An implantable ventilator augments inspiration in an *in vivo* porcine model

Lucy Hu

Massachusetts Institute of Technology <https://orcid.org/0000-0002-0619-3195>

Mossab Saeed

Harvard Medical School

Manisha Singh

Massachusetts Institute of Technology

Ellen Roche (✉ etr@mit.edu)

Massachusetts Institute of Technology <https://orcid.org/0000-0002-8952-2993>

Article

Keywords:

Posted Date: December 30th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1182615/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Nature Biomedical Engineering on December 12th, 2022. See the published version at <https://doi.org/10.1038/s41551-022-00971-6>.

Abstract

Severe diaphragm dysfunction can lead to respiratory failure, requiring permanent mechanical ventilation. Permanent tethering to a mechanical ventilator via a patient's mouth or tracheostomy can interfere with quality of life and autonomy by hindering activities like speech and swallowing. We present a diaphragm assist system that intervenes internally at the diaphragm as opposed to the mouth. By implanting contractile, soft robotic actuators above the diaphragm to push downwards and augment diaphragm motion during inspiration, this diaphragm assist system functions as an implantable ventilator. We demonstrate the proof-of-concept feasibility of this system to augment physiological metrics of ventilation in an *in vivo* porcine model of varied respiratory insufficiency. Synchronized actuation of the assist system with native respiratory effort augmented the tidal volume by up to a 100 mL increase and was capable of improving minute ventilation into a normal range. The diaphragm assist system has the potential to provide a new therapeutic ventilation option that aims to restore respiratory performance without sacrificing quality of life.

Introduction

The diaphragm is the major muscle responsible for inspiration, and contributes to up to 70% of the inspiratory tidal volume in a healthy individual.^{1,2} Diaphragm dysfunction can result from a variety of etiologies including phrenic nerve trauma³ and neuromuscular disease^{4,5}. Owing to the degenerative nature of many of these etiologies, mechanical respiratory failure exists as a continuous spectrum of dysfunction. Severe diaphragm dysfunction or paralysis can lead to chronic respiratory failure. When disease progresses beyond the treatment capacity of noninvasive treatment, patients must make the difficult decision to opt for permanent invasive ventilation via a tracheostomy or to pursue palliative care with an understanding of the terminal nature of their disease. Invasive ventilation can interfere with many aspects of a patient's quality of life, such as hindering speech, requiring full-time care, and possibly necessitating the patient move into a care facility. There is an urgent need for new therapeutic ventilation options that restore respiratory performance without sacrificing quality of life, especially for those with the most severe cases of diaphragm dysfunction.

Respiration is a fundamentally mechanical system. The diaphragm is a dome-shaped muscle that drives up to 70% of respiration^{1,6}. Soft robotic actuators are ideal for reproducing complex, repetitive muscle contractions, such as that of the diaphragm, while interfacing nondestructively with biological tissue. Previously, soft actuators have shown the ability to augment heart function^{7,8} and have had utility in other biological applications^{9,10}. Due to the mechanical nature of respiratory failure, especially in the context of conditions like muscular dystrophy, implanted soft robotic actuators applied to the diaphragm have the potential to mechanically support and augment its function. There is minimal prior work investigating soft robotics applied to the augmentation of respiration; one of the few examples reports a dielectric elastomer sheet used to completely replace an excised diaphragm and generate motion.^{10,11} Contrastingly, the work presented here leaves the native diaphragm intact while demonstrating function in

terms of clinically-relevant physiological metrics (ventilation flows, volumes, and pressures) in an *in vivo* porcine model as opposed to replicating diaphragm motion to act as a replacement.

Here, we demonstrate a diaphragm assist system that functions as an implantable ventilator by using soft robotic actuators to mechanically augment diaphragm function during inhalation, increasing inspiration. As a proof-of-concept, we simulate a range of respiratory insufficiency within each animal—specifically, we induce respiratory depression via anesthetics and diaphragm paralysis by severing the phrenic nerve—and then demonstrate the ability of the assist system to augment respiratory flows, volumes, and pressures. We also investigate specific metrics of inspiratory function including peak inspiratory flow and transdiaphragmatic pressure¹². We show that in order to achieve effective inspiration assistance, the actuation of the assist system must be synchronized to the subject's underlying respiratory effort. To achieve this, we have built a control system in which actuation is triggered by the beginning of inspiration. Through an analysis of the respiratory waveforms, we investigate the optimal alignment of actuation with the subject's native respiratory effort. By augmenting diaphragm function in a biomimetic fashion, we demonstrate the replication and augmentation of the native biomechanics of respiration in which a negative pleural and alveolar pressure drives airflow, as opposed to the positive pressure ventilation of standard mechanical ventilation.

Results

Soft robotic design strategy applied to mechanically assisting inspiration.

As depicted in the schematic in Fig. 1a, when the diaphragm contracts, the arclength of the diaphragm shortens, and the entire sheet of the diaphragm moves downwards, acting as a pump. The thoracic cavity volume increases and pressure decreases, ultimately driving respiration.

