

MASTER THESIS TECHNICAL MEDICINE  
MEDICAL SENSING AND STIMULATION

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**The use of nasal high-flow therapy to treat  
central sleep apnoea in patients with  
congestive heart failure**

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**Sietske van der Leest, BSc.**

**January 18, 2018**



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January 18, 2018

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## Preface

This thesis has been written to fulfil the graduation requirements of the Technical Medicine master program at the University of Twente (UT). I was engaged in researching and writing this thesis from February 2017 to January 2018 at the Center of Home Mechanical Ventilation at the University Medical Center in Groningen. There have been plenty of people who supported me during my graduation year, which I would like to thank.

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Best regards,

Sietske van der Leest

Groningen, January 18, 2018



## Abstract

**Introduction:** Central sleep apnoea (CSA) is a common syndrome in patients with congestive heart failure. The combination of CSA and congestive heart failure is associated with higher morbidity and mortality rates. However, there is no safe and effective therapy available for treating CSA in these patients. Nasal high-flow therapy (nHFT) is a novel therapy that provides high levels of flow ranging between 10-50 L/min of heated and humidified air through an open nasal cannula, with or without oxygen. The aim of the study is to evaluate the effectiveness of nHFT stabilising ventilation in patients with congestive heart failure and CSA.

**Methods:** Ten patients with severe congestive heart failure and untreated moderate to severe CSA will be treated with nHFT during the night for 4 weeks. The apnoea hypopnoea index (AHI) before and after nHFT is compared. The patients will be initiated on nHFT during a titration night, in which different nHFT settings, with and without oxygen, are applied. Many physiological effects of nHFT, such as the generated pressure, work of breathing, neural breathing drive and heart rate variability (HRV), will be measured to determine the optimal nHFT setting and gain more information about the mechanisms of action.

**Results:** Currently, the study is on-going. So far, three patients have been included. Preliminary results showed low compliance rates: 2 patients dropped-out due to non-tolerance, and the only patient who has finished the study, did not decide to continue therapy afterwards. Complaints included nose irritation, a too large nasal cannula, and an uncomfortable high flow rate. The AHI of the patient who finished the study decreased from 30 to 12 events per hour with nHFT. During the titration night, the AHI was lower when additional oxygen was given. When the nHFT flow rate was higher, an increase of the pharyngeal pressure was not measured, the work of breathing decreased when the patient slept with the mouth closed, and the neural breathing drive seemed to decrease. nHFT did not influence HRV.

**Discussion:** There are indications that nHFT with the addition of oxygen makes ventilation more stable in patients with congestive heart failure and CSA. Especially oxygen addition seems to be effective reducing AHI. More patients need to be included in the study to verify this result. Patients were not satisfied with nHFT. Probably, low humidity levels and a large nasal cannula might explain the low compliance. A humidity level between 34-37 °DP and a smaller nasal cannula are advised. Furthermore, the high flow rate made exhaling more difficult, which is uncomfortable. It is recommended to analyse whether a nHFT device, in which the flow rate decreases when there is resistance, would increase the compliance. Moreover, it was difficult to determine the optimal nHFT setting during the titration night due to poor sleep quality. The sleep quality during the titration night and compliance might increase when patients get used to sleeping with the nHFT device one week before the titration night. The pharyngeal pressure was not measured properly due to occlusion of the catheter by secretions. When occlusion by secretions was prevented, the pharyngeal pressure increased linearly with a higher nHFT flow rate. A 20 ml/h airflow produced by a microinfusor at the inlet of the catheter might avoid occlusion of the catheter by secretions. There are indications that a higher flow rate reduces the work of breathing and the neural breathing drive, which indicates that patients can relax their muscles more with a higher flow rate. No clear HRV changes due to nHFT were found, since the sleep stages influenced HRV a lot. HRV should be compared before and after nHFT to analyse HRV changes due to nHFT.

**Conclusion:** nHFT with the addition of oxygen might stabilise ventilation in patients with congestive heart failure and CSA. However, due to the poor compliance so far, nHFT does not seem to be an optimal treatment for these patients.



## Nederlandse samenvatting

**Introductie:** Het centraal slaapapneu-syndroom (CSAS) komt veel voor bij patiënten met hartfalen. De combinatie van CSAS met hartfalen is geassocieerd met een hogere morbiditeit en mortaliteit. Echter is er nog geen veilige en effectieve therapie beschikbaar om CSAS te behandelen in deze patiënten. Nasal high-flow therapie (nHFT) is een nieuwe therapie dat verwarmde en bevochtigde lucht, met of zonder zuurstof, met een hoge luchtstroom tussen de 10-50 L/min aanbiedt aan de patiënt via een neusbril. Het doel van de studie is om de effectiviteit van nHFT in het stabiliseren van de ademhaling in patiënten met hartfalen en CSAS te analyseren.

**Methodes:** Tien patiënten met ernstig hartfalen en onbehandeld matig tot ernstig CSAS worden behandeld met nHFT gedurende 4 weken tijdens de nacht. De Apneu-Hypopneu Index (AHI), het aantal ademstops per uur, voor en na nHFT worden met elkaar vergeleken. De patiënten worden ingesteld op nHFT tijdens een titratienacht, waarin verschillende nHFT instellingen, met en zonder zuurstof, worden toegepast. Veel fysiologische effecten van nHFT, zoals de creëerde drukken, de ademarheid, de aansturing van de spieren en de hartslagvariabiliteit (HRV), worden bekeken om de optimale nHFT instelling te bepalen en om meer over het werkingsmechanisme van nHFT te weten te komen.

**Resultaten:** Op dit moment loopt de studie en zijn er drie patiënten geïnccludeerd. Voorlopige resultaten laten een lage compliantie zien: 2 patiënten stopten vroegtijdig met de studie, en de enige patiënt die de studie afmaakte, wilde niet doorgaan met de therapie. Patiënten klaagden over neus irritaties, een te grote neusbril en een oncomfortabele hoge luchtstroom. De AHI van de patiënt die de studie afmaakte, verlaagde van 30 naar 12 ademstops per uur met nHFT. Tijdens de titratienacht was de AHI lager wanneer zuurstof werd toegevoegd. Bij een verhoogde luchtstroom van de nHFT steeg de farynx druk niet, verlaagde de ademarheid als de patiënt met de mond dicht sliep, en leek de aansturing van de spieren te verlagen. De nHFT had geen invloed op de HRV.

**Discussie:** Er zijn aanwijzingen dat de ademhaling van patiënten met hartfalen en CSAS meer stabiel wordt door nHFT met zuurstof. Vooral zuurstof lijkt effectief te zijn in het verlagen van de AHI. Meer patiënten moeten worden geïnccludeerd om dit resultaat te verifiëren. Patiënten waren niet tevreden met de therapie. Een te laag bevochtigingslevel en een te grote neusbril kan deels de lage compliantie verklaren. Een bevochtigingslevel tussen 34-37 °DP en een kleinere neusbril wordt aangeraden. Daarnaast maakte de hoge luchtstroom het uitademen moeilijker, wat niet aangenaam is. Het wordt aanbevolen om te analyseren of de compliantie omhoog gaat als een ander nHFT apparaat gebruikt wordt, waarbij de luchtstroom verlaagd wanneer het apparaat weerstand voelt. De patiënten sliepen slecht tijdens de titratienacht, wat het moeilijk maakte om de optimale nHFT instelling te bepalen. De slaapkwaliteit tijdens de titratienacht en de compliantie zouden kunnen verbeteren als de patiënten één week voor de titratienacht al wennen aan het slapen met de nHFT. De farynx druk werd niet juist gemeten, doordat de katheter verstopt raakte met slijm. De farynx druk steeg lineair met een verhoogde luchtstroom van de nHFT wanneer verstopping met slijm werd voorkomen. Het aanbieden van een continue luchtstroom van 20 ml/h aan de katheter zou een verstopping van de katheter kunnen voorkomen. Er zijn aanwijzingen dat een verhoogde luchtstroom de ademarheid en de aansturing van de ademhalingspijpen doet verminderen, waardoor patiënten hun ademhalingspijpen meer kunnen ontspannen. Er werden geen duidelijke HRV veranderingen gezien met nHFT, aangezien de slaapstadia de HRV erg beïnvloedden. De HRV voor en na nHFT zouden met elkaar vergeleken moeten worden om te analyseren wat voor effect nHFT heeft op de HRV.

**Conclusie:** nHFT met zuurstof lijkt de ademhaling van patiënten met hartfalen en CSAS te stabiliseren. Echter lijkt nHFT niet een geschikte therapie te zijn voor deze patiënten vanwege de lage compliantie.



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## List of Abbreviations

$\Delta P_{di}$	Amplitude of the transdiaphragmatic pressure
$\int P_{di}$	Integral of the transdiaphragmatic pressure
$\Delta P_{es}$	Amplitude of the oesophageal pressure
$\Delta P_{pha}$	Amplitude of the pharyngeal pressure
<b>6MWD</b>	Six minute walk distance
<b>AHI</b>	Apnoea hypopnoea index
<b>amp</b>	Amplitude
<b>ANOVA</b>	Analysis of variance
<b>ASV</b>	Adaptive servo-ventilation
<b>AUC</b>	Area under the curve
<b>AUC<sub>c</sub></b>	Area under the curve during central apnoeas
<b>AUC<sub>EMG</sub></b>	Area under the curve of the EMGdi <sub>fse</sub> signal
<b>AUC<sub>EMG1</sub></b>	AUC <sub>EMG</sub> calculated from the neural onset to the neural onset of the consecutive breath
<b>AUC<sub>EMG2</sub></b>	AUC <sub>EMG</sub> calculated from the neural onset to the neural offset
<b>AUC<sub>n</sub></b>	Area under the curve during normal breathing
<b>AUC<sub>o</sub></b>	Area under the curve during obstructive apnoeas
<b>BiPAP</b>	Bi-level positive airway pressure
<b>CO<sub>2</sub></b>	Carbon dioxide
<b>COPD</b>	Chronic Obstructive Lung Disease
<b>CPAP</b>	Continuous Positive Airway Pressure
<b>CSA</b>	Central sleep apnoea
<b>ECG</b>	Electrocardiogram
<b>EEG</b>	Electroencephalogram
<b>EMG</b>	Electromyography
<b>EMGdi</b>	Electromyography signals from the frontal diaphragm
<b>EMGdi<sub>fse</sub></b>	Fixed sample entropy analysis of the EMGdi signal
<b>ESS</b>	Epworth Sleepiness Scale
<b>FiO<sub>2</sub></b>	Fractional inspired oxygen
<b>FOSQ</b>	Functional Outcomes of Sleep Questionnaire
<b>GOLD</b>	Global Initiative for Chronic Obstructive Lung Disease
<b>HF</b>	High frequency (f>0.2 Hz and f<1 Hz) power per minute
<b>HRV</b>	Heart rate variability
<b>HRV<sub>ECG</sub></b>	Heart rate variability estimated with the ECG signals of the polysomnography
<b>HRV<sub>EMG</sub></b>	Heart rate variability estimated with the EMGdi signals
<b>I<sub>off</sub></b>	End of inspiration

$I_{on}$	Start of inspiration
<b>KDE</b>	Kernel density estimation
<b>LF</b>	Low frequency ( $f > 0.04$ Hz and $f < 0.2$ Hz) power per minute
<b>LF/HF ratio</b>	The ratio of the normalised LF power to the normalised HF power
<b>LVEF</b>	Left ventricular ejection fraction
<b>nHFT</b>	Nasal high-flow therapy
$nt_{off}$	Neural offset
$nt_{on}$	Neural onset
<b>NTproBNP</b>	N-terminal natriuretic peptide
$O_2$	Oxygen
<b>OSA</b>	Obstructive sleep apnoea
<b>PaCO<sub>2</sub></b>	Partial pressure of carbon dioxide in arterial blood
<b>PaO<sub>2</sub></b>	Partial pressure of oxygen in arterial blood
$P_{di}$	Transdiaphragmatic pressure
$P_{es}$	Oesophageal pressure
$P_{ga}$	Gastric pressure
$P_{pha}$	Pharyngeal pressure
<b>PRP</b>	Pressure-rate product
<b>PTP</b>	Pressure-time product
<b>PSG</b>	Polysomnography
<b>REM</b>	Rapid Eye Movement
<b>RMSSD</b>	Root-mean-square of the successive normal sinus R-R intervals
<b>RR</b>	Respiratory rate
<b>SDB</b>	Sleep-disordered breathing
<b>SDNN</b>	Standard deviation of the successive normal sinus R-R intervals
$T_e$	Expiration time
$T_i$	Inspiration time
$t_{off}$	End of inspiration determined from flow signal
$t_{on}$	Start of inspiration determined from flow signal
<b>Total power</b>	Average power (VLF + LF + HF) per minute
<b>VLF</b>	Very low frequency ( $f < 0.04$ Hz) power per minute

## Outline of the thesis

This thesis consists of two different parts. Part I, the main part of this thesis, describes a clinical study to evaluate the effectiveness of nasal high-flow therapy stabilising ventilation in patients with congestive heart failure and central sleep apnoea. The clinical study is performed together with Petra Meijer, a nurse specialist at the Center of Home Mechanical Ventilation at the University Medical Center in Groningen. Currently, the clinical study is on-going. So far, three patients have been included. Part I is about the preliminary results of these three patients.

During the clinical study, transcutaneous electromyography data have been collected. Part II describes the additional value of electromyography data detecting both obstructive and central sleep apnoea and estimating heart rate variability. To answer the additional research question of part II, the electromyography signals recorded during the clinical study have been analysed.



# 1 PART I: The effects of nasal high-flow therapy (nHFT)

## 1.1 Introduction

Congestive heart failure is a common disease with a prevalence of 26 million people worldwide<sup>1</sup>. It is expected that this prevalence will increase by 46% in the next 15 years<sup>2</sup>. Patients with congestive heart failure suffer from severe dyspnoea d'effort and fatigue due to an impaired pump function of the heart, which has a great influence on quality of life<sup>3</sup>. However, these symptoms could also be caused by sleep-disordered breathing (SDB)<sup>4</sup>, from which almost 46% of the patients with severe congestive heart failure suffer<sup>5</sup>. The combination of congestive heart failure with severe SDB is associated with decreased cardiac output and increased morbidity and mortality rates<sup>6;7</sup>, since SDB can have adverse effects on cardiac function<sup>3;4;8-10</sup> and can induce arrhythmias<sup>3;7;11</sup>. An effective treatment for SDB could result in decreased morbidity and improved survival<sup>6</sup>. However, many patients with congestive heart failure are not treated for SDB, since the diagnosis of SDB is often missed due to overlapping symptoms between congestive heart failure and SDB<sup>11</sup>.

SDB in patients with congestive heart failure can have an obstructive origin (obstructive sleep apnoea) or a central origin (central sleep apnoea), with or without a crescendo-decrescendo breathing pattern with oscillating tidal volumes, called Cheyne-Stokes respiration<sup>3;4</sup>. In patients with congestive heart failure and SDB, 80% suffer from central sleep apnoea (CSA) and 20% suffer from obstructive sleep apnoea (OSA)<sup>12</sup>. Both OSA and CSA are characterised by repetitive episodes of absence of airflow (apnoea) or a reduction of airflow (hypopnoea)<sup>13</sup>, which can result in nocturnal oxygen desaturations, arousals and sympathetic activation<sup>14</sup>. OSA is caused by a collapse of the upper airways while respiratory muscles continue working to maintain an adequate airflow<sup>15</sup>. CSA is caused by a reduced or absent central neural breathing drive, resulting in absent rib cage or abdominal excursions<sup>15</sup>.

Treatment of OSA or CSA in patients with congestive heart failure is targeted to decrease the amount of apnoeas and hypopnoeas. The number of apnoeas and hypopnoeas per hour is expressed as the apnoea hypopnoea index (AHI)<sup>16</sup>. OSA can be treated adequately with Continuous Positive Airway Pressure (CPAP), which keeps the upper airways open<sup>17</sup>. However, treatment of CSA in congestive heart failure patients, especially with Cheyne-Stokes respiration, is more challenging due to complex pathophysiological mechanisms. Hypocapnia, hypoxemia, increased chemosensitivity, increased circulation time and narrow oxygen (O<sub>2</sub>) reserve, all contribute to the existence of CSA and/or Cheyne-Stokes respiration<sup>4</sup>. There are several therapies available for the treatment of CSA in patients with congestive heart failure, such as nocturnal oxygen therapy<sup>8;14;16</sup>, acetazolamide<sup>16;18-20</sup>, and ventilation with adaptive servo-ventilation (ASV)<sup>9</sup>, CPAP<sup>5;8-11;16;21;22</sup> or Bi-level positive airway pressure (BiPAP)<sup>23;24</sup>. There is no agreement on how to treat patients with congestive heart failure and CSA effectively, since studies showed inconclusive results in clinical outcomes, were short-term and/or showed no sufficient clinical improvements. Moreover, some studies even showed adverse effects of the therapies. For instance, ASV therapy increased the mortality in patients with congestive heart failure, while it decreased the AHI<sup>9</sup>. The reasons for this increased mortality are unknown<sup>9</sup>. Furthermore, the compliance of CPAP is low, which limits the effectiveness of this therapy<sup>17</sup>. Overall, there is an urgent need for a safe and effective therapy for treating CSA in these patients.

