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Mask Continuous Positive Airway Pressure Increases Diaphragm Thickening Fraction in Healthy Subjects

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Keywords
Diaphragm thickening fraction · Ultrasound · Respiratory effort · Non-invasive ventilation · Continuous positive airway pressure

Abstract
Introduction: The most widespread treatment for obstructive sleep apnoea and obesity hypoventilation syndrome is continuous positive airway pressure (CPAP). The addition of inspiratory support is a potential alternative. This is a physiological study to determine the effect of CPAP and inspiratory support pressure on respiratory effort measured by diaphragm thickening fraction (DTF) in healthy volunteers. ***Methods:*** DTF was measured in spontaneously breathing, healthy volunteers during 4 phases: (I) without connection to a ventilator, (II) on a ventilator without any applied pressures, (III) with a CPAP of 5 cmH_2O, and (IV) with an additional inspiratory support pressure of 5 cmH_2O. ***Results:*** Twenty-nine individuals agreed to participate. DTF was similar during the first two phases (32 ± 13% and 35 ± 22%). A considerable increase in DTF to 51 ± 21% was noted in phase III. The introduction of inspiratory support pressure during phase IV led to a reduction in DTF back to 36 ± 23% ($p < 0.001$). Tidal volume and minute ventilation were both slightly higher in phase IV compared to phase III. ***Conclusion:*** CPAP without inspiratory support pressure increases respiratory effort measured by DTF in healthy subjects. Further research is required to investigate this phenomenon in a clinical setting.

Introduction

In obesity hypoventilation syndrome (OHS) and obstructive sleep apnoea (OSA), the application of nocturnal continuous positive airway pressure (CPAP) is an effective therapy [1, 2]. In both entities, an inspiratory pressure may be successfully added to provide non-invasive ventilation (NIV) [2, 3]. The differences in the effects of CPAP and NIV on the respiratory system are however inadequately understood in this context. Masa

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et al. found both NIV and CPAP to improve clinical symptoms and polysomnographic parameters in OHS with concomitant OSA, but NIV led to better results in spirometry, 6-min walk distance, and quality of life compared to CPAP [2]. In a study by Howard et al. [4], relevant differences between CPAP and NIV could not be shown, which may be attributable to the relevantly smaller cohort (57 vs. 221). Ishak et al. [3] demonstrated improved therapy adherence and symptom control of NIV in patients that had low CPAP adherence. One reason for the depicted findings might lie in the difference in respiratory effort between these modalities. Respiratory effort is increased in multiple aetiologies of acute or chronic respiratory failure. The term refers to the work required by the patient's muscles to achieve sufficient ventilation. Among all muscles contributing to the ventilatory pump, the diaphragm is the most important [5, 6]. Respiratory support may be used not only to increase oxygen supply but also to unload ventilatory muscles and reduce the respiratory effort through assisted or controlled ventilation. Sonographic measurement of the diaphragm thickening fraction (DTF) has been adapted to monitor respiratory effort during mechanical ventilation and weaning [7, 8], although multiple other methods are available for this purpose. The assessment of DTF in the context of non-invasive respiratory support is less well studied, although its ability to predict NIV failure has been shown [9, 10]. During non-invasive respiratory support, DTF is one of the few practicable ways to approximate respiratory effort as ultrasound is a bedside tool used to assist decision-making in a variety of critical care problems. The estimation of respiratory effort using oesophageal and gastral manometry in this setting has also been reported [11], although it demands additional equipment and expertise. The nasogastric probe required for this method may also interfere with the ventilation mask. Furthermore, a good correlation between the respiratory effort measured by manometry and DTF in invasive [12, 13] and non-invasive [14] pressure support ventilation has been found. One study has demonstrated the reduction of DTF by increasing inspiratory support pressures in post-extubation NIV [14].

In acute respiratory failure, CPAP may also reduce respiratory effort through antagonizing intrinsic PEEP and/or optimizing lung compliance [11, 15, 16]. However, its effect on respiratory effort in aetiologies with healthy lungs and diaphragm such as OSA and OHS remains unclear. To our knowledge, DTF has never been used to assess the effect of non-invasive CPAP and pressure support ventilation on respiratory effort. For this aim, we designed this physiological pilot study.

Materials and Methods

Study Design

This is a physiological study in healthy volunteers.