Our strategy aims to harness the contractile function of pneumatic artificial muscles (PAMs) to mimic and augment the native contraction of the diaphragm. We opt for a McKibben type PAM—a classical soft actuator type with a simple fabrication process and high force generation¹³ that is capable of mimicking and augmenting biological systems.^{7–9} The McKibben actuators used in this work were capable of generating up to 50 N of contractile force under 20 psi pressurization (see Supplementary Information). At their simplest, McKibben actuators are composed of an expandable weaved mesh surrounding a bladder connected to an airline (Fig. 1b) (see Methods). When the bladder is pressurized, the mesh expands radially and drives linear contraction (Fig. 1c). Conceptually, we harness the linear contraction of these PAMs by placing them superior to the native diaphragm so that the relaxed PAM conforms to the native curvature of the diaphragm (Fig. 1d). Mimicking the native diaphragm, we anchor the ends of the PAMs to the ribs (see Methods). With pressurization, the length of the PAM shortens, the arclength shortens, and the PAM mechanically pushes the diaphragm downwards (shown *in situ* in Fig. S1).

In contrast to the dielectric artificial diaphragm described by Bashkin, et al.,¹⁰ our diaphragm assist system uses a set of two linear PAMs, leaves the native diaphragm intact, and has a low profile presence

(deflated: 5 mL volume, inflated: 17 mL volume). To test this concept in a live porcine model, we surgically implanted a pair of McKibben actuators in an anterior-to-posterior direction lateral to the heart. The actuator placement is visualized in a 3D rendering in Fig. 1e. Fluoroscopy of the diaphragm was taken throughout the experiments. The lateral cross-sectional view from the fluoroscopy shows the realization of our soft robotic strategy in an *in vivo* pig model (Fig. 1f,g).

Augmenting tidal volume and peak inspiratory flow in vivo.

To evaluate the ability of our diaphragm assist system to augment respiratory function, the animals were instrumented to collect physiological data, including respiratory flows, volumes, and pressures within the respiratory system (Fig. S2). The pressurization of the soft robotic actuators was controlled via a custom-built control system; the actuation pressure data was input into the same high-resolution data acquisition system as the physiological data (see Methods).

Ventilation is key to driving CO₂ exchange, so we first examine the flow and volume waveforms as metrics of ventilatory function. Flow is measured by a spirometer. Peak inspiratory flow can be used as a clinical metric of inspiratory function¹², which yields a direct measurement of the effect of the diaphragm assist system. Integrating the flow with respect to time yields a volume waveform over time. The volume of each breath (tidal volume) and its rate (minute ventilation) are the most relevant parameters of directly measuring ventilation. Pressures within the respiratory system, such as pleural and abdominal pressures, reveal information about the respiratory biomechanics that physically drive ventilation and are discussed later in this work.

To start each study, the animal was anesthetized appropriately with isoflurane and placed on mechanical ventilation. Isoflurane induces a respiratory depression with decreased tidal volumes and increased respiratory rate that ultimately combine to a reduced minute ventilation¹⁴. The respiratory depression secondary to the isoflurane is used as our baseline animal model of respiratory insufficiency due to hypoventilation. Each subject has a reduced but non-zero respiratory drive and response to CO₂. Mechanical ventilation is used to support the animal throughout the implantation surgery. Within each subject, we introduce a series of respiratory challenges, collecting data during periods of unassisted ventilation (in which any spontaneous respiration is due to the native respiratory drive) and during periods of actuator assisted ventilation. Mechanical ventilation is used to restore and maintain a state of normoventilation after and between respiratory challenges. To investigate the effect of the diaphragm assist system, a representative respiratory challenge was chosen per subject. The phrenic nerve is intact for all data shown in Fig. 2.

In a vignette from the best responding subject (Fig. 2a), we show that the assist system has the direct capacity to augment the peak inspiratory flow from 0.18 L/s to 0.59 L/s and the tidal volume from 55 mL to 161 mL. When the assist is resumed after a short period of unassisted respiration, the augmentation effect of the actuation on the flow and volume waveforms is reestablished nearly immediately over the course of 2 breaths.

An example of a full respiratory challenge is shown in Fig. 2b. During the unassisted ventilation at the start of the challenge, the subject models a state of hypoventilation. During this period, the tidal volumes and flows have a slight increase over time, indicating the baseline respiratory drive is responding to the increasing CO₂ status due to the unassisted low minute ventilation (0.9 L/min). When assist is switched on (as indicated by the actuator pressure waveform and the black arrow), there is a clear jump in the peak inspiratory flow (+0.20 L/s, 95%CI +0.19 L/s to +0.22 L/s), tidal volumes (63mL, 95% CI 58 mL to 68 mL), and minute ventilation (0.9 L/min to 3.1 L/min). The actuators cycle between a pressurized and unpressurized state for 10 minutes. At the end of the respiratory challenge when the respiratory effort has reached a steady state, the assist is switched off and we see that the respiratory effort drops slightly (peak inspiratory flow: -0.09 L/s, 95% CI -0.08 to -0.10; tidal volume: -10 mL, 95% CI -7 to -13) but much less than the jump seen at the start of the respiratory challenge.

The respiratory drive is a slow but dynamic factor underlying all of the respiratory physiology data. As seen in the first 200 s of Fig. 2b, the respiratory drive visibly increases as the low minute ventilation leads to CO₂ buildup. This response to CO₂ is dynamic and varies between subjects based on each animal's response to isoflurane. By examining the breaths immediately before and after these transition points (off-to-on and on-to-off), we can examine the direct effect of the diaphragm assist system in terms of augmenting volume and peak inspiratory flow while minimizing the influence of the changing baseline.