Nasal high-flow therapy (nHFT) could be a new safe and effective treatment option for patients suffering from congestive heart failure and CSA. nHFT provides high levels of flow ranging between 10-50 L/min of heated and humidified air through an open nasal cannula, with or without oxygen<sup>25</sup>. There are several working mechanisms of nHFT proposed, which could be beneficial for patients with congestive heart failure and CSA. The provided flow can generate end-expiratory pharyngeal pressures which can reduce upper airway obstruction, reduce left ventricular afterload and stabilise ventilation<sup>26-28</sup>. This is sufficient to reduce AHI in patients with OSA when using sufficient high levels of flow<sup>29;30</sup>. Oxygen addition can prevent oxidative stress and reduce

chemosensitivity (the degree whether metabolic changes result in changes in minute ventilation), which can lead to a reduction of periods of apnoea<sup>4;8;31</sup>. Furthermore, nHFT can reduce the inspiratory resistance by providing adequate flow, which can reduce the related work of breathing<sup>25;32;33</sup>. Moreover, because of the heated and humidified air, high oxygen concentrations can be delivered, airway dryness can be avoided and the metabolic work associated with gas conditioning can be reduced<sup>32;34</sup>. Additionally, compliance rates of this therapy are promising<sup>32;35</sup>. Studies show that nHFT reduced breathing frequency<sup>32</sup>, work of breathing<sup>36</sup>, frequency of arousals, AHI, and increased nocturnal oxygen saturation and sleep quality<sup>29;32</sup>. However, there are also some possible disadvantageous working principles of nHFT for patients with congestive heart failure and CSA. For example, nHFT reduces the anatomical dead space resulting in a decreased carbon dioxide (CO<sub>2</sub>) level, which might induce apnoeas<sup>27</sup>. Furthermore, high levels of flow can promote hyperventilation due to a ventilatory overshoot<sup>28</sup>. Altogether, the mechanisms of action are not fully understood<sup>27;34;37</sup>. Thereby, there are no studies performed to assess the effectiveness of nHFT reducing AHI in patients with congestive heart failure and CSA. Moreover, it is not known which nHFT setting should be used in these patients and how the optimal setting could be determined.

In this study, the effectiveness of nHFT stabilising ventilation in patients with congestive heart failure and CSA is being studied. Ten patients with congestive heart failure and untreated CSA will use nHFT during the night for 4 weeks and the AHI before and after the use of nHFT will be compared. The patients will be initiated on nHFT during a titration night, in which different nHFT settings are applied. Many physiological effects of nHFT, such as the generated pressure, work of breathing, neural breathing drive and heart rate variability, will be measured to determine the optimal nHFT setting and to gain more information about the mechanisms of action.

### 1.1.1 Research questions

This part of the study answers three research questions. The first research question is:

1) *Can ventilation of patients with congestive heart failure and moderate to severe CSA be stabilised by applying nHFT for four weeks during the night?*

This research question is answered by comparing the AHI before and after applying nHFT.

At this moment, the mechanisms of action of nHFT on patients with congestive heart failure and CSA are not known. Therefore, the second research question is:

2) *What are the mechanisms of action of nHFT on patients with congestive heart failure and CSA?*

Another goal of this study is to gain information about how the optimal nHFT setting can be determined during the titration night. Therefore, the third research question is:

3) *How can the optimal nHFT setting reducing AHI in patients with congestive heart failure and CSA be determined during the titration night?*

To answer the second and the third research question, the effect of different nHFT settings on pharyngeal pressure, work of breathing, neural breathing drive, heart rate variability and respiratory rate is analysed.

## 1.2 Background

Firstly, the normal breathing physiology will be discussed. Thereafter, more information will be given about the pathophysiology of CSA and Cheyne-Stokes respiration in relation with congestive heart failure. Finally, the expected effects of nHFT on patients with congestive heart failure and CSA will be discussed more extensively.

### 1.2.1 Normal breathing physiology

During the day, ventilation is regulated by higher suprapontine influences and by metabolic processes, namely changes in  $PaO_2$  (partial pressure of oxygen in arterial blood),  $PaCO_2$  (partial pressure of carbon dioxide in arterial blood) or pH. During sleep, ventilation is regulated by metabolic processes only, which should be sufficient to regulate ventilation during sleep. Metabolic control of ventilation is mainly done by the chemoreceptors in the aorta, carotids and brainstem (see Figure 1). The receptors responding mainly to changes in  $PaO_2$  are the peripheral chemoreceptors in the carotid and aortic bodies. When these receptors detect a decrease in  $PaO_2$ , the afferent activity of the receptors increase resulting in an increase in minute ventilation. The degree of increase of the minute ventilation depends on the hypoxic chemosensitivity. When the hypoxic chemosensitivity is high, small changes in  $PaO_2$  cause huge changes in minute ventilation resulting in ventilatory instability. When the hypoxic chemosensitivity is decreased, a decrease in  $PaO_2$  results in a too limited increase in minute ventilation.  $PaCO_2$  changes are sensed by peripheral chemoreceptors in the carotid and aortic bodies and by central chemoreceptors, from which the central chemoreceptors are more important in regulating  $PaCO_2$ . The central chemoreceptors are located in the brainstem (more specific in the ventral surface of the medulla) and can react on changes in the pH, which is related to  $PaCO_2$ . When the chemoreceptors detect a low pH, minute ventilation increases, which decreases  $PaCO_2$  and increases pH. The  $CO_2$  chemosensitivity is the degree whether changes in pH and  $PaCO_2$  are aligned with changes in minute ventilation. When the  $CO_2$  chemosensitivity is increased, this leads to instability and central apnoeas.<sup>13</sup>

	<b>Regulated mainly by:</b>	<b>Working principle:</b>
$PaO_2$	Peripheral chemoreceptors in the carotid and aortic bodies	$\downarrow PaO_2 = \uparrow$ minute ventilation $= \uparrow PaO_2$
$PaCO_2$	Central chemoreceptors in the brainstem	$\downarrow$ pH $= \uparrow$ minute ventilation $= \downarrow PaCO_2$ $= \uparrow$ pH

Figure 1: Summary of the regulation of ventilation by metabolic processes.

Besides these metabolic processes that influence ventilation during sleep, other factors are also important. For example, a decrease in tonic activity of the pharyngeal muscles during sleep, especially during REM (Rapid Eye Movement) sleep, may lead to a collapse of the upper airway once a negative intraluminal pressure is generated during inspiration<sup>13</sup>. Normally, despite this loss of tonic activity of the pharyngeal dilator muscles, the tonic activity is still sufficient to prevent a collapse<sup>13</sup>.

Another factor that influences ventilation during sleep is the  $CO_2$  reserve. The  $CO_2$  reserve is defined as the difference between the sleep eupneic  $PaCO_2$  set point, which is the  $PaCO_2$  level during stable breathing, and the apnoea threshold, which is the level of  $PaCO_2$  leading to an apnoea. Normally, this difference is around 2-6 mmHg. When this  $CO_2$  reserve is decreased, the ventilatory system is less stable.<sup>13</sup>

### 1.2.2 Central sleep apnoea and the relation with congestive heart failure

There is a high prevalence of CSA in patients with congestive heart failure (around 36%)<sup>12;21</sup>, of which Cheyne-Stokes respiration is the most common form<sup>5</sup>. CSA is characterized by an instable ventilatory control<sup>13</sup>. This

instability is characterised by periods of central apnoeas and periods of hyperventilation<sup>7;13</sup>. In patients with Cheyne-Stokes respiration, hyperventilation results into a PaCO<sub>2</sub> level below the apnoeic threshold triggering a central apnoea<sup>4</sup>. Due to this central apnoea, the PaCO<sub>2</sub> level raises above the apnoeic threshold. When chemoreceptors detect this increased PaCO<sub>2</sub> level, the patient starts to hyperventilate bringing the PaCO<sub>2</sub> level below the apnoeic threshold again (shown in Figure 2 in the circle)<sup>4</sup>. This instability is often present in non-REM sleep, when ventilation is almost solely driven by metabolic processes<sup>4;13</sup>.

The presence of CSA can aggravate congestive heart failure. Oxygen desaturations and arousals increase sympathetic activity, causing arrhythmias and cardiotoxicity<sup>4</sup>. Moreover, the periods of hyperventilation increase work of breathing<sup>4</sup>. This ventilatory control instability in patients with congestive heart failure can have several origins (illustrated in Figure 2).

1) The circulation time increases due to a decreased cardiac output in patients with congestive heart failure. Due to a prolonged circulation time, the detection of changes in PaCO<sub>2</sub> or PaO<sub>2</sub> in the blood by chemoreceptors is delayed<sup>13;38</sup>. This delayed detection results in an increased chemosensitivity, leading to an increased ventilatory response resulting in hypocapnia<sup>6;11;13;21;38</sup>. It is hypothesized that exposure to intermittent hypoxia results in an increased chemosensitivity as well<sup>13</sup>.

2) An increased exhalation gain could result in ventilatory control instability. An increased exhalation gain means that a small change in minute ventilation results in huge changes in PaCO<sub>2</sub><sup>13;31</sup>. A decreased lung volume in patients with congestive heart failure due to pulmonary oedema increases the exhalation gain<sup>13;31;39</sup>.

3) A narrow CO<sub>2</sub> reserve could cause ventilatory control instability, since the sleep eupneic CO<sub>2</sub> set point is then close to the apnoea threshold<sup>13</sup>. A narrow CO<sub>2</sub> reserve can be caused by chronic hyperventilation and/or hypocapnia, since this decreases the sleep eupneic CO<sub>2</sub> set point bringing it closer to the apnoea threshold<sup>31</sup>. When there is a narrow CO<sub>2</sub> reserve, small changes in PaCO<sub>2</sub> result in central apnoeas<sup>13</sup>. These central apnoeas result in a deteriorated gas exchange. When a narrow CO<sub>2</sub> reserve is combined with fluctuations in PaCO<sub>2</sub> due to an increased chemosensitivity and/or exhalation gain, this causes cycles of hypercapnia and hypocapnia induced central apnoeas<sup>13</sup>.

4) A decrease in tonic dilator muscle activity results, next to obstructive apnoeas, in central apnoeas as well. The negative pressure and the increased upper airway resistance can cause a ventilatory overshoot, resulting in hypocapnia and a central apnoea.<sup>13</sup>

5) Patients with CSA can suffer from sleep-wake instability, meaning that patients often have arousals. Normally the eupneic PaCO<sub>2</sub> set point is 3-8 mmHg higher during sleep compared to the awake state<sup>13</sup>. If a patient has an arousal, the ventilatory drive increases and the eupneic PaCO<sub>2</sub> decreases to the awake set point. When falling asleep again, the eupneic PaCO<sub>2</sub> set point crosses or approaches the apnoea threshold, which is near the awake set point. This causes central apnoeas and results in ventilatory instability. Patients with high chemosensitivity often suffer from more arousals<sup>13</sup>.

### 1.2.3 Potential effects of nHFT

It is hypothesised that nHFT will stabilise ventilation in patients with congestive heart failure and CSA, with or without Cheyne-Stokes respiration. There are several known working mechanisms of nHFT that might be responsible for this effect (illustrated in Figure 3).

The first working principle of nHFT is the generation of positive (upper) airway pressure by the given flow<sup>26</sup>. The generated pressure is strongly related with the level of flow given<sup>37</sup>. This pressure increases the mean lung volume by recruiting the lungs or upper airways<sup>4;25;31</sup>, which decreases the exhalation gain<sup>13;39</sup>. This decreased exhalation gain makes ventilation more stable, since the magnitude of change in PaCO<sub>2</sub> will be less when minute ventilation changes. By preventing airway collapse by the generated pressure, work of breathing of respiratory muscles could be decreased<sup>4;34</sup> and hypocapnia due to a ventilatory overshoot can be prevented<sup>13</sup>. Moreover, the created pressure could reduce the left ventricular afterload, which results in a decreased heart rate and prevents left ventricular remodelling<sup>4;6</sup>. A difficulty using nHFT is that the delivered airway pressure cannot be controlled completely, since it depends not only on the flow rate, but also on the amount of leak and on the

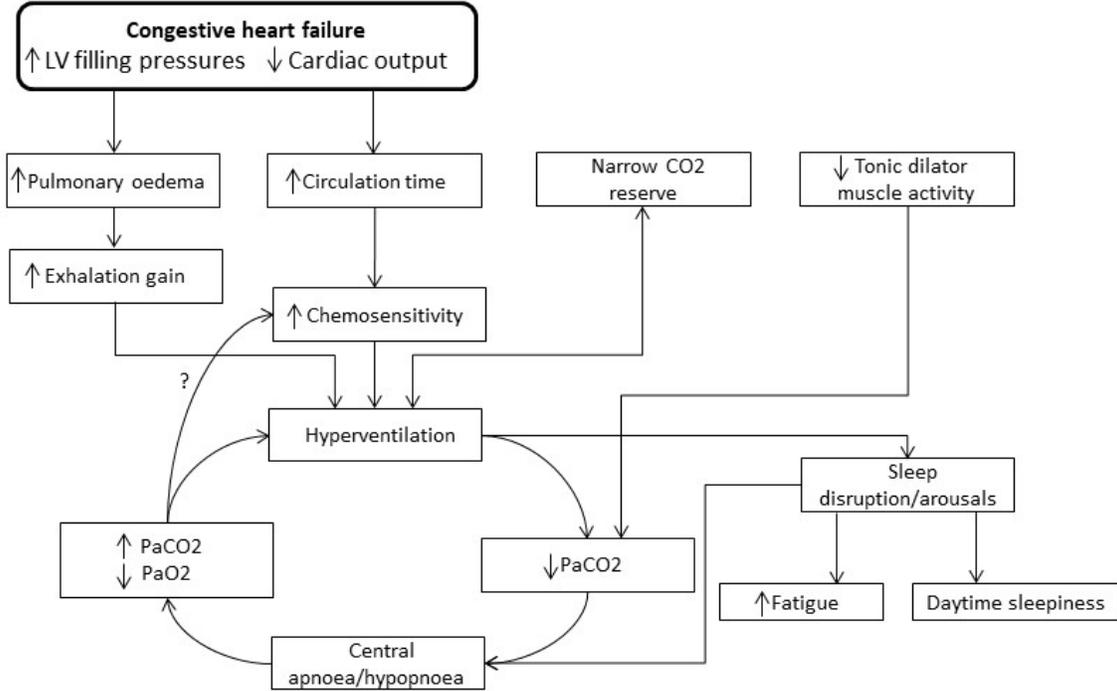


Figure 2: Central sleep apnoea in relation with congestive heart failure. LV = left ventricular.

relation between the nasal cannula and the nasopharyngeal anatomy<sup>25;37</sup>. Therefore, it is important to analyse the delivered airway pressure for each flow rate<sup>37</sup>.

Secondly, the flow can reduce the inspiratory resistance, which reduces the related work of breathing<sup>25;40</sup>.

Thirdly, oxygen addition stimulates the storage of oxygen in haemoglobin instead of carbon dioxide<sup>8</sup>. This ensures that more free carbon dioxide is in the arterial blood, rising the PaCO<sub>2</sub> levels above the apnoea threshold<sup>8</sup>. This reduces chemosensitivity and periods of apnoea<sup>4;31</sup>. Moreover, oxygen addition reduces the amount of oxygen desaturations, which prevents oxidative stress, and prevents an increase in sympathetic activity and work of breathing due to hyperventilation in response to hypoxia<sup>8</sup>.

Fourthly, the applied flow may washout the nasopharyngeal dead space, improving oxygenation<sup>25;33</sup>. Normally, air with high CO<sub>2</sub> and low O<sub>2</sub> levels remains in the anatomical dead space and is rebreathed at the beginning of the inspiration<sup>33</sup>. nHFT continuously flushes the nasopharyngeal dead space with air with low concentrations of CO<sub>2</sub>, which washouts the air in the anatomical dead space<sup>33</sup>. A higher flow probably flushes the low CO<sub>2</sub> levels deeper in the nasal cavity and reduces the volume of inspired CO<sub>2</sub> up to 65%<sup>33</sup>. The washout of the nasopharyngeal dead space improves the effectiveness of ventilation, since alveolar ventilation is a greater fraction of the minute ventilation<sup>25</sup>. This can decrease the respiratory rate<sup>25;27;32;36</sup>. However, the degree of washout created by the flow depends on the size of the cannula in comparison to the nasopharyngeal anatomy<sup>33</sup>.

Finally, warmed and humidified gas is more comfortable for patients than dry and cold air, which might increase the compliance with the therapy and thereby the effectiveness<sup>25;32;37</sup>. Moreover, it reduces the metabolic work associated with gas conditioning, it prevents bronchoconstriction due to cold air and it prevents a dry and irritating airway<sup>25;26;32</sup>. Furthermore, the administration of warmed and humidified gas is associated with an increased clearance of secretions, less atelectasis and improved mucociliary function compared to cold and dry air<sup>26;32</sup>.

