Animal Ventilator for Gated Hyperpolarized Helium MRI: Primary Validation and Second Generation Development

BME 400
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Team Members
Ashley Anderson III
Micah Brown
Matt Smith
Chris Wegener

Advisor
Dr. Willis Tompkins
Department of Biomedical Engineering
University of Wisconsin-Madison

Client
Dr. Sean Fain
Department of Medical Physics
University of Wisconsin-Madison

Abstract

The use of hyperpolarized 3-helium as a contrast agent in functional magnetic resonance imaging (fMRI) is an emerging technique for diagnosing diseases or abnormalities in the respiratory tract. Current methodology allows for fMRI scans to be taken during inhalation of helium every fourth breath. A device and/or method is needed to function as an oxygen ventilator and serve as a means to integrate hyperpolarized helium into the respiratory tract of small animals on every breath. This report includes a design that delivers user defined volumes of gas variable frequencies.

Contents

§1 Problem Statement

Create or redesign a small-animal ventilator capable of delivering constant volumes of hyperpolarized 3-helium and oxygen gas (1-20 mL) at user-specified frequencies (1-100 cycles/min) for safe and compatible use in fMRI.

§2 Introduction

Imaging the respiratory tract using traditional MRI methods is very difficult. Our client, Dr. Sean Fain of the Medical Physics Department at the University of Wisconsin – Madison, is using hyperpolarized 3-helium as a contrast agent for fMRI imaging of the respiratory tract. A first generation device has been previously developed by the authors of this report to effectively deliver helium and oxygen into a small animal respiratory tract simultaneously, as to allow for imaging of the tract on every breath. This device will help to save our client and other researchers valuable scan time and allow other types of experimental variables to be implemented quickly and easily. This report will focus on first generation device calibration and design improvements made on the second generation device after delivery of the first generation device.

§3 Background

Helium MRI

Medical imaging systems are useful in diagnosis and physiological verification. Helium Magnetic Resonance Imaging is a fairly newer technique. It utilizes the same scanner as the conventional MR Imaging, except instead of tuning the scanner to Hydrogen, it is tuned to Helium (48.6 MHz). Therefore, the scanner receives the signal that is coded specifically from Helium. The Helium is typically inhaled while the MR scanner performs the imaging. The anatomical

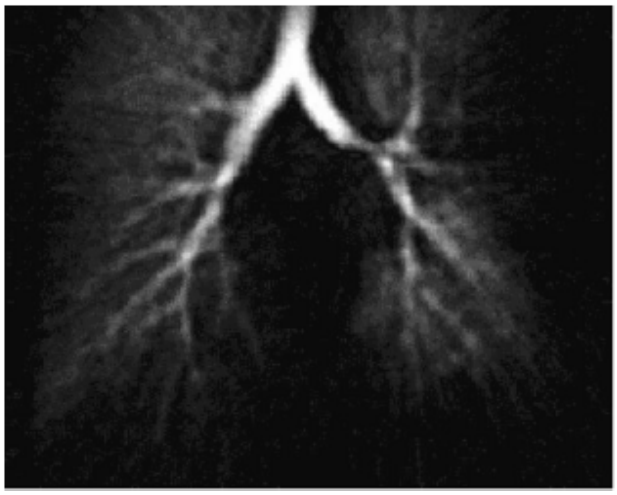


Figure 1. Helium MRI during onset of inhalation. [1]

structures usually imaged with Helium MRI are the respiratory channels and lung systems. During the onset of inhalation, it is possible to see the Helium traveling down the trachea in humans (see Figure 1).

The traditional MR scanner receives signal from the hydrogen already in the body. The Helium, however, needs to be hyperpolarized (3-He) in order to be used in this process. The hyperpolarization gives the Helium a heightened spin state. However, oxygen has a paramagnetic effect that destroys the polarization of 3-He. Therefore, great care is taken to avoid mixing the two gases prior to the scanning.

