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Original article

Respiratory inductive plethysmography as a method for measuring ventilatory parameters in conscious, non-restrained dogs

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ABSTRACT

Introduction: Assessing the effects of new chemical entities on respiratory function in animal models is an essential component of preclinical drug safety evaluation. Methods currently available for measuring ventilatory parameters in conscious dogs generally utilize a plethysmograph chamber or a face mask equipped with a pneumotachograph attached to the snout of the animal. These methods require restraint and allow for only short, periodic measurements. Because of these limitations, respiratory inductive plethysmography (RIP) was evaluated as a possible new methodology that will allow for continuous monitoring of respiratory parameters in non-restrained dogs for extended periods of time. **Methods:** Straps containing inductive coils were placed around the thorax and abdomen to measure thoracic and abdominal excursions. The straps were contained within a protective jacket that was placed on the dogs and the electrical signals from the inductive coils were transmitted by telemetry to a receiver. The data were acquired and analyzed using the Vivometrics® LifeShirt® PreClinical System. Because postural changes can alter tidal volume measurements using RIP, the jacket also contained an accelerometer that was used to record postural changes during ventilatory measurements. **Results:** Measurement of ventilatory parameters in dogs following manual placement in different positions (e.g., standing, sitting, lateral recumbent) or during the different postures in non-restrained dogs demonstrated that changes in posture had only a minimal influence ($\leq$10% difference) on tidal volume measurements in conscious dogs. Conscious, restrained male beagle dogs given a single intravenous dose of 0.25 mg/kg morphine (respiratory depressant) or exposed to a gas mixture containing 8% CO_2 (respiratory stimulant) had values for tidal volume, respiratory rate and minute volume obtained using RIP that were within 7, 3 and 9% of values obtained using a facemask with an attached pneumotachograph. All of the expected changes in tidal volume, respiratory rate and minute volume were also detected in conscious, non-restrained male dogs using RIP following a single intravenous dose of 10 mg/kg doxapram (respiratory stimulant), a single intravenous dose of 0.5 mg/kg acepromazine (respiratory stimulant) and a single subcutaneous dose of 2 mg/kg morphine (respiratory depressant). **Discussion:** The results of this study demonstrate that RIP is an acceptable method for measuring ventilatory parameters in conscious non-restrained dogs. RIP expands current methodologies in that it allows for continuous monitoring of ventilatory parameters over extended periods of time. This added capability will allow for respiratory monitoring during both the awake and sleep states, which is significant since control of respiratory drive differs between the awake and sleep states and treatment related effects such as sleep apnea or sleep disordered breathing can have adverse health consequences. Combined with cardiovascular telemetry, this methodology will also allow for the combined monitoring of cardiovascular and respiratory parameters in conscious, non-restrained dogs.

1. Introduction

Assessing the effects of new chemical entities on respiratory function in animal models is an essential component of preclinical drug safety evaluation. Methods currently available for measuring ventilatory parameters in conscious dogs utilize a head-out or head-enclosed plethysmograph chamber, or a face mask equipped with a pneumotachograph attached to the snout of the animal (Murphy, 2005). These methods require restraint and, consequently, allow for only short, periodic measurements. Because of these limitations, respiratory inductive plethysmography (RIP) was evaluated as a possible method for continuous monitoring of respiratory parameters in non-restrained dogs for extended periods of time.

RIP utilizes straps containing inductive coils placed around the thorax and abdomen to measure lung volume changes. A continuous,

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low voltage electrical current is passed through the inductive coils and current changes that are proportional to the changes in length of the inductive coil straps are produced by the expansion and contraction of the thorax and abdomen during breathing. Changes in the inductive current are used to continuously monitor changes in the diameter of the thorax and abdomen and analysis software can be used to calculate volume changes and breathing rate (Neumann et al., 1998). Both thoracic and abdominal measurements are obtained since an increase in lung volume involves both expansion of the rib cage and depression of the diaphragm, the latter of which is determined by expansion of the abdomen. RIP is routinely used in humans to accurately monitor ventilatory parameters (Carry et al., 1997). However, this procedure is generally used in non-ambulatory subjects since a change in body posture is known to influence tidal volume measurements (Zimmerman et al., 1983). As such, additional calibrations and adjustments to the algorithms for calculating tidal volume have to be made. Because of this limitation, the potential effect of body posture changes on tidal volume measurements in the dog were evaluated in this study. The effects of a known respiratory stimulant and depressant on ventilatory parameters measured using RIP and a pneumotachograph were compared to demonstrate that RIP can accurately measure ventilator parameters in the dog. In addition, the effects respiratory stimulants and a depressant were also evaluated in non-restrained dogs using RIP to demonstrate that this methodology is capable of detecting ventilatory changes in conscious, non-restrained dogs.

2. Methods

2.1. Animals

All animals used in this study were cared for and used humanely in accordance with the requirements specified by the GlaxoSmithKline Animal Care and Use Committee (ACUC) and in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Research Council, NIH Publication No. 85-23, revised 1996).