Test Methods

Voluntary participants were recruited from the University Medical Centre Mannheim and settled in semi-recumbent position with their torso elevated by a 30-degree incline. A mask for non-invasive respiratory support that covers mouth and nose was used. The first phase assessed baseline values. Thus, the mask was fastened but not connected to a ventilator. The second phase was designed to discriminate the impact of the airway resistance introduced by the respiratory circuit, i.e., ventilator, tubing, and heat and moisture exchange filter. The mask was connected to a HAMILTON-C3® (Hamilton Medical AG, Switzerland) turbine ventilator, with PEEP and inspiratory support pressure set to 0 cmH_2O. In the third phase, PEEP was set to 5 cmH_2O (i.e., CPAP). For the fourth phase, an inspiratory support pressure of 5 cmH_2O was added. Measurements were performed after 2 min in each phase, when subjects had adapted to the new setup and were breathing steadily.

Diaphragm ultrasound was acquired at the zone of apposition in the right mid-axillary line. B-Mode loops of three respiratory cycles were recorded for each measurement. End-inspiratory and end-expiratory diaphragm thickness (DT) was measured in each cycle. DTF was calculated as:

$$\mathrm{DTF} = 100 \times \left[\frac{(\text{endinspiratory DT}) - (\text{endexpiratory DT})}{(\text{endexpiratory DT})} \right]$$

The median DTF was documented. The investigators were not blinded to the study phases. Respiratory rates were recorded for all phases. Minute ventilation measured by the ventilator was recorded for phases 2–4. Tidal volume was calculated by division of minute ventilation by the respiratory rate. To monitor for potential correlation between subjective discomfort and DTF that may influence the findings, after the trial period, participants were asked to retrospectively rate their discomfort during each trial phase from 1 (no discomfort) to 5 (very uncomfortable).

Rationale for Recording B-Mode Instead of M-Mode Ultrasound

B-Mode and M-Mode acquisition of DT are reported methods for the measurement of DTF. When the diaphragm is not exactly perpendicular to the ultrasound beam, M-Mode measurements are distorted in relation to the extent of deviation from the 90° angle, leading to an overestimation of DT. The thickening fraction, being independent from absolute values, is unaffected when inspiratory and expiratory diaphragm measurements are performed at the same angle. However, any angular deviation between the two measurements leads to incorrect calculations of DTF. Thus, we opted for measurements of DT in the two-dimensional B-Mode.

Analysis

Statistical analyses were performed using IBM® SPSS® Statistics version 28.0.1.0 (IBM, Armonk, NY, USA). Qualitative variables are given in absolute numbers and group-related percentages. Metric variables are given as mean and standard deviation.

Differences between males and females were compared with a two-sided independent samples *t* test. Differences between measurements between phases were compared using the related-samples Friedman's two-way analysis of variance by ranks.

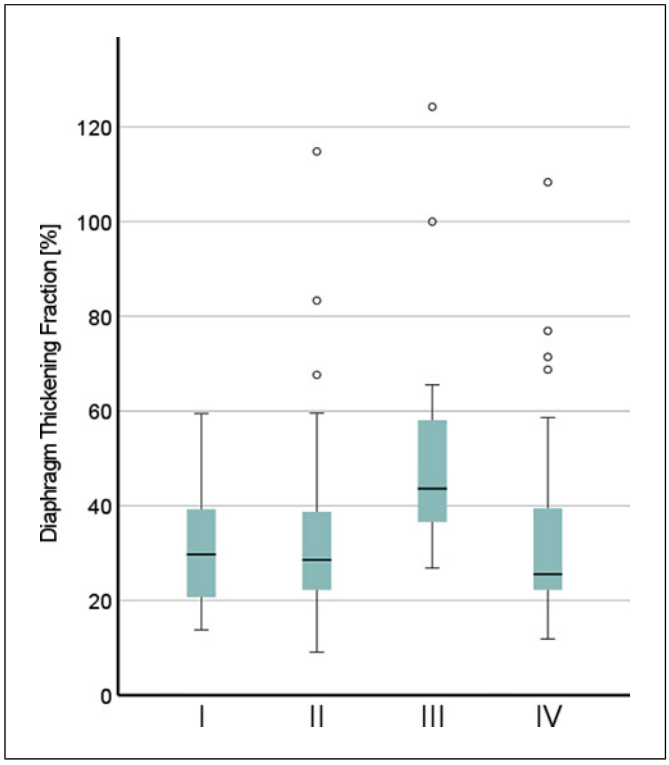

Fig. 1. Distribution of DTF during the four phases: (I) without connection to a ventilator, (II) on a ventilator without any applied pressures, (III) with CPAP, and (IV) with additional inspiratory support pressure. Circles mark data outliers. Between group difference: $p < 0.001$.

Results

Participants

Among the medical ICU staff and medical students, 29 healthy volunteers agreed to participate in this study. Mean age was 26 ± 5 years, mean body mass index 22 ± 2 kg/m^2, and 17 (59%) were female.