This analysis was conducted for one representative respiratory challenge per subject. We see a spectrum of responsiveness to the diaphragm assist system across 5 subjects (Fig. 2c,d,e). The subjects are ordered from largest change in tidal volume at the start of the challenge to the smallest (best responder to worst responder according to Fig. 2d). We find the diaphragm assist system generates much larger respiratory augmentations at the beginning of a trial—when mechanical ventilation support has just been removed, minute ventilation drops suddenly, and the animal's CO₂ state rises rapidly—than at the end of the respiratory challenge when the respiratory baseline is relatively more stabilized (Fig. 2c,d,e).

Subject A was much more responsive to the assist system than any other subject. In terms of tidal volume, 4 of the 5 subjects show an augmentation of >30 mL per breath at the beginning, whereas only 1 of the subjects shows substantial augmentation to the tidal volume at the end. Of the 4 less responsive subjects (B,C,D,E), 3 of them show a mild response at the end while in the worst responder (E), the actuation overall decreased the ventilation metrics (Fig. 2c-e). The subject with the weakest response had the highest baseline weight-normalized minute ventilation at the beginning of the trial (Fig. 2e) compared to other subjects.

Body weight normalized minute ventilation is used to compare these results to normal physiology. Minute ventilation is a metric of the ventilation rate, taking into account both tidal volume and the respiratory rate. In a normal, conscious pig, the expected body weight normalized minute ventilation is 198 mL/min/kg $\pm$ 41 mL/min/kg with a range of 104 mL/min/kg to 262 mL/min/kg¹⁵. Actuator assisted ventilation allowed all 5 subjects to reach the lower range of normal physiology, and 2 of the subjects even achieved a minute ventilation corresponding to one standard deviation below the normal mean

(Fig. 2e). However, we note that this minute ventilation is achieved with low tidal volumes and high respiratory rates, which results in a lower alveolar ventilation than the same minute ventilation achieved with high tidal volumes and low respiratory rates.

Synchronizing with the underlying respiratory effort.

Like with standard mechanical ventilation^{16,17}, patient-ventilator synchrony in our system is critical to the ability to augment respiration. Asynchronous ventilation can destructively interfere with the underlying respiratory effort, leading to worse ventilation with assistance than without.

In order to synchronize the actuation of our assist system with the subject's underlying respiratory effort, we built a control system (Fig. 3a,b) that can actuate based on the respiratory flow rate. The system uses the spirometry flow sensor as the source data. The flow data is read into our data acquisition system. The associated data analysis software allows a user-set threshold voltage; this threshold voltage was manually titrated during every respiratory trial to achieve qualitatively good synchronization. When the flow rate passes this set threshold, a digital pulse is triggered and sent to the microcontroller in our control box. The microcontroller triggers a pre-set actuation pressure waveform of one cycle of pressurization and depressurization in the electropneumatic regulator, filling and emptying the PAMs with pressurized air (further details in Methods).

Our control system can implement both a set, rhythmic control scheme independent of the native respiratory effort or a dynamic control scheme synchronized with the underlying respiratory effort. Due to the phase and frequency mismatch between the independent actuation and the underlying respiratory effort, the mixed interference of the actuator and the underlying respiratory effort can be seen in both the flow and volume waveform (Fig. 3c). Contrastingly, the well synchronized actuation reveals much more homogenous flow and volume waveforms. (Fig. 3d).

Within each subject, we compare the tidal volumes and peak inspiratory flows in one representative challenge of independent actuation with one representative challenge of synchronized actuation (details in methods). We find that synchronized actuation consistently produces much less variance in the tidal volumes (Fig. 3e,f). Although in some subjects—such as subject A—independent actuation achieved a few higher maximum tidal volumes, the independent actuation also achieved lower minimum tidal volumes across all subjects due to the misalignment of actuations with the underlying respiratory effort leading to destructive interference or due to actuation with no underlying breath—representing a breath that is solely actuator driven.

Factors in optimizing synchronization.

As seen by the mixed interference in Fig. 3c, the alignment of the actuation with the underlying respiratory effort will critically determine the constructive versus destructive nature of the interference. In respiratory challenges that had an independent actuation scheme or a poorly synchronized actuation scheme, we

found the datasets that provide a natural variation in the timing of the actuation in relationship to the underlying respiratory effort.

Because mechanical respiratory failure exists as a continuous spectrum of loss of function, we looked at the implications of synchronization in different levels of baseline respiratory effort. As seen in Fig. 2, there is variance in the underlying respiratory function between subjects. To simulate a controlled change in the underlying respiratory function within the same subject, we severed the phrenic nerve in some subjects, simulating diaphragm paralysis in combination with the respiratory depression due to the isoflurane (see Methods). Fig. 4 depicts the analysis of aligning the actuator synchronization to the underlying respiratory effort for two respiratory challenges within subject B: (1) the subject with preserved diaphragm function (Fig. 4, left) and (2) the subject with a severed phrenic nerve (Fig. 4, right).

