Safety and Feasibility of Noninvasive Electromagnetic Stimulation of the Phrenic Nerves

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BACKGROUND: Mechanical ventilation is widely used in ICU patients as a lifesaving intervention. Diaphragmatic atrophy and thinning occur from lack of contractions of the diaphragm during mechanical ventilation. It may prolong weaning and increase the risk of respiratory complications. Noninvasive electromagnetic stimulation of the phrenic nerves may ameliorate the atrophy seen with ventilation. The objective of this study was to show that noninvasive repetitive electromagnetic stimulation is safe, feasible, and effective to stimulate the phrenic nerves in both awake individuals and anesthetized patients. METHODS: A single-center study with 10 subjects overall, 5 awake volunteers and 5 anesthetized subjects. We used a prototype electromagnetic, noninvasive, simultaneous bilateral phrenic nerve stimulation device in both groups. In the awake volunteers, we assessed time-to-first capture of the phrenic nerves and safety measures, such as pain, discomfort, dental paresthesia, and skin irritation. In the anesthetized subjects, time-to-first capture as well as tidal volumes and airway pressures at 20%, 30%, and 40% stimulation intensity were assessed. RESULTS: Diaphragmatic capture was achieved in all the subjects within a median (range) of 1 min (1 min to 9 min 21 s) for the awake subjects and 30 s (20 s to 1 min 15 s) for the anesthetized subjects. There were no adverse or severe adverse events in either group, nor any dental paresthesia, skin irritation, or subjective pain in the stimulated area. Tidal volumes increased in all the subjects in response to simultaneous bilateral phrenic nerve stimulation and increased gradually with increasing stimulation intensity. Airway pressures corresponded to spontaneous breathing of ~2 cm H_2O. CONCLUSIONS: Noninvasive phrenic nerve stimulation can be safely performed in awake and anesthetized individuals. It was feasible and effective in stimulating the diaphragm by induction of physiologic and scalable tidal volumes with minimum positive airway pressures. *Key words: diaphragm; intensive care; muscle atrophy; phrenic nerve stimulation; prevention; respiratory muscles; ventilation.* [Respir Care 2023;68(5):602–610. © 2023 Daedalus Enterprises]

Introduction

Mechanical ventilation is used as a life-saving tool in patients with respiratory failure but has disadvantages, such as non-physiologic pulmonary pressures and rapid diaphragmatic atrophy. Most patients exhibit ventilator-induced diaphragmatic dysfunction as a direct effect of mechanical ventilation,[1-3] and this may adversely affect outcomes. Diaphragmatic dysfunction is often associated with extubation failure, prolonged mechanical ventilation, an increased risk of infection, damage to lung tissue attributable to high positive pressures from the ventilator, a longer stay in the ICU, and an increase in mortality.[4-7] One solution to address this is to preserve the diaphragmatic muscle with early induction of a training stimulus. Analysis of previously published data shows that relatively brief time periods of phrenic nerve stimulation reduces diaphragm atrophy.[8,9]

There is recent ongoing research in the area of phrenic nerve stimulation by invasive or partly invasive techniques.[10,11] Noninvasive phrenic stimulation has been the subject of study for decades,[12-14] with renewed interest in recent years.[15,16] Determining whether a patient will benefit from noninvasive stimulation devices is a clinical decision that is informed by the literature. Research has shown that diaphragmatic atrophy occurs within the first day of mechanical ventilation.[1-3] Therefore, to prevent diaphragmatic atrophy, very early induction of stimulation is necessary. Noninvasive techniques may be advantageous because they are applied and removed more quickly and easily than

invasive techniques. This study concentrated on a noninvasive technique of phrenic nerve stimulation. The objective of this study was to show that noninvasive electromagnetic stimulation, by using a ramp stimulation protocol, is safe and feasible with repetitive stimulation to the phrenic nerves. The stimulation generates physiologic diaphragm contractions that result in tidal volumes (V_T) with minimal positive pressures in both awake as well as anesthetized subjects.

