Published in final edited form as:

Exp Lung Res. 2011 June ; 37(5): 301–309. doi:10.3109/01902148.2011.561399.

Dynamic Determination of Oxygenation and Lung Compliance in Murine Pneumonectomy

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Abstract

Thoracic surgical procedures in mice have been applied to a wide range of investigations, but little is known about the murine physiologic response to pulmonary surgery. Using continuous arterial oximetry monitoring and the FlexiVent murine ventilator, we investigated the effect of anesthesia and pneumonectomy on mouse oxygen saturation and lung mechanics. Sedation resulted in a dose-dependent decline of oxygen saturation that ranged from 55–82%. Oxygen saturation was restored by mechanical ventilation with increased rate and tidal volumes. In the mouse strain studied, optimal ventilatory rates were a rate of 200/minute and a tidal volume of 10ml/kg. Sustained inflation pressures, referred to as a "recruitment maneuver," improved lung volumes, lung compliance and arterial oxygenation. In contrast, positive end expiratory pressure (PEEP) had a detrimental effect on oxygenation; an effect that was ameliorated after pneumonectomy. Our results confirm that lung volumes in the mouse are dynamically determined and suggest a threshold level of mechanical ventilation to maintain perioperative oxygen saturation.

Introduction

Pulmonary surgical procedures in mice have been applied to a wide range of investigations including studies of gene expression (12), tumor biology (4) and lung regeneration (13). The economic benefits of *Mus musculus*, including its small size and short reproductive cycle, complement the experimental advantages of widely available and well-characterized inbred mouse strains (17). Further, recent sequencing of the murine genome has facilitated the experimental manipulation of gene expression (20). Using murine models, genes of interest can be enhanced (overexpression), suppressed (knockout) or even conditionally expressed in selected tissues (2, 11).

Despite the experimental advantages of mice, surprisingly little is known about murine surgical anatomy and the physiologic response to pulmonary surgery. Mice have a 2mm diameter trachea with 1mm diameter mainstem bronchi (9); the small anatomy has limited the routine use of the endotracheal intubation and positive pressure ventilation required for pulmonary surgery. Murine lobar anatomy is unusual among mammals with 4 right lung lobes: 3 lobes (anterior, middle and posterior) within the right pleural space and a single

medial lobe (median, cardiac or infracardiac) abutting the diaphragm to the left of the inferior vena cava. The left lung is a single lobe with occasional variation consisting of an oblique fissure reminiscent of the left major fissure in humans (3). Mice have a prominent ventral junctional line suggesting a common intrathoracic pressure.

From a physiologic viewpoint, allometry predicts many of the respiratory parameters in mice. Murine respiratory rate, lung compliance and work of breathing are consistent with size-based allometric equations (7, 15); however, an exception is the very compliant mouse chest wall (6). Similar to newborn mammals (8), the compliant mouse chest wall means that the resting or relaxation volume of the lung approaches closing volume (19); that is, the volume at which all airways are closed. The functional consequences of anesthesia, or even moderate sedation, are diminished lung volumes and the prospect of compromised gas exchange.

In this report, we investigated the use of anesthesia and pneumonectomy on mouse oxygen saturation and lung mechanics. Using continuous arterial oxygen saturation monitoring, we demonstrated rapid oxygen desaturation with sedation. Mechanical ventilation with increased frequency, increased tidal volume or sustained insufflation (recruitment maneuver) improved both lung compliance and oxygen saturation. These results confirm that lung volumes in the mouse are dynamically determined and suggest practical strategies for perioperative management.

Methods

Mice

C57/B6 mice (Jackson Laboratory, Bar Harbor, ME), 22 to 30gm, were used in all experiments. The care of the animals was consistent with guidelines of the American Association for Accreditation of Laboratory Animal Care (Bethesda, MD).

Pulse oximetry

The MouseOx (STARR Life Sciences, Oakmont, PA) is a pulse oximeter with a proprietary plethysmographic waveform analysis algorithm optimized for rats and mice. The MouseOx photodiode was placed on the shaved skin overlying either the neck or proximal thigh. For each animal, a MouseOx data file was saved in tabular format and exported to Excel for analysis. The MouseOx has been previously validated by a comparison with Instrumentation Laboratories IL-682 SaO₂ (16). Briefly, the MouseOx arterial oxygen saturation values were nearly identical to the IL-682 with no detectable bias in the MouseOx values (16). Based on these studies in the anesthetized, nonventilated rat, the MouseOx reflects arterial oxygen saturations from 100% to less than 20%.