Baseline DT and DTF

Mean end-expiratory DT during breathing without connection to the ventilator was 1.6 ± 3 mm, and DTF was 32 ± 13%. Female participants had a thinner diaphragm than males (1.4 ± 2 mm vs. 1.8 ± 2 mm; $p < 0.001$) and a slightly higher DTF (34 ± 14% vs. 29 ± 12%; $p = 0.329$).

DT during the Trial Phases

DTF was similar during the first two phases (32 ± 13% and 35 ± 22%). An increase in DTF to 50 ± 21% was noted in the phase with CPAP (PEEP but without support pressure). The introduction of inspiratory support pressure during the fourth phase led to a reduction in DTF back to 36 ± 23% ($p < 0.001$) (shown in Fig. 1). Respiratory rates were similar in all phases (14 ± 3 bpm, 14 ± 2 bpm, 14 ± 3 bpm, 14 ± 4 bpm; $p = 0.833$) (shown in Fig. 2 a). Tidal volume per predicted body weight increased slightly from phases 2–4 (13.9 ± 4.1 mL/kg PBW, 14.3 ± 3.9 mL/kg PBW, 14.9 ± 3.7 mL/kg PBW; $p = 0.048$), as did minute ventilation (12.2 ± 2.9 L/min, 12.1 ± 2.7 L/min, 13.4 ± 2.3 L/min; $p = 0.005$) (shown in Fig. 2b, c).

Expiratory DT was similar throughout all phases (1.6 ± 0.3 mm, 1.7 ± 0.3 mm, 1.7 ± 0.3 mm, 1.7 ± 0.3 mm, $p = 0.079$), whereas inspiratory thickness was highest in the third phase (2.1 ± 0.4 mm, 2.3 ± 0.5 mm, 2.6 ± 0.5 mm, 2.3 ± 0.4 mm; $p < 0.001$) (shown in online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000535990).

Participant Discomfort during the Trial Phases

After the trial period, participants were asked to retrospectively rate their discomfort during each trial phase from 1 (no discomfort) to 5 (very uncomfortable). Discomfort levels increased during the trial period. Mean discomfort ratings were 1.6 (phase I), 2.1 (phase II), 2.5 (phase III), and 2.6 (phase IV).

Discussion

This physiological study assesses changes in respiratory effort induced by different modes of respiratory support in healthy volunteers using DTF. We found that during the third phase, DTF increased compared to the other phases. This increase was not accompanied by substantial changes in respiratory rate, tidal volume, or minute ventilation. DTF was reduced to baseline levels when an inspiratory support pressure was introduced, accompanied by slight increases in tidal volume and minute ventilation. Participant discomfort increased throughout all study phases but was similar in phases III and IV. This suggests that the increase in DTF may be attributable to an increased respiratory effort introduced by PEEP during CPAP that was alleviated when support pressure was added. The reasons for this finding are unclear. The increase in DTF cannot be ascribed to resistance in the breathing circuit as the ventilator was already connected in phase II. PEEP may have caused hyperinflation, leading to degraded respiratory system compliance. This should have been in effect during phase IV as well; however, the inspiratory support pressure of 5 cmH_2O may have been sufficient to reduce respiratory effort to baseline values.

In acute exacerbation of chronic obstructive pulmonary disease, CPAP has been shown to decrease diaphragmatic effort by antagonizing intrinsic PEEP [11]. How CPAP affects respiratory effort in other

