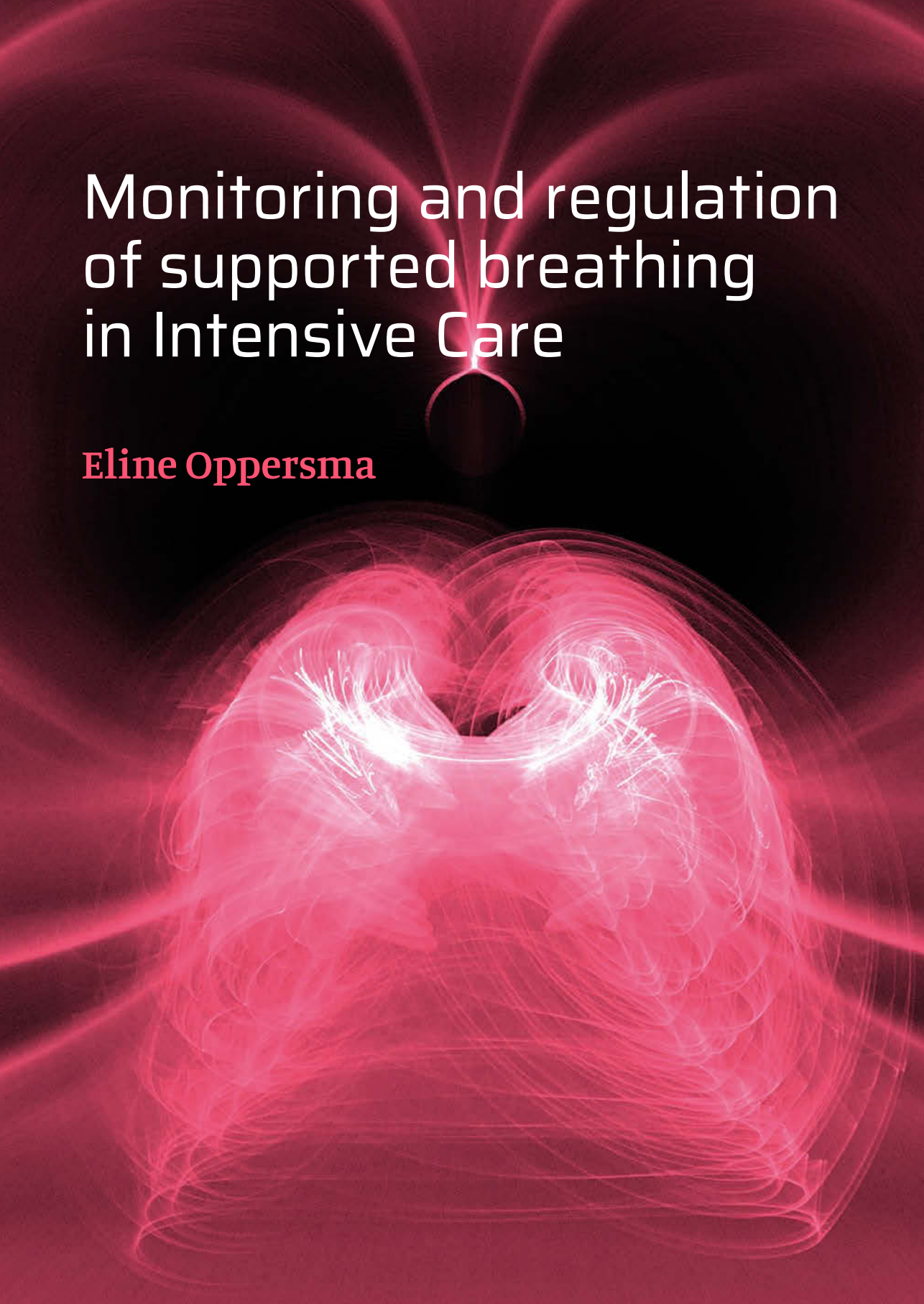
Monitoring and regulation of supported breathing in Intensive Care

Eline Oppersma



Monitoring and regulation of supported breathing in Intensive Care

Eline Oppersma

Composition of the Graduation Committee

Chairman and secretary

Prof. dr. J.N. Kok	*University of Twente*

Supervisors

Prof. dr. ir. P.H. Veltink	*University of Twente*
Prof. dr. L.M.A. Heunks	*Amsterdam UMC, location VUmc*
Prof. dr. J.G. van der Hoeven	*Radboud university medical center*

Members – internal

Prof. dr. ir. M.J.A.M. van Putten	*University of Twente*
Dr. ir. F.H.C. de Jongh	*University of Twente*

Members – external

Prof. dr. P.J. Wijkstra	*University Medical Center Groningen*
Prof. dr. D.A.M.P.J. Gommers	*Erasmus University Medical Center*
Dr. C.S. Brülls	*RWTH Aachen University, Germany*

Monitoring and regulation of supported breathing in Intensive Care
Academic thesis, University of Twente, Enschede, the Netherlands, with a summary in Dutch.

Author Eline Oppersma
Design Arthur Veugelers
Printed by Gildeprint

ISBN 978-90-365-4642-3
DOI 10.3990/1.9789036546423

The author gratefully acknowledges financial support for the publication of this thesis by the University of Twente.

MONITORING AND REGULATION OF SUPPORTED BREATHING IN INTENSIVE CARE

DISSERTATION

to obtain
the degree of doctor at the University of Twente,
on the authority of the rector magnificus
Prof. Dr. T.T.M. Palstra
on account of the decision of the graduation committee,
to be publicly defended
on Wednesday the 31st of October, 2018 at 14:45

by

Eline Oppersma

born on the 26th of November, 1987
in Enschede, the Netherlands

This dissertation has been approved by the supervisors:

Prof. dr. ir. P. H. Veltink
Prof. dr. L. M. A. Heunks
Prof. dr. J. G. van der Hoeven

Table of contents

1 Introduction

In the Netherlands each year, over 85.000 patients are admitted to the Intensive Care Unit (ICU) (1). Patients with acute respiratory failure, coma, acute exacerbation of chronic obstructive pulmonary disease, and neuromuscular disorders may benefit from mechanical ventilation (MV) (3). In 2016 in the Netherlands, 58.3 % of the patients with pneumonia on the ICU needed MV during the first 24 hours in the ICU (4) and the median duration of MV for these patients is 7.1 days (5). MV aims to decrease work of breathing and reverse life-threatening hypoxemia or acute progressive respiratory acidosis. Nowadays clinicians focus on the prevention of ventilator-induced lung injury while maintaining adequate gas exchange (3,6).

The relevant parameters in the interaction between a patient and a mechanical ventilator are pressure and flow. More specifically to understand MV, we are interested in the pressure necessary to cause a flow of gas to enter the airway and increase the volume of the lungs. In terms of physical systems theory pressure is an effort and flow a flow variable, their product being the power of the physical interaction (7). During MV, the ventilator replaces or supplements the spontaneous breathing effort (8), introducing two interacting physical systems that influence each other and jointly realize adequate ventilation: spontaneous breathing and mechanical ventilation. Mechanical ventilators use closed-loop control to maintain consistent pressure and flow waveforms with changing patient conditions, to provide continu-

ous support. Figure 1 introduces a feedback control system of these two interacting systems involved in mechanical ventilation. The input for the controller is a clinically relevant criterion to be realized by supported ventilation. This can be a preset inspiratory pressure or flow, but, most important, should reference to a clinical measure of good ventilation and oxygenation: minimal mechanical support resulting in adequate gas exchange. The controller compares the preset criterion with the sensed parameters and imposes a pressure, flow or relation between these parameters via the hardware of the ventilator, providing mechanical ventilatory support. The sensed variables can be the pressure and flow acting at the interface between patient and ventilator. A more central variable to sense and provide information about the interaction could be the electrical activity of the diaphragm, our main respiratory muscle. This concept will be discussed in further detail in a following paragraph. The physical interaction between the patient and the ventilator, indicated by a bond graph in Figure 1, is represented by the pressure and flow acting at the interface between the ventilator and the patient, that are jointly generated by these interacting systems (7). The more a patient is able to deliver effective ventilation from spontaneous breathing drive, the less the mechanical ventilator should need to support to meet the preset criterion. Timing of this interaction during breathing is essential and will be discussed later this chapter. Following from Figure 1, it is important that the interaction between the patient and the ventilator should balance between providing support to maintain adequate gas exchange on the one hand, while the patient maintains sufficient spontaneous breathing effort. Adaptation of the breathing pattern of the patient over time to mechanical ventilatory support may result in failure when ventilatory support is reduced aiming to return to spontaneous breathing (called weaning), as will be discussed later this chapter.

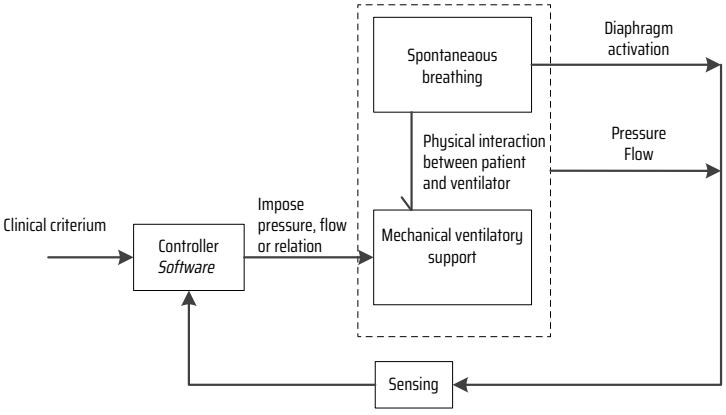


Figure 1
Feedback control system of the interaction between spontaneous and mechanical ventilation

Figure 2 introduces the relation between two important concepts during MV; invasiveness and level of support. Mechanical ventilatory support can be provided invasively, via an endotracheal tube or tracheostoma, or noninvasively, via a nose- or facemask. The level of support ranges on the horizontal axis from no support during healthy spontaneous breathing, to full support ventilation with absent spontaneous breathing drive, with all levels of partial assisted ventilatory support in between. These concepts will be discussed in the following paragraphs.

Invasive ventilation

In case of a patient in need for maintenance and protection of the upper airway, high inspired oxygen concentrations or application of positive pressure to the airway, an endotracheal tube is indicated (9).

Full support ventilation

When spontaneous breathing is absent, full support mechanical ventilation should be provided. Although this is sometimes called 'controlled ventilation', in this Introduction chapter we will use the term full support ventilation, to avoid vagueness with respect to the controller in the feedback control system, which is also present in other forms of supported breathing. Full support ventilation can be explained by absence of spontaneous breathing effort, the upper block in Figure 1. The interaction between the patient and the ventilator is still present but the duration and frequency of the inspiratory phase is completely regulated by the ventilator and the patient does not need to contribute (10). The clinical criterion to deliver breaths, defined as a positive airway flow towards the patient relative to baseline, can be set as pressure-controlled or volume-controlled. For example in pressure-control modes, airway pressure is used as the feedback signal to control airflow from the ventilator. However, the respiratory muscles and particularly the diaphragm are completely inactive during full support ventilation, resulting in the rapid development of diaphragmatic weakness due to both atrophy and contractile dysfunction (11–13). Diaphragm weakness develops rapidly: muscle fiber atrophy in the human diaphragm occurs already after only 18–69 hours of full support mechanical ventilation and a reduction of approximately 30 % is found in twitch airway pressure,

Figure 2
Relation between invasiveness and level of support during MV: both invasive and noninvasive ventilation can be provided over a continuous scale of support level, from full to no support.

induced by magnetic phrenic nerve stimulation, in the first 5 to 6 days of invasive mechanical ventilation (14,15). Despite growing evidence that respiratory muscle dysfunction develops in critically ill patients and contributes to weaning failure (15–17), the respiratory muscles are poorly monitored in the ICU and usually unrecognized (18). Today, measurement of transdiaphragmatic pressure using esophageal and gastric balloons is the gold standard to assess effort of the diaphragm. However, this technique is invasive and requires expertise, and interpretation may be complex (18,19). Several studies demonstrated the utility of ultrasonography for diaphragm muscle imaging, as B-mode or M-mode ultrasonography, where fractional thickening of the diaphragm has been used to quantify effort of the diaphragm. However, low correlations between transdiaphragmatic pressure and diaphragmatic thickening fraction have been reported, indicating limited validity of fractional thickening to quantify diaphragm effort (20,21).

Partial support ventilation

With partial support ventilation, patients are required to trigger the ventilator, allowing the patient to time the delivery of the assist to the inspiratory effort (10). This is shown in Figure 1 by the contribution of the interaction between both systems to ventilatory functioning. Although both partial and full support MV results in diaphragmatic atrophy, the MV-induced diaphragmatic atrophy that occurs during partial ventilatory support occurs at a slower rate compared with the atrophy induced by full ventilatory support (13). As it is believed that partial support modes can reduce side effects and complications associated with full supported mechanical ventilation, partial assisted ventilation is in most cases preferred over full support ventilation in case the patient is capable of triggering the ventilator. Only in patients generating high tidal volumes despite low levels of partial assist, clinicians may prefer controlled ventilation. In these patients the control of lung protection is lost due to the high drive and high tidal volumes, increasing work of breathing (22). During partial ventilatory support, inspiration is started when a preset variable (pressure, volume, flow or time), reaches a preset value. The patient effort required to trigger inspiration is determined by the ventilator's sensitivity setting. When the ventilator is triggered to deliver a breath, a preset pressure, flow or volume is targeted. Finally, inspiration is terminated when the preset value of the so-called cycling-off variable is reached (a preset pressure, volume, flow or time) (8,10). During the proportional neurally adjusted ventilatory assist mode of ventilation, the electrical activity of the diaphragm of the patient controls triggering, targeting and cycling-off of the ventilator (2). This will be discussed in a following paragraph.

Noninvasive ventilation

Although invasive MV is often lifesaving, it is also associated with serious complications. Even before initiation of MV, endotracheal intubation is a critical procedure

in which patients are at risk, but also risks related to the direct mechanical effects of the intrathoracic pressures generated by the ventilator, to alveolar and systemic inflammation or to neural stimulation are present (23).

Noninvasive ventilation (NIV) is an alternative approach to mechanical ventilation, that was developed to avoid complications caused by the use of artificial airways that may lead to infectious complications and injury to the trachea (24). An important goal of NIV is to prevent endotracheal intubation and thereby reduce the complications related to invasive ventilation (25,26). NIV is increasingly used in acute respiratory failure, for instance in patients with exacerbation of chronic obstructive pulmonary disease (COPD) or acute heart failure (25,27,28). NIV in patients with an acute exacerbation of COPD is indicated to reverse acute respiratory acidosis, and such to prevent endotracheal intubation and invasive mechanical ventilation for mild to moderate acidosis and respiratory distress, and as an alternative to invasive ventilation for severe acidosis (29). Particularly, NIV is indicated in COPD patients with a respiratory acidosis with a pH of 7.25–7.35, but contraindicated in patients with severe hypoxaemia, or copious respiratory secretions (30). COPD patients showed to benefit from NIV because such exacerbations may be rapidly reversed and because the hypercapnic ventilatory failure seems to respond well to NIV (24). Also after extubation, prophylactic use of NIV may benefit patients at risk for respiratory failure and reintubation, such as elderly patients with COPD or congestive heart failure (23). During NIV, positive pressure support is provided via an interface: a mouthpiece, nasal mask, nasal pillows, oronasal mask, total face mask, or helmet (31,32). These interfaces however promote air leaks, and the added mechanical dead space compared to endotracheal tubes could cause CO_2 rebreathing during NIV, thereby reducing the efficiency of NIV and increasing patient-ventilator asynchrony, which will be discussed in further detail in the following paragraph (33). Factors for successful NIV include properly timed initiation, a comfortable and well-fitting interface, coaching and encouragement of patients, careful monitoring and a skilled and motivated team (34). The resulting marker for success is defined as an increasing pH within 1 to 2 hours after initiation of NIV (34,35). However, in 5–40 % of COPD patients NIV fails (36) and endotracheal intubation is required. The pathophysiology of NIV failure is incompletely understood and difficult to monitor. It is known that glottic narrowing during inspiration increases upper airway resistance in lambs and may limit effective ventilation, but this requires further research (37).

NAVA

During neurally adjusted ventilatory support (NAVA) ventilation, the ventilatory support is adjusted to the electrical activity of the diaphragm. NAVA can be used to trigger both invasive and noninvasive ventilation. As direct measurement of the output of the respiratory center is not possible, neural drive is represented by elec-

trical activity of the diaphragm, see Figure 3. Electrical activity of the diaphragm can be measured by electrodes mounted on a catheter which is inserted via the nose and positioned in the lower esophagus. In Figure 1 this is represented by the activation of the diaphragm, which is sensed and used by the controller. The magnitude of the mechanical support will vary on a moment-by-moment basis according to the diaphragmatic electrical activity times a gain factor, which can be selected on the machine by the clinician. This allows the patient's respiratory center to be in direct control of the mechanical support provided throughout the course of each breath, allowing any variation in neural respiratory output to be matched by a corresponding change in ventilatory assistance

Patient-ventilator interaction

In case of a fully paralyzed patient and an intact ventilator, a modern ventilator will easily deliver full support ventilation, where synchrony is not an issue. As described previously and in Figure 1 the patient creates 'noise' in the interaction with the mechanical ventilator by having a spontaneous breathing drive, particularly during partial ventilatory support. This potentially causes patient-ventilator asynchrony, in which more effort (mechanic work of breathing per time) is needed to effect adequate ventilation (8,10). For the most effective unloading of the inspiratory muscles, the ventilator should cycle in synchrony with the activity of a patient's own respiratory rhythm. However, asynchronies are reported to occur in a range from 25 % (38) up to 80 % (39) of mechanically ventilated patients, a rate that is affected by several factors such as underlying disease, the patient's breathing pattern and drive, ventilator settings, and sedative drugs (39). The interaction between the two interacting systems is complex, and problems can arise at several phases in the respiratory

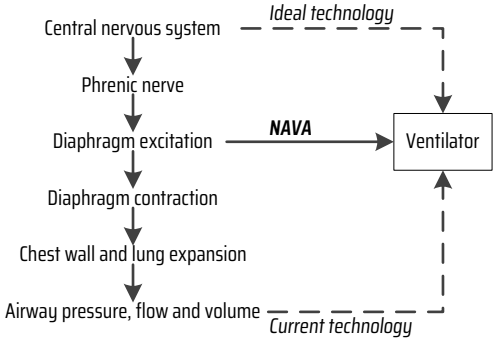


Figure 3
Steps to transform central respiratory drive into an inspiration with levels at which technology able to control a mechanical ventilator could be implemented (2)

cycle: the onset of ventilator triggering, the rest of inspiration after triggering, the switch from inspiration to expiration (cycling-off), and the end of expiration (40). By the mismatch in this case between the mechanical and natural respiratory cycles, the patient 'fights' the ventilator, causing discomfort, inefficiency in adequate gas exchange and cardiovascular impairment (2,40). In particular with high levels of invasive pressure support ventilation, a quarter to a third of a patient's inspiratory efforts may fail to trigger the machine and the number of ineffective triggering attempts increases in direct proportion to the level of ventilator assistance (41). Cycling-off on the other hand can be delayed when the ventilator delivers the set tidal volume before the end of a patient's neural inspiratory time; ventilator assistance will cease while the patient continues to make an inspiratory effort. The likely consequence for this single effort is double triggering, two ventilator breaths (40).

Although it is believed that partial support modes of ventilation can reduce side effects and complications associated with full support mechanical ventilation, coordination between spontaneous breathing and mechanical assistance is not guaranteed. As earlier discussed, airway pressure, flow or volume is mainly used to initiate and regulate the ventilatory support. However, synchrony would be ideal when matched to the output of the respiratory center in the brain. As discussed in a previous paragraph, electrical activity of the diaphragm can be used to estimate respiratory center output and regulate timing and gain of mechanical ventilation during NAVA (2). Numerous studies showed that NAVA improves patient-ventilator interaction especially at higher levels of assist, compared to pressure support ventilation (42,43).

Weaning failure

In most patients, mechanical ventilation can be discontinued as soon as the underlying reason for acute respiratory failure has been resolved (44). However, 20 % to 30 % of patients have difficulties to pass a spontaneous-breathing trial or need to be reintubated within 48 hours following extubation, defining weaning failure (45). The pathophysiology of weaning failure is complex and often multifactorial, and can at least partly be caused by adaptation of the patients own spontaneous breathing mechanisms to the ventilatory support. Possible causes of weaning failure are in airway and lung dysfunction, brain dysfunction, cardiac dysfunction, diaphragm dysfunction or endocrine dysfunction (44). The earlier discussed weakness of the diaphragm is a risk of MV by adaptation to the ventilator, and is thought to be an important contributor to the difficulties that are encountered during weaning and returning to spontaneous breathing (14). Another important mechanism of adaptation to mechanical ventilation during weaning in the scope of this thesis is acid-base regulation. In patients with COPD who are weaning from mechanical ventilation, acid- base disorders as chronic respiratory acidosis and metabolic alkalosis are fre-

quently observed (46). Metabolic compensation for respiratory acidosis by bicarbonate production or retention results in posthypercapnic alkalosis with an increased arterial bicarbonate concentration (47). This could result in an increase in the buffer capacity for CO_2, resulting in decreased sensitivity of the respiratory centers to increased inhaled CO_2 during the HCVR test; so-called reduced chemosensitivity of breathing. Reduced chemosensitivity may affect the respiratory drive during loaded breathing, which may result in difficult weaning in patients with COPD.

Research questions and thesis outline

This thesis describes several chapters related to monitoring and regulation of breathing. The main goal is to provide better insight in the interaction between spontaneous breathing and mechanical ventilatory support. This will provide more adequate ventilatory support and reduction of adaptation issues. Both healthy subject and patient characteristics of breathing regulation and related anatomical, physiological and medical device aspects are studied. The thesis deals with the following research questions:

1. How is the neural respiratory drive influenced by arterial bicarbonate levels?
2. How can diaphragm function be noninvasively assessed using speckle tracking ultrasound?
3. How is the synchrony between the patient and the ventilator influenced by different modes and settings of noninvasive ventilation?

This thesis is divided in three parts to answer the above stated research questions. The first part refers to the earlier introduced adaptation problems specifically of the respiratory drive, arising during mechanical ventilatory support (research question 1). The second part refers also to the adaption problems, by measurement of the contribution of the diaphragm to the ventilatory output (research question 2). The third part refers to the synchrony between the patient, and more specifically the upper airway of the patient, and the ventilator (research question 3).

To assess central regulating mechanisms of breathing, chapter 2 describes the effect of metabolic alkalosis on the ventilatory response in healthy subjects. When gas exchange fails and patients develop acute respiratory failure (48), the respiratory acidosis can end up in posthypercapnic alkalosis with an increased arterial bicarbonate concentration, by metabolic compensatory mechanisms. As an answer to the first research question, this study hypothesized that the increased bicarbonate levels influence the respiratory drive. Elevated plasma bicarbonate levels might increase the buffer capacity for CO_2, resulting in decreased sensitivity of the respiratory centers, called reduced chemosensitivity of breathing (49,50). This could cause difficulties in weaning from mechanical ventilation.

Although neural drive can be assessed by the electrical activity of the diaphragm, this requires a nasogastric catheter and extensive signal- and data analysis, which can be challenging in particular in critically ill patients. Fractional thickening during inspiration assessed by ultrasound has been used to estimate diaphragm effort. However, correlations between electrical activity of the diaphragm and diaphragm thickening are low. As it is important to gain information about the diaphragm effort as part of the interaction between patient and ventilator, in chapter 3 we evaluated the performance of speckle tracking imaging to quantify diaphragm function to answer the second research question. Speckle tracking imaging is an ultrasound technique which enables angle-independent, two-dimensional quantification of muscle deformation and deformation velocity during muscle contraction. This could be a noninvasive alternative to assessing the neural drive compared to using the current invasive nasogastric catheter.

To answer the third research question, this thesis studies the above discussed interaction between the mechanical ventilator and the spontaneous breathing drive in patients with an acute exacerbation of COPD during noninvasive ventilation. More specifically the interaction of the mechanical ventilator with the behavior of the upper airways is studied in different ventilatory modes and settings. Chapter 4 of this thesis reviews the effect of positive pressure ventilation on upper airway patency and its possible clinical implications. It is known that regulation of the upper airway is complex and influenced by NIV, but mostly based on animal data. Understanding of the laryngeal reactions during different modes and settings of NIV in patients will be crucial to determine whether a diminished upper airway patency contributes to NIV failure. In chapter 5 we performed a study aiming to analyze this patency of the glottis during inspiration in patients with chronic obstructive pulmonary disease. To analyze the interaction between patient and ventilator, the electrical activity of the diaphragm, flow, pressure and video recordings of the glottis were synchronously acquired. From these video frames the angle of the vocal cords was calculated, as a measure of the patency of the upper airways, to perform a detailed physiological analysis of the upper airway patency during different modes and levels of the ventilator. In chapter 6 we evaluated patient-ventilator interaction during low and high levels of noninvasive PSV and NAVA in patients with an exacerbation of chronic obstructive pulmonary disease. Automated analysis of patient-ventilator interaction showed a progressive mismatch between neural effort and pneumatic timing with increasing levels of PSV. During noninvasive NAVA the patient-ventilator interaction improved and showed no difference with increasing NAVA levels.

References

1. Stichting Nice. Basisgegevens IC units voor het jaar 2016. [cited 2018 16 January] Available from: https://stichting-nice.nl/datainbeeld/public?subject=BASIC&year=2016&hospital=-1&icno=0
2. Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, Gottfried SB, Lindstrom L. Neural control of mechanical ventilation in respiratory failure. Nature medicine 1999; 5: 1433–1436.
3. Tobin MJ. Advances in mechanical ventilation. The New England journal of medicine 2001; 344: 1986–1996.
4. Stichting Nice. Jaarboek 2016. [cited 2018 16 January] Available from: https://stichting-nice.nl/doc/jaarboek-2016-web.pdf
5. Stichting Nice. Beademingsduur voor het jaar 2016. [cited 2018 16 January] Available from: https://stichting-nice.nl/datainbeeld/public?subject=BASIC&year=2016&hospital=-1&icno=0
6. Del Sorbo L, Goligher EC, McAuley DF, Rubenfeld GD, Brochard LJ, Gattinoni L, Slutsky AS, Fan E. Mechanical Ventilation in Adults with Acute Respiratory Distress Syndrome. Summary of the Experimental Evidence for the Clinical Practice Guideline. Annals of the American Thoracic Society 2017; 14: S261-S270.
7. Breedveld P. Concept-Oriented Modeling of Dynamic Behavior. In: Borutzky W, editor. Bond Graph Modelling of Engineering Systems: Springer Science+Business Media; 2011.
8. Chatburn RL, Mireles-Cabodevila E. Closed-loop control of mechanical ventilation: description and classification of targeting schemes. Respiratory care 2011; 56: 85–102.
9. Tobin MJ, McGraw-Hill C. Principles and practice of mechanical ventilation. 2013. Available from: http://accessmedicine.mhmedical.com/book.aspx?bookid=520
10. Tobin MJ. Principles and practice of mechanical ventilation. McGraw-Hill Companies; 2013.
11. Powers SK, Wiggs MP, Sollanek KJ, Smuder AJ. Ventilator-induced diaphragm dysfunction: cause and effect. American journal of physiology Regulatory, integrative and comparative physiology 2013; 305: R464–477.
12. Hudson MB, Smuder AJ, Nelson WB, Bruells CS, Levine S, Powers SK. Both high level pressure support ventilation and controlled mechanical ventilation induce diaphragm dysfunction and atrophy. Critical care medicine 2012; 40: 1254–1260.
13. Goligher EC, Fan E, Herridge MS, Murray A, Vorona S, Brace D, Rittayamai N, Lanys A, Tomlinson G, Singh JM, Bolz SS, Rubenfeld GD, Kavanagh BP, Brochard LJ, Ferguson ND. Evolution of Diaphragm Thickness during Mechanical Ventilation. Impact of Inspiratory Effort. American journal of respiratory and critical care medicine 2015; 192: 1080–1088.
14. Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, Zhu J, Sachdeva R, Sonnad S, Kaiser LR, Rubinstein NA, Powers SK, Shrager JB. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. The New England journal of medicine 2008; 358: 1327–1335.
15. Jaber S, Petrof BJ, Jung B, Chanques G, Berthet JP, Rabuel C, Bouyabrine H, Courouble P, Koechlin-Ramonatxo C, Sebbane M, Similowski T, Scheuermann V, Mebazaa A, Capdevila X, Mornet D, Mercier J, Lacampagne A, Philips A, Matecki S. Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. American journal of respiratory and critical care medicine 2011; 183: 364–371.
16. Laghi F, Cattapan SE, Jubran A, Parthasarathy S, Warshawsky P, Choi YS, Tobin MJ. Is weaning failure caused by low-frequency fatigue of the diaphragm? American journal of respiratory and critical care medicine 2003; 167: 120–127.
17. Hermans G, Agten A, Testelmans D, Decramer M, Gayan-Ramirez G. Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: a prospective observational study. Critical care 2010; 14: R127.

18. Doorduin J, van Hees HW, van der Hoeven JG, Heunks LM. Monitoring of the respiratory muscles in the critically ill. American journal of respiratory and critical care medicine 2013; 187: 20–27.
19. ATS/ERS Statement on Respiratory Muscle Testing. American journal of respiratory and critical care medicine 2002; 166: 518–624.
20. Oppersma E, Hatam N, Doorduin J, van der Hoeven JG, Marx G, Goetzenich A, Fritsch S, Heunks LMA, Bruells CS. Functional assessment of the diaphragm by speckle tracking ultrasound during inspiratory loading. Journal of applied physiology 2017; 123: 1063–1070.
21. Goligher EC, Laghi F, Detsky ME, Farias P, Murray A, Brace D, Brochard LJ, Bolz SS, Rubenfeld GD, Kavanagh BP, Ferguson ND. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. Intensive Care Med 2015; 41: 734.
22. Doorduin J, Nollet JL, Roesthuis LH, van Hees HW, Brochard LJ, Sinderby CA, van der Hoeven JG, Heunks LM. Partial Neuromuscular Blockade during Partial Ventilatory Support in Sedated Patients with High Tidal Volumes. American journal of respiratory and critical care medicine 2017; 195: 1033–1042.
23. Pham T, Brochard LJ, Slutsky AS. Mechanical Ventilation: State of the Art. Mayo Clinic proceedings 2017; 92: 1382–1400.
24. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, Simonneau G, Benito S, Gasparetto A, Lemaire F, Isabey D, Harf A. Noninvasive Ventilation for Acute Exacerbations of Chronic Obstructive Pulmonary Disease. New England Journal of Medicine 1995; 333: 817–822.
25. Brochard L, Mancebo J, Elliott MW. Noninvasive ventilation for acute respiratory failure. European Respiratory Journal 2002; 19: 712–721.
26. Boldrini R, Fasano L, Nava S. Noninvasive mechanical ventilation. Current opinion in critical care 2012; 18: 48–53.
27. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 2008; 10: 933–989.
28. Chandra D, Stamm JA, Taylor B, Ramos RM, Satterwhite L, Krishnan JA, Mannino D, Sciurba FC, Holguin F. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998–2008. American journal of respiratory and critical care medicine 2012; 185: 152–159.
29. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, Navalesi PMOTSC, Antonelli M, Brozek J, Conti G, Ferrer M, Guntupalli K, Jaber S, Keenan S, Mancebo J, Mehta S, Raoof SMOTTF. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 2017; 50.
30. British Thoracic Society Standards of Care C. Non-invasive ventilation in acute respiratory failure. Thorax 2002; 57: 192–211.
31. Hess DR. Patient-ventilator interaction during noninvasive ventilation. Respiratory care 2011; 56: 153–165; discussion 165–157.
32. Costa R, Navalesi P, Antonelli M, Cavaliere F, Craba A, Proietti R, Conti G. Physiologic evaluation of different levels of assistance during noninvasive ventilation delivered through a helmet. Chest 2005; 128: 2984–2990.

