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Executive Summary of the Thesis

Development of a Portable Animal Ventilator for Hyperpolarized ^{129}Xe MRI and MRE at 9.4 Tesla

Laurea Magistrale in Biomedical Engineering - Ingegneria Biomedica

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1. Introduction

Pulmonary pathologies have a profound impact on the morphology and mechanical properties of lung parenchyma, encompassing alterations in airway geometry and tissue stiffness (elasticity). These alterations can detrimentally affect the efficiency of gas exchange regions within the alveoli, leading to a decrease in the effective surface area for respiration or creating impediments in the respiration process due to fibrotic tissue stiffening. The urgency of addressing this issue stems from the critical need for improved noninvasive and non-ionizing radiation methods that can accurately quantify regional gas exchange efficiency and the intrinsic mechanical properties of lung tissue, particularly in cases of diffuse or localized fibrosis or the presence of tumors [1].
Conventional magnetic resonance imaging (MRI) techniques that rely on water (proton) signals face significant limitations in imaging the lungs, primarily because of the presence of air and the tissue/air boundaries that complicate image interpretation. In this context, hyperpolarized (HP) ^{129}Xe MRI has shown considerable promise as a method capable of regionally quantifying ventilation and gas exchange efficiency [5]. The degradation of gas exchange efficiency, which manifests as chronic shortness of breath, has been notably observed in conditions such as Covid-19 and post-acute sequelae (PASC or "long") Covid [2]. Therefore, the development and implementation of new lung imaging techniques are crucial not only for addressing the broader challenges posed by pulmonary pathologies but also for understanding and managing the long-term effects of Covid-19.
Moreover, MR elastography (MRE) represents a non-invasive phase-contrast MRI technique that offers quantitative maps of soft-tissue stiffness, providing valuable insights into the mechanical properties of biological tissues [3]. Given the challenges associated with proton-based MRE when applied to lung imaging, the innovative application of MRE using HP ^{129}Xe MRI holds significant potential in advancing our understanding of lung tissue mechanics and its alterations in various pulmonary pathologies.
Nevertheless, utilizing HP ^{129}Xe MRI and MRE with small animal models presents distinctive technical challenges. Achieving precision involves tightly controlling the volume and timing of HP gas alongside anesthesia administration to the breathing animals [4]. Furthermore, the experimental process necessitates meticulous

instrumentation and adherence to the stringent requirements of ultra-high field MRIs. This ensures that the HP gas remains effective, preventing depolarization and preserving image quality. One feasible approach entails continuously supplying HP gas to anesthetized mice that are spontaneously breathing. However, this method can be problematic due to irregular and varying-depth breathing patterns, potentially resulting in motion artifacts or limitations in image resolution.
A more robust solution involves mechanically ventilating the animals with positive pressure while incrementally conducting full 3D encoding over multiple breathing cycles. This approach effectively suppresses respiratory motion, ensuring image quality and consistency.
The primary aim of this project, which was conducted both at Politecnico di Milano and the University of Illinois at Chicago, is to create a portable hyperpolarized (HP) gas ventilator capable of enabling high-resolution three-dimensional (3D) imaging of dissolved and gas-phase ^{129}Xe within the lungs. This device is specifically designed to work seamlessly with the 9.4 Tesla preclinical MRI system at the UIC RRC Preclinical Imaging Core, Figure 1.

Figure 1: 9.4 Tesla preclinical MRI system within the UIC RRC Preclinical Imaging Core.

2. Methods

2.1. Ventilator Requirements

To achieve this aim, several critical considerations are essential when developing the device:

- Mixing paramagnetic oxygen and HP gas as late as possible to prevent Xenon depolarization.
- Ensuring that HP gas is handled using only materials without ferrous impurities.
- Constructing the ventilator from non-magnetic materials, such as aluminum, brass, or plastic, to avoid magnetic field interference with the MRI scanner.
- Providing consistent tidal volume delivery and precise lung positioning throughout each cycle for collecting image data over multiple breaths.
- Ensuring user-friendliness with straightforward controls for technicians or research students, along with ease of mobility in and out of the MRI room.