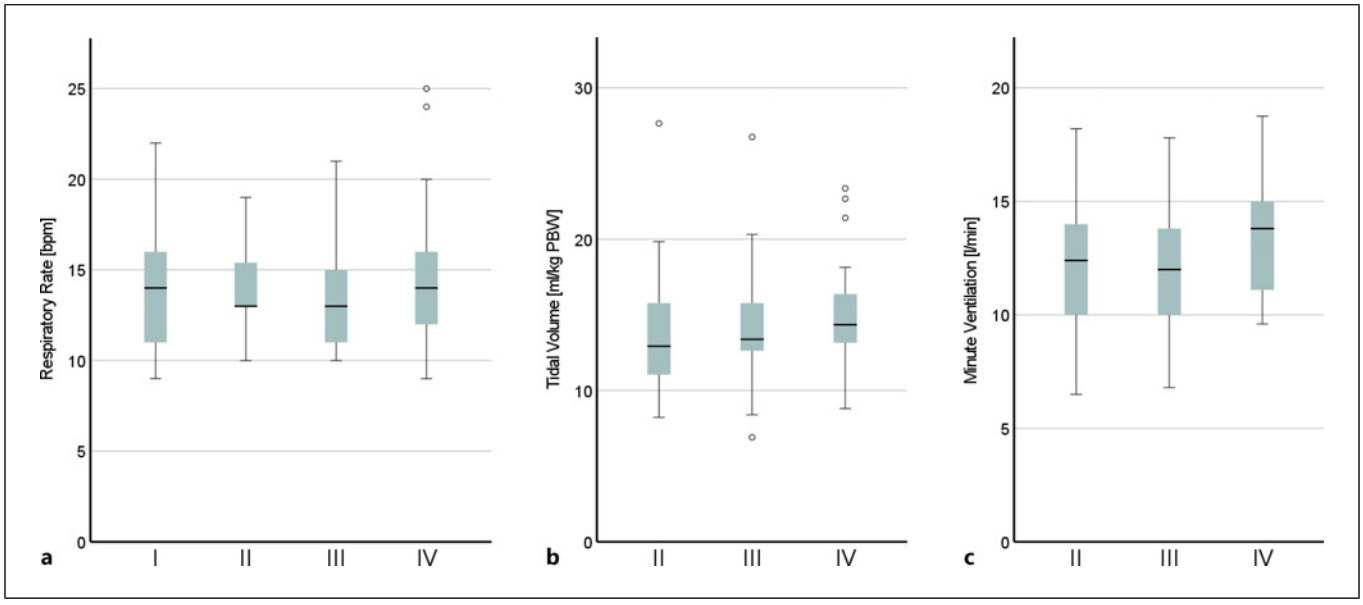

Fig. 2. Distribution of recorded variables during the four phases: (I) without connection to a ventilator, (II) on a ventilator without any applied pressures, (III) with CPAP, and (IV) with additional inspiratory support pressure. **a** Respiratory rate. Between group difference: $p = 0.833$. **b** Tidal volume. Between group difference: $p = 0.048$. **c** Minute ventilation. Between group difference: $p = 0.005$. Circles mark data outliers.

aetiologies remains unclear. Adequate levels of CPAP will lower upper airway resistance in OSA and OHS. However, as they usually present with healthy lungs, similar effects as found in our study may be expected on lung and diaphragm. Our findings might be explanatory to the differences between CPAP and NIV described in OSA and OHS, where increased respiratory effort in CPAP may lead to less favourable outcomes compared to NIV [2, 3]. Further studies are needed to support this hypothesis.

Still being far from routine practice, DTF is a promising tool in the context of non-invasive respiratory support. It has shown good correlation with other, more intricate tools for the quantification of respiratory effort [14] and may even predict failure of non-invasive respiratory support in acute respiratory failure [9, 10]. More investigations are needed to further explore and delimit the use of DTF. Formulation of target values would be helpful to guide the titration of support pressure.

Limitations of This Study

The main limitation of this physiological study is that measurements were performed in healthy, young subjects of normal weight and the relatively small sample size. The same sequence was applied in each subject, and investigators were not blinded to the study phases. No direct conclusions should be drawn for clinical practice and for the treatment of patients.

Conclusion

This physiological pilot study suggests that CPAP increases respiratory effort measured by DTF in healthy subjects. With the addition of pressure support, this effect could be alleviated. Future trials should investigate this phenomenon. Ultrasound assessment of DTF could be a valuable tool to optimize NIV.

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Statement of Ethics

This physiological study was conducted according to the principles of the 1964 Helsinki Declaration and its later amendments. The Ethics Committee II of the Heidelberg University and

medical faculty of University Medical Centre Mannheim approved the study protocol, approval number 2023-509. Written informed consent was obtained from all individual participants included in the study.

Conflict of Interest Statement

Daniel Duerschmied is supported by the German Research Foundation (DFG CRC1366 B08, Project #394046768, and CRC1425 P07, Project #422681845) and the German Centre for Cardiovascular Research (MaBo-05). All other authors have no conflicts of interest to declare.

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Author Contributions

Simon Lindner, Jan Teichert, Clara Hoermann, Julia D. Michels, Felix J. F. Herth, Daniel Duerschmied, and Simone Britsch contributed to the study conception and design and read and approved the final manuscript. Material preparation and data collection and analysis were performed by Simon Lindner, Jan Teichert, and Clara Hoermann. The first draft of the manuscript was written by Simon Lindner. Jan Teichert, Clara Hoermann, Julia D. Michels, Felix J. F. Herth, Daniel Duerschmied, and Simone Britsch commented on previous versions of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons. Anonymized data are available from the corresponding author upon reasonable request.

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