33. Vignaux L, Grazioli S, Piquilloud L, Bochaton N, Karam O, Levy-Jamet Y, Jaecklin T, Tourneux P, Jolliet P, Rimensberger PC. Patient-ventilator asynchrony during noninvasive pressure support ventilation and neurally adjusted ventilatory assist in infants and children. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2013; 14: e357–364.

34. Antonelli MA, Conti GC, Moro MM, Esquinas AE, Gonzalez-Diaz GG-D, Confalonieri MC, Pelaia PP, Principi TP, Gregoretti CG, Beltrame FB, Pennisi MP, Arcangeli AA, Proietti RP, Passariello MP, Meduri GM. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Medicine 2001; 27: 1718–1728.

35. Confalonieri M, Garuti G, Cattaruzza MS, Osborn JF, Antonelli M, Conti G, Kodric M, Resta O, Marchese S, Gregoretti C, Rossi A, Italian noninvasive positive pressure ventilation study g. A chart of failure risk for noninvasive ventilation in patients with COPD exacerbation. The European respiratory journal 2005; 25: 348–355.

36. Moretti M, Cilione C, Tampieri A, Fracchia C, Marchioni A, Nava S. Incidence and causes of non-invasive mechanical ventilation failure after initial success. Thorax 2000; 55: 819–825.

37. Moreau-Bussiere F, Samson N, St-Hilaire M, Reix P, Lafond JR, Nsegbe E, Praud JP. Laryngeal response to nasal ventilation in nonsedated newborn lambs. Journal of applied physiology 2007; 102: 2149–2157.

38. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med 2006; 32: 1515–1522.

39. Colombo D, Cammarota G, Alemani M, Carenzo L, Barra FL, Vaschetto R, Slutsky AS, Della Corte F, Navalesi P. Efficacy of ventilator waveforms observation in detecting patient-ventilator asynchrony. Critical care medicine 2011; 39: 2452–2457.

40. Tobin MJ, Jubran A, Laghi F. Patient-ventilator interaction. American journal of respiratory and critical care medicine 2001; 163: 1059–1063.

41. Leung P, Jubran A, Tobin MJ. Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea. American journal of respiratory and critical care medicine 1997; 155: 1940–1948.

42. Schmidt M, Kindler F, Cecchini J, Poitou T, Morawiec E, Persichini R, Similowski T, Demoule A. Neurally adjusted ventilatory assist and proportional assist ventilation both improve patient-ventilator interaction. Critical care 2015; 19: 56.

43. Spahija J, de Marchie M, Albert M, Bellemare P, Delisle S, Beck J, Sinderby C. Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilatory assist. Critical care medicine 2010; 38: 518–526.

44. Heunks LM, van der Hoeven JG. Clinical review: the ABC of weaning failure–a structured approach. Critical care 2010; 14: 245.

45. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, Pearl R, Silverman H, Stanchina M, Vieillard-Baron A, Welte T. Weaning from mechanical ventilation. The European respiratory journal 2007; 29: 1033–1056.

46. Faisy C, Meziani F, Planquette B, Clavel M, Gacouin A, Bornstain C, Schneider F, Duguet A, Gibot S, Lerolle N, Ricard JD, Sanchez O, Djibre M, Ricome JL, Rabbat A, Heming N, Urien S, Esvan M, Katsahian S, Investigators D. Effect of Acetazolamide vs Placebo on Duration of Invasive Mechanical Ventilation Among Patients With Chronic Obstructive Pulmonary Disease: A Randomized Clinical Trial. JAMA 2016; 315: 480–488.

47. Banga A, Khilnani GC. Post-hypercapnic alkalosis is associated with ventilator dependence and increased ICU stay. Copd 2009; 6: 437–440.

48. Roussos C, Koutsoukou A. Respiratory failure. The European respiratory journal Supplement 2003; 47: 3s-14s.

49. Heinemann HO, Goldring RM. Bicarbonate and the regulation of ventilation. The American journal of medicine 1974; 57: 361–370.
50. Rialp G, Raurich JM, Llompart-Pou JA, Ayestaran I, Ibanez J. Respiratory CO2 response depends on plasma bicarbonate concentration in mechanically ventilated patients. Medicina intensiva 2014; 38: 203–210.

Eline Oppersma
Jonne Doorduin
Johannes G van der Hoeven
Peter H Veltink
Jeroen WH van Hees
Leo MA Heunks

Respiratory Physiology & Neurobiology
2018, Volume 249, Pages 47–53.

2 The effect of metabolic alkalosis on the ventilatory response in healthy subjects

Abstract

Background Patients with acute respiratory failure may develop respiratory acidosis. Metabolic compensation by bicarbonate production or retention results in posthypercapnic alkalosis with an increased arterial bicarbonate concentration. The hypothesis of this study was that elevated plasma bicarbonate levels decrease respiratory drive and minute ventilation.

Methods In an intervention study in 10 healthy subjects the ventilatory response using a hypercapnic ventilatory response (HCVR) test was assessed, before and after administration of high dose sodium bicarbonate. Total dose of sodiumbicarbonate was 1000 ml 8.4 % in 3 days.

Results Plasma bicarbonate increased from 25.2 ± 2.2 to 29.2 ± 1.9 mmol/L. With increasing inspiratory CO_2 pressure during the HCVR test, RR, V_t, P_{di}, EA_{di} and V_E increased. The clinical ratio $\Delta V_E/\Delta P_{et}CO_2$ remained unchanged, but P_{di}, EA_{di} and V_E were significantly lower after bicarbonate administration for similar levels of inspired CO_2.

Conclusion This study demonstrates that in healthy subjects metabolic alkalosis decreases the neural respiratory drive and minute ventilation, as a response to inspiratory CO_2.

Introduction

Respiratory centers in the brainstem control the respiratory drive. Among other factors, activity of these respiratory centers is modulated by pH (1). Patients with acute hypoventilation, will develop arterial carbon dioxide (CO_2) retention, and therefore respiratory acidosis. To maintain homeostasis, metabolic compensation via bicarbonate (HCO_3^-) production or retention develops, which will shift plasma pH towards normal. Controlled mechanical ventilation can restore minute ventilation and normalize the CO_2 surplus. The slow adaptation of bicarbonate remaining in the blood may result in posthypercapnic alkalosis (2). This alkalosis may cause a reduced ventilatory response to hypercapnia in patients with moderate to severe chronic obstructive pulmonary disease (COPD), as demonstrated by a decreased response in minute ventilation (V_E) for a given change in end-tidal carbon dioxide ($P_{et}CO_2$) (3). However, Oren and colleagues showed that chronic metabolic acid-base changes do not alter the hypercapnic ventilatory response (HCVR) in 4 healthy subjects (4). Because of the limited number of subjects and several methodological issues in that study, uncertainty remains concerning the effect of bicarbonate retention on the ventilatory response (4). Electrical activity of the diaphragm (EA_{di}) has been used to quantify the respiratory drive (5,6) and is therefore a useful tool to study the effect of metabolic alkalosis on respiratory drive to the diaphragm.

In the present study, we hypothesize that increased plasma bicarbonate levels result in a decreased respiratory drive and reduced minute ventilation during a HCVR test. To test this hypothesis, we studied the effect of sodium bicarbonate administration on the HCVR and neural respiratory drive, as assessed by electrical activity of the diaphragm, in healthy subjects. Part of this work has previously been presented at the international conference of the European Respiratory Society (7).

Materials and methods

Subject characteristics

Subjects were eligible when meeting the following inclusion criteria: no relevant past medical history, in particular no neurological, respiratory or cardiac disorders reported, no current use of prescribed drugs, age > 18 years, non-smoking, not pregnant and body weight between 60 and 80 kg. The strict weight criterion was set to achieve corresponding levels of arterial bicarbonate with the same dosage of sodium bicarbonate, for each subject. The study was conducted at the Radboud university medical center and the protocol was approved by the local ethics review committee and conducted in accordance with the Declaration of Helsinki and its later amendments. All subjects gave their written informed consent.

Study protocol

In this before-after study design, physiological measurements were performed before and after sodium bicarbonate administration.

Arterial blood was obtained through arterial puncture at baseline for bicarbonate and gas analysis using an i-STAT handheld device with EG7+ cartridges (Abbott Point of Care Inc., Princeton, USA). A multi-electrode esophageal catheter with two balloons (NeuroVent Research Inc, Toronto, Canada) was inserted and positioned, as described previously (8). The ventilatory response to inhaled CO_2 was assessed by a HCVR test (3,4); subjects were seated in upright position with uncast abdomen and wearing a nose clip, breathing through a mouthpiece. First, subjects were breathing ambient air via a one-way valve from a reservoir breathing bag, which was continuously filled with ambient air. Thereafter every 2 min the inspiratory CO_2 pressure ($P_{insp}CO_2$) was increased by 1 kPa, by adding CO_2 to the breathing bag. Subjects were instructed to breathe normally and endure the test as long as possible.

After the first part of the measurements, participants were instructed to orally ingest 100 ml of 8.4 % sodium bicarbonate solution, thrice daily (7:00 a.m., 2:00 p.m. and 10:00 p.m.) for a total number of 10 doses. This regimen is adopted from previous studies that demonstrated increased plasma bicarbonate (4,9,10,11,12). Within 4 h after the last ingestion initial measurements were repeated. Figure 1 provides a schematic representation of the study protocol.

Data acquisition

During the HCVR test, all variables were continuously recorded. $EAdi$ signals were amplified and digitized (Porti 16, 22 bits, 71.5 µV/least significant bit, TMSi; The Netherlands) at a sampling frequency of 2 kHz. CO_2 pressure of the in- and exhaled air

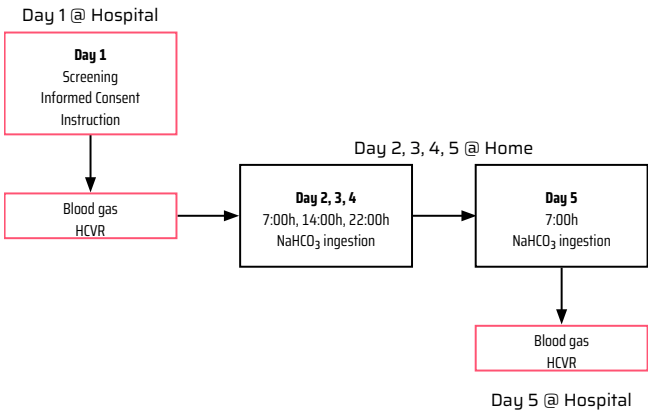


Figure 1
Schematic description of the protocol.

was continuously acquired with the NICO cardiopulmonary measurement device (Philips Respironics, The Netherlands). Pressure signals and flow were digitized (Porti 16, 22 bits, 1.4 μV/least significant bit, TMSi; The Netherlands) at a sampling frequency of 2 kHz. Data were stored and buffered on an external drive for offline analysis. Transdiaphragmatic pressure (P_{di}) was calculated as $P_{ga} - P_{es}$. Tidal volume was obtained by digital integration of the flow signal.

Data analysis

Measurement variables were analyzed offline in Matlab R2013a (The Mathworks, Natick, MA).

For every step of $P_{insp}CO_2$ during the HCVR test (both before and after sodium bicarbonate administration), the mean respiratory rate (RR), tidal volume (V_t), minute ventilation (V_E), P_{es} swings, P_{di}, EA_{di} (as the root mean square of the EA_{di} signal) and endtidal CO_2 pressure ($P_{et}CO_2$) was calculated during 30 s of stable signal at the end of a period of constant $P_{insp}CO_2$.

The commonly used clinical endpoint of the HCVR test, the ratio between the maximal V_E in respect to its baseline value (ΔV_E) and the maximal $P_{et}CO_2$ in respect to its baseline value ($\Delta P_{et}CO_2$), was calculated (3).

For further analysis only data where all 10 subjects endured the test were analyzed.

Neuromechanical efficiency (NME) is a specific measure for contractile efficiency of the diaphragm; the ability to generate inspiratory pressure for a given neural respiratory effort ($NME = P_{di}/EA_{di}$) (8,13,14). Neuroventilatory efficiency (NVE) defines the tidal volume generated for a given neural respiratory effort ($NVE = V_t/EA_{di}$) (14). Both NME and NVE were calculated.

To assess variability in the breathing pattern the coefficient of variation (CV; ratio of standard deviation (SD) to mean) was calculated for EA_{di} and V_E during 30 s at the start of the HCVR test and 30 s at the last step of $P_{insp}CO_2$ where all 10 subjects endured the test, both before and after sodium bicarbonate administration.

The center frequency of the power spectrum of the EA_{di} signal (CF_{di}) was used to assess muscle fiber conduction velocity (8,15). The CF_{di} was calculated during 30 s at the start of the HCVR test and 30 s at the last step of $P_{insp}CO_2$ where all 10 subjects endured the test, both before and after sodium bicarbonate administration.

Statistics

Statistical analyses were performed with OriginPro 9.1.0 (OriginLab Corporation, Northampton, USA). All values are given in mean ± Standard Error of the Mean (SEM), and $p \leq 0.05$ was considered significant. Descriptive statistics were determined for the subject characteristics. Paired-samples t-tests were performed to assess differences between before and after sodium bicarbonate administration for blood gases and breathing parameters, as well as the ratio $\Delta V_E/\Delta P_{et}CO_2$, the maximal achievable $P_{insp}CO_2$, EA_{di}, CF and CV. The difference between begin and end of the test was also assessed for the CF and CV using a paired-samples t-test.

Table 1

Subjects' characteristics, blood gas values and baseline breathing in mean of all subjects with standard error of the mean of the paired samples t-test.

Subject characteristics	mean ± SEM		
Subjects: male/female	7/3		
Age (y)	22.5 ± 0.7		
Body mass index (kg/m²)	21.9 ± 0.5		
	before	after	*p* value
Blood gas values			
HCO_3^- (mmol/L)	25.2 ± 0.7	29.2 ± 0.6	0.00*
pH	7.41 ± 0.004	7.44 ± 0.005	0.00*
pCO_2 (kPa)	5.3 ± 0.2	5.7 ± 0.1	0.00*
Na^+ (mmol/L)	139 ± 0.4	142 ± 0.5	0.00*
K^+ (mmol/L)	3.9 ± 0.1	3.8 ± 0.1	0.13
Baseline (breathing ambient air)			
V_E(L/min)	9.9 ± 1.6	9.7 ± 1.3	0.78
$P_{et}CO_2$ (kPa)	4.5 ± 0.3	4.6 ± 0.2	0.65
EA_{di} (μV)	10.0 ± 1.5	6.4 ± 1.0	0.05*
V_t	934.9 ± 105.6	814.6 ± 63.8	0.21
RR	11.3 ± 1.7	12.5 ± 2.1	0.14
P_{es} (*n* = 8/10)	−5.6 ± 1.1	−3.2 ± 0.8	0.01*

** Significant difference between before and after sodium bicarbonate administration ($p \leq 0.05$)*

Repeated measures two-way ANOVA was used to analyze within subjects effects of $P_{insp}CO_2$ and bicarbonate and their interaction for all parameters (EA_{di}, P_{es}, P_{di}, V_E, V_t, RR, neuroventilatory efficiency and neuromechanical efficiency). Tukey post hoc tests were applied when ANOVA showed significant differences between before and after increased bicarbonate levels.

Results

Subject characteristics

Eleven subjects were enrolled in this study, 1 subject withdrew after the first ingestion of sodium bicarbonate due to abdominal discomfort and 7 other subjects experienced minor abdominal discomfort but could complete the study. Subject characteristics and blood gas are presented in Table 1. This table also demonstrates the effects of sodium bicarbonate administration on plasma HCO_3^-, pH, pCO_2, Na^+ and K^+.

Ventilatory response

Flow, $P_{insp}CO_2$, $P_{et}CO_2$ and EA_{di} were recorded for every subject during both HCVR tests before and after sodium bicarbonate administration. Means of all parameters were calculated for every step of $P_{insp}CO_2$ as described in the methods section.

HCVR test

A representative response to inspiration of CO_2 during the HCVR test is shown in Figure 2. The inspiratory CO_2 is represented by the minimum values of the CO_2-curve for each breath, expiratory CO_2 by the maximum values of the curve for each breath. Increasing inspiratory CO_2 results in an increase in ventilation, EA_{di} and flow, to clear the excess CO_2. An example of V_E as a function of $P_{insp}CO_2$ and $P_{et}CO_2$ for 1 subject during the HCVR test is shown in Figure 3.

Sodium bicarbonate administration

While breathing ambient air at baseline, EA_{di} decreased after sodium bicarbonate administration (p = 0.05, Table 1). V_E and $P_{et}CO_2$ were not affected by sodium bicarbonate administration.

The commonly used clinical measure for the HCVR ($\Delta V_E/\Delta P_{et}CO_2$) did not change after sodium bicarbonate administration (Table 2). There was no significant difference between before and after sodium bicarbonate administration in maximal achievable $P_{insp}CO_2$, although the paired samples t-test shows a trend to increase from 6.7 kPa before to 7.3 kPa at after sodium bicarbonate administration (p = 0.06) and accordingly the V_E max did increase (Table 2).

The maximal $P_{insp}CO_2$ level where all subjects still endured the test was 5 kPa, so further analysis was restricted to $P_{insp}CO_2$ from 0 kPa to 5 kPa.

Both the ratio and the separate parameters of the clinical endpoint of the HCVR test (ΔV_E and $\Delta P_{et}CO_2$), as mean for all subjects until a $P_{insp}CO_2$ of 5 kPa, did not change after sodium bicarbonate administration (Table 2).

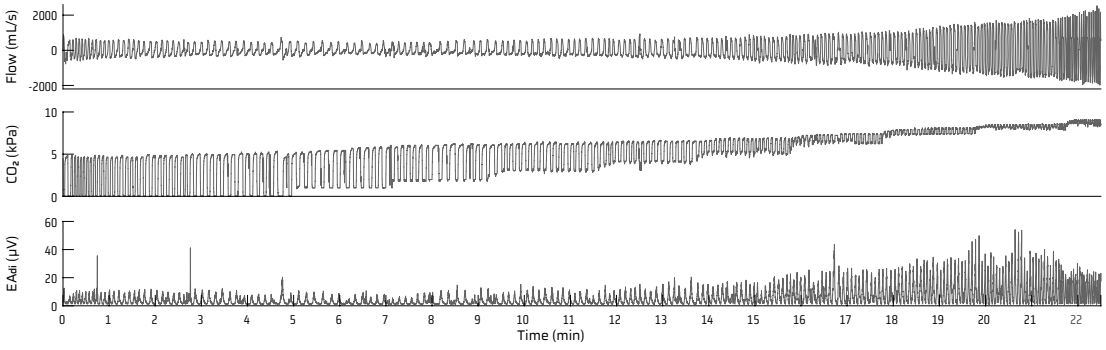


Figure 2

Flow, CO_2 and EA_{di} tracings during a HCVR test. Inspiratory CO_2 is given by the minimum values of the curve for each breath, expiratory CO_2 by the maximum values of the curve for each breath.

Table 2

Results of the HCVR test in mean of all subjects with standard error of the mean of the paired samples t-test.

	before	after	*p* value
HCVR test			
$\Delta V_E/\Delta P_{et}CO_2$ (L/min/kPa)	8.2 ± 1.7	7.9 ± 1.2	0.70
max $P_{insp}CO_2$ (kPa)	6.7 ± 0.3	7.3 ± 0.2	0.06
max V_E (L/min)	30.9 ± 2.1	35.9 ± 2.6	0.04*
$P_{insp}CO_2$ 0–5 kPa			
ΔV_E (L/min)	9.5 ± 2.0	7.7 ± 1.4	0.28
$\Delta P_{et}CO_2$ (kPa)	1.9 ± 0.2	2.0 ± 0.1	0.54
$\Delta V_E/\Delta P_{et}CO_2$ (L/min/kPa)	6.3 ± 1.6	4.3 ± 0.9	0.14
Center Frequency			
CF start test (Hz)	95.9 ± 2.4	97.0 ± 5.8	0.29
CF at $P_{insp}CO_2$ 5 kPa (Hz)	100.8 ± 5.4	82.7 ± 11.0	0.86
Coefficient of variation			
CV EA_{di} start test	0.31 ± 0.08	0.14 ± 0.04	0.08
CV EA_{di} at $P_{insp}CO_2$ 5 kPa	0.20 ± 0.04	0.19 ± 0.03	0.81
CV V_E start test	0.18 ± 0.11	0.26 ± 0.13	0.69
CV V_E at $P_{insp}CO_2$ 5 kPa	0.13 ± 0.03	0.12 ± 0.05	0.79

** Significant difference between before to after sodium bicarbonate administration ($p \leq 0.05$)*

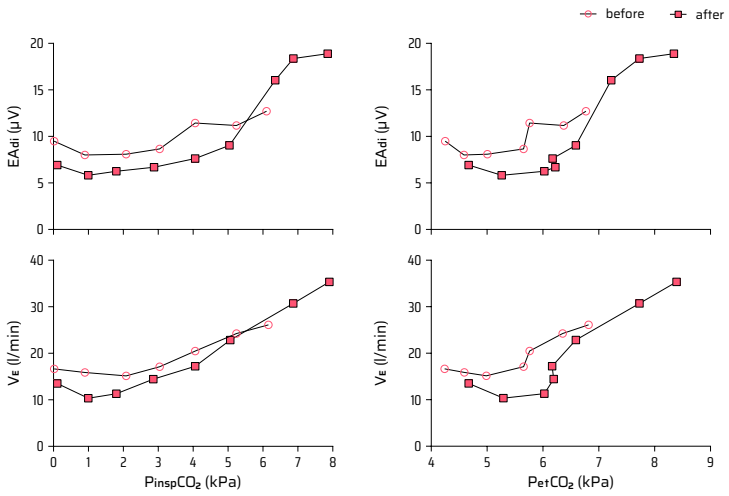


Figure 3

EA_{di} and minute ventilation (V_E) as function of inspiratory CO_2 pressure ($P_{insp}CO_2$) and endtidal CO_2 pressure ($P_{et}CO_2$) for one subject during the HCVR test before and after sodiumbicarbonate administration.

However, Figure 4 shows that both EAdi (p = 0.03) and VE (p = 0.03) significantly decreased after bicarbonate administration. Tukey post hoc tests showed that the difference between before and after sodium bicarbonate administration was significant within a level of $P_{insp}CO_2$ of 4 and 5 kPa. As a result of elevated levels of $P_{insp}CO_2$, RR (p = 0.00), Vt (p = 0.00), EAdi (p = 0.00) and VE (p = 0.00) all increased (Figure 4). Pes data was excluded for 2 subjects due to noise in the signal. Pes significantly decreased after bicarbonate administration (p = 0.01), according to Tukey's post hoc test within a level of $P_{insp}CO_2$ of 4 and 5 kPa. Due to noise in the Pdi signal, 4 subjects were excluded from further analysis regarding Pdi and NME. Pdi significantly decreased

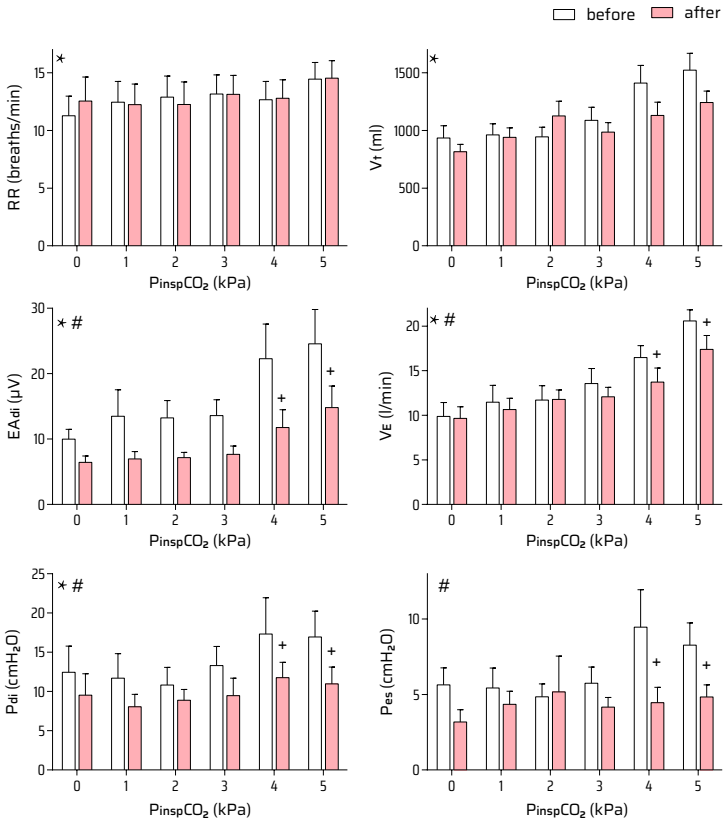


Figure 4

Mean and SEM for RR, Vt,VE, EAdi, Pdi and Pes before and after sodium bicarbonate administration for all subjects, as function of $P_{insp}CO_2$.

* Significant increase with increasing $P_{insp}CO_2$ with ANOVA.

\# Significant decrease from before to after sodium bicarbonate administration with ANOVA.

\+ Tukey's post hoc difference between before and after sodium bicarbonate administration.

Note: Pes is analyzed for 8 subjects and Pdi is analyzed for 6 subjects.

after bicarbonate administration (p = 0.05), within a level of $P_{insp}CO_2$ of 4 and 5 kPa according to the Tukey post hoc test. P_{di} also increased as a result of elevated levels of $P_{insp}CO_2$ (p = 0.01). There was an interaction between $P_{insp}CO_2$ and bicarbonate administration for V_E (p = 0.04) and V_t (p = 0.01).

NVE was not significantly influenced by increasing inspiratory CO_2 levels, but did increase after sodium bicarbonate administration (Figure 5). NME showed a significant decrease due to increasing $P_{insp}CO_2$, but only between 2 and 5 kPa. NME was not influenced by sodium bicarbonate administration (Figure 5).

The coefficient of variation of EA_{di} and V_E did not change within the tests (begin test versus $P_{insp}CO_2$ of 5 kPa), or between before and after sodium bicarbonate administration (Table 2). This implies that the CV was not influenced by increased bicarbonate levels.

The center frequency of diaphragm did not change within the tests (begin test versus $P_{insp}CO_2$ of 5 kPa) or between before and after sodium bicarbonate administration (Table 2), implying there is no change in muscle fiber conduction velocity due to the increased bicarbonate. This could however be analyzed for respectively 9 and 8 subjects due to noise in the signal.

Discussion

This is the first study to evaluate neural respiratory drive and resulting minute ventilation in healthy subjects with compensated metabolic alkalosis. Neural drive is represented by the electrical activity of the diaphragm (16). The main finding of this study is that an increased arterial bicarbonate level causes a decrease in the

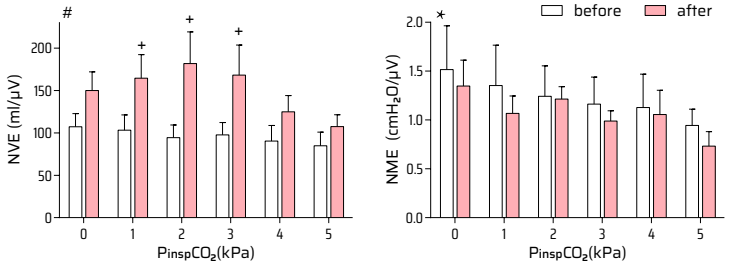


Figure 5

Mean and SEM for NVE and NME before and after sodium bicarbonate administration for all subjects, as function of $P_{insp}CO_2$.

* Significant increase with increasing $P_{insp}CO_2$ with ANOVA.

\# Significant decrease from before to after sodium bicarbonate administration with ANOVA.

\+ Tukey's post hoc difference between before and after sodium bi-carbonate administration.

Note: NME is analyzed for 6 subjects.

mean EA_{di} and minute ventilation of all subjects during a hypercapnic ventilatory response test at normal plasma pH levels.

Effect of elevated plasma bicarbonate on respiratory drive

We hypothesized that elevated plasma bicarbonate levels increase the buffer capacity for CO_2 resulting in decreased sensitivity of the respiratory centers to increased inhaled CO_2 during the HCVR test; so-called reduced chemosensitivity of breathing (17,18).

We found that when breathing ambient air, elevated plasma bicarbonate did not affect the HCVR test ($\Delta V_E/\Delta P_{et}CO_2$), V_E or $P_{et}CO_2$. However, baseline EA_{di} was lower after bicarbonate administration. In addition, further analysis of the ventilatory response to elevated $P_{insp}CO_2$ demonstrated different patterns before and after sodium bicarbonate administration. The respiratory centers respond differently to inhaled CO_2 when arterial bicarbonate levels are increased. This is probably as a result of the enhanced buffer capacity; more arterial bicarbonate supplies more capacity to buffer CO_2 before the respiratory centers sense an increased arterial CO_2.

First, the respiratory drive, represented by the electrical activity of the diaphragm (5,6), is decreased with increasing arterial bicarbonate levels, resulting in a decreased V_E. This is different from the findings of Oren in 1991; that study showed no difference in minute ventilation related to $P_{et}CO_2$ between pre and post sodium bicarbonate administration (arterial bicarbonate from 25.5 ± 0.6 to 30.6 ± 1.7 mEq/l in 3 days) (4). Also van de Ven et al. found no difference in ventilatory response in normocapnic and hypercapnic COPD patients under varying acid-base conditions (12). An explanation for this difference with the study of van de Ven could be that in the current study healthy subjects are measured, whereas van de Ven included COPD patients, with a possibility of changed respiratory mechanics influencing the hypercapnic ventilatory response. Our study adds measurement of EA_{di}, reflecting motor output of the central nervous system to the diaphragm muscle (5), which causes contraction of the diaphragm. EA_{di} is thereby a more specific and sensitive reflective of neural respiratory drive than V_E, which could also be influenced by mechanical properties of the respiratory system (6). Herrera and Kazemi studied the phrenic nerve output in dogs, as an index of neural output from the respiratory centers in the brain, and found that its response to hypoxia is significantly decreased when bicarbonate levels in the cerebrospinal fluid are increased (19). Although minute ventilation is not measured in these anesthetized dogs, this adheres to the findings of the current study.

Second, NVE appears to increase after sodium bicarbonate administration. This is due to EA_{di} decreasing more than V_E: less diaphragm electrical activity is needed to generate the same tidal volumes. The most likely explanation is a change in respiratory pump function, by recruitment of accessory muscles additional to the diaphragm.

Lastly, the maximal achievable V_E after sodium bicarbonate administration was higher than before. Although the maximal achievable $P_{insp}CO_2$ was not significantly increased, the *p* value of 0.06 shows a trend towards longer endurance of the test after sodium bicarbonate administration. Longer endurance implies subjects also reach a higher minute ventilation.