To optimize for maximum inspiratory augmentation, we investigate the relationship of the timing of different waveform features to the resulting tidal volume and peak inspiratory flow of each breath. The high frequency sampling of our data acquisition system (1000 Hz) allows for millisecond temporal resolution. Custom software was written to analyze the actuation pressure, flow, and volume data.

We identify the breath bounds as determined by the local minima in the volume waveform (the locations of V_0), and then finds the time distance between identified waveform features for each individual breath (further details in Methods). Waveform features analyzed include the start of an actuation waveform (P_0), peak inspiratory flow (F_{pk}), the start of inspiration (V_0), the start of expiration (V_{pk}), and others (Fig. 4a,b, and Fig. S3).

The distances between features act as different metrics of alignment and elucidate what factors are important to consider in optimizing synchronization. There are many different features and feature distances that can be analyzed. Fig. 4c-f shows the time relationship of the start of expiration to the actuation pressure ($V_{pk}-P_0$), but other metrics are shown in Fig. S3.

We examine the influence of these time metrics on tidal volume and peak inspiratory flow. We find the most important predictor variables are time metrics related to the start of expiration (V_{pk}). With diaphragm function preserved, there is a weak linear relationship between $V_{pk}-P_0$ and the peak inspiratory flow ($R^2 = 0.31$, $p < 0.001$) (Fig. 4c), and no significant relationship to the tidal volume ($R^2 = 0.04$, $p = 0.001$) (Fig. 4e). However, when the diaphragm function is removed by severing the phrenic nerve, a clear linear relationship emerges between $V_{pk}-P_0$ and tidal volume ($R^2 = 0.84$, $p < 0.001$) (Fig. 4f) and a weaker relationship with peak inspiratory flow ($R^2 = 0.30$, $p < 0.001$) (Fig. 4d).

Notably, we do not find these relationships when using the timing between the start of actuation and the start of inspiration ($P_0 - V_0$) as a metric. There is no linear relationship between $P_0 - V_0$ and the peak inspiratory flow or tidal volume for both the cases with and without diaphragm function (Fig. S4)

Comparing respiratory biomechanics.

To compare the respiratory biomechanics of different modes of respiration and ventilation, pleural pressure (P_{pl}), abdominal pressure (P_{ab}), and transdiaphragmatic pressure (P_{di} ; $P_{di} = P_{ab} - P_{pl}$) waveforms are analyzed. Transdiaphragmatic pressure is a metric of diaphragm function^{6,18,19}. Pleural pressure and abdominal pressure are approximated by a sensor mounted on a balloon catheter placed in the esophagus and stomach, respectively. As these sensors approximate P_{pl} and P_{ab} , the measurements are interpreted as relative measurements and not absolute measurements (see Methods for information about instrumentation and normalization). When analyzing relative pressure waveforms, the most informative metric is the maximum change in pressure per each breath.

In Fig. 5a-c, we show that across subjects (subject C was not instrumented for pressure measurements, and is therefore not shown), actuator assisted ventilation more closely matches the respiratory biomechanics of spontaneous respiration than in mechanical ventilation. Mechanical ventilation pushes air into the lungs, increasing pleural pressure with inspiration, whereas both actuator assisted ventilation and spontaneous respiration generate a negative pleural pressure to drive airflow. As the diaphragm is passive in mechanical ventilation, we see a negligible change in the abdominal pressure, whereas the caudal movement of the diaphragm in both actuator assisted ventilation and spontaneous respiration increases abdominal pressure.

In the representative waveforms from subject A (Fig. 5d-f), the case of highest responsiveness as seen in Fig. 3b-f, the actuator assisted ventilation not only more closely resemble that of spontaneous respiration, but also augments all of the pressure waveforms. Actuator assisted ventilation generates more negative changes in pleural pressure, greater increases in abdominal pressure, and ultimately greater increases in transdiaphragmatic pressure per breath.

A graphical technique used to measure work of breathing (WOB) is the Campbell diagram, referencing pleural pressure with lung volume. Using the pressure and volume data from subject A, we generate the pressure-volume (PV) loops of a Campbell diagram (Fig. 5g). Work of breathing is calculated from this PV loop as the internal area between the inspiratory edge of the loop and the passive chest wall compliance derived from the mechanical ventilation PV data. Normal WOB is 0.35-0.7 J/L.^{12,20,21} During attenuated spontaneous breathing, the subject's WOB is 0.10 J/L. During actuator assisted ventilation, the assist system shares the WOB and increases the total average WOB to 0.17 J/L, a 66% increase.

Discussion

In this work, we use pneumatic soft robotic actuators to support and augment physiological metrics of respiration, demonstrating proof-of-concept. A set of two McKibben-style PAMs surgically implanted superior to the diaphragm are capable of providing mechanical support to the diaphragm in a large animal model of respiratory insufficiency.

We report varied responsiveness to our soft robotic system between subjects, with one subject (A) showing a strong and substantive response in the peak inspiratory flow (a direct metric of inspiratory

function), and tidal volume and minute ventilation (metrics of ventilation). Subject A had the highest change in peak inspiratory pressure, tidal volume, and minute ventilation; the corresponding large augmentation in peak inspiratory pressure indicates that the volume and minute ventilation augmentation are specifically due to the soft robotic actuators augmenting the diaphragm's inspiratory function.

