, but the change in FRC seems to be short-lived. In our study IC decreased significantly with the PEP-mask (flow resistor) but not with the PEP-bottle (threshold resistor). It is possible that the expiratory resistance produced by the water seal affects IC, i.e. FRC, differently than other threshold resistors like a spring-loaded valve.

4.4 The effect of changes in ambient air pressure on CPAP device performance

The performance of the flow resistor CPAP device and the threshold resistor CPAP device differed when simulated altitude increased. During static pressure measurements, the measured pressure level increased with the flow resistor CPAP device every time the simulated altitude increased. With the threshold resistor CPAP device, measured pressures were close to the preset pressure level regardless of simulated altitude. To ensure that the results seen with the flow resistor CPAP device was not due to the rotameter, four different flow selectors were also tested. As the altitude increased measured pressure levels increased regardless of a rotameter or any of the four flow selectors was connected to the flow resistor CPAP device.

This difference in performance between the flow resistor CPAP device and the threshold resistor CPAP device may be explained by differences in mechanical construction.

In a study by Fromm et al (114), the performance of four different fan driven CPAP machines used for treating sleep apnea, three non-pressure compensated CPAP machines and one CPAP machine with a pressure-sensor (i.e. threshold resistor), were tested at different simulated altitudes. Contrary to data in our study, where the pressure level increased as the altitude increased for the flow resistor CPAP device, the non-pressure compensated CPAP machines decreased the pressure level
at increasing altitudes. However, as in our study the CPAP machine with the pressure-sensor maintained the pressure level regardless of altitude and preset CPAP level. As a consequence of the results from the study by Fromm et al, today most CPAP machines used for treating sleep apnea come with the option of altitude adjustment (119).

The collective fan laws describe how changes in air density affect the performance of fan driven CPAP machines. If air density is decreased and the power to the fan is constant, airflow through the fan will be reduced. To maintain the flow rate, the power to the fan has to be increased (114). Poiseuille’s law state how changes in air density affect flow rate through a fixed tube. With decreased air density, constant temperature and constant pressure, airflow through a fixed tube will increase. In our study, airflow was delivered at a constant pressure level to the CPAP devices with a 3.5 bar pressure regulator. As simulated altitude increased, resulting in decreased air density, the resistance through the rotameter and the flow resistor CPAP device decreased which resulted in increased airflow through the CPAP device. Since the CPAP level in the flow resistor CPAP device is determined by the velocity of airflow, the measured pressure level increased.

4.5 Perceived exertion
In our experience, the PEP-bottle causes some patients to become dyspneic but if they use a PEP-mask instead, they can perform their breathing exercises without getting out of breath. We therefore investigated how strenuous different breathing devices and different resistors are perceived. To this end, the Borg CR10 scale was chosen since it has been widely used for measuring dyspnea. The results showed a wide range of estimations of perceived exertion within the different breathing devices, but the median perceived exertion was quite low for all four breathing devices and for different CPAP levels. The highest median estimated perceived exertion amounted to three. A rating of three on the Borg CR10 scale is anchored as moderate perceived exertion. The lowest median estimated perceived exertion amounted to 0.7 which is anchored between extremely weak and very weak perceived exertion. The highest rating amounted to 7, which reflects a very strong perceived exertion. Considering the wide range of estimations for perceived exertion in healthy volunteers it is easy to understand that patients’ capacity to breathe with different breathing devices differ. To optimize patient treatment the choice of breathing device needs to be individualized.
4.6 Methodological considerations

Three out of four breathing devices investigated in this thesis are commercial products, but the PEP-bottle is not. Mestriner et al (115) has investigated the optimum design for a “homemade” PEP-bottle. With the tube submerged 10 cm below water surface, they showed that if expiratory airflow through the tube was 25 L/min (0.42 L/s), the inner diameter of the tube had to be $\geq 0.8$ cm to avoid adding flow dependent properties to the PEP-bottle. Christensen el al (6) showed that the T-valve from the PEP-mask could in itself act as a flow resistor. The tubes used in paper I and paper III had an inner diameter of $\geq 1$ cm. In paper I, mean expiratory airflow was lower (0.33 L/s) but peak expiratory airflow was higher (0.98 L/s) than 25 L/min. If these flow levels added flow dependent properties has not been elucidated in this thesis. We had a T-valve connected to the PEP-bottle in paper I and III. Both the use of a T-valve and the velocity of airflow might explain why the measured PEP-level was higher than the preset PEP level in the PEP-bottle. The measured pressure level for the PEP-mask was lower than the intended PEP level of 10 cm H$_2$O in both paper I and III. This might be due to participants changing their breathing pattern between the practice phase and the actual measurement phase. To avoid affecting the participants breathing during the measurements, changes in breathing pattern was not met with further instructions or comments.

Normally when patients use the PEP-bottle, they close their lips around the tube submerged into the water. They then breathe in through the nose and exhale through the tube. In paper I, a mouthpiece was used to mimic normal conditions as much as possible. In paper III, a facemask was used during all measurements, including measurements with the PEP-bottle. The reason for this choice was to have the same interface between the participants and the equipment during all IC measurements to ensure that the interface did not affect the results.