QUICK LOOK

Current knowledge

Mechanical ventilation may lead to rapid diaphragmatic atrophy and can create injurious high pulmonary pressures. Early pilot studies in awake subjects showed that electromagnetic stimulation of the phrenic nerves may ventilate patients by active contraction of the diaphragm and thereby prevent atrophy. Noninvasive phrenic nerve stimulation by electromagnetic induction has not been tested in anaesthetized patients with a ramp-shaped stimulation protocol.

What this paper contributes to our knowledge

Noninvasive electromagnetic stimulation of the phrenic nerves was safe and feasible to generate contractions of the diaphragm muscle in awake and in anaesthetized subjects. We showed that this method could ventilate the subjects by producing V_T without producing positive pressures in the lung tissue.

Methods

Statement of Ethics and Study Approval

The research described in this study was conducted in accordance with the World Medical Association Declaration of Helsinki and the study protocol has been approved by the ethics committee of central and northwestern Switzerland, EKNZ (2021-00755), and Swissmedic (102651402). All the subjects gave written informed consent before study participation.

Study Registration

This study was registered on clincaltrials.gov before inclusion of the first subjects (NCT04884698).

Design and Study Population

This single-center safety and feasibility study investigated the activation of the diaphragm via electromagnetic stimulation of the phrenic nerves by using a novel device (STIMIT prototype, STMIT, Biel, Switzerland). The study was performed in 2 parts with 5 awake subjects and 5 anesthetized subjects on ventilation after elective surgery. Inclusion and exclusion criteria for both groups are shown in Table 1.

Investigational Device

The electromagnetic stimulation device STIMIT prototype is the first of its kind that uses a proprietary stimulation protocol with dual coils. These coils are designed to target the phrenic nerves simultaneously, gradually increasing stimulation, which creates a ramp. This device consists of a european conformity marked magnetic stimulator (Mag & More, Munich, Germany) and a dual-coil system (STIMIT) developed to produce a spatial electric field for phrenic nerve stimulation. Electromagnetic fields are induced by pulsed electrical currents flowing through a coil, which creates a transient local magnetic field, which depolarizes the phrenic nerves within a confined target region. This depolarization takes place with a frequency of 25 Hz, 2 s of train duration (0.5 s ramp and 1.5 s plateau), and individual intensity (100% corresponds to 2,365 volt), which activates the diaphragm noninvasively in a physiologic pattern to cause a contraction. In this study, stimulation intensities were chosen between 20% and 40%.

Procedures and Measurements

The study subjects received 2 visits. The first visit was to perform screening, which consisted of assessment of

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Table 1. Inclusion and Exclusion Criteria for the Awake and the Anesthetized Subject Groups

Criteria	Awake Subjects	Anesthetized Subjects
Inclusion criteria		
Age ≥ 18 y	×	×
Written informed consent given before participation	×	×
Planned for elective orthopedic surgery of the lower extremities with general anesthesia	NA	×
Exclusion criteria		
Chronic lung diseases	×	×
Known diaphragmatic weakness	×	×
Known neurologic conditions with motor weakness	×	×
Known paralysis of the phrenic nerves	×	×
Conditions that limit the mobility of the diaphragm	×	×
Skin lesions or infections or strictures in the neck area	×	×
Implanted electronic devices	×	×
Pregnancy	×	×
Persons deprived of liberty by administrative or judicial decision or under legal guardianship	×	×
Participation in another clinical trial in the 30 d preceding the study participation	×	×
Not able to read and understand German	×	×
Relevant preexisting conditions that correspond to the American Society of Anesthesiologists level III or higher	NA	×
Unstable patient after induction of anesthesia and intubation	NA	×

NA = not applicable

demographic information, medical history, and a physical examination by the study physician (EA). For women with childbearing potential, a pregnancy test was performed. The second visit was conducted before the study procedure. Informed consent was obtained from the subjects at this time. The study subjects were equipped with multiple sensors: a diaphragm pressure belt (Löwenstein Medical, Bad Ems, Germany) to monitor single-breath diaphragm excursions with different stimulation intensities, flow/pressure sensors in the ventilator tubing, and standard blood pressure, heart rate, and oxygen saturation sensors were placed on the upper arm and finger.