Variance in responsiveness is likely dependent on a combination of many factors. One factor is the level of preserved respiratory baseline. The weak response in the subject with a relatively high preserved weight-normalized minute ventilation (E) suggests that the assist system may have weak augmentation or even a disruptive effect in cases of well-preserved diaphragm function. Other potential factors include precise actuator placement, actuator fit, and anatomical variations. Future work aims to further understand what factors in system design and implantation can replicate high responsiveness.

Our system could generate the low end of acceptable minute ventilations but relied on high respiratory rates to do so. Due to the ventilation of dead space, this results in less alveolar ventilation than if the same minute ventilation achieved with higher tidal volumes and a lower respiratory rate. A core goal of the next generation system is to further improve the tidal volume augmentation. In this work, we use the widely used, classic McKibben actuator; a more application-specific or customized actuator type may allow for further increases in tidal volumes in future work. Other factors in actuator design, such as the number, layout, and positioning of actuators, will also be critical.

We show that synchronization with the native respiratory effort is a critical design element in our system. Like standard mechanical ventilation, off-cycle actuation of the actuators can lead to a destructive interference with the underlying respiratory effort. Synchronous actuation is key to consistent, low-variance respiratory waveforms and tidal volumes. When we actuate the system independent of the baseline respiratory effort, we see a range of mixed interference due to the phase mismatch.

The control system used in this study was a simple but effective first-generation system with many directions for improvement. In order to achieve consistent assistance from breath to breath, the synchronization must be optimized for the alignment that maximizes constructive interference. The system relied on a manually titrated threshold set for the flow sensor data. It is designed to be triggered at start of an inspiratory flow effort, which is related to V_0 . However, the manual nature of the system meant that if the threshold was set too low, noise in the flow signal could cause pre-emptive or false triggering (as evidenced by the negative values for $P_0 - V_0$). Flow is an easily instrumented signal for triggering in this study, but it is a very downstream signal of the respiratory system. Using a more upstream signal (such as neuromuscular signals) would allow for a more robust control system.

An ideal smart control system should be automated, to remove the error that can result from manual titration. Our alignment analysis reveals two important considerations for improvements towards this goal.

The first consideration is that the influence of alignment changes with the degree of preserved respiratory function, as seen with the difference in results between the intact and severed the phrenic nerve. When the phrenic nerve is severed, all diaphragm motion is governed by the actuators, and misaligned actuation with the remaining native respiratory effort—expansion of the ribcage—results in more consequential destructive interference. Whereas when the phrenic nerve is intact, the net diaphragm motion results from a combination of native diaphragm function and the effect of the actuators, because the actuators only operate along 2 discrete lines on the diaphragm. The contraction of the rest of the native diaphragm motion is still synchronized with the ribcage motion, so the effects of misalignment are less apparent. This implies that optimal alignment parameters may be different for different disease states and the control system will need to be dynamic and adaptive to changes in respiratory function, even within the same patient.

The second consideration is that the actuation curve's relationship to the beginning of expiration (V_{pk}) is more influential than the relationship to the beginning of inspiration (V_0). This implies that an updated system should trigger off of a signal related to expiration as opposed to the beginning of inspiration. Future work lies in building a next generation control system; this includes triggering from a more upstream signal, creating a system that is cognizant of V_{pk} as opposed to V_0 , and further investigation of dynamic actuation curves.

Ultimately, we show that the strategy to augment the native function of the diaphragm with soft robotics acts as a form of negative pressure ventilation by driving ventilation through the generation of a negative pressure in the thoracic cavity. Our diaphragm assist system is biomechanically similar to that of spontaneous breathing, sharing a substantial portion of the work of breathing in our best responding subject. By functioning as an assist device—as opposed to completely overtaking breathing—our system has the potential to be compatible with voluntary use of the diaphragm. Maneuvers such as voluntary deep breaths or drinking through a straw—abilities related to patient autonomy and quality of life—can be preserved with this implantable ventilator strategy.

Additionally, in contrast to current modes of mechanical ventilation, recapitulation of native biomechanics, as shown with this system, can avoid the deleterious effects that arise secondary to the use of positive pressure ventilation, such as barotrauma^{22,23} or hemodynamic changes in patients with concurrent cardiac pathologies^{24,25}.

Although this technology requires further advancements in the net tidal volumes it can generate before it can fully match the ventilation capacity of a current mechanical ventilator, it is the first study to report the ability to rescue ventilation with an implantable ventilator. We envision further translational potential of this technology when combined with the development of smaller and more portable pneumatic energy sources^{26,27} as the field of soft robotics advances. With the integration of a portable pump and control system in the future, this technology could provide an additional level of patient autonomy via increased mobility. Motivated by the encouraging results of this study, we believe this technology, with optimized

design, has the potential to provide a radically different ventilation technology that preserves key metrics of quality of life for people with end-stage mechanical respiratory failure.

^

Methods

Study design.

There were two main objectives of our study. First, we sought to demonstrate the proof-of-concept capability to augment ventilation via implanted soft robotic actuators in an animal model of respiratory muscle weakness. To evaluate ventilation metrics, we measured spirometric flow and volume. Second, we aimed to demonstrate that this soft robotic strategy replicates more native respiratory biomechanics than standard mechanical ventilation. To evaluate the respiratory biomechanics, we evaluated the respiratory pressure data along with the spirometry data.