Six purebred male beagle dogs obtained from Marshall Farms USA, Inc., North Rose, NY, were used in this study. Five of the six dogs were selected for use with the restraint procedures, while three of the six dogs were used for the non-restrained part of the study. Dogs were approximately 3 to 4 years of age (approximately 8.2 to 8.8 kg) at the initiation of dosing. Each dog was identified by a unique number tattooed inside the ear. All dogs were housed individually in stainless-steel cages and were acclimated to local housing conditions for at least seven days prior to the initiation of measurements.

The environmental controls were set to maintain temperature within the range 64 to 84°F and relative humidity within the range 30 to 70%, with an approximately 12-hour light/dark cycle.

A daily allotment of approximately 300 g of LabDiet™ brand Certified Laboratory Canine Diet #5007 (PMI™ Nutrition International, Richmond, IN, USA) was offered for approximately 3 h per day, at which time any remaining food was removed. On each day of treatment, food was removed approximately 2 h prior to treatment and was offered approximately 1 h after dosing. Filtered tap water (supplied by Aqua Pennsylvania, Inc. and periodically analyzed) was available ad libitum from an automatic watering source.

2.2. Body weight and acclimation

The body weight of all test animals was obtained for dose calculations prior to each dose (within 14 days of dosing). To reduce stress related to the use of a facemask, all dogs were acclimated to restraint and placement of the face mask on the snout on approximately five occasions for periods of up to 30 min. This was found to be an appropriate acclimation schedule as indicated by the acceptance of the animal for the facemask and no overt evidence of animal stress. Non-restrained dogs were acclimated to wearing a custom-fit jacket that contained the inductive coil straps and accelerometer by placing the jacket on each animal for increasing periods of time up to a target time of approximately 26 h. Acclimation to the jacket on at least one occasion for a period of 4 to 6 h and a second occasion for 20 to 24 h was found to be an appropriate acclimation schedule as indicated by the acceptance of the animal for the jacket and no overt evidence of animal stress. Most dogs adapted well to these procedures. Only one of the 10 dogs evaluated for use in this study were rejected because of poor behavior related to acceptance of these procedures.

2.3. Preparation and administration of test treatments

A gas mixture containing 8% CO_2, 21% O_2 and 71% N_2 (Praxair Mediblend™, compressed gases N.O.S.) was administered by inhalation using a facemask placed on the snout. Inhalation of air containing elevated CO_2 was used to produce a sustained increase in respiration within seconds after exposure (Saupe et al., 1992).

Morphine sulphate (injectable USP) was obtained from Baxter Healthcare Corp., Deerfield, IL. For intravenous administration, a solution at a concentration of 1 mg/mL in 0.9% sodium chloride for injection was prepared on the day of dosing. Dogs were given an intravenous bolus dose of 0.25 mg/kg at a dose volume of 0.25 mL/kg. For subcutaneous administration, the preformulated stock solution at a concentration of 10 mg/mL in 0.9% sodium chloride for injection was used and dogs were given a subcutaneous dose of 2 mg/kg at a dose volume of 0.2 mL/kg. Morphine is an opioid analgesic and was used to produce a decrease in respiratory drive. Maximal respiratory depressant effects generally occur within minutes after dosing in dogs, due primarily to a direct effect on the brainstem respiratory centers (Lewis & Kirchner, 1981).

Doxapram hydrochloride (Respiram™) was obtained from Hanna's Pharmaceutical Supply Co., Inc. (Wilmington, DE). Doxapram was obtained as a preformulated solution at a concentration of 20 mg/mL. Dogs were given an intravenous bolus dose of 10 mg/kg at a dose volume of 0.5 mL/kg. Doxapram is a respiratory stimulant in dogs and appears to act primarily by stimulating carotid and aortic chemoreceptors (Kato & Buckley, 1964; Ruiz, 1975).

Acepromazine maleate was obtained from Phoenix Pharmaceuticals (St. Joseph, MO) and was stored at room temperature. Acepromazine was obtained as a preformulated solution at a concentration of 10 mg/mL. Dogs were given an intravenous bolus dose of 0.5 mg/kg at a dose volume of 0.05 mL/kg. A preliminary study in our laboratory demonstrated that an intravenous dose of 0.5 mg/kg Acepromazine can increase tidal volume and minute volume in conscious, non-restrained (resting) dogs. Although the mechanism is unknown, evidence suggests that acepromazine (a phenothiazine derivative) may act by blocking the inhibitory effect of endogenous dopamine on peripheral chemoreceptors (Llados & Zapata, 1978; Bisgard et al., 1979).

Concentration and stability analyses of the dosing solutions used in this study were not conducted. Consequently, all test agents were stored according to the manufacturer's instructions and all dosing formulations were prepared on the day of dosing. All doses are expressed as mg/kg of the salt form.