The awake subjects were breathing with a full face mask connected to a ventilator (Evita 600, Dräger Medical, Lübeck, Germany) in the volume-controlled intermittent mandatory mode with 0 cm H_2O PEEP and 3–4 cm H_2O pressure support to compensate for the resistance of the tube. The anesthetized subjects were all intubated for the surgery and connected to an anesthesia workstation (Atlan A350, Dräger Medical). Ventilator settings of the anesthetized subjects are described in the stimulation procedure. The measuring devices described above were used to determine the effectiveness of the stimulation. None of the measuring devices influenced the subject's ventilation. All devices were European conformity marked medical devices and were used within their respective intended use. The STIMIT prototype study device is a class IIa device under the Medical Device Regulation 2017/745, Rule 9. The critical respiratory parameters included airway pressure (P_{aw}), V_T, and maximum flow from the ventilator. The awake and the anesthetized subjects were monitored and recorded by a surveillance camera (Sonata, Löwenstein Medical). The recording provided documentation of all feedback signals. The technical study setup is shown in Figure 1.

Stimulation Procedure

On completion of the elective surgery, the anesthetized subjects' ventilation parameters were set to volume-controlled continuous mandatory ventilation mode. Before the start of the study-specific measures and procedures, hemodynamic and respiratory stability were verified. The contact surfaces of the coils were positioned over the phrenic nerves at the level of the lower third sternocleidomastoid muscle. Phrenic nerve capture was performed with single trains of simultaneous bilateral stimulations at 25 Hz of frequency, 2 s of train duration, and 20%–30% of intensity for the awake subjects and 30% of intensity for the anesthetized subjects. Capture was defined as an increase in V_T seen with electromagnetic stimulation of the phrenic nerves while the mechanical ventilator was set in spontaneous breathing mode with minimum pressure support of 2–4 cm H_2O in the awake subjects and spontaneous breathing mode with a PEEP of 0 cm H_2O in the anesthetized subjects.

Phrenic nerve capture was confirmed by abdominal palpation and/or a change in ventilator pressure and flow curves. When capture was not found or diaphragm contraction was