§4 First Generation Device

A dual piston device was designed and developed by the authors of this report. For information regarding the process and design specifications for the first generation device please refer to Anderson, et al. [2]. Figure 2 shows a graphical rendering of the original device.

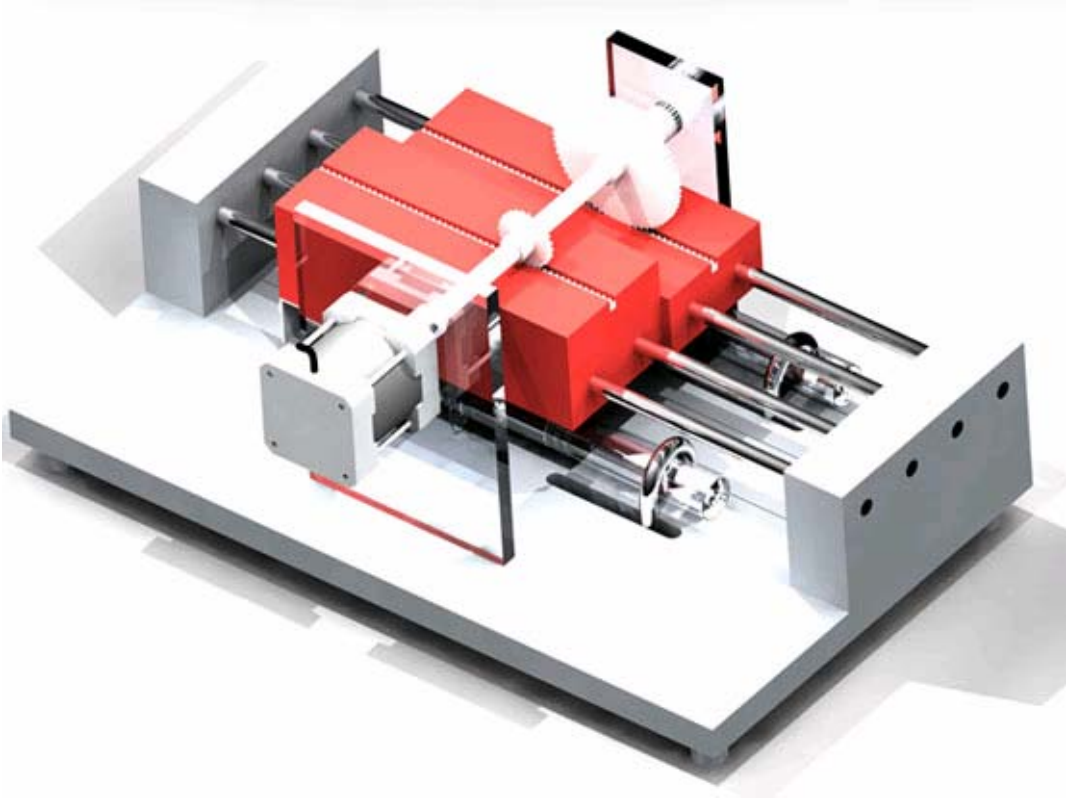


Figure 2. Rendering of first generation device.

§5 First Generation Calibration and Testing

Prior to delivery of the first generation device to the client, several calibration tests were conducted to create an accurate calibration curve for the device. This calibration data was then used to create an equation used to tell the LabVIEW program how many steps the motor must run depending on the user-defined tidal volumes. A target steps/mL was attempted to be found.

Several trials were performed over a range of motor steps, from 250-400 steps. Device output was measured by connecting the prototype to a manometer (tubing mounted to a meter stick) and recorded the water level. After one tidal volume of a specified number of steps, we recorded the end water level. Calculating the difference in water level and dividing by the number of steps gave us "inches/step". We first converted linear inches to mL volume by using the cross sectional area of the inner diameter of the tube and the displacement height of the water (calculated by hand to be 0.201 mL/inch). Inverting this ratio we got our desired step/mL. We then calculated the mL output given by the specified number of steps.

The average steps/mL were then graphed and a line fit to the data (Figure3). The equation for the line served as our calibration equation.