In order to evaluate the system performance under varying conditions within a single animal, a series of respiratory challenges were performed. Prior to the first and between each subsequent respiratory challenge, volume control mechanical ventilation operated through the facility's Dräger ventilator (Drägerwerk AG, Lübeck, Germany) was used to maintain the animal's ventilation needs and recover from respiratory challenges if needed. Each respiratory challenge was initiated by switching the ventilator to a manual mode of ventilation. During each challenge, data for a mix of unsupported ventilation and actuator-supported ventilation was collected. Vital signs and respiratory status were monitored.

Fabrication and characterization of pneumatic artificial muscles. The actuators were a modified version of the PAM actuators previously described in Roche, E.T. et al⁷, and Payne, C., et al²⁸. Specifically, McKibben pneumatic artificial muscles were fabricated according to the protocol detailed in the Supplementary Methods. They consist of a thermoplastic elastomer bladder (Stretchlon 200, FibreGlast Developments Corp.), a thermoplastic polyurethane tubing (1/8" Tubing, 5648K226, McMaster, Inc) and an expandable braided mesh (PT00.25BK, TechFlex, Inc.). Prior to use *in vivo*, actuators were fatigue tested to a pressurization of 20 psi for >1000 cycles on the benchtop. Mechanical characterization was performed on an Instron 5499 Universal Testing System (Instron Corp, Norwood, MA, USA). Further details can be found in the Supplementary Information.

Live animal studies

All studies were conducted according to protocol #19-05-3907 approved by the Boston Children's Hospital (BCH) Institutional Animal Care and Use Committee (IACUC) policy.

Procedures were carried out at Boston Children's Hospital in accordance with BCH IACUC under protocol #19-05-3907 and MIT IACUC under protocol #0118-006-21. Protocol reviews were conducted in

accordance with the standards outlined in the National Research Council's Guide for the Care and Use of Laboratory Animals and BCH's Animal Welfare Assurance.

Female Yorkshire 30-40kg swine were sourced from Parson's Farm (Hadley, MA, USA). We used a total of nine swine during the development and testing of our system, and we present data from six swine in the manuscript. Animals were acclimated and cared for according to standard facility protocols. Each experiment was conducted under 2-3% isoflurane anesthesia, titrated to each animal to maintain a stable anesthetic plane. Anesthesia and mechanical ventilation were controlled through the facility's Dräger ventilator (Drägerwerk AG, Lübeck, Germany). Vital signs were monitored via a SurgiVet monitor (Smiths Medical, Inc., Minneapolis, MN, USA). After completing the study and acquiring the data, animals were euthanized using Fatal-Plus Solution (Vortech Pharmaceuticals, Dearborn, Michigan) at a dose of 110 mg/kg/body weight.

Surgical procedure.

After induction of anesthesia, the animal was intubated and placed on mechanical ventilation. A transesophageal EKG catheter was placed to monitor the heart rate. A carotid arterial sheath and jugular venous line were placed using cut-down technique for animal systemic and central venous pressures monitoring respectively. Two balloons were placed, one in the esophagus and one in the stomach for pressure monitoring. A Foley catheter was placed for urine output monitoring.

Following that, the chest cavity was accessed through midline sternotomy. Next, we opened both pleural cavities and placed one soft actuator along the diaphragm curvature on each cavity. We passed each actuator posteriorly at lowest intercostal space to outside chest cavity and fixed it to the skin using sutures. Then, we fixed the other end to the sternum using sutures and we passed the actuation lines through separate opening through the skin. To monitor the diaphragm movement with the actuators, we attached two magnetic trackers near the actuators on the diaphragm on each side. Next, we approximated the sternum using sternal wires and close the subcutaneous layers and the skin in layers using sutures. After the sternotomy was closed, the negative pressure in the thoracic cavity was restored via chest tube, and the respiratory challenges were conducted with a closed chest.

Simulating varying levels of respiratory function.

In order to simulate varying levels of respiratory functions, two animal models of respiratory muscle weakness were used. The first method relied on the respiratory depressive effects of isoflurane. Isoflurane levels were held between 2-3% and titrated to a stable plane of anesthesia while still maintaining a depressed but non-zero level of spontaneous respiration during respiratory challenges. The second method modeled diaphragm paralysis via mechanically severing both the left and right phrenic nerves. This model is still conducted under the setting of the isoflurane, and thus combines the effects of the isoflurane and severed phrenic nerve and represents a more severe model of respiratory model weakness.

Data acquisition.

The biomedical sensors and instrumentation data were input into a PowerLab 35 series (PL3516, ADInstruments, Dunedin, New Zealand) high performance data acquisition system with a 1000Hz sampling frequency for all channels. During the experiments, data was monitored live via LabChart software (ADInstruments, Dunedin, New Zealand). After the experiments, data was exported into and processed in MATLAB (MathWorks, Portola Valley, CA, USA).

Spirometry instrumentation.

An analog spirometer (Gas Flow Sensor, ES Systems, Filothei-Psychiko, Greece) was placed in line between the ventilator Y-tubing and the endotracheal tube. Analog data was input into the PowerLab. The data was converted from mass flow to volumetric flow according to manufacturer specifications

Respiratory pressure instrumentation and measurement.