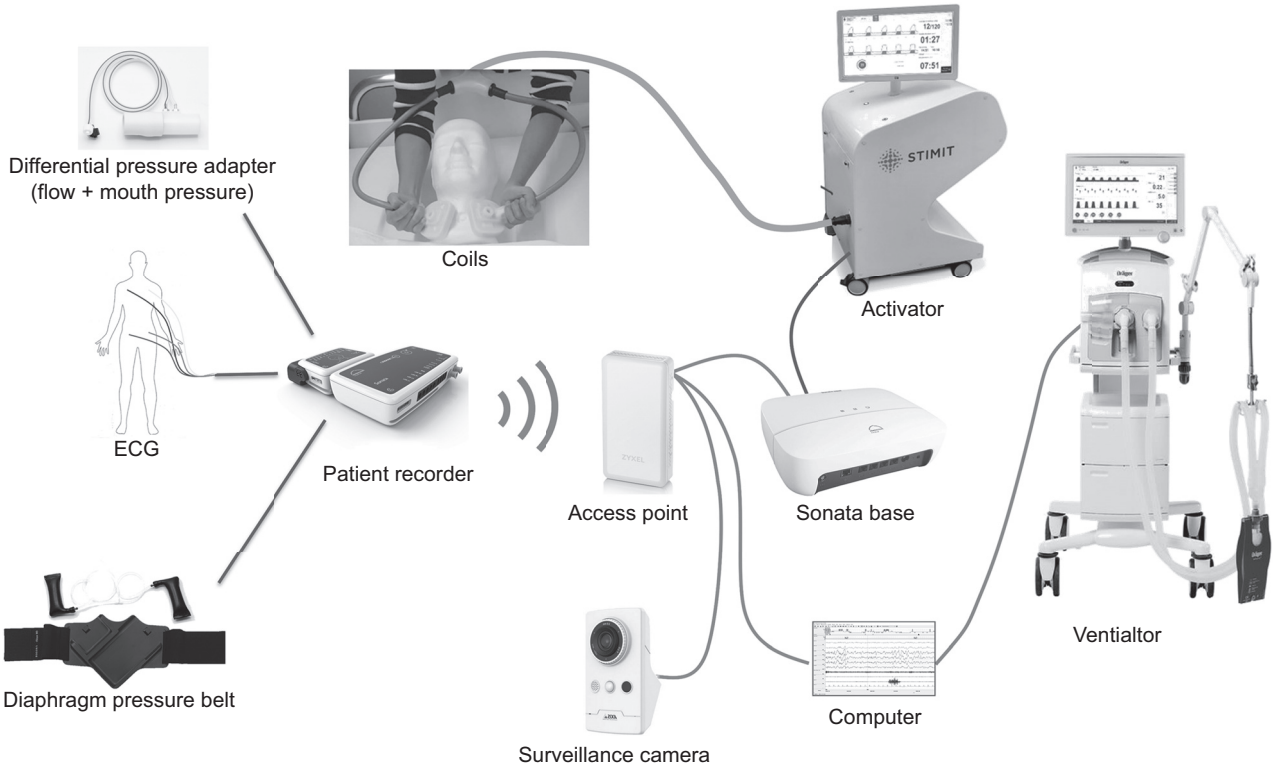

Fig. 1. Technical study setup. ECG = electrocardiography.

not sufficient, readjustment of the coils and/or an increase in stimulation intensity was made until adequate diaphragm contraction was achieved. The time to find optimal capture of the phrenic nerve in the neck area was measured by a conventional stopwatch. Time was calculated from the start of phrenic nerve capture search until 2 persons (GM, SK) confirmed a clear visible or palpable contraction of the diaphragm and effects of the stimulation on the flow curves seen on the ventilator. Typically, several stimulation cycles were necessary.

After phrenic nerve capture was confirmed, 3 different sets of 10 breaths each were recorded:

(1) 10 consecutive ventilator-induced breaths for baseline values (procedure I, no stimulation).
(2) 10 stimulated breaths with manual stimulation of every second breath (procedure II, stimulation plus mechanical ventilation).
(3) 10 consecutively stimulated breaths (procedure III, stimulation only, ventilator off).

For the awake subjects, procedures II and III were performed with the same stimulation intensity as phrenic nerve capture was successful. For the anesthetized subjects, procedures II and III were performed 3 times each at 20%, 30%, and 40% stimulation intensity. Ventilator settings in the anesthetized subjects for procedures I and II were set to the volume-controlled continuous mandatory ventilation mode, PEEP of 5 cm H_2O with peak inspiratory pressure to achieve a V_T of 6–8 mL/kg body weight (peak inspiratory pressure of 12–22 cm H_2O); for procedure III, the ventilator was set to the spontaneous breathing mode, with 0 cm H_2O PEEP. The pause duration between the stimulation trains were adjusted to accommodate individual breathing patterns. For the awake subjects, stimulation was applied at the beginning of the inspiration and continued until the beginning of the expiration. For the anesthetized subjects, the time of stimulation duration/pause duration were set to 1:2 to 1:1.5 (eg, 2-s stimulation/4-s pause or 2-s stimulation/3-s pause) to maintain the breathing frequency between 12 and 16 breaths/min. For the anesthetized subjects, when the ventilator was off (procedure III), each trigger for induction of stimulation has been performed manually by directly interfacing with the stimulator device.

Measured Safety Parameters

The following were continually assessed in both groups during and after the procedure: vital signs that consisted of blood pressure, heart rate, electrocardiogram, and oxygen saturation. Skin reaction in the stimulated area and collateral muscle stimulation was also assessed. Additional monitoring for the awake subjects included subjective pain (1–10), discomfort measured by a visual analog scale (from 0 to 10),

and before and after procedure paresthesia in the dental area (awake subjects). Adverse events (AE) or severe AEs (SAE) were assessed as well for each subject and all the procedures. The definitions of AEs and SAEs are the following:

AEs: AEs are all unexpected medical problems that happen during treatment.