In order to evaluate baseline changes in EELV (FRC) and breathing pattern before an IC maneuver it is recommended that the tester is able to look at the volume-time plot during measurements (107). The equipment used for measuring IC recorded airflow and airway pressure. Volume is later acquired by integrating the recorded airflow signal. No real-time assessment of the baseline prior to the IC maneuver could therefore be performed. Since the respective CPAP device was still running during the second IC maneuver, conditions during the second IC maneuver differed slightly depending on whether a PEP device or a CPAP device was being tested.

In paper IV, at ground level the spring-loaded valve in the threshold resistor CPAP device provided a CPAP level that was a little lower than set pressure levels, 5 and 10 cm H$_2$O, respectively. During measurements the spring loaded valve was placed in a horizontal position. If vertically
oriented, the self-weight of the spring-loaded valve would have increased measured pressure levels. Christensen et al (6) made the same observation, that the spring-loaded valve produced lower pressure levels than set pressure levels, especially when airflow was lower. However, they do not describe the position of the spring-loaded valve during tests.

We choose the rotameter for flow delivery to the flow resistor CPAP device, since it enabled titration of airflow to the respective predetermined CPAP level.

Measurements in this thesis have been performed in healthy volunteers and in a hypobaric chamber and need to be repeated in patients and during actual inflight conditions.

4.7 Clinical implications and future research
To summarize, this thesis has shown that there is a difference between the PEP bottle and the PEP-mask. Breathing with the PEP-bottle, using the current instructions, does not automatically result in increased FRC. The results also suggest that we need to be more attentive to how our patients exhale during PEP breathing. Furthermore, in the clinical setting, it can no longer be argued, as it has been done in this region of the country, that we, as physiotherapists, only need one PEP device and that is the PEP-bottle to treat our patients.

The Boussignac CPAP does not maintain stable pressure levels during increased breathing efforts and should therefore not be used in patients with increased respiratory frequency. However, if the aim with CPAP treatment is to increase FRC in patients with normal respiratory frequency, the Boussignac CPAP is suitable.
A comparison between the threshold resistor CPAP device and the flow resistor CPAP device at different ambient pressures, as during flight, showed that the threshold resistor CPAP performed better at lower ambient pressures. Therefore, CPAP devices used in flight should have a pressure adaptive function.

In this field of physiotherapy, we need to find methods to measure, in the clinical setting, what we claim to accomplish physiologically with different breathing devices, e.g. changes in FRC and reduced atelectatic area. Only then can we find explanations for how different breathing devices actually affect different respiratory parameters and also why breathing devices might fail to achieve desired results. Having the ability to measure patients’ physiological responses to different breathing devices could optimize breathing instructions different kinds of patients receive to achieve desired therapeutic goals.
5 Conclusions

- Effects on airway pressure, airflow, IC and the effect of changes in ambient air pressure differ between different kinds of resistance breathing devices.

- The relationship between airway pressure and airflow differ between the PEP-bottle and the PEP-mask.

- The performance of the Boussignac CPAP device is sufficient during normal breathing.

- During forced breathing the Boussignac CPAP device is unable to maintain the CPAP level close to the preset CPAP.

- Changes in IC could be used as an indirect measure of changes in FRC.

- Three of the four investigated resistance breathing devices, the PEP-mask, the flow resistor CPAP and the threshold resistor CPAP, but not the PEP-bottle decreased IC, i.e. increased FRC.

- The performance of the threshold resistor CPAP device is more robust than the flow resistor CPAP device when ambient air pressure decreases as during flight.

- There is a great variety in perceived exertion when different people breathe with a certain resistance breathing device.

- The differences in device performance should be taken into consideration when choosing a resistance breathing device for a patient.
Acknowledgements

I would like to express my sincere gratitude to everyone who has, in one way or the other, contributed to this thesis. I would especially like to thank:

All the volunteers who participated in the different studies.

Ola Winsø, my main supervisor, for believing in my ideas, for standing behind me and making this journey possible.

Fredrik Öhberg, my supervisor, for valuable collaboration, skillful technical assistance and support whenever I needed.

Karin Wadell, my supervisor, for valuable collaboration, quick feedback and positive energy.

Göran Johansson, my co-author, Excel tutor and statistician.

Siv Sandkvist Törnell, my co-author and project partner in paper II.

Helge Brändström, my co-author, for sharing your knowledge in aviation medicine and for delivering the idea resulting in paper IV.

Michael Haney, my co-author, for sharing your knowledge in aviation medicine.

Jan Skedebrandt and Andreas Eriksson, for valuable help with lung function measurements.

Hans G von Wovern and Kurt Svensson, FRM, for valuable help with the hyperbaric chamber measurements in paper IV.

Gabriel Granåsen, for valuable help with the linear mixed models in paper IV.

Mona Jakobsson, for valuable help with participants in paper III.

All doctoral students at Physiotherapy and at Anesthesiology and Intensive Care Medicine, and especially Camilla Brorsson and Sofie Jacobsson for shared knowledge, frustration and laughter.

Colleagues and friends, for valuable support.

My brother Ola and my nieces, Moa and Ida, for joy and laughter.

My parents, Helén and Runo, for endless support and encouragement.

This work was supported with grants from Västerbotten County Council, the Medical Faculty of Umeå University and the Swedish Association of Registered Physiotherapists.
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