Coefficient of variation

Variability of ventilation has been shown to improve oxygenation in animals and also in humans such high variability might be beneficial (20,21,22). For example, Schmidt et al. showed that in patients who were mechanically ventilated in a partially supported mode, reducing the load increased variability of breathing. So the more unloading of the respiratory muscles is achieved by the ventilator, the higher the variability of breathing, by improved neuromechanical coupling (21). However, effects of increased inspiratory CO_2 levels on variability of electrical activity of the diaphragm and ventilation are variable. Busha et al. found that increased inspired CO_2 in rats resulted in a decrease of the CV of peak EA_{di} but also an increased breath-to-breath variability, indicating a difference in short- and long-term correlations in the variability of breathing (23), whereas Fiamma et al. found that hypercapnia decreased the breath-to-breath variability of ventilation (24). It is proposed by Nattie (23,25,26) that there are multiple sites of chemoreception throughout the brain stem where different chemosensors may be more or less active during different levels of CO_2. With increasing inspired CO_2, a greater number of inputs drives the respiratory centers resulting in more dynamic behaviour of the output (25,26). However, because in the current study bicarbonate levels are increased, we hypothesize that the inspired CO_2 will be buffered and the behaviour of the respiratory center will not change. We indeed found no effect of sodiumbicarbonate on the coefficient of variation which confirms our hypothesis that CV is not changed by an increased plasma bicarbonate level during the HCVR test.

Center frequency

Administration of sodiumbicarbonate changes the electrolyte status, and could thereby influence the membrane potentiation of the diaphragm. CF_{di} is a measure for muscle fiber conduction velocity, which is known to decrease during loaded breathing (8) and fatigue, attributed to many factors including a decreased extracellular sodium concentration which inhibits force development (27,28). In this study CF_{di} remains constant, although the administration of sodium bicarbonate resulted in a significant increased plasma sodium concentration, indicating no effect on diaphragm fiber conductivity probability of fatigue of the diaphragm.

Methodological issues

Arterial bicarbonate levels can be safely increased in healthy subjects as shown in this study. Sodium bicarbonate administration resulted in a relevant increase in bicarbonate levels exceeding standard laboratory reference values (HCO_3^- 22–28 mmol/L), whereas pH remained within reference value limits (pH 7.35–7.45). The response of

the respiratory drive to an increased arterial bicarbonate level was evaluated by administering a fixed dose to all subjects. Although only subjects with a weight of 60–80 kg were included, this results in a varying dose for each subject within these margins and thereby a varying arterial bicarbonate level. This resulted in a dosage of 0.3–0.4 g/kg/day (during 3 days), where i.e. Oren administered 0.7 g/kg/day (during 3 days) and Douroudos administered 0.3–0.5 g/kg/day (during 5 days) [4,11]. Resulting arterial bicarbonate levels were all comparably high (29.2 mmol/L, 30.6 mmol/L and 29.8–32.3 mmol/L respectively) and also pH was comparable and did not explain the difference in minute ventilation between the studies (7.44, 7.47 and 7.45–7.47). The HCVR test is used to assess the response of the respiratory centers to increased inspiratory CO_2 concentrations and provides a measure of the chemosensitivity of the brain. The chemosensitivity influences regulation of V_E and the response of various physiological and pathophysiological states to V_E [4]. There are various protocols to test the hypercapnic ventilatory response, all aiming at measuring the increase in V_E by increasing $P_{insp}CO_2$ [3,4,5]. This study used an adapted version of these protocols, and succeeded in changing V_E and $P_{et}CO_2$ as a result of increased $P_{insp}CO_2$. Baseline tidal volumes were high, probably due to a high instrumental dead space. We found that after sodium bicarbonate administration, the maximal achievable V_E and $P_{insp}CO_2$ were significantly higher, which could also be due to the familiarization of the subjects to the experimental protocol, without a placebo control group in this setup. However, subjects were unaware of the results of the previous test, of the duration of the HCVR test and of the current $P_{insp}CO_2$. Next to that, we showed that EA_{di} decreased with elevated levels of arterial bicarbonate. We have however no data of the electrical activity of other (accessory) respiratory muscles to analyze their behaviour during this state and in particular the interaction between the diaphragm and other muscles, which could possibly explain the behaviour of the diaphragm and the decrease in EA_{di}.

Clinical implications

The results of the current study may be relevant for the approach of patients difficult to wean from mechanical ventilation and of patients with COPD. Metabolic alkalosis is common in these patients [2] and our data indicate that this may affect breathing pattern, in particular respiratory drive during loaded breathing. Although in our study the healthy subjects were able to maintain adequate ventilation at baseline, ventilation during the HCVR test did decrease after administration of sodium bicarbonate. Patients with COPD could have mechanical difficulties and be unable to maintain adequate ventilation. These patients that suffer from (an exacerbation of) COPD or other causes of acute respiratory failure mostly require (noninvasive) mechanical ventilation to recover adequate minute ventilation, which restores the hypercapnia and thus pH to normal levels. Bicarbonate on the other hand is found to remain elevated in patients with posthypercapnic alkalosis [2]. It is suggested that excreting bicarbonate could correct metabolic alkalosis and, subsequently, increase

minute ventilation and improve oxygenation, facilitating weaning from mechanical ventilation in patients with COPD or other pulmonary diseases (29). Recently, Faisy et al. showed in a randomized trial that the use of acetazolamide did not result in a significant reduction in the duration of mechanical ventilation compared to placebo (30). However, serum bicarbonate levels were decreased after acetazolamide administration and there was a clinically substantial decrease (median 16 h) in duration of mechanical ventilation (30). This supports the findings of the current study that increased arterial bicarbonate levels suppress ventilation and excreting bicarbonate in patients with metabolic alkalosis could stimulate the respiratory centers.

Conclusions

In conclusion, the present study in healthy subjects demonstrates that an increased arterial bicarbonate level decreased the respiratory drive to the diaphragm and consequently decreased minute ventilation.

References

1 Feldman, J.L., Del Negro, C.A., Gray, P.A., 2013. Understanding the rhythm of breathing: so near, yet so far. Annu. Rev. Physiol. 75, 423–452.

2 Banga, A., Khilnani, G.C., 2009. Post-hypercapnic alkalosis is associated with ventilator dependence and increased ICU stay. COPD 6, 437–440.

3 Nickol, A.H., Dunroy, H., Polkey, M.I., Simonds, A., Cordingley, J., Corfield, D.R., Morrell, M.J., 2009. A quick and easy method of measuring the hypercapnic ventilatory response in patients with COPD. Respir. Med. 103, 258–267.

4 Oren, A., Whipp, B.J., Wasserman, K., 1991. Effects of chronic acid-base changes on the rebreathing hypercapnic ventilatory response in man. Respir. Int. Rev. Thorac. Dis. 58, 181–185.

5 American Thoracic Society/European Respiratory Society, 2002. ATS/ERS statement on respiratory muscle testing. Am. J. Respir. Crit. Care Med. 166, 518–624.

6 Jolley, C.J., Luo, Y.M., Steier, J., Rafferty, G.F., Polkey, M.I., Moxham, J., 2015. Neural respiratory drive and breathlessness in COPD. Eur. Respir. J. 45, 355–364.

7 Oppersma, E., Doorduin, J., van der Hoeven, J., Veltink, P., Heunks, L., 2016. Influence of Bicarbonate on Ventilatory Drive in Healthy Subjects [Abstract]. European Respiratory Society, London, UK.

8 Doorduin, J., Sinderby, C.A., Beck, J., Stegeman, D.F., van Hees, H.W., van der Hoeven, J.G., Heunks, L.M., 2012. The calcium sensitizer levosimendan improves human diaphragm function. Am. J. Respir. Crit. Care Med. 185, 90–95.

9 Cohen, B., Laish, I., Brosh-Nissimov, T., Hoffman, A., Katz, L.H., Braunstein, R., Sagi, R., Michael, G., 2013. Efficacy of urine alkalinization by oral administration of sodium bicarbonate: a prospective open-label trial. Am. J. Emerg. Med. 31, 1703–1706.

10 Coppoolse, R., Barstow, T.J., Stringer, W.W., Carithers, E., Casaburi, R., 1997. Effect of acute bicarbonate administration on exercise responses of COPD patients. Med. Sci.Sports Exerc. 29, 725–732.

11 Douroudos, I.I., Fatouros, I.G., Gourgoulis, V., Jamurtas, A.Z., Tsitsios, T., Hatzinikolaou, A., Margonis, K., Mavromatidis, K., Taxildaris, K., 2006. Dose-related effects of prolonged NaHCO3 ingestion during high-intensity exercise. Med. Sci. Sports Exerc. 38, 1746–1753.

12 van de Ven, M.J., Colier, W.N., van der Sluijs, M.C., Oeseburg, B., Vis, P., Folgering, H., 2002. Effects of acetazolamide and furosemide on ventilation and cerebral blood volume in normocapnic and hypercapnic patients with COPD. Chest 121, 383–392.

13 Doorduin, J., Nollet, J.L., Roesthuis, L.H., van Hees, H.W., Brochard, L.J., Sinderby, C.A., van der Hoeven, J.G., Heunks, L.M., 2017. Partial neuromuscular blockade during partial ventilatory support in sedated patients with high tidal volumes. Am. J. Respir.Crit. Care Med. 195, 1033–1042.

14 Liu, L., Liu, H., Yang, Y., Huang, Y., Liu, S., Beck, J., Slutsky, A.S., Sinderby, C., Qiu, H., 2012. Neuroventilatory efficiency and extubation readiness in critically ill patients. Crit. Care 16, R143.

15 Sinderby, C., Spahija, J., Beck, J., 2001. Changes in respiratory effort sensation over time are linked to the frequency content of diaphragm electrical activity. Am. J. Respir. Crit. Care Med. 163, 905–910.

16 Beck, J., Gottfried, S.B., Navalesi, P., Skrobik, Y., Comtois, N., Rossini, M., Sinderby, C., 2001. Electrical activity of the diaphragm during pressure support ventilation in acute respiratory failure. Am. J. Respir. Crit. Care Med. 164, 419–424.

17 Heinemann, H.O., Goldring, R.M., 1974. Bicarbonate and the regulation of ventilation. Am. J. Med. 57, 361–370.

18 Rialp, G., Raurich, J.M., Llompart-Pou, J.A., Ayestaran, I., Ibanez, J., 2014. Respiratory CO2 response depends on plasma bicarbonate concentration in mechanically ventilated patients. Med. Intensiva 38, 203–210.

19 Herrera, L., Kazemi, H., 1982. Modification of phrenic nerve output to hypoxia after twohours of hypercapnia and increased cerebrospinal fluid [HCO3-]. Am. Rev. Respir. Dis. 126, 70–774.

20 Arold, S.P., Mora, R., Lutchen, K.R., Ingenito, E.P., Suki, B., 2002. Variable tidal volume ventilation improves lung mechanics and gas exchange in a rodent model of acute lung injury. Am. J. Respir. Crit. Care Med. 165, 366–371.

21 Schmidt, M., Demoule, A., Cracco, C., Gharbi, A., Fiamma, M.N., Straus, C., Duguet, A.,Gottfried, S.B., Similowski, T., 2010. Neurally adjusted ventilatory assist increases respiratory variability and complexity in acute respiratory failure. Anesthesiology 112, 670–681.

22 Suki, B., Alencar, A.M., Sujeer, M.K., Lutchen, K.R., Collins, J.J., Andrade Jr., J.S.,Ingenito, E.P., Zapperi, S., Stanley, H.E., 1998. Life-support system benefits from noise. Nature 393, 127–128.

23 BuSha, B.F., Stella, M.H., 2002. State and chemical drive modulate respiratory variability.J. Appl. Physiol. (1985) 93, 685–696.

24 Fiamma, M.N., Straus, C., Thibault, S., Wysocki, M., Baconnier, P., Similowski, T., 2007. Effects of hypercapnia and hypocapnia on ventilatory variability and the chaotic dynamics of ventilatory flow in humans. Am. J. Physiol. Regul. Integr. Comp. Physiol.292, R1985–1993.

25 Nattie, E., 1999. CO2: brainstem chemoreceptors and breathing. Prog. Neurobiol. 59, 299–331.

26 Nattie, E., 2000. Multiple sites for central chemoreception: their roles in response sensitivity and in sleep and wakefulness. Respir. Physiol. 122, 223–235.

27 Fortune, E., Lowery, M.M., 2009. Effect of extracellular potassium accumulation on muscle fiber conduction velocity: a simulation study. Ann. Biomed. Eng. 37, 2105–2117.

28 Overgaard, K., Nielsen, O.B., Clausen, T., 1997. Effects of reduced electrochemical Na+ gradient on contractility in skeletal muscle: role of the Na+-K+ pump. Pflugers Arch.: Eur. J. Physiol. 434, 457–465.

29 Heming, N., Urien, S., Faisy, C., 2012. Acetazolamide: a second wind for a respiratory stimulant in the intensive care unit? Crit. Care 16, 318.

30 Faisy, C., Meziani, F., Planquette, B., Clavel, M., Gacouin, A., Bornstain, C., Schneider, F., Duguet, A., Gibot, S., Lerolle, N., Ricard, J.D., Sanchez, O., Djibre, M., Ricome, J.L.,Rabbat, A., Heming, N., Urien, S., Esvan, M., Katsahian, S., Investigators, D., 2016. Effect of acetazolamide vs placebo on duration of invasive mechanical ventilation among patients with chronic obstructive pulmonary disease: a randomized clinical trial. JAMA 315, 480–488.

Eline Oppersma*
Nima Hatam*
Jonne Doorduin
Johannes G van der Hoeven
Gernot Marx
Andreas Goetzenich
Sebastian Fritsch
Leo MA Heunks*
Christian S Bruells*

* authors contributed equally

Journal of Applied Physiology
2017, Volume 123, Pages 1063–1070

NEW & NOTEWORTHY

Transdiaphragmatic pressure using esophageal and gastric balloons is the gold standard to assess diaphragm effort. However, this technique is invasive and requires expertise, and the interpretation may be complex. We report that speckle tracking ultrasound can be used to detect stepwise increases in diaphragmatic effort. Strain and strain rate were highly correlated with transdiaphragmatic pressure, and therefore, diaphragm electric activity and speckle tracking might serve as reliable tools to quantify diaphragm effort in the future.

3 Functional assessment of the diaphragm by speckle tracking ultrasound during inspiratory loading

Abstract

Assessment of diaphragmatic effort is challenging, especially in critically ill patients in the phase of weaning. Fractional thickening during inspiration assessed by ultrasound has been used to estimate diaphragm effort. It is unknown whether more sophisticated ultrasound techniques such as speckle tracking are superior in the quantification of inspiratory effort. This study evaluates the validity of speckle tracking ultrasound to quantify diaphragm contractility. Thirteen healthy volunteers underwent a randomized stepwise threshold loading protocol of 0–50 % of the maximal inspiratory pressure. Electric activity of the diaphragm and transdiaphragmatic pressures were recorded. Speckle tracking ultrasound was used to assess strain and strain rate as measures of diaphragm tissue deformation and deformation velocity, respectively. Fractional thickening was assessed by measurement of diaphragm thickness at end-inspiration and end-expiration. Strain and strain rate increased with progressive loading of the diaphragm. Both strain and strain rate were highly correlated to transdiaphragmatic pressure (strain r^2 = 0.72; strain rate r^2 = 0.80) and diaphragm electric activity (strain r^2 = 0.60; strain rate r^2 = 0.66). We conclude that speckle tracking ultrasound is superior to conventional ultrasound techniques to estimate diaphragm contractility under inspiratory threshold loading.

Introduction

Under physiological conditions, the pressure developed by the inspiratory muscles is only ± 5 % of maximum inspiratory pressure (1). However, under pathological conditions, such as an acute exacerbation of chronic obstructive pulmonary disease or a failed trial of weaning from mechanical ventilation, the load imposed on the respiratory muscles increases considerably (2,3). Excessive inspiratory muscle loading may result in fatigue or injury of the diaphragm (4,5,6). Accordingly, in selected patients, evaluating respiratory muscle effort may be of clinical relevance (7,8). Today, measurement of transdiaphragmatic pressure (P_{di}) using esophageal and gastric balloons is the gold standard to assess effort of the diaphragm. However, this technique is invasive and requires expertise, and interpretation may be complex (7,9).

Diaphragmatic function has been studied by B-mode and M-mode ultrasound (10,11,12). Fractional thickening (FT) of the diaphragm has been used in previous studies to quantify effort of the diaphragm (10,13,14). However, Goligher et al. (15) reported low correlations (r^2 = 0.28) in healthy subjects between P_{di} and diaphragmatic thickening fraction, indicating limited validity of FT to quantify diaphragm effort.

Two-dimensional deformation ultrasound or speckle tracking (ST) ultrasound is an innovative ultrasound technique enabling distinct assessment of muscle function (16). The gray value pattern in ultrasound images remains relatively constant for any small region in muscle tissue; this is called a speckle. In the speckle tracking technique, a defined cluster of speckles is tracked from one frame to another during a contractile cycle. This enables the angle-independent, two-dimensional quantification of the percentage of deformation (strain; %) and deformation velocity (strain rate; s). For readers with additional interest in basic deformation imaging methodology, we may humbly refer to the references of Collier et al. (17) and Smiseth et al. (18).

Speckle tracking echocardiography has become a popular tool for both research and clinical purposes (16,19,20,21). Previously, we have demonstrated the feasibility of ST of the diaphragm during respiratory muscle unloading with noninvasive ventilation (22). ST has not been validated as a measure of diaphragm contractility using P_{di} as a gold standard. We hypothesize that strain and strain rate, obtained by ST, can be used to quantify diaphragm contractility during inspiratory loading, and this study aims to investigate the validity of these parameters. Part of this work has been presented previously at the international conference of the European Respiratory Society (23).

Materials and methods

Subjects

We enrolled 15 healthy volunteers with a body mass index of < 25 kg/m². This study was conducted at the Radboud University Medical Center, and the protocol was approved by the local ethics review committee and conducted in accordance with the Declaration of Helsinki and its later amendments. All subjects gave their written informed consent. Preexisting neuromuscular disorders or lung diseases were defined as exclusion criteria.

Measurements

A multielectrode esophageal catheter with two balloons (NeuroVent Research, Toronto, ON, Canada) was inserted, and the balloons were inflated with air, as described previously (24,25). The flow, electric activity of the diaphragm (EAdi), esophageal pressure (Pes), and gastric pressure (Pga) were recorded continuously (24). EAdi signals were amplified and digitized (Porti 16, 22 bits, 71.5 μV/least significant bit; TMSi) at a sampling frequency of 2 kHz. Pressure signals and flow were digitized (Porti 16, 22 bits, 1.4 μV/least significant bit; TMSi) at a sampling frequency of 2 kHz. Data were stored and buffered on an external drive for offline analysis. Transdiaphragmatic pressure (Pdi) was calculated as Pes subtracted from Pga. Tidal volume (Vt) was obtained by digital integration of the flow signal. Diaphragm ultrasound was performed using a 9-MHz linear transducer with a Vivid E 9TM ultrasound machine (General Electric Healthcare, Horton, Norway).

Study protocol

The protocol starts with the measurement of maximum inspiratory pressure (MIP). The mean mouth pressure (Pmo) during sustained maximum inspiration for 1 s, as recommended by the ATS/ERS statement on respiratory muscle testing (9) against a closed valve at functional residual capacity, is defined as the MIP. The maneuver is repeated at least five times until three reproducible efforts, with < 10 % variance, are obtained. Subjects were seated in the upright position

Inspiratory loading

An in-house-developed inspiratory threshold apparatus, modified from Chen et al. (26), was used to perform negative pressure threshold loading. In short, the device consisted of a cylindrical adjustable pressure chamber, which was connected to a nonrebreathing valve. The negative pressure was generated by a powerful commercially available vacuum cleaner. Pressure in the chamber was measured continuously using a differential pressure transducer (range ± 375 mmHg; Freescale). The dead space of the device can be estimated at ~600 ml. Subjects were seated in the uprightposition with uncast abdomen, breathing through a mouthpiece while wearing a nose clip. Inspiratory loading of 0, 10, 20, 30, 40, and 50 % of MIP was applied in random order. Every loading task was applied for 3 min and alternated

with 5 min of unloaded breathing. During the loading tasks, EA_{di}, P_{es}, P_{ga}, P_{mo}, and flow were recorded continuously (Figure 1).

Ultrasound recording

The ultrasound transducer was positioned in the right anterior axillary line longitudinal to the body axis (between the 9th–11th intercostal space) (Figure 2 top, and Supplemental Video S1). We chose the strongly longitudinal approach vs. the individual intercostal space to reduce angle dependence of the measurements. The hemidiaphragm is thereby displayed above the liver as a central, less echogenic layer between the peritoneal and pleural echogenic layer (Figure 2 top, and Supplemental Video S1). The region of interest (ROI) was positioned as described below during the offline data analysis (Figure 2, bottom). This probe position was marked on the skin for the purpose of standardization (15). Ultrasound recordings of the diaphragm were made at the final minute of every inspiratory loading task. A 10-s recording with the highest possible frame rate was used for offline analysis. Strain describes the relative change in length between an initial reference state (L_0) and the compressed/shortened state (L). The conventional strain is defined as: $\varepsilon = (L - L_0)/L_0$. Positive strain means stretching, whereas negative strain means shortening. An increase

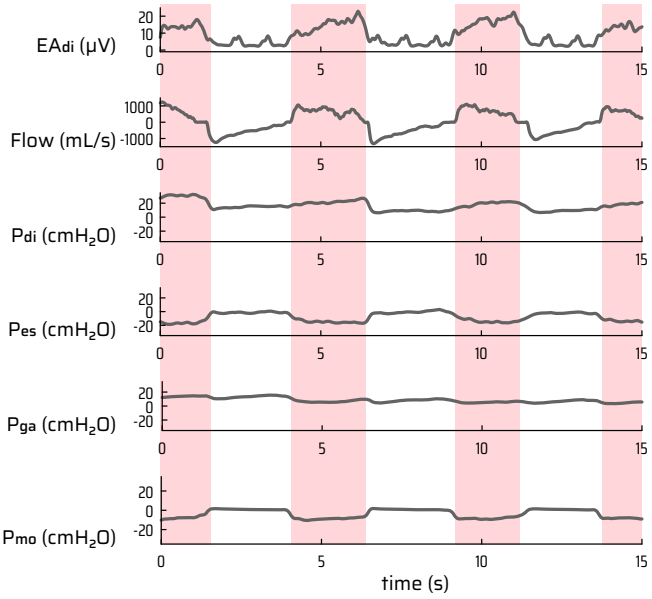


Figure 1

Representative tracing of electric activity of the diaphragm (EA_{di}), flow, electric activity of the diaphragm (P_{di}), esophageal pressure (P_{es}), gastric pressure (P_{ga}), and mean mouth pressure (P_{mo}) during inspiratory threshold loading [20 % of maximum inspiratory pressure (MIP); random subject]. Shaded areas are inspiration.

in strain, as described in the following data presentation, refers to a more negative value of strain, and thus an increase in shortening; e.g., −10 to −15 % corresponds to an increase in strain (or shortening).

Strain rate indicates the rate of deformation as follows: $\varepsilon'' = d\varepsilon/dt$. Strain rate is an instantaneous measurement not requiring a relation to a reference state. Examples for insufficient and sufficient tracking are displayed in Supplemental Videos S1 and S4.

Data analysis

$EAdi$, Pes, Pga, Pdi, Pmo, and flow were analyzed offline using algorithms developed in Matlab R2013a (The Mathworks, Natick, MA). $EAdi$ refers to a method using a standard electrode, acquisition, and analysis system to overcome signal filtering and processing effects when quantifying the diaphragm, as described previously (24).

Pes at end expiration was calculated as a measure of lung volume and corrected for active expiration (27). The recorded ultrasound data were analyzed offline, with

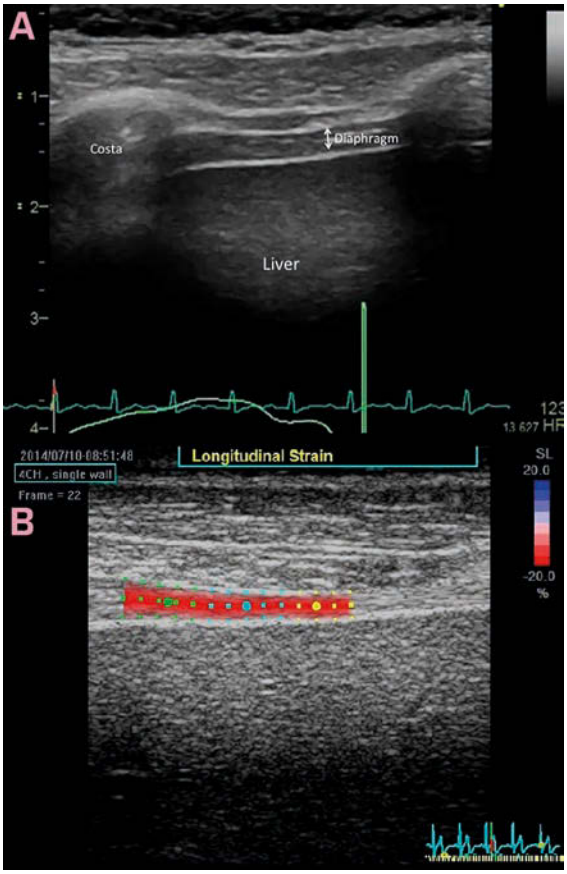


Figure 2
A B-mode picture of a scanned diaphragm area between chest wall and liver. Double arrow indicates the diaphragm between to hyperechoic lines, which are the equivalent to the border between diaphragm/pleura and peritoneum. Note the gray "dots" inside the diaphragm ("speckles").
B Region of interest tracked by the software.

the speckle tracking technique using the two-dimensional (2D) strain modality of EchoPac's Q-analysis tool (software version BT 12; General Electric Healthcare). Although the GE software is designed to trigger by the ECG signal by default, the cine loops were adjusted to one entire breathing cycle based upon simultaneously recorded respiratory curves. The software allows for manually moving the loop to the desired cycle, resulting in an adequate measurement independent of the cardiac cycle. The ROI was placed at the lower echogenic line (peritoneal line) to the upper echogenic line (pleural line) starting at the right side of the sector (cranial) and ending at the left sector side (caudal) with approximately five to seven points (Figure 2 bottom, and Supplemental Videos S2 and S3). In some loops, especially in the higher loading steps (40 and 50 % MIP), several attempts of ROI placement were necessary to achieve proper tracking. Here, fewer points with a narrower ROI had to be selected to allow adequate tracking. We refer to Supplemental Videos S4 for an example of not appropriate tracking. In general, these offline measurements can be finished in several minutes.

FT was also calculated from the ultrasound images. In the 2D image, diaphragmatic thickness at end expiration and end inspiration was measured at the same point following the longitudinal downward motion of the respective location. FT was measured at minimum in three different breaths and calculated by the following equation: (thickness at inspiration – thickness at expiration)/thickness at expiration. The quality of the recorded loops varied in some volunteers, depending on the load and general movement of the thorax, especially in high-loading steps. Loops were discarded from the analysis if no sufficient border tracking could be developed (see Supplemental Videos S5 and S6).

Statistical analysis

Values are presented as means ± SD, and $p < 0.05$ was considered significant. Statistical analyses were performed with SPSS 21.0 (SPSS, Chicago, IL). Repeated-measures one-way ANOVA was used to test the effect of inspiratory loading on EA_{di}, P_{es} at end expiration, P_{di}, strain, strain rate, and FT. Correlations between EA_{di}, P_{di}, FT, and strain and strain rate were assessed using repeated-observations correlation (28,29). This method accounts for multiple measurements within subjects by removing the differences between subjects and looking only at changes within subjects.

Results

Subjects

All included subjects (baseline characteristics: male/female, 7/8; age, 21.3 ± 2.3 yr; BMI 21.6 ± 1.7 kg/m^2) completed the protocol without adverse effects. Two data sets were lost from analysis due to technical issues (file damage). Mean MIP value for the group was 100 ± 32 cmH_2O.

Physiological measurements

Mean mouth pressure for all subjects was −1.2 ± 0.4, −13.7 ± 4.6, −26.3 ± 7.6, −37.9 ± 11.7, −49.9 ± 14.3, and −59.7 ± 16.9 cmH_2O for 0–50 % inspiratory loading. The stepwise increase in inspiratory loading resulted in an increase in both P_{di} and EA_{di} (Figure 3). P_{di} increased from 14.3 ± 5.9 cmH_2O at unloaded breathing via the mouthpiece to 60.8 ± 24.4 cmH_2O at 50 % loading. Likewise, EA_{di} increased from 20.3 ± 11.3 μV at zero loading to 66 ± 23.2 μV at 50 % loading. P_{es} at end expiration decreased from −3.7 ± 3.7 cmH_2O at zero loading to −6.0 ± 5.3 cmH_2O at 50 % loading ($p = 0.03$). There were no changes in V_t or respiratory frequency during the different inspiratory loading steps (Table 1).

Ultrasound assessment

In all assessable data sets, a ROI could be tracked in the offline ultrasound analysis during diaphragm contraction and relaxation. Table 2 shows the thickness of the diaphragm at end expiration, end inspiration, and thickening fraction as well as the repeatability coefficients. Repeated-measures one-way ANOVA showed that with increasing load both strain and strain rate increased ($p < 0.001$). Strain increased from −22 ± 7.6 % at zero loading to −41.5 ± 10.1 at 50 % loading. Consistent with strain, strain rate increased from −0.48 ± 0.2 s at zero loading to −1.5 ± 0.7 s at 50 % loading (Figure 3).

Strain and strain rate were both significantly correlated with EA_{di} and P_{di}. Strain vs. EA_{di} showed a correlation of $r^2 = 0.60$ ($p < 0.0001$), whereas strain vs. P_{di} data showed a correlation of $r^2 = 0.72$ ($p < 0.0001$). Correlations between strain rate and P_{di} ($r^2 = 0.80$, $p < 0.0001$) and between strain rate and EA_{di} ($r^2 = 0.66$, $p < 0.0001$) were even higher than those reported for strain (Figure 4).

Diaphragm thickness during zero loading was 2.4 ± 0.7 and 3.8 ± 1.2 mm during end expiration and end inspiration, respectively, and did not change during inspiratory loading (Table 1). Consequently, FT was not affected by incremental inspiratory loading ($p = 0.70$). Also, no significant correlations between EA_{di} and FT ($p = 0.790$), between P_{di} and FT ($p = 0.495$), or between FT and strain ($p = 0.654$) and strain rate ($p = 0.364$) were found.

Discussion

The present study is the first to evaluate speckle tracking ultrasound of the diaphragm during inspiratory muscle loading. We found that the ST parameters strain and strain rate are highly correlated with P_{di}, the gold standard for diaphragmatic contractility, and also with EA_{di}. Strain rate had the highest correlation with P_{di} and EA_{di}. Furthermore, ST proved to be superior to diaphragm fractional thickening, as assessed by conventional ultrasound to quantify diaphragmatic effort.

Validation of the physiological model.