SAEs: SAEs include AEs that result in death, require either in-patient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or major disability and/or incapacity, or result in a congenital anomaly and/or defect.

Outcome Measures

The primary outcomes for both groups included any AEs or SAEs. Moreover, for the awake subjects, the level of pain and subjective discomfort during the whole procedure was assessed. For the anesthetized subjects, the change in P_{aw} during stimulation was an additional assessed safety measure. Secondary outcome measures for both groups were the time until first capture of the phrenic nerves, oxygen saturation, blood pressure, and heart rate before and after stimulation. Additional outcome measures for the awake subjects were the following: stimulation-induced local skin reactions or muscle activation that led to paresthesia in the dental area. For the anesthetized subjects, additional outcome measures were the following: diaphragmatic contraction at 20%, 30%, and 40% stimulation intensity at the optimal stimulation site, with 25 Hz and 2-s stimulation time measured as generated V_T, maximum flows per breath and diaphragm belt excursions. All data were documented in paper case report forms and entered by the study staff into the electronic database secuTrial (Interactive Systems GmbH, Berlin, Germany) after completion of the study procedure.

Statistical Analysis

Due to the small number of subjects, the study data were analyzed descriptively. The awake subjects and the anesthetized subjects were analyzed separately. Data are reported as median (range) for continuous variables and frequency (%) for categorical and ordinal data, and were analyzed using SPSS v 25 (IBM, Armonk, NY). Applied stimulation intensity (output power %) in relation to diaphragmatic contraction (measured by relative breath volume, ie, mL/kg body weight) was calculated for the anesthetized subjects. For procedure II, the difference of the critical respiratory parameters (V_T, maximum flow, and P_{aw}) with and without phrenic nerve stimulation (every second breath stimulated) were calculated to demonstrate the effect of the stimulation. The following equations were applied:

$$\Delta V_T = V_T \text{ stimulation} - V_T \text{ without stimulation}$$

$$\Delta \text{Relative } V_T = (V_T \text{ stimulation} - V_T \text{ without stimulation})/\text{weight}$$

$$\Delta \text{Maximum flow (F)} = \text{F stimulation} - \text{F without stimulation}$$

$$\Delta P_{aw} = P_{aw} \text{ stimulation} - P_{aw} \text{ without stimulation}$$

To gather points of interest (peak diaphragm belt extension), the MATLAB 2021 software from MathWorks (Natick, MA), was used to automatically detect peak values of the belt sensor. This method aids in capturing the values of interest quickly and precisely. The same has been done with the flow and pressure signals to confirm the values obtained by the ventilators.

Results

Demographics

Inclusion of the awake subjects started on June 26, 2021 (first subjects in), and assessments of the last anesthetized subjects were completed on December 13, 2021 (last subjects out). Five awake and 5 anesthetized subjects were included in this study. The 5 awake subjects consisted of 3 male and 2 female volunteers, with a median (range) age of 45 (26–57) y, height 184 (156–188) cm, and weight 75 (52–107) kg. Of the 5 anesthetized subjects, 4 men and 1 woman, with a median age of 58 (45–63) y height 182 (174–187) cm, and weight of 90 (75–102) kg.

Safety Measures

There were no AEs or SAEs in either group. There was no dental paresthesia, skin irritation, or subjective pain in the stimulated area of the awake subjects. The subjective discomfort by using the visual analog scale during the procedures in the awake subjects was the following: 1.2 (0–4.1) after the time-to-capture assessment, 0.2 (0.1–6.2) after procedure II, which consisted of 10 stimulation cycles of every second breath; and 1.1 (0–5.8) after procedure III, which consisted of 10 consecutive stimulated breaths. No cardiac arrhythmias were observed on electrocardiogram recordings, no signs of glottis closure that resulted in the sudden stop of stimulated breaths and no relevant changes in blood pressure or oxygen saturation. Stimulation bursts had no effects on electrocardiogram recordings. There was a minimal amount of co-stimulation of local muscles and the brachial plexus at 30% or 40% stimulation intensity. Co-stimulation effects resulted in individual small movements, dependent on the exact positioning of the stimulation coils. These movements included shoulder and/or arm

