Animal Ventilator for Gated Hyperpolarized Helium MRI

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Abstract- The use of hyperpolarized helium (He-3) as a contrast agent in functional magnetic resonance imaging (fMRI) is an emerging and promising technique for diagnosing diseases and abnormalities in the respiratory tract. Current methodology for animal studies allows fMRI imaging to be performed during inhalation of 100% He-3 every fourth breath. This limitation leads to average scan times of approximately 8 minutes for a diagnostic scan (scan parameters with breath gating). This paper will discuss the production of a ventilation device that delivers an 80:20 ratio of hyperpolarized helium and oxygen gas mixture so that image acquisition can be performed with every breath, decreasing scan time by a factor of 4. This device is needed to function as an oxygen ventilator and serve as the means to integrate He-3 into the respiratory tract of anesthetized small animals with every breath.

Index Terms- animal ventilator, hyperpolarized helium, He-3 MRI, fMRI

I. Introduction

Medical imaging systems have proven their capabilities in diagnostic means and physiological verification. Magnetic Resonance Imaging (MRI) is superior in detecting soft tissue contrast. Another advantage with MRI, unlike Computed Tomography (CT), is the ability to image in oblique planes. This is very advantageous in a number of

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different applications, such as interventional MRI and the diagnosis of abnormal tissues. Due to the highly configurable nature of MRI, various pulse sequences can be written to highlight different aspects of the subject anatomy or physiology.

A relatively newer technique in MRI is the use of hyperpolarized Helium (He-3) as a source of signal. In order for Helium to have the magnetic properties that allow it to be imaged with MRI it must be hyperpolarized (He-3). The hyperpolarization gives the Helium a heightened spin state that is required to give an MR signal. Although there is no natural He-3 in the human body, it can be safely inhaled to achieve signal in the respiratory tract and lung systems, which are often difficult areas to image with conventional MRI because of the air interfaces. Oxygen has a paramagnetic effect that depolarizes He-3, destroying the property that allows it to be imaged[1]. Therefore, great care is taken to avoid mixing the two gases prior to the scanning.

The conventional clinical MRI detects signal from the H^1 protons in the body that resonate within the main magnetic field at 42.58 MHz/T. There are other potential sources of signal in the body, like ^{31}P (11.26 MHz/T) and ^{13}C (10.71 MHz/T) that can be imaged with MRI as well[3]. He-3 MRI utilizes the same magnet except instead of tuning the receiver to detect the signal from H^1, it is tuned to He-3 which resonates at 32.43 MHz/T. Therefore, the scanner detects the signal specifically and solely from He-3. The gas is typically inhaled while the MR scanner acquires the signal. Conventional image reconstruction techniques can be performed with the acquired data to yield images of the signal. During the onset of He-3 inhalation, it is possible in the time-resolved image set to view the signal traveling down the trachea in humans much like the bolus of contrast in Contrast Enhanced MRI (CE-MRI). Thus, He-3 MRI can reveal physiological information about both the structure and therefore function of the respiratory system. Current animal studies are being performed to test the ability and effectiveness of He-3 MRI in diagnosing respiratory diseases. The He-3 MRI interpretation of a respiratory disease can be compared to both Positron Emission Tomography (PET) images and histological examination (see Figure 1).

During current studies the anesthetized small animals are vitally sustained through an oxygen ventilator system (MRI-1 Volume Ventilator, Ardmore PN) that uses pneumatic valves to control breathing rates and tidal volume gas delivery. Previous

integration of He-3 into the animal suppressed the ventilator every fourth breath to allow a stepper motor controlled syringe to deliver the appropriate tidal volume of He-3. Through this method, image acquisition can only be performed every fourth breath when the He-3 is the animal's airways. In order to acquire He-3 signal with every breath and decrease necessary scan time by a factor of four, a dual syringe system was developed. This system integrated oxygen at 20% of the tidal volume through one syringe to sustain life and He-3 at 80% of the tidal volume through the second syringe to allow adequate signal detection from the respiratory system. The following sections will discuss the production of the He-3/Oxygen delivery system, the software developed for user interface and parameter control, the calibration techniques used, and validation testing results.