Two methods for loading of the diaphragm have been described in the literature: inspiratory threshold loading and inspiratory resistive loading. The load imposed by the latter method is highly dependent on the inspiratory flow generated by the subject; low flow will result in minimal loading. We used a threshold load, as this may best reflect loading in intensive care patients where elastic properties of the respiratory system are increased due to pulmonary edema, chest wall edema, and pleural fluid. Our setup for inspiratory threshold loading was modified from Chen et al. (26). Figure 1 shows a representative example of one subject at loading of 10% of MIP. It should be noted that at 0% inspiratory loading P_{di}, EA_{di}, V_t, and FT were higher than expected for a healthy subject (24). This is most likely the result of the additional resistance and instrumental dead space imposed by the experimental device. As expected, increasing the inspiratory load as a percentage of MIP resulted in an increase in P_{di} (Figure 3).

Speckle tracking ultrasound of the diaphragm.

Tracking of unique grayscale scatter patterns, i.e. "speckles", is one of the most useful tools in cardiac imaging to assess cardiac function and is closely correlated with contractile myocardial function and outcome (16,20,21,30). These speckle patterns are the ultrasonic correlate of interferences of ultrasound inside the tissue, i.e., different tissue patterns (muscle fibers, epimysium, etc.) and their movement toward each other. Movement of speckle patterns reflects myofibrils/muscle tissue during its contraction, although speckles do not represent specific single myofibrils. It is important to mention that strain and strain rate approximate contractile function but are not equal to contraction (31,32).

Software tools to derive deformation data out of two- or three-dimensional ultrasonic cine loops are usually designed to track speckles in between endomyocard and epimyocard as hyperechoic leading structures. The parameters strain and strain rate define different but load-dependent variables; muscle deformation (strain) and deformation velocity (strain rate) can be inferred. Importantly, in contrast to conventional ultrasound techniques, this measure is probe angle independent, which is of fundamental importance if the diaphragm is investigated. An important advantage of ST is that, compared with conventional ultrasound, the ST software recognizes the same region of the diaphragm. A limitation is that defining ROIs and the software calculations are based on an algorithm patented by GE, which is not open to the public.

Within the current study, we did not assess intra- and interobserver variability. This has been evaluated extensively by Orde et al. (33). Their study demonstrated that ST of the right diaphragm is feasible and reproducible (33). Diaphragm images were recorded from the end of expiration through the end of inspiration at 60% maximal inspiratory capacity. The current study is the first to demonstrate that diaphragm strain and strain rate are highly correlated with P_{di}, the gold standard for

diaphragm effort. In addition, a high correlation was found between these two ST measures and EAdi.

Fractional thickening during inspiratory loading.

Diaphragm FT during inspiration as a measure for loading has been studied previously (15,34,35,36). Umbrello et al. (35) found that diaphragm thickening is a reliable

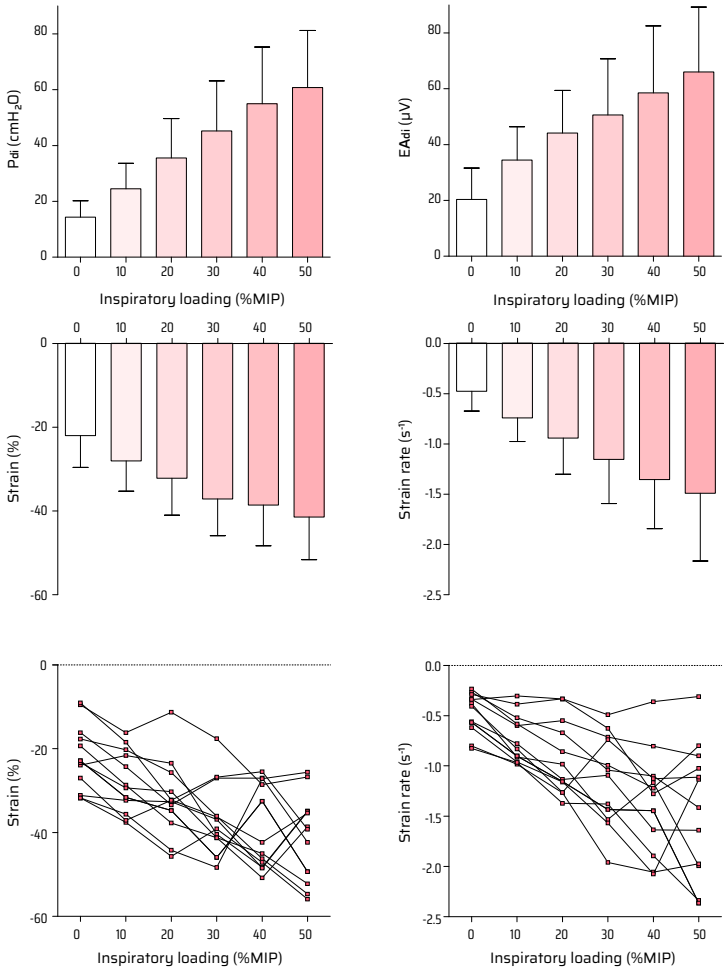


Figure 3

Top and middle: means ± SD of EAdi, Pdi, strain, and strain rate as function of inspiratory loading (%MIP) for all subjects. Repeated measures 1-way ANOVA showed a significant effect of increased loading on all variables ($p < 0.001$).

Bottom: individual data of all subjects, strain, and strain rate as function of inspiratory loading (%MIP).

Table 1
Physiological response to the different loading steps

	Inspiratory loading (%MIP)						
	0	10	20	30	40	50	*p* value
V_T (ml)	1076 ± 350	1183 ± 427	1147 ± 425	1053 ± 346	1049 ± 418	936 ± 329	0.161
Resp. frequency (breaths/min)	13.5 ± 4.2	15.3 ± 4.4	15.6 ± 5.4	16.7 ± 6.1	16.1 ± 5.7	17.3 ± 5.7	0.133
Diaphragm thickness end expiration (mm)	2.4 ± 0.7	2.4 ± 0.6	2.6 ± 0.5	2.6 ± 0.7	2.5 ± 0.6	2.4 ± 0.7	0.783
Diaphragm thickness end inspiration (mm)	3.8 ± 1.2	4.0 ± 1.5	4.1 ± 1.7	3.9 ± 1.8	4.0 ± 1.4	3.6 ± 1.4	0.452

Values are means ± SD. MIP, maximum inspiratory pressure; V_T, tidal volume. p value is given of repeated-measures 1-way ANOVA.

indicator of respiratory effort, and Vivier et al. (36) as well found a parallel decrease in FT and the diaphragmatic pressure-time product per breath during noninvasive ventilation with increasing levels of support. Goligher et al. (15) reported a rather low but significant correlation (r^2 = 0.3; p < 0.01) for FT vs. both P_{di} and EA_{di} in healthy subjects (n = 5) (15). In the current study, no significant correlation between FT and P_{di} or EA_{di} was found. To evaluate whether insufficient ultrasound training of our investigators contributed to this discrepancy, the repeatability coefficient of thickness at end expiration was calculated, as this measure is unaffected by our loading protocol (Table 2). This demonstrates that the relatively high variation in FT in the present study is due mainly to the variation in thickness at end inspiration but also that the repeatability at end expiration in our study was relatively high compared with the study by Goligher et al. (1.07 vs. 0.2 mm in the current study and the Goligher et al. study, respectively) (15).

Another possible explanation for the apparent discrepancy with the study by Goligher et al. (15) is the difference in inspiratory loading protocol used. In their study, thickness was measured at different lung volumes, whereas in our study inspiratory threshold loading was imposed, whereas volume was kept more or less constant (Table 1), which may have important implications. Finally, the current study is a single point study and not a follow-up study where patients were ventilated; our population consisted of healthy, not ventilated subjects, which also may account for the discrepancy with the study by Goligher et al. (15). In a study by Cohn et al. (37), healthy subjects were instructed to target specific lung volumes up to total lung capacity. A nonlinear relationship was found for FT vs. lung volume (polynomial equation was calculated with an r^2 of 0.99). Because subjects were instructed to keep the glottis open, the diaphragm was active at the targeted lung volumes, and thus changes in diaphragm thickness resulted from changes in volume and pressure. When thickness is measured at different lung volumes with closed glottis (diaphragm relaxed),

Table 2
Thickness of the diaphragm at end expiration and end inspiration and thickening fraction

	End-Expiration Thickness	End-Inspiration Thickness	Thickening Fraction, %
0 %	2.4 ± 0.7	3.8 ± 1.2	59.9 ± 32.1
10 %	2.4 ± 0.6	4.0 ± 1.5	67.9 ± 35.0
20 %	2.6 ± 0.5	4.1 ± 1.7	55.0 ± 39.2
30 %	2.6 ± 0.7	3.9 ± 1.8	48.9 ± 34.7
40 %	2.5 ± 0.6	4.0 ± 1.4	61.5 ± 48.1
50 %	2.4 ± 0.7	3.6 ± 1.4	50.6 ± 46.7
Repeatability coefficient	1.07 mm	2.54 mm	85.2 %

Data are shown as means ± SD in mm for all subjects. Bottom row shows the values for the repeatability coefficient of the measurements.

volume affects diaphragm thickness only at lung volume > 50 % of vital capacity (15). Finally, Ueki et al. (38) measured diaphragm during maximal inspiratory effort against a closed valve (isovolumetric). They reported a strong correlation between maximum inspiratory pressure and diaphragm FT (r^2 = 0.67). The relationship between isometric inspiratory pressure and FT was not studied systematically.

Apparently, the relationship between diaphragm thickness and effort (Pdi, EAdi), is complex and depends upon other possible factors on the pressure developed, lung volume and thoracic cage configuration (15,37,38), which may explain the poor or absent correlation between FT and Pdi in the studies discussed. However, because chest cage configuration was not controlled in this study, we cannot derive any conclusions about the influence of the chest cage configuration on the relation between diaphragm thickness and effort.

The strong correlation between Pdi and strain as well as strain rate in the current study indicates that speckle tracking ultrasound-derived parameters may provide a good estimation of diaphragm effort, at least under inspiratory threshold loading. The performance of speckle tracking ultrasound under different loading conditions (isometric contractions, high inspiratory volume) remains to be evaluated.

Future perspectives and clinical implications.

Regarding deformation analysis of the diaphragm, the software deriving the ST data has to be adapted to diaphragmatic ultrasonic morphology, allowing quick, easy, and reproducible analysis, preferably on site. The offline setting of the actual data analysis is currently the only way to ensure proper data analysis, which hampers its use as bedside tool. In echocardiography, most vendors provide a simplified software tool for ST, allowing measurements on site.

Only a few days of controlled mechanical ventilation are associated with atrophy of the diaphragm (39,40). The reduction in diaphragm force, assessed by bilateral magnetic stimulation of the phrenic nerves, is ~30 % in the first 5–6 days of invasive mechanical ventilation, indicating the rapid development of diaphragm weakness

(41). Despite the growing evidence that diaphragm weakness develops in critically ill patients and contributes to weaning failure and thus prolonged ventilation (41,42,43), respiratory muscle function is poorly monitored in these patients. Importantly, current state of the art techniques for monitoring, such as EA_{di} and P_{di}, are invasive and not widely available, and their interpretation may be rather complex (7). An ideal assessment of diaphragm function must be available at bedside, fast and easy to acquire, and allow standardized quantification. Guiding of ventilator weaning and assessing diaphragm contractile force during spontaneous breathing trials and/or pressure support ventilation might allow us to adapt ventilation and weaning protocols individually. Both sufficient loading and prevention of excessive loading are decisive for weaning success. ST of the diaphragm might serve as a diagnostic tool that can provide direct insight into diaphragm activity and force generation.

In conclusion, speckle tracking ultrasound as noninvasive techniques can be used to detect stepwise increases in diaphragmatic effort. Deformation (strain) and deformation velocity (strain rate) were highly correlated with transdiaphragmatic pressure and electric activity of diaphragm. Speckle tracking ultrasound might serve as reliable tool to guide weaning at the bedside in the future.

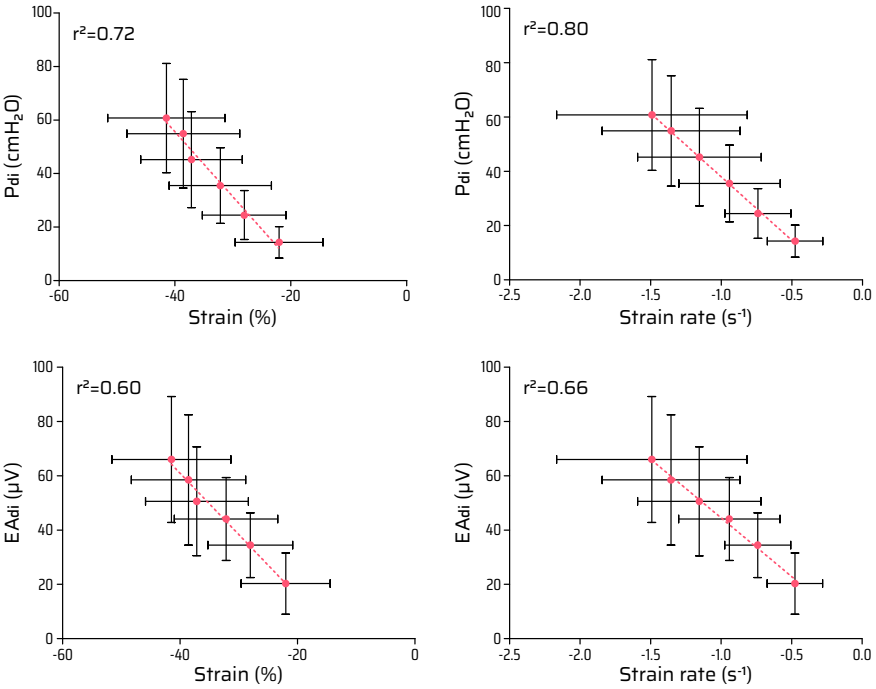


Figure 4
Correlation of P_{di} and EA_{di} vs. strain and strain rate for all subjects during inspiratory loading from 0 to 50 %.

Supplemental videos

Supplemental videos for this article are provided at the *Journal of Applied Physiology* web site.
To view the Supplemental Videos online, scan this QR code or use the short URL underneath.

https://j.mp/2JD1mQ4

References

1. Gandevia SC, McKenzie DK, Plassman BL. Activation of human respiratory muscles during different voluntary manoeuvres. J Physiol 428: 387–403, 1990. doi:10.1113/jphysiol.1990.sp018218.
2. Carlucci A, Ceriana P, Prinianakis G, Fanfulla F, Colombo R, Nava S. Determinants of weaning success in patients with prolonged mechanical ventilation. Crit Care 13: R97, 2009. doi:10.1186/cc7927.
3. McKenzie DK, Butler JE, Gandevia SC. Respiratory muscle function and activation in chronic obstructive pulmonary disease. J Appl Physiol (1985) 107: 621–629, 2009. doi:10.1152/japplphysiol.00163.2009.
4. Ebihara S, Hussain SN, Danialou G, Cho WK, Gottfried SB, Petrof BJ. Mechanical ventilation protects against diaphragm injury in sepsis: interaction of oxidative and mechanical stresses. Am J Respir Crit Care Med 165: 221–228, 2002. doi:10.1164/ajrccm.165.2.2108041.
5. Orozco-Levi M, Lloreta J, Minguella J, Serrano S, Broquetas JM, Gea J. Injury of the human diaphragm associated with exertion and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164: 1734–1739, 2001. doi:10.1164/ajrccm.164.9.2011150.
6. Reid WD, Belcastro AN. Time course of diaphragm injury and calpain activity during resistive loading. Am J Respir Crit Care Med 162: 1801– 1806, 2000. doi:10.1164/ajrccm.162.5.9906033.
7. Doorduin J, van Hees HW, van der Hoeven JG, Heunks LM. Monitoring of the respiratory muscles in the critically ill. Am J Respir Crit Care Med 187: 20–27, 2013. doi:10.1164/rccm.201206–1117CP.
8. Heunks LM, Doorduin J, van der Hoeven JG. Monitoring and preventing diaphragm injury. Curr Opin Crit Care 21: 34–41, 2015. doi:10.1097/ MCC.0000000000000168.
9. American Thoracic Society/European Respiratory Society. ATS/ERS statement on respiratory muscle testing. Am J Respir Crit Care Med 166: 518–624, 2002. doi:10.1164/rccm.166.4.518.
10. Ayoub J, Cohendy R, Prioux J, Ahmaidi S, Bourgeois JM, Dauzat M, Ramonatxo M, Préfaut C. Diaphragm movement before and after cholecystectomy: a sonographic study. Anesth Analg 92: 755–761, 2001. doi:10.1213/00000539-200103000-00038.
11. Lerolle N, Guérot E, Dimassi S, Zegdi R, Faisy C, Fagon JY, Diehl JL. Ultrasonographic diagnostic criterion for severe diaphragmatic dysfunction after cardiac surgery. Chest 135: 401–407, 2009. doi:10.1378/chest. 08–1531.
12. Matamis D, Soilemezi E, Tsagourias M, Akoumianaki E, Dimassi S, Boroli F, Richard JC, Brochard L. Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. Intensive Care Med 39: 801–810, 2013. doi:10.1007/s00134-013-2823-1.
13. Goligher EC, Fan E, Herridge MS, Murray A, Vorona S, Brace D, Rittayamai N, Lanys A, Tomlinson G, Singh JM, Bolz SS, Rubenfeld GD, Kavanagh BP, Brochard LJ, Ferguson ND. Evolution of diaphragm thickness during mechanical ventilation. impact of inspiratory effort. Am J Respir Crit Care Med 192: 1080–1088, 2015. doi:10.1164/ rccm.201503-0620OC.
14. Kim WY, Suh HJ, Hong SB, Koh Y, Lim CM. Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. Crit Care Med 39: 2627–2630, 2011. doi:10.1097/CCM. 0b013e3182266408.

15. Goligher EC, Laghi F, Detsky ME, Farias P, Murray A, Brace D, Brochard LJ, Bolz SS, Rubenfeld GD, Kavanagh BP, Ferguson ND. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. Intensive Care Med 41: 642–649, 2015. [Erratum. Intensive Care Med 41: 734, 2015.] 10. 1007/s00134-015-3724-2.

16. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, Støylen A, Ihlen H, Lima JA, Smiseth OA, Slørdahl SA. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 47: 789–793, 2006. doi:10.1016/j.jacc. 2005.10.040.

17. Collier P, Phelan D, Klein A. A test in context: myocardial strain measured by speckle-tracking echocardiography. J Am Coll Cardiol 69: 1043–1056, 2017. doi:10.1016/j.jacc.2016.12.012.

18. Smiseth OA, Torp H, Opdahl A, Haugaa KH, Urheim S. Myocardial strain imaging: how useful is it in clinical decision making? Eur Heart J 37: 1196–1207, 2016. doi:10.1093/eurheartj/ehv529.

19. Crosby J, Amundsen BH, Hergum T, Remme EW, Langeland S, Torp H. 3-D speckle tracking for assessment of regional left ventricular function. Ultrasound Med Biol 35: 458 –471, 2009. doi:10.1016/ j.ultrasmedbio.2008.09.011.

20. Kusunose K, Agarwal S, Marwick TH, Griffin BP, Popović ZB. Decision making in asymptomatic aortic regurgitation in the era of guidelines: incremental values of resting and exercise cardiac dysfunction. Circ Cardiovasc Imaging 7: 352–362, 2014. doi:10.1161/CIRCIMAGING.113.001177.

21. Yingchoncharoen T, Gibby C, Rodriguez LL, Grimm RA, Marwick TH. Association of myocardial deformation with outcome in asymptomatic aortic stenosis with normal ejection fraction. Circ Cardiovasc Imaging 5: 719 –725, 2012. doi:10.1161/CIRCIMAGING.112. 977348.

22. Hatam N, Goetzenich A, Rossaint R, Karfis I, Bickenbach J, Autschbach R, Marx G, Bruells CS. A novel application for assessing diaphragmatic function by ultrasonic deformation analysis in noninvasively ventilated healthy young adults. Ultraschall Med 35: 540–546, 2014. doi:10. 1055/s-0034-1366090.

23. Oppersma E, Hatam N, Doorduin J, van der Hoeven JG, Marx G, Goetzenich A, Heunks LM, Bruells CS. Speckle tracking echography allows sonographic assessment of diaphragmatic loading (Abstract). Eur Respir J 48: PA3564, 2016.

24. Doorduin J, Sinderby CA, Beck J, Stegeman DF, van Hees HW, van der Hoeven JG, Heunks LM. The calcium sensitizer levosimendan improves human diaphragm function. Am J Respir Crit Care Med 185: 90–95, 2012. doi:10.1164/rccm.201107-1268OC.

25. Doorduin J, Sinderby CA, Beck J, van der Hoeven JG, Heunks LM. Assisted ventilation in patients with acute respiratory distress syndrome: lung-distending pressure and patient-ventilator interaction. Anesthesiology 123: 181–190, 2015. doi:10.1097/ALN.0000000000000694.

26. Chen RC, Que CL, Yan S. Introduction to a new inspiratory threshold loading device. Eur Respir J 12: 208–211, 1998. doi:10.1183/09031936. 98.12010208.

27. Parthasarathy S, Jubran A, Laghi F, Tobin MJ. Sternomastoid, rib cage, and expiratory muscle activity during weaning failure. J Appl Physiol (1985) 103: 140–147, 2007. doi:10.1152/japplphysiol.00904.2006.

28. Bland JM, Altman DG. Calculating correlation coefficients with repeated observations: Part 1–Correlation within subjects. BMJ 310: 446, 1995. doi:10.1136/bmj.310.6977.446.

29. Bland JM, Altman DG. Calculating correlation coefficients with repeated observations: Part 2–Correlation between subjects. BMJ 310: 633, 1995. doi:10.1136/bmj.310.6980.633.

30. Urheim S, Edvardsen T, Torp H, Angelsen B, Smiseth OA. Myocardial strain by Doppler echocardiography. Validation of a new method to quantify regional myocardial function. Circulation 102: 1158–1164, 2000. doi:10.1161/01.CIR.102.10.1158.

31. D'hooge J, Heimdal A, Jamal F, Kukulski T, Bijnens B, Rademakers F, Hatle L, Suetens P, Sutherland GR. Regional strain and strain rate measurements by cardiac ultrasound: principles, implementation and limitations. Eur J Echocardiogr 1: 154–170, 2000. doi:10.1053/euje.2000. 0031.

32. Waldman LK, Fung YC, Covell JW. Transmural myocardial deformation in the canine left ventricle. Normal in vivo three-dimensional finite strains. Circ Res 57: 152–163, 1985. doi:10.1161/01.RES.57.1.152.

33. Orde SR, Boon AJ, Firth DG, Villarraga HR, Sekiguchi H. Diaphragm assessment by two dimensional speckle tracking imaging in normal subjects. BMC Anesthesiol 16: 43, 2016. doi:10.1186/s12871-016-0201-6.

34. DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. Thorax 69: 423–427, 2014. doi:10.1136/thoraxjnl-2013-204111.

35. Umbrello M, Formenti P, Longhi D, Galimberti A, Piva I, Pezzi A, Mistraletti G, Marini JJ, Iapichino G. Diaphragm ultrasound as indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation: a pilot clinical study. Crit Care 19: 161, 2015. doi:10.1186/s13054-015-0894-9.

36. Vivier E, Mekontso Dessap A, Dimassi S, Vargas F, Lyazidi A, Thille AW, Brochard L. Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. Intensive Care Med 38: 796– 803, 2012. doi:10.1007/s00134-012-2547-7.

37. Cohn D, Benditt JO, Eveloff S, McCool FD. Diaphragm thickening during inspiration. J Appl Physiol (1985) 83: 291–296, 1997.

38. Ueki J, De Bruin PF, Pride NB. In vivo assessment of diaphragm contraction by ultrasound in normal subjects. Thorax 50: 1157–1161, 1995. doi:10.1136/thx.50.11.1157.

39. Hooijman PE, Beishuizen A, Witt CC, de Waard MC, Girbes AR, Spoelstra-de Man AM, Niessen HW, Manders E, van Hees HW, van den Brom CE, Silderhuis V, Lawlor MW, Labeit S, Stienen GJ, Hartemink KJ, Paul MA, Heunks LM, Ottenheijm CA. Diaphragm muscle fiber weakness and ubiquitin-proteasome activation in critically ill patients. Am J Respir Crit Care Med 191: 1126–1138, 2015. doi:10.1164/ rccm.201412-2214OC.

40. Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, Zhu J, Sachdeva R, Sonnad S, Kaiser LR, Rubinstein NA, Powers SK, Shrager JB. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 358: 1327–1335, 2008. doi:10.1056/ NEJMoa070447.

41. Jaber S, Petrof BJ, Jung B, Chanques G, Berthet JP, Rabuel C, Bouyabrine H, Courouble P, Koechlin-Ramonatxo C, Sebbane M, Similowski T, Scheuermann V, Mebazaa A, Capdevila X, Mornet D, Mercier J, Lacampagne A, Philips A, Matecki S. Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. Am J Respir Crit Care Med 183: 364–371, 2011. doi:10.1164/ rccm.201004-0670OC.

42. Hermans G, Agten A, Testelmans D, Decramer M, Gayan-Ramirez G. Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: a prospective observational study. Crit Care 14: R127, 2010. doi:10.1186/cc9094.

43. Laghi F, Cattapan SE, Jubran A, Parthasarathy S, Warshawsky P, Choi YS, Tobin MJ. Is weaning failure caused by low-frequency fatigue of the diaphragm? Am J Respir Crit Care Med 167: 120–127, 2003. doi:10.1164/rccm.200210-1246OC.

Eline Oppersma
Jonne Doorduin
Erik HFM van der Heijden
Johannes G van der Hoeven
Leo MA Heunks

Critical Care
2013, Volume 17:245

4 Noninvasive ventilation and the upper airway: should we pay more attention?

Abstract

In an effort to reduce the complications related to invasive ventilation, the use of noninvasive ventilation (NIV) has increased over the last years in patients with acute respiratory failure. However, failure rates for NIV remain high in specific patient categories. Several studies have identified factors that contribute to NIV failure, including low experience of the medical team and patient–ventilator asynchrony. An important difference between invasive ventilation and NIV is the role of the upper airway. During invasive ventilation the endotracheal tube bypasses the upper airway, but during NIV upper airway patency may play a role in the successful application of NIV. In response to positive pressure, upper airway patency may decrease and therefore impair minute ventilation. This paper aims to discuss the effect of positive pressure ventilation on upper airway patency and its possible clinical implications, and to stimulate research in this field.

Introduction

Noninvasive ventilation (NIV) is increasingly used in acute respiratory failure, for instance in patients with exacerbation of chronic obstructive pulmonary disease or acute heart failure (1-3). An important goal of NIV is to prevent endotracheal intubation and thereby reduce the complications related to invasive ventilation (1,4). However, failure rates of NIV range between 5 and 50 % (5,6) and most of these patients require endotracheal intubation (5-9). Several factors have been identified that increase the success rate of NIV. These factors include careful selection of patients, properly timed intervention, a comfortable and well-fitting interface, coaching and encouragement of patients, careful monitoring, and a skilled and motivated team (6,8,10). In particular, careful selection is of major importance in patients with chronic obstructive pulmonary disease. A low pH (< 7.25) is a strong predictor of NIV failure (10,11), but an improvement in pH 1 to 2 hours after the initiation of NIV accurately predicts NIV success (5,11-13).

Today, the pathophysiology of NIV failure is incompletely understood. How can ventilation be inadequate with NIV, but adequate with similar levels of support after endotracheal intubation? An important difference in the application of NIV versus invasive ventilation is, evidently, the involvement of the upper airway. During invasive ventilation the endotracheal tube bypasses the upper airway and the cuff of the endotracheal tube provides an air-tight seal in the trachea. In contrast, during NIV the upper airway might play a role in the efficiency of delivered ventilation. Indeed, ventilator settings during NIV affect the patency of the upper airway (14,15). This effect implies that deviant behavior of the upper airway may play a role in

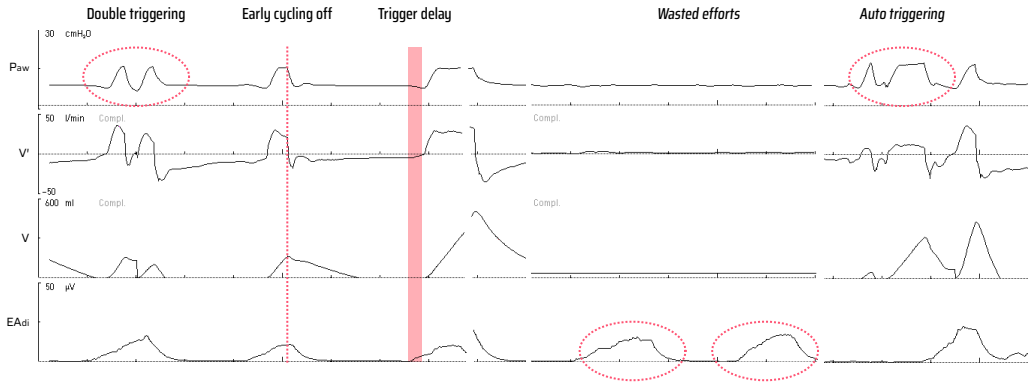


Figure 1
Screenshots from a ventilator in noninvasive ventilation pressure support mode. Tracings from top to bottom: airway pressure (P_{aw}), airway flow (V'), tidal volume (V), and diaphragm electrical activity (EA_{di}). Different types of patient ventilator asynchrony and dyssynchrony are shown: double triggering, early cycling off, trigger delay, wasted efforts and auto triggering (18,19).

the failure of NIV. The present concise review discusses the physiology and current understanding on the effects of NIV on upper airway patency. We will discuss the clinical relevance of the available studies and will list important points to stimulate research in this field.

Noninvasive ventilation and upper airway physiology

Patient-ventilator asynchrony

The aim of NIV is to decrease the work of breathing and/or improve oxygenation and ventilation. The most frequently used mode of NIV is pressure support ventilation (PSV). For the most effective unloading of the inspiratory muscles, the ventilator should cycle in synchrony with the patient's neural respiratory drive (16). Although triggering and cycling of mechanical support during PSV depends on the patient's respiratory effort, asynchrony between the patient and ventilator occurs frequently (17). Several types of asynchrony and dyssynchrony between the patient's neural drive and ventilator support have been identified and are shown in Figure 1 (18,19). Suboptimal synchrony between the patient and the ventilator may be affected by respiratory mechanics, the breathing pattern, neural drive, ventilator settings, the type of interface and the amount of air leak (18,20-23). The consequences of patient–ventilator asynchrony are poorly understood, but a high incidence of asynchrony is associated with discomfort and a prolonged duration of NIV (17).

The above-discussed types of asynchrony are related to the interaction between the activity of the inspiratory muscles and the ventilator's response. Indeed, this is sufficient for patients requiring invasive ventilation. However, during NIV it is

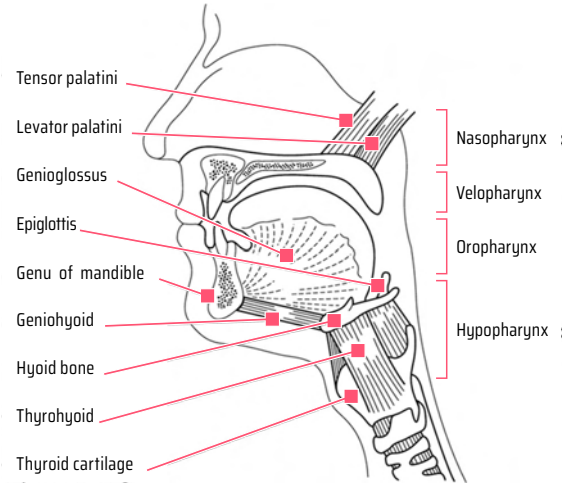


Figure 2
Anatomical representation of the upper airway and the important muscles controlling airway patency. From (26).

also important that the ventilator acts in synchrony with the upper airway muscles. Glottic narrowing during inspiration increases upper airway resistance and may limit effective ventilation. We will discuss this type of asynchrony after briefly summarizing the knowledge of upper airway physiology relevant to the topic of this review.