2.4. Measurement of ventilatory parameters and postures

Ventilatory parameters were measured either by measuring mouth airflow using a face mask equipped with a pneumotachograph or by measuring thoracic and abdominal excursions using RIP. Analog flow waveforms from the pneumotachograph were detected by a differential pressure transducer (Model MP-45, Validyne Engineering, Northridge, CA), amplified and converted into telemetry signals using an analog to frequency converter (model C12V, Data Sciences International Inc., (DSI), St. Paul, MN) and either connected to an A.R.T. Analog Output System

(Version 1.0, DSI, St. Paul, MN) and input into the Life Science Suite™ PONEMAH Physiology Platform P3 software system (Version 3.322, DSI, Valley View, OH) or input into the Life Science Suite™ PONEMAH Physiology Platform P3 software system (Version 4.2 with OpenART Version 2.3, DSI, Valley View, OH) for acquisition and analysis. Respiratory parameters obtained using RIP involved fitting dogs with a custom-fit jacket equipped with inductive sensor straps woven into the jacket to fit around the chest and abdomen to detect chest and abdomen excursions and an accelerometer that allows the system to continuously monitor the relative posture and movement of the animal (The LifeShirt® PreClinical System , Vivometrics® ,Ventura, CA). Respiratory and posture data were transmitted wirelessly from a transmitter inside the jacket to a receiver for input into the VivoMonitor™ data acquisition system (Vivometrics®, Version 2.0, Ventura, CA). The data was subsequently imported into the VivoLogic™ software application (Vivometrics®, Version 3.1, Ventura, CA) for analysis. The distance between the inductive straps was adjusted such that one strap was located at the level of the fourth to fifth rib and the other located just caudal to the ribcage. These locations provided for stable measurements, as strap adjustments were not required for measurement periods of up to 24 h. Volume measurements were monitored during the adjustment of inductive strap tensions to ensure maximal sensitivity. The LifeShirt® system was programmed to report posture as the following discrete positions: upright, prone, supine or lateral recumbent (right or left). The supine position (lying on the back) could not be evaluated in this study since the dogs struggled when placed in this position. This was not considered to be a limitation since dogs rarely, if ever, are in this position while non-restrained. Prone is defined as standing on all four legs or positioned with the stomach and abdomen on the cage floor. Dogs in the sitting position or standing erect on their hind legs are considered to be in the upright position, while dogs lying on their side are considered to be in the lateral recumbent position. Certain behaviors (e.g., eating/drinking, barking, jumping, panting) noted in non-restrained dogs produced abnormal volume waveforms that were excluded from data analysis. These behaviors were relatively infrequent and generally account for less than approximately 5% of the total recording time over a 24 h period.

To calibrate volume measurements of the RIP system, a qualitative diagnostic calibration (QDC) and a fixed volume calibration were performed each time the jacket was placed on an animal according to the procedure described by Sackner et al. (1989). QDC computes a calibration factor (k) that defines the proportional relationship between abdominal and thoracic volumes using breaths of constant tidal volume. Fixed volume was used to calculate the total volume amplification factor (M) and uses a known tidal volume from a pneumotachograph. The calibration procedure involved (1) fitting the animal with a jacket containing the inductive straps and placing the animal on a table in a prone (standing) position, (2) allowing the animal to take normal breaths for a period of approximately 5 min and calculating the ratio of the standard deviations of the abdominal (ΔV_{AB}) to thoracic (ΔV_T) excursions (ratio $= k$), (3) placing a face mask with a calibrated pneumotachograph on the animal's snout and (4) adjusting the amplifier gain until the pneumotachograph and RIP system tidal volume values were identical (amplifier multiple $= M$). The calibrated tidal volume (ΔV_{cal}) is then be calculated using the equation $\Delta V_{cal} = M[(K\Delta V_T) + \Delta V_{AB}]$.

2.5. Parameters measured

Ventilatory parameters (tidal volume, respiratory rate and minute volume) obtained using both a face mask equipped with a