Sedation and anesthesia

Awake oxygen saturation measurements were assessed by the MouseOx collar clip on a shaved neck. In experiments designed to assess the effects of sedation, baseline arterial oxygen saturation measurements were obtained with the MouseOx-collar clip on a shaved mouse. The mice were sedated with either 100mg/kg or 200mg/kg intraperitoneal (IP) ketamine (Fort Dodge Animal Health, Fort Dodge, IA). Measurements were obtained until oxygen saturation stabilized for 60 seconds.

Orotracheal intubation

Anesthesia for oro tracheal intubation was a mixture of 100mg/kg Ketamine (Fort Dodge Animal Health) and 6mg/kg Xylazine (Phoenix Scientific, Inc., St. Joseph, MO) administered IP. The animal was then suspended by the incisors and the tongue gently

retracted anteriorly. A 20G angiocatheter (BD Insyte, Sandy, Utah) was passed between the vocal cords under direct illumination.

FlexiVent

After intubation, mice were transferred to the FlexiVent (SCIREQ, Montreal, PQ, Canada) system for pulmonary function testing. The FlexiVent technique involved several maneuvers or "perturbations" used to determine lung mechanics. The whole-lung dynamic compliance and lung resistance was obtained by fitting the linear single-compartment model using multiple linear regression. The mice were ventilated at various breathing frequencies. With the recruitment maneuver (RM) perturbation (named TLC by SCIREQ), the mouse was ventilated with a 3sec ramp to a 3sec 30cm H₂O plateau pressure. During the RM, the following parameters were determined: mean displaced volume (V_{end}), V_{end} relative to weight, and mean delivered volume. A "snapshot perturbation" maneuver was used to measure resistance (R), compliance (C), and elastance (E) of the whole respiratory system (airways, lung, and chest wall). Maximal pressure-volume loops were generated using ramp pressure-regulated perturbations.

Frequency and Tidal Volume

For frequency investigations, the animal was initially ventilated at a respiratory rate of 150/min, a tidal volume of 8mL/kg, PEEP of 2 cmH₂O and a pressure limited constant flow profile. After five minutes, the animal was removed from the ventilator, and allowed to desaturate. When the oxygen saturation had stabilized, the animal was reattached to the FlexiVent at predetermined ventilator rates (typically 200, 250 or 300/minute). For tidal volume experiments, the animal was initially ventilated at a respiratory rate of 200/min, a tidal volume of 8mL/kg PEEP of 2cmH₂O and a pressure limited constant flow profile. After five minutes, the animal was removed from the ventilator, and allowed to desaturate. When the oxygen saturation had stabilized, the animal was reattached to the FlexiVent at predetermined tidal volumes (typically 10, 12 and 14 mL/kg).

PEEP and recruitment maneuvers

After anesthesia and intubation, the hind limb was shaved to the inguinal crease and a MouseOx thigh clip was applied. The animal was initially ventilated with a respiratory rate of 200, tidal volume of 8mL/kg, 0 PEEP and a pressure limited constant flow profile and. After 5min, the PEEP was increased to 2cmH₂O. PEEP levels of 4, 6, 8, and 10cmH₂O were sequentially applied. After reaching a PEEP of 10, the PEEP trap was returned back to 0, and a RM was performed. The animal was ventilated for 5 minute intervals with PEEP increases and a RM at the end of each interval.

Pneumonectomy

After anesthesia and intubation, the animal was ventilated on a Flexivent (SCIREQ, Montreal, QC Canada) at ventilator settings of 200 bpm, 10mL/kg, and PEEP of 2cmH₂O with a pressure limited constant flow profile. A thoracotomy was created in the left fifth intercostal space, and the lung gently removed from the chest. The hilum was ligated with a 5-0 surgical silk tie (Ethicon, Somerville, NJ) and the lung was sharply excised distal to the tie. The hilum was allowed to retract into the chest, and a recruitment maneuver was performed while closing the thoracotomy with a single silk stitch. At the completion of the procedure, the animal was removed from the ventilator and observed for spontaneous respirations. Once spontaneous muscle activity was noted, the animal was extubated and transferred to a warmed cage.