Next to the expected advantages of nHFT, there are also possible disadvantages. For example, the high flow of

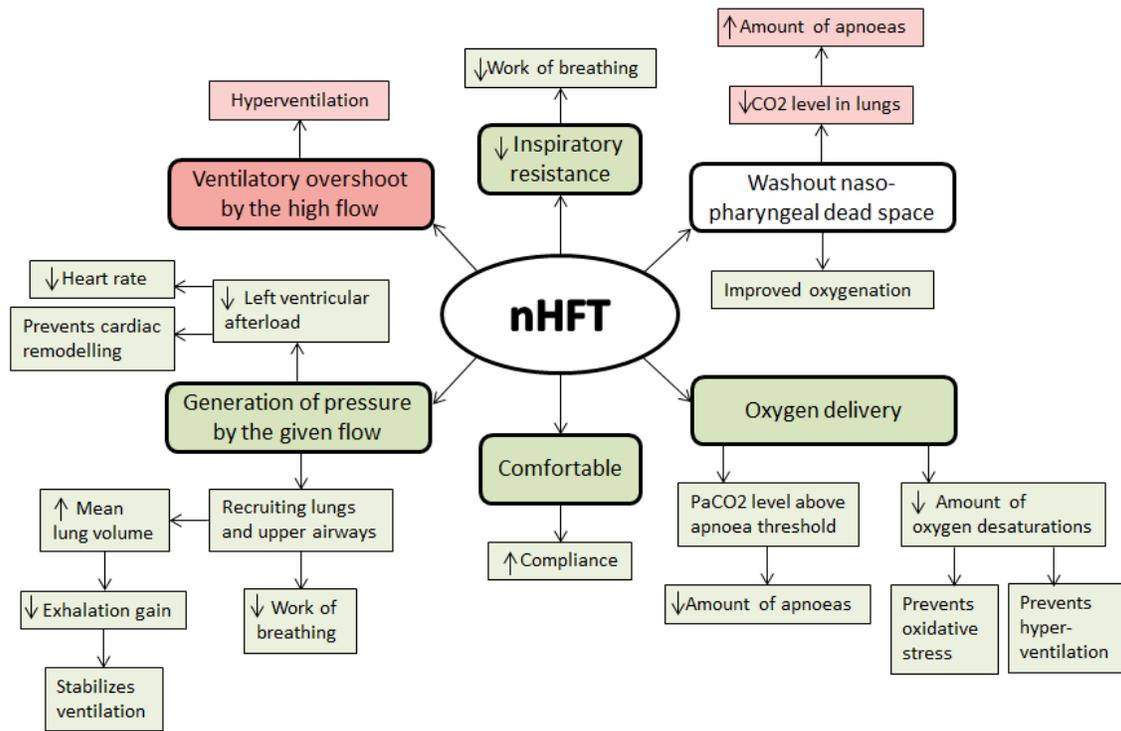


Figure 3: Potential effects of nasal high-flow therapy (nHFT).

air could give a ventilatory overshoot, promoting hyperventilation and thereby ventilatory instability<sup>28</sup>. Furthermore, the pressure generated by the flow is not exactly known and depends on several variables. Therefore, the effectiveness of the therapy could not always be predicted, which makes the application of nHFT difficult<sup>37</sup>. In addition, the washout of the anatomical dead space reduces the CO<sub>2</sub> level, which might induce apnoeas<sup>27</sup>. Finally, the flow applied with nHFT is possibly too low to prevent apnoeas. In a previous study, the AHI did not change with the use of nHFT, since the apnoeas changed into hypopnoeas<sup>28</sup>. In summary, there are several expected advantages of nHFT, such as decreased work of breathing, increased lung volume, decreased left ventricular afterload and good compliance. However, there is also a possibility that patients do not benefit from nHFT, since its effect on decreasing apnoeas and hyperinflation is not known yet. Therefore, a pilot study is needed to investigate the effects of nHFT on patients with congestive heart failure and CSA.

## 1.3 Methods

### 1.3.1 Patient population

At the University Medical Center Groningen, ten patients with severe congestive heart failure (with a left ventricular ejection fraction (LVEF) below 45%) combined with a moderate to severe CSA (AHI $\geq$ 15, with at least 50% central apnoeas) will be included in the study. Patients are excluded from the study when they are treated with CPAP or ASV, and when having other diseases affecting the breathing negatively, such as neuromuscular diseases, thoracic deformations and Chronic Obstructive Lung Disease (COPD) stage III and IV according the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline. Ethical approval is obtained (registered under the University Medical Center Groningen research register number 201700147) and informed consent will be retrieved from all patients. When writing this thesis, the study is on-going. So far, three patients have been included in the study. This thesis is written about the preliminary results of these three patients.

### 1.3.2 Study design

The study is an single-armed intervention pilot study to assess the effectiveness of nHFT for four weeks at home in patients with congestive heart failure and CSA. A flow diagram of the study design can be found in Figure 4.

After patients were included in the study, they came to the hospital for a baseline visit. During the baseline visit complaints were evaluated, venous blood was taken to determine the N-terminal natriuretic peptide (NTproBNP), the six minute walk distance (6MWD) was determined and the Epworth Sleepiness Scale (ESS) and the Functional Outcomes of Sleep Questionnaire (FOSQ) were filled in. Additionally, a polysomnography (PSG) was performed, of which the sleep quality, AHI, and heart rate variability were assessed.

After the baseline visit, patients were hospitalised for a titration night in which nHFT was applied with different settings. During the titration night a PSG was performed, the pressure produced by nHFT was assessed by measuring the pharyngeal pressure ( $P_{pha}$ ), work of breathing was assessed by measuring the oesophageal pressure ( $P_{es}$ ) and the gastric pressure ( $P_{ga}$ ), and neural breathing drive was measured using electromyography (EMG). The nHFT device called SoftFlow 50<sup>®</sup>homecare system (TNI Medical AG, Wurzburg, Germany) was used in this study. First, measurements were performed with different SoftFlow 50<sup>®</sup>settings (0 L/min, 10 L/min, 20 L/min, 30 L/min and 40 L/min) while the patient was awake, during which the patients were asked to breath normally for 3 minutes with the mouth open and for 3 minutes with the mouth closed. Thereafter, the patients were asked to hold the breath for 10 seconds, to sigh and sniff three times, which could help to synchronise the data in the signal analysis phase. When the patients went to bed, nHFT was initially set to a flow rate of 10 L/min. When the patients were asleep, four different nHFT settings were applied during a period of 45-90 minutes, based on the individual expected length

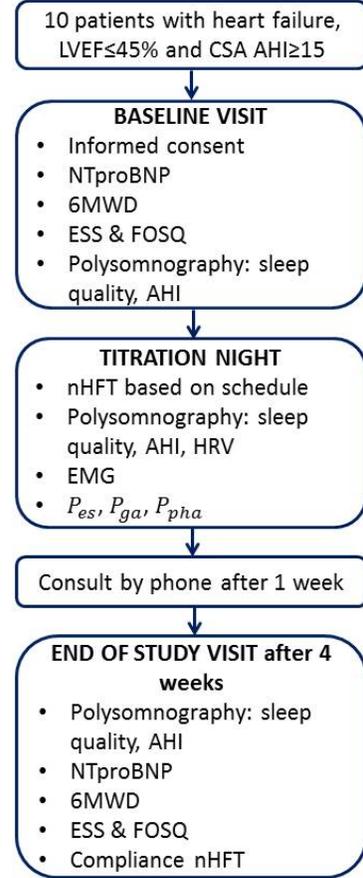


Figure 4: A flow diagram of the study design. LVEF=Left ventricular ejection fraction. CSA=central sleep apnoea. AHI=apnoea hypopnoea index. NTproBNP=natriuretic peptide. 6MWD=six minute walk distance. ESS=Epworth sleepiness scale. FOSQ=Functional Outcomes of Sleep Questionnaire. HRV=Heart rate variability

Table 1: nHFT settings applied to the patient during titration night.

Moderate flow rate: 20 L/min without additional oxygen
High flow rate: 30-40 L/min without additional oxygen
Moderate flow rate: 20 L/min with a FiO <sub>2</sub> of 28%
High flow rate: 30-40 L/min with a FiO <sub>2</sub> of 28%

Table 1. The different nHFT settings applied to the patients for a 45-90 minute period during the titration night. These different settings were applied to the patient in a randomised sequence. When a flow was applied to the patient without additional oxygen, the fractional inspired oxygen (FiO<sub>2</sub>) was equal to 21%, compared with room air. An FiO<sub>2</sub> of 28% was reached by giving additional oxygen.

of sleep. The different nHFT settings can be found in Table 1. The sequence of the settings was randomised for each patient. When all settings were applied to the patients, nHFT was set to a zero flow rate without additional oxygen to measure a baseline. The nHFT setting reducing the amount of apnoea/hypopnoea events the most, was considered as the optimal setting.

After the titration night, the patients used nHFT with the optimal setting for four weeks at home. After one week the patients were contacted by the researcher to evaluate the treatment. After four weeks of treatment the patients came back to the hospital for the final visit. During this visit nHFT usability was evaluated, NT-proBNP and 6MWD were determined, and the questionnaires were addressed (ESS and FOSQ). Additionally, a PSG was performed and compliance with the therapy was assessed. The AHI before and after treatment were compared to assess the efficacy.

### 1.3.3 Measurement setup of titration night

The measurements and/or devices used during the titration night are described below.

#### 1.3.3.1 SoftFlow 50<sup>®</sup>

The nHFT device used in this study, the SoftFlow 50<sup>®</sup>, is shown in Figure 5. A constant, humidified and warm flow, with or without oxygen, was applied to the patient via a nasal cannula. When using the SoftFlow 50<sup>®</sup> it is important that the system is below head height, with at least a distance of 40 cm to the floor or wall and a distance of 80 cm to other electrical devices<sup>41</sup>.



Figure 5: The nasal high-flow therapy device SoftFlow 50<sup>®</sup> homecare system used in the study.

### 1.3.3.2 Polysomnography

PSG was used to monitor patients overnight and to select the best nHFT setting for each patient. A previous study suggested that the therapy could be more successful and less harmful when patients with congestive heart failure and CSA are initiated under PSG monitoring<sup>10</sup>. Normally, a PSG includes an electroencephalogram (EEG) of the brain, oxygen saturation measures at the finger, heart rate variability measures using the electrocardiogram (ECG), measurements of inspiratory airflow with a separate nasal pillow device, measurements of chest and abdominal movements with body plethysmography and measurements of movements of the legs, eyes and chin with EMG.

The EEG and the legs, eyes and chin movements were used to determine sleep stages, sleep quality, total sleep time, sleep efficiency, sleep latency, hours of REM sleep and periodic limb movement.

To detect apnoeas and hypopnoeas, oxygen saturation, measurements of the chest and abdominal movements, and inspiratory airflow were used. The sleep technician scoring the apnoeas and hypopnoeas was blinded to the ventilator settings and subjective evaluation. The AHI was scored on basis of the 2012 American Academy of Sleep Medicine rules<sup>42;43</sup>. An apnoea was detected when there was a drop in airflow of at least 90% of the pre-event baseline for at least 10 seconds, measured by the nasal pillow device<sup>42</sup>. A central apnoea was distinguished from an obstructive apnoea with the use of the chest and abdominal movements, reflecting respiratory effort. A central apnoea was detected when there was an absence of airflow without chest and abdominal movements; and an obstructive apnoea was detected when there was an absence of airflow with chest and abdominal movements (see Figure 6). A hypopnoea was detected when there was a decrease of airflow of at least 30% of the pre-event baseline measured by the nasal device for at least 10 seconds, followed by an oxygen desaturation of at least 3% compared to the pre-event baseline<sup>42</sup>. A respiratory event was scored as Cheyne-Stokes respiration when there

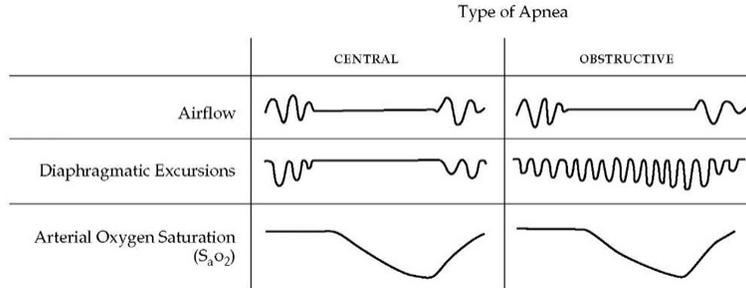


Figure 6: Central apnoea versus obstructive apnoea. In both cases there is an absence of airflow and there is an oxygen saturation drop. With a central apnoea there are no diaphragmatic excursions and with obstructive apnoea there is. The diaphragmatic excursions are equal to chest and abdominal movements<sup>44</sup>.

were three consecutive central apnoeas and/or central hypopnoeas, separated by a crescendo and decrescendo change in breathing amplitude, which took at least 40 seconds<sup>42</sup>. Moreover, when someone is diagnosed with Cheyne-Stokes respiration, the patient must have at least 5 cycles of Cheyne-Stokes breathing per hour<sup>42</sup>. An example of a Cheyne-Stokes breathing pattern is shown in Figure 7.

The ECG was used to determine heart rate variability (HRV). HRV is the variation of time intervals between heartbeats, reflecting the function of the autonomic nerve system that controls the heart rate<sup>46</sup>. The effect of different nHFT settings on HRV was assessed. In previous research, the use of CPAP has shown to decrease HRV, despite its beneficial effects on sympathetic overactivation<sup>47</sup>. This was probably due to a more stable breathing, since the breathing rate and depth also influences HRV<sup>47</sup>. A similar effect of the nHFT on HRV was expected.

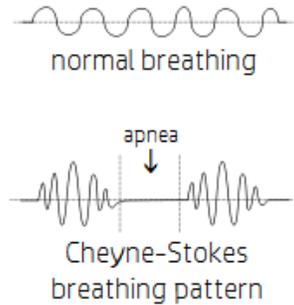


Figure 7: An example of a normal breathing pattern versus a Cheyne-Stokes breathing pattern<sup>45</sup>.

### 1.3.3.3 Pharyngeal pressure

The  $P_{pha}$  was measured to analyse whether nHFT was able to generate a positive (upper) airway pressure. The  $P_{pha}$  was measured by a feeding catheter (3.5 French, equally to 1.17 mm) for premature infants with two holes at the distal end, connected to a pressure transducer. The feeding catheter was introduced proximally in the pharynx through the nose. The pharyngeal pressure signal was recorded with the Dipha-16<sup>®</sup> (DEMCON macawi respiratory systems, Eindhoven, the Netherlands), a battery powered amplifier, which sent the data to a laptop via an USB dongle<sup>48</sup>. The sample frequency was 500 Hz.

### 1.3.3.4 Oesophageal and gastric pressure

The  $P_{es}$  and  $P_{ga}$  were measured to determine work of breathing. Previous studies showed that nHFT could reduce work of breathing by the flow and created  $P_{pha}$ <sup>29;36;40;49</sup>. The work of breathing was determined to analyse the influence of the different nHFT settings on work of breathing. The work of breathing was calculated using transdiaphragmatic pressure ( $P_{di}$ ), which is the pressure that the diaphragm creates to initiate a breathing. The  $P_{di}$  was calculated by subtracting  $P_{ga}$  from  $P_{es}$ . The  $P_{ga}$  and  $P_{es}$  were measured by two balloon catheters connected to pressure transducers, which were introduced through the nose into the oesophagus and the stomach under local anaesthesia in the nose (lidocain spray 1%)<sup>50</sup>. The oesophagus catheter was placed at the distal third of the oesophagus to obtain a signal without cardiac artefacts<sup>49</sup>. Both  $P_{es}$  and  $P_{ga}$  signals were recorded with the Dipha-16<sup>®</sup> with a sample frequency of 500 Hz as well.

### 1.3.3.5 Electromyography signals

EMG signals were derived from respiratory muscles in order to measure neural breathing drive. The influence of the different nHFT settings on neural breathing drive was analysed. EMG signals were measured from the intercostal muscles and frontal diaphragm using transcutaneous electrodes (Inbiolab, Groningen, the Netherlands)<sup>48</sup>. Only EMG signals from the frontal diaphragm and intercostal muscles were measured, since these signals contain less movement artefacts and better muscle activity compared to other respiratory muscles, such as the scalene muscles<sup>48</sup>. Two electrodes were bilaterally placed at the costal margin in the nipple line to measure the activity of the frontal diaphragm and two electrodes were placed bilaterally in the second intercostal space, about 3 cm parasternal, to measure the activity of the intercostal muscles<sup>48</sup>. A common ground electrode was placed on the sternum<sup>48</sup>. The EMG signals were recorded with the Dipha-16<sup>®</sup> with a sample frequency of 500 Hz as well.

### 1.3.4 Data analysis

#### 1.3.4.1 Data recording and synchronisation

The EMG,  $P_{es}$ ,  $P_{ga}$  and  $P_{pha}$  signals were recorded using Polybench<sup>®</sup> data-acquisition package (Applied Biosignals GMBH, Weener, Germany). PSG data were recorded using BrainRT<sup>®</sup>Shell+ (OSG, Rumst, Belgium). Both data recorded with Polybench<sup>®</sup> and BrainRT<sup>®</sup> were loaded in Matlab<sup>®</sup> (v. R2016a, the Mathworks, Natick, Massachusetts, United States), in which further signal processing was conducted.