Upper airway

The upper airway comprises the nose, oral cavity, pharynx and larynx. The upper airway is involved in chewing, swallowing, speech and smell, and its primary functions are to act as a conductor of air, to humidify and warm the inspired air and prevent foreign materials from entering the tracheobronchial tree (24). The nose and oral cavity are mainly static in their conducting function, whereas the pharynx and larynx predominantly are muscular structures and thus may alter the patency of the upper airway (15,25). A simplified representation of the muscles of the upper airway is shown in Figure 2 and a view of the intrinsic muscles of the larynx shown in Figure 3 (26,27).

Stella and England studied the effect of pressure and flow in isolated piglet upper airway (28). They showed that the presence of negative pressure in the upper airway and flow during inspiration results in phasic respiratory activity of the posterior cricoarytenoid muscle above tonic levels, which results in glottic widening during inspiration and reduces resistance to airflow. This response effectively unloads the inspiratory muscles. Positive pressure and flow during expiration results in phasic activity of the thyroarytenoid muscle, resulting in glottic narrowing and therefore increased resistance to the expiratory flow. Accordingly, this study shows that, at least in an animal model, respiratory flow patterns affect the activity of the upper airway muscles.

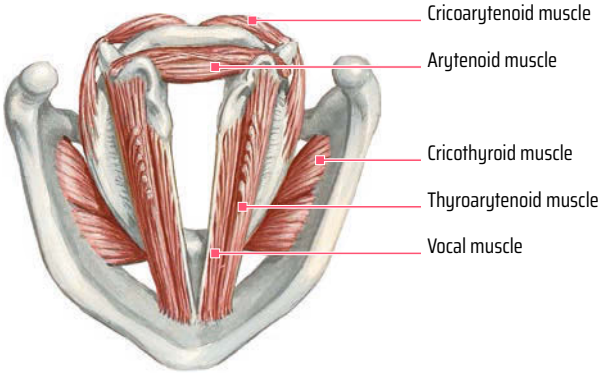


Figure 3
Intrinsic muscles of the larynx. From (27).

Table 1

Relevant respiratory receptors and their location and effect

Receptors		Location	Stimulus	Effect
C-fiber	Pulmonary	Between alveolar epithelium and pulmonary capillary	Large mechanical deformations, chemical stimuli and temperature increases	Inhibitory effects as apnea, hypotension and bradycardia
	Bronchial	In the walls of conducting airway		
Rapidly adapting		In epithelium close to bronchial venules	Very sensitive to mechanical stimuli and slow response to chemical stimuli	Irritant receptors cause cough and expiration reflexes
Pulmonary stretch		In close association with airway smooth muscle	Mechanical changes, stretch of airway wall	Terminate inspiration and extend expiration (Hering–Breuer reflex)

Earlier, Sant'Ambrogio and colleagues showed that flow receptors actually respond to temperature changes from body to room temperature (thermoreceptors) (29). Stella and England used these findings to analyze the laryngeal muscle response to continuous versus oscillating flow patterns and different body and room temperatures. They reported that a negative pressure and inspiratory flow results in increased posterior cricoarytenoid activity (opening of the glottis), independent of the stimulus modality. Furthermore, positive pressure and expiratory flow increased the thyroarytenoid activity for all stimuli, although constant room air applied to the upper airway results in more activity of the thyroarytenoid muscle than an oscillatory stimulus, implying that constant room air results in enhanced constriction of the glottis. Accordingly, both pressure and flow receptors play an important role in muscle activity of the upper airway during respiration (28,30).

Receptors in the upper and lower airway modulate activity of the upper airway muscles. The most prominent receptors are the bronchopulmonary C-fiber receptors, rapidly adapting receptors (RARs) and slowly adapting pulmonary stretch receptors (PSRs) (Table 1).

Pulmonary C-fiber receptors are located between the alveolar epithelium and the pulmonary capillaries, whereas bronchial C-fiber receptors have been identified in the conducting airway. The receptors' fiber endings extend into the space between epithelial cells or form a plexus immediately under the basement membrane. C-fiber receptors are excited by large mechanical deformations, chemical stimuli (for example, capsaicin and carbon dioxide), lung edema by increased interstitial fluid volume, or increased temperature (31,32). C-fiber receptor activation evokes inhibitory effects (apnea or bradypnea; hypotension and bradycardia). C-fiber receptor stimulation can result in closing of the upper airway by glottic narrowing to protect the respiratory system against inhalation of gaseous irritants, by activation of laryngeal muscles (33).

RARs are located in and under the epithelium throughout the respiratory tract from the nose to the bronchi. The receptors respond in reaction to mechanical (extremely sensitive) and chemical stimuli, and produce mainly excitatory effects such as tachypnea (33,34). The RARs in the larynx are usually called irritant receptors because of their activation by inhaled irritants such as ammonia or cigarette smoke, and they probably cause cough and expiration reflexes. When the laryngeal mucosa is stimulated, RAR reflexes elicit laryngoconstriction and bronchoconstriction, which may be part of the glottal closure seen during cough. However, the exact modulation of laryngeal upper airway muscle activities by RARs is incompletely understood (31,33,34).

PSRs do not affect patency of the upper airway but modulate the respiratory cycle: they terminate inspiration and extend expiration (35). PSRs are activated by stretching the airway wall and fire throughout the respiratory cycle (tonic activity) or in response to lung inflation (phasic activity). The discharge rate is progressively increased as a function of lung volume. PSRs are also widely known as the receptors responsible for the Hering–Breuer reflex, one of the first negative feedback loops in physiology. Hering and Breuer found that lung inflation decreases the tidal volume and increases the respiratory rate, thereby protecting the lungs from hyperinflation, while maintaining constant alveolar ventilation: an inspiratory off-switch (33,36).

To summarize, respiration and in particular patency of the upper airway depends on a complex, but incompletely understood, interplay between several inhibitory and excitatory pathways. Physical conditions such as pressure, flow and temperature affect upper airway patency. NIV may affect these physical characteristics and therefore affect patency of the upper airway.

Interaction between the upper airway and noninvasive ventilation

Moreau-Bussière and colleagues studied the effect of NIV on activity of the glottal constrictor (thyroarytenoid) and dilator (cricothyroid) muscles in awake lambs. Figure 4 shows thyroarytenoid, cricothyroid and diaphragm muscle activity during spontaneous breathing or NIV with PSV (37). During spontaneous breathing, both the thyroarytenoid and cricothyroid muscles are active — thyroarytenoid muscle activity occurring primarily at the end of inspiration. However, with application of pressure support during NIV, inspiratory cricothyroid activity disappears whereas activity of the thyroarytenoid muscle increases. This results in glottal narrowing and restricted ventilation, as reflected by respiratory inductance phlethysmography (37).

A subsequent study demonstrated that increased glottal constrictor muscle activity during NIV depends mainly on activation of bronchopulmonary receptors.

After bilateral vagotomy, the increase in inspiratory activity of the thyroarytenoid muscle previously observed with increasing support during NIV was absent (14).

There are limited data that demonstrate a similar response to NIV in humans. Rodenstein and colleagues exposed healthy subjects to increasing levels of support with NIV while their glottis was continuously monitored through a fiberoptic bronchoscope. The higher the level of support, the narrower the glottic aperture and the higher the airway resistance. This effect led to a progressive decrease in the percentage of tidal volume effectively reaching the lungs, apparently at least partly due to the behavior of the glottis (15,38,39).

In summary, studies in animals and humans indicate that positive pressure ventilation reduces patency of the upper airway during neural inspiration.

Neurally adjusted ventilator assist (NAVA) is a relatively new mode of noninvasive ventilatory support. The key features of NAVA are that the ventilator is cycled by diaphragm electrical activity, thereby improving patient–ventilator synchrony (40,41), and that the level of support is proportional to the electrical activity of the diaphragm (42). The electrical activity of the diaphragm is measured by an array of bipolar electrodes mounted on a nasogastric feeding tube.

In contrast to PSV, glottal constrictor muscle activity does not increase with NAVA during inspiration in lambs (43). Apparently, NAVA induces less glottal closure and more synchronous ventilation and may thus be advantageous compared with PSV during NIV. A possible underlying mechanism for the absence of glottal constrictor activity during inspiration with NAVA is that the pressure rise mimics the normal progressive recruitment of the diaphragmatic motor units, whereas during PSV insufflation from the ventilator is performed with a constant level of pres-

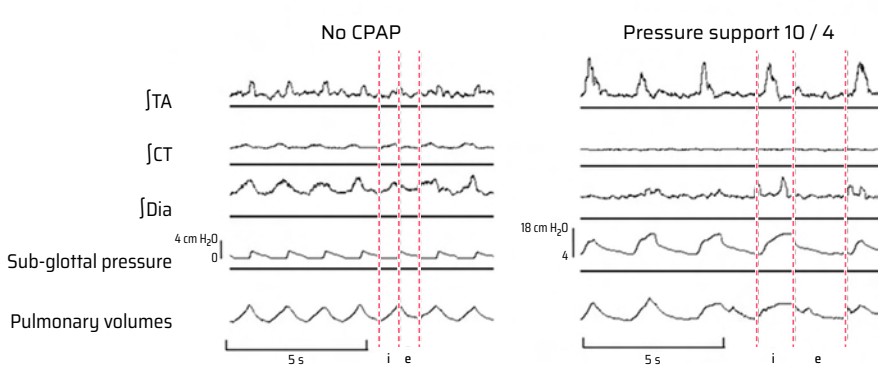


Figure 4
Moving time averaged electrical activities of muscles during noninvasive ventilation. Moving time averaged electrical activities of thyroarytenoid (TA), cricothyroid (CT), and diaphragm (Dia) muscles during noninvasive ventilation in wakefulness, without continuous positive airway pressure (CPAP) and with pressure support ventilation, in newborn lambs (37). i, inspiration; e, expiration.

sure (decelerating flow pattern), often with a short inspiratory rise time to further decrease the patient's inspiratory work. The consequent rapid nonphysiological rise in airway pressure at the onset of inspiration with PSV could be responsible for activating, in a reflex manner, the inspiratory activity of the glottal constrictor muscles and thus limits the efficiency of NIV (43). This hypothesis should be the subject of further clinical research.

Monitoring muscles of the upper airway

The importance of monitoring inspiratory muscle activity during mechanical ventilation has been stressed in the literature (44). In contrast, little is known about the role of monitoring upper airway activity during NIV — probably related to the complexity of monitoring the upper airway function in these patients.

Activation of intrinsic laryngeal muscles affects glottis opening and thus affects resistance to flow into and out of the lungs (28). Monitoring the recruitment of upper airway dilator muscles during inspiration could be clinically relevant because the phasic activity of upper airway dilator muscles increases with respiratory constraints, as in patient–ventilator asynchrony (45,46). Cheng and colleagues studied the upper airway in healthy subjects, using magnetic resonance imaging with tagging (47). This study showed not only that the genioglossus muscle but also nonmuscular soft tissues surrounding the upper airway move before the onset of inspiratory flow (47). Movement of certain reference points on the genioglossus muscle was greater during normal inspiration than during loaded inspiration, suggesting that the increase in activity of the muscle during loaded inspiration does not result in dilation but in stiffening of the upper airway (47). Moreover, this study demonstrated that movement of nonmuscular soft tissue affects upper airway patency.

A complex interaction exists between movement of nonmuscular soft tissue and genioglossus muscle activity. Although laryngeal muscle (for example, genioglossus or cricothyroid muscle) electromyography is feasible during NIV (37,45), one should note that electromyography does not provide information about nonmuscular soft tissue movement. Additional techniques should therefore be used to evaluate upper airway patency. Magnetic resonance imaging probably provides the most reliable information but it is expensive and cumbersome, particularly in patients on NIV. Recently, a study showed that the upper airway could be visualized with ultrasound, although the value of assessing upper airway patency with this technique has not been studied (48). In addition, endoscopy has been used to assess upper airway patency, but ideally should be used at different levels in the upper airway.

Clinical relevance and future research

Increasing the success rate of NIV is of major clinical importance. In contrast to invasive ventilation, the upper airway plays an important role as a conductor of air during NIV. Current literature suggests that during NIV it is important that the

ventilator acts in synchrony with the upper airway muscles to allow adequate ventilation. In lambs and piglets, the patency of the upper airway is influenced by ventilator-induced changes in pressure and flow (14,30,37,43). However, we do not know whether this phenomenon can be extrapolated to humans. The involved reflexes are similar in humans to those in newborn lambs, but are thought to be less pronounced.

Today, there are limited data on the effects of NIV on upper airway physiology in patients with acute respiratory failure. It is reasonable to assume that when the ventilator cycles in synchrony with the upper airway, this will improve efficiency of ventilation. As discussed, upper airway patency is linked to neural respiratory drive. Therefore, improved synchrony between the ventilator and respiratory drive may improve ventilation partly by limiting wasted ventilation at the level of the upper airway. Currently, it would be preliminary to provide recommendations on how the level of assist, level of positive end-expiratory pressure and flow pattern should be adapted to enhance patency of the upper airway in patients with acute respiratory failure.

Future research should therefore aim at studying the effect of different ventilator modes and settings on the patency of the upper airway in patients. For example, NAVA ventilation in lambs has been shown to decrease glottal constrictor muscle activity compared with PSV during NIV. Settings of the ventilator such as the rise time, trigger sensitivity, and the level of pressure support and positive end-expiratory pressure should also be the subject of further research. These settings could influence the behavior of the upper airway and potentially limit adequate lung ventilation. Currently, a study is investigating the effect of ventilator settings during NIV on upper airway patency in patients with an exacerbation of chronic obstructive pulmonary disease (Clinicaltrials.gov ID: NCT01791335). Our recommendations for further research focus on inspiration, but expiration could also be influenced by upper airway patency.

Conclusions

In conclusion, we have shown that regulation of the upper airway is complex and influenced by NIV. The latter findings are mostly based on animal data. Understanding of the laryngeal reactions during different modes and settings of NIV in patients will be crucial to determine whether a diminished upper airway patency contributes to NIV failure.

References

1 Brochard L, Mancebo J, Elliott MW: Noninvasive ventilation for acute respiratory failure. Eur Respir J 2002, 19:712–721.

2 Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, ESC Committee for Practice Guidelines: ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 2008, 10:933–989.

3 Chandra D, Stamm JA, Taylor B, Ramos RM, Satterwhite L, Krishnan JA, Mannino D, Sciurba FC, Holguin F: Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998–2008. Am J Respir Crit Care Med 2012, 185:152–159.

4 Boldrini R, Fasano L, Nava S: Noninvasive mechanical ventilation. Curr Opin Crit Care 2012, 18:48–53.

5 Moretti M, Cilione C, Tampieri A, Fracchia C, Marchioni A, Nava S: Incidence and causes of non-invasive mechanical ventilation failure after initial success. Thorax 2000, 55:819–825.

6 Antonelli M, Conti G, Moro ML, Esquinas A, Gonzalez-Diaz G, Confalonieri M, Pelaia P, Principi T, Gregoretti C, Beltrame F, Pennisi MA, Arcangeli A, Proietti R, Passariello M, Meduri GU: Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med 2001, 27:1718–1728.

7 Lightowler JV, Wedzicha JA, Elliott MW, Ram FS: Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. BMJ 2003, 326:185.

8 Carlucci A, Richard JC, Wysocki M, Lepage E, Brochard L: Noninvasive versus conventional mechanical ventilation. An epidemiologic survey. Am J Respir Crit Care Med 2001, 163:874–880.

9 Keenan SP, Mehta S: Noninvasive ventilation for patients presenting with acute respiratory failure: the randomized controlled trials. Respir Care 2009, 54:116–126.

10 Confalonieri M, Garuti G, Cattaruzza MS, Osborn JF, Antonelli M, Conti G, Kodric M, Resta O, Marchese S, Gregoretti C, Rossi A, Italian Noninvasive Positive Pressure Ventilation (NPPV) Study Group: A chart of failure risk for noninvasive ventilation in patients with COPD exacerbation. Eur Respir J 2005, 25:348–355.

11 Mehta S, Hill NS: Noninvasive ventilation. Am J Respir Crit Care Med 2001, 163:540–577.

12 Meduri GU, Turner RE, Abou-Shala N, Wunderink R, Tolley E: Noninvasive positive pressure ventilation via face mask. First-line intervention in patients with acute hypercapnic and hypoxemic respiratory failure. Chest 1996, 109:179–193.

13 Ambrosino N, Foglio K, Rubini F, Clini E, Nava S, Vitacca M: Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: correlates for success. Thorax 1995, 50:755–757.

14 Roy B, Samson N, Moreau-Bussière F, Ouimet A, Dorion D, Mayer S, Praud J-P: Mechanisms of active laryngeal closure during noninvasive intermittent positive pressure ventilation in nonsedated lambs. J Appl Physiol 2008, 105:1406–1412.

15 Parreira VF, Jounieaux V, Aubert G, Dury M, Delguste PE, Rodenstein DO: Nasal two-level positive-pressure ventilation in normal subjects. Effects of the glottis and ventilation. Am J Respir Crit Care Med 1996, 153:1616–1623.

16 Tobin MJ, Jubran A, Laghi F: Patient–ventilator interaction. Am J Respir Crit Care Med 2001, 163:1059–1063.

17 Vignaux L, Vargas F, Roeseler J, Tassaux D, Thille A, Kossowsky M, Brochard L, Jolliet P: Patient–ventilator asynchrony during non-invasive ventilation for acute respiratory failure: a multicenter study. Intensive Care Med 2009, 35:840–846.

18 Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L: Patient–ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med 2006, 32:1515–1522.

19 Sassoon C: Triggering of the ventilator in patient-ventilator interactions. Respir Care 2011, 56:39–51.

20 Colombo D, Cammarota G, Alemani M, Carenzo L, Barra FL, Vaschetto R, Slutsky AS, Della Corte F, Navalesi P: Efficacy of ventilator waveforms observation in detecting patient–ventilator asynchrony. Crit Care Med 2011, 39:2452–2457.

21 Leung P, Jubran A, Tobin MJ: Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea. Am J Respir Crit Care Med 1997, 155:1940–1948.

22 Navalesi P, Costa R: New modes of mechanical ventilation: proportional assist ventilation, neurally adjusted ventilatory assist, and fractal ventilation. Curr Opin Crit Care 2003, 9:51–58.

23 Murata S, Yokoyama K, Sakamoto Y, Yamashita K, Oto J, Imanaka H, Nishimura M: Effects of inspiratory rise time on triggering work load during pressure-support ventilation: a lung model study. Respir Care 2010, 55:878–884.

24 Des Jardins TR: Cardiopulmonary Anatomy & Physiology: Essentials for Respiratory Care. 5th edition. Clifton Park, NY: Thomson Delmar Learning. London: Thomson Learning (distributor); 2008.

25 Mittal RK: Motor Function of the Pharynx, Esophagus, and its Sphincters. Morgan & Claypool Life Sciences: San Rafael, CA; 2011.

26 Fogel RB, Malhotra A, White DP: Sleep. 2: pathophysiology of obstructive sleep apnoea/hypopnoea syndrome. Thorax 2004, 59:159–163.

27 Netter medical illustration used with permission of Elsevier. All rights reserved. [http://www.netterimages.com/image/20362.htm]

28 Stella MH, England SJ: Modulation of laryngeal and respiratory pump muscle activities with upper airway pressure and flow. J Appl Physiol 2001, 91:897–904.

29 Sant'Ambrogio G, Tsubone H, Sant'Ambrogio FB: Sensory information from the upper airway: role in the control of breathing. Respir Physiol 1995, 102:1–16.

30 Stella MH, England SJ: Laryngeal muscle response to phasic and tonic upper airway pressure and flow. J Appl Physiol 2001, 91:905–911.

31 Kubin L, Alheid GF, Zuperku EJ, McCrimmon DR: Central pathways of pulmonary and lower airway vagal afferents. J Appl Physiol 2006, 101:618–627.

32 Lee LY, Pisarri TE: Afferent properties and reflex functions of bronchopulmonary C-fibers. Respir Physiol 2001, 125:47–65.

33 Bailey EF, Fregosi RF: Modulation of upper airway muscle activities by bronchopulmonary afferents. J Appl Physiol 2006, 101:609–617.

34 Sant'Ambrogio G, Widdicombe J: Reflexes from airway rapidly adapting receptors. Respir Physiol 2001, 125:33–45.

35 Davies A, Pirie L, Eyre-Todd RA: Adaptation of pulmonary receptors in the spontaneously breathing anaesthetized rat. Eur Respir J 1996, 9:1637–1642.

36 Boron WF, Boulpaep EL: Medical Physiology: A Cellular and Molecular Approach. Updated 2nd edition. Philadelphia, PA: Saunders; 2012.

37 Moreau-Bussière F, Samson N, St-Hilaire M, Reix P, Lafond JR, Nsegbe É, Praud J-P: Laryngeal response to nasal ventilation in nonsedated newborn lambs. J Appl Physiol 2007, 102:2149–2157.

38 Jounieaux V, Aubert G, Dury M, Delguste P, Rodenstein DO: Effects of nasal positive-pressure hyperventilation on the glottis in normal sleeping subjects. J Appl Physiol 1995, 79:186–193.

39 Jounieaux V, Aubert G, Dury M, Delguste P, Rodenstein DO: Effects of nasal positive-pressure hyperventilation on the glottis in normal awake subjects. J Appl Physiol 1995, 79:176–185.

40 Piquilloud L, Tassaux D, Bialais E, Lambermont B, Sottiaux T, Roeseler J, Laterre PF, Jolliet P, Revelly JP: Neurally adjusted ventilatory assist (NAVA) improves patient-ventilator interaction during non-invasive ventilation delivered by face mask. Intensive Care Med 2012, 38:1624–1631.

41 Bertrand PM, Futier E, Coisel Y, Matecki S, Jaber S, Constantin JM: Neurally adjusted ventilator assist versus pressure support ventilation for noninvasive ventilation during acute respiratory failure: a cross-over physiological study. Chest 2013, 143:30–36.

42 Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, Gottfried SB, Lindstrom L: Neural control of mechanical ventilation in respiratory failure. Nat Med 1999, 5:1433–1436.

43 Hadj-Ahmed MA, Samson N, Bussieres M, Beck J, Praud JP: Absence of inspiratory laryngeal constrictor muscle activity during nasal neurally adjusted ventilatory assist in newborn lambs. J Appl Physiol 2012, 113:63–70.

44 Doorduin J, van Hees HW, van der Hoeven JG, Heunks LM: Monitoring of the respiratory muscles in the critically ill. Am J Respir Crit Care Med 2013, 187:20–27.

45 Hug F, Raux M, Morelot-Panzini C, Similowski T: Surface EMG to assess and quantify upper airway dilators activity during non-invasive ventilation. Respir Physiol Neurobiol 2011, 178:341–345.

46 Schmidt M, Chiti L, Hug F, Demoule A, Similowski T: Surface electromyogram of inspiratory muscles: a possible routine monitoring tool in the intensive care unit. Br J Anaesth 2011, 106:913–914.

47 Cheng S, Butler JE, Gandevia SC, Bilston LE: Movement of the human upper airway during inspiration with and without inspiratory resistive loading. J Appl Physiol 2011, 110:69–75.

48 Cheng SP, Lee JJ, Liu TP, Lee KS, Liu CL: Preoperative ultrasonography assessment of vocal cord movement during thyroid and parathyroid surgery. World J Surg 2012, 36:2509–2515.

Eline Oppersma
Jonne Doorduin
Petra J Gooskens
Lisanne H Roesthuis
Erik HFM van der Heijden
Johannes G van der Hoeven
Peter H Veltink
Leo MA Heunks

Respiratory Physiology & Neurobiology
2018, in press

5 Glottic patency during noninvasive ventilation in patients with chronic obstructive pulmonary disease

Abstract

Background Non-invasive ventilation (NIV) provides ventilatory support for patients with respiratory failure. However, the glottis can act as a closing valve, limiting effectiveness of NIV. This study investigates the patency of the glottis during NIV in patients with acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD).

Methods Electrical activity of the diaphragm, flow, pressure and videolaryngoscopy were acquired. NIV was randomly applied in pressure support (PSV) and neurally adjusted ventilatory assist (NAVA) mode with two levels of support. The angle formed by the vocal cords represented glottis patency.

Results Eight COPD patients with an acute exacerbation requiring NIV were included. No differences were found in median glottis angle during inspiration or at peak inspiratory effort between PSV and NAVA at low and high support levels.

Conclusions The present study showed that patency of the glottis during inspiration in patients with an acute exacerbation of COPD is not affected by mode (PSV or NAVA) or level of assist (5 or 15 cmH_2O) during NIV.

Background

Noninvasive ventilation (NIV) can provide inspiratory support for patients with acute respiratory failure. In particular patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) have been shown to benefit from NIV (1–3). However, in 5–40 % of these patients NIV fails (4) and endotracheal intubation is required. Factors for successful NIV include properly timed initiation, a comfortable and well-fitting interface, coaching and encouragement of patients, careful monitoring and a skilled and motivated team (5). The resulting marker for success is defined as an increasing pH within 1 to 2 hours after initiation of NIV (5,6). A major physiological difference between NIV and endotracheal intubation is the involvement of the upper airways. The larynx can act as a closing valve, limiting the effectiveness of delivering inspiratory support under NIV. In normal breathing, the upper airways actively dilate before initiation of inspiratory flow (7). This is a highly effective response as narrowing of the upper airways during inspiration would result in elevated inspiratory resistance (8). Studies in lambs showed that during NIV with pressure support ventilation (PSV) the activity of the constricting muscle of the glottis (the thyroarytenoid muscle) increases, resulting in decreased upper airway patency (9). In this model, this decreased patency reduces effectiveness of the delivery of tidal volume during NIV. It has been hypothesized that the instantaneous increase in flow in the PSV mode plays an important role in the response of the upper airways during noninvasive ventilation. Neurally adjusted ventilatory assist (NAVA) is a relatively new mode of partially supported ventilation that uses electrical activity of the diaphragm (EAdi) to control the ventilator. During NAVA mode, the level of inspiratory support and the cycling of the ventilator is proportional to the electrical activity of the diaphragm (10). Accordingly, the inspiratory flow pattern follows a more physiological breathing pattern, which may cause upper airway constriction during NIV. Indeed, it was shown in lambs that no glottal constrictor muscle activity is present with NAVA ventilation applied during NIV (11). There are only limited data about the effect of NIV on upper airway patency in humans. In healthy subjects tidal volume is not necessarily increased as a result of increasing noninvasive inspiratory pressure, at least partly due to glottis narrowing (12–14). Today, no studies have been conducted in patients with a clinical indication for NIV. Therefore, it is of interest to compare NAVA mode and PSV mode on upper airway patency in patients with acute exacerbation of COPD. In the current study we aimed to investigate the effects of NIV on upper airway opening in patients with acute exacerbation of COPD, both in PSV and NAVA mode. We hypothesized that patency of the glottis during inspiration decreased with higher inspiratory pressures under PSV. In addition, we hypothesized that NAVA limits the effects of positive pressure on this decreased patency of the glottis.

Materials and methods

For this intervention study, we enrolled 8 patients with an acute exacerbation of COPD. Patients were included when meeting the clinical indication for NIV in the Intensive Care Unit (ICU), and having a NAVA catheter in situ (12 French; Maquet Critical Care, Solna, Sweden). This catheter is used to acquire EA_{di}, measured by nine electrodes placed at the distal end of the catheter (10,15). The catheter was positioned at the level of the diaphragm, according to manufacturer's instructions using dedicated software available on the ventilator. This catheter tracks EA_{di} in all ventilator modes. However, only in the NAVA mode EA_{di} is used to control the ventilator. Exclusion criteria included upper airway- mouth- or face pathology, recent nasal bleeding (to allow nasal introduction of a video laryngoscope), or pre-existent muscle disease. The protocol was approved by the Ethical Committee of the Radboud University Medical Centre and registered at ClinicalTrials.gov (NCT01791335). All subjects gave their written informed consent.

Study protocol

The study protocol included four phases: two levels of inspiratory support (5 versus 15 cmH_2O) and two different ventilator modes (PSV versus NAVA) were randomly applied. The gain of NAVA ventilation was set to match peak pressure as delivered in PSV using manufacturer-supplied software.

A flexible video laryngoscope was passed through the facemask and the nostril and positioned ± 2 cm cranial to the vocal cords allowing its continuous visualization. To minimize discomfort during insertion of the video laryngoscope, topical anaesthesia (Xylocaine spray 10 %) was applied to the nasal cavity, but care was taken not to apply Xylocaine to the larynx. Each phase started with a run-in period of 30 seconds in which the subject could familiarize with the ventilator setting followed by at least ten breaths of good quality video recording of the glottis. The rise time in PSV was standardized at 0.05 seconds. Trigger sensitivity was set at 5 % of peak flow (0.5 microvolt for NAVA) and the inspiratory oxygen fraction was titrated to obtain peripheral oxygen saturation > 95 %. Positive end expiratory pressure was kept constant at 5 cmH_2O.

Data acquisition and analysis

NIV was delivered with a SERVO-i ventilator (Maquet Critical Care, Solna, Sweden). As an interface, a full facemask (Respironics PerforMax, Philips, Best, The Netherlands) was used in all patients.

A unique measurement setup was developed in which parameters from the ventilator and flexible video laryngoscopy were recorded simultaneously, using LabVIEW (version 11.0 National Instruments). Airway flow, airway pressure and EA_{di}, were acquired (f_s = 100 Hz) using Servo Tracker, a software tool for the collection and presentation of performance data from SERVO-i. The data acquired by Servo Tracker

was converted with the NI-USB 6229 and NI-USB 6211 modules (National Instruments) to import in LabVIEW.

Real time videos of the glottis (f_s = 25 Hz) were obtained with a fiberoptic flexible bronchoscope (Pentax EB-1170 (11 Fr)). A PCI analog color image acquisition device (NI PCI-1411) acquired the video frames of the bronchoscope in LabVIEW.

Synchronicity of data was ensured in LabVIEW by a phase indicator controlled by the flow of the ventilator. Data were stored and buffered on an external hard disk and analysed offline in Matlab R2017a (The Mathworks, Natick, MA). Of each mode and setting the last 5 to 10 breaths of good quality of the video were used for analysis. The same time frame for EAdi and flow data was analysed. Good quality was defined as video images allowing the identification of the borders and the anterior commissure of the vocal cords. The aperture of the glottis was assessed for each frame of the video, by measuring the angle formed by the vocal cords at the anterior commissure. A schematic representation of the assessment of the angle is shown in Figure 1. The contrast between the vocal folds and the rima glottidis was used to detect the edges of the vocal folds, and the angle between two lines fitted through the vocal cords was calculated. The resulting 25 angles per second were averaged over each 3 samples.

Statistics

Statistical analyses were performed with SPSS 21.0 (SPSS, Chicago, IL). Descriptive statistics were determined for the subject characteristics, given in mean ± Standard Error of the Mean (SEM).