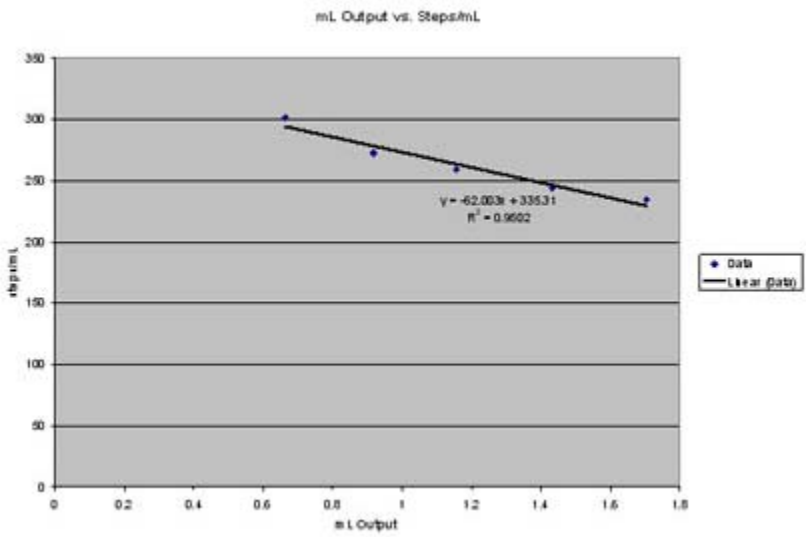


Figure 3. Calculated calibration curve and corresponding fit line.

When the equation that described the output with a given input and entered it into the appropriate LabVIEW VI file, it was attempted to verify that indeed a desired output volume was actually outputted. However, this was not the case. Every time a verification trial was performed, the output was consistently off by no more than 0.3 mL. Although precise, the actual output is not yet accurate. Other trials were done, and equations tried, with no better accuracy. The problem was most likely caused by a deeply rooted constant found somewhere within the large LabVIEW code.

Since the volume delivered was consistently low, the device was able to be used for single piston helium delivery as was used in the client's original set-up.

§6 Second Generation Improvements

This was the second semester of design work done on the device. Several improvements were made to minimize several sources of error shown by the first generation prototype as well as be able to deliver much smaller tidal volumes (>1 mL) to accommodate a mouse. The design elements altered are described below. Descriptions of materials used to construct the second generation device as well as the 2-D part drawings are appended.

Material Selection

Since our device will be used in an MRI environment, choice of materials is very important. Last semester our design team chose to use high-density polyethylene (HDPE). HDPE is a very inexpensive plastic that suited the needs for our first generation prototype. After some deliberation over the wear resistance and machinability of the HDPE, the design team decided to choose another non-ferrous material for bulk parts. While Delrin™ was considered due to its prior use in the project as well as high strength and durability, Nylon-66 was an attractive choice due to its similar material properties and machinabilty at half the cost.

The first generation prototype included a stainless steel axel. The gears were attached to this axel after machining and provided the proper rotation of the gears in order to move the sliders, and therefore the syringes. In an attempt to create a less ferro-magnetic device as well as lower the total weight of the prototype, the switch to

aluminum was made. During the production of the second prototype, it was found that the aluminum was indeed a better choice, as both production time on the lathe and total weight were nearly cut in half

Slider Design

The first design dictated that the syringes were to be placed underneath the sliders. This would keep the syringes in-line with the sliders as well as save space. However, it became nearly impossible to interchange the large and small syringes needed for rats and mice respectively. In the new design, the syringes are placed on the sides of the slider blocks to allow for ease of access and replacement of syringes. Furthermore, the sliders were reduced in size in an attempt to lessen the overall size of the device. This was made possible because the length of travel for the largest syringe to be used was found to be significantly less than originally planned. The new slider design can be easily seen in Figure 4 with drawn plans appended.

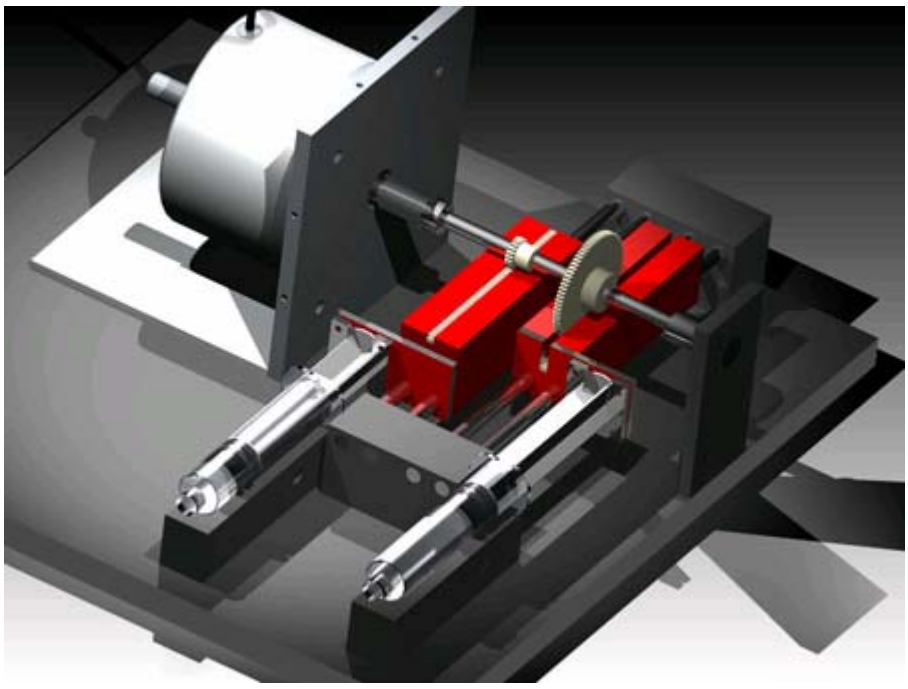


Figure 4. Second generation device rendering. Note reduced size of the overall design as well as the placement of the syringes.

Clip Design

In the first prototype, syringes were clamped to the slider with an L-shaped clamp that had been bent using a single piece of steel and a single thumbscrew. After testing of the device, it was found that this type of clamp design produced an inconsistent volume delivery due to independent clip movement, termed "flexing". The new U-shaped clips allow for four stationary attachment points directly on the slider material. This will provide a more solid connection between the slider and the syringe, and therefore will eliminate any "flexing" or inconsistencies in volume delivery as displayed in the previous design. Refer to Figure 5 for a close up of the design or the drawings in the appendix.

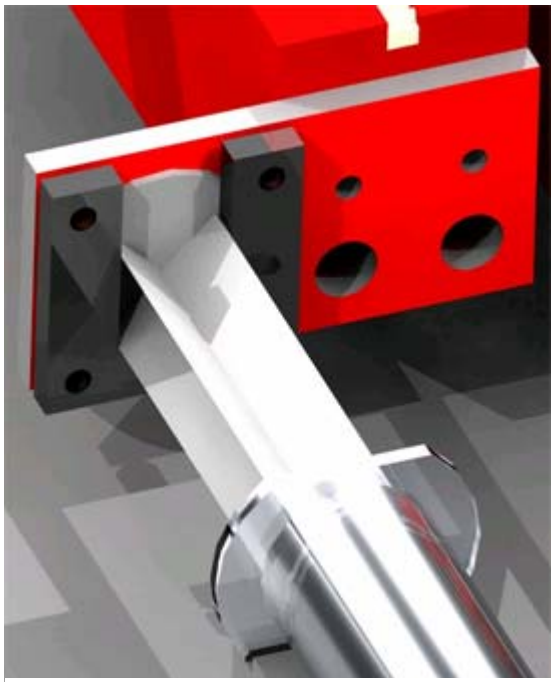


Figure 5. New syringe attachment design features an aluminum clamp tightened with