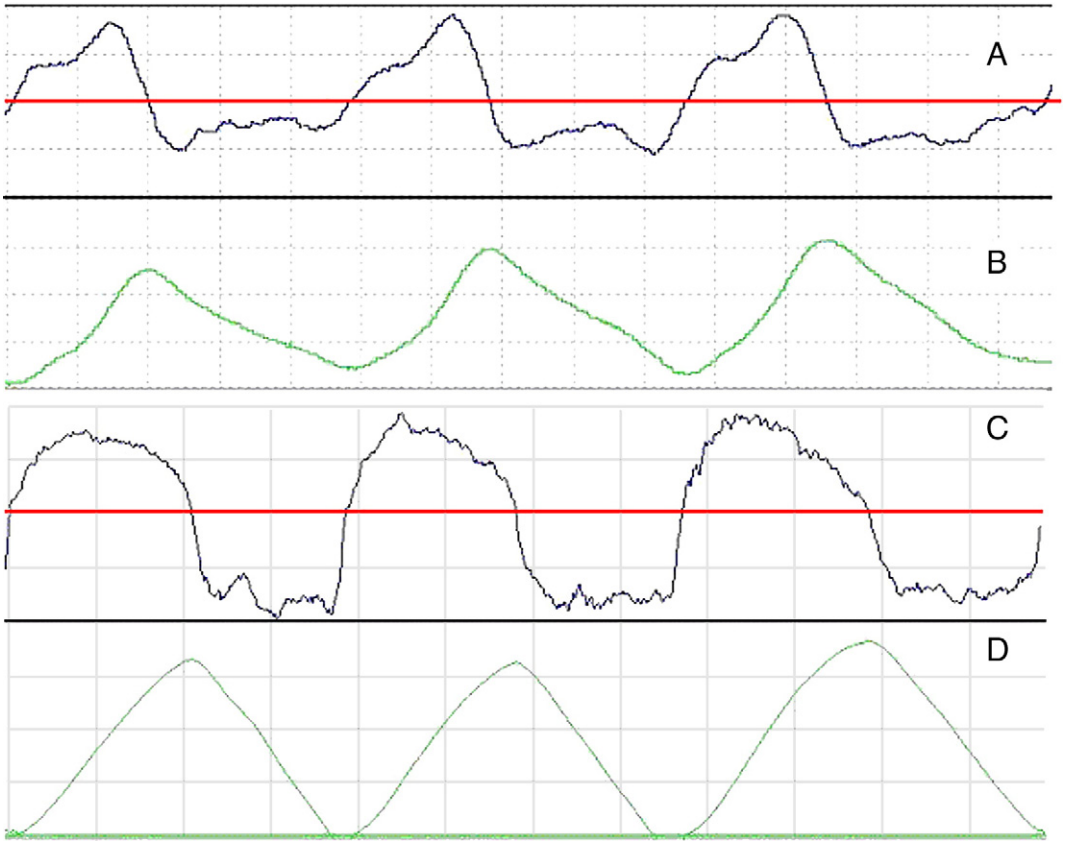

Fig. 1. Flow and volume waveforms from a pneumotachograph and RIP. Flow and volume waveforms were obtained in conscious, restrained dogs using a face mask equipped with a pneumotachograph and simultaneously with respiratory inductive plethysmography (RIP). Tracings A and C are the flow waveforms from the RIP and pneumotachograph, respectively, and tracings B and D are the volume waveforms from RIP and pneumotachograph, respectively. Zero flow is indicated by the horizontal line in tracings A and C (inspiration is up and expiration is down) and all scales are relative. RIP tracings are the sum of the thoracic and abdominal movements.

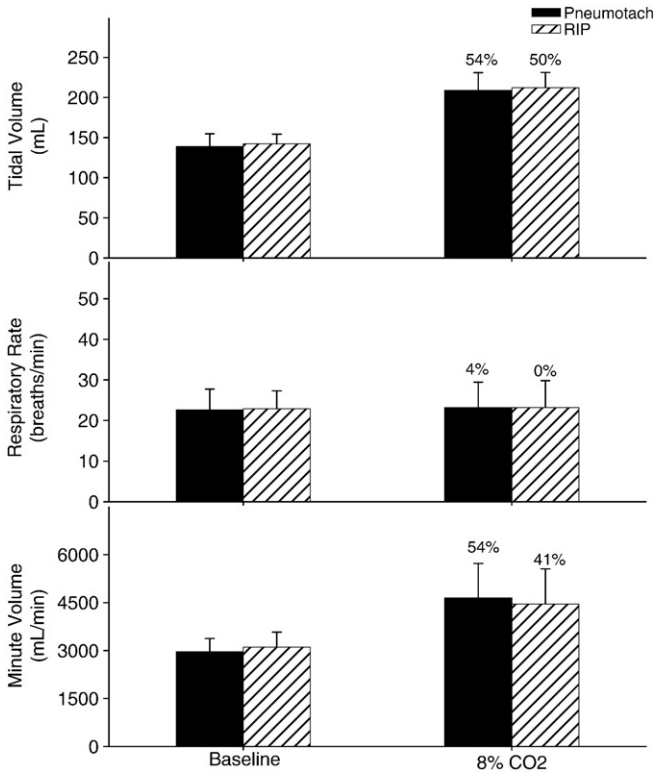

Fig. 2. Effect of exposure to 8% CO_2 in conscious, restrained dogs. Ventilatory parameters were monitored in conscious, restrained dogs while standing and wearing a face mask equipped with a pneumotachograph and simultaneously with respiratory inductive plethysmography (RIP). Each value is the mean of 3 dogs and error bars are ±SEM. Each animal was exposed to a gas mixture containing 8% CO_2 for approximately 5 min. The percent values represent percent changes from baseline.

pneumotachograph attached to the snout of the animal and the RIP system and body postures obtained using the RIP system were measured in both restrained and non-restrained conscious dogs. To evaluate the ability of the accelerometer to accurately monitor body position in non-restrained animals, video recordings were collected during respiratory measurements to verify body positions.

2.6. Analysis of data

Statistical analyses of the differences between drug treatments and vehicle control treatment in the conscious non-restrained dogs were conducted at each measurement period after dosing. To adjust for possible differences in baseline (predose) values, all postdose values were analyzed as change from predose. A crossover design was used to compare the effects of vehicle to each drug treatment group. Each dog received vehicle and each drug treatment with at least 1 week between treatments. For each measurement period following treatment, a Dunnett's test (Dunnett, 1965) was used to test for differences between the treatments and vehicle control. If the p value of the Dunnett's test was <0.05, the difference between the mean values of the drug treatment and the vehicle control treatment was considered to be statistically significant.