Normality was tested with the Shapiro-Wilk test. Repeated measures two-way ANOVA was used to assess the effect of mode (PSV and NAVA) and level (low and high) of ventilation on the mean EAdi of all 8 subjects.

To compare the angle of the glottis during inspiration between the different settings of the ventilator, histograms were made for each setting for each patient, of all the angles during inspiration. Inspiration was defined as EAdi from > 2 μV to 80 % of peak EAdi. The median angle was calculated from the histogram, reported for all

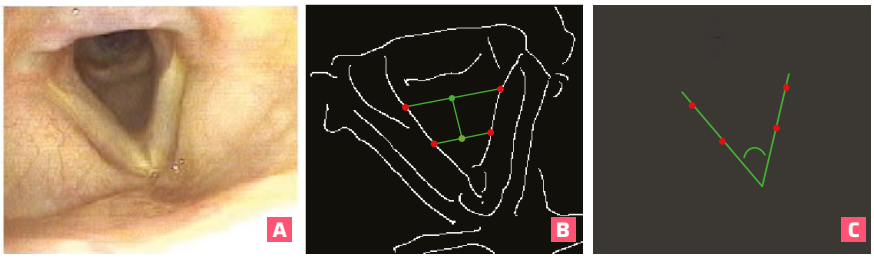


Figure 1
Schematic representation of angle determination. From video frame (A) to edge detection (B) to determination of glottis angle (C).

Table 1
Patient characteristics, blood values *n* = 7

	Mean ± SEM
Age (years)	65.3 ± 3.0
pCO_2 (kPa)	8.4 ± 0.5
pO_2 (kPa)	9.4 ± 1.2
pH	7.34 ± 0.02
Bicarbonate (mmol/L)	33.9 ± 2.5
Base Excess (mmol/L)	6.2 ± 2.4

subjects as mean ± SEM, and the settings were compared with repeated measures two-way ANOVA.

To compare the glottis angle during peak inspiratory effort, as defined by the peak EAdi, the mean angle from −5 to +5 samples of the peak EAdi was calculated for each breath. The angles during peak inspiratory effort were reported as mean ± SEM and compared among the settings with repeated measures two-way ANOVA.

A *p* value ≤ 0.05 was considered significant.

Results

Eight patients were included in this study (male/female 4/4, patient characteristics in Table 1). Blood gases could not be obtained in 1 patient. Total time for data acquisition for this study was less than 30 minutes per patient.

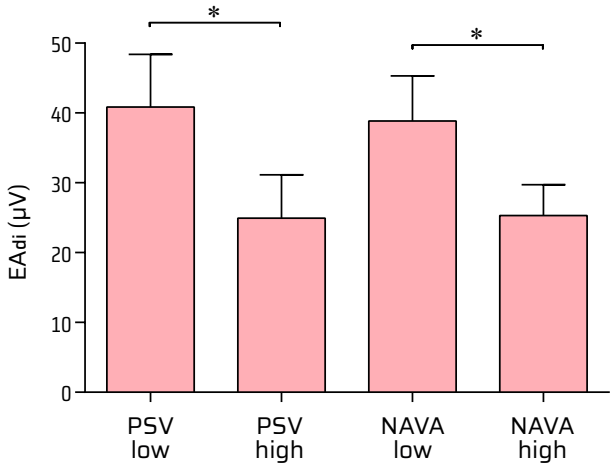


Figure 2
Bargraph of EAdi of all patients during the 4 phases of the protocol. *significant difference.

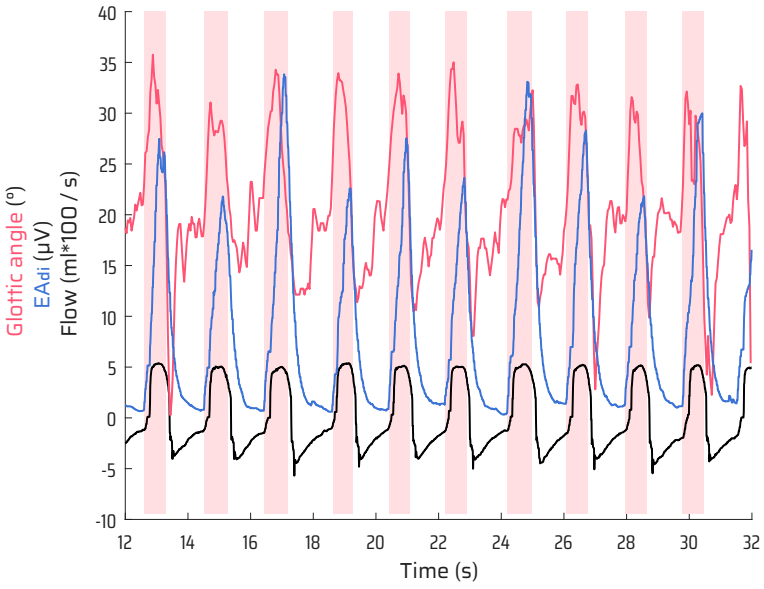


Figure 3
Example of EAdi, flow and angle of the glottis of 1 subject during 1 setting. Shaded areas represent inspiration based on EAdi, from > 2 µV to 80 % of peak EAdi.

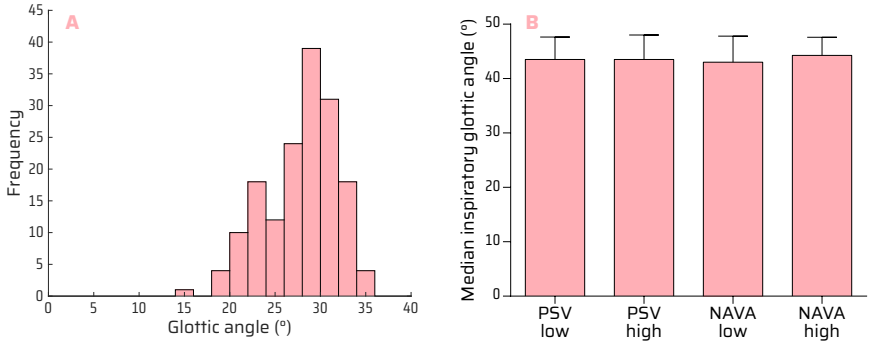


Figure 4
A Example of a histogram of all angles during inspiration of 1 subject during 1 setting
B Bargraph of median angle during inspiration of all patients for the four conditions. No differences between the settings were found.

Shapiro–Wilk tests showed that mean EAdi, median angle during inspiration and mean angle during peak inspiratory effort were normally distributed. Figure 2 shows a bargraph of the EAdi of all patients during the 4 phases of the study. As dictated by the protocol, EAdi levels for PSV and NAVA were equal at low (p = 0.40) and high (p = 0.92) levels of support, showing that the level of inspiratory support was similar for the different modes. As expected, EAdi at PSV low was higher than at PSV high (p = 0.05), and EAdi at NAVA low was higher than at NAVA high (p = 0.01).

Figure 3 shows a representative image of the acquired EAdi, flow and angle of the glottis of 1 subject under PSV with a low level of support. The pattern of glottis opening varied within and between subjects; some patients showed cyclic behavior of the glottis as in figure 3, related to the breathing cycle, but some showed more chaotic patterns of glottis behavior. The online available supplemental videos E1 and E2 illustrate this.

An example of a histogram with all the angles during inspiration of 1 subject is shown in Figure 4A. A bargraph of the median angle during inspiration for all patients is shown in Figure 4B. Mean ± SEM value of the angles during inspiration for all subjects was 43.5° ± 4.1°during PSV low, 43.5° ± 4.5° during PSV high, 43.0° ± 4.8° during NAVA low and 44.3° ± 3.4° during NAVA high. No significant differences were found.

The mean ± SEM value for the glottic angle at peak inspiratory effort for all subjects was 39.1° ± 3.9° during PSV low, 42.8° ± 4.7° during PSV high, 39.6° ± 4.7° during NAVA low and 40.3° ± 3.3° during NAVA high. There was no significant difference between the glottic angle at peak inspiratory effort between the different modes and levels of inspiratory support (Figure 5).

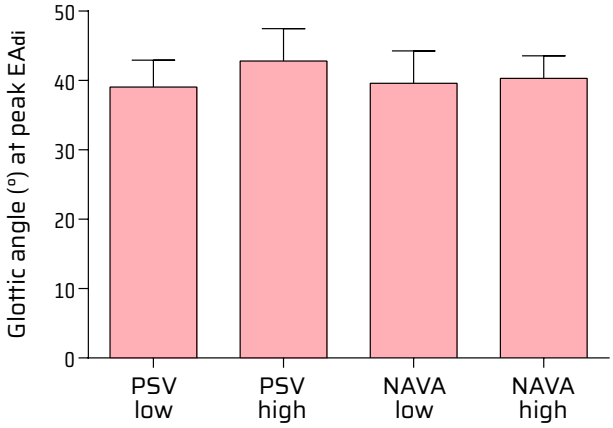


Figure 5
Bargraph of the glottic angle at peak EAdi for all patients. No differences between the settings were found.

Discussion

This is the first study to evaluate the patency of the glottis during NIV in patients with acute exacerbation of COPD. Specifically, we evaluated the effects of the level of inspiratory support (low and high) and two different ventilator modes (PSV and NAVA) characterized by different flow patterns. We found that neither the level of inspiratory pressure, nor inspiratory flow pattern did affect the patency of the glottis in these patients. These data are in apparent conflict with earlier studies in newborn lambs and healthy subjects (9,12-14).

Patency of the glottis

The vocal cords largely determine the variations in laryngeal resistance during the normal breathing cycle, and thereby regulate the resistance to airflow of the upper airways (8). It is known that in resting or anesthetized animals the vocal cords are abducted during inspiration (8). The constricting muscle of the glottis (the thyroarytenoid muscle) is responsible for this contraction in early expiration (9,16) and the dilation during inspiration is a result of activity of the dilating muscle (the cricothyroid muscle) (9).

However, studies in newborn lambs showed that the electrical inspiratory activity of the thyroarytenoid muscle increased during NIV. The activity of the cricothyroid muscle on the other hand decreased, while it normally acts as a dilator during inspiration (9). These results suggest that modifications in laryngeal muscle activity regulate active glottal narrowing during noninvasive positive pressure ventilation in lambs (9,16). From an evolutionary point of view, closing of the upper airways and the glottis might be an effective protective response, as high pressure delivered to the lungs may induce alveolar overdistension (16). However, these glottal responses may negatively affect the efficiency of ventilatory support delivered to the lungs during NIV (9,16), result in leaking of the interface of NIV or insufflation of air into the digestive system (11) and thereby potentially influence failure rates.

A better understanding of the behaviour of the glottis of human subjects under different modes and settings of NIV will thus help to obtain better compliance, more effective tidal volumes and thereby higher success rates for NIV.

Several studies analyzed minute ventilation in healthy subjects during nasal two-level positive pressure ventilation in controlled and spontaneous modes (14,17), and during sleep and wakefulness (12,13). The main findings are more or less consistent with results from lambs. Effective ventilation was not increased or even reduced with increasing levels of inspiratory pressure. Only high inspiratory pressures (20 cmH_2O) in a spontaneous mode resulted in an increased minute ventilation, resulting from an increase of tidal volume (17). The main factor regulating effective tidal volume during NIV in awake humans appeared to be the additional resistance of the upper airways by closure of the glottis. The glottis narrowed during passive hyperventilation in the absence of respiratory muscle activity, whereas

activation of the diaphragm resulted in a significant inspiratory widening of the vocal cords (13). As adding CO_2 to the inspired air could widen the glottis, it was suggested that glottic narrowing could be caused by extreme hypocapnia, to attempt to reverse the hypocapnia induced by NIV (12,13). Glottic narrowing as a result of NIV increased during sleep compared to wakefulness and effective ventilation was also lower during sleep than during wakefulness (12). Besides, a very wide interindividual variability in glottis behavior and effective ventilation is observed, especially during wakefulness (14). Although in lambs as well as in healthy subjects the glottis narrows with increasing inspiratory pressure during NIV, the results of the current study showed no closure of the glottis during NIV. The current study showed that the glottis of human adults with COPD is not influenced by increasing inspiratory pressure levels during noninvasive pressure support ventilation.

An important explanation for this difference between lambs and humans could be that reflexes alter with maturation and therefore adult population in this study is incomparable by age to the lambs that have been studied earlier (11,18,19). Although sheep are, by equality in size and structure of the tissue with human lungs, suitable for various types of research (20), the human lung still is different in for example anatomy of the lobes. The difference in species could therefore account for differences in behavior of the glottis.

A third important difference is that the reflex pathways in the COPD patients with an acute exacerbation, as in the current study, are probably different from healthy subjects. Mechanical factors such as tidal volume and flow are known to trigger glottis closure, effected by receptors at laryngeal or upper airway level, to avoid hyperventilation in NIV (13). It is probable that the COPD population in the current study has harmed reflex pathways, by their chronic exposure to CO_2 by smoking. The C-fiber receptors, which are excited by chemical stimuli as carbon dioxide and can induce glottis narrowing, are affected in COPD patients by chronic carbon dioxide inhalation (21), which makes the behavior of the glottis incomparable to healthy subjects.

NAVA

During PSV the ventilator insufflates air with a constant level of pressure for each breath, with a decelerating flow pattern. The resulting rapid airway pressurization at the onset of inspiration in PSV could be responsible for triggering, in a reflex manner, the inspiratory activity of the glottal constrictor muscles (11). In NAVA ventilation, the pressure rise is thought to mimic the normal progressive recruitment of the diaphragmatic motor units, inducing more synchronous ventilation than NIV with PSV (10). It is shown that in contrast with nasal PSV, nasal NAVA does not induce inspiratory glottal constrictor muscle activity in nonsedated newborn lambs, even at maximal achievable NAVA levels (11). This absence of inspiratory electrical activity of the thyroarytenoid muscle may partly account for improvement of patient-ventilator interaction and success rates of NIV during NAVA (11,22). Although NAVA improves

glottis patency during inspiration with respect to PSV in newborn lambs, in the current study no difference is found in glottis patency during NAVA. However, as the patency of the glottis is not decreased during PSV, the hypothesized improvement with NAVA is less probable.

Measurement setup

This study was designed as a proof of concept study, identifying the behavior of the glottis of patients with an acute exacerbation of COPD. A unique measurement setup was created which ensures synchronous data acquisition, in which the level of support and the modus of the ventilator could be analyzed. This is, to our knowledge, the first study in which the behavior of the glottis is synchronously related to the neural drive, represented by the electrical activity of the diaphragm. The studies in healthy subjects discussed above, measured the widest angle of the vocal cords during the inspiratory phase of the mechanical insufflation on a video screen using a flexible protractor (14). The automated image analysis to calculate the angle of the vocal cords used in the current study, provides a state-of-the-art method for analysis of patency of the glottis. We consider analysis of the angle of the vocal cords considered more reliable than other measures, such as the widest distance between the vocal cords or the surface of the opening. Other measures need the whole glottis without any anatomical structures in view, which appeared practically impossible for more than one breath. However, there were some limitations to this study. The NAVA catheter in situ, which is used for the measurement of EAdi, might influence the behaviour of the glottis. Although the tube does not pass the laryngeal space, it might touch the epiglottis or surrounding tissue and thereby cause reflective non-physiological movement patterns of the glottis. Also the video laryngoscope might influence the physiological behaviour of the vocal cords.

Although the duration of the current study is relatively short, we are confident that if changes would have occurred in glottic patency, these would have been captured within the time frame of the study protocol (maximum 30 minutes). The change in glottis behaviour is expected to be caused by fast reflexes of the upper airway receptors to changes in the inspiratory flow pattern, which are known to occur in newborn lambs (9,11)

There was no pattern in the behaviour of the glottis, or subgroups to define based on behaviour of the glottis or blood gas characteristics. Although all patients included in this study were in need of noninvasive mechanical ventilation due to COPD, the degree of the illness and probably resulting reflex pathways were different. However, this study is the first to show the high variability in glottis behaviour among patients.

Conclusion

In conclusion, in patients with an acute exacerbation of COPD, patency of the glottis during inspiration is not affected by ventilator mode (PSV or NAVA) or the level of inspiratory assist (5 and 15 cmH_2O) during NIV.

Supplemental videos

Supplemental videos for this article are provided at the *Respiratory Physiology & Neurobiology* web site.
To view the Supplemental Videos online, scan this QR code or use the short URL underneath.

https://j.mp/2NseBG1

References

1 Brochard L, Mancebo J, Elliott MW. Noninvasive ventilation for acute respiratory failure. European Respiratory Journal. 2002;19(4):712–21.

2 Chandra D, Stamm JA, Taylor B, Ramos RM, Satterwhite L, Krishnan JA, et al. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998–2008. American journal of respiratory and critical care medicine. 2012;185(2):152–9.

3 Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail. 2008;10(10):933–89.

4 Moretti M, Cilione C, Tampieri A, Fracchia C, Marchioni A, Nava S. Incidence and causes of non-invasive mechanical ventilation failure after initial success. Thorax. 2000;55(10):819–25.

5 Antonelli MA, Conti GC, Moro MM, Esquinas AE, Gonzalez-Diaz GG-D, Confalonieri MC, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Medicine. 2001;27(11):1718–28.

6 Confalonieri M, Garuti G, Cattaruzza MS, Osborn JF, Antonelli M, Conti G, et al. A chart of failure risk for noninvasive ventilation in patients with COPD exacerbation. The European respiratory journal. 2005;25(2):348–55.

7 Ludlow CL. Central nervous system control of the laryngeal muscles in humans. Respiratory physiology & neurobiology. 2005;147(2-3):205–22.

8 Bartlett D, Jr. Respiratory functions of the larynx. Physiological reviews. 1989;69(1):33–57.

9 Moreau-Bussiere F, Samson N, St-Hilaire M, Reix P, Lafond JR, Nsegbe E, et al. Laryngeal response to nasal ventilation in nonsedated newborn lambs. Journal of applied physiology. 2007;102(6):2149–57.

10 Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, et al. Neural control of mechanical ventilation in respiratory failure. Nature medicine. 1999;5(12):1433–6.

11 Hadj-Ahmed MA, Samson N, Bussieres M, Beck J, Praud JP. Absence of inspiratory laryngeal constrictor muscle activity during nasal neurally adjusted ventilatory assist in newborn lambs. Journal of applied physiology. 2012;113(1):63–70.

12 Jounieaux V, Aubert G, Dury M, Delguste P, Rodenstein DO. Effects of nasal positive-pressure hyperventilation on the glottis in normal sleeping subjects. J Appl Physiol. 1995;79(1):186–93.

13 Jounieaux V, Aubert G, Dury M, Delguste P, Rodenstein DO. Effects of nasal positive-pressure hyperventilation on the glottis in normal awake subjects. J Appl Physiol. 1995;79(1):176–85.

14 Parreira VF, Jounieaux V, Aubert G, Dury M, Delguste PE, Rodenstein DO. Nasal two-level positive-pressure ventilation in normal subjects. Effects of the glottis and ventilation. Am J Respir Crit Care Med. 1996;153(5):1616–23.

15 Doorduin J, Sinderby CA, Beck J, Stegeman DF, van Hees HW, van der Hoeven JG, et al. The calcium sensitizer levosimendan improves human diaphragm function. American journal of respiratory and critical care medicine. 2012;185(1):90–5.

16 Roy B, Samson N, Moreau-Bussiere F, Ouimet A, Dorion D, Mayer S, et al. Mechanisms of active laryngeal closure during noninvasive intermittent positive pressure ventilation in nonsedated lambs. Journal of applied physiology. 2008;105(5):1406–12.

17 Parreira VF, Delguste P, Jounieaux V, Aubert G, Dury M, Rodenstein DO. Glottic aperture and effective minute ventilation during nasal two-level positive pressure ventilation in spontaneous mode. American journal of respiratory and critical care medicine. 1996;154(6 Pt 1):1857–63.

18 Arsenault J, Moreau-Bussiere F, Reix P, Niyonsenga T, Praud JP. Postnatal maturation of vagal respiratory reflexes in preterm and full-term lambs. Journal of applied physiology. 2003;94(5):1978–86.

19 Abu-Shaweesh JM. Maturation of respiratory reflex responses in the fetus and neonate. Seminars in neonatology : SN. 2004;9(3):169–80.

20 Meeusen EN, Snibson KJ, Hirst SJ, Bischof RJ. Sheep as a model species for the study and treatment of human asthma and other respiratory diseases. Drug Discovery Today: Disease Models. 2009;6(4):101–6.

21 Oppersma E, Doorduin J, van der Heijden EH, van der Hoeven JG, Heunks LM. Noninvasive ventilation and the upper airway: should we pay more attention? Critical care. 2013;17(6):245.

22 Vignaux L, Vargas F, Roeseler J, Tassaux D, Thille AW, Kossowsky MP, et al. Patient-ventilator asynchrony during non-invasive ventilation for acute respiratory failure: a multicenter study. Intensive care medicine. 2009;35(5):840–6.

Clinical trial registration

Retrospectively registered 12 February 2013 at ClinicalTrials.gov (NCT01791335), https://clinicaltrials.gov/ct2/show/NCT01791335

Eline Oppersma
Jonne Doorduin
Lisanne H Roesthuis
Hans JG van der Hoeven
Peter H Veltink
Leo MA Heunks

Submitted for publication

6 Patient-ventilator interaction during noninvasive ventilation in patients with acute exacerbation of COPD: effect of support level and ventilator mode

Purpose Patient-ventilator synchrony in chronic obstructive pulmonary disease (COPD) patients is at risk during noninvasive ventilation (NIV). NIV in neurally adjusted ventilatory assist (NAVA) mode improves synchrony compared to pressure support ventilation (PSV). The current study investigated patient-ventilator interaction during two levels of NAVA and PSV mode in patients with acute exacerbation of COPD.

Methods NIV was randomly applied in two levels (5 and 15 cmH_2O) of PSV and NAVA. Patient-ventilator interaction was evaluated by comparing airway pressure and EA_{di} waveforms with automated computer algorithms.

Results Eight patients were included. Trigger delay was longer in PSV high (268 ± 40 ms) than in PSV low (161 ± 42 ms) and trigger delay during NAVA was shorter than PSV for both low (49 ± 9 ms for NAVA) and high (79 ± 27 ms for NAVA) support. No difference in cycling-off error for low and high levels of PSV (PSV low −100 ± 40 ms and PSV high 56 ± 111 ms) or NAVA (NAVA low −5 ± 6 ms, NAVA high 12 ± 13 ms) and no difference between PSV and NAVA was found.

Conclusions Increasing PSV levels during NIV caused a progressive mismatch between neural effort and pneumatic timing. Patient-ventilator interaction during NAVA was more synchronous than during PSV, independent of inspiratory support level.

Introduction

Noninvasive ventilation (NIV) improves outcome of patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) (1,2). More specifically, NIV decreases work of breathing and increases alveolar ventilation by increasing tidal volume and decreasing respiratory rate (3). In patients with COPD, NIV reduces endotracheal intubation rate and related complications compared to conventional medical therapy, thereby shortening hospital stay and decreasing mortality (1,2). However, synchrony between the patient and the ventilator, defined as a match between the patient's neural inspiratory and expiratory times and the ventilator's mechanical inspiratory and expiratory times (4), is at risk especially in patients with COPD during NIV, due to the presence of pulmonary hyperinflation and leaks (5). Patient-ventilator asynchronies have been associated with failure of NIV, and may eventually result in invasive mechanical ventilation (6,7). In COPD patients delayed cycling, defined as prolonged pressurization by the machine into the patient's expiratory phase, can result in inadequate emptying of the lungs and dynamic hyperinflation with increasing levels of inspiratory support, increasing the trigger delay and respiratory workload (8,9). In neurally adjusted ventilatory assist (NAVA) mode, the ventilator is controlled by electrical activity of the diaphragm (EAdi) (10). Ventilator triggering, cycling-off and the level of assist is based on EAdi. During invasive mechanical ventilation, high levels of inspiratory support with NAVA have significantly shorter trigger delays and less cycling-off errors compared to high levels of pressure support ventilation (PSV) (11,12). Ineffective triggering increases with the level of PSV, because of the risk of dynamic hyperinflation (4). Previously, we have shown that noninvasive NAVA improves patient-ventilator interaction relative to equal inspiratory pressures during noninvasive PSV (13). Trigger delays were substantially longer during PSV than during NAVA. Cycling-off errors during NAVA were negligible, whereas PSV showed a large variability in early and late cycling-off (13). Although increasing inspiratory support progressively unloads the respiratory muscles and is aimed to improve gas exchange in patients with respiratory failure, it is unknown what the effect is of increasing the level of inspiratory support on patient-ventilator interaction during noninvasive PSV and NAVA in patients with an acute exacerbation of COPD. We hypothesize that patient-ventilator asynchrony increases during PSV with high levels of inspiratory pressure, whereas patient-ventilator interaction during NAVA improves and is independent of the level of inspiratory pressure.

Methods

The current study presents data derived from a previous study by our group, registered at ClinicalTrials.gov (NCT01791335). Eight patients with an acute hypercapnic exacerbation of COPD with a clinical indication for NIV in the ICU and the presence

of a NAVA catheter (12 French; Maquet Critical Care, Solna, Sweden) were included. The protocol was approved by the Ethical Committee of the Radboud University Medical Center (NL40582.091.12) and conducted in accordance with the Declaration of Helsinki. All subjects gave their written informed consent.

Study protocol

The study protocol included four ventilator settings: two levels of inspiratory support (5 and 15 cmH_2O) and two different ventilator modes (PSV and NAVA), which were randomly (assigned by an online randomizer) applied. A flexible video laryngoscope was inserted through the nose for acquisition of video images of the glottis, as required by the protocol of the study for which these data originally were acquired. Each ventilator setting started with a run-in period of 30 seconds in which the subject could familiarize with the ventilator setting, followed by data acquisition during at least ten breaths of good quality video recording of the glottis. The NAVA level was set to match peak pressure as delivered in PSV using manufacturer-supplied software. The rise-time in PSV was standardized at 0.05 seconds. Trigger sensitivity was set at 5 % of peak flow during PSV (0.5 microvolt for NAVA) and the inspiratory oxygen fraction was titrated to obtain peripheral oxygen saturation > 95 %. Positive end expiratory pressure (PEEP) was kept constant at 5 cmH_2O throughout the study.

Data acquisition and analysis

NIV was delivered with a SERVO-i ventilator (Maquet Critical Care, Solna, Sweden). A full facemask (Respironics PerforMax, Philips, Best, The Netherlands) was used in all patients. Airway flow, airway pressure (P_{aw}) and EA_{di} were acquired (f_s = 100 Hz) using Servo Tracker, a software tool for the collection and presentation of performance data from the SERVO-i.

Data were stored and buffered on an external hard drive and analysed offline in Matlab R2017a (The Mathworks, Natick, MA). Peak EA_{di} and peak P_{aw} were calculated from the last 30 seconds of each ventilator setting. Neural respiratory rate was calculated as the number of EA_{di} peaks per minute.

Patient-ventilator interaction was evaluated by comparing P_{aw} and EA_{di} waveforms with an automated computer algorithm (13,14). Dyssynchronies, trigger delays and cycling-off errors, were calculated as percentages of neural inspiratory time periods and neural expiratory time periods, respectively. Synchrony was defined as ≤ 20 % difference between pneumatic and neural timing, as after timing errors reach 20 % the incidence of wasted efforts increase (13). Asynchronous breaths such as wasted efforts (inspiratory efforts not rewarded by ventilatory assist), auto-triggering (ventilatory assist without inspiratory effort), and multiple EA_{di} peaks during a single ventilator-assisted breath, where EA_{di} and P_{aw} were completely dissociated, were assigned 100 % error.

Statistics

Statistical analyses were performed with OriginPro 9.1.0 (OriginLabCorporation, Northampton, MA, USA). Descriptive patient characteristics were given in

mean ± Standard Error of the Mean (SEM) and respiratory study variables were reported as median and interquartile ranges. Repeated measures two-way ANOVA with post-hoc Tukey was used to assess the effect of ventilation mode (PSV and NAVA) and ventilator support level (low and high) on trigger delay and cycling-off error, given in mean ± SEM and $p \leq 0.05$ was considered significant.

Results

Eight patients (4 female/4 male) were enrolled in this study. Patient characteristics are shown in Table 1. Results for breathing pattern and respiratory drive are presented in Table 2. As dictated by the protocol, peak EA_{di} for both PSV and NAVA was comparable at low and high levels of support, and decreased with increasing inspiratory support for both PSV and NAVA.

PSV

Figure 1 shows mean values for trigger delay (delay of pneumatic timing compared to neural inspiration) and cycling-off error (error of pneumatic timing compared to neural expiration) during each ventilator setting for all individual patients. The mean trigger delay was longer during PSV high (268 ± 40 ms) than during PSV low (161 ± 42 ms, $p = 0.04$). There was no difference in mean cycling-off error between low and high PSV (PSV low −100 ± 40 ms and PSV high 56 ± 111 ms). Figure 2 shows a plot for all 4 ventilator settings, all breaths of all patients, of the relative timing errors of triggering (Y-axis) versus the relative timing error of cycling-off (X-axis). A box was inserted marking synchrony as acceptable, whereas larger errors (> 20 %) represent dyssynchrony. With increasing levels of PSV, incidence of dyssynchronous breaths increases. The pie charts in Figure 3 show the distribution of breaths defined as synchronous, dyssynchronous and asynchronous. Increasing the inspiratory support increases the occurrence of dyssynchronies from 33 % to 54 % of all breaths. Although wasted efforts were the most prevalent asynchronies which occurred in 18 % of all breaths during low level PSV, during high level PSV the incidence of wasted efforts did not increase (16 %). Multiple EA_{di} during assist and auto-triggering occurred in minimal percentages (≤ 3 %) during PSV.

NAVA

During NAVA the mean trigger delay, as shown in Figure 1, was the same for low and high level of support, but shorter than both PSV with low (49 ± 9 ms for NAVA, $p = 0.03$) and high (79 ± 27 ms for NAVA, $p = 0.00$) level of support. No difference was found in mean cycling-off error for NAVA with low or high inspiratory support. Also, cycling-off error during NAVA was not different from PSV (NAVA low −5 ± 6 ms, NAVA high 12 ± 13 ms). Figure 2 shows that with increasing levels of support in NAVA mode the percentage of dyssynchronies did not increase, and that timing of the breaths was more condensed inside the 20 %-box during NAVA than during both low and high level PSV. The distribution of breaths in Figure 3 showed relatively similar synchrony

(81 % of all breaths for low level NAVA and 78 % of all breaths for high level NAVA) and dyssynchrony (13 % of all breaths for low level NAVA and 12 % of all breaths for high level NAVA). Wasted efforts only occurred in 4 % and 1 % of all breaths during respectively low and high level assist in NAVA mode, which is less than during both low and high level PSV. However, auto-triggering increased from 4 % of all breaths during low level NAVA to 9 % during high level NAVA, which is more than during both low level PSV (2 %) and high level PSV (3 %).

Discussion

The current study provides new insights in the effects of inspiratory support levels and ventilator mode on patient-ventilator interaction during NIV in patients with an acute exacerbation of COPD. First, we found that patient-ventilator synchrony decreased with increasing inspiratory pressure during PSV, due to progressive inci-

Table 1

Patient characteristics. Pulmonary function tests (FEV1, FVC and FEV1/FVC) were of maximal one year before or after the study took place.

