SOUTHERN RESEARCH

Legendary Discoveries. Leading Innovation.

PERFORMANCE OF THE SOUTHERN RESEARCH NONHUMAN PRIMATE PLETHYSMOGRAPHY SYSTEM

J.K. BOHANNON, Z.N. Llewellyn, J.E. Trombley, J.A. Boydston, and L.E. Bowen

Abstract

Background

Respiratory dosimetry for nonhuman (NHP) primates requires the estimation or measurement of the respiratory ventilation. Several formulas based on weight are available to estimate NHP ventilation. However they are usually determined using alert animals and are not directly applicable to testing with anesthetized animals. Therefore, Southem Research tested a custom plethysmography system with a cylindrical head-out plethysmography plenum, amplifier, pneumotachographs, pressure transducer, and IOX software (emka TECHNOLOGIES USA, Falls Church, VA) for NHPs.

Methods

The plethysmography system was calibrated by injection of a known volume of air into the sealed plethysmography plenum. The volume of air was dependant on the body weight range of the NHPs. The pressure drop propagated across the pneumotachographs was detected by the pressure transducer and relayed to the amplifier. The amplified pressure signal was integrated into a flow rate using the IOX software. NHPs were lightly sedated and fitted with rubber dental dam collars prior to testing. The collars fit snuggly enough to provide a good seal but did not restrict ventilation. NHPs were placed in the plethysmography plenum in a supine position and the dental dam collar was placed around the animal's neck. Respiratory frequency, tidal volume, and minute ventilation were collected.

Results

The plethysmography system was calibrated using simulated tidal volumes of 30 ml, 40 ml, and 60 ml. NHPs weighing 2.5 - 4.0 kg were tested using the plethysmography system. The mean breathing frequency was 15.6 ± 3.5 breaths per minute, the mean tidal volume was 31.8 ± 16.0 cm^3, and the mean minute ventilation was 0.5 ± 0.2 L/min.

Conclusions

The head-out plethysmography system was calibrated and used to determine respiratory frequency, tidal volume, and minute ventilation data in anesthetized NHPs. Our results are consistent with published data.

Introduction

Bioaerosol concentration, minute ventilation, and inhalation challenge duration are required to determine respiratory dosimetry in NHPs. NHPs are usually anesthetized during bioaerosol inhalation challenge which depresses respiration and makes the use of mathematical equations to estimate minute ventilation impractical. Plethysmography can be used to accurately measure NHP inspiratory tidal volume and breathing frequency which can be integrated to give minute ventilation. Southern Research tested the emka TECHNOLOGIES head-out NHP plethysmography system which includes a custom designed cylindrical plethysmograph. The plethysmograph has a portal with an attached platform that slides in and out of the plethysmograph body for easy loading and unloading of the NHP. The portal is fitted with a pre-cut section of dental dam material that fits securely around the neck of the NHP and is sealed by an o-ring on the plethysmograph body. A picture of the NHP head-out plethysmograph is shown in Figure 1. Two pneumotachographs, located at the back of the plethysmograph, use a series of 200 mesh stainless steel screens to produce a change in pressure detected by a transducer. The pressure signal is amplified, processed by the A/D convertor, and integrated by the IOX software into the respiratory functional components.

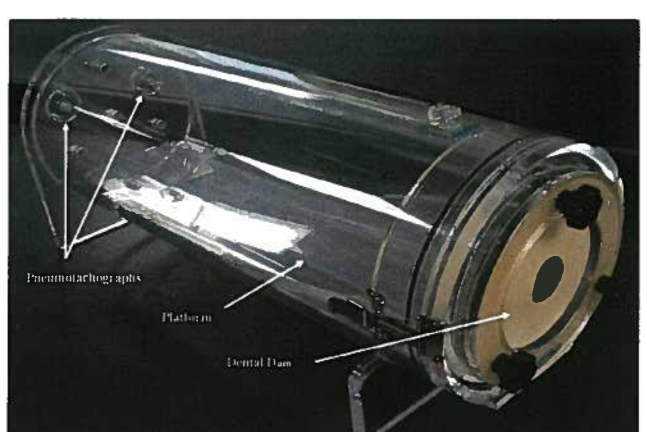

Figure 1. The Southern Research NHP Head-out Plethysmograph

Introduction (Continued)

The IOX software displays a real-time pulmonary wave form of an anesthetized NHP. The views edit screen can display multiple pulmonary parameters simultaneously.