Pleural pressure and abdominal pressure were measured via an esophageal balloon catheter (Cooper Surgical, Trumbull, CT, USA) placed in the esophagus and stomach respectively, each connected to a pressure transducer (PRESS-S-000, PendoTech, Princeton, NJ, USA).

Respiratory pressure data was normalized in the MATLAB post-processing. For a given segment of interest, the average of the pressure reading at the breath bounds was set to zero, to allow the analysis to show the change in pressure over the course of one breath.

Control system design and instrumentation.

Our group has built a custom electropneumatic control system utilizing electropneumatic pressure regulators and valves (SMC Pneumatics, SMC Corp, Tokyo, Japan) controlled by a custom software described in Horvath, Hu et al²⁹. The software is designed to allow custom pressure waveforms to be input. The control system can generate a desired waveform via an analog input to the electropneumatic regulators. The nominal peak pressure for all waveforms was 20 psi. The regulators also output an analog signal of the actual pressure waveform; this data is input into the PowerLab system.

Independent and synchronized actuation.

The custom control system is capable of generating a manual timing set to a frequency of actuation that is initiated by user input. This set timing initiates the custom pressure waveform programmed into the system. This timing is independent of the subject's native breathing.

In order to implement synchronization in our system, the Fast Response Output add-on for LabChart (ADInstruments, Dunedin, New Zealand). Analog spirometry flow data was used as the input channel. Voltage and hysteresis settings were manually titrated between a voltage range equivalent to 0.01 L/s to 0.07 L/s and a hysteresis range between 2-5% during every respiratory trial to achieve qualitatively good synchronization, as visually recognized by the homogeneity of the real-time flow and volume waveforms.

The digital output channel on the PowerLab was used to send a trigger pulse to a digital input channel in the microcontroller of the custom control system described above.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Hutchinson, D. & Whyte, K. Neuromuscular disease and respiratory failure. *Pract. Neurol.* **8**, 229–237 (2008).
2. Groth, S. S. & Andrade, R. S. Diaphragm Plication for Eventration or Paralysis: A Review of the Literature. *ATS* **89**, S2146–S2150 (2010).
3. Col Henry Tripp, L. F. & Col W Randolph Bolton, L. J. Phrenic Nerve Injury Following Cardiac Surgery: A Review. *J Card Surg* **73**, 218–223 (1998).
4. Leung, D. G. & Wagner, K. R. Therapeutic advances in muscular dystrophy. *Ann. Neurol.* **74**, 404–411 (2013).
5. Kurtzke, J. F. Epidemiology of amyotrophic lateral sclerosis. *Adv. Neurol.* **36**, 281–302 (1982).
6. Caruso, P. *et al.* Diagnostic methods to assess inspiratory and expiratory muscle strength. *J. Bras. Pneumol.* **41**, 110–123 (2015).
7. Roche, E. T. *et al.* Soft robotic sleeve supports heart function. *Sci. Transl. Med.* **9**, 1–12 (2017).
8. Payne, C. J. *et al.* Soft robotic ventricular assist device with septal bracing for therapy of heart failure. *Sci. Robot.* **2**, eaan6736 (2017).
9. Cianchetti, M., Laschi, C., Menciassi, A. & Dario, P. Biomedical applications of soft robotics. *Nat. Rev. Mater.* 2018 **36** **3**, 143–153 (2018).
10. Bashkin, J. S., Heim, J. & Prahlad, H. Medical Device Applications of Dielectric Elastomer Based Artificial Muscles. in *Medical Device Materials IV: Proceedings of the 2007 Materials and Processes for Medical Devices Conference* (2007).
11. Bashkin, J. S., Kornbluh, R., Prahlad, H. & Wong-Foy, A. Biomedical Applications of Dielectric Elastomer Actuators. in *Biomedical Applications of Electroactive Polymer Actuators* (eds. Carpi, F. & Smela, E.) 395–410 (John Wiley & Sons, Ltd, 2009).
12. de Vries, H., Jonkman, A., Shi, Z.-H., Man, A. S. & Heunks, L. Assessing breathing effort in mechanical ventilation: physiology and clinical implications. *Ann. Transl. Med.* **6**, 387–387 (2018).
13. Daerden, F. & Lefeber, D. Pneumatic Artificial Muscles: actuators for robotics and automation. *Eur. J. Mech. Environ. Eng.* (2002).
14. Cohen, I. T., Deutsch, N. & Motoyama, E. K. Induction, Maintenance, and Recovery. *Smith's Anesth. Infants Child.* 365–394 (2011). doi:10.1016/B978-0-323-06612-9.00013-4