A few steps were taken to synchronise the data recorded with Polybench<sup>®</sup> and BrainRT<sup>®</sup>. First, the starting time difference between the two measurements was corrected to synchronise the data roughly. Thereafter, the data were synchronised more exactly by using the manoeuvres (holding the breath, sighing and sniffing) which could be found in both measurements. To check whether the synchronisation succeeded, it was verified whether the heart activity measured with the EMG was synchronised with the ECG measurement of the PSG. If not, the synchronisation was corrected by synchronising the pattern of the R-R intervals between successive R-peaks of both the heart activity measured with the EMG and the ECG signal of the PSG. The calculation of the R-R intervals is outlined in section 1.3.4.6.

#### 1.3.4.2 AHI per nHFT setting

The AHI per nHFT setting was estimated by counting the amount of apnoea/hypopnoea events during a 30-minute period and multiplying it by two. Each 30-minute segment was during non-REM sleep. Paired sample t-tests were performed to test for differences in AHI between nHFT settings. The assumption of normality was checked with the Shapiro-Wilk test. A 2-way repeated measures analysis of variance (ANOVA) statistical test was used to test whether 1) there was a significant interaction between the nHFT flow rate and oxygen addition on AHI, 2) nHFT flow rate and oxygen addition has a significant effect on AHI. A significance level of 5% was used. SPSS Statistics<sup>®</sup> (version 24.0, IBM Corporation, Armonk, New York, United States) was used for all analysis.

#### 1.3.4.3 Relationship of delivered flow and the pharyngeal pressure

To analyse the relation between the delivered flow and  $P_{pha}$ , the data from the measurements with different nHFT flow rates, while the patients were awake, were used. From each flow setting, the 3-minute period with the mouth open and mouth closed were used for the analysis. The influence of the mouth open and mouth closed was analysed, since previous research showed that the openness of the mouth has a big influence on the pressures reached in the airway and the pharynx<sup>26</sup>. After the data selection, the signals were pre-processed to remove

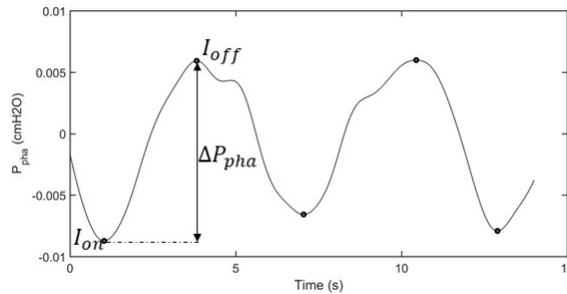


Figure 8: Detection of the pharyngeal pressure amplitude ( $\Delta P_{pha}$ ).  $I_{on}$  is the start of inspiration and  $I_{off}$  is the end of inspiration.

the drift. The low frequencies of the  $P_{pha}$  signal were filtered with a fourth order Butterworth high-pass filter

with a cut-off frequency of 0.1 Hz. The start of inspiration ( $I_{on}$ ) and end of inspiration ( $I_{off}$ ) of each breath were estimated by detecting the most negative and positive peaks using the *findpeaks* function in Matlab<sup>®</sup>. The minimal peak distance between two consecutive breaths was empirically estimated. The amplitude of each breath ( $\Delta P_{pha}$ ) was considered as the difference in  $P_{pha}$  between  $I_{on}$  and  $I_{off}$ , as shown in Figure 8. Breaths with an  $\Delta P_{pha}$  twice the average  $\Delta P_{pha}$  were not included in the analysis. The average  $\Delta P_{pha}$  was calculated for each setting, with the mouth open and mouth closed.

#### 1.3.4.4 Assessment of work of breathing per nHFT setting

For each nHFT setting, a 5-minute period in both REM (when present) and non-REM sleep without artefacts was selected. First, the low frequencies were filtered from both  $P_{es}$  and  $P_{ga}$  signals with a fourth order Butterworth high-pass filter with a cut-off frequency of 0.1 Hz in order to remove the drift. Thereafter, the  $P_{di}$  was calculated using the following equation:

$$P_{di} = P_{ga} - P_{es} \quad (1)$$

For each breath, the change of  $P_{di}$  from baseline to peak ( $\Delta P_{di}$ ) was calculated (shown in Figure 9C), since the  $\Delta P_{di}$  reflects the inspiratory effort of the diaphragm.

The pressure-rate product (PRP) and pressure-time product (PTP), which are measures of work of breathing, were calculated thereafter<sup>36;49</sup>. The PRP was calculated by multiplying the change in  $P_{es}$  ( $\Delta P_{es}$  in Figure 9A) with the respiratory rate (RR)<sup>36</sup>. The  $P_{es}$  is a surrogate for pleural pressure or the pressure required to distend the lung and the chest wall<sup>36</sup>.

$$PRP = \Delta P_{es} * RR \quad (2)$$

The RR was determined by calculating the amount of breaths per minute.

The PTP quantifies inspiratory effort of the muscles. The PTP of the diaphragm was calculated using the following equation<sup>49</sup>:

$$PTP = \int_{t_{on}}^{t_{off}} P_{di} * RR \quad (3)$$

in which  $t_{on}$  is the beginning of inspiration and  $t_{off}$  the end of inspiration.  $t_{on}$  and  $t_{off}$  were determined by the start and end of the inspiratory flow, which are equal to the points where the flow was zero (as shown in Figure 9B). Prior to determining these zero-crossings, the flow signal, measured with the nasal pillow device, was resampled from 32 Hz to 500 Hz. This provided a more accurate detection of the zero-crossings.

The average work of breathing ( $\Delta P_{di}$ , PRP and PTP) was calculated for each setting through these parameters.

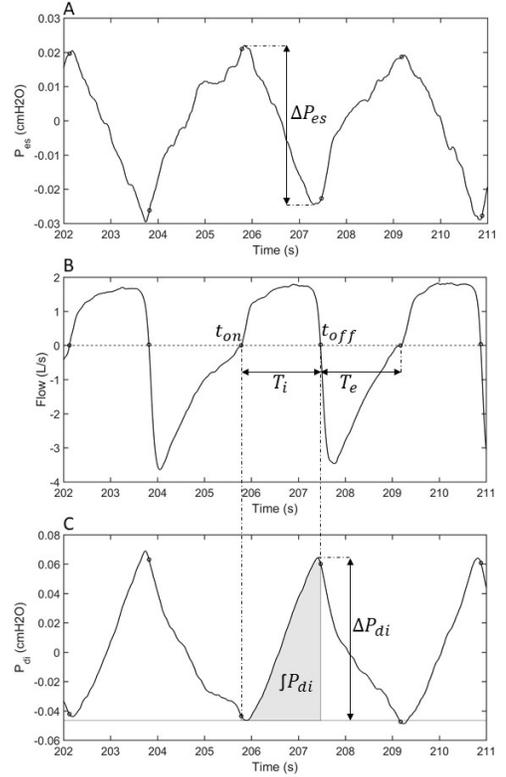


Figure 9: Analysis of work of breathing. **A.** Calculation of the amplitude of the oesophageal pressure ( $\Delta P_{es}$ ), ranging from the maximal point to the minimal point. **B.** Determining the beginning of inspiration ( $t_{on}$ ) and the end of inspiration ( $t_{off}$ ) from the flow signal. The inspiration time ( $T_i$ ) was considered as the time between  $t_{on}$  and  $t_{off}$  and the expiration time ( $T_e$ ) was considered as the time between  $t_{off}$  and  $t_{on}$ . **C.** Calculation of the integral of the transdiaphragmatic pressure ( $\int P_{di}$ ) and the amplitude of the transdiaphragmatic pressure ( $\Delta P_{di}$ ). The  $\int P_{di}$  was calculated from  $t_{on}$  to  $t_{off}$ . The  $\Delta P_{di}$  was considered as the difference in  $P_{di}$  between  $t_{on}$  and the maximal peak.

### 1.3.4.5 Assessment of neural breathing drive per nHFT setting

The selected data used to assess work of breathing were also used to assess neural breathing drive. The EMG signals from the frontal diaphragm ( $EMG_{di}$ ) were used for this analysis. The electrical heart activity was removed from the  $EMG_{di}$  using fixed sample entropy analysis ( $EMG_{di_{fse}}$ ), a non-linear method to analyse non-stationary biomedical signals. This method is less sensitive to electrical heart activity compared to other conventional methods, such as the root mean square value<sup>51</sup>. Based on previous studies<sup>51;52</sup>, the moving window was set to 1 second, the embedding dimension was set to 1, the step size was set to 0.1 times the window size and the fixed tolerance value was set to 0.3 times the standard deviation of the signal.

Thereafter, the neural onset ( $nt_{on}$ ) and neural offset ( $nt_{off}$ ) were determined for each breath (see Figure 10). First, the maximal peak of each breath was selected by using the function *findpeaks* in Matlab<sup>®</sup>. When the  $EMG_{di_{fse}}$  was noisy, and the difference between noise and breathing signal was small, peaks in the  $EMG_{di_{fse}}$  corresponding to a peak in the  $P_{es}$  signal were considered as breaths only. The maximal peak of each breath was then selected by determining each peak in the pre-processed  $P_{es}$  signal and selecting the corresponding  $EMG_{di_{fse}}$  peak. The maximal deviation between the corresponding  $EMG_{di_{fse}}$  peak and the peak in the  $P_{es}$  signal was set to 1 second.

A dynamic threshold was used for determining  $nt_{on}$ . The dynamic threshold was considered as the maximal peak in the amplitude distribution between two consecutive peaks<sup>53</sup>. This maximal peak in the amplitude distribution was considered as the baseline  $EMG_{di_{fse}}$  level when there is no breathing. When the  $EMG_{di_{fse}}$  level crosses the threshold for the last time before a breathing peak, it was considered as the  $nt_{on}$ . The kernel density estimation (KDE) method, a nonparametric method that estimates the probability density function, was used to calculate the amplitude distribution<sup>53</sup>.

The  $nt_{off}$  was considered as the point where the  $EMG_{di_{fse}}$  has decreased to 70% of its maximal peak value, as shown in Figure 10C<sup>53;54</sup>.

Several neural breathing drive parameters were derived from the  $EMG_{di_{fse}}$ . The area under the curve of the  $EMG_{di_{fse}}$  ( $AUC_{EMG}$ ) was calculated for each breath from  $nt_{on}$  to  $nt_{on}$  of the consecutive breath ( $AUC_{EMG1}$ ) and from  $nt_{on}$  to  $nt_{off}$  ( $AUC_{EMG2}$ ), multiplied by the RR. Only the  $AUC_{EMG1}$  is shown in Figure 10C. The amplitude of the  $EMG_{di_{fse}}$  (amp in Figure 10C) was calculated as the difference between  $nt_{on}$  and the maximal peak, multiplied by the RR. Finally, the neural inspiration time ( $T_i$ ) was considered as the time between  $nt_{on}$  and  $nt_{off}$  and the neural expiration time ( $T_e$ ) was considered as the time between  $nt_{off}$  and  $nt_{on}$  of the consecutive peak.

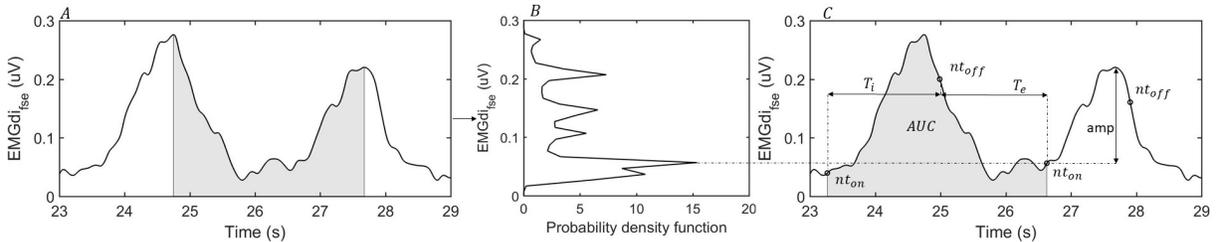


Figure 10: Neural breathing drive analysis<sup>53</sup>. **A.** The area between two consecutive peaks from which the amplitude distribution is determined. **B.** The amplitude distribution, calculated with the kernel density estimation method. The highest peak was considered as the dynamic threshold. **C.** The neural breathing drive parameters determined for each breath. The  $nt_{on}$  is the neural onset, determined with the dynamic threshold. The  $nt_{off}$  is the neural offset at 70% of the maximal peak height. The area under the curve of the  $EMG_{di_{fse}}$  ( $AUC_{EMG}$ ) was determined from  $nt_{on}$  to  $nt_{on}$  of the consecutive peak. The amplitude (amp) of the  $EMG_{di_{fse}}$  was calculated as the difference between  $nt_{on}$  and the maximal peak. The neural inspiration time ( $T_i$ ) was considered as the time between  $nt_{on}$  and  $nt_{off}$ . The neural expiration time ( $T_e$ ) was considered as the time between  $nt_{off}$  and  $nt_{on}$  of the consecutive peak.

### 1.3.4.6 Assessment of heart rate variability per nHFT setting

The total length of the ECG signal during each nHFT setting was used to determine HRV for each setting. The time intervals between heart beats (R-R interval) were determined by calculating the time between two consecutive R-peaks (illustrated in Figure 11). The R-peak from each heart beat was detected using the *findpeaks* function in Matlab<sup>®</sup>. Thereafter, two time domain HRV features (SDNN, RMSSD) were determined, of which a

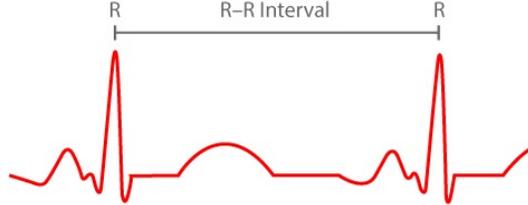


Figure 11: An example of an R-R interval<sup>55</sup>.

description and/or calculation can be found in Table 2<sup>56</sup>. The SDNN reflects the variation in the R-R intervals, which gives insight into the total power in the R-R interval frequency spectrum<sup>46</sup>. The RMSSD reflects the higher frequency variations in the R-R intervals, which decreases when there is less parasympathetic activity<sup>46</sup>. Consequently, five frequency domain HRV features (VLF, LF, HF, total power and the LF/HF ratio) were determined, of which a description can be found in Table 2 as well<sup>57</sup>. In order to calculate the frequency domain HRV features, the successive R-R intervals were resampled at 4 Hz using a cubic spline interpolation. Thereafter, the power spectral density of the resampled signal was calculated using the function *periodogram* in Matlab<sup>®</sup>. The power spectral density in three different frequency bands (VLF, LF and HF), the total power and the LF/HF ratio were calculated, as shown in Table 2. Different frequency bands reflect different (patho)physiological mechanisms. The LF component reflects mainly the sympathetic activity that controls the heart rate and maintains the blood pressure<sup>46;57</sup>. The HF component reflects the parasympathetic control of the heart rate that influences the respiratory sinus arrhythmia<sup>46</sup>. The VLF component is higher in patients with congestive heart failure<sup>57</sup>. When the LF/HF ratio is higher, the sympathetic activity is predominant<sup>57</sup>.

Table 2: Heart rate variability features.

SDNN	Standard deviation of the successive normal sinus R-R intervals.
RMSSD	Root-mean-square of the successive normal sinus R-R intervals.
VLF	Very low frequency ( $f < 0.04$ Hz) power per minute.
LF	Low frequency ( $f > 0.04$ Hz and $f < 0.2$ Hz) power per minute.
HF	High frequency ( $f > 0.2$ Hz and $f < 1$ Hz) power per minute.
Total power	Average power (VLF + LF + HF) per minute.
LF/HF ratio	The ratio of the normalised LF power to the normalised HF power.

## 1.4 Results

### 1.4.1 Tolerance and side effects

From the three patients included in the study so far, the first and third patient dropped out because of non-compliance. The second patient finished the study, but did not decide to continue nHFT afterwards. The first and second patient reported a running nose and nose irritation. Furthermore, the nasal cannula was too large, the light of the device continued to burn, and the device was noisy. No dry throat was reported. After evaluating the complaints of the first two patients, there was decided to use a smaller nasal cannula and to set the humidity between 34-37 °DP to avoid nose irritation. The third patient used nHFT only for two nights due to short of breathing and too high flow rates. No nose irritation and complaints about the nasal cannula were reported. Table 3 shows the compliance with the therapy during the four weeks at home for the second

Table 3: Compliance with the therapy.

	Compliance (%)	Average use (h · day <sup>-1</sup> )
1st patient	85	7.09
2nd patient	71	6.18

patient. The compliance of the first patient with the therapy, during the three weeks he used the therapy at home, is shown as well. On average, the SoftFlow 50<sup>®</sup> was used 78% of the days, with an average using time of 6.64 hours.

### 1.4.2 Effectiveness of nHFT

Table 4 shows the AHI, NTproBNP, 6MWD, ESS and FOSQ before and after nHFT for the second patient. The AHI improved with nHFT. From the apnoea/hypopnoea events detected, 94% were apnoeas and 6% were hypopnoeas during the measurements at T0, and 39% were apnoeas and 61% were hypopnoeas during the measurements at T3. The ESS and FOSQ showed contradicting and inconclusive results. Furthermore, both the NTproBNP and the 6MWD were slightly higher during nHFT.

Table 4: Parameters change after nasal high-flow therapy.