Valve Timing

Three pneumatic lines control the inspiratory and expiratory check valves, as well as a helium/oxygen selection valve. Figure 1 shows the configuration of the three valves. The red arrows represent the red pneumatic lines. The valves are controlled by the MRI-1 ventilator which receives instructions from the LabVIEW program. The LabVIEW program initiates three counters on an NB-MIO-16 board I/O board. Two of these counters serve to signal the pneumatic lines on the ventilator, while the third is used to monitor the first two. The first counter (counter A) controls both the inspiratory and expiratory check valves. The second counter (counter B) alternates between two signals, *b1* and *b2*, and it controls the helium/oxygen selection valve. This counter switches between the two patterns (*b1* and *b2*) based on a certain interval or number of breaths. Each valve

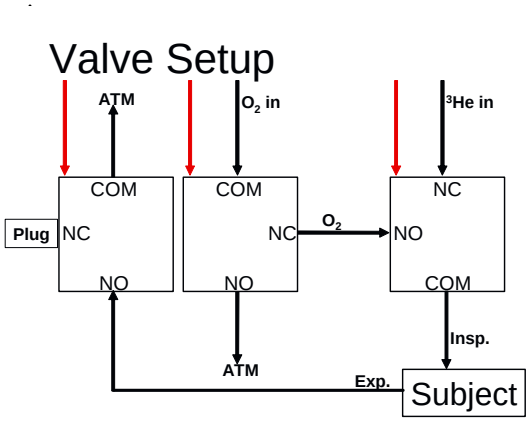
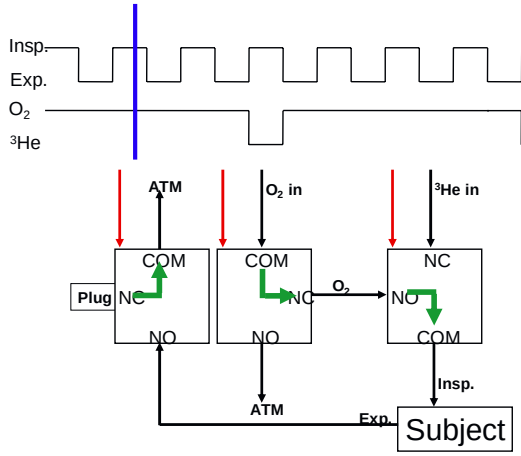
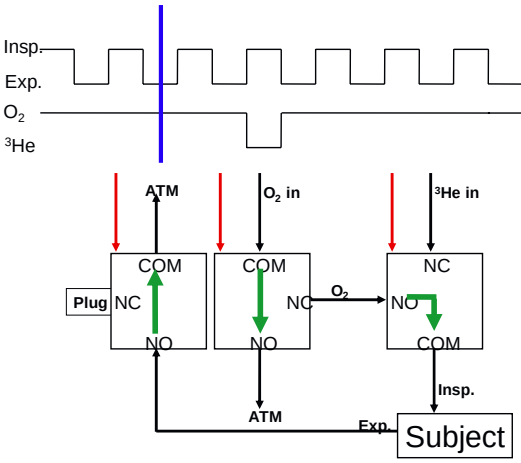


Figure 6. Valve Configuration – From left to right; expiratory check valve, inspiratory check valve, and helium/oxygen selection valve.

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.

In the client's original setup, an issue with the timing of the valves caused a burst of oxygen to be delivered to the subject immediately after every helium breath. This problem was inherited by our first semester design, because that portion of the software was unchanged. Figure 7 is a four-paned sequence showing the valve states for particular counter values. Accompanying descriptions make note of the status of various gasses throughout the ventilation sequence.