2.2. Ventilator Architecture

The system comprises two sections: an MR-compatible mechanical part and a non-MR-compatible electronic module.
The electronic module serves as the primary user interface, allowing for the modification of the breathing pattern and continuous monitoring of pressures and tidal volume. More specifically, this module encompasses the power supplies, different conditioning circuits, and two separate microcontrollers: a Raspberry Pi and an Arduino. Arduino is employed for firmware development in its integrated development environment (IDE). It manages fundamental system tasks, including time control and signal sampling.
Conversely, Raspberry Pi operates as a single-board computer with a Linux-based operating system, interfaced with a keyboard and monitor. Its primary function revolves around rendering the user interface, which is constructed using Processing, a Java-based platform. Within this framework, all essential computations and signal processing activities are conducted.
The MRI-compatible mechanical part of the system, which includes sensors and valves, manages gas delivery for the ventilator, regulating a mixture of oxygen, anesthesia, nitrogen, and hyperpolarized (HP) gas, Figure 2. During normal breathing, it provides a mix of 75% nitrogen and 25% oxygen. For HP gas imaging, it replaces nitrogen with HP gas. The system has oxygen and nitrogen lines with anesthesia, their pressures are controlled by regulators and also checked by analog pressure sensors.
During normal breathing, the delivery of these

two gasses is controlled by solenoid valves, while when there is the need to ventilate the animal with the HP gas, the line of nitrogen is turned off. The administration of HP gas is controlled by using a pneumatic valve made entirely of fluoropolymer, as opposed to the fast-switching metal solenoid valves that control the delivery of nitrogen and oxygen. A solenoid valve is used to open and close this pneumatic valve in response to pressure variations.
The delivery of hyperpolarized (HP) gas involves a Tedlar bag located within a rigid chamber that is pressurized by nitrogen (N_2). To ensure the preservation of HP gas polarization, oxygen and either xenon or nitrogen are kept separate for as long as possible. They are combined in the trachea of the animal to prevent depolarization of the HP gas. A pneumotachometer (PNT), 3, monitors tidal volume on the exhale line, and there's an option to release gas or capture it for reuse, improving gas management efficiency.

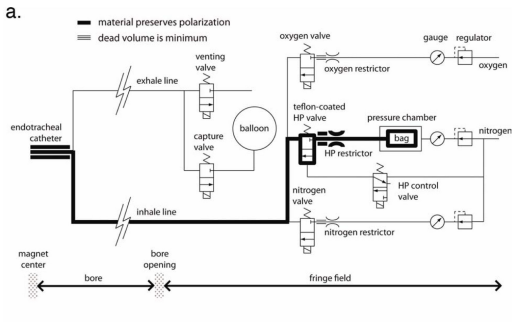

Figure 2: Ventilator Schematic presented by Nouls et al. in 2011.

To calibrate the pneumotachometer, a syringe with a known volume of 12.5 mL was utilized. The air of this volume was passed through the interior of the pneumotachometer, and the pressure sensor measured the resulting pressure difference across the PNT. In the meanwhile, the firmware executed an interrupt routine to capture pressure data. This simultaneous operation enabled real-time measurements of pressure differentials, providing accurate and continuous monitoring of the dynamic airflow within the PNT.