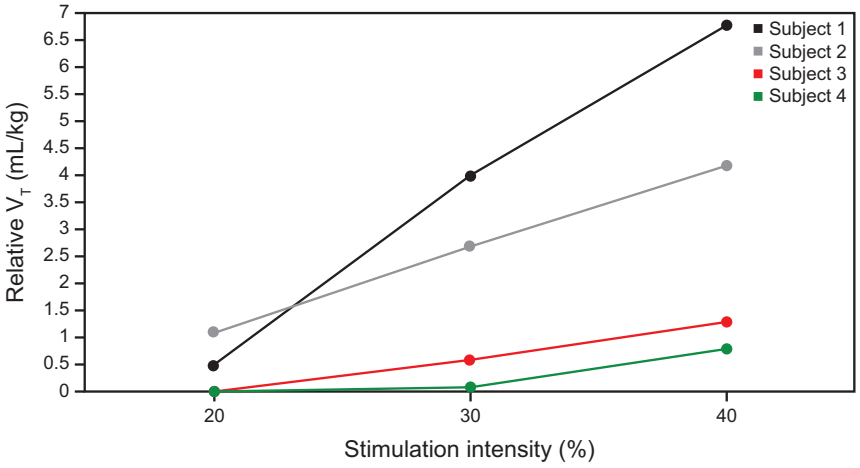

Fig. 2. Individual relative tidal volumes generated during procedure III at the selected stimulation intensity.

Table 2. Anesthetized Subjects, Differences Between Stimulated and Not Stimulated Breaths ($n = 5$)*

Intensity, %	Tidal Volume, mL	Maximum Flow, L/min	Airway Pressures, cm H_2O	Diaphragm Belt Excursion, mV
20	167 (19–280)	8.9 (0.5–16.2)	1.5 (0.1–2.7)	13.1 (9.2–25.5)
30	239 (141–369)	16.8 (6.8–25.7)	2.6 (1.6–3.0)	16.4 (12.2–27.9)
40	324 (252–423)	20.5 (13.3–34.1)	3.9 (2.8–4.4)	25.5 (14.2–34.7)

Data are median (range) unless otherwise noted.
*Difference between stimulated and not stimulated breaths during ventilation of procedure II.

Table 3. Anesthetized Subjects, Stimulated Breaths Without Ventilation (10 consecutive breaths) of Procedure III ($n = 4$)

Intensity, %	Tidal Volume, mL	Maximum Flow, L/min	Airway Pressures, cm H_2O	Diaphragm Belt Excursion, mV
20	21 (0–106)	8.1 (0.0–13.4)	1.0 (0.0–2.0)	5.8 (0.0–14.5)
30	166 (14–332)	17.8 (8.0–29.7)	2.0 (0.6–2.0)	15.5 (2.3–31.4)
40	279 (80–557)	24.1 (16.8–36.5)	2.0 (1.5–2.0)	13.3 (6.0–37.2)

Data are median (range) unless otherwise noted.

movements or contractions of local neck muscles. When observed co-stimulation patterns were noted, these were not deemed uncomfortable in the awake patient group. The procedures were continued without interruptions in both groups.

Phrenic Nerve Stimulation

The time-to-first capture was 1 min (60 s to 9 min 21 s) for the awake subjects and 30 s (20 s to 1 min 15 s) for the anesthetized subjects, which resulted in 25% (20%–40%) and 30% stimulation intensity, respectively. In procedure II, the awake subjects demonstrated a median of 25% stimulation intensity, the difference (Δ) in V_T between stimulated and non-stimulated breaths was 191 (27–405) mL. The differences in maximum flows were 9.9 (0.4–17.1) L/min and no differences were observed in P_{aw} 0.05 (0.02–0.47) cm H_2O between stimulated and non-stimulated breaths. No differences in stimulated breaths between procedure II (every second breath stimulated) and procedure III (10 consecutive breaths stimulated) were observed for volumes, maximum flows and P_{aw}.

In the anesthetized subjects, V_T increased gradually with increasing stimulation intensity but with large inter-individual variability (Fig. 2). Respiratory values for the investigated intensities at 20%, 30%, and 40% are detailed in Table 2 (procedure II) and Table 3 (procedure III). In 1 anesthetized subject, during procedure III, the ventilator settings were set on spontaneous breathing mode with a PEEP of 10 cm H_2O instead of 0 cm H_2O. When PEEP is set at 10 cm H_2O, functional residual capacity is elevated in comparison with 0 cm H_2O PEEP. As a result, the inspiratory capacity is decreased, which may lead to reduced V_T. For this reason, the subject was excluded from analysis of procedure III data. Individual pressure-volume curves of the anesthetized subjects in the baseline procedure I, without

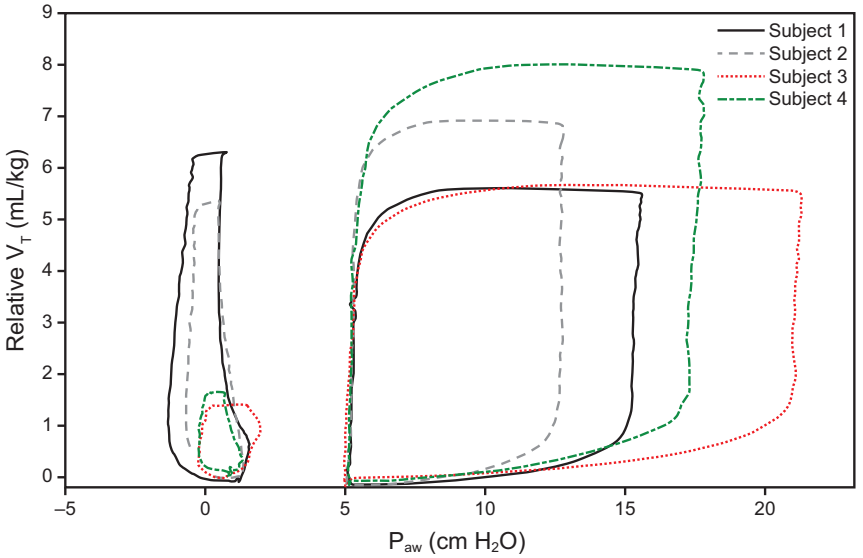

Fig. 3. Pressure-volume loops (mL/kg body weight) of the anesthetized subjects. Right loops: procedure I (ventilated, without stimulation); and left loops: procedure III (stimulated without ventilation), at 40% stimulation intensity. The shown curves are means over 10 breaths of the 4 subjects with PEEP set to 0 cm H_2O.

stimulation, in volume-controlled continuous mandatory ventilation mode, and in procedure III at 40% stimulation intensity in spontaneous breathing mode are shown in Figure 3.

Discussion

Results establish that noninvasive, magnetic phrenic nerve stimulation is safe and capable of generating repetitive diaphragmatic contractions in awake and anesthetized subjects. Higher V_T are generated with increasing stimulation intensities; however, large inter-individual differences were observed. This correlates with recently published studies on noninvasive electric[15] or electromagnetic[16] phrenic nerve stimulation. Both studies reported large inter-individual differences.[15,16] The abstract by Panelli et al[16] shows that individuals who are obese required even higher stimulation intensities (50%) to achieve a sufficient V_T.