II. Ventilator Design

The ventilator described in the following sections was designed to provide the same Oxygen delivery as the conventional ventilator and thus is used both to maintain the animal breathing during anesthesia and to provide the He-3 signal for imaging. Until the imaging is performed during the study, the anesthetized animal receives Oxygen through the original ventilator. Once ready, the Oxygen delivery responsibility is transferred to our ventilator. The ventilator design (see Figure 2) incorporates the use of two sliders traveling on two aluminum rods respectively. Each slider is controlled by a rack and pinion gear system. The diameters of each of the two gears are integral dimensions for determining the ratio of He-3 and Oxygen delivered to the animal. Important aspects of the ventilator design are discussed further in this section including material selection, slide design, syringe clip design, pneumatic valve timing, and motor selection.

A. Material Selection

Since this device is used in an MRI environment, choice of materials is extremely important and limited. After some deliberation, Nylon-66 was chosen for the bulk of the materials because of its high strength, durability, ease of machining, and cost. The motor axle containing the gears was machined from an aluminum stock (1 ft. x ¾" diam.) and the motor enclosure and syringe clips made from 1/8" aluminum sheet stock. All machined pieces were attached together using brass screws because brass is non-

ferromagnetic and thus is a MR-compatible metal. It creates minimal adverse artifacts only in the field surrounding the metal. Since the ventilator is kept at the end of the scanner couch, it will not interfere with image quality.

Medical-grade plastic syringes were used as the volume-delivering pistons on the device. The syringes come in two different sizes depending on application: 12 mL syringes for rat ventilation (tidal volumes from 1mL-15mL) and 1mL syringes for mouse ventilation (tidal volumes from 0mL-1mL).

B. Slider Design

This device is used to scan both rats and mice, and therefore the syringes used for delivery of the gasses must be interchangeable. The syringes were placed in front of the sliders to allow for easy access and replacement. Furthermore, the sliders' maximum length was dictated by the maximum stroke length needed for each syringe to deliver the predetermined tidal volume.

C. Clip Design

U-shaped aluminum clips (see Figure 3) allow for four stationary attachment points directly on the slider material. This provides a solid connection between the slider and the syringe, and therefore eliminates any "flexing" or inconsistencies in volume caused by unwanted material movement. The syringe clips are interchangeable as well, and can accompany different syringe sizes as dictated by the animal being scanned.

D. Valve Timing

Three pressure lines control the inspiratory and expiratory pneumatic valves, as well as a He-3/air selection valve. Each valve has three ports, COM, NC and NO. Depending on the pressure in the pneumatic line, the valves selectively connect either NC or NO to COM. Figure 4 shows the configuration of the three valves. The red arrows represent the pressurized lines that control the valves. The valves are controlled by the MRI-1 ventilator on air lines separate from ventilation lines. Two counters are initiated on the NI-6022 which communicate with the MRI-1 ventilator to control the valve states.

The first counter (counter A) controls both the inspiratory and expiratory check valves. The second counter (counter B) controls the He-3/oxygen selection valve. During a scan, counter B maintains the He-3/air selection valve in the He-3 position. Counter A alternates between inspiration and exhalation positions according to the input respiratory rate and percent inspiration time. This system allows the MRI-1 ventilator to support the subject using its internal settings while the software is not running.

E. Motor Selection

For this device a NEMA size 34 stepper motor was used to drive the new ventilator's syringes. This motor was necessary to produce the torque needed to overcome the friction of the syringes. The motor functions in "absolute position" mode, so the software can indicate precisely where the axle should rotate to. A linear function based on calibration data (Figure 5) relates tidal volume to a number of steps for the motor to move with each stroke.

III. Software

To drive the motor component, software was developed using National Instruments (Austin, Texas) LabVIEW 8.2 and a National Instruments NI-6022 Data Acquisition card. The LabVIEW program interacts with the motor's driver/controller via a serial port directly from the computer, interacts with the animal ventilator through a serial port on the NI-6022, and communicates to the scanner via a BNC connection on the NI-6022.