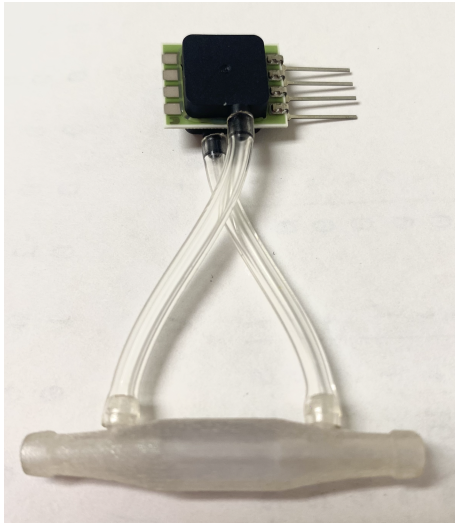

Figure 3: PNT with the differential pressure transducer

2.3. Volume and End-Expiratory Pressure Management

Upon flow calculation, understanding the flow-volume relationship becomes crucial. Flow measurements require integration over time to determine volume, with the trapezoidal rule as a simple numerical integration method. This method divides the curve into trapezoids, and the sum of their areas provides an integrated value.
Moreover to establish a favorable positive end-expiratory pressure at the oral cavity of the subject, diverse strategies have been explored. The Bubble-Continuous Positive Airway Pressure method is a straightforward yet effective technique that offers a safe and practical way to provide continuous positive airway pressure (CPAP). Hydrostatic pressure is applied to the complete respiratory circuit by submerging the expiratory end limb and channeling it via an underwater seal.

2.4. User Interface

The user interface for the ventilator system was implemented using the Java programming language through the Processing framework. In the initial user interface screen, the user is prompted to input various parameters. These include the calibration-derived coefficients 'm' and 'q' for flow calculation, the sampling frequency of flow during calibration for volume determination, and additional parameters such as inspiration, expiration, and breathhold times to accommodate different animal requirements, en-

hancing ventilator flexibility.
Subsequently, a new screen displays pressure values for each line, along with flow and volume metrics. The interface operates in different modes, starting with the ventilator turned off, where pressure monitoring is the sole focus. If the pressure values meet the desired criteria, the ventilator can be activated using a switch. Following this, a second switch allows the transition from normal breathing, utilizing oxygen and nitrogen, to HP gas mode, utilizing oxygen and Xenon for hyperpolarization instead of nitrogen. In the Figure 4 it is shown the userInterface during normal breathing.

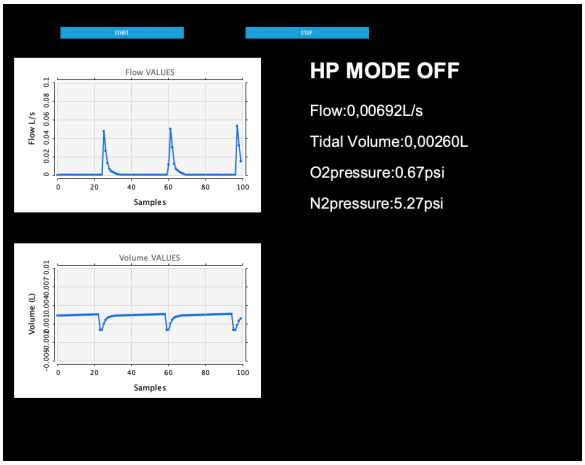

Figure 4: The interface displays the Ventilation during normal ventilation, with flow and volume graphs and nitrogen pressure

3. Results

The initial validation was conducted on the overall system to assess its responsiveness to the provided commands. The algorithm was structured into distinct phases. In the initial phase, all valves were turned off, and the pressure of individual channels was monitored. To validate each tube, a comparison was made between the data displayed on the user interface and that obtained from a commercially available digital pressure gauge. If these data matched, a switch was used to transition to the "Ventilator ON" mode.
Within this mode, two mutually exclusive settings are available through a switch: "Normal Breathing," administering oxygen and nitrogen, and "Hyperpolarized Gas" mode, in which nitrogen was replaced by HP (high-pressure) gas. In both modes, ventilation was divided into three phases: an inspiration phase with inhale valves opened and the expiratory valve closed; a breath-hold period with all valves closed; and finally, an expiration period with only the expiratory valve closed. During this breathing cycle, the graphycal data of Flow and Volume on the user interface were evaluated, Figure 4. In order to assess that the valve opening and closing times matched those set by the user, an oscilloscope was employed as a reliable tool for capturing and analyzing the electrical signals sent to the valves. This allowed for precise monitoring of the duration during which the input signal to the valves remained in the high or low state.
The validation of the Pneumotachometer (PNT) is conducted to ensure control over the volume displayed in the user interface. It is carried out as follows: at the PNT's termination point, a tube was connected, leading to an inverted cylinder filled with water 5. With each cycle, the volume in the cylinder decreased, allowing for a comparison with the reading from the PNT.