15. Hannon, J. P., Bossone, C. A. & Wade, C. E. Normal Physiological Values for Conscious Pigs Used in Biomedical Research. (1989).
16. Thille, A. W., Rodriguez, P., Cabello, B., Lellouche, F. & Brochard, L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med.* 2006 3210 **32**, 1515–1522 (2006).
17. Bailey, J. M. Management of Patient-Ventilator Asynchrony. *Anesthesiology* **134**, 629–636 (2021).
18. Davis, J. N., Goldman, M., Loh, L. & Casson, M. Diaphragm function and alveolar hypoventilation. *Q. J. Med.* **45**, 87–100 (1976).
19. Panitch, H. B. The Pathophysiology of Respiratory Impairment in Pediatric Neuromuscular Diseases. *Pediatrics* **123**, S215–S218 (2009).
20. Hess, D. R. Respiratory mechanics in mechanically ventilated patients. *Respir. Care* **59**, 1773–1794 (2014).
21. Mancebo, J. *et al.* Comparative effects of pressure support ventilation and intermittent positive pressure breathing (IPPB) in non-intubated healthy subjects. *Eur. Respir. J.* **8**, (1995).
22. Boussarsar, M. *et al.* Relationship between ventilatory settings and barotrauma in the acute respiratory distress syndrome. *Intensive Care Med.* 2002 284 **28**, 406–413 (2002).
23. Ioannidis, G. *et al.* Barotrauma and pneumothorax. *J. Thorac. Dis.* **7**, S38 (2015).
24. Thomson, A. The role of negative pressure ventilation. *Arch. Dis. Child.* **77**, 454–458 (1997).
25. Shekerdemian, L. S. *et al.* Cardiopulmonary interactions in healthy children and children after simple cardiac surgery: the effects of positive and negative pressure ventilation. *Heart* **78**, 587–593 (1997).
26. Wehner, M. *et al.* An integrated design and fabrication strategy for entirely soft, autonomous robots. *Nat.* 2016 5367617 **536**, 451–455 (2016).
27. Zhang, J. *et al.* Robotic Artificial Muscles: Current Progress and Future Perspectives. *IEEE Trans. Robot.* **35**, 761–781 (2019).
28. J., P. *et al.* An Implantable Extracardiac Soft Robotic Device for the Failing Heart: Mechanical Coupling and Synchronization. <https://home.liebertpub.com/soro> **4**, 241–250 (2017).
29. Horvath, M. A. *et al.* An organosynthetic soft robotic respiratory simulator. *APL Bioeng.* **4**, 026108 (2020).

Figures

Figure 1

Overview of using implantable pneumatic artificial muscles for augmenting respiratory muscle function. **a**, Schematic depicting the lateral cross-sectional of the native diaphragm anchored to the ribs in a relaxed (left) and contracted (right) state. **b** Schematic of the components that make up a single pneumatic artificial muscle (PAM). **c**, Pictures of a single PAM in an unpressurized and pressurized state. **d**, Lateral cross-sectional schematic of the strategy to augment diaphragm motion by placing PAMs

superior to the diaphragm. The PAM conforms to the relaxed diaphragm in its unpressurized (left) state and pushes the diaphragm caudally in its pressurized (right) state. **e**, Visualization of the placement of PAMs (in black) superior to the diaphragm in a live pig model. **f, g**, Lateral fluoroscopy view of the *in vivo* porcine diaphragm with PAMs in an (**f**) unpressurized and (**g**) pressurized state (fluoroscopic videos available as Supplementary Video 1). The air-filled balloon of the actuator is outlined with a dashed line and indicated with an arrow. *A* and *P* indicate the anterior and posterior direction of the animal.

Figure 2

Ability to augment tidal volume and peak inspiratory flow *in vivo*. **a**, A representative, continuous segment of actuation pressure, flow, and tidal volume waveforms from the respiratory challenge with the largest augmentation. Gray shading indicates the period of time where the diaphragm assist system is off and the subject's respiration is unsupported. **b**, A representative set of actuation pressure, flow, and tidal volume waveforms for one full respiratory challenge. Gray shading indicates the period of time where the system is off and respiration is unassisted. **c,d**, Comparison of the average (**c**) peak inspiratory flow and (**d**) tidal volume immediately before and after the point where the assist is turned on at the beginning (left two bars per subject) and off at end (right two bars per subject) of the respiratory challenge (indicated by arrows in **b**) across 5 subjects. Each gray dot represents one breath. **e**, Body weight normalized minute ventilation achieved during the period immediately before and after the assist is turned on at the beginning and off at the end of the respiratory challenge. The range of normal minute ventilation, as reported by Hannon et al¹⁵, is indicated by the light green shading; the solid line indicates the mean; the dashed lines indicate the standard deviation. In **c-d**, bar plots show mean $\pm$ s.d., *** $p < 0.001$ using a Wilcoxon rank-sum test.

Figure 3

Synchronous actuation with the native respiratory effort. **a**, Schematic of the control system. The spirometry flow sensor data is fed into the data acquisition system; when the flow sensor crosses a set threshold a trigger pulse is sent to the control box which triggers a set pressure actuation curve in the electropneumatic regulator, modulating the pressure inside the pneumatic artificial muscles. **b**, A set of idealized waveforms (indicated by the green background) showing the mechanism of synchronization.

c,d, A representative set of collected waveform data—actuation pressure, flow, and tidal volume—for (c) a set independent actuation scheme and (d) a synchronized actuation scheme. **e,f**, A swarm plot comparing the (e) tidal volumes and (f) peak inspiratory flows generated in one respiratory challenge with independent actuation with one respiratory challenge with synchronized actuation for 6 different subjects.

Figure 4

Effect of the time alignment of actuation and native respiratory effort in two levels of respiratory

insufficiency. a,b, Representative actuation pressure, flow, and volume waveforms for a single breath from one respiratory challenge with (a) an intact phrenic nerve and one with (b) a severed phrenic nerve. Circles mark features that can be identified from the waveforms including the start of actuation (P_0), