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RESEARCH PAPER

Influence of the mode of ventilation on ketamine/xylazine requirements in rabbits

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Abstract

Objective To evaluate the effect of the mode of mechanical ventilation (MV) on the dose of intravenous anesthetic during 3 hours of ketamine/xylazine anesthesia.

Study design Prospective laboratory study.

Animals Sixty-one adult male New Zealand White rabbits.

Methods Rabbits were anesthetized (ketamine/xylazine 35 + 5 mg kg^{-1}, IM), the trachea was intubated and randomized to four groups – (1) CMV-1 ($n = 14$), ventilated with traditional conventional volume-cycled MV [$V_T = 12$ mL kg^{-1}, RR = 20, positive end-expiratory pressure (PEEP) = 0 cmH_2O]; (2) CMV-2 ($n = 13$), ventilated with a modern lung-protective regimen of volume-cycled MV ($V_T = 6$ mL kg^{-1}, RR = 40, PEEP = 5 cmH_2O); (3) HFPV ($n = 17$) ventilated with high-frequency percussive ventilation [high-frequency oscillations (450 $minute^{-1}$) superimposed on 40 $minute^{-1}$ low-frequency respiratory cycles, I:E ratio = 1:1], oscillatory continuous positive airway pressure (CPAP) of 7–10 cmH_2O, and demand CPAP of 8–10 cmH_2O. (4) A fourth group, spontaneously ventilating (SV, $n = 17$), was anesthetized, intubated, but not ventilated mechanically. FiO_2 in all groups was 0.5. Anesthesia was maintained at a surgical plane by IV administration of a ketamine/xylazine mixture (10 + 2 mg kg^{-1}, as necessary) for 3 hours after intubation. Total dose of xylazine/ketamine administered and the need for yohimbine to facilitate recovery were quantitated.

Results The total dose of xylazine/ketamine was significantly higher in the HFPV and SV groups compared with CMV-1 ($p < 0.01$). Fewer animals required yohimbine to reverse anesthesia in the HFPV than CMV-1 group ($p < 0.05$).

Conclusions The HFPV mode of MV led to higher doses of ketamine/xylazine being used than the other modes of MV.

Clinical relevance In rabbits, anesthetic dose for the maintenance of anesthesia varied with the mode of MV used. Investigators should be aware of the possibility that changing the mode of ventilation may lead to an alteration in the amount of drug required to maintain anesthesia.

Keywords ketamine, mechanical ventilation, rabbits, xylazine.

Introduction

The combination of ketamine and xylazine has been used for many species over the years and remains a popular combination for intramuscular (IM) and intravenous (IV) anesthesia in rabbits (Difilippo et al. 2004). Aye & Milne (2002) reported that an

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advantage of ketamine was the maintenance of spontaneous ventilation during anesthesia. This feature makes ketamine very attractive for veterinary use. However, ketamine administration is insufficient for a surgical plane of anesthesia and high doses could lead to serious respiratory depression, including apnea (Gonzalez et al. 2002; Sumitra et al. 2004), and death (Borkowski et al. 1990). Thus it has commonly been combined with xylazine in experimental animal studies (Borkowski et al. 1990).

It could be postulated that mechanical ventilation (MV) would increase the safety of ketamine/xylazine anesthesia and reduce the possibility of complications related to gas exchange. Nevertheless, information about MV in ill or healthy rabbits is limited. There is minimal information provided on methods and modes of MV in veterinary anesthesia texts (Short 1987; Flecknell 1996; Paddleford 1996; Vogler 1997; Haskins 2003). The main sources of information on MV in rabbits are brief descriptions in the articles in which these animals were used as experimental animals. It is obvious that the aims of each study often determined the specific modes of ventilation, and in many cases they could not be recommended for general veterinary practice.