Figure 5: Small graduated cylinder submerged in a water bath is utilized to measure tidal volume over a specified number of breaths.

To obtain a readable volume, this cycle was repeated ten times, and the cumulative volume was recorded. The experiment was replicated three times for various pressure settings and the data has been plotted on MATLAB (Fig 6).

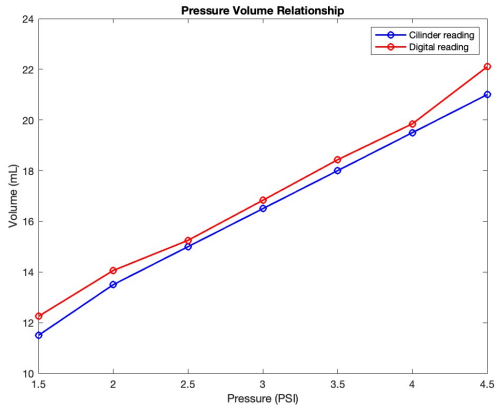

Figure 6: Pressure Volume Relationship: on x-axis pressure ranges, on y-axis Volume displacement after 10 cycles.

4. Discussions

The volume of airflow delivered to the mouse is contingent upon a multitude of variables, encompassing the pressure parameters established by the regulators, the impedance characteristics inherent in the tubing, and the unique impedance profile of the mouse's pulmonary system. Consequently, this complex interplay among these elements engenders a degree of variability in the ultimate volume of air supplied, a phenomenon that becomes especially significant when dealing with exceedingly low flow rates.
To address this inherent challenge, the utilization of flow restrictors is crucial in mechanical ventilation. Flow restrictors, characterized by their pronounced resistance, effectively relegate the resistive attributes of the tubing and the lung tissues to a relatively negligible status within the ventilation process. This strategic incorporation of flow restrictors enables precise control over tidal volume, regardless of any potential disruptions stemming from tubing impedance or variations in lung impedance, which may occur during the imaging process.
Another recurring challenge in the realm of mechanical ventilation pertains to issues associated with flow integration, leading to unintended volume drift. Owing to the inherent limitations of measurement instruments, achieving absolute precision at a 100% level is an unattainable objective, invariably resulting in the presence of a consistent offset. Over time, this offset accumulates, giving rise to a linear drift in volume measurements. The attainment of a flawless offset compensation remains beyond reach, and this predicament is further exacerbated with prolonged utilization of the flow meter.
In response to this issue, a practical solution entails the deliberate practice of resetting the volume measurement to zero at the conclusion of each ventilation cycle. This proactive measure effectively mitigates the cumulative impact of offset discrepancies, particularly when dealing with extended periods of flow meter usage.

5. Conclusions

The achievements of this project encompassed several key objectives:

- Extensive review of literature on commercially available mechanical ventilators.
- Meticulous selection of components based on research, technical specifications, compatibility, and reliability.
- Design and development of 3D components for constructing the ventilator box using Solidworks.
- Establishment of hardware connections to enable seamless communication and interaction between components and subsystems.
- Development of software capable of executing hardware commands, and adjusting ventilation parameters.
- Development of a user interface providing real-time monitoring of vital parameters and results.
- Calibration and validation of the pressure and flow sensing device (PNT) for accurate monitoring of tidal volume.

This thesis project represents an initial step towards a broader undertaking aimed at utilizing ^{129}Xenon Magnetic Resonance Elastography (MRE) to acquire information about the mechanical properties of the lungs, specifically lung stiffness. By developing a functional mechanical ventilator system and integrating advanced imaging techniques, researchers aim to enhance our understanding of lung mechanics and improve patient care in respiratory medicine.

6. Acknowledgements

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