	**1. Oxygen Inspiration** Counter A is high (inspired) and counter B is high (oxygen). Counter B is currently in the *b1* state, which has a duty cycle of 1. Oxygen flows into valve 2 from the O2 supply line, then through valve 3 into the subject. Valve 1 obstructs flow through the expiratory tube.
	**2. Oxygen Expiration** Counter B remains high because it is still in the *b1* state with a duty cycle of 1. Counter A has fallen to low, however, which changes the state of both valves 1 and 2. Oxygen now flows directly through valve 2 into the room atmosphere, and the subject is able to passively exhale through valve 1. The state of valve 2 prevents exhaled gas from flowing into the inspiratory pathway.

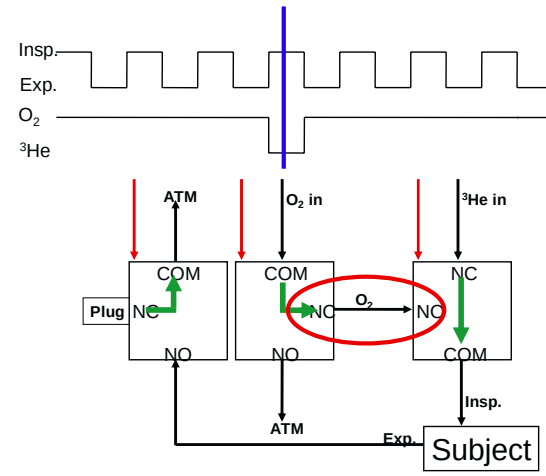
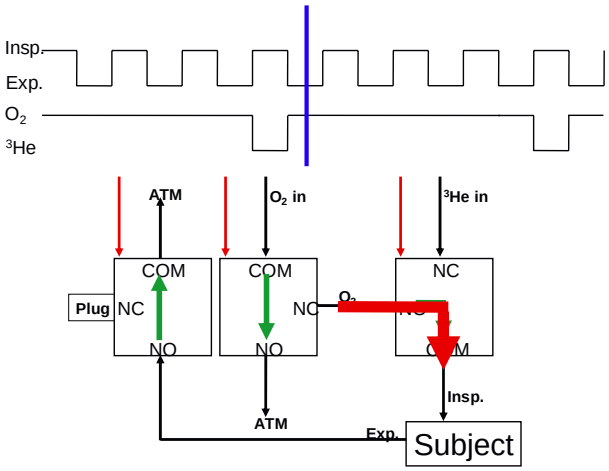
	**3. Helium Inspiration** Counter A is now high again, while counter B has switched to the *b2* state and is low. In the *b2* state counter B has a duty cycle of 0.4, which is based on the inspiration time setting on the ventilator. Here helium (from the syringe pump) flows through valve 3 into the subject. Valve 1 is in the inspiratory, so no gas is able to flow out from the subject. This is where the problem begins. Pressure builds in the line connecting valves 2 and 3 as oxygen is not vented properly.
	**4. Helium Expiration** Counter A falls back to low, and counter B returns to high for the remainder of the *b2* cycle. The pressure that built up in stage 3 is now released and delivered to the subject through valve 3 as an "oxygen chaser." Meanwhile the subject is (attempting to) passively exhale through valve 1. After this breath, counter B would begin producing the *b1* signal for a predetermined number of breaths.

Figure 5. Valve states corresponding to different counter values.

This problem will be irrelevant when our device is used to deliver helium and oxygen simultaneously, and the valve setup will need further reconfiguration. However, our client plans to continue using our device to deliver helium only until we have verified the concentrations of the gasses delivered. To solve the "oxygen chaser" problem, we changed the duty cycle of counter *b2* to zero. This causes valve 3 to remain low through the helium expiration phase, allowing any extra pressure in the line between valve 2 and 3 to bleed off.

Motor Selection

The original motor for our device was a NEMA size 17 stepper motor. This motor lacked the required torque to move the sliders with the syringes in place. To solve this problem, we took the NEMA size 34 stepper motor from our client's previous design and adapted our prototype to accommodate it. This required us to create an extension to the base of our design, a new RF shielding enclosure, and an adapter for our old axle. With the new motor in place, our device worked smoothly with the client's original software and controller setup.