3. Results and discussion

3.1. Ventilatory measurements in conscious, restrained dogs

Flow and volume waveforms were obtained in conscious, restrained dogs simultaneously using a face mask equipped with a pneumotachograph and with the RIP system. In general, the morphology of the volume waveforms obtained with RIP was similar to that obtained with the pneumotachograph (Fig. 1). However, minor differences in the flow waveforms were evident with differences in peak inspiratory flows and the pattern of flow changes during both inspiration and expiration. This is an expected difference since the pneumotachograph is measuring lung volume by monitoring airflows external to the thoracic cavity during inspiration and expiration, whereas, the inductive straps are measuring lung volume by monitoring excursions of thorax and abdomen. Excursions of thorax and abdomen are based not only on airflow into and out of the lung, but also changes in air volume due to changes in the compressive forces, temperature and humidity within the thoracic cavity. The fact that overall respiratory rate (total time for each breath) and tidal volume (maximum volume for each breath) were the same between the pneumotachograph and RIP indicates that despite the minor differences in the morphology of the flow waveforms, RIP is able to accurately measure total pulmonary ventilation in the dog.

To assess the accuracy of the RIP measurements, ventilatory parameters (tidal volume, respiratory rate and minute volume) were monitored in three conscious, restrained dogs while standing and wearing a face mask equipped with a pneumotachograph and simultaneously using RIP. Exposure to 8% CO_2 produced an approximate 54% increase in total pulmonary ventilation (minute volume) relative to predose when measured using the pneumotachograph and an approximate 41% increase in minute volume when measured using RIP (Fig. 2). A single intravenous bolus dose of 0.25 mg/kg morphine produced 13 to 19% decreases in total pulmonary ventilation (minute volume) at 15 min and 3 h after dosing when measured using either the pneumotachograph or RIP (Fig. 3). These findings indicate that RIP provides a measure of ventilatory function following increases and

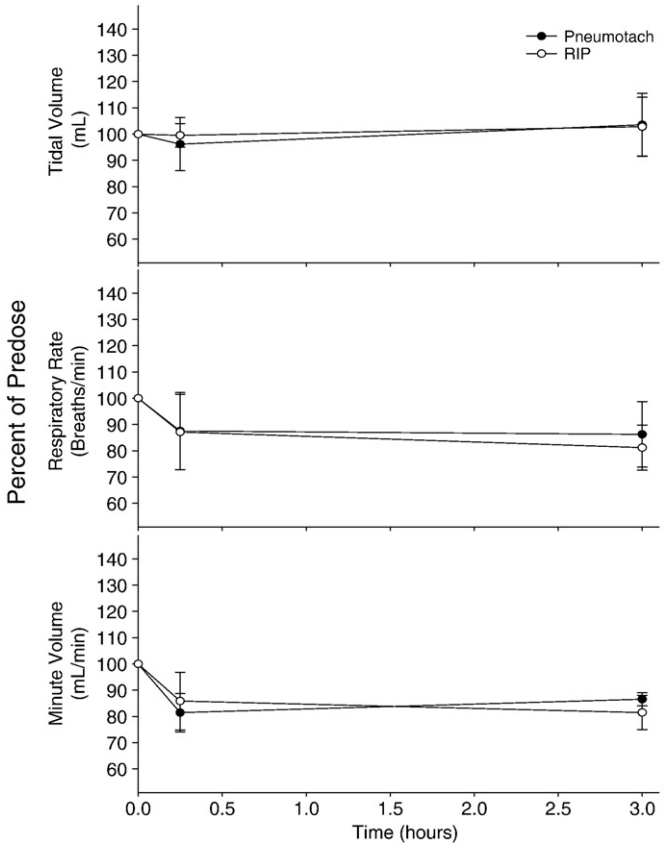

Fig. 3. Effect of morphine in conscious, restrained dogs. Ventilatory parameters were monitored in conscious, restrained dogs while standing and wearing a face mask equipped with a pneumotachograph and simultaneously with respiratory inductive plethysmography (RIP). Each value is the mean of 3 dogs and error bars are ±SEM. Each animal was given a bolus intravenous dose of 0.25 mg/kg morphine at time 0. The changes are the % of an average predose value (time 0), which is the mean of the 2 h interval immediately prior to dosing.

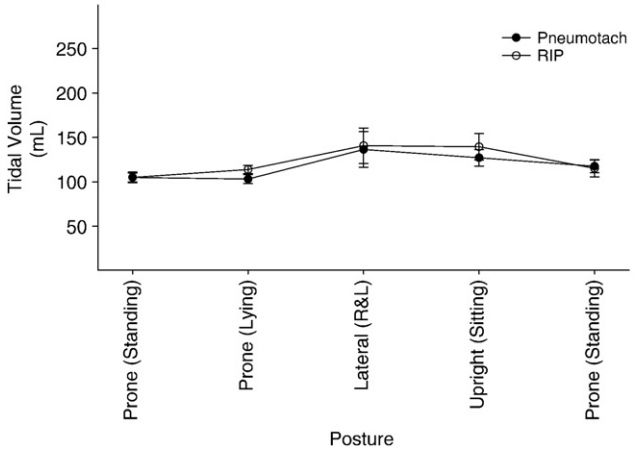

Fig. 4. Effect of posture on tidal volume in conscious, restrained dogs. Tidal volume was measured in conscious, restrained dogs using a face mask equipped with a pneumotachograph and respiratory inductive plethysmography (RIP). Each dog was placed in the positions listed above in the order presented on two separate occasions. Each value is the mean of 6 measurements (3 dogs on 2 occasions) and error bars are ± SEM. The RIP system was calibrated to the pneumotachograph measurements in the first prone position.

decreases in respiratory drive that are comparable to the values obtained using a pneumotachograph.