The program functions as a "switch" between the normal animal ventilator and the new He-3 ventilator. Upon initialization, a target breath rate, tidal volume, and percent inspiration (a value 0-100 which determined by the ratio of inspiration to expiration) are set as parameters. Upon clicking the "Start Ventilation" button on the user interface, the program places the MRI-1 animal ventilator on hold. Two counters on the NI-6022 card synchronize the pneumatic valves with the syringe ventilation. Additionally a TTL pulse ("scan trigger") is sent to the scanner at the onset of every breath.

When the He-3 ventilation sequence is completed, the program will end communications with the motor, MRI-1 ventilator, and the scanner. This resumes normal oxygen animal ventilation using the internal settings of the MRI-1 ventilator.

IV. Results

The device was tested using the developed software with He-3 MR imaging. A small bag (2x2 in) was ventilated with a 0_2/He-3 gas mixture. Both gases began in their respective reservoirs and were pumped by their respective syringes at the appropriate 20% 0_2 : 80% He-3 volumes dictated by a 2mL tidal volume. An 80 breath per minute breathing rate was used and passive exhalation was utilized. Scan time was ~9 minutes.

The MRI unit (1.5T General Electric, Waukesha, WI) was properly tuned to pick up the He-3 signal and a conventional protocol was performed for small animal He-3 MR imaging. Projection MR imaging was performed over the time course of a breath and a half and over many trials to get adequate Signal to Noise (SNR) and temporal resolution. The final time data set of images allowed viewing of individual slices of the bag over the time taken for one and a half breaths. Inflow of signal was visible down the delivery tube and entry into the bag as shown in Figure 6. The time resolved data set demonstrates the adequate He-3 delivery by the developed ventilator.

V. Conclusions and Future Work

At the time of submission of this article, calibration had only been performed on the large (12mL) syringes. As one function of this device is to ventilate mice as well as rats, calibration with small (1mL) syringes are also required to accurately deliver tidal volumes on the order of 1mL.

Calculations showed the motor has the capability of delivering to a resolution of 41.9μL for the large syringe and 14.5μL for the small syringe. Since calibration was performed using a rather crude method of manometric analysis (1/8” tubing taped to a meter stick), the accuracy of these resolutions was not confirmed or denied. Higher

quality equipment would be desirable to test the actual resolutions and volumes delivered.

All calibration information was taken performed at a constant motor acceleration and velocity, 50 and 50, respectively. As long as the acceleration and velocity are held constant during ventilation, delivery is extremely accurate. However, during some calibration testing it was found that output volumes changed when these motor parameters were altered. Slower velocities and accelerations resulted in larger delivered volumes.

Preliminary tests to determine why this phenomenon occurs included monitoring output pressure and backflow, neither of which showed signs of variance during fast or slow delivery. Further analyses will be conducted to characterize the effects of delivery speed on volume output.

It is already known from the phantom images shown earlier that the ventilator is delivering enough He-3 for adequate MR signal generation. However, the actual ratio of delivered He-3 to oxygen is yet to be confirmed. It is important that we confirm the gas composition of 80% He-3 and 20% oxygen to ensure adequate oxygen availability for the animal. This test will be accomplished through a direct volumetric study of the pistons' outputs using a manometer or other volumetric tool. If results seem satisfactory, animal testing will be the final step before using the device in animal studies.

After testing, calibration, and validation, the device will be put to use in small animal research studies. Delivering both oxygen and He-3 every breath will reduce the average scan time by a factor of 4 while maintaining image quality. Additionally, high resolution images (acquired through signal averaging) will be obtainable without sacrificing the animal, which makes long term studies possible. Hopefully these benefits will facilitate progress in the field of diagnostic lung imaging.