Number	Age (y)	BMI (kg/m²)	FEV1 (% pred.)	FVC (% pred.)	FEV1/FVC	GOLD class.	pH at ICU submission	pH at study inclusion
1	66	34	24	63	28	4	7.24	7.35
2	59	23	24	42	45	4	7.30	7.41
3	69	19	51	74	55	2	7.16	7.36
4	52	20	27	77	29	4	7.32	7.35
5	73	35	30	45	49	4	7.29	7.31
6	78	31	39	109	29	3	7.26	7.32
7	56	20	18	71	22	4	7.24	7.37
8	66	22	17	76	16	4	7.26	7.24

BMI: body mass index; FEV1: forced expired volume in 1 second; FVC: forced vital capacity; GOLD class: Global Initiative for Chronic Obstructive Lung Disease classification.

Table 2

Breathing pattern and respiratory drive shown as median with interquartile range (IQR).

	PSV low	PSV high	NAVA low	NAVA high
Peak EA_{di} (μV)	37.2 (11.8–60.4)	21.4* (8.9–46.1)	34.8 (16.2–58.2)	19.8* (8.7–42.8)
Peak airway pressure (cmH_2O)	9.9 (9.3–10.1)	17.2* (16.4–19.1)	11.8 (9.5–14.1)	16.3* (15.9–18.7)
Neural resp. rate (breaths/min)	24.0 (13.5–29.5)	21.0 (15.0–27.0)	25.0 (18.5–29.5)	27.0# (20.5–31.5)

* *significant difference between low and high inspiratory support.*
\# *significant difference between PSV and NAVA for high support.*

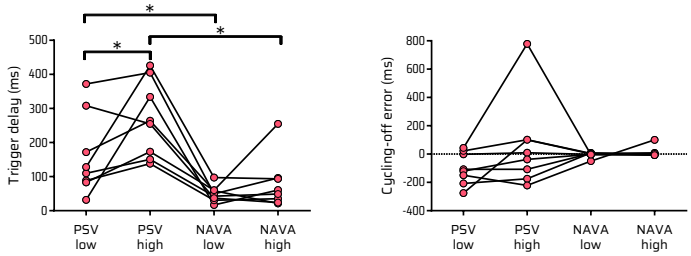


Figure 1

Trigger delay (left) and cycling-off error (right) for the 4 ventilator settings. Positive y-values indicate late cycling-off, and negative y-values indicate early cycling-off. * $p \leq 0.05$.

dence of trigger delays. Second, patient-ventilator interaction in NAVA mode was independent of the level of inspiratory support; no differences in trigger delay and cycling-off error were found with increasing level of support. Third, patient-ventilator interaction in NAVA mode was superior compared to both low and high level PSV during NIV.

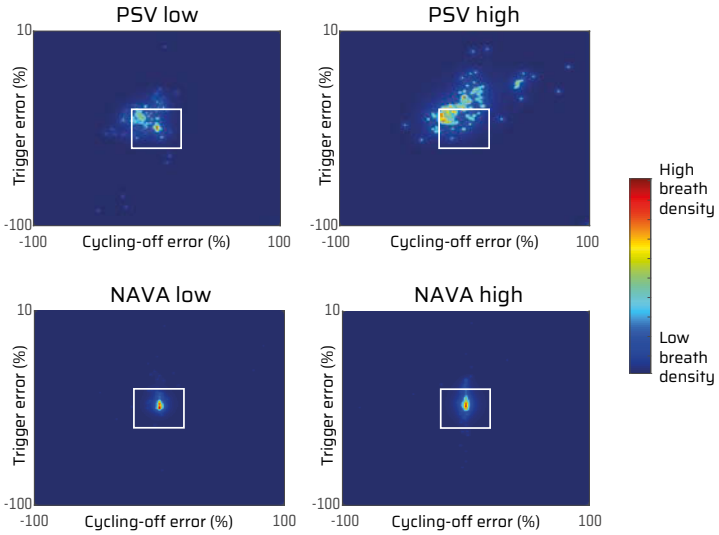


Figure 2

Breath density graph for relative trigger (Y-axis) and cycling-off (X-axis) errors, for all breaths in all patients, during each ventilator setting. The white box in each graph indicates the limit (20 %) between synchrony and dyssynchrony.

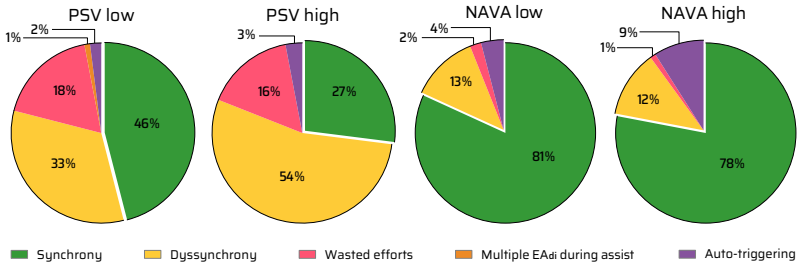


Figure 3
Percentage of synchronous, dyssynchronous (trigger delay and cycling-off errors) and asynchronous (wasted efforts, auto-triggering and multiple EA_{di} during assist) breaths for the 4 ventilator settings.

Patient-ventilator interaction

For effective unloading of the inspiratory muscles during NIV, the ventilator should cycle in synchrony with the neural respiratory drive of the patient (7). Previous studies have reported the presence of trigger delays and cycling-off errors in PSV and NAVA mode under NIV (13,15,16). In those studies inspiratory pressures were different for each patient. However, it is known that during invasive ventilation increasing the level of inspiratory assistance may worsen ineffective triggering (4,17). To the best of our knowledge, this is the first study to compare noninvasive PSV and NAVA both with two levels of inspiratory support for each patient.

PSV

We applied two levels (5 and 15 cmH_2O) of inspiratory pressure to all subjects. By increasing the level of assistance, the inspiratory muscles were progressively unloaded as indicated by reduced peak electrical activity of the diaphragm. Because of the increased inspiratory pressure support, tidal volumes may increase and the respiratory rate tends to decrease. However, increasing inspiratory assistance may also result in more leaks. As during NIV leaks are found to be a major contributing factor to the prevalence of patient-ventilator asynchronies by preventing the flow from reaching the pre-set expiratory trigger (5), this could be an important cause of increased patient-ventilator asynchrony with increasing inspiratory support. However, leaks are not quantified in the current study so this hypothesis cannot be verified.

Although dyssynchronies increased from 33% to 54%, incidence of wasted efforts did not increase with increasing inspiratory pressure. It is known that increasing inspiratory pressure during invasive ventilation induces more wasted efforts, mainly as a result of a decrease in respiratory drive and an increase in tidal volume resulting in hyperinflation, which makes it harder to reach the preset trigger (17). The respiratory drive in the current study, represented by a median peak

EAdi of 21.4 μV, was not associated with more wasted efforts, whereas previously an increase of dyssynchronies and wasted efforts was shown even with a comparable median peak EAdi of 25.6 μV (13). The increase in dyssynchronies from low to high level PSV in the current study was thus mainly caused by increased trigger delay, which may be the result of more leakages, less emptying of the lungs and increased hyperinflation whereby the preset trigger is reached with a delay.

It should be noted that one patient showed a remarkably high cycling-off delay during high support PSV (see Figure 1). As COPD is characterized by obstructive lung mechanics and elevated compliance, expiration requires relatively more time than inspiration. The rise of the inspiratory flow should be fast, to avoid hyperinflation and increasing intrinsic PEEP (18). By increasing the inspiratory pressure and thus inspiratory flow during PSV, with equal compliance, this patient did not receive the extra time needed to inhale, which results in increased cycling-off delays during high support PSV.

NAVA

NAVA was applied with two levels of support, matching peak pressure as delivered in PSV. Similar to PSV, increasing the level of assistance resulted in more unloading of the inspiratory muscles and the peak EAdi decreased. Both trigger delays and cycling-off errors during NAVA were in a comparable range with previous findings (13,15,16), without distinction between low and high inspiratory support.

One patient in the current study showed a high trigger delay during NAVA with a high level of support (see Figure 1). This patient exhibited an irregular EAdi pattern, with many small peaks in between breaths. This EAdi pattern caused the ventilator to switch to backup PSV mode, by which the synchrony decreased. For this patient, NAVA was probably not the most appropriate mode of support.

Compared to PSV, the mean trigger delay was shorter during NAVA for both low and high inspiratory support, in a range comparable with previous studies on noninvasive NAVA (13,15,19). Cycling-off error was not significantly different for both modes and levels of noninvasive ventilation. Although the incidence of dyssynchronies is less during both levels of NAVA than during both PSV with low and high support, auto-triggering during NAVA occurs slightly more than during PSV, and even increases from 4 % to 9 % from low to high level NAVA. Auto-triggering is a known phenomenon especially with NAVA (15). The ventilator will cycle on due to even a small increase in EAdi, including increases due to signal artifacts or any 'subrespiratory' diaphragmatic activity. However, as the peak EAdi is relatively low, the ventilator will promptly cycle off again and its detrimental effect on the patients respiratory pattern will be limited (15).

The current study showed in all modes more dyssynchronies than a previous study by our group (13). The current study showed 33 % dyssynchronies for PSV low and 54 % for PSV high, whereas the previous study showed 30.5 % dyssynchronies during PSV. During low and high level NAVA, respectively 13 % and 12 % of breaths

were dyssynchronous, compared to 3.3 % in the previous study. The difference between the current study and the previous study by our group (13) may be explained by patient selection. The previous study included 4 out of the total 12 subjects with other indications for NIV than an exacerbation of COPD. More important, mean arterial blood pH was 7.38, whereas mean arterial blood pH at time of inclusion of the patients in the current study was 7.34. Although from time of submission to the ICU to the moment of study inclusion the arterial blood pH was already increased by supported breathing during NIV in the current study (see Table 1), these patients were still in an acute phase of their exacerbation and in need of NIV. As it is known that intrinsic PEEP in COPD patients is the most common cause of ineffective inspiratory triggering (20), these patients in the current study being in a more acute phase of their COPD exacerbation than the previous study by our group (13) could be causing the decreased patient-ventilator synchrony. Other plausible explanations could be the presence of the videolaryngoscope, a different interface (fullface mask versus oronasal mask) and the difference in inspiratory pressure and PEEP. In the current study the inspiratory pressures were 5 and 15 cmH_2O for all patients, whereas the mean inspiratory pressures in the previous study was 6.9 cmH_2O with a standard deviation of 1.8 cmH_2O. Whereas PEEP was not changed in the current study, mean PEEP in the previous study was 6.1 cmH_2O with a standard deviation of 1.2 cmH_2O. As it is thought that increasing inspiratory pressure could increase the risk of leaks and leaks might induce patient-ventilator asynchrony, these factors could explain the difference in asynchrony between these two studies.

Methodological considerations

It should be noted that data discussed here were acquired for different purposes, as mentioned in the Methods section, for which a fiberoptic flexible bronchoscope (Pentax EB-1170 (11 Fr)) was inserted via the nose and positioned ± 2 cm cranial to the vocal cords. The presence of the scope might have influenced the interaction between the patient and the ventilator by reflective mechanisms resulting from contact of the scope with, for example, epiglottic tissue. The current study provides no data recorded without the scope in situ to support this.

Patient-ventilator interaction was quantified by an automated method, allowing detection of dyssynchronies (trigger delays and cycling-off errors) and asynchronies (wasted efforts, auto-triggering and multiple EA_{di} during assist) in a standardized manner (13,14). This method might provide a future clinical tool to monitor patient-ventilator asynchrony, and more importantly, to analyze whether patient-ventilator asynchrony occurs more often in severely ill patients, or whether patient-ventilator asynchrony itself is responsible for the poor prognosis (21). It should be noted that for the automated analysis of patient-ventilator interaction in this study the last 30 seconds of each dataset were used. This is a shorter time period than in previous studies (4,13,14).

The proportion of synchronous and dyssynchronous breaths is affected by the applied criterion. A previous study by our group defined 20 % of relative inspiratory and expiratory neural time to be synchronous (13), whereas another study defined 33 % to be synchronous (14). As it is shown that after timing errors reach 20 % the wasted efforts increase, the current study adhered to this criterion, but it should be noted that this definition influences the percentages in Figure 3.

Conclusion

Automated analysis of patient-ventilator interaction showed that there is a progressive mismatch between neural effort and pneumatic timing with increasing levels of PSV during NIV. During noninvasive NAVA the patient-ventilator interaction improved as compared to PSV, independent of the level of inspiratory support.

References

1 Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, et al. Noninvasive Ventilation for Acute Exacerbations of Chronic Obstructive Pulmonary Disease. New England Journal of Medicine. 1995;333(13):817–22.

2 Chandra D, Stamm JA, Taylor B, Ramos RM, Satterwhite L, Krishnan JA, et al. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998–2008. Am J Respir Crit Care Med. 2012;185(2):152–9.

3 Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. The Lancet. 2000;355(9219):1931–5.

4 Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med. 2006;32(10):1515–22.

5 Vignaux L, Vargas F, Roeseler J, Tassaux D, Thille AW, Kossowsky MP, et al. Patient-ventilator asynchrony during non-invasive ventilation for acute respiratory failure: a multicenter study. Intensive care medicine. 2009;35(5):840–6.

6 Kondili E, Prinianakis G, Georgopoulos D. Patient-ventilator interaction. British journal of anaesthesia. 2003;91(1):106–19.

7 Tobin MJ, Jubran A, Laghi F. Patient-ventilator interaction. American journal of respiratory and critical care medicine. 2001;163(5):1059–63.

8 Nava S, Bruschi C, Fracchia C, Braschi A, Rubini F. Patient-ventilator interaction and inspiratory effort during pressure support ventilation in patients with different pathologies. Eur Respir J. 1997;10(1):177–83.

9 Jolliet P, Tassaux D. Clinical review: patient-ventilator interaction in chronic obstructive pulmonary disease. Critical care. 2006;10(6):236.

10 Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, et al. Neural control of mechanical ventilation in respiratory failure. Nature medicine. 1999;5(12):1433–6.

11 Schmidt M, Kindler F, Cecchini J, Poitou T, Morawiec E, Persichini R, et al. Neurally adjusted ventilatory assist and proportional assist ventilation both improve patient-ventilator interaction. Critical care. 2015;19:56.

12 Spahija J, de Marchie M, Albert M, Bellemare P, Delisle S, Beck J, et al. Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilatory assist. Critical care medicine. 2010;38(2):518–26.

13 Doorduin J, Sinderby CA, Beck J, van der Hoeven JG, Heunks LM. Automated patient-ventilator interaction analysis during neurally adjusted non-invasive ventilation and pressure support ventilation in chronic obstructive pulmonary disease. Critical care. 2014;18(5):550.

14 Sinderby C, Liu S, Colombo D, Camarotta G, Slutsky AS, Navalesi P, et al. An automated and standardized neural index to quantify patient-ventilator interaction. Critical care. 2013;17(5):R239.

15 Piquilloud L, Tassaux D, Bialais E, Lambermont B, Sottiaux T, Roeseler J, et al. Neurally adjusted ventilatory assist (NAVA) improves patient-ventilator interaction during non-invasive ventilation delivered by face mask. Intensive care medicine. 2012;38(10):1624–31.

16 Longhini F, Pan C, Xie J, Cammarota G, Bruni A, Garofalo E, et al. New setting of neurally adjusted ventilatory assist for noninvasive ventilation by facial mask: a physiologic study. Critical care. 2017;21(1):170.

17 Leung P, Jubran A, Tobin MJ. Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea. Am J Respir Crit Care Med. 1997;155(6):1940–8.

18 Tassaux D, Gainnier M, Battisti A, Jolliet P. Impact of expiratory trigger setting on delayed cycling and inspiratory muscle workload. American journal of respiratory and critical care medicine. 2005;172(10):1283–9.

19 Schmidt M, Dres M, Raux M, Deslandes-Boutmy E, Kindler F, Mayaux J, et al. Neurally adjusted ventilatory assist improves patient-ventilator interaction during postextubation prophylactic noninvasive ventilation. Crit Care Med. 2012;40(6):1738–44.

20 Chao DC, Scheinhorn DJ, Stearn-Hassenpflug M. Patient-ventilator trigger asynchrony in prolonged mechanical ventilation. Chest. 1997;112(6):1592–9.

21 Piquilloud L, Jolliet P, Revelly JP. Automated detection of patient-ventilator asynchrony: new tool or new toy? Critical care. 2013;17(6):1015.

Clinical trial registration

Retrospectively registered 12 February 2013 at ClinicalTrials.gov (NCT01791335), https://clinicaltrials.gov/ct2/show/NCT01791335

7 General discussion and future perspectives

Mechanical ventilation (MV) provides breathing support to maintain adequate gas exchange in patients with respiratory failure. According to the feedback control system explained in the Introduction of this thesis (see Figure 1 in Chapter 1), there is a continuous interaction between spontaneous breathing of the patient and the provided mechanical ventilatory support. Although MV is often lifesaving, the balance of these interacting components is crucial. A sufficient level of synchronized ventilatory support should be provided to ensure adequate breathing function, at the same time minimizing the provided support in order to prevent adaptation of the patient to the provided mechanical support. This thesis aimed at providing better insight in monitoring and regulation of breathing support. Relevant issues considered in this thesis include weaning difficulties, assessment of diaphragm weakness, and patient-ventilator interaction. These issues were investigated in both healthy subjects and patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) requiring noninvasive ventilation in the Intensive Care Unit (ICU). First the 3 research questions as stated in the Introduction of this thesis will be discussed separately. Subsequently, the general contribution of this thesis to current knowledge about the interaction between spontaneous breathing and mechanical ventilatory support will be discussed. Lastly, future perspectives will be presented.

How is the neural respiratory drive influenced by arterial bicarbonate levels?

Chapter 2 of this thesis showed that metabolic alkalosis in healthy subjects decreased the neural respiratory drive and resulting minute ventilation. This is of clinical importance, because a decreased respiratory drive could lead to difficulties in weaning of the ventilator when the underlying reason for acute respiratory failure has been resolved. Under physiological conditions, inspiratory carbon dioxide (CO_2) causes an increase in respiratory drive and minute ventilation. However, after administration of sodiumbicarbonate, which increased plasma bicarbonate levels, the ventilatory response to inspiratory CO_2 appeared to be decreased. With respect to the feedback control mechanism stated in the Introduction of this thesis, posthypercapnic alkalosis can be considered as a consequence of adaptation to the mechanical ventilation. Acute hypoventilation results in arterial CO_2 retention. As a consequence, bicarbonate production or retention will shift the acidotic pH level towards normal by metabolic compensatory mechanisms. Mechanical ventilation will restore minute ventilation and normalize CO_2 levels, but adaptation of bicarbonate in the arterial blood is a considerably slower process, resulting in posthypercapnic alkalosis (1). The results presented in chapter 2 of this thesis adhere to the hypothesis that the elevated arterial bicarbonate levels increase the buffer capacity for CO_2, thus reducing the chemosensitivity of breathing and depressing the neural respiratory drive (2,3). However, the results were different from previous literature. In other studies, no difference in minute ventilation related to endtidal CO_2 pressures was shown after sodiumbicarbonate administration to healthy subjects (4). In COPD patients no difference in ventilatory response was found with elevated arterial bicarbonate levels as well (5). It is important to note that mechanical properties of the respiratory system, as the pressure-generating capacity of the diaphragm, compliance of the lungs and chest wall or hyperinflation, could change the relation between bicarbonate levels and minute ventilation (6). The most important addition of the study in this thesis to the current knowledge about metabolic alkalosis and minute ventilation, is the measurement of neural respiratory drive. Neural drive is represented by the electrical activity of the diaphragm (EAdi) (7). EAdi reflects motor output of the central nervous system to the diaphragm muscle (8), eliciting contraction of the diaphragm. Therefore, EAdi is a more specific and sensitive measure of neural respiratory drive than minute ventilation alone. Indeed, in contrast with previous studies (4,5), minute ventilation in the study in this thesis decreased significantly, there was a stronger decrease in EAdi. As long as patients are capable of maintaining sufficient ventilation, by recruiting for example accessory respiratory muscles, an increased plasma bicarbonate level might not lead to decreased minute ventilation. This implies that neuroventilatory efficiency should increase, as shown in the study in this thesis. Although we hypothesized that the recruitment of

accessory respiratory muscles explained the increasing neuroventilatory efficiency, activity of these muscles was not assessed in the study in this thesis. However, as we showed that even in healthy subjects elevated bicarbonate levels decrease the respiratory drive, the clinical relevance in COPD patients in acute respiratory distress becomes evident. These patients may not have the reserve capacity to increase their neuroventilatory efficiency. The inability to maintain sufficient ventilation with a decreased respiratory drive might lead to difficulties in retaining spontaneous breathing during weaning from the ventilator.

Two main topics for further research can be identified. First, the cause of increased neuroventilatory efficiency found in chapter 2 should be analyzed. Changes in the activity of accessory muscles with increased bicarbonate levels was expected to result in equal minute ventilation with decreased diaphragm activity, expressed as EA_{di}. As the study in chapter 2 provided no data to support this, further research is needed. Second, as we showed that neural respiratory drive decreased with increased plasma bicarbonate levels, it is of clinical importance to determine the characteristic time of this adaptation process. The time course of the weaning process should occur in accordance with the characteristic time of the adaptation process of respiratory drive depending on plasma bicarbonate levels. Although it is shown that the duration of mechanical ventilatory support is not significantly reduced by excretion of bicarbonate, decreased bicarbonate levels were associated with a clinically substantial decrease in duration of mechanical ventilation (9). Therefore, we consider the decrease in respiratory drive during metabolic alkalosis a relevant topic that should be included in the structured approach of weaning failure analysis as proposed in literature (10). Most importantly, the relation between plasma bicarbonate levels and neural respiratory drive should be analyzed in patients with acute respiratory failure due to an exacerbation of COPD, as this is the population that is known to suffer from metabolic alkalosis and resulting weaning difficulties.

How can diaphragm function be noninvasively assessed using speckle tracking ultrasound?

Chapter 3 of this thesis showed that strain and strain rate, derived with speckle tracking ultrasound, were highly correlated with gold standard measures of diaphragmatic function.

According to the feedback control mechanism in the Introduction chapter, there is an interaction between a patient's spontaneous breathing and the mechanical ventilatory support that is provided. Mechanical ventilatory support takes over (part of) the respiratory muscle function, mainly of the diaphragm. This may result in diaphragm atrophy, contractile dysfunction and development of diaphragm weakness (11,12). Diaphragm weakness may develop rapidly: muscle fiber atrophy in the

human diaphragm occurs already after only 18–69 hours of full support mechanical ventilation and a reduction of approximately 30 % is found in twitch airway pressure, induced by magnetic phrenic nerve stimulation, in the first 5 to 6 days of invasive mechanical ventilation (13,14). As respiratory muscle dysfunction develops in critically ill patients and contributes to weaning failure (14–16), it is of utmost importance to retrieve objective information about the functioning and possible degeneration of the diaphragm. However, the respiratory muscles are poorly monitored in the ICU and weakening is usually unrecognized (17). Currently, measurement of transdiaphragmatic pressure (P_{di}) using esophageal and gastric balloons is the gold standard to assess effort of the diaphragm. However, this technique is invasive and requires expertise, and interpretation may be complex (8,17). Ultrasound can be used to noninvasively evaluate thickness, thickening during inspiration and displacement of the diaphragm at the bedside (18). The fractional thickening (FT) of the diaphragm has been used in previous studies to quantify effort of the diaphragm, but low correlations between P_{di} and FT are reported in healthy subjects (19).

The high correlation between P_{di} and strain rate found in chapter 3 of this thesis, implied that speckle tracking ultrasound can be used to noninvasively estimate diaphragm contractility during inspiratory loading in healthy subjects. The strain and strain rate showed to be superior to the FT derived from conventional ultrasound in quantifying functionality of the diaphragm. As it is shown previously that speckle tracking of the diaphragm is feasible and reproducible (20) speckle tracking could possibly be used to estimate diaphragm contractile force and guide weaning in ventilated patients in the future.

Although the correlation between P_{di} and strain rate was as high as 0.8, it should be noted that this was found under inspiratory threshold loading. The correlation between speckle tracking and physiological measures under different loading conditions, like isometric contraction or high inspiratory volumes, remains to be evaluated. Most important point of concern is the offline analysis that is currently required, which hampers its use as a bedside tool. This analysis method requires further research and development by companies that produce ultrasound machines. Lastly, future research should focus on the applicability of this technology in patients receiving mechanical ventilatory support with weakened diaphragms, instead of healthy subjects.

How is the synchrony between the patient and the ventilator influenced by different modes and settings of noninvasive ventilation?

Whereas the first 2 research questions in this thesis handle two adaptive processes regarding the interaction between spontaneous breathing and mechanical ventilatory support, the third research question concerns the momentary effectiveness

of the provided mechanical ventilatory support. Chapter 6 of this thesis showed that the patient and the ventilator acted more in synchrony, defined as the match between the patient's neural inspiratory and expiratory times and the ventilator's mechanical inspiratory and expiratory time, during noninvasive neurally adjusted ventilatory assist (NAVA) mode than during noninvasive pressure support ventilation (PSV) mode in patients with an exacerbation of COPD. Inspiratory triggering was more synchronous with NAVA than during PSV, and remained synchronous with increasing inspiratory levels of support. The percentage of dyssynchronous breaths increased with increasing PSV from 33 % to 54 %, whereas during both levels of NAVA this was only 12 %. In chapter 4 the synchrony between the ventilator and the patient's upper airway was reviewed. The most important determinant of synchronicity for patients receiving invasive ventilation, is the interaction between the activity of the diaphragm and the ventilator's response. The upper airways are bypassed by the endotracheal tube, which ensures patency of the upper airway. During noninvasive ventilation (NIV), the upper airways are part of the interaction between the patient and the ventilator. Receptors in the upper and lower airways modulate activity of the upper airway muscles, by for example changes in pressure, flow and temperature stimuli (21–23). During NIV, the glottis might thereby increase upper airway resistance during inspiration and limit effective alveolar ventilation. The study in chapter 5 showed that patency of the glottis, in patients with an exacerbation of COPD, was independent of mode and level of noninvasive inspiratory support. The angle formed by the vocal cords during inspiration was equal during low or high levels of PSV or NAVA, although a very wide interindividual variability in glottis behavior was observed. This implies that patients with an exacerbation of COPD benefit from noninvasive NAVA ventilation over PSV regarding patient diaphragm-ventilator interaction, but specific modes do not have any beneficial effects on upper airway patency. In addition, increasing the inspiratory support during NAVA did not decrease the synchrony between the patient, its upper airway and the ventilator.

It should be noted that both chapter 5 and 6 were based on the same results found in a small population of 8 patients. Thereby, COPD is known to be a heterogeneous disease (24), in which the presence of airflow limitation alone is not adequate to fully assess the severity of the disease (25). As an example, the harmed upper airway receptors by chronic carbon dioxide exposure during chronic cigarette smoking could be an important component in the heterogeneous pattern of the disease. The high variability of glottis behavior which was found in analyzing the videolaryngoscopy images could be a consequence. Although we are convinced that the applied measurement setup ensures synchronous data acquisition and the automated image analysis, used to calculate the angle of the vocal cords, provides a state-of-the-art method for analysis of the patency, some points of concern remain. First, video images were not continuously of sufficient quality to calculate

the angle of the vocal cords throughout the breathing cycle. Change of the laryngoscope position, airway secretions and coughing for example leaded to inadequate images and thereby missing information about the behavior of the glottis, whereas these might be the moments when patency is changed and influenced by mode or level of NIV. Second, no data is available of COPD patients or healthy subjects without noninvasive ventilatory support. Although no change in patency is found with different modes and settings, it is unknown whether patency is decreased or increased compared to unassisted breathing. Third, the presence of the NAVA catheter and the videolaryngoscope both might influence the behavior of the glottis in such way that the influence of the ventilator mode (PSV or NAVA) and setting (low or high support) is imperceptible with the used method. This study should be regarded as a pilot study which requires extensive further research. A larger cohort of patients should be a first step, which will require an improvement in the image analysis as well. Although the image analysis is automated, calculating and checking all the angles still is very time consuming for both the computer and the researcher. In case no decreased patency is confirmed in a larger cohort of COPD patients during NIV, the reason of failure of NIV in COPD patients should of course still be subject to further research.

General conclusion

This thesis elucidates the interaction between a patients spontaneous breathing and the provided mechanical ventilatory support (see Figure 1 in the Introduction). Although further research is necessary, new tools and insights are provided to improve mechanical ventilation and weaning. The optimal interaction between a patient and a ventilator deals with short and long term effects. On the short term it is essential for the interaction to deliver efficient and synchronous ventilation, reducing the work of breathing for the patient without fighting the ventilator. However, on the longer term it is important to deliver a level of support where adaptation to the ventilator is minimized. Adaptation to the ventilator could result in problems during weaning of the ventilator, when the cause of the respiratory failure is resolved. This thesis investigated two aspects which are relevant with respect to the adaptation effect: the metabolic adaptation and noninvasive monitoring of diaphragm function. We showed that neural respiratory drive is influenced by metabolic alkalosis and should be considered as a possible adaptation effect of mechanical ventilation. The difference in time between restoring of adequate gas exchange by mechanical ventilation and the slower compensatory increase of bicarbonate in the arterial blood might result in posthypercapnic alkalosis which could become a problem during weaning of the ventilator. In addition, the first step is set towards noninvasive monitoring of diaphragm contractility, using speckle tracking ultrasound to quantify functioning of the diaphragm during inspiratory loading.

Speckle tracking ultrasound could be used in the future to identify weakening of the diaphragm by adaptation to the provided ventilatory support. Regarding the short term requirements, the behavior of the COPD patient and its upper airways interacting with noninvasive mechanical ventilation was clarified. Synchrony between the patient and the ventilator decreased with increasing inspiratory pressure during PSV, whereas NAVA ventilation increased the synchrony between the patient and the ventilator. The patency of the upper airways of COPD patients showed a variable but mostly cyclic behavior related to the neural respiratory drive, which was independent of mode or level of noninvasive ventilation.

Future perspectives

Setting the ventilator in such way that the patient receives just sufficient support to improve gas exchange and reduce the work of breathing, while adaptation to the support is minimized, remains a challenging clinical task. It is unknown and of course very patient specific when this balance is shifted and diaphragm atrophy or metabolic changes are occurring more than the needed unloading of the respiratory muscles. Although we know that for example diaphragm weakening starts already after 18–69 hours of full support mechanical ventilation, these timing characteristics are unknown for the metabolic changes on a patient specific level. Besides, reversing these processes for example in training of the diaphragm is an important aspect in weaning and should be subject of further research. Future research should focus on noninvasive monitoring methods to identify this: can we identify the patient specific timing of diaphragm weakening, how is the evolvement in time of bicarbonate levels in the arterial blood when this adaptation to the ventilator will reduce the neural respiratory drive and prevent the patient from weaning from the ventilator? Ultimately, ventilatory support should be provided in a continuous feedback loop where not only a preset pressure or volume is used to target mechanical support. An adequate (but minimal) level of breathing support should be constantly estimated from a combination of neural respiratory drive, diaphragm effort, accessory muscle activity and blood gas values, on a breath by breath basis.

References

1 Banga A, Khilnani GC. Post-hypercapnic alkalosis is associated with ventilator dependence and increased ICU stay. Copd 2009; 6: 437–440.

2 Heinemann HO, Goldring RM. Bicarbonate and the regulation of ventilation. The American journal of medicine 1974; 57: 361–370.

3 Rialp G, Raurich JM, Llompart-Pou JA, Ayestaran I, Ibanez J. Respiratory CO2 response depends on plasma bicarbonate concentration in mechanically ventilated patients. Medicina intensiva 2014; 38: 203–210.

4 Oren A, Whipp BJ, Wasserman K. Effects of chronic acid-base changes on the rebreathing hypercapnic ventilatory response in man. Respiration; international review of thoracic diseases 1991; 58: 181–185.

5 van de Ven MJ, Colier WN, van der Sluijs MC, Oeseburg B, Vis P, Folgering H. Effects of acetazolamide and furosemide on ventilation and cerebral blood volume in normocapnic and hypercapnic patients with COPD. Chest 2002; 121: 383–392.

6 Jolley CJ, Luo YM, Steier J, Rafferty GF, Polkey MI, Moxham J. Neural respiratory drive and breathlessness in COPD. Eur Respir J 2015; 45: 355–364.

7 Beck J, Gottfried SB, Navalesi P, Skrobik Y, Comtois N, Rossini M, Sinderby C. Electrical activity of the diaphragm during pressure support ventilation in acute respiratory failure. American journal of respiratory and critical care medicine 2001; 164: 419–424.

8 American Thoracic Society/European Respiratory S. ATS/ERS Statement on respiratory muscle testing. American journal of respiratory and critical care medicine 2002; 166: 518–624.

9 Faisy C, Meziani F, Planquette B, Clavel M, Gacouin A, Bornstain C, Schneider F, Duguet A, Gibot S, Lerolle N, Ricard JD, Sanchez O, Djibre M, Ricome JL, Rabbat A, Heming N, Urien S, Esvan M, Katsahian S, Investigators D. Effect of Acetazolamide vs Placebo on Duration of Invasive Mechanical Ventilation Among Patients With Chronic Obstructive Pulmonary Disease: A Randomized Clinical Trial. JAMA 2016; 315: 480–488.

10 Heunks LM, van der Hoeven JG. Clinical review: the ABC of weaning failure–a structured approach. Critical care 2010; 14: 245.

11 Powers SK, Wiggs MP, Sollanek KJ, Smuder AJ. Ventilator-induced diaphragm dysfunction: cause and effect. American journal of physiology Regulatory, integrative and comparative physiology 2013; 305: R464–477.

12 Hudson MB, Smuder AJ, Nelson WB, Bruells CS, Levine S, Powers SK. Both high level pressure support ventilation and controlled mechanical ventilation induce diaphragm dysfunction and atrophy. Critical care medicine 2012; 40: 1254–1260.

13 Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, Zhu J, Sachdeva R, Sonnad S, Kaiser LR, Rubinstein NA, Powers SK, Shrager JB. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. The New England journal of medicine 2008; 358: 1327–1335.

14 Jaber S, Petrof BJ, Jung B, Chanques G, Berthet JP, Rabuel C, Bouyabrine H, Courouble P, Koechlin-Ramonatxo C, Sebbane M, Similowski T, Scheuermann V, Mebazaa A, Capdevila X, Mornet D, Mercier J, Lacampagne A, Philips A, Matecki S. Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. American journal of respiratory and critical care medicine 2011; 183: 364–371.

15 Laghi F, Cattapan SE, Jubran A, Parthasarathy S, Warshawsky P, Choi YS, Tobin MJ. Is weaning failure caused by low-frequency fatigue of the diaphragm? American journal of respiratory and critical care medicine 2003; 167: 120–127.

16 Hermans G, Agten A, Testelmans D, Decramer M, Gayan-Ramirez G. Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: a prospective observational study. Critical care 2010; 14: R127.

17 Doorduin J, van Hees HW, van der Hoeven JG, Heunks LM. Monitoring of the respiratory muscles in the critically ill. American journal of respiratory and critical care medicine 2013; 187: 20–27.

18 Matamis D, Soilemezi E, Tsagourias M, Akoumianaki E, Dimassi S, Boroli F, Richard JC, Brochard L. Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. Intensive Care Med 2013; 39: 801–810.

19 Goligher EC, Laghi F, Detsky ME, Farias P, Murray A, Brace D, Brochard LJ, Bolz SS, Rubenfeld GD, Kavanagh BP, Ferguson ND. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. Intensive Care Med 2015; 41: 734.

20 Orde SR, Boon AJ, Firth DG, Villarraga HR, Sekiguchi H. Diaphragm assessment by two dimensional speckle tracking imaging in normal subjects. BMC anesthesiology 2016; 16: 43.

21 Stella MH, England SJ. Modulation of laryngeal and respiratory pump muscle activities with upper airway pressure and flow. J Appl Physiol (1985) 2001; 91: 897–904.

22 Stella MH, England SJ. Laryngeal muscle response to phasic and tonic upper airway pressure and flow. J Appl Physiol (1985) 2001; 91: 905–911.

23 Sant'Ambrogio G, Tsubone H, Sant'Ambrogio FB. Sensory information from the upper airway: role in the control of breathing. Respiration physiology 1995; 102: 1–16.

24 Di Marco F, Santus P, Scichilone N, Solidoro P, Contoli M, Braido F, Corsico AG. Symptom variability and control in COPD: Advantages of dual bronchodilation therapy. Respiratory medicine 2017; 125: 49–56.

25 Gruffydd-Jones K, Jones MM. NICE guidelines for chronic obstructive pulmonary disease: implications for primary care. The British journal of general practice : the journal of the Royal College of General Practitioners 2011; 61: 91–92.

8 Summary Samenvatting

Summary

This thesis describes several chapters related to monitoring and regulation of breathing. The main goal is to provide better insight in the interaction between spontaneous breathing and mechanical ventilatory support. In **chapter 2** we investigated the effect of metabolic alkalosis on the ventilatory response. In this intervention study the ventilatory response was assessed in 10 healthy subjects, using a hypercapnic ventilatory response (HCVR) test, before and after administration of high dose sodium bicarbonate. After bicarbonate administration P_{di}, EA_{di} and V_E were significantly lower for similar levels of inspired CO_2. We demonstrated that the respiratory centers respond differently to inhaled CO_2 when arterial bicarbonate levels are increased, probably as a result of the enhanced buffer capacity; more arterial bicarbonate supplies more capacity to buffer CO_2 before the respiratory centers sense an increased arterial CO_2. These findings could implicate that patients with metabolic alkalosis suffering from suppressed ventilation, and resulting weaning difficulties, could benefit from excreting bicarbonate to stimulate the respiratory centers.

To analyze whether speckle tracking ultrasound can be used to noninvasively quantify diaphragm contractility, in **chapter 3** this technique is used in healthy sub-

jects undergoing a randomized stepwise threshold loading protocol. Speckle tracking ultrasound was used to assess strain and strain rate as measures of diaphragm tissue deformation and deformation velocity. Strain and strain rate increased with progressive loading of the diaphragm and were both highly correlated to transdiaphragmatic pressure and diaphragm electric activity. We concluded that speckle tracking ultrasound is superior to conventional ultrasound techniques to estimate diaphragm contractility under inspiratory threshold loading and, although this requires further research, might serve as a reliable tool to guide weaning at the bedside in the future.

Chapters 4, 5 and 6 of this thesis focus on the interaction between the two parallel systems involved in providing adequate ventilation: the patient and more specific its upper airway, and the ventilator. We studied this interaction in patients with an acute exacerbation of COPD during noninvasive ventilation. This topic is initiated by reviewing, in **chapter 4**, the effect of positive pressure ventilation on upper airway patency and its possible clinical implications during NIV. First we emphasized the importance of not only the interaction between the inspiratory muscle activity and the ventilator's response, but during NIV mainly the synchrony between the ventilator and the upper airway muscles. Both pressure and flow receptors play an important role in muscle activity of the upper airway during respiration, whereas pulmonary C-fiber receptors, rapidly adapting receptors and slowly adapting pulmonary stretch receptors affect the patency of the upper airway. Although it is known in lambs and piglets that the patency of the upper airway is influenced by changes in pressure and flow during mechanical ventilation, we do not know whether this can be extrapolated to humans.

In **chapter 5** this is followed by studying the patency of the glottis during inspiration in patients with chronic obstructive pulmonary disease, during two modes and two levels of NIV. The electrical activity of the diaphragm, flow, pressure and video recordings of the glottis were synchronously acquired. From these video frames the angle of the vocal cords was calculated, as a measure of the patency of the upper airways. Patterns of glottis angle varied between and within patients. The median angle of the glottis during inspiration and at peak inspiratory effort were compared but no differences were found between PSV and NAVA at low and high levels of support. Although this pilot study showed no dependence of patency of the glottis on mode or level of NIV in COPD patients, it should be noted that COPD patients are prone to have harmed reflex pathways by CO_2 exposure during smoking, and thereby incomparable to lambs or healthy subjects.

The last chapter of this thesis, **chapter 6**, focused on patient-ventilator interaction. Synchrony between the patient and the ventilator, defined as a match between the patient and ventilator inspiratory and expiratory times, is at risk especially during NIV, due to the presence of leaks at the patient-mask interface. In NAVA mode, EA_{di} controls the ventilator and it has been shown that noninvasive NAVA improves

patient-ventilator interaction relative to equal inspiratory pressures during noninvasive PSV. Increasing invasive NAVA has been shown to result in significantly lower trigger delays compared to increasing PSV. Patient-ventilator interaction was evaluated by comparing airway pressure and EA_{di} waveforms with automated computer algorithms. We showed a progressive mismatch between neural effort and pneumatic timing with increasing levels of PSV during NIV. During noninvasive NAVA the patient-ventilator interaction improved and this was independent of increasing NAVA levels.

Samenvatting

Dit proefschrift richt zich op monitoring en regulatie van de ademhaling. Het belangrijkste doel is om beter inzicht te krijgen in de interactie tussen spontane ademhaling en mechanische ondersteuning van de ademhaling. In **hoofdstuk 2** onderzochten we het effect van metabole alkalose op de ventilatoire respons. In deze interventiestudie werd de ventilatoire respons gemeten bij 10 gezonde proefpersonen, met behulp van een hypercapnische ventilatoire respons (HCVR) test, voor en na toediening van een hoge dosis natriumbicarbonaat. Na toediening van bicarbonaat waren de transdiafragmale druk (P_{di}), electrische activiteit van het diafragma (EA_{di}) en minuutventilatie (V_E) significant lager voor vergelijkbare niveaus van inspiratoir CO_2. We hebben aangetoond dat wanneer het arterieel bicarbonaat niveau verhoogd is, de ademhalingscentra anders reageren op het inademen van CO_2, waarschijnlijk als gevolg van de verbeterde buffercapaciteit; meer arterieel bicarbonaat levert meer capaciteit op om CO_2 te bufferen voordat de ademhalingscentra een verhoogde arteriële CO_2 detecteren. Deze bevindingen impliceren dat patiënten met metabole alkalose, die lijden aan een verminderde ademdrang en daardoor problemen ondervinden tijdens het ontwennen van de beademing, baat zouden kunnen hebben bij excretie van bicarbonaat om zo de ademhalingscentra te stimuleren.

In **hoofdstuk 3** hebben we geanalyseerd of speckle-tracking echografie gebruikt kan worden om contractiliteit van het diafragma niet-invasief te kwantificeren. Een gerandomiseerde stapsgewijze inspiratoire belasting werd opgelegd aan gezonde proefpersonen. Speckle-tracking echografie werd gebruikt om vervorming (strain) en vervormingssnelheid (strain rate) van het diafragma te bepalen. De vervorming en vervormingssnelheid namen toe met de progressieve belasting van het diafragma en waren beide sterk gecorreleerd aan P_{di} en EA_{di}. We concludeerden dat speckle-tracking echografie superieur is aan conventionele echografie technieken om de contractiliteit van het diafragma te schatten tijdens inspiratoire belasting. Hoewel verder onderzoek vereist is, kan speckle-tracking echografie mogelijk een betrouwbaar hulpmiddel zijn bij het ontwennen van de beademing. Hoofdstukken 4, 5 en 6 van dit proefschrift richten zich op de interactie tussen de twee parallelle systemen die betrokken zijn bij adequate ondersteuning van de ademhaling: de patiënt en meer specifiek de bovenste luchtwegen, en de beademingsmachine. We hebben deze interactie bestudeerd in patienten met een acute exacerbatie van COPD tijdens niet-invasieve beademing.

In **hoofdstuk 4** is het effect bekeken van positieve druk beademing op de doorgankelijkheid van de bovenste luchtwegen en de mogelijke klinische implicaties tijdens NIV. Allereerst werd het belang benadrukt van niet alleen de interactie tussen de inspiratoire spieractiviteit en de respons van de beademingsmachine, maar

tijdens NIV vooral de synchronie tussen de beademingsmachine en de spieractiviteit in de bovenste luchtwegen. Zowel druk- als flowreceptoren spelen een belangrijke rol bij de spieractiviteit van de bovenste luchtwegen tijdens de ademhaling, en kunnen zo de doorgankelijkheid van de bovenste luchtwegen beïnvloeden. Hoewel het bij lammeren en biggen bekend is dat de doorgankelijkheid van de bovenste luchtwegen beïnvloed wordt door veranderingen in druk en stroming tijdens mechanische ventilatie, weten we niet of dit kan worden geëxtrapoleerd naar mensen.

In **hoofdstuk 5** volgt een studie naar de doorgankelijkheid van de glottis tijdens inspiratie bij patiënten met COPD, tijdens twee modi en twee niveaus van NIV. De elektrische activiteit van het diafragma, de luchtflow, druk aan de mond en video-opnamen van de glottis zijn synchroon geacquireerd. Uit de videoframes is de hoek van de stembanden berekend als een maat voor de doorgankelijkheid van de bovenste luchtwegen. Gedrag van de glottishoek varieerde onderling en binnen patiënten. De mediane hoek van de glottis tijdens inspiratie en tijdens de piek van de inspiratie zijn vergeleken, maar er zijn geen verschillen gevonden tussen PSV en NAVA bij lage en hoge niveaus van ondersteuning. Hoewel deze pilotstudie laat zien dat de doorgankelijkheid van de glottis niet afhankelijk is van de modus of het niveau van NIV bij COPD-patiënten, moet worden opgemerkt dat de reflexen van COPD-patiënten beschadigd kunnen zijn door CO_2-blootstelling tijdens het roken, en daarmee onvergelijkbaar zijn met lammeren of gezonde proefpersonen.

Het laatste hoofdstuk van dit proefschrift, **hoofdstuk 6**, is gericht op de interactie tussen patiënt en beademingsmachine. Synchronie tussen de patiënt en het beademingsmachine, gedefinieerd als een match van in- en expiratie tussen patiënt en beademingsmachine, is met name tijdens NIV in het geding, vanwege de kans op lekkage van het beademingsmasker. In de NAVA-modus bestuurt EAdi de beademingsmachine en het is aangetoond dat niet-invasieve NAVA de interactie tussen patiënt en machine verbetert ten opzichte van gelijke inspiratoire druk tijdens niet-invasieve PSV. Daarnaast is aangetoond dat toenemende ondersteuning tijdens invasieve NAVA resulteerde in significant minder vertraging van het triggeren van de beademingsmachine in vergelijking met het verhogen van PSV. De patiënt- beademingsmachine interactie is geëvalueerd door luchtwegdruk en EAdi-golfvormen te vergelijken door middel van geautomatiseerde computeralgoritmen. We toonden een progressieve mismatch aan tussen neurale inademing en pneumatische timing met toenemende niveaus van PSV tijdens NIV. Tijdens niet-invasieve NAVA verbeterde de patient- beademingsmachine interactie, onafhankelijk van toenemende NAVA niveaus.

9 Addenda

List of abbreviations

CF	Center frequency of the power spectrum
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CT	Cricothyroid
CV	Coefficient of variation
E_{di}	Electrical activity of the diaphragm
EA_{di}	Electrical activity of the diaphragm
FT	Fractional thickening
HCO_3^-	Bicarbonate
HCVR	Hypercapnic ventilatory response
ICU	Intensive Care Unit
MIP	Maximum inspiratory pressure
MV	Mechanical ventilation
NAVA	Neurally adjusted ventilatory assist
NIV	Noninvasive ventilation
NME	Neuromechanical efficiency
NVE	Neuroventilatory efficiency
P_{aw}	Airway pressure
P_{di}	Transdiaphragmatic pressure
P_{es}	Esophageal pressure
$P_{et}CO_2$	End-tidal carbon dioxide pressure
P_{ga}	Gastric pressure
$P_{insp}CO_2$	Inspiratory carbon dioxide pressure
P_{mo}	Mouth pressure
PSR	Pulmonary stretch receptor
PSV	Pressure support ventilation
RAR	Rapdily adapting receptor
ROI	Region of interest
RR	Respiratory rate
ST	Speckle tracking
TA	Thyroarytenoid
V	Volume
V'	Airway flow
V_t	Tidal volume
V_E	Minute ventilation

Co-authors

- Jonne Doorduin
  Department of Critical Care Medicine and Department of Neurology, Radboud university medical center, Nijmegen, the Netherlands
- Petra J Gooskens
  Department of Critical Care Medicine, Radboud university medical center, Nijmegen, the Netherlands
  Cardiovascular and Respiratory Physiology, University of Twente, Enschede, the Netherlands
- Lisanne H Roesthuis
  Department of Critical Care Medicine, Radboud university medical center, Nijmegen, the Netherlands
- Erik HFM van der Heijden
  Department of Pulmonology, Radboud university medical center, Nijmegen, the Netherlands
- Johannes G van der Hoeven
  Department of Critical Care Medicine, Radboud university medical center, Nijmegen, the Netherlands
- Peter H Veltink
  Biomedical Signals and Systems, University of Twente, Enschede, the Netherlands
- Leo MA Heunks
  Department of Critical Care Medicine, Radboud university medical center, Nijmegen, the Netherlands
  Department of Intensive Care Medicine, Amsterdam UMC, location VUmc, the Netherlands
- Nima Hatam
  Department of Thoracic and Cardio-Vascular Surgery, University Hospital RWTH Aachen, Germany
- Gernot Marx
  Department of Intensive Care, University Hospital RWTH Aachen, Germany
- Andreas Goetzenich
  Department of Thoracic and Cardio-Vascular Surgery, University Hospital RWTH Aachen, Germany
- Sebastian Fritsch
  Department of Intensive Care, University Hospital RWTH Aachen, Germany
- Christian S Brülls
  Department of Intensive Care, University Hospital RWTH Aachen, Germany
- Jeroen WH van Hees
  Department of Pulmonology, Radboud university medical center, Nijmegen, the Netherlands

List of publications

Oppersma E, Doorduin J, Gooskens PJ, Roesthuis LH, van der Heijden EHFM, van der Hoeven JG, Veltink PH, Heunks LMA. Glottic patency during noninvasive ventilation in patients with chronic obstructive pulmonary disease. Respir Physiol Neurobiol. 2018. doi: 10.1016/j.resp.2018.07.006. [Epub ahead of print]

Oppersma E, Doorduin J, van der Hoeven JG, Veltink PH, van Hees HWH, Heunks LMA. The effect of metabolic alkalosis on the ventilatory response in healthy subjects. Respir Physiol Neurobiol. 2018 Feb;249:47–53. doi: 10.1016/j.resp.2018.01.002.

Oppersma E, Hatam N, Doorduin J, van der Hoeven JG, Marx G, Goetzenich A, Fritsch S, Heunks LMA, Bruells CS. Functional assessment of the diaphragm by speckle tracking ultrasound during inspiratory loading. J Appl Physiol (1985). 2017 Nov 1;123(5):1063–1070. doi: 10.1152/japplphysiol.00095.2017.

Eijsvogel MM, Ubbink R, Dekker J, **Oppersma E**, de Jongh FH, van der Palen J, Brusse-Keizer MG. Sleep position trainer versus tennis ball technique in positional obstructive sleep apnea syndrome. J Clin Sleep Med. 2015 Jan 15;11(2):139–47. doi: 10.5664/jcsm.4460.

Oppersma E, Doorduin J, van der Heijden EH, van der Hoeven JG, Heunks LM. Noninvasive ventilation and the upper airway: should we pay more attention? Crit Care. 2013 Dec 5;17(6):245. doi: 10.1186/cc13141. Review.

Presentations at conferences

A novel method to evaluate upper airway patency during non-invasive ventilation
Oral presentation — NVvTG conference — 2013-10

De invloed van bicarbonaat op de ventilatoire drive in gezonde proefpersonen
Oral presentation — Nederlandse Intensivisten Dagen — 2016-01

Influence of bicarbonate on ventilatory drive in healthy subjects
Thematic poster discussion — ERS conference London — 2016-09

Speckle tracking echogaphy allows sonographic assessment of diaphragmatic loading
Thematic poster discussion — ERS conference London — 2016-09

The effect of metabolic alkalosis on the ventilatory response in healthy subjects
Oral presentation — MIRA day — 2016-11

Glottic patency during two levels of pressure support and neurally adjusted noninvasive ventilation in patients with acute exacerbation of chronic obstructive pulmonary disease
Thematic poster discussion — ESICM Lives Forum Madrid — 2018-05

Biography

Eline Oppersma was born on November 26th, 1987 in Enschede. She grew up in Hengelo and graduated from the gymnasium in 2005 at the Bataafse Kamp.

The same year she started to study Technical Medicine at the University of Twente, followed by the master Medical Signaling. She did clinical research internships in the Radboudumc in Nijmegen at the departments of Intensive Care and Clinical Neurophysiology and after that in the MST Enschede at the Pulmonary Function department and Neonatology. During her clinical internship in the last year of her education, she studied respiratory physiology at the pulmonary function department of the MST, and graduated with a thesis entitled *Pulmonary diffusion: searching for a new standard.*

In November 2011 she started to work as a teacher and researcher at the Technical Medicine program focused on respiratory physiology. Some months later she started a PhD-project in cooperation with the Intensive Care of the Radboudumc, which led to this thesis under supervision of prof. L.M.A. Heunks, prof. J.G. van der Hoeven and prof P.H. Veltink.

In 2015 she completed her University Teaching Qualification, won the educational prize of the faculty of Life, Science and Technology of the University of Twente and won an 'Excellence grant in physiology' for part of her work during the international conference of the European Respiratory Society in London in 2016. From November 2017 she became part of the new research group Cardiovasular and Respiratory Physiology, where she will continue to combine research and education.

Eline is married to Bob Mos and together they have a son, Pepijn.

Dankwoord

Daar is dan eindelijk het laatste hoofdstuk van mijn proefschrift: het dankwoord. Als je dat mag gaan schrijven, dan is het echt bijna klaar. Ik heb zo kunnen genieten van het onderzoek doen en het schrijven van dit proefschrift dankzij heel wat mensen, die ik graag wil bedanken.

Als eerste wil ik graag alle patiënten en proefpersonen die meegewerkt hebben bedanken. Zonder hun medewerking waren deze onderzoeken nooit mogelijk geweest.

Prof. dr. Leo Heunks, beste Leo, eind 2011 kwamen we met elkaar in contact en ik was direct enthousiast over al je onderzoeksplannen. Toen we vanaf 2012 samen gingen werken aan wat dit proefschrift zou worden, kwam ik er achter dat die bron van plannen onuitputtelijk is. Ik heb groot respect voor je wetenschappelijke kwaliteiten, je altijd kritische blik en opbouwende feedback. Al jouw bezigheden naast de klinische werkzaamheden, in combinatie met mijn niet zo standaard combinatie van onderzoek en onderwijs, maakten het niet altijd makkelijk om in contact te blijven. Maar er ligt een prachtig proefschrift en ik ben erg dankbaar voor al je hulp, inspiratie en enthousiasme de afgelopen jaren.

Prof. dr. Hans van der Hoeven, beste Hans, ook al was je niet mijn eerste aanspreekpunt, altijd als ik je sprak was je op de hoogte van mijn projecten en altijd wist je precies de goede kritische vragen te stellen. Ik heb daar grote bewondering voor. Je steun aan ons – toch nog steeds wel nieuwe – beroep is ontzettend waardevol en ik ben erg dankbaar dat ik mijn studies op jouw afdeling mocht uitvoeren.

Prof. dr. ir. Peter Veltink, beste Peter, je kwam na een aantal jaren als mijn promotor vanuit de UT erbij en ik heb erg veel van je geleerd. Het is voor mij als Technisch Geneeskundige ongelooflijk waardevol om naast de fysiologische blik, ook de technologische kijk op klinische problemen mee te nemen. Dankzij onze gesprekken en discussies kon ik mijn eigenheid als TG'er in dit proefschrift duidelijk profiel geven. Mijn dank daarvoor.

Grote waardering gaat ook uit naar alle co-auteurs, voor jullie commentaar dat ieder artikel beter heeft gemaakt.

De promotiecommissie, bestaande uit prof. dr. Gommers, dr. ir. De Jongh, prof. dr. ir. Van Putten en prof. dr. Wijkstra wil ik hartelijk danken voor het kritisch bestuderen van mijn proefschrift en het opponeren tijdens de openbare verdediging. Dr. Brülls, vielen Dank für Ihre Bereitschaft meine Dissertation kritisch zu lesen und für die Verteidigung nach Enschede zu kommen.

Beste IC research groep, bedankt voor de gezelligheid op jullie afdeling als ik in het Radboud ziekenhuis in Nijmegen was. Speciaal dank aan Yvonne Kaspers: altijd sta je klaar, zelfs voor een promovendus die zomaar aan komt waaien. Jij maakte dat ik me altijd welkom voelde! Jonne en Lisanne, ik vond het erg leuk om als TG'ers samen op de IC het beademings-onderzoek invulling te geven.

In 2011 studeerde ik af en mocht ik komen werken in het ECTM. Ik heb dit ervaren als een grote snoepwinkel: ik mocht een plek uitzoeken om onderzoek te doen, onderwijs geven over wat ik het allerleukste vond, en ook nog eens werken met de Human Patient Simulator. Remke, dank voor de vrijheid en het vertrouwen daarin! Ik ben alle collega's van TG en het ECTM dankbaar voor de prettige en gezellige omgeving om in te werken. Paul, jij wees me in 2011 op de vacature bij het ECTM. Ik ben blij dat je dit gedaan hebt en dat je altijd tijd maakt als ik je heldere psychologenblik weer eens nodig heb. Marleen, bedankt dat we de nadelen van het buitenbeentje zonder vakgroep zijn en de publicatieperikelen altijd kunnen delen. Erik ten Berge, wat werken wij al die jaren al fijn samen als dokter en TG'er. Ik vind jouw klinische blik zo waardevol in het onderwijs. Bedankt voor je interesse in mijn promotie en natuurlijk ook voor je interesse in Pepijn zijn eeuwigdurende hoest en snot in de winter!

Ik begon op een kamer bij Benno; een van de eerste bijna-TG'ers, ik bewonder hoe hard jij werkte. Van jou leerde ik dat onderwijs en onderzoek heel goed samen gaan, bedankt daarvoor! Daarna kwam Lex. Wat ben ik blij met jou als kamergenoot en vooral om je nu als paranimf naast me te hebben staan. Ik kan nog wat leren van jouw rust en relativeringsvermogen, dankjewel daarvoor. Vooral bedankt voor het aanhoren van al mijn frustraties de afgelopen jaren, zowel werk als privé. Ik vind het toch ook wel fijn dat je mijn babyverhalen over slaap- en poepritmes nu zelf ook ondervindt. Mathilde, bedankt voor je altijd optimistische toevoeging aan onze groep. Het is heel fijn om te weten dat jij altijd een oplossing bedenkt en voor de groep klaarstaat.

De 'Wij-TGers' appgroep bestaat niet voor niks. Ik ben blij met zo'n groep enthousiaste TG-collega's met wie we niet alleen de frustraties delen rondom de altijd lastige balans tussen onderwijs en onderzoek, maar ook de taart bij elke dubbel en dwars verdiende publicatie! Lex, Mathilde, Marije, Jordy, Erik en Tim – bedankt voor jullie gezelligheid! En Anique, wat zijn wij elkaar goed gaan snappen de afgelopen jaren, bedankt voor het altijd bieden van een luisterend oor!

Als ik iets doe, dan moet het ook tot in de perfectie geregeld zijn. Zo mooi als mijn proefschrift er nu uitziet, heb ik het echter niet zelf kunnen doen. Arthur, wat een prachtige stijl heb je voor me gecreëerd. Ik heb genoten van het proces om dit samen te maken, maar ik blijf toch ook zoeken naar die gimmick die je volgens mij ergens hebt verstopt...

Heleen, jouw visie heeft een belangrijke bijdrage geleverd aan mijn professionele ontwikkeling. Ik ben je dankbaar voor je ongekende doorzettingsvermogen om TG te ontwerpen en te blijven innoveren, maar vooral voor hoe je mij inspireert en altijd tijd maakt voor wijze lessen over de wereld en mezelf.

Lieve schoonfamilie, ik weet dat het niet altijd duidelijk is waar ik nou zo druk mee ben geweest, maar jullie gezelligheid als we elkaar zien heeft zeker bijgedragen aan dit proefschrift. Bedankt daarvoor! Lieve Joke en Alwy, ik heb het getroffen met

jullie als schoonouders. Ik heb me bij jullie altijd heerlijk thuis gevoeld en weet dat ik altijd verwend word als we bij jullie zijn. Dank jullie wel voor alle steun!

Lieve oma, ook al woon je niet in de buurt, gelukkig ben je altijd op de hoogte van hoe het met ons gaat. Dankjewel hiervoor, voor je interesse en natuurlijk voor de reisjes naar Marbella en alle verwennerij als we langskomen!

Zus, het is zover, je bent mijn elfje (hoezo 'paranimf'...) en wat ben ik daar blij mee. Hoewel we elkaar vroeger wel konden knijpen als we ruzie hadden, kunnen we nu echt niet meer zonder elkaar. Je bent er altijd voor mij en voor ons (het liefst vooral voor Pepijn dan) en daar prijs ik mezelf gelukkig mee. Ik geniet er enorm van dat Sven en jij, maar vooral Liam en Mats, zo dichtbij wonen en dat we na een dag werken even een espressootje samen kunnen drinken zodat de '3 broers' nog even met elkaar kunnen spelen.

Lieve papa en mama, ik zou nog een boek vol kunnen schrijven met wat jullie allemaal doen voor mij, waardoor ik kan doen wat ik wil. Zonder jullie had ik het niet gekund; niet zonder de praktische steun en oppas, maar bovenal niet zonder jullie eindeloze en onvoorwaardelijke geloof in mij. Jullie hebben er mede voor gezorgd dat ik kon worden wie ik ben en ik ben van plan nog van heel veel vakanties, etentjes en gezelligheid samen met jullie te genieten.

De allerbelangrijksten heb ik bewaard voor het laatst.

Lieve Pepijn, mijn kleine eigenwijze draak, ik zie je elke dag de wereld onderzoeken. Ik vind dat het allermooiste wat er is.

Lieve Bob, diepe dalen of grote euforie, met jou kan ik het aan. Jouw vertrouwen in mij en jouw kunst om te zeggen: "Komt wel goed, schatje", zijn terecht gebleken. Onze gezamenlijke kwaliteit om te genieten van het leven, van eten, drinken en vakantie vieren (en selfies maken) is mijn grootste geluk!