3.2. Effect of body posture on tidal volume

A change in body posture can influence tidal volume measurements obtained using RIP and can limit its usefulness in ambulatory subjects. To evaluate the effect of posture on tidal volume measurements, three dogs were manually restrained and placed sequentially in the prone (standing), prone (lying), lateral recumbent (right and left), upright (sitting) and back to the prone (standing) position and tidal volumes measured using the face mask equipped with a pneumotachograph and simultaneously with RIP. Tidal volume was either unchanged or changed in a similar manner as that detected using the pneumotachograph in the different postures (Fig. 4). Tidal volume values obtained with RIP in the prone (lying), lateral recumbent (right and left), upright (sitting) and prone (standing) postures were approximately +10, +3, +10 and −2%, respectively, of the values obtained using the pneumotachograph. These values are considered to be comparable since, in general, variability of ±10% is considered to be acceptable for measurements of ventilatory parameters in conscious dogs.

The effect of posture on tidal volume measurements was also evaluated in conscious, non-restrained dogs. The accuracy of the posture being reported by the LifeShirt® system accelerometer was verified using a digital video capture system. A total of approximately 30 h of video recordings were used to verify the accuracy of the postures being reported by the accelerometer. The accelerometer was 100% accurate in detecting the specific posture of the animal at a given time. During a 12-hour measurement period, one dog was only observed to be in the prone and upright positions and not in the lateral recumbent position (left or right), whereas two other dogs were observed to be in the prone and lateral recumbent positions (both left and right), but not in the upright position (Table 1). To quantify tidal volumes for each position in these non-restrained dogs, tidal volume measurements were collected as 1 min means and the average of these 1 min values for each position was calculated. Only positions in which 60 min of data could be collected were used. In general, average tidal volume values did not change significantly when the posture of the non-restrained animals changed. The maximal differences in average tidal volume values among the different postures for each of the three dogs were 3, 7 and 10% (Table 1). The data obtained in the restrained and non-restrained dogs indicate that postural changes have only a minimal influence (<10%) on tidal volume measurements in conscious dogs.

Table 1
Effect of posture on tidal volume in conscious, non-restrained dogs. Tidal volume was measured in conscious, non-restrained dogs using respiratory inductive plethysmography. The data were collected over a 12 h period during the light photoperiod. Each tidal volume value is the mean (±SEM) value for at least 60 one minute mean values obtained in the posture indicated. "–" indicates that the animal was in the posture indicated for less than 2% of the total collection period and insufficient data was available for analysis.

Tidal volume (mL)				
Postures				
Animal number	Prone (standing)	Upright (sitting)	Left lateral recumbency	Right lateral recumbency
8694	130 (2.9)	134 (1.8)	–	–
1259	162 (3.8)	–	174 (2.9)	168 (2.5)
3651	148 (2.8)	–	141 (2.8)	135 (2.7)

3.3. Ventilatory measurements in conscious, non-restrained dogs

Changes in tidal volume, respiratory rate and minute volume measured continuously over a 24-hour period in a non-treated dog on two separate occasions demonstrated that RIP is sensitive enough to detect diurnal changes in the respiratory pattern of conscious, non-restrained dogs. The dark photoperiod was characterized by a slower deeper breathing pattern with no change in total pulmonary ventilation (Fig. 5). Similar data were obtained from two other dogs (data not presented).

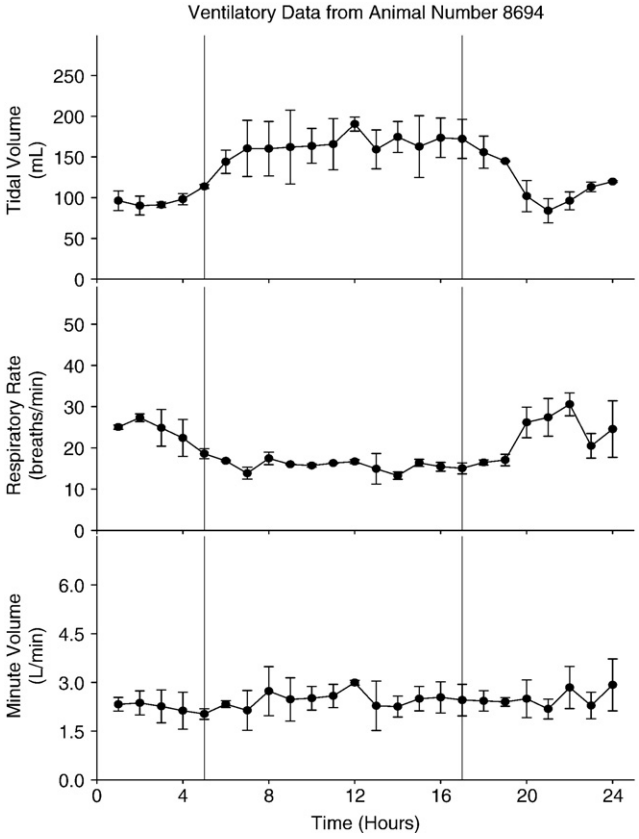

Fig. 5. Diurnal changes in ventilatory parameters in a conscious, non-restrained dog. Ventilatory parameters were monitored in a conscious, non-restrained dog using respiratory inductive plethysmography for a total time of approximately 24 h. Each value is the 1-hour mean from 1 dog collected on two separate occasions and error bars are ±SEM. Data between the horizontal drop lines indicate the dark photoperiod.