The existing software was calibrated to work with the syringe used in the client's original design. To accommodate our syringes, a few modifications were made to the software. Initially, the software used the given respiratory rate to determine the amount of time allotted to the inspiratory phase. This time, as well as the tidal volume, was used in an equation that determined the "target velocity" for the motor to achieve. This target velocity was the maximum of a trapezoidal piecewise function (Figure 8) representing the acceleration and peak velocity of the motor. The area under this curve represented the linear distance the plunger was withdrawn, thus it was directly proportional to the volume to be delivered. We removed this method in favor of using a calibration curve that relates volume to a number of steps. We achieved moderate success with this new method, and the problems we encountered are attributed to the flawed clip design as discussed in a previous section.

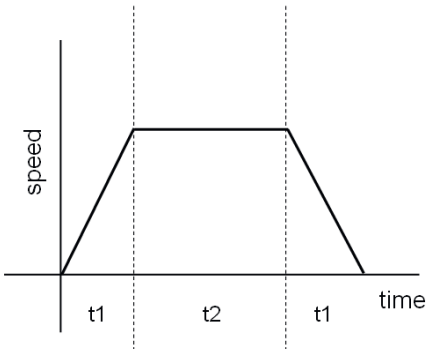


Figure 6. Motor "schedule" as determined by time and volume constraints

§7 Future Work

There is still work to be done in the area of creating a better LabVIEW program to accommodate our second generation device as well as developing a good method for valve integration with our device. There are things that need to be considered when developing the software-mediated aspects of the apparatus. What happens during device failure to ensure that the animal does not suffocate, exhalation timing, and being able to create a full-helium breaths without changing the set-up are just a few.

There are to be three other main areas of future work; tidal volume verification, helium mixing and backflow, and animal efficacy trials.

Tidal Volume Verification

To verify the actual tidal volumes delivered, will require initial testing similar to the procedure described in the first generation prototype calibration section. Some error may have been introduced into our system by the crude manometer created for the test. Commercial manometers and/or flow meters should be pursued for second generation testing. Volumes of oxygen and helium delivered will be measured independently as well as total volume delivered to ensure proper 20/80 ratio will be supplied.

Helium Mixing and Backflow

Another key element in the design of the device is to make sure no mixing of helium or oxygen occurs prior to the desired spot in the tubing. If oxygen does make it into the helium tubes or reservoir, spontaneous depolarization of the hyperpolarized helium will transpire. This reduces the contrast quality and results in a poor image of the respiratory tract.

To ensure this mixing does not occur, actual imaging of the delivery lines will be conducted using either the hyperpolarized helium gas and oxygen or a similar test using gadolinium and another liquid can be used. Reduction of the contrast agent intensity in the MR image or appearance of the contrast agent in undesired areas of the tubing will point to design failure.

Animal Efficacy Trials

Perhaps the most important test that can be run is an *in vivo* test. Upon confirmation of appropriate volume ratio and delivery, the imaging procedure will be tested on an actual rat or mouse subject. This will reveal in the end if the designs success.

§8 References

[1] Hedlund, LW, Moller, HE, Chen XJ, Chawla, MS, Cofer GP, Johnson, GA. (2000) *Mixing oxygen with hyperpolarized He for small-animal lung studies*. NMR Biomed. 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/

Appendix A. Product Design Specifications

Project Design Specification

February 17, 2006

Team Members: Matt Smith, Micah Brown, Chris Wegener, Ashley Anderson

Function:

The function of our device is to deliver a set ratio of a helium/oxygen mix in order to image the airways and lungs of an anesthetized rat within an MRI machine. Currently, the scanning time is longer since the helium contrast agent can only be administered once every four breaths. By incorporating the oxygen into each breath, our client will be able to image every breath and therefore reduce the scan time by a factor of four.

Client Requirements:

- *Must be compatible with MRI scanners. However, since the injection system will be outside the magnet bore, ferromagnetic materials are permissible as long as they are away from the magnetic field.*
- *Oxygen/Helium must be at a ratio of 20%:80%*
- *Title volume of breaths must be variable and controlled by computer*
- *Must minimize the time the oxygen and helium are mixed to reduce the amount of helium depolarization.*

Design Requirements:

1. Physical and Operational Characteristics

a. Performance Requirements- The device must be able to inject a set title volume of 20%:80% oxygen/helium mix into an anesthetized rat every breath.

b. Safety- The device's ferromagnetic components must be outside the magnetic field created by the MR scanner in order to reduce the danger of attraction and presence of artifacts in the scans. Also, the device may not cause any harm to the animals being tested.

c. Accuracy and Reliability- Device must be able to deliver set title amount and set oxygen/helium ratio every breath continuously for the entire scan time (average scan time is 3 minutes)

d. Shelf Life- The device must last up to 5 years, for the entire duration of the client's study.

e. Operating Environment- Must be operated outside the magnetic field of 1.5T produced by the MR scanner. Must be able to withstand daily cleaning with industrial strength disinfectants for sterilization purposes.

f. Ergonomics- The device should be easily transported, set-up, and torn down to reduce the total scan time on the animal.

g. Size and Shape- The device will be incorporated into a 1' cubic box. This will reduce the weight of the device, as well as make setting up the device very easy.

h. Weight- No more than 20 lbs. in order to make the device easily transported.

i. Materials- Ferromagnetic materials are allowed to be used in this design, as the device will be outside of the magnetic field. Aluminum and other light metals will be used to reduce the weight of the device.

j. Aesthetics – It doesn't have to look pretty, function is more important.

2. Product Characteristics:

a. Quantity – Only one device is needed.

b. Target Product Cost- The device should stay within the client budget of $1,000.

3. Miscellaneous:

a. Standards and Specifications- The device should comply to the guidelines setup up by the FDA for medical instruments. Further information is available online at the FDA's website, but it's too extensive to specifically list. The device is subject to performance and safety standards without exemption, for its classification.

b. Patient-related concerns- The patient in this case is an anesthetized rat. The device must not harm the animal in any way.

c. Competition-No known devices exist for the injection of a helium contrast agent to be used for the imaging of a rat's airways and lungs.

Appendix B. Parts List

Black Nylon 6/6 Rectangular Bar 1" Thick, 2" Width, 2' Length	$26.60
Black Nylon 6/6 Sheet 1/2" Thick, 12" X 12"	$34.99
Alloy 6061 Aluminum Hard Anodized Coated Rod 1/4" Diameter, 1' Length	$3.06
Alloy 6061 Aluminum Hard Anodized Coated Rod 1/4" Diameter, 3' Length	$7.57
Knurled Small Diameter Head Shoulder Screw Brass, 6-32 Thread, 1" Length, Packs of 25	$10.79
Brass Flat Head Phillips Machine Screw 6-32 Thread, 1" Length, Packs of 100	$10.49
Alloy 5052 Aluminum Sheet W/Mill Finish .125" Thick, 12" X 24"	$26.27
Molded Nylon 14-1/2 Deg Angle Spur Gear 48 Pitch, 20 Teeth, 0.417" Pitch Dia, 1/8" Bore	$2.82
Molded Nylon 14-1/2 Deg Angle Spur Gear 48 Pitch, 80 Teeth, 1.667" Pitch Dia, 1/4" Bore	$4.34
Molded Nylon 14-1/2 Deg Angle Spur Gear Rack, 48 Pitch, 1/8" Face Width, 1/8" H O'all, 1'L	$4.24
Rubber Bumper W/ Out Metal Core Recessed, 1/2" Diameter, 6-32 Threaded Stud, Packs of 25	$4.98
Loctite Black Max 380 Super Glue .10 oz Tube, Begins To Harden In 90 Seconds	$4.19
	$140.34

(All parts ordered from McMaster-Carr)

Appendices C-H. 2-D Part Drawings

Axle
Base
Motor Support
Large Syringe Plate
Slider Support
U-Clamp Plate
Large Gear Slider
Small Gear Slider