Safety

Analysis of the data showed that no AEs or SAEs occurred in either group for any interventions. No skin irritation, cardiac arrhythmia, signs of glottis closure, extreme changes in blood pressure or oxygen saturation were detected in any of the 10 included subjects. The study by Sander et al[14] reported dental paresthesia after electromagnetic stimulation, whereas none of our awake subjects reported any signs of dental paresthesia. This could be due to a slightly lower stimulation intensity and more targeted magnetic field that resulted from a new smaller coil design and the ramp-shaped stimulation protocol.[17] Co-stimulation resulted mostly in the shoulder, arm, or local neck muscles, which produced minimal movement. According to the subjective rating of the awake subjects, none of these effects were disturbing and the procedures could be continued. Subjective pain and discomfort in the stimulated area was minimal, hence application of this procedure may also be possible in an ICU setting with patients partially sedated or awake.

P_{aw} and V_T

This study showed that the generation of physiologic diaphragm-induced breathing volumes without generation of relevant pulmonary positive pressures was possible by noninvasive phrenic nerve stimulation in the anesthetized subjects applied with or without mechanical ventilation. In the future, noninvasive phrenic stimulation might be used to ameliorate detrimental effects of positive-pressure ventilation on the diaphragm. Overstimulation may generate excessive V_T, and we should be cognizant of creating volutrauma by limiting volumes to 4–6 mL/kg body weight.

Volumes generated by a set stimulation intensity substantially varied between individuals. They increased in a linear fashion between 20% and 40% stimulation intensity (Fig. 2). These findings are consistent with Panelli et al[16] who used similar stimulation devices in subjects who were obese. These subjects required intensities of up to 50% to reach physiologic breathing volumes.[16] The V_T generated by electromagnetic phrenic nerve stimulation is a simple easy-to-measure parameter, which may indicate the strength of diaphragmatic contraction. To address this, a diaphragm pressure belt was mounted and showed diaphragmatic movement increases with increasing stimulation intensity (Tables 2 and 3). Exceptions may exist in patients

with chest wall stiffness or other diseases. Keogh et al[15] showed comparable breathing volumes that resulted from electric phrenic nerve stimulation in another recently published study. Research on noninvasive phrenic nerve stimulation techniques demonstrated potential clinical value for ICU patients on ventilation. As technology advances, an increase in clinical implementation may be realized.

Limitations

This pilot study was limited by its small size, and, therefore, the generalized applicability of the results obtained is limited. Analysis of 10 subjects showed the ability to noninvasively stimulate the phrenic nerve may vary substantially among individuals due to differences in body habitus.

Potential Clinical Benefits of Noninvasive Phrenic Nerve Stimulation

Application of phrenic nerve stimulation on mechanically ventilated ICU patients may preserve or even improve diaphragm thickness and function with regular training sessions and thereby prevent ventilator-induced diaphragmatic dysfunction.[10] Decreased weaning times as well as lower rates of respiratory infections may result. Ventilation by stimulation of the phrenic nerves is physiologically more appropriate than mechanical ventilation and may result in lower P_{aw} than during mechanical ventilation (Fig. 3). This technology may further reduce lung stress and strain during stimulated breaths with reduced high positive P_{aw}, which can cause damage to the lung tissue. Patients may benefit from reduced pressures if ventilation is achieved solely with stimulation. When noninvasive phrenic stimulation is applied instead of mechanical ventilation or as a supplement to long-term ventilation, several other factors should be considered: first, induction of diaphragmatic fatigue with overstimulation; second, the prevention of pressure areas; and third, movement that resulted in loss of phrenic capture. Work is being done to develop a special headset to fix the coils in the optimal position for stimulation. In the absence of continuous application, diaphragm stimulation may still result in potentially better recruitment of dorsal alveoli and reduce dorsal atelectasis, improving gas exchange.[18] Additional positive effects may include reduced hippocampal inflammation and increased venous return.[18]

Conclusions

Noninvasive phrenic nerve stimulation can be safely performed in both awake and anesthetized subjects. It was effective in stimulating the diaphragm by induction of physiologic and scalable V_T and only minimal positive P_{aw}. Diaphragm capture was achieved within 1 min. This method may have the potential to ventilate patients with 2 principle advantages: (1) by not producing positive P_{aw}, and (2), the preservation of the diaphragm muscle and its contractility. Future clinical trials in patients with respiratory failure are needed to determine clinical efficacy and safety.

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