Rabbits are often used for studies of pulmonary diseases, such as adult respiratory distress syndrome (ARDS) (Imai et al. 2003). In these experiments, aggressive methods of MV may be necessary for the development of severe ventilator-induced lung injury (VILI) and for subsequent exacerbation of ARDS. In some studies of ARDS, tidal volumes (V_T) applied to rabbits during MV reached 30 mL kg^{-1} (Maeda et al. 2004; Qiu et al. 2004), that is, 2.5–3 times higher than V_T traditionally recommended (10–12 mL kg^{-1}) (Hummler et al. 2000). On the other hand, recent investigations of VILI have led to development of a new approach to the conventional volume-cycled MV (CMV), described as a 'lung-protective' mode (Petrucci & Iacovelli 2004). This approach recommended a low V_T (6 mL kg^{-1}) with an appropriate level of positive end-expiratory pressure (PEEP) in the airways that is slightly higher than the low inflection point of the pressure–volume curve. In recent years, this 'lung-protective' mode of CMV has become more popular in human critical care units and is gradually displacing the more traditional modes of MV that are now believed to cause injury to the lung. In addition, some modes of high frequency ventilation, including high-frequency percussive ventilation (HFPV), have also been described as being lung-protective (Salim et al. 2004).

As a part of a larger study evaluating modes of MV in a rabbit model of pneumonia, the present report evaluated the dose of ketamine/xylazine used to maintain anesthesia in rabbits breathing spontaneously or ventilated with three different modes of MV during a 3-hour ventilation period prior to the inoculation of bacteria. In addition, the number of side effects and complications (variations in heart rate, inadequate gas exchange, delayed recovery from anesthesia) were compared among the four groups. In the present report the dose of ketamine/xylazine was compared in two ways. First, ventilated rabbits were compared with spontaneously ventilating (SV) rabbits to evaluate the general effects of MV. Second, anesthetic dose in 'lung-protective' modes of CMV and HFPV were compared with rabbits ventilated by the conventional CMV-1 mode to determine any variation in the use of anesthetics specific to a particular mode of MV. To our knowledge, this is also the first report on the use of HFPV in rabbits.

Materials and methods

The study was approved by the US Army Institute of Surgical Research Research Council Animal Care and Use Committee (IACUC) and followed the National Research Council's Guide for the Care and Use of Laboratory Animals.

Male Specific Pathogen Free New Zealand white rabbits (4.75 ± 0.25 kg) were obtained. After arrival, all animals were placed in quarantine for 7 days in individual cages and fed *ad libitum* commercial feed. Water was freely available. The health status of each rabbit was confirmed by the Institute's veterinary staff before commencing each experiment.

On the day of the experiment, rabbits were premedicated with glycopyrrolate (0.008 mg kg^{-1}, IM), anesthetized with ketamine hydrochloride/xylazine hydrochloride (35 mg kg^{-1}/5 mg kg^{-1}, IM), and after 2–3 minutes of inhalation of 100% O_2 (through a face mask), the tracheas intubated with a 3.5–4 mm cuffed tube (ETT). Intubations were performed blindly and sounds of breathing through the ETT, noticeable expirations of air and water vapor in the lumen of the ETT were helpful for confirmation of correct positioning. Auscultation was also used to confirm correct placement. No neuromuscular blocking agents were used during