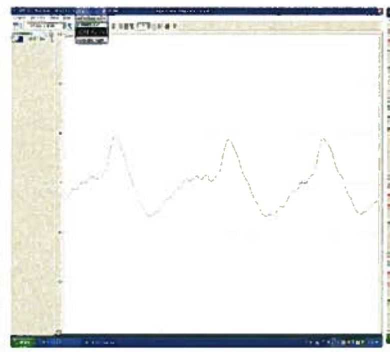

Figure 2. Signal screen of NHP pulmonary wave form.

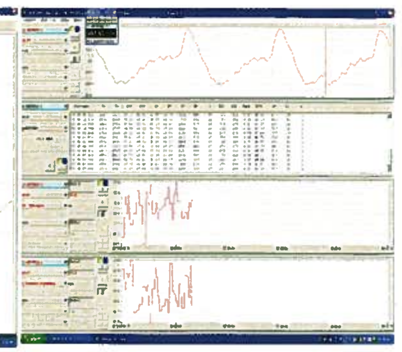

Figure 3. Views screen of pulmonary wave form, data table, Tidal Volume and Accumulated Volume trend graphs.

Methods

- The plethysmograph was calibrated before each experiment by injecting a 30 mL, 40 mL, or 60 mL bolus of air into the sealed plenum to simulate a NHP tidal volume.
- NHPs were pre-anesthetized with Ketamine HCl and a catheter was placed in a saphenous vein.
- NHPs were anesthetized with a continuous infusion of Propofol™ using a syringe pump.
- Anesthetized female NHPs weighing 2.5-4.0 kg were placed into the plethysmograph and fitted with a dental dam collar.
- An exposure mask was placed over the snout of the NHP to simulate a bioaerosol challenge.
- The pressure differential generated across the pneumotachographs was detected by the pressure transducer, amplified, and integrated by the IOX software.
- NHP tidal volume, breathing frequency, and minute ventilation were recorded for approximately 10 minutes.
- NHP Minute Ventilation estimates were calculated using Guyton's Formula[1] with a mean body weight of 3.03 kg.
  - $Vm = 2.10 \times (g)^{0.75}$
- NHP Minute Ventilation estimates were calculated using Bides' Formula[2] with a mean body weight of 3.03 kg.
  - $Vm = 0.499 \times (kg)^{0.809}$
- A schematic of the plethysmograph with an anesthetized NHP is shown in Figure 4.

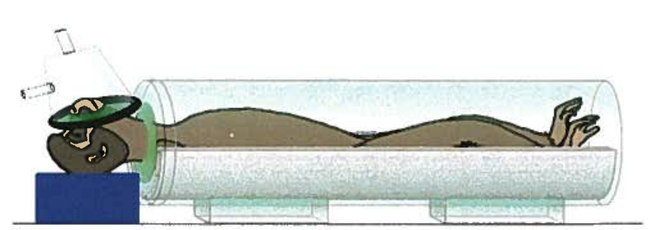

Figure 4. Anesthetized NHP Inside Plethysmograph

Results

- The mean inspiratory tidal volume was 31.8 ± 16.0 cm^3
- The mean breathing frequency was 15.6 ± 3.5 breaths per minute
- The mean minute ventilation was 0.5 ± 0.2 L/min

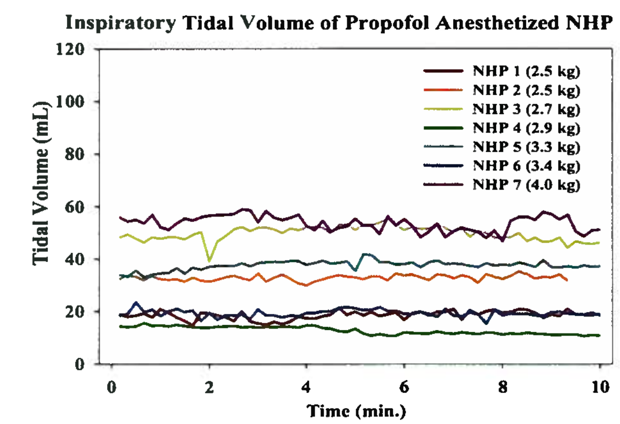

Figure 5. NHP Inspiratory Tidal Volume

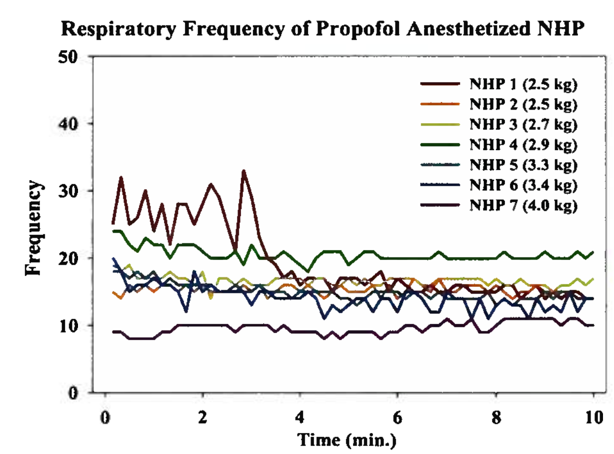

Figure 6. NHP Breathing Frequency

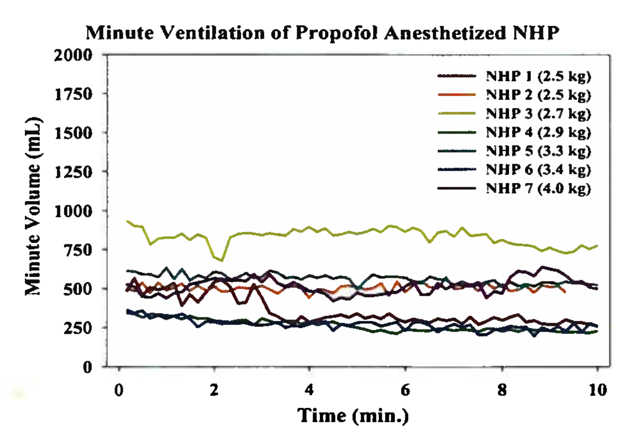

Figure 7. NHP Minute Ventilation. Minute Ventilation = Tidal Volume x Frequency

Results (Continued)

- Mean Minute ventilation estimates for NHPs calculated using Guyton's and Bide's equations were 0.8 L/min. and 1.2 L/min., respectively as compared to observed minute ventilation of 0.5 L/min. See Figure 8.

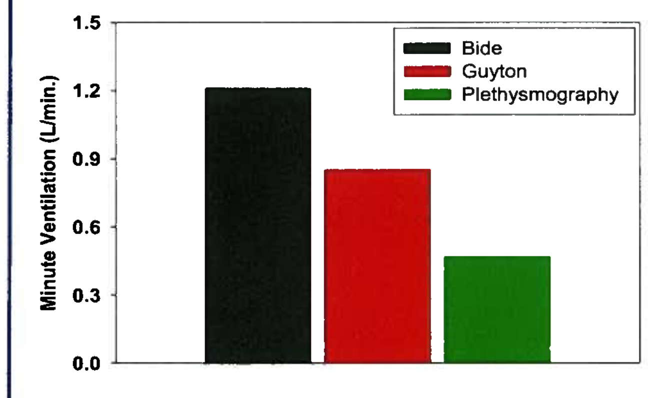

Figure 8. Minute Ventilation Estimates

Discussion

- Respiratory dosimetry for NHPs requires the estimation or measurement of minute ventilation. Guyton and Bide formulas are based on weight to estimate NHP ventilation. However, they are usually determined using alert animals and are not directly applicable to testing with anesthetized NHPs because anesthesia depresses respiratory rate.
- Guyton's and Bide's estimated minute ventilation for alert NHPs overestimated minute ventilation results observed from anesthetized NHPs
- Real-time plethysmography demonstrates a more reliable measurement of minute ventilation when using anesthetized NHPs for inhalation exposures.

Conclusions

The head-out plethysmography system demonstrated that estimated respiratory functions based on animal weight are not applicable for anesthetized NHPs. Our data shows actual respiratory frequency, tidal volume, and minute ventilation in anesthetized NHPs vary from calculated estimates and are consistent with published data.

References

1. Guyton, A.C. Measurement of the Respiratory Volumes of Laboratory Animals. Am J Physiol, 150, 70-77, 1947
2. Bide, RW, et al Journal of Applied Toxicology, 20, 273–290, 2000

Acknowledgements

This work was funded by the National Institutes of Health, National Institute of Allergy and Infectious Disease. Contract N01-AI-30063.

2000 Ninth Avenue South • Birmingham, AL 35205 • www.SouthernResearch.org • BusDev@SouthernResearch.org • (888) 322-1166 • 001 (205) 581-2830