	T0	T3
AHI (events/hour)	30	12
NTproBNP (ng/L)	1726	1837
6MWD (m)	400	440
ESS (0-24)	7	5
FOSQ (0-120)	118	109

Table 4. AHI=apnoea hypopnoea index. NTproBNP=N-terminal natriuretic peptide. 6MWD=Six minute walk distance. ESS=Epworth Sleepiness Scale. FOSQ=Functional Outcomes of Sleep Questionnaire. The ESS has a range from 0 to 24, in which a lower score means less sleepiness problems. The FOSQ has a range from 0 to 120, in which a higher score means less impact of sleepiness on functional outcomes.

### 1.4.3 AHI per nHFT setting during titration night

Figure 12 shows the AHI per nHFT setting for each patient. Since all three patients finished the titration night, the results of all patients are shown. The lowest AHI levels were reached with the addition of oxygen for all patients. The effect of oxygen addition on AHI was significant ( $p=0.046$ ). When looking more specific, oxygen addition showed only significant difference in AHI when the flow rate was 30 L/min ( $p=0.025$ ). A moderate or high flow rate without the addition of oxygen did not decrease AHI below 10 events/hour. A higher nHFT flow rate did also not have a significant effect on AHI ( $p=0.258$ ). There was no significant interaction between the nHFT flow rate and oxygen addition on AHI ( $p=0.635$ ).

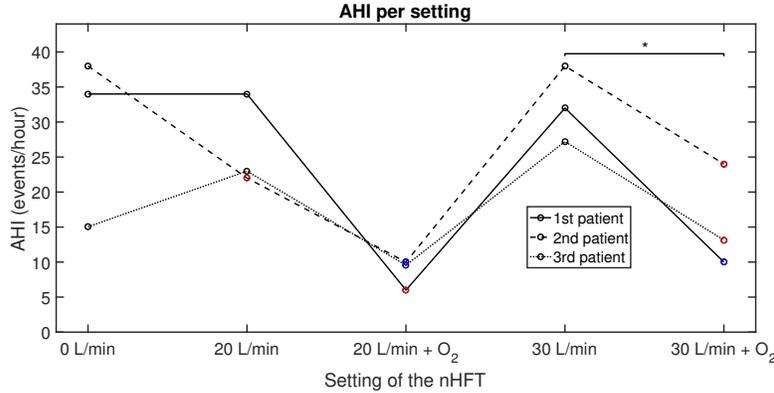


Figure 12: The apnoea hypopnoea index (AHI) per nasal high-flow therapy (nHFT) setting. The nHFT setting is on the x-axis and AHI is on the y-axis. Each line represents the results of one patient. The red dots indicate that during that setting the patient was barely asleep, which gives most likely an undervaluation of AHI. The blue dots indicate the setting which is chosen as the optimal setting for that patient in decreasing AHI. The \* means that the difference in AHI between those two settings was significant ( $p=0.025$ ).

In Table 5, additional parameters (AHI, sleep stage and mouth openness) during each nHFT setting are shown for each patient. Patient 1 slept the whole night with the mouth open and patient 2 slept the whole night with the mouth closed. Patient 3 slept almost the whole night with the mouth open. Patient 1 and 2 did not have any periods of REM sleep during the titration night. Patient 3 had only a REM period at the end of the night, when the flow rate was 0 L/min.

### 1.4.4 Relationship of delivered flow rate and pharyngeal pressure

Figure 13 shows the relationship between the nHFT flow rate and the  $\Delta P_{pha}$ , for both mouth open and mouth closed. The  $\Delta P_{pha}$  with the mouth closed was higher compared to the  $\Delta P_{pha}$  with the mouth open for every flow rate. The pressures measured with both the mouth open and mouth closed were negligible, since all pressures were close to zero.

### 1.4.5 Assessment of work of breathing per nHFT setting during titration night

Figure 14 shows the  $\Delta P_{di}$ , PRP, PTP and RR during each nHFT setting for the first two patients. The data of patient 3 were missing, since he did not tolerate the balloon catheters. The  $\Delta P_{di}$ , PRP and PTP were higher in patient 2 compared to patient 1. For both patients, the  $\Delta P_{di}$  remained around the same level during most nHFT settings, as shown in Figure 14A. Only the setting with a flow rate of 20 L/min with additional oxygen showed an increased  $\Delta P_{di}$  for patient 1 and a decreased  $\Delta P_{di}$  for patient 2.

The PRP was comparable to the PTP (see Figure 14B&C). For patient 1, the PRP and PTP remained around

Table 5: Additional parameters during each nHFT setting for each patient. AHI = apnoea hypopnoea index. The percentage of each sleep stage during each nHFT setting was determined.

<b>1st patient</b>	0 L/min	20 L/min	20 L/min + O <sub>2</sub>	30 L/min	30 L/min + O <sub>2</sub>
AHI	34	34	6	32	10
Awake (%)	48	50	53	21	21
Light sleep (%)	52	43	47	79	56
Deep sleep (%)	0	7	0	0	23
REM sleep (%)	0	0	0	0	0
Mouth openness	open	open	open	open	open
<b>2nd patient</b>	0 L/min	20 L/min	20 L/min + O <sub>2</sub>	30 L/min	30 L/min + O <sub>2</sub>
AHI	38	22	10	38	24
Awake (%)	8	21	9	0	32
Light sleep (%)	85	79	12	81	68
Deep sleep (%)	7	0	79	19	0
REM sleep (%)	0	0	0	0	0
Mouth openness	closed	closed	closed	closed	closed
<b>3rd patient</b>	0 L/min	20 L/min	20 L/min + O <sub>2</sub>	30 L/min	30 L/min + O <sub>2</sub>
AHI	15	23	10	27	13
Awake (%)	29	17	36	5	37
Light sleep (%)	57	52	64	66	63
Deep sleep (%)	4	30	0	29	0
REM sleep (%)	10	0	0	0	0
Mouth openness	open	open and closed	open and closed	open	open

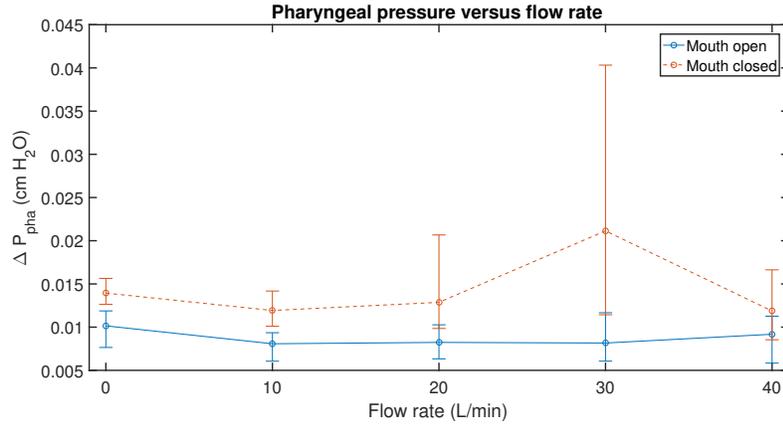


Figure 13: The relationship between the delivered flow by nasal high-flow therapy (nHFT) and the amplitude of the pharyngeal pressure ( $\Delta P_{pha}$ ), for both mouth open (the blue line) and mouth closed (the dashed red line). The nHFT flow rate is on the x-axis and the average  $\Delta P_{pha}$  is on the y-axis. The vertical lines indicate the spread between patients.

the same level for each nHFT setting. For patient 2, the PRP and PTP decreased with a higher nHFT flow rate.

The RR was variable between the different settings for both patients, as shown in Figure 14D. For patient 1, the

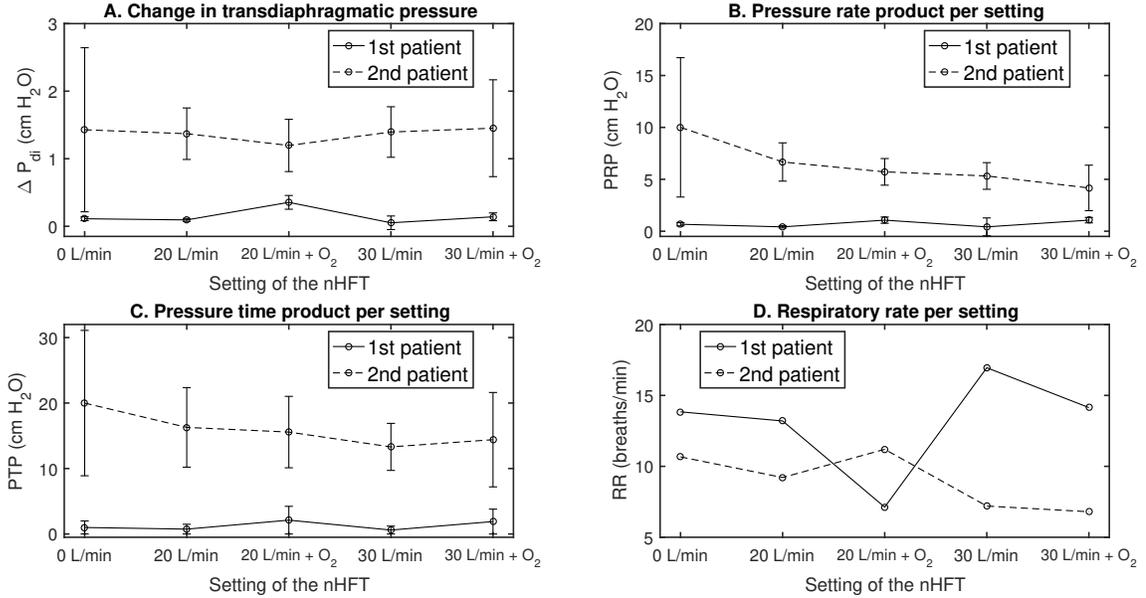


Figure 14: Several work of breathing parameters during each nasal high-flow therapy (nHFT) setting for two patients (differentiated with different lines). **A.** The average amplitude of the transdiaphragmatic pressure ( $\Delta P_{di}$ ) during each nHFT setting, indicated with a dot. The vertical lines show the standard deviation. **B.** The pressure-rate product (PRP) during each nHFT setting, indicated with a dot. The vertical lines show the standard deviation. **C.** The average pressure-time product (PTP) during each nHFT setting, indicated with a dot. The vertical lines show the standard deviation. **D.** The respiratory rate (RR) during each nHFT setting.

RR during the setting with an oxygen enriched flow rate of 20 L/min was lower compared to the other settings. For patient 2, the RR was lower with a flow rate of 30 L/min compared to the settings with a flow rate of 0 L/min and 20 L/min.

#### 1.4.6 Assessment of neural breathing drive per nHFT setting during titration night

Figure 15 shows the average  $AUC_{EMG}$  from  $nt_{on}$  to  $nt_{on}$  of the consecutive peak ( $AUC_{EMG1}$ ), the average  $AUC_{EMG}$  from  $nt_{on}$  to  $nt_{off}$  ( $AUC_{EMG2}$ ), and the average amplitude during each nHFT setting. For patient 1, both  $AUC_{EMG1}$  and  $AUC_{EMG2}$  increased with a higher flow rate and decreased slightly with the setting providing a flow rate of 30 L/min with additional oxygen. The average amplitude for patient 1 fluctuated, but showed an increasing trend with a higher flow rate. However, the results of patient 1 are not reliable, since the EMG signals of patient 1 were noisy, which made the analysis difficult to perform.

For patient 2, the average  $AUC_{EMG2}$  and average amplitude decreased with a higher flow rate and were slightly higher with an oxygen enriched flow rate of 30 L/min. The average  $AUC_{EMG1}$  for patient 2 was lower with an oxygen enriched flow rate of 20 L/min and a flow rate of 30 L/min, and was higher with a flow rate of 30 L/min with additional oxygen.

For patient 3, the average  $AUC_{EMG1}$ , the average  $AUC_{EMG2}$ , and the average amplitude were lower with the settings with additional oxygen. Furthermore, the neural breathing drive parameters were all lower with a flow rate of 30 L/min than with a flow rate of 20 L/min.

The average inspiratory and expiratory time during each nHFT setting for all patients are shown in Table 6. For patient 1, the inspiratory time was higher when additional oxygen was given. The expiratory time was higher

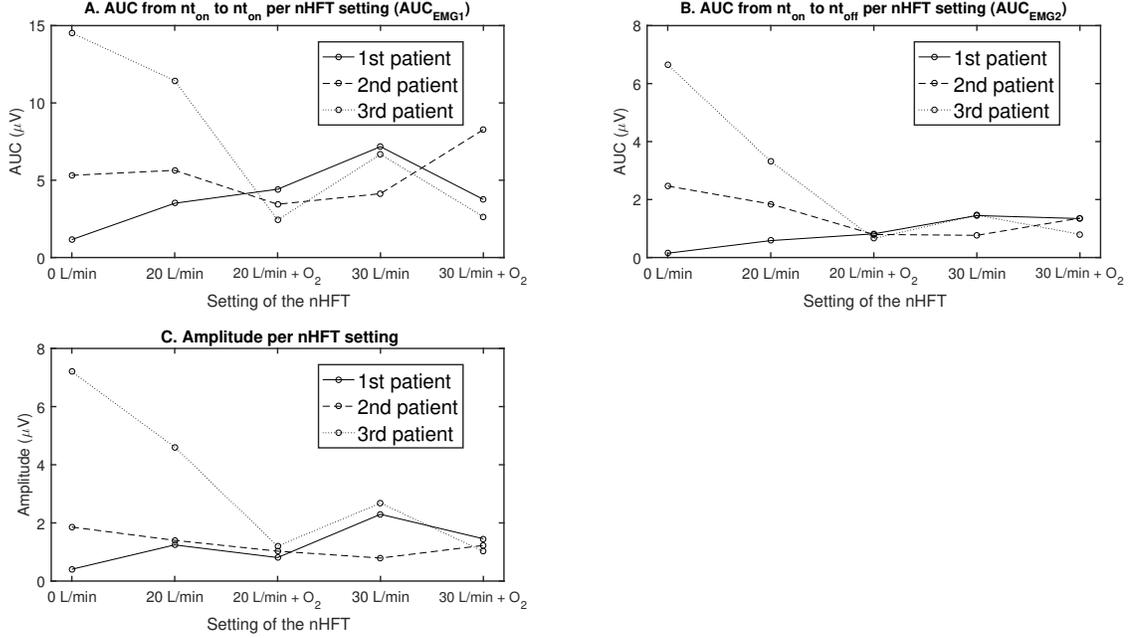


Figure 15: Neural breathing drive parameters during each nasal high-flow therapy (nHFT) setting for all patients (differentiated with different lines). **A.** The average area under the curve of the EMG $_{di_{fse}}$  ( $AUC_{EMG}$ ) from the neural onset ( $nt_{on}$ ) to  $nt_{on}$  of the consecutive breath ( $AUC_{EMG1}$ ). **B.** The average  $AUC_{EMG}$  from  $nt_{on}$  to the neural offset ( $nt_{off}$ ) ( $AUC_{EMG2}$ ). **C.** The average amplitude.

Table 6: Inspiratory ( $T_i$ ) and expiratory ( $T_e$ ) time per nasal high-flow therapy setting for all patients.

$T_i - T_e$ (s)	0 L/min	20 L/min	20 L/min + O <sub>2</sub>	30 L/min	30 L/min + O <sub>2</sub>
1st patient	0.92 — 3.20	0.84 — 3.74	2.05 — 6.55	1.05 — 3.04	1.34 — 2.31
2nd patient	2.16 — 3.40	2.19 — 4.11	1.26 — 3.43	1.56 — 5.95	1.90 — 5.20
3rd patient	1.70 — 2.29	1.27 — 1.80	1.03 — 2.08	1.12 — 1.97	1.36 — 2.60

with a flow rate of 20 L/min with and without additional oxygen and was lower with a flow rate of 30 L/min. For patient 2, the inspiratory time decreased with a higher flow rate and the expiratory time increased with a higher flow rate. For patient 3, the inspiratory and expiratory time were comparable for all nHFT settings.

#### 1.4.7 Assessment of heart rate variability per nHFT setting during titration night

Table 7 shows the HRV features during each nHFT setting for patient 2 and 3. HRV analysis could not be performed for patient 1 due to noisy ECG signals.

For patient 2, the SDNN, reflecting the variation in R-R intervals, was higher with the settings with a flow rate of 20 L/min and 30 L/min with additional oxygen. More high frequency variations were present in the R-R intervals with the settings with a flow rate of 20 L/min and 30 L/min with additional oxygen, reflected by a higher RMSSD and a higher power in the HF frequency band. The total power was higher with these settings as well. A higher power in the VLF frequency band and LF frequency band was present with the setting with

Table 7: Heart rate variability parameters per nasal high-flow therapy setting for patient 2 and 3.

<b>2nd patient</b>	0 L/min	20 L/min	20 L/min + O <sub>2</sub>	30 L/min	30 L/min + O <sub>2</sub>
SDNN (s)	0.37	0.42	0.37	0.33	0.46
RMSSD (s)	0.53	0.60	0.53	0.47	0.63
VLF (s <sup>2</sup> *60/Hz)	4.48	12.20	3.67	4.62	46.36
LF (s <sup>2</sup> *60/Hz)	13.03	25.15	12.07	18.03	44.26
HF (s <sup>2</sup> *60/Hz)	30.95	47.74	30.34	24.52	42.62
Total power (s <sup>2</sup> *60/Hz)	48.46	94.37	46.06	47.17	133.24
LF/HF ratio	0.42	0.72	0.40	0.74	1.04
<b>3rd patient</b>	0 L/min	20 L/min	20 L/min + O <sub>2</sub>	30 L/min	30 L/min + O <sub>2</sub>
SDNN (s)	0.24	0.27	0.20	0.23	0.25
RMSSD (s)	0.29	0.36	0.29	0.30	0.34
VLF (s <sup>2</sup> *60/Hz)	2.06	5.88	0.78	0.86	3.37
LF (s <sup>2</sup> *60/Hz)	5.66	10.17	2.43	4.43	3.82
HF (s <sup>2</sup> *60/Hz)	10.45	16.48	7.70	12.36	9.08
Total power (s <sup>2</sup> *60/Hz)	18.17	32.53	10.92	17.66	16.27
LF/HF ratio	0.54	0.62	0.32	0.36	0.42

an oxygen enriched flow rate of 30 L/min. Sympathetic activity was predominant with the settings with a flow rate of 20 L/min, 30 L/min and 30 L/min with additional oxygen, reflected by a higher LF/HF ratio.

For patient 3, all HRV features were higher with the setting with a flow rate of 20 L/min. Additionally, the SDNN, reflecting the variation in R-R intervals, was lower with the setting with an oxygen enriched flow rate of 20 L/min. The power in the VLF frequency band was lower with the settings with a flow rate of 20 L/min with additional oxygen and 30 L/min. The sympathetic activity was more predominant with the setting with a flow rate of 0 L/min, reflected by a higher LF/HF ratio.

## 1.5 Discussion

The first aim of this study was to analyse whether ventilation of patients with congestive heart failure and moderate to severe CSA could be stabilised by applying nHFT for four weeks during the night. The preliminary results of one patient, showing a decreased AHI after nHFT, gives indications that applying nHFT for four weeks during the night makes ventilation more stable in these patients.

The second aim of the study was to investigate what the mechanisms of action are of nHFT on patients with congestive heart failure and CSA. Especially oxygen addition reduced AHI. An increase of the pharyngeal pressure with a higher nHFT flow rate was not measured. Work of breathing reduced with a higher flow rate in one patient. Furthermore, nHFT reduced the neural breathing drive, but did not influence HRV.

The third research question of the study was to analyse how the optimal nHFT setting reducing AHI in patients with congestive heart failure and CSA could be determined during the titration night. Since the titration nights were not representative for a normal night due to low sleep efficacy, this question could not be answered.

These preliminary results are further discussed in the subsections below. Thereafter, limitations of the study and directions for future research are given.

### 1.5.1 Effectiveness of nHFT in stabilising ventilation

The AHI decreased in the only patient who has finished the study so far. This indicates that nHFT might stabilise ventilation in patients with congestive heart failure and CHF. However, AHI has substantial night-to-night variations<sup>58</sup>. So, more patients need to be measured to confirm the effectiveness of nHFT reducing AHI. A previous study showed that AHI did not change with nHFT in patients with OSA, since the apnoeas changed into hypopnoeas<sup>28</sup>. In our patient, less apnoeas and more hypopnoeas were measured as well after nHFT, which indicates that nHFT indeed could change apnoeas into hypopnoeas. More patients are needed to confirm this as well.

### 1.5.2 Mechanisms of action of nHFT

The expected mechanisms of action of nHFT were outlined in section 1.1 and 1.2. Each expected mechanism of action is discussed in the paragraphs below.

#### 1.5.2.1 Generation of positive (upper) airway pressure

It was expected that nHFT would generate a positive (upper) airway pressure<sup>26</sup>, which stabilises ventilation<sup>13</sup>, decreases work of breathing<sup>4;34</sup> and prevents left ventricular remodelling<sup>4;6</sup>. In this subsection it is discussed whether nHFT was able to generate a positive (upper) airway pressure, and whether it was able to stabilise ventilation by this created pressure. The influence of nHFT on work of breathing is discussed in subsection 1.5.2.2 and its influence on the heart is discussed in subsection 1.5.2.7.

#### *Generation of positive (upper) airway pressure*

The  $P_{pha}$  was measured to analyse whether nHFT was able to generate a positive (upper) airway pressure. The measured  $P_{pha}$  was negligible, indicating that nHFT was not able to generate a positive (upper) airway pressure. A previous study<sup>59</sup> showed an average pressure of 1.93 cm H<sub>2</sub>O with a flow rate of 30 L/min. Physiologically, the pressures measured in this previous study are more reasonable than the pressures measured in this study. The results might be lower than expected due to a leak of flow. However, since the  $P_{pha}$  measured with the mouth closed was negligible as well and the researchers did not hear any leak, this is not likely. Moreover, the production of saliva might have blocked the two holes at the distal end of the catheter, which might have induced a wrong measurement of  $P_{pha}$ .

To analyse whether the production of saliva blocked the distal end of the catheter, the feeding catheter (3.5 French) and the SoftFlow 50<sup>®</sup> were introduced to one healthy subject. Different SoftFlow 50<sup>®</sup> settings (0 L/min,

10 L/min, 20 L/min, 30 L/min and 40 L/min) were applied while the healthy subject was awake, during which the healthy subject was breathing normally for 1 minute with the mouth open and 1 minute with the mouth closed. To prevent occlusion of the catheter by saliva during the measurements, the feeding catheter was flushed with 4 ml of air every 5 minutes and after the healthy subject swallowed. During the measurements, the real time  $P_{pha}$  showed a decreased amplitude after the healthy subject swallowed, indicating that indeed the production of saliva can obstruct the catheter. The relationship between the nHFT flow rate and  $\Delta P_{pha}$  for this healthy subject, for both the mouth open and mouth closed, is shown in Figure 16A. The  $\Delta P_{pha}$  increased with

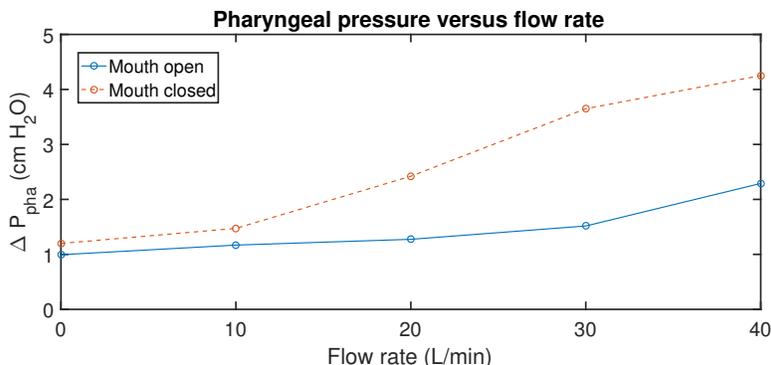


Figure 16: The relationship between the delivered flow rate by the nasal high-flow therapy (nHFT) and the amplitude of the pharyngeal pressure ( $\Delta P_{pha}$ ), for both the mouth open (the blue line) and mouth closed (the dashed red line), for a healthy subject. The nHFT flow rate is on the x-axis and the average  $\Delta P_{pha}$  is on the y-axis.

both the mouth open and mouth closed, but increased faster with the mouth closed. With the mouth open, there is leakage of flow and therefore the  $\Delta P_{pha}$  was lower. This is in agreement with previous studies<sup>26;59</sup>. Since the  $\Delta P_{pha}$  was higher with the mouth closed, this might have an effect on stabilising ventilation. Thus, if possible, patients should sleep with the mouth closed when using nHFT.

The measured pressures were slightly higher compared to a previous study (3.65 cm H<sub>2</sub>O versus  $1.93 \pm 1.25$  cm H<sub>2</sub>O for a flow rate of 30 L/min)<sup>59</sup>. A different nHFT device was used in the previous study (Optiflow<sup>®</sup> produced by Fisher & Paykel Healthcare), which might explain the different results. Both nHFT devices use a different nasal cannula. The size and shape of the nasal cannula influences the resistance<sup>25;37</sup> and therefore might influence the pressure generated by the applied flow rate. Moreover, there is also variation between different persons, which might explain the difference as well.

The results of this healthy subject indicate that the  $\Delta P_{pha}$  measured in the three patients were indeed lower due to saliva production, which obstructed the catheters. Therefore, it is likely that the  $\Delta P_{pha}$  did increase with a higher flow rate in these patients, but it could not be measured. Airway collapse could be prevented when the  $\Delta P_{pha}$  did increase with a higher nHFT flow rate.

It is recommended to apply a 20 ml/h airflow produced by a microinfusor at the inlet of the catheter to avoid occlusion of the catheter by secretions<sup>40</sup>. This could be applied in the remaining seven patients that need to be included in the study. The data of these seven patients could be used to perform a linear regression analysis to analyse whether there is a linear relation between the flow rate and the  $\Delta P_{pha}$ .

### ***Stabilising ventilation by the created pressure***

During the titration night, AHI did not decrease significantly when a moderate or high nHFT flow rate was applied without additional oxygen. This indicates that a flow rate alone, and thereby the generation of positive (upper) airway pressure by the given flow, does not reduce AHI. It was hypothesised that an increased positive (upper) airway pressure would increase mean lung volume<sup>4;25;31</sup>, which decreases the exhalation gain<sup>13</sup>. These results indicate that either nHFT is not able to increase mean lung volume, or a decreased exhalation gain does

not reduce the amount of central apnoeas. However, since there were only three patients, the statistical results are not fully reliable. Therefore, a bigger sample size is required to reliably validate this result. Although, since the AHI did not decrease with a moderate or high flow rate without additional oxygen in these patients, it is not expected that the flow rate will significantly decrease AHI when more patients are included.

### 1.5.2.2 Reduction of inspiratory resistance and related work of breathing

It was expected that the nHFT flow rate would reduce inspiratory resistance, which reduces the related work of breathing<sup>25;40</sup>. Additionally, by preventing an airway collapse by the creation of positive (upper) airway pressure, work of breathing could be reduced as well<sup>4;34</sup>. In this section there is discussed whether nHFT was able to reduce both work of breathing and neural breathing drive.

#### *Assessment of work of breathing per nHFT setting during titration night*

PRP and PTP are measures of work of breathing, and previous research showed that nHFT could reduce work of breathing<sup>29;36;40;49</sup>. In patient 2, work of breathing did indeed decrease with a higher nHFT flow rate. This indicates that a higher nHFT flow rate might reduce inspiratory resistance, since reduced inspiratory resistance is related with reduced work of breathing<sup>25;40</sup>. Moreover, the generated pressure by the given flow could have prevented an airway collapse, which could also have decreased work of breathing<sup>4;34</sup>. Patient 1 did not show a decreased work of breathing with a higher nHFT flow rate, which does not support the hypothesis that nHFT could reduce work of breathing. As discussed in section 1.5.2.1, the pressure created by the flow depends on the amount of leak through the mouth<sup>25;37</sup>. Since patient 1 only slept with the mouth open, this might explain that the work of breathing did not decrease with a higher flow rate.

For both patients, the  $\Delta P_{di}$  did not differ a lot between the different nHFT settings. The variation within the patients could be explained by the variation in the RR. For instance, the RR during the setting with an oxygen enriched flow rate of 20 L/min was the lowest for patient 1, while the  $\Delta P_{di}$  during this setting was the highest. When the RR is lower, there is also more time to breath deeper, resulting in an increased transdiaphragmatic pressure. To assess work of breathing per breath, the RR must be taken into account. Therefore, conclusions according work of breathing during different settings must be taken from the PRP and PTP results and cannot be taken from the change in  $P_{di}$  without correcting for the influence of the RR.

#### *Assessment of neural breathing drive per nHFT setting during titration night*

The EMG signals of patient 1 were noisy, and the analysis of the neural breathing drive was therefore difficult to perform. Hence, the results of the neural breathing drive of the first patient are not reliable. For patient 1, the neural breathing drive increased with a higher flow rate and decreased with the setting with a flow rate of 30 L/min with additional oxygen. This is not expected, since the muscles should be more relaxed when they are supported by nHFT. For all patients, the EMG was applied in the same way and therefore this cannot explain the noisy EMG signals of patient 1. However, the Diphera-16<sup>®</sup> was not working optimally during the night for patient 1, since it stopped measuring every 6 minutes. Furthermore, one electrode on the frontal diaphragm disconnected during the night, which might explain the noisy EMG signals as well.

For patient 2, the average  $AUC_{EMG2}$  and average amplitude were comparable to the PTP (see Figures 15B&C and 14C). This is expected, since there is less neural breathing drive when the muscles need to perform less work of breathing. This also indicates that patient 2 could relax his muscles more during inspiration with a higher flow rate. The average  $AUC_{EMG1}$  does also include the work of the muscles between breaths, so including the expiration. The muscles were able to relax more between breaths with the settings with an oxygen enriched flow rate of 20 L/min and with a flow rate of 30 L/min. The setting with a flow rate of 30 L/min with additional oxygen did increase the work of the muscles between breaths. These results could not be explained. Possibly, cross-talk of the abdominal muscles contribute to the neural breathing drive measured during expiration. The cross-talk is especially expected with a higher nHFT flow rate, since more effort is needed to exhale against this flow rate. However, this could not explain the different results between the settings with a flow rate of 30

L/min with and without oxygen. More patients are needed to further analyse this.

For patient 3, all neural breathing drive parameters were lower with the settings with additional oxygen. Furthermore, the neural drive parameters were lower with the settings with a flow rate of 30 L/min compared to a flow rate of 20 L/min. This indicates that the patient could relax the muscles more with a higher flow rate and with additional oxygen.

The inspiratory time decreased and expiratory time increased with a higher flow rate for patient 2. A higher flow rate reduces the inspiratory resistance, which makes it easier for the patient to breath in<sup>25;40</sup>. Less time is needed to breath in with a higher flow rate and therefore the inspiratory time decreases. However, the continuous flow of nHFT increases the expiratory resistance, since the patient needs to exhale against this flow rate. Therefore, more expiratory time is needed to overcome this increased expiratory resistance. However, the results of the inspiratory time and the expiratory time of patient 1 were contradicting: the expiratory time decreased and the inspiratory time increased with a higher flow rate. This was not expected, since the inspiratory resistance decreases and the expiratory resistance increases with a higher flow rate. However, since the signals of patient 1 were noisy, these results are not reliable as well. The different settings did not change the inspiratory and expiratory time in patient 3, indicating that the settings did not influence the inspiratory and expiratory time in this patient.

### 1.5.2.3 Reduction of periods of apnoeas by the addition of oxygen

During the titration night, AHI was significantly decreased with the addition of oxygen and did not decrease significantly with a higher nHFT flow rate. This indicates that especially oxygen addition makes ventilation more stable in patients with congestive heart failure and CSA. As discussed in section 1.2, oxygen addition stabilises ventilation by preventing oxygen desaturations and increasing the storage of oxygen in haemoglobin, which reduces chemosensitivity and periods of apnoea<sup>8</sup>. The AHI was probably not significantly different between the nHFT settings with a flow rate of 20 L/min with and without oxygen due to the low sample size. This has a great influence on statistically significant results. More patients should be measured to verify whether oxygen addition has indeed a significant effect on decreasing AHI.

### 1.5.2.4 Washout of the nasopharyngeal dead space

It was expected that nHFT would improve the effectiveness of ventilation due to the washout of the nasopharyngeal dead space<sup>25;33</sup>. This could reduce the RR. The results (shown in Figure 14D) showed that indeed the RR decreased with a higher nHFT flow rate for patient 2. This gives an indication that nHFT did washout the nasopharyngeal dead space, which improved the effectiveness of ventilation<sup>25</sup>. However, for patient 1 the RR did not decrease with a higher flow rate. Other factors could also influence the RR, such as the sleep stage or the number of apnoeas during that period, which could explain the opposite results. Therefore, the RR only could not be used to determine whether there was a washout of the nasopharyngeal dead space.

The washout of the nasopharyngeal dead space could have negative side effects. For instance, it could induce apnoeas, since it reduces the CO<sub>2</sub> level in the lung<sup>27</sup>. The AHI was not higher with a higher nHFT flow rate. This indicates that 1) the washout of the nasopharyngeal dead space does not induce apnoeas, or 2) the effect of the generation of a positive (upper) airway pressure on AHI is higher than the effect of the washout of the nasopharyngeal dead space.

### 1.5.2.5 High compliance due to warmed and humidified air

It was expected that the compliance would be high due to the warmed and humidified air, which should be comfortable<sup>25;32;37</sup>. Furthermore, compliance rates of previous studies were high<sup>32;35</sup>.

The results so far showed a poor satisfaction: there was a 66% drop out, and the only patient who finished the study, did not decide to continue nHFT afterwards. The average using time per day was high compared to the average using time per day of CPAP therapy (3.6 hours<sup>17</sup>). More patients need to be included to further

evaluate the compliance and compare it to CPAP therapy.

The reported complaints of a running nose and nose irritation could be explained by a too low humidity level. At the beginning, the patients were told to choose their own humidity level, instead of advising a humidity level between 34-37 °DP. It is expected that these complaints could be prevented by a higher humidity level. A too large nasal cannula was another complaint: after the second patient complaining about the large nasal cannula as well, smaller nasal cannulas were used, and the third patient did not report complaints about the nasal cannula. The complaints about the device (burning light and noisy) will be reported to the company. The complaints could have contributed to the low compliance. Another complaint, reported during the titration night, was that the flow rate was high and that patients could not exhale easily. This complaint is discussed more extensively in subsection 1.5.2.6.

### 1.5.2.6 Hyperventilation due to a ventilatory overshoot

High flow of air could give a ventilatory overshoot, promoting hyperventilation and thereby ventilatory instability<sup>28</sup>. Since AHI did not increase with a higher flow rate, it seems that nHFT does not induce ventilatory instability. The researchers even noticed that the patients needed more time to exhale when the applied flow was higher than 20 L/min. The patients indicated as well that they found it difficult to exhale when using nHFT with flow rates higher than 20 L/min. To confirm these findings, the RR in the healthy subject, which was measured to compute the  $P_{pha}$  without occlusion of the catheter, was determined during each flow setting with the mouth open and mouth closed (see Figure 17). The RR with the mouth closed was lower compared

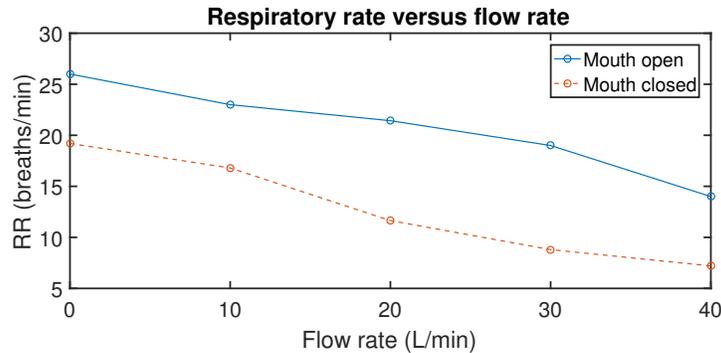


Figure 17: The relationship between the delivered flow by nHFT and the respiratory rate (RR), for both the mouth open (the blue line) and mouth closed (the dashed red line), for a healthy subject. The nHFT flow rate is on the x-axis and the RR is on the y-axis.

to the RR with the mouth open. Moreover, the RR decreased when applying a higher nHFT flow rate, and did not increase as expected when a high flow rate induces hyperventilation. The RR decreased, since the healthy subject needed more time to exhale against the increasing generated flow and the associated increasing created pressure (which was 4.25 cm H<sub>2</sub>O with a flow rate of 40 L/min). Less pressure was generated with the mouth open, which could explain why the RR was higher with the mouth open compared to the mouth closed.

A decreased RR might be beneficial for patients with CSA, since this prevents hyperventilation and an associate low CO<sub>2</sub> level triggering a central apnoea. However, there is also a risk of hyperinflation when patients do not take enough time to exhale. Although, an increased lung volume decreases the exhalation gain<sup>13</sup>, which is beneficial for stabilising ventilation as well.

### 1.5.2.7 Effect of nHFT on the heart

In the only patient who finished the study, NTproBNP was slightly higher after nHFT. Whether this is due to nHFT or due to common day-to-day variations<sup>60</sup>, could not be determined. More patients need to be included to study the effect of nHFT on the NTproBNP.

The results of patient 2 showed that HRV during the titration night was influenced by sleep stages a lot, which was shown in previous studies as well<sup>61-64</sup>. Autonomic control is closely related with sleep stages, which could explain this correlation<sup>61</sup>. For instance, all HRV features, except for the LF/HF ratio, were lower with the nHFT settings in which patient 2 had periods of deep sleep, and were higher when patient 2 was awake. This pattern was seen in previous studies as well for the HRV features SDNN, VLF and LF<sup>62;63</sup>.

In previous studies, the RMSSD and the power in the HF frequency band, both reflecting the parasympathetic activity<sup>46</sup>, were higher in periods with deep sleep compared to light sleep in healthy patients<sup>63</sup>, which is inconsistent to our results. However, another study of Penzel et al.<sup>62</sup> showed the same unexpected results. Possibly, the underlying disease influences the parasympathetic activity during different sleep stages<sup>62</sup>. More patients need to be measured to analyse what the influence of sleep stages is on the parasympathetic activity in patients with central sleep apnoea and congestive heart failure.

No correlation was found between the AHI during the titration night and all HRV features in patient 2, except for the LF/HF ratio. A previous study showed a decrease in both spectral and time domain HRV features with CPAP therapy in patients with congestive heart failure and central sleep apnoea<sup>47</sup>. It was expected that the time and spectral domain HRV features would be decreased when AHI was lower during that specific nHFT setting. However, since the sleep stages influenced HRV, these effects were probably not visible. Moreover, the patient did not sleep well, which could have influenced these results as well. A previous study compared HRV before and after the therapy<sup>47</sup>. The confounding effect of sleep stages should be lower when comparing two complete nights. If nHFT is able to decrease AHI, a reduced HRV is expected after the therapy.

The results showed the highest sympathetic activity (highest LF/HF ratio) with the setting in which patient 2 was most awake (an oxygen enriched flow rate of 30 L/min). However, the LF/HF ratio was also higher with the setting with a flow rate of 30 L/min, in which the patient was not awake. Normally, sympathetic activity is more predominant during awake, reflected by higher LF/HF ratios<sup>61;62</sup>. However, the LF/HF ratio is also higher in patients with SDB<sup>61;65</sup>. The AHI was the highest with the setting with a flow rate of 30 L/min, which might explain the higher LF/HF ratio during this setting. The lowest LF/HF ratio was found with the nHFT setting that provided the longest period of deep sleep and the least SDB, which was expected, since parasympathetic activity is more predominant in deep sleep<sup>61-64</sup>.

For patient 3, there was no correlation between the HRV features and both the sleep stages and AHI. All HRV features were higher with the setting providing a flow rate of 20 L/min, which was not expected, since different HRV features react differently on for instance sleep stages. Possibly, there was an artefact during this setting, which might have influenced the results. Furthermore, the SDNN, reflecting the variation in R-R intervals, is mathematically similar to the total power<sup>46</sup>, which can explain the correlation between these two HRV features. Finally, the power in the VLF frequency band was higher in patients with congestive heart failure and correlated with mortality in another study<sup>57</sup>. For patient 3, the power in the VLF frequency band was lower with the settings with a flow rate of 20 L/min with additional oxygen and with 30 L/min, indicating that these settings were supportive for this patient. For patient 2, the power in the VLF frequency band was higher with the setting with a flow rate of 30 L/min with additional oxygen suggesting that this setting was not supportive for this patient.

In summary, no clear HRV changes due to nHFT were found during the titration night, since the sleep stages influenced HRV a lot. HRV should be compared before and after nHFT to analyse HRV changes due to nHFT.

### 1.5.3 Titration of the optimal nHFT setting

The titration night was not representative for a normal night, due to low sleep efficacy. During the titration night, patients needed to sleep with many sensors and the researchers came into the room about every hour,

which disturbs a normal sleep. Furthermore, the patients used nHFT for the first time during the titration night, which could disturb the sleep as well. This abnormal sleep pattern made it difficult to determine the optimal nHFT setting reducing AHI for a normal sleep situation based on PSG.

Other signals were analysed, but also due to the sub-optimal titration night and the low number of patients, it is difficult to decide which signals could be used to determine the optimal setting reducing AHI. More patients need to be measured to analyse this.

#### 1.5.4 Limitations and recommendations

Until now, only three patients are included in the RELAX study. Therefore, the statistical results are not fully reliable and conclusions could hardly be drawn. The previous conclusions and discussion points are only indications and need to be confirmed with more data. It is advised to continue with the pilot study, to be able to analyse whether nHFT might be effective reducing AHI. Note that the inclusion is difficult for this study. This was not expected, since almost 46% of the patients with congestive heart failure suffer from SDB<sup>5</sup>, from which 80% suffer from CSA<sup>12</sup>. This gives indications that indeed the diagnosis of SDB is often missed.

There was a low compliance with the therapy. Especially the first two patients faced problems with the device and the nasal cannula, which probably influenced the compliance. It is questionable whether the patients quit the therapy due to non-compliance with the SoftFlow 50<sup>®</sup> or due to non-compliance with nHFT. It would be interesting to analyse whether there is a poor compliance with for instance another nHFT device, the Optiflow<sup>®</sup> produced by Fisher & Paykel Healthcare, as well. For instance, the producers of the SoftFlow 50<sup>®</sup> mentioned that the SoftFlow 50<sup>®</sup> always produces the same amount of flow, also when there is a resistance, and that the Optiflow<sup>®</sup> is not able to do that. Although, nHFT might be more comfortable if a lower flow is given when there is resistance due to exhaling.

The titration night in the hospital was not representative for a normal night. Therefore, some analysis could not be performed and the results could hardly be used to determine the optimal nHFT setting. For instance, no periods of REM were present during the use of nHFT at the hospital, which is abnormal. Therefore, the nHFT effect during REM sleep could not be analysed in these patients.

Moreover, the amount of apnoeas/hypopnoeas depends on the sleep stages as well<sup>4,13</sup>. Within one nHFT setting, multiple periods with and without apnoeas/hypopnoeas were present. Since patients did not have the same sleep stages during each nHFT setting, it was hard to choose the optimal nHFT setting without influence of the sleep stages. It is possible that the optimal nHFT setting reducing AHI was based on the moment when the patient had the optimal sleep stage during the titration night. Therefore, it is doubtful whether a titration night at the hospital is the way to calibrate the optimal nHFT setting.

The Diphera<sup>®</sup> device measuring EMG and several pressures did not work optimally for patient 1. The EMG contained lots of noise, which made the signal analysis unreliable. Moreover, during the titration night of patient 1, the Diphera<sup>®</sup> device stopped measuring every six minutes. Thus, every six minutes the Diphera<sup>®</sup> device needed to be restarted. This made the titration night and the signal analysis labour intensive. Moreover, mistakes could be made in the signal analysis due to missing data. To prevent this from happening again, a second Diphera<sup>®</sup> device was bought.

#### 1.5.5 Directions for future research

When the results of this pilot study will show that nHFT is effective reducing AHI, a randomised controlled trial should be conducted to analyse the effectiveness of nHFT compared to both CPAP and oxygen therapy, the most commonly used therapies for patients with congestive heart failure and CSA. However, when the results indicate that AHI only reduces when additional oxygen is given with nHFT, a randomised controlled trial should be performed to evaluate the effectiveness of oxygen therapy versus a placebo. Until now, studies on the effectiveness of oxygen therapy were short-term, included rather small populations and/or did not include control patients<sup>8</sup>. Therefore, the effects of oxygen therapy, especially on the long-term, are unknown<sup>8</sup>.

In this study, patients acquainted with the SoftFlow 50<sup>®</sup> for the first time during the titration night, during which lots of other measurements were performed as well. This first negative acquaintance could influence the compliance with the therapy negatively in the four weeks using the therapy at home. It is advised that the patients already use the SoftFlow 50<sup>®</sup> for one week at home with a low flow setting (for instance 10 L/min) before the titration night. In this way patients can get used to the device before additional measurements are performed. After this week, the patients will come to the hospital for the titration night and the optimal setting is determined. In this way, patients will get a more positive acquaintance with the device, and less measurements and devices are new to the patient during the titration night, which might influence the quality of the titration night and the compliance with nHFT positively. After the titration night, the patients will use nHFT for four weeks at home with the optimal setting determined during the titration night. In this study, there is contact with the patient after one week after the initiation of nHFT at home. It is advised to already get contact with the patient after one night too, to give advice in an early stage when patients face problems with nHFT.

## 1.6 Conclusion

There are indications that nHFT with the addition of oxygen makes ventilation more stable in patients with congestive heart failure and CSA. Especially oxygen addition seems to be effective reducing AHI. More patients need to be included in the study to verify this result. Patients were not satisfied with nHFT. Probably, low humidity levels and a large nasal cannula might explain the low compliance. A humidity level between 34-37 °DP and a smaller nasal cannula are advised. Furthermore, the high flow rate made exhaling more difficult, which is uncomfortable. It is recommended to analyse whether a nHFT device, in which the flow rate decreases when there is resistance, would increase the compliance. Moreover, it was difficult to determine the optimal nHFT setting during the titration night due to poor sleep quality. The sleep quality during the titration night and compliance might increase when patients get used to sleeping with the nHFT device one week before the titration night. The pharyngeal pressure was not measured properly due to occlusion of the catheter by secretions. When occlusion by secretions was prevented, the pharyngeal pressure increased linearly with a higher nHFT flow rate. A 20 ml/h airflow produced by a microinfusor at the inlet of the catheter might avoid occlusion of the catheter by secretions. There are indications that a higher flow rate reduces the work of breathing and the neural breathing drive, which indicates that patients can relax their muscles more with a higher flow rate. There were no clear HRV changes due to nHFT found, since the sleep stages influenced HRV a lot. HRV should be compared before and after nHFT to analyse HRV changes due to nHFT.

In conclusion, nHFT with the addition of oxygen might stabilise ventilation in patients with congestive heart failure and CSA. However, due to the poor compliance so far, nHFT does not seem to be an optimal treatment for these patients.



## 2 PART II: Added value of transcutaneous electromyography (EMG)

### 2.1 Introduction

This part of the study focuses on the added value of transcutaneous EMG. EMG is a simple, reproducible and sensitive non-invasive method to evaluate the activity of respiratory muscles<sup>48;66</sup>. In this study it is analysed whether EMGdi signals can also be used to detect 1) both OSA and CSA, and to assess 2) HRV.

1) Especially in patients with congestive heart failure and CSA this additional analysis would be of added value. As discussed in section 1.1, the diagnosis of SDB is often missed due to overlapping symptoms with congestive heart failure<sup>4;11</sup>. Nowadays, patients need at least a polygraphy measurement to analyse whether they suffer from SDB, which is time-consuming<sup>67</sup> and expensive. In practice, only patients suspected of having SDB receive a polygraphy measurement. As a consequence, many patients are not diagnosed with SDB and therefore are not treated for it<sup>4;11</sup>. An EMG measurement is much more simple and less time-consuming compared to a polygraphy measurement. When SDB patterns could be automatically detected in an EMGdi signal, many more patients with congestive heart failure could be easily screened for SDB.

2) HRV is the variation in the time interval between heart beats, which reflects the function of the autonomic nerve system that controls the heart rate<sup>46</sup>, as discussed in section 1.3. HRV is less variable in patients with severe congestive heart failure and is a predictor of mortality<sup>47;68;69</sup>. Normally, HRV is measured with a 24-hour Holter measurement. When measuring EMGdi, heart activity is detected with the transcutaneous electrodes as well. Normally, this heart activity is removed by advanced signal processing techniques in order to analyse the activity of the respiratory muscles<sup>51</sup>. When HRV could also be determined using the raw EMGdi signal, the 24-hour Holter measurement is superfluous to measure HRV continuously with the neural breathing drive of the diaphragm.

The research question of this part of the study is:

*Can sleep apnoea and HRV be detected with transcutaneous EMG of the diaphragm?*

When it is possible to measure sleep apnoea and HRV using transcutaneous EMG, less invasive and uncomfortable measurements would be needed during the titration night of the study described in part I.

## 2.2 Methods

### 2.2.1 Data acquisition

The EMG and PSG data from the titration night, as discussed in section 1.3, were used for the analysis of this part as well. Additionally, data from one patient with a double sided diaphragm paralysis, which got a PSG with EMG during the night, were also used to assess HRV with EMG. Section 1.3.3.5 and section 1.3.3.2 describe how EMG and PSG were measured, respectively.

### 2.2.2 Detection of sleep apnoea with EMG

To investigate whether periods of OSA and CSA could be detected with EMG, the  $EMGdi_{fse}$  during periods of apnoea were compared with the  $EMGdi_{fse}$  during normal breathing. The method of determining  $EMGdi_{fse}$  was outlined in section 1.3.4.5. To exclude the influence of nHFT and sleep stages on  $EMGdi_{fse}$ , only data when the patient was in light sleep without using nHFT were analysed.

For each CSA event, the area under the  $EMGdi_{fse}$  curve was calculated ( $AUC_c$ ), as shown in Figure 18. There was corrected for the length of the CSA event by dividing the  $AUC_c$  by the length of the CSA event. The area under the  $EMGdi_{fse}$  curve was calculated for OSA events ( $AUC_o$ ) and for normal breathing ( $AUC_n$ ) in the same way. The difference in AUC in percentages between both the two types of apnoea ( $AUC_c$  and  $AUC_o$ ) and normal breathing ( $AUC_n$ ) was determined.

Additionally, the envelope of the  $EMGdi_{fse}$  was calculated using spline interpolation over local maximal points separated by at least 1.5 seconds, which could be a way to distinguish normal breathing with apnoeas.

It was expected that the  $AUC_o$  and the envelope during an OSA event were increased compared to the  $AUC_n$  and the envelope during normal breathing, since the patient need to breath against an obstruction. It was expected that the  $AUC_c$  and the envelope during a CSA event were decreased compared to the  $AUC_n$  and the envelope during normal breathing, since there is no neural breathing drive during a CSA event.

### 2.2.3 Assessment of heart rate variability with EMG

To investigate whether HRV can be estimated with EMG signals ( $HRV_{EMG}$ ),  $HRV_{EMG}$  was compared to the HRV estimated using the ECG signals of the PSG ( $HRV_{ECG}$ ) during the whole night. The analysis of  $HRV_{ECG}$  is already explained in section 1.3.4.6. In addition, the parts of the ECG data which contained noise, were not analysed. The raw EMG was used to calculate  $HRV_{EMG}$ , since heart activity is still present in the raw EMG. The R-peaks from each heart beat were detected using the *findpeaks* function in Matlab<sup>®</sup> and the R-R intervals were determined by assessing the difference between consecutive R peaks. The time domain and frequency domain features of HRV, which are shown in Table 2 in section 1.3.4.6, were calculated for each 5 minute interval. Bland Altman plots<sup>70</sup> were constructed to compare  $HRV_{ECG}$  with  $HRV_{EMG}$  per 5-minute segment.