the experiment. After endotracheal intubation, rabbits were positioned in sternal recumbency and randomized into four groups. Rabbits in group 1 (CMV-1; $n = 14$) were ventilated with a volume-cycled conventional mode of mechanical ventilation (CMV): $V_T = 12$ mL kg^{-1}, PEEP = 0 cmH_2O; RR = 20 minute^{-1}, $FiO_2 = 0.5$, inspiratory:expiratory (I:E) ratio = 1:2. Group 2 animals (CMV-2; $n = 13$) were ventilated with volume-cycled 'lung-protective' CMV: $V_T = 6$ mL kg^{-1}, PEEP = 5 cmH_2O; RR = 40 minute^{-1}, $FiO_2 = 0.5$, I:E ratio = 1:2. Rabbits from group CMV-1 and CMV-2 were ventilated using a Siemens Servo 300-A ventilator (Siemens AG, Munich, Germany). Rabbits in the third group (HFPV; $n = 17$) were ventilated with HFPV (VDR 4; Percussionaire Corporation, Sandpoint, ID, USA): high-frequency oscillations (450 minute^{-1}) superimposed on 40 minute^{-1} low-frequency respiratory cycles, I:E ratio = 1:1, oscillatory continuous positive airway pressure (CPAP) of 7–10 cmH_2O and demand CPAP of 8–10 cmH_2O, $FiO_2 = 0.5$. Rabbits from group 4 (SV; $n = 17$) were anesthetized, the trachea intubated, and breathed air supplemented with oxygen ($FiO_2 = 0.5$) spontaneously. Rabbits were placed on a heating pad to maintain body temperature at 38–40 °C, measured using a rectal probe (Suckow & Douglas 1997). The duration of the ventilation period was 3 hours. All experiments were performed under the same conditions and with a similar level of anesthesia using established criteria, as indicated by monitoring heart rate, lack of a righting reflex and jaw tone and testing the palpebral and pedal withdrawal reflexes every 7–10 minutes as previously described (Wyatt et al. 1989; Borkowski et al. 1990). Additional doses of ketamine/xylazine (10 mg kg^{-1}/2 mg kg^{-1}; IV) were administered intravenously as necessary to maintain anesthesia at a plane deep enough to prevent spontaneous movement, other than respiration, according to the above criteria. Animals were observed continuously. Generally from our earlier experience, if we noticed intense blinking or a slight movement or twitching of the animal, we had approximately 30–45 seconds, but no more than 1 minute, to administer additional anesthetic agents before the animal showed movement, such as extension of the legs or chewing on the ETT. After 3 hours, the rabbits were allowed to recover. If the animal remained fully anesthetized without purposeful movement at 3 hours and 15 minutes, the α_2-adrenergic receptor antagonist, yohimbine (0.2 mg kg^{-1}; IV), was administered to reverse the effects of xylazine and hence hasten recovery. This was to assure that all rabbits received additional treatment (beyond the scope of this report) at a similar time after the end of the MV period.

Select hemodynamic parameters and temperature-corrected blood gases were monitored during the experiment to maintain animals within normal physiologic limits. According to the study protocol these included: heart rate and oxyhemoglobin saturation (SpO_2) using a pulse oximeter, and end-tidal carbon dioxide ($P_E'CO_2$), by nondispersive infrared gas concentration measurement by an HP Anesthetic Gas Module M1026A (Hewlett-Packard, Andover, MD, USA). Gas sampling for the $P_E'CO_2$ determinations was made via a side stream port at the proximal end of the ETT. Arterial blood gases (ABG), drawn from the central artery in the ear, were determined at 15 minutes, and 1, 2, and 3 hours after intubation using the AVL Omni Modular System (AVL Medical Instruments; Roche Omni Systems, Basle, Switzerland). pH, $PaCO_2$, PaO_2, HCO_3^-, base excess (BE), and lactate concentration in arterial blood obtained from the ABG and co-oximeter, were selected for subsequent statistical analyses. Co-oximeter data were not corrected for hemoglobin concentrations as these remained unchanged through the course of this study. Physiologic dead space was calculated from the Bohr equation: $PaCO_2 - P_E'CO_2/PaCO_2$.

The following intervals in controlled parameters were considered as 'acceptable norms' for the present study: heart rate = 200–300 beats minute^{-1}, SpO_2 >90% (on $FiO_2 = 0.5$), $P_E'CO_2$ = 35–45 mmHg; pH = 7.30–7.50; $PaCO_2$ 20–46 mmHg; PaO_2 85–102 mmHg; HCO_3^- = 24–28 mEq L^{-1}; standard BE = 0 ± 2.5 mEq L^{-1}; lactate concentration <2 mmol L^{-1} (Wyatt et al. 1989; Suckow & Douglas 1997).

Statistical analysis

When appropriate, data are presented as mean ± SD. To compare the distribution of controlled parameters among groups, analysis of variance was performed using SPSS version 10.1 (SPSS Inc., Chicago, IL, USA). *Post hoc* tests among groups utilized *t*-tests using Bonferroni correction for multiple comparisons ($f < 0.0125$ for $p < 0.05$). The Fisher's exact test was used to compare categorical variables (yohimbine administration). $p < 0.05$ was considered significant.

