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Impact of unilateral denervation on transdiaphragmatic pressure

Luther C. Gill[a], Carlos B. Mantilla[a,b], Gary C. Sieck[a,b,*]

[a] Department of Physiology and Biomedical Engineering, Mayo Clinic, 200 First Street SW, Rochester, MN, USA
[b] Department of Anesthesiology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

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ABSTRACT

The diaphragm muscle (DIAm) has a large reserve capacity for force generation such that in rats, the transdiaphragmatic pressure (Pdi) generated during ventilatory behaviors is less than 50% of maximal Pdi (Pdi_{max}) elicited by bilateral phrenic nerve stimulation. Accordingly, we hypothesized that following unilateral denervation (DNV), the ability of the contralateral DIAm to generate sufficient Pdi to accomplish ventilatory behaviors will not be compromised and normal ventilation (as determined by arterial blood gas measurements) will not be impacted, although neural drive to the DIAm increases. In contrast, we hypothesized that higher force, non-ventilatory behaviors requiring Pdi generation greater than 50% of Pdi_{max} will be compromised following DIAm hemiparalysis, i.e., increased neural drive cannot fully compensate for lack of force generating capacity. Pdi generated during ventilatory behaviors (eupnea and hypoxia (10% O_2)–hypercapnia (5% CO_2)) did not change after DNV and arterial blood gases were unaffected by DNV. However, neural drive to the contralateral DIAm, assessed by the rate of rise of root mean squared (RMS) EMG at 75 ms after onset of inspiratory activity (RMS_{75}), increased after DNV ($p < 0.05$). In contrast, Pdi generated during higher force, non-ventilatory behaviors was significantly reduced after DNV ($p < 0.01$), while RMS_{75} was unchanged. These findings support our hypothesis that only non-ventilatory behaviors requiring Pdi generation greater than 50% of Pdi_{max} are impacted after DNV. Clinically, these results indicate that an evaluation of DIAm weakness requires examination of Pdi across multiple motor behaviors, not just ventilation.

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1. Introduction

Mechanical activation of the diaphragm muscle (DIAm) mediates airflow into the lungs by generating a pressure difference across the muscle—transdiaphragmatic pressure (Pdi). Previous work from our lab in cats (Fournier and Sieck, 1988b; Sieck and Fournier, 1989), hamsters (Sieck, 1994), rats (Mantilla et al., 2010) and more recently in mice (Greising et al., 2013) used Pdi measurements to estimate DIAm force generation across a range of ventilatory (rhythmic gas exchange) and higher force, non-ventilatory behaviors. In these studies we found that Pdi generated during ventilatory behaviors is consistently less than 50% of maximal Pdi (Pdi_{max}) elicited by bilateral phrenic nerve stimulation. For example, Pdi generated during quiet rhythmic breathing (eupnea) ranged from 10% to 27% of Pdi_{max} depending on species (Greising et al., 2013; Mantilla et al., 2010; Sieck and Fournier, 1989; Watchko et al., 1986). Stimulating breathing by exposure to a hypoxic–hypercapnic (10% O_2–5% CO_2) gas mixture increased Pdi generated during ventilatory behaviors; however, Pdi never exceeded 36% of Pdi_{max} across several species (Greising et al., 2013; Mantilla et al., 2010; Sieck and Fournier, 1989; Watchko et al., 1986).

Although lung inflation may result, the goal of higher force, non-ventilatory behaviors of the DIAm is not gas exchange. Often DIAm activation during these behaviors is preparatory for expulsive airway clearance, e.g., coughing or sneezing. The Pdi generated during higher force, non-ventilatory behaviors is substantially greater than that generated during ventilatory behaviors (Greising et al., 2013; Mantilla et al., 2010; Sieck and Fournier, 1989; Watchko et al., 1986). For example in cats, mechanical stimulation of the oropharynx induces a gagging/coughing behavior in which Pdi approximates Pdi_{max} (Sieck and Fournier, 1989). Also in cats, the Pdi generated during sneezing induced by mechanical stimulation of the nasopharynx was found to be maximal (comparable to Pdi_{max}). Similarly in rats, a sneezing behavior induced by intranasal injection of capsaicin is associated with generation of near maximal Pdi (94% of Pdi_{max}) (Mantilla et al., 2010). The Pdi's generated during other higher force, non-ventilatory behaviors of the DIAm are

* Corresponding author at: Department of Physiology and Biomedical Engineering, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.
Tel.: +1 507 284 6850; fax: +1 507 255 7300.
E-mail address: Sieck.Gary@mayo.edu (G.C. Sieck).

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also greater than during ventilatory behaviors. For example, during sustained airway occlusion, Pdi ranges from 43% to 70% of Pdi_{max} across species (Greising et al., 2013; Mantilla et al., 2010; Sieck and Fournier, 1989; Watchko et al., 1986).

The DIAm comprises separate left and right hemidiaphragms, each with its own phrenic nerve innervation, with no crossover of innervation (Fournier and Sieck, 1988a). Accordingly, unilateral denervation (DNV) (Argadine et al., 2009; Geiger et al., 2001; Gosselin et al., 1994; Sieck, 1994; Sieck and Zhan, 2000) induces DIAm hemi-paralysis, reducing maximum force generating capacity of the DIAm by ~50%. We hypothesized that following unilateral DNV, the ability of the contralateral DIAm to generate sufficient Pdi to accomplish ventilatory behaviors will not be compromised and normal ventilation (as determined by arterial blood gas measurements) will not be impacted, although neural drive to the DIAm increases. In contrast, we hypothesized that those higher force, non-ventilatory behaviors requiring Pdi generation greater than 50% of Pdi_{max} will be compromised following DIAm hemiparalysis, i.e., increased neural drive cannot compensate for lack of force generating capacity.

2. Methods

All experiments were approved by the Institutional Animal Care and Use Committee of the Mayo Clinic. A total of 18 adult, male Sprague-Dawley rats (300–350 g) from Harlan Laboratories (Indianapolis, IN) were used for this study. Rats were anesthetized via intramuscular ketamine (90 mg/kg) and xylazine (10 mg/kg) injections for all experimental procedures. Animals were randomly assigned to either the sham control ($n = 6$) or DNV ($n = 6$) groups. Additional animals ($n = 6$) were used to measure changes in ventilatory parameters and blood gases before and after DNV.

2.1. Denervation

The right phrenic nerve was isolated in the lower neck and sectioned. A 10–20 mm length of the nerve was removed to ensure complete DIAm DNV. In all animals, DIAm hemiparalysis was verified by the absence of EMG activity in the ipsilateral (right) DIAm. The sham group underwent a similar surgical procedure as the animals in the DNV group, but the right phrenic nerve remained intact.

2.2. Transdiaphragmatic pressure measurements

Measurements of Pdi were performed based on the difference between esophageal and gastric pressures as previously described (Fournier and Sieck, 1988a; Greising et al., 2013; Mantilla et al., 2010; Sassoon et al., 1996; Sieck and Fournier, 1989; Watchko et al., 1986). In anesthetized animals, two 3.5 French Millar solid-state pressure catheters (SPR-524; Millar Instruments, Houston, TX) were inserted through the mouth into the esophagus and stomach, spanning the thoracic and abdominal borders of the DIAm, respectively. Correct catheter position was determined based on the direction of signal deflection and postmortem analysis. Measurements were collected during the following conditions and sequence: (1) breathing of room air (eupnea) for 5 min, (2) exposure to a hypoxia (10% O_2)–hypercapnia (5% CO_2) gas mixture for 5 min, (3) sustained airway occlusion (by covering nose and mouth for ~40 s), (4) maximum Pdi (Pdi_{max}) obtained by supramaximal bilateral phrenic nerve stimulation (using a stimulus isolation unit to control the current pulse) at 75 Hz (0.5 ms duration pulses in 300 ms trains repeated each s) using bipolar electrodes (FHC, Bowdoin, ME); and (5) sneezing, induced by intranasal infusion of 10 μl of 30 μM capsaicin. Measurements were also obtained when animals took deep breaths ("sighs") defined as spontaneously occurring inspiratory events that were >2 times eupneic Pdi amplitude. Rats were given 5–10 min intervals between behaviors to allow for re-acclimatization to a tidal breathing condition and for Pdi amplitude to return to eupneic values.