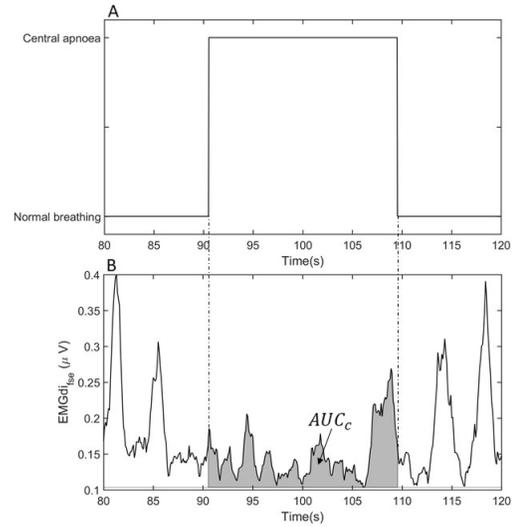


Figure 18: Analysis of detecting sleep apnoea with EMG. **A.** An example of a central apnoea. The time is on the x-axis and the apnoea analysis is on the y-axis. **B.** The  $EMGdi_{fse}$  during the same time frame. The area under the  $EMGdi_{fse}$  curve was determined during the central apnoea ( $AUC_c$ ), indicated with the grey area.

## 2.3 Results

### 2.3.1 Detection of sleep apnoea with EMG

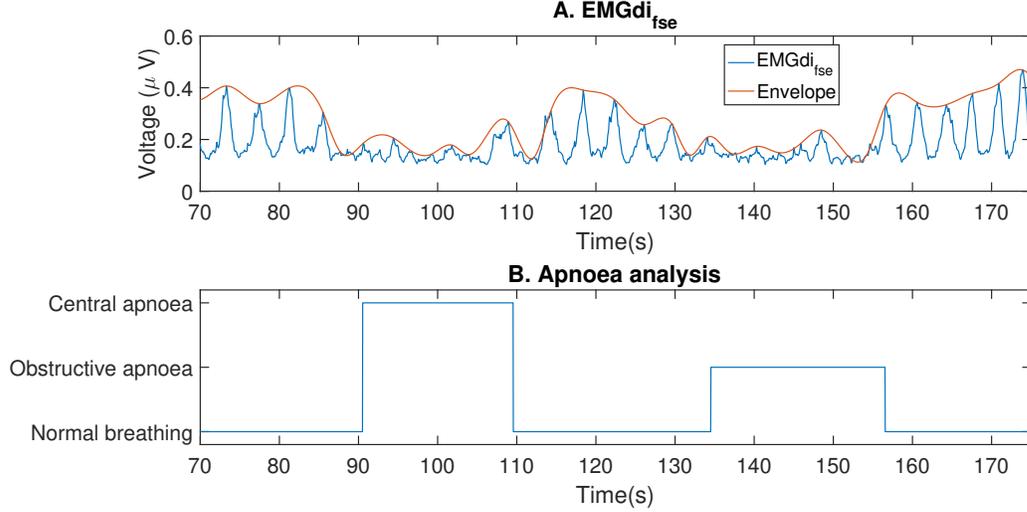


Figure 19: Change of the AUC of the EMGdi<sub>fse</sub> during an obstructive and central apnoea. **A.** The EMGdi<sub>fse</sub> signal is shown in blue. The envelope of the EMGdi<sub>fse</sub> is shown in red. The time is on the x-axis and the voltage is on the y-axis. **B.** The apnoea analysis during the same time frame. The time is on the x-axis and the type of apnoea is on the y-axis.

Table 8 shows the difference in AUC of the EMGdi<sub>fse</sub> in percentages between CSA and normal breathing and between OSA and normal breathing. Both types of sleep apnoea showed a lower AUC of the EMGdi<sub>fse</sub> compared to normal breathing. In the first two patients, OSA showed a higher AUC of the EMGdi<sub>fse</sub> than CSA.

Figure 19 shows an example of the change in EMGdi<sub>fse</sub> during an OSA and CSA event. During both types of apnoea the EMGdi<sub>fse</sub> signal and the envelope of this signal decreased. This suggests that both apnoeas might have been of central origin and that the second event was incorrectly defined as an OSA event with the PSG.

Table 8: AUC difference (%) of the EMGdi<sub>fse</sub> between both central and obstructive sleep apnoea and normal breathing.

	Patient 1	Patient 2	Patient 3
AUC <sub>c</sub> /AUC <sub>n</sub>	32%	59%	78%*
AUC <sub>o</sub> /AUC <sub>n</sub>	50%	84%	-

Table 8. A '\*' indicates that this is a percentage of central hypopnoeas and not apnoeas, due to an absence of central apnoeas. A '-' indicates that there were no obstructive events present.

### 2.3.2 Assessment of heart rate variability with EMG

Figure 20 shows the agreement between HRV<sub>ECG</sub> and HRV<sub>EMG</sub> for all patients through Bland-Altman plots of four HRV features: SDNN, RMSSD, LF/HF ratio and total power. The Bland-Altman plots of the other HRV features are not shown, since they were comparable. The mean difference and standard deviation between HRV<sub>ECG</sub> and HRV<sub>EMG</sub> of the four HRV features are included in Table 9 together with the percentage of data within the limits of agreement. The mean difference between the ECG and EMG-based SDNN was almost zero, which indicates that the SDNN<sub>ECG</sub> was comparable to the SDNN<sub>EMG</sub>. When looking at Figure 20A, most data points were at the zero level. Especially, there were a few outliers around the mean of 0.2, in which the SDNN<sub>ECG</sub> was lower than the SDNN<sub>EMG</sub>. These outliers increased the limits of agreement.

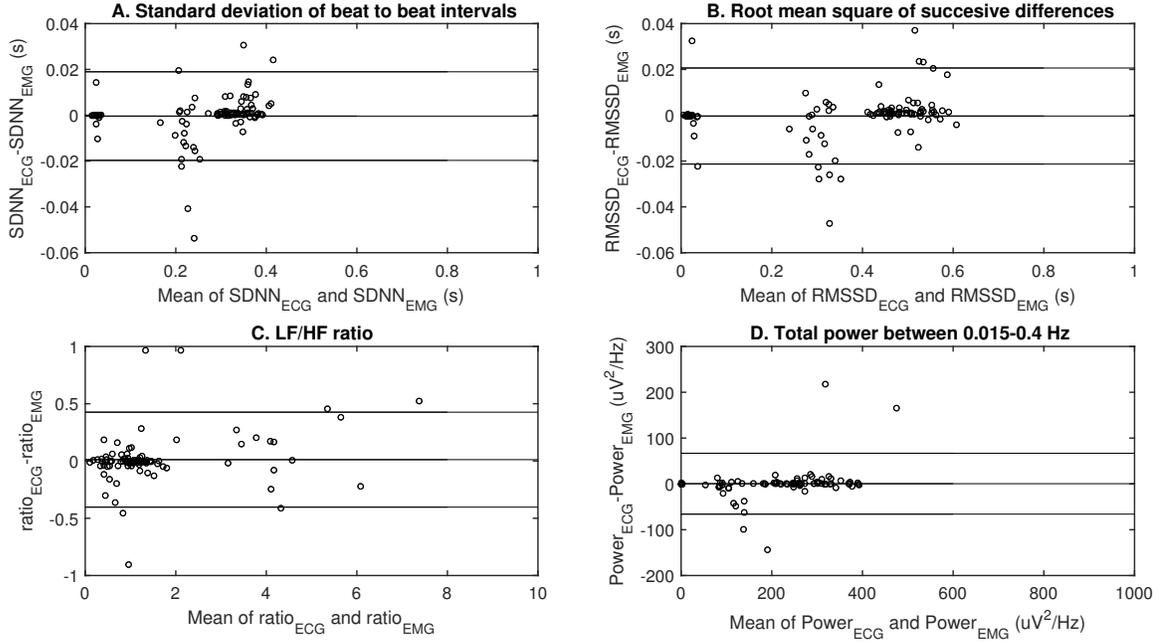


Figure 20: Bland-Altman plots of four HRV features, in which  $HRV_{EMG}$  is compared with  $HRV_{ECG}$ . Each circle reflect a 5-minute segment. The HRV analysis of all patients are plotted in this figure. The y-axis shows the difference between  $HRV_{ECG}$  and  $HRV_{EMG}$ . The x-axis shows the mean of the  $HRV_{ECG}$  and  $HRV_{EMG}$ . The top and bottom line in the Bland-Altman plots reflect the upper and lower limits of agreement, calculated through the average  $\pm 1.96$  times the standard deviation. The middle line is the mean difference between  $HRV_{ECG}$  and  $HRV_{EMG}$ . **A.** The Bland-Altman plot of the HRV feature SDNN. **B.** The Bland-Altman plot of the HRV feature RMSSD. **C.** The Bland-Altman plot of the HRV feature LF/HF ratio. **D.** The Bland-Altman plot of the HRV feature total power between 0.015-0.4 Hz.

The comparison of the  $RMSSD_{ECG}$  with the  $RMSSD_{EMG}$  showed the same pattern (shown in Figure 20B) as the comparison of the  $SDNN_{ECG}$  with the  $SDNN_{EMG}$ . Most outliers were present when the mean of the  $RMSSD_{ECG}$  and the  $RMSSD_{EMG}$  was around 0.3.

The mean difference of the LF/HF ratio was above zero. Figure 20C shows that most data points were around zero. Especially there were two outliers when the mean of the LF/HF ratio $_{ECG}$  and LF/HF ratio $_{EMG}$  was between 1 and 2, in which the LF/HF ratio $_{ECG}$  was higher than the LF/HF ratio $_{EMG}$ . This probably contributes to a mean difference of the LF/HF ratio above zero.

The mean difference of the total power was above zero, which means that the Power $_{ECG}$  was slightly higher than the Power $_{EMG}$ . Figure 20D shows that there were a few outliers, which increased the limits of agreement.

Table 9: The average difference between  $HRV_{ECG}$  and  $HRV_{EMG}$ , the standard deviation (std) and the percentage of data points within the limits of agreement (LOA).

	mean	std	LOA (%)
SDNN (s)	-0.0004	0.0099	94
RMSSD (s)	-0.0004	0.0107	90
LF/HF ratio	0.0117	0.2115	93
Total power (s <sup>2</sup> *60/Hz)	0.4383	33.9060	96

## 2.4 Discussion

There are indications that sleep apnoea can be distinguished from normal breathing with EMG. Moreover, the time domain HRV features could be determined using EMG. However, the limits of agreement of the spectral domain HRV features were too high to determine these with EMG. The results are further discussed in the subsections below.

### 2.4.1 Detection of sleep apnoea with EMG

A difference in the AUC of the  $EMGdi_{f_{se}}$  between sleep apnoea and normal breathing was shown. However, more patients need to be analysed to assess whether there is a statistical difference.

The detected CSA events did have a smaller AUC of the  $EMGdi_{f_{se}}$  than the OSA events. The highest AUC of the  $EMGdi_{f_{se}}$  for CSA events was found in patient 3. Since only hypopnoeas were analysed in this patient, in which there is still some airflow, it can be explained that the highest AUC was found in this patient. More patients need to be included to analyse whether there is a significant difference between the AUC of the  $EMGdi_{f_{se}}$  during OSA and CSA events.

The results of OSA were not as expected. It was expected that the AUC of the  $EMGdi_{f_{se}}$  would increase compared to normal breathing. However, these OSA events were detected in patients who mainly suffer from CSA. These OSA events might contain a central element, which might decrease the  $EMGdi_{f_{se}}$ , but not completely. Therefore, possibly these events were incorrectly determined as OSA events by the PSG. When this is the case, OSA and CSA events might even be distinguished better using EMG than using PSG analysis.

### 2.4.2 Assessment of heart rate variability with EMG

The mean difference between the ECG and EMG-based SDNN and RMSSD was low. When looking at Table 7, the SDNN and RMSSD of the different nHFT settings could still be distinguished when using  $HRV_{EMG}$ , since the limits of agreement were small. Literature shows that the limits of agreement must be below 0.03s to be able to analyse SDNN and RMSSD using EMG<sup>56;62;67</sup>, which was the case for both the SDNN and RMSSD. Furthermore, on average 92% of the data points was within the limits of agreement. This indicates that  $HRV_{EMG}$  could be used to determine the SDNN and RMSSD. However, more patients need to be included to analyse whether the EMG signal could be used to determine the time domain HRV features in other patients as well.

The mean difference between the ECG and EMG-based LF/HF ratio was small, which indicates that the EMG signal would be a good alternative to estimate the LF/HF ratio. However, the limits of agreement and the standard deviation were too high to analyse for instance the difference in LF/HF ratio between the different nHFT settings. In addition, literature shows that the limits of agreement must be below 0.3s to be able to analyse LF/HF ratio using EMG<sup>63</sup>, while the limits of agreement of the comparison between the ECG and EMG-based LF/HF ratio was around 0.4s. More data points were above zero, which indicates that the ECG-based LF/HF ratio was higher than the EMG-based LF/HF ratio. This indicates that the ECG-based R-R intervals contained less high frequencies and more low frequencies than the EMG-based R-R intervals. Possibly, this difference might be explained by missing R-peaks in the ECG-signal, since R-peak detection was difficult to perform due to noisy ECG signals. When R-peaks are missing, less high frequency oscillations are detected, which results in a higher ECG-based LF/HF ratio.

The mean difference between the ECG and EMG-based total power was above zero, which indicates that there was more power in the ECG-based R-R intervals compared to the EMG-based R-R intervals. However, this mean difference above zero was probably mostly due to the outliers. Furthermore, the limits of agreement were too high to distinguish the difference in total power between different nHFT settings. However, the few outliers did also increase these limits of agreement.

For all HRV features, there were a few outliers, which increased the mean differences and the limits of agreement. These outliers were mainly due to a noisy ECG signal, which changed  $HRV_{ECG}$  results. This noisy ECG signal

makes it difficult to validate the  $HRV_{EMG}$  method. The parts of the ECG signal with lots of noise were removed from this analysis. However, when the ECG signal contained only a little noise, this could still influence the  $HRV_{ECG}$ . Therefore, it seems that the ECG signal of the PSG is not a good gold standard to validate the  $HRV_{EMG}$  method. The EMG signal did not contain noise which disturbed the heart signal. Therefore, the EMG signal seems to be a more reliable signal to determine the HRV than the PSG-based ECG signal. More patients need to be included to further analyse this.

### **2.4.3 Limitations and recommendations**

#### **2.4.3.1 Detection of sleep apnoea with EMG**

EMG signals between patients differ a lot: some patients show noisy EMG signals and in some patients the breathing signal could be derived perfectly from the EMG signals. Therefore, more patients need to be studied to assess whether sleep apnoea could be identified from EMG signals.

Another recommendation is to analyse the relation between OSA events and the EMG in purely OSA patients too. It is expected that the EMG amplitude increases during an OSA event in patients with OSA and decreases during an OSA event in patients with especially CSA.

#### **2.4.3.2 Detection of heart rate variability with EMG**

The ECG data contained lots of artefacts and the EMG results needed to be validated with the ECG data. The official gold standard of measuring HRV is a 24-hour Holter measurement. It is recommended to perform EMG measurements together with a 24-hour Holter measurement to validate the use of EMG data estimating HRV. This needs to be performed in at least 10 subjects, to analyse whether EMG is suitable to determine HRV in different subjects. Since the results of the validation of  $HRV_{EMG}$  showed that EMG might be a good technique to determine HRV, a good correlation with the 24-hour Holter measurement is expected.

## 2.5 Conclusion

There are indications that sleep apnoea can be distinguished from normal breathing with EMG, since the neural breathing drive decreased during an apnoea compared to normal breathing. More patients need to be analysed to determine whether there is a statistical difference in neural breathing drive between periods of apnoea and normal breathing. The neural breathing drive decreased during both OSA and CSA events, while it was expected that the neural breathing drive would increase during an OSA event. Possibly, the OSA events contained a central element, since the events were measured in patients suffering mainly from CSA. The neural breathing drive during an OSA event in patients with OSA should be analysed as well to study whether this differs from OSA events in patients with mainly CSA.

The difference between the time domain HRV features determined with ECG and the time domain HRV features determined with EMG was small. This gives indications that the time domain HRV features could be estimated using EMG. The limits of agreement of the difference between the ECG and EMG analysis of the spectral domain HRV features were too high. This indicates that the spectral domain HRV features could not be determined with EMG. More measurements should be performed to analyse whether the HRV time domain features could also be determined using EMG in other patients. Furthermore, the ECG data of the PSG is not appropriate to validate the HRV analysis using EMG, since the ECG data contained lots of noise. The HRV analysis using EMG data should be validated with a 24-hour Holter measurement instead.

Once the method has been validated better, EMG is nevertheless a promising technique to detect sleep apnoea and to monitor its consequences on the heart easily and non-invasive, also for the home situation.



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