Results

There were no significant differences among the groups in the rabbits' average body weights, temperatures and initial heart rates (data not shown). All 61 rabbits were successfully pre-medicated, anesthetized, intubated, mechanically ventilated (except the SV group), allowed to recover from anesthesia and the trachea extubated. No life-threatening complications were recorded in any animal during the 3-hour period.

Comparing ventilated and SV groups of animals, the CMV-1 group received fewer doses of ketamine/xylazine than the SV group ($p < 0.001$), while the HFPV group received more ($p < 0.05$) during the 3 hour experimental period (Fig. 1). It was observed that the interval between ketamine/xylazine doses in the CMV-1 and CMV-2 groups averaged 49 ± 6 and 46 ± 10 minutes, respectively, whereas the intervals between doses in the HFPV and SV groups were 36 ± 6 and 35 ± 6 minutes, respectively. As a consequence, among ventilated rabbits, the total number of ketamine/xylazine injections required to maintain anesthesia was lowest in the CMV-1 group and highest in the HFPV group (3.0 *versus* 5.0, $p < 0.05$) (Fig. 1). When compared with CMV-1 as the standard mode of MV, ketamine/xylazine dose in the HFPV group was significantly higher (Fig. 1).

Yohimbine was administered more often to rabbits in the CMV-1 group (in 50% of rabbits) compared with HFPV and SV groups (12%; $p < 0.05$; Fig. 1). The use of yohimbine did not correlate with the total dose of anesthetic drugs among the groups of rabbits (Fig. 1). In addition, the time of the last dose of ketamine/xylazine did not relate to whether the animal received yohimbine.

In all groups of rabbits at least a few abnormalities in monitored parameters were detected during the experiment. Although lactate concentration did not differ significantly among groups, the averages were higher than our institutional reference norm (<2 mmol L^{-1}) in all groups at the first time point (15 minutes after intubation). For example, lactate concentration was highest in the CMV-1 group (4.9 ± 3.3 mmol L^{-1}) and lowest in the SV group (3.1 ± 2.4 mmol L^{-1}). This remained high over the next hour in the CMV-1 and HFPV groups (3.3 ± 2.4 and 3.1 ± 2.4 mmol L^{-1}, respectively). BE was slightly higher than the reference range in all groups of rabbits throughout the duration of the experiment, and differences among groups were not statistically significant (data not shown). The highest mean BE was observed at 2 hours after intubation in the SV group (+6.5 ± 4.3 mEq L^{-1}).

No significant differences in heart rate (Fig. 2), SaO_2, $P_E'CO_2$, and HCO_3^- were observed in the groups of rabbits at any time points (data not shown). Other measured physiologic and laboratory parameters (pH, PaO_2, and $PaCO_2$) had significant differences among the groups only at some time points (Fig. 2). PaO_2 in the SV group was significantly higher than in the other groups at 15 minutes, which was attributed to initial hyperventilation in these animals. PaO_2 was similar among groups through the remainder of the experiment. In all groups average $PaCO_2$ values