Intra-thoracic and abdominal pressures were measured independently and recorded with a PowerLab 8/35 data acquisition system with an integrated amplifier following the manufacturer recommended calibration procedure. Pressure data were sampled at 100 Hz using LabChart (Millar Instrumentation) and band-pass filtered (0.3–30 Hz). Data from LabChart was exported to MATLAB for custom-designed automated analyses of peak pressure amplitudes and corresponding baselines on an event-by-event (e.g., breath-by-breath) basis. Baseline pressure values were determined systematically from the average of all inflection points in the segment preceding each peak. Data were analyzed and averaged across behaviors for 2 min of eupnea, 2 min of hypoxia–hypercapnia, and 5 maximal breaths during occlusion, all spontaneous deep breaths, all sneezes, and the maximal value obtained during bilateral phrenic nerve stimulation at 75 Hz. Pdi measurements across all conditions were obtained before and after unilateral DIAm DNV. Across all behaviors, movement of the abdomen was constrained using a custom-made binder to approximate isometric conditions (determined by Pdi response) and to minimize changes in functional residual capacity (FRC) of the lung.

2.3. Diaphragm electromyography (EMG)

In all animals, DIAm EMG was measured using methods similar to those previously described (Dow et al., 2006; Mantilla et al., 2010, 2011; Sieck and Fournier, 1990; Trelease et al., 1982). Briefly, pairs of multistranded fine wire, insulated (stripped to expose ~2 mm segment) stainless steel electrodes (0.28 mm diameter—model AS631, Cooner Wire Inc., Chatsworth, CA) were implanted (~3 mm apart) into the mid-costal regions of both right and left sides of the DIAm following laparotomy. The compound EMG signal was differentially amplified (2000×), bandpass filtered (20–1000 Hz) using an analog amplifier (Model 2124, DATA Inc.) and digitally sampled at a frequency of 2 kHz using a data acquisition board (National Instruments, Austin, TX) controlled by a custom-made program (LabView 8.2; National Instruments). The root-mean squared (RMS) of the EMG signal was computed using a 100-ms window. Respiratory rate, inspiratory burst duration, duty cycle, the RMS value at 75 ms after the onset of DIAm activity (RMS_{75}—an estimate of neural drive, Seven et al., 2014), and peak RMS (RMS_{peak}) were determined from the EMG signal. The maximum DIAm RMS EMG value was estimated based on the positive linear relationship between DIAm RMS EMG and Pdi measurements that we previously observed (Mantilla et al., 2010). Accordingly, in each animal, the maximum DIAm RMS EMG value was extrapolated from RMS EMG and Pdi measurements obtained in other behaviors.

2.4. Plethysmography

A commercially available whole-body plethysmography system (Buxco Inc., Wilmington, NC, USA) was used to quantify ventilation in additional anesthetized animals. The plethysmograph was calibrated by injecting known volumes of gas into a Plexiglas recording chamber using a 5-mL syringe. The chamber pressure, temperature and humidity, and atmospheric pressure as well as the rectal temperature of the rat were used in an equation first described by (Drorbaugh and Fenn, 1955) to calculate respiratory volumes, and peak airflow rates before and after DNV. Ventilatory parameters were calculated from the airflow traces, which were continuously sampled at 500 Hz. During the experiments, gas mixtures flowed

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