Acknowledgements

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References

[1] Hedlund, LW.; Moller, H.E.; Chen, X.J.; Chawla, M.S.; Cofer G.P.; Johnson, G.A. (2000) *Mixing oxygen with hyperpolarized He for small-animal lung studies*. NMR Biomed. (2000). Jun;13(4):202-6

[2] Anderson, A, Brown, M, Smith, M, Wegener, C. (2006) *Animal Ventilator for Gated Hyperpolarized Helium MRI*. Dept of Biomedical Engineering, University of Wisconsin. http://homepages.cae.wisc.edu/~bme200/animal_ventilator_f06/

[3] Prince, J.; Links,J.; *Medical Imaging Signals and Systems*. Pearson Education. Upper Saddle River, NJ. (2006).

[4] Holmes et al. *Noninvasive Mapping of Regional Response to Segmental Allergen Challenge Using Magnetic Resonance Imaging and [F-18]Fluorodeoxyglucose Positron Emission Tomography*. Magnetic Resonance in Medicine. (2005). 53:1243-1250.

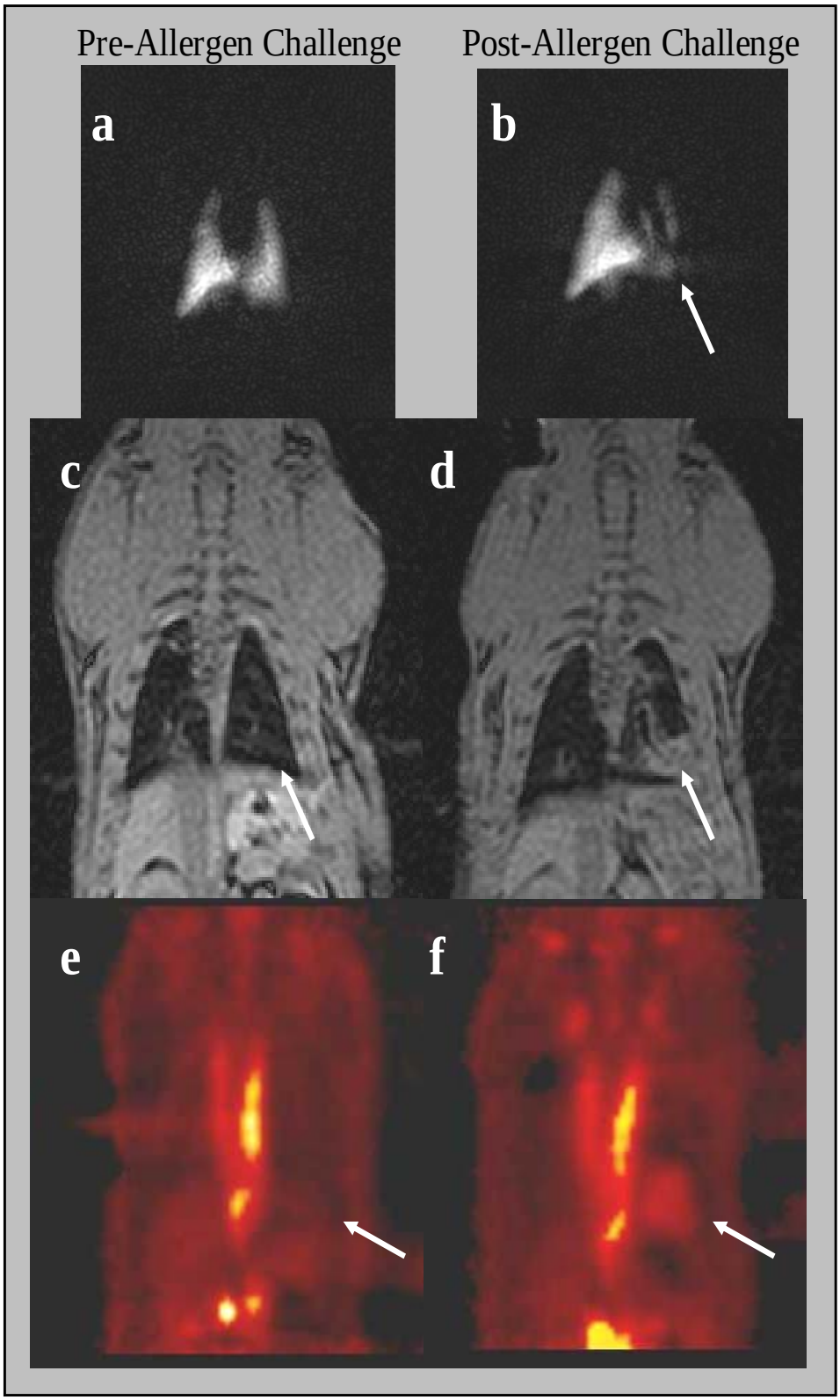

Figure 1. [4].

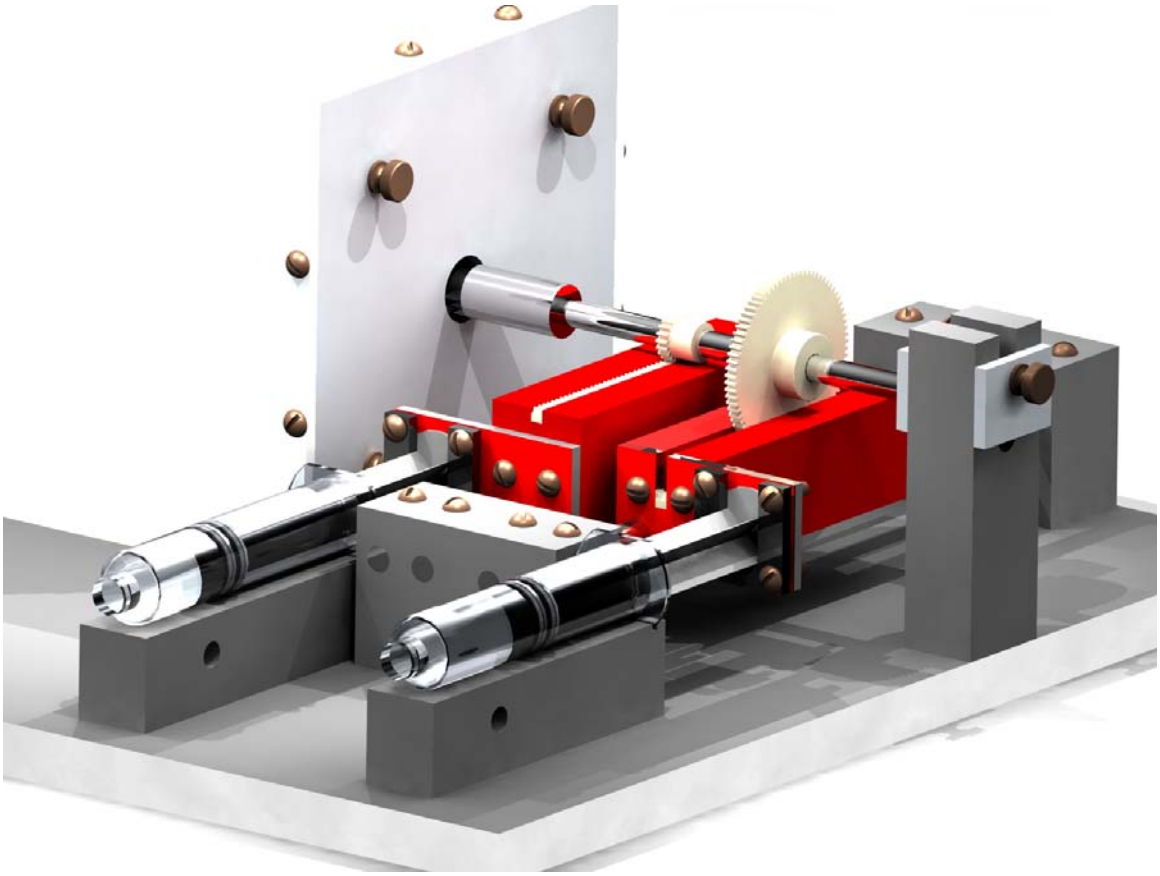

Figure 2. Animal ventilator device showing rack and pinion operation method.

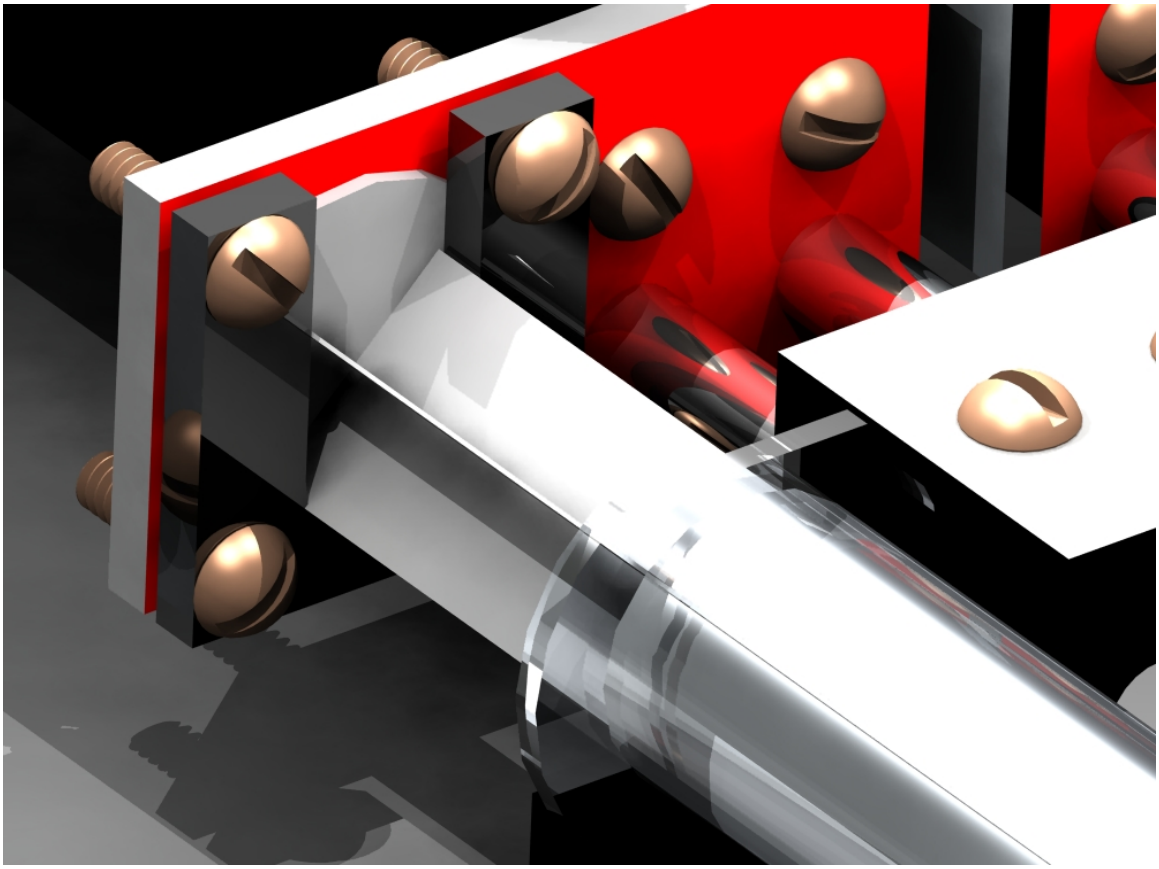

Figure 3. U-clamp design shown with brass screws.