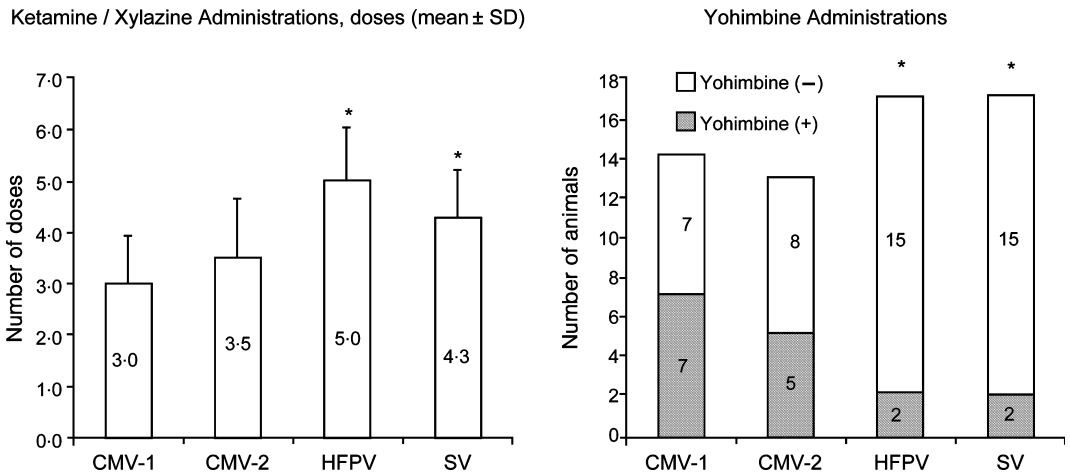

Figure 1 Effect of different modes of ventilation on number of doses and frequency of yohimbine use in rabbits (mean ± SD). *$p < 0.05$ (from CMV-1).

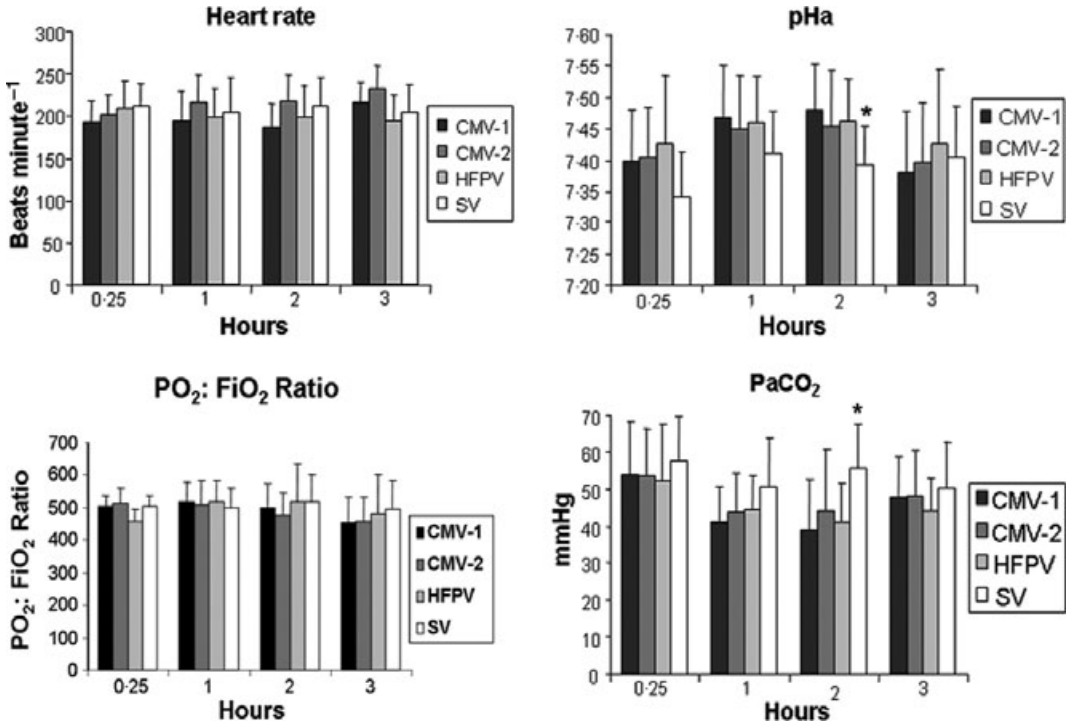

Figure 2 Effects of different modes of ventilation on heart rate, pH, $PaCO_2$ and PaO_2 (mean ± SD). *$p < 0.05$ (from CMV-1).

were >45 mmHg by 15 minutes after intubation (Fig. 2). This parameter normalized over time in all groups of rabbits with the exception of the SV group, which remained above 45 mmHg throughout the study (Fig. 2). At 2 hours after intubation, $PaCO_2$ was higher and pH lower in SV animals than in ventilated rabbits, but these variables were similar among groups at the other times (Fig. 2). In addition, there were no significant differences in physiologic dead space among the groups at the start or end of the 3 hour study period. Physiologic dead space values 15 minutes after the start of ventilation were (in mL kg^{-1}): CMV-1, 0.24 ± 0.05; CMV-2, 0.27 ± 0.07; HFPV, 0.26 ± 0.05; and SV, 0.29 ± 0.04. At 3 hours, these values were (in mL kg^{-1}): 0.21 ± 0.08, 0.28 ± 0.07, 0.24 ± 0.08, and 0.25 ± 0.08, respectively.