Statistical analysis

The statistical analysis was based on measurements in at least three different mice. The unpaired Student's t test for samples of unequal variances or repeated measure ANOVA was used to calculate statistical significance. The data was expressed as mean $\pm$ one standard deviation. The significance level for the sample distribution was defined as $P < .05$.

Results

Sedation and oxygen saturation

To measure the effect of sedation on gas exchange, we assessed arterial oxygen saturation prior to and after IP sedation with ketamine. Within 60 seconds of administration, oxygen saturation declined (Figure 1A). The rate and depth of desaturation was dose-related; larger doses of ketamine resulted in more rapid decline and lower absolute level of desaturation (Figure 1B). Sedation also lowered both respiratory rate and heart rate. Oxygen desaturation was associated with a mean $66 \pm 5\%$ decrease in respiratory rate and a $57 \pm 4\%$ decrease in heart rate (N=8 mice) at ketamine doses between 100mg/kg and 200mg/kg.

Frequency and tidal volume

To test the effect of increased breathing rate and tidal volumes on oxygenation, the sedated mice were intubated and ventilated at various frequencies and tidal volumes. Increasing the ventilatory rate increased oxygen saturation within 3 minutes (Figure 2A). The rate of improvement in oxygen saturation was associated with increasing ventilator frequency (Figure 2B). A ventilator rate of 200/minute was a consistent threshold for improvement in oxygenation. Similarly, an increased tidal volume resulted in an increase in oxygen saturation (Figure 2C). The improvement in oxygen saturation was associated with a threshold tidal volume of 10mL/kg (Figure 2D). These observations were consistent with dynamically determined lung volumes; that is, increased frequency and tidal volumes led to increased functional residual capacity and an improvement in gas exchange.

Recruitment and PEEP

Two additional strategies were used to increase lung volumes: sustained inflation pressures--here referred to as a "recruitment maneuver" (RM)--and positive end expiratory pressure (PEEP). The RM was a 3 second linear ramp to a 3 second plateau at 30cm H₂O airway pressure (Figure 3A). In addition to recruiting lung volume, the slow continuous (ramp) inflation to 30cm was used to assess nonlinearities in pressure-volume loops and measure quasi-static compliance. The pressure controlled RM demonstrated a significant improvement in lung compliance (Figure 3B). In pulmonary mechanics studies of N=8 mice, there was an improvement in both lung compliance (Figure 3C) and airway resistance (Figure 3D) after RM. RM had a consistently positive effect on oxygen saturation (see Figure 2A and 2C). In contrast, the application of PEEP had a deleterious effect on oxygenation (Figure 4A). PEEP at 6cm H₂O produced oxygen saturation levels of 60%. The adverse effect of PEEP was ameliorated with RM prior to each increment in PEEP level. With RM prior to each increase in PEEP, higher levels of PEEP (10cm H₂O) were required before the oxygen saturation neared 60% ($p < 0.01$) (Figure 4B). Increases in PEEP were consistently associated with decreasing oxygen saturation and increasing heart rate (N=20 mice).

Effect of pneumonectomy

To optimize lung mechanics and gas exchange, mice were maintained on a rate of 200/minute and 10ml/kg TV during left pneumonectomy procedures. After the pneumonectomy, oxygen saturations remained above 90% (Figure 5A). Lung mechanics measurements

demonstrated the predicted decrease in compliance and increase in resistance and elastance (Figure 5B–C). To investigate the effect of pneumonectomy on PEEP-induced desaturation, post-pneumonectomy mice were ventilated with various levels of PEEP. In contrast to mice with two lungs, pneumonectomy ameliorated the detrimental effect of PEEP on oxygen saturation ($p < .01$) (Figure 5D). In all mice, 0.25 l/min supplemental oxygen restored oxygen saturations to $>90\%$.

Discussion

In several small mammals, including rodents, the chest wall is significantly more compliant than larger animals (6); a mechanical feature reminiscent of newborn mammals (8). In the setting of a compliant chest wall, the static balance between opposing elastic recoil of the lung and chest wall results in low resting or relaxation volumes of the lung. In the mouse, the low relaxation volume is only slightly above the volume at which all airways are closed (19). This small expiratory reserve volume is inconsistent with efficient gas exchange.

Using continuous arterial oximetry monitoring in mice, we confirmed the inefficiency of sedation-associated gas exchange. Sedation resulted in a dose-dependent decrease in oxygen saturation. The effect of the sedation appeared to be related to breathing frequency and tidal volume. Mechanical ventilation with either increased frequency or tidal volume restored oxygen saturation to awake baseline levels. These observations are consistent with the hypothesis that lung volumes, and indirectly gas exchange, are dynamically determined.

In awake mice, an additional mechanism has been implicated in maintaining an increased functional residual capacity; namely, expiratory braking (19). Braking is persistent inspiratory muscle activity or increased glottal resistance that results in the retardation of expiratory flow (14). Prior to these studies, we suspected that PEEP would have a similar functional effect in maintaining expiratory airway pressure and functional residual capacity. An unexpected observation was the adverse effect of PEEP on oxygen saturation; as little as 2 cmH₂O PEEP resulted in significant arterial desaturation.

There are several plausible mechanisms for the adverse effect of PEEP on murine arterial oxygen saturation. The commonest explanation in humans for adverse effects of PEEP is an increase in mean intrathoracic pressure. The increased airway pressure can result in systemic circulatory insufficiency and/or the inefficient redistribution of blood flow in the lungs. The potential effect of PEEP-associated crowding within the chest likely contributes to inefficient gas exchange because pneumonectomy reduced the adverse effects of PEEP-induced desaturation. A second possibility is that the increased airway pressure associated with PEEP may have a direct effect on juxta-alveolar vascular resistance. Increased vascular resistance may redistribute blood flow away from well-aerated alveoli and toward nonaerated regions of the lung. A third possibility is that the dominant effect of PEEP was to maintain airway patency and blood flow to otherwise poorly ventilated alveoli. The finding that supplemental oxygen normalized oxygen saturation is consistent with this possibility. Because of the complex interactions between breathing frequency, lung volume, tidal volume and volume history, the ability to distinguish between these mechanisms will be limited until quantitative and instantaneous measurements of interstitial pressure and blood flow are available.

A contribution of this study was the concomitant use of continuous oxygen saturation monitoring and the FlexiVent mechanical ventilator. Measuring the rapid changes in arterial oxygen saturation was enabled by the recent development of continuous arterial oxygen saturation monitoring in mice. An extension of photoplethysmography (PPG) technology, mouse oximetry uses the optical measurement technique that has been clinically adapted in

humans (5). PPG is commonly employed as the detected reflectance of a red or a near infrared wavelength light; the most recognizable waveform feature of the reflected light is the peripheral pulse. The pulsatile component of the PPG waveform (often called the 'AC' component) has a fundamental frequency linked to the heart rate (1). The challenge of adapting pulse oximetry to the mouse is not only the small scale, but a heart rate in mice that is 8-fold higher than in humans (10). The recent development of analytic algorithms that permit noninvasive pulse oximetry is particularly useful given the limitations of invasive monitoring in mice.

The other technology used to assess murine physiology was the FlexiVent. The FlexiVent is a rodent ventilator, requiring endotracheal intubation, designed to provide an instantaneous assessment of the pressure-flow relationship (impedance). Based on impedance measurements, the flow resistance and reactance of the respiratory system can be calculated. Two major limitations of the FlexiVent are 1) the requirement for tracheal intubation, and 2) the requirement for complete relaxation to avoid extrapulmonary artifact. In survival experiments, tracheal intubation must be performed skillfully to avoid glottic edema and airway obstruction. Because of the need for complete relaxation, and the limitations of paralytic agents in mice, the use of the FlexiVent requires careful data analysis.

Mice have well-established differences in lung mechanics over time and between strains (18). A practical limitation of our study is that we examined only one strain of mice (C57/B6) within a narrow age range. Although specific ventilatory parameters may vary with age and strain, we suspect the basic management principles will be equally applicable to not only other mouse strains, but rats and many small mammals as well.

The results of our study highlight the both the similarities and differences between mice and humans. In humans, sedation results in desaturation only after prolonged hypoventilation and hypercarbia. In contrast, sedation in mice results in rapid and significant oxygen desaturation. Our studies suggest that these differences are not the result of intrinsic differences in lung function, but a consequence of the hypercompliant chest wall and the high rate of oxygen consumption characteristic of the mouse. The awake mouse uses breathing frequency and tidal volume to maintain functional residual capacity and efficient gas exchange. Any anesthetic or surgical procedure that compromises ventilatory rate and tidal volumes risks substantial hypoxemia. The practical consequence of these observations for murine procedures is the meticulous attention to mechanical ventilation parameters and the optional use of supplemental oxygen.

Acknowledgments

The authors would like to thank Drs. Andrew Hoffman and Dr. Robert Voswinckel for their generous suggestions and technical advice.

Supported in part by NIH Grant HL47078, HL75426 and HL94567

Abbreviations

C	compliance
E	elastance
IP	intraperitoneal
TV	tidal volume
PEEP	positive end expiratory pressures

PPG	photoplethysmography
RM	recruitment maneuver
R	resistance
SD	standard deviation

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Figure 1. Effect of sedation on arterial oxygen saturation. A) Representative oximetry profiles of two mice after a dose of ketamine (100mg/kg and 200mg/kg) anesthesia at time=zero. B) Comparison of oxygen saturations in mice administered either 100mg/kg or 200mg/kg ketamine at time=zero. Oxygen saturations were recorded at 15sec intervals (mean $\pm$ SD; N=8 mice in each group).

Figure 2.

Effect of respiratory frequency and tidal volume on oxygen saturation. A) Representative oximetry profile of a mouse with sedation-related desaturation rescued with intubation and ventilation. Increased ventilator rate (100/minute) improved oxygen saturations over 3 minutes. Further improvement followed a recruitment maneuver (RM) at 30cmH₂O (see Methods). B) Relationship of ventilator rate to oxygen saturation at 3 frequencies; oximetry values were averaged over the 15sec interval (mean±SD; N=8 in each group). C) Representative oximetry profile of a mouse with sedation-related desaturation rescued with intubation and ventilation. Increase in tidal volume (2mL/kg) improved oxygen saturations over 2 minutes (arrow denotes a "snapshot" perturbation; see Methods). Further improvement followed a sustained inflation at 30cmH₂O (RM). D) Relationship of ventilator tidal volume to oxygen saturation at 3 tidal volumes; oximetry values were averaged over the 15sec interval (mean±SD; N=6 in each group).

Figure 3.

Effect of recruitment maneuver (RM) on pulmonary mechanics. A) The RM was a positive pressure insufflation maneuver consisting of a 3sec ramp and 3sec plateau at 30cmH₂O. The improved compliance after the initial RM (RM1) was maintained on subsequent RM maneuvers (RMn). The increase in functional residual capacity is reflected by the inflation volume difference between the initial and subsequent RM (asterisk). B) Quasi-static flow-volume loops show the improvement in lung volumes and compliance. RM resulted in a significant (C) decrease in airway resistance ($p < .01$; $N=6$) and (D) increase in lung compliance ($p < .01$; $N=6$).

Figure 4.

The effect of PEEP on oxygen saturation. A) A representative oximetry profile of a mouse with sedation-related desaturation rescued with intubation and ventilation. Sedation administered at time=zero; oxygen saturations were 85% prior to instituting progressive levels of PEEP. Recruitment maneuvers (RM) were performed prior to the change of PEEP levels during the second phase (1000 to 2400 seconds). B) The effect of different levels of PEEP on oxygen saturation with or without RM prior to each increase in PEEP ($p < 0.01$).

Figure 5.

The effect of pneumonectomy on oxygen saturation and pulmonary mechanics. The effect of pneumonectomy on airway resistance (A), parenchymal compliance (B) and elastance (C) is shown ($p < .05$; $N = 6$ mice). D) The effect of PEEP on oxygen saturation in mice with or without pneumonectomy ($p < .01$; $N = 6$ mice).