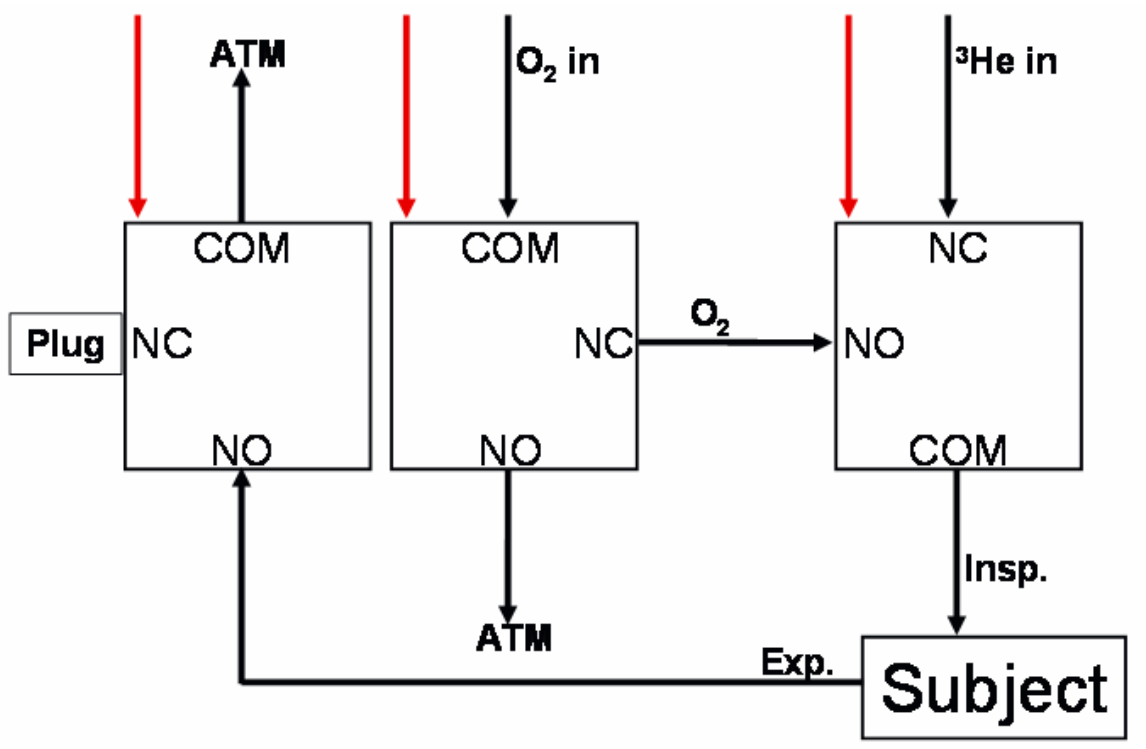

Figure 4. Valve Configuration – From left to right; expiratory check valve, inspiratory check valve, and helium/oxygen selection valve.

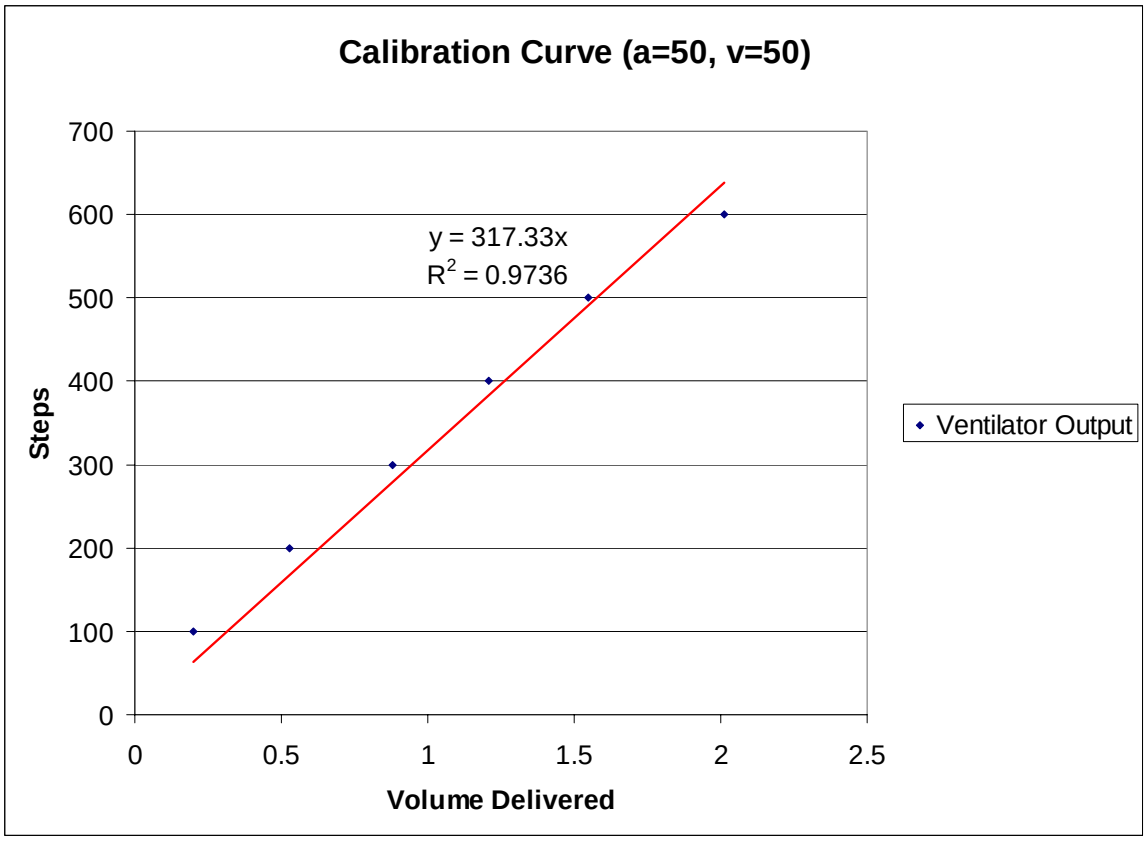
Calibration Curve (a=50, v=50)
700
600
500
400
300
200
100
0
Steps
y = 317.33x
R2 = 0.9736
0
0.5
1
1.5
2
2.5
Volume Delivered
Ventilator Output

Figure 5.

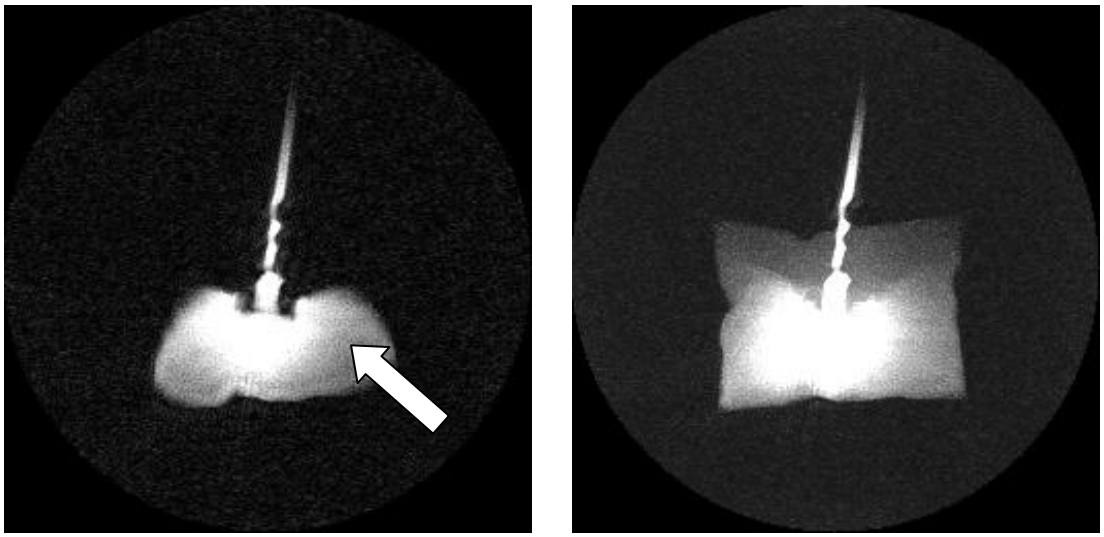

Figure 6. (Left) He-3 image of small ventilated bag with developed ventilator. Gas delivery line is visible. Signal is brightest where gas delivery line opens into the bag (white arrow). (Right) Maximum Intensity Projection of ventilated bag using all slices during one time interval.