Discussion

To our knowledge, this is the first study to investigate the influence of different modes of MV on dose requirements for anesthesia in rabbits. The results indicated that some modes of MV affected ketamine/xylazine use differently than others. For example, it was found that rabbits subjected to CMV-1 and CMV-2 regimes of ventilation required fewer doses of anesthetic. As the average time between anesthetic doses was longer in these groups than in the HFPV and SV groups, these animals often remained anesthetized at the end of the 3 hour experimental period. Consequently, more animals in CMV-1 and CMV-2 received yohimbine for anesthesia reversal than rabbits in the other groups. The results also indicated that HFPV ventilation was associated with a comparatively shorter duration of anesthesia compared with the other ventilation groups. In our experiment, settings for HFPV were based on the manufacturer's instructions for pediatric clinical practice. However, it is not known whether these were the ideal settings for rabbits.

In the present study, no relationship between anesthetic use and monitored ventilation-related metabolic features was found. However, it could be hypothesized that the shorter times between anesthetic doses in the HFPV group could be related to the distinctive features of HFPV, such as constant vibration of the thorax and upper abdomen associated with the high-frequency component of ventilation. Possibly, this vibration intensifies liver blood flow and results in more effective metabolism of ketamine/xylazine. It is well known that the meta-

bolism of anesthetics can be affected by change in body temperature or hemodynamics. In the present study, body temperature was maintained relatively constant. However, positive pressure ventilation can reduce cardiac output in both humans and experimental animals (Cournand et al. 1948; Pepe et al. 2003, 2004). In addition, ketamine has been reported to increase cardiac output, while xylazine decreased it (Wyatt et al. 1989). In the present study, we did not determine cardiac output, so it remains unknown whether HFPV or the other modes of MV investigated in the current study had an affect on cardiac output sufficient enough to alter metabolism of the anesthetics.

It is possible that thoracic and abdominal trembling, as seen in animals ventilated with HFPV, could be a source of continuous mechanical stimuli for sensory neurons that result in additional activation of the central nervous system. At present, the exact cause for the differential requirement for ketamine/xylazine in this study remains unknown. Based on the results of the current study, continuous ketamine administration may be more preferable in rabbits ventilated with HFPV than bolus IV injections. Further studies to address the unique effects of HFPV in rabbits seem warranted.

In the present study, rabbits in the SV group showed some gas exchange changes manifested by hypercapnia and a respiratory acidosis. In contrast to a previous study (Wyatt et al. 1989), hypoxemia was rare in the present study, possibly related to the differences in FiO_2 between the two studies. From the PaO_2 values reported by Wyatt et al. (1989), it would appear that their animals breathed room air, whereas the FiO_2 in the present study was 0.5. In addition, lactate concentrations remained similar or deceased over the 3 hour period, also suggesting that systemic hypoxia was not developing in these animals.

Conclusion

To our knowledge, this is the first study to evaluate different modes of MV (particularly HFPV) in rabbits anesthetized with ketamine/xylazine. The mode of respiratory support appeared to affect anesthetic dose but further work needs to be carried out to ascertain the reasons for this change. In adult New Zealand white rabbits during anesthesia with a ketamine/xylazine mixture, respiration could be successfully supported with HFPV and different modes of CMV: traditional (with high V_T) and modern (with low V_T). Anesthesia with ketamine/xylazine in spontaneously breathing rabbits resulted in respiratory depression which should be considered when this mixture is used for extended periods in studies where pulmonary function is being evaluated.