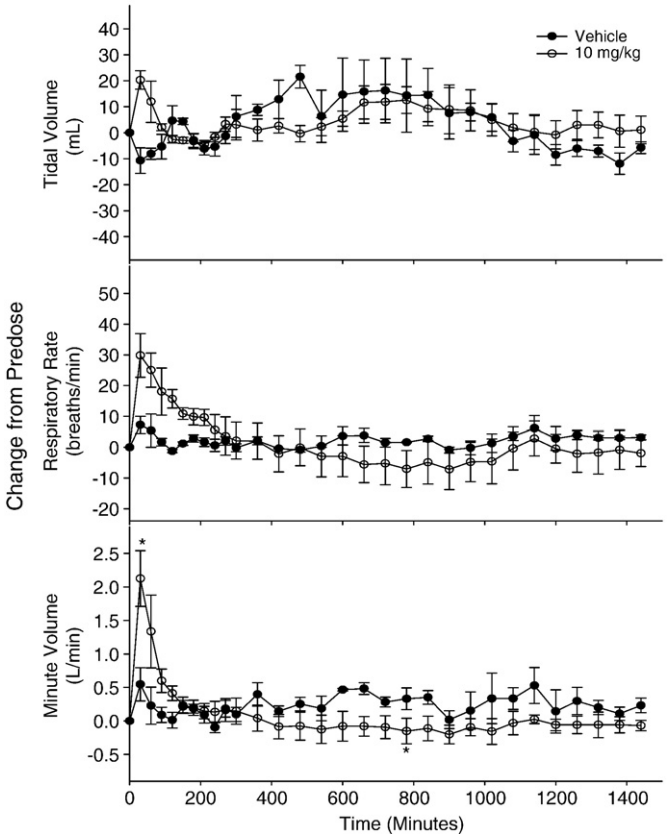

Fig. 6. Effect of doxapram on ventilatory parameters in conscious, non-restrained dogs. Ventilatory parameters were monitored in conscious, non-restrained dogs using respiratory inductive plethysmography for a total time of approximately 24 h. Doxapram was administered as an intravenous bolus dose at time 0. Each value is the mean of 3 dogs and error bars are ± SEM. The changes are the difference from an average predose value (time zero), which is the mean of the 2 h interval immediately prior to dosing. An asterisk indicates that the mean value is statistically different from the mean value of the vehicle control group ($p<0.05$).

Three dogs were given vehicle (0.9% sodium chloride), doxapram, acepromazine and morphine on separate occasions with at least 7 days between each treatment to evaluate the ability of RIP to detect drug-induced changes in respiratory drive in conscious, non-restrained dogs. A single intravenous bolus dose of 10 mg/kg doxapram (respiratory stimulant) produced an increase in total pulmonary ventilation (minute volume) for up to two hours after dosing (Fig. 6). The maximal change occurred at approximately 30 min after dosing and at this time, the baseline-adjusted increase in minute volume relative to the vehicle control value was approximately 1.6 L/min, or an increase of approximately 88% of the mean absolute vehicle control value. The increase in ventilation at this time was due to increases in respiratory rate and tidal volume, with a less proportionate increase in tidal volume. This was the expected change in ventilatory parameters based on the dose and known pharmacology of the compound (Kato & Buckley, 1964; Ruiz, 1975).

A single subcutaneous dose of 2 mg/kg morphine (respiratory depressant) produced a decrease in total pulmonary ventilation (minute volume) between 1 and 24 h after dosing (Fig. 7). Maximal changes occurred between approximately 6 and 11 h after dosing and, during these times, the maximum baseline-adjusted decrease in minute volume relative to the vehicle control values was approximately 1.2 L/min, or a decrease of approximately 74% of the mean absolute vehicle control values. The decreases in ventilation were due to a decrease in respiratory rate, with only minimal changes in tidal volume. This was the expected change in ventilatory parameters based on the dose and known pharmacology of the compound (Lewis & Kirchner, 1981).

A single intravenous bolus dose of 0.5 mg/kg acepromazine (respiratory stimulant) produced an increase in total pulmonary ventilation (minute volume) between approximately 1 and 10 h after dosing (Fig. 8). The maximal change occurred at approximately 4 h after dosing and at this time, the baseline-adjusted increase in minute volume relative to the vehicle control value was approximately 1.2 L/min, or an increase of approximately 108% of the mean absolute vehicle control value. The increase in ventilation was due to an increase in tidal volume with no change in respiratory rate.