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References

Aye T, Milne B. (2002) Ketamine anesthesia for pericardial window in a patient with pericardial tamponade and severe COPD. Can J Anaesth 49, 283–286.

Borkowski GL, Danneman PJ, Russell GB (1990) An evaluation of three intravenous anesthetic regimens in New Zealand rabbits. Lab Anim Sci 40, 270–276.

Cournand A, Hurley ML, Werko L et al. (1948) Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. Am J Physiol 152, 162–174.

Difilippo SM, Norberg PJ, Suson UD et al. (2004) A comparison of xylazine and medetomidine in an anesthetic combination in New Zealand White Rabbits. Contemp Top Lab Anim Sci 43, 32–34.

Flecknell PA (1996) Special techniques. In: Laboratory Animal Anaesthesia (2nd edn). Academic Press, London, UK, pp. 105–109.

Gonzalez GA, Illera JC, Silvan G et al. (2002) Changes in hepatic and renal enzyme concentrations and heart and respiratory rates in New Zealand White rabbits after anesthetic treatments. Contemp Top Lab Anim Sci 41, 30–32.

Haskins SC (2003) Positive pressure ventilation. In: Textbook of Small Animal Surgery (3rd edn). Slatter D (ed.). Saunders, Philadelphia, PA, pp. 2623–2629.

Hummler HD, Schulze A, Pohlandt F et al. (2000) Dynamics of breathing during partial liquid ventilation in spontaneously breathing rabbits supported by elastic and resistive unloading. Pediatr Res 47, 392–397.

Imai Y, Parodo J, Kajikawa O (2003) Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. JAMA 289, 2104–2112.

Maeda Y, Fujino Y, Uchiyama A (2004) Effects of peak inspiratory flow on development of ventilator-induced lung injury in rabbits. Anesthesiology 101, 722–728.

Paddleford RR (1996) Pulmonary dysfunction. In: Lumb & Jones' Veterinary Anesthesia (3rd edn). Thurmon J,

Tranquilli W, Benson G (eds). Williams & Wilkins, Baltimore, MD, pp. 771–775.

Pepe PE, Raedler C, Lurie KG et al. (2003) Emergency ventilatory management in hemorrhagic states: elemental or detrimental? J Trauma 54, 1048–1057.

Pepe PE, Lurie KG, Wigginton JG et al. (2004) Detrimental hemodynamic effects of assisted ventilation in hemorrhagic states. Crit Care Med 32, S414–S420.

Petrucci N, Iacovelli W (2004) Ventilation with smaller tidal volumes: a quantitative systematic review of randomized controlled trials. Anesth Analg 99, 193–200.

Qiu HB, Yan YL, Yang Y (2004) Effect of lung protective ventilation strategy on pulmonary inflammatory response in a rabbit model of acute respiratory distress syndrome. Zhonghua Jie He He Hu Xi Za Zhi 27, 298–301.

Salim A, Miller K, Dangleben D et al. (2004) High-frequency percussive ventilation: an alternative mode of ventilation for head-injured patients with adult respiratory distress syndrome. J Trauma 57, 542–546.

Short CE (1987) Principles and Practice of Veterinary Anesthesia. Williams & Wilkins, Baltimore, MD, p. 425.

Suckow MA, Douglas FA (1997) The Laboratory Rabbit. CRC Press, Boca Raton, FL, p. 7.

Sumitra M, Manikandan P, Rao KV et al. (2004) Cardiorespiratory effects of diazepam-ketamine, xylazine-ketamine and thiopentone anesthesia in male Wistar rats – a comparative analysis. Life Sci 75, 1887–1896.

Vogler GA (1997) Anesthesia equipment: types and uses. In: Anesthesia and Analgesia in Laboratory Animals. Kohn D, Wixon S, White W, Benson G (eds). Academic Press, San Diego, CA, pp. 105–147.

Wyatt JD, Scott RA, Richardson ME (1989) The effects of prolonged ketamine-xylazine intravenous infusion on arterial blood pH, blood gases, mean arterial blood pressure, heart and respiratory rates, rectal temperature and reflexes in the rabbit. Lab Anim Sci 39, 411–416.

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