4. Conclusion

The results of this study demonstrate that respiratory inductive plethysmography (RIP) is an acceptable method for measuring ventilatory parameters in conscious, non-restrained dogs. A comparison with a standard method for measuring ventilation (facemask with attached pneumotachograph) demonstrated that ventilatory parameters (tidal volume, respiratory and minute volume) could be accurately measured in the conscious dog and, importantly, that changes in posture did not have a significant effect on tidal volume measurements. The absence of postural effects allows this methodology to accurately assess ventilatory parameters in ambulatory subjects. The RIP methodology was able to detect the diurnal changes in ventilatory patterns as well as drug-induced stimulation and depression of ventilation in conscious, non-restrained dogs using a relatively small group size ($n=3$). RIP expands current methodologies in that it allows for continuous monitoring of ventilatory

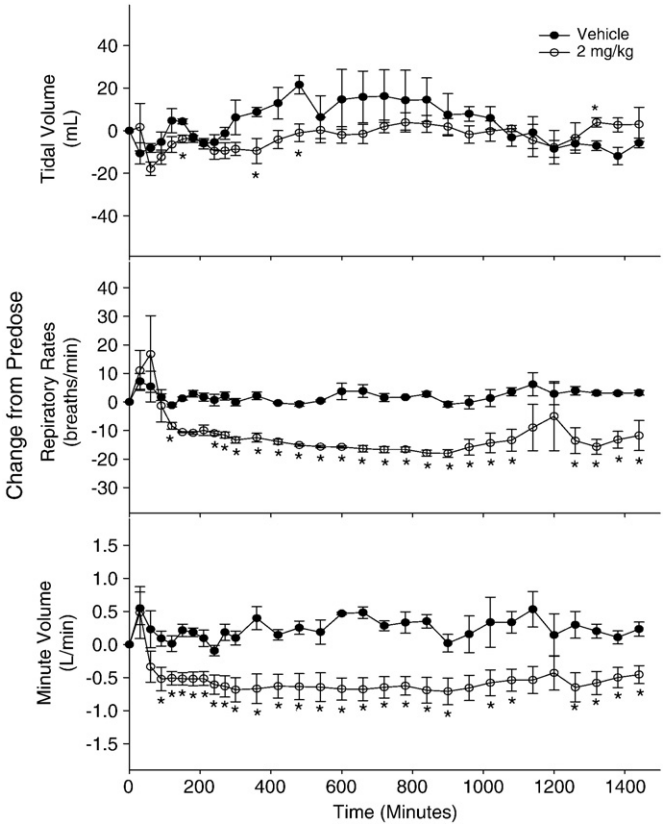

Fig. 7. Effect of morphine on ventilatory parameters. Ventilatory parameters were monitored in conscious, non-restrained dogs using respiratory inductive plethysmography for a total time of approximately 24 h. Morphine was administered as a subcutaneous dose at time 0. Each value is the mean of 3 dogs and error bars are ± SEM. The changes are the difference from an average predose value (time zero), which is the mean of the 2 h interval immediately prior to dosing. An asterisk indicates that the mean value is statistically different from the mean value of the vehicle control group ($p<0.05$).

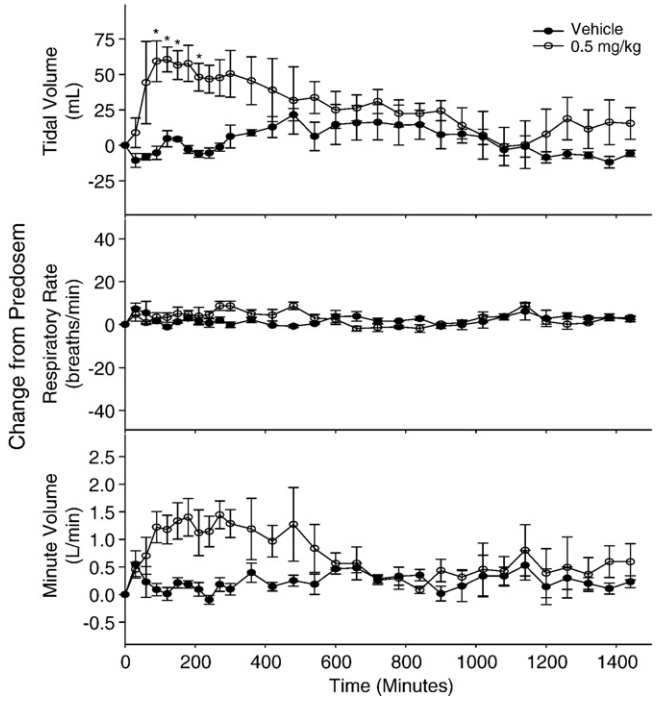

Fig. 8. Effect of acepromazine on ventilatory parameters. Ventilatory parameters were monitored in conscious, non-restrained dogs using respiratory inductive plethysmography for a total time of approximately 24 h. Acepromazine was administered as an intravenous bolus dose at time 0. Each value is the mean of 3 dogs and error bars are ±SEM. The changes are the difference from an average predose value (time zero), which is the mean of the 2 h interval immediately prior to dosing. An asterisk indicates that the mean value is statistically different from the mean value of the vehicle control group ($p<0.05$).

parameters over extended periods of time. This added capability will allow for respiratory monitoring during both the awake and sleep states, which is significant since control of respiratory drive differs between the awake and sleep states and drug-induced effects such as sleep apnea or sleep disordered breathing can have adverse health consequences (Benjamin & Lewis, 2007). Combined with cardiovascular telemetry, this methodology will also allow for the combined monitoring of cardiovascular and respiratory parameters in conscious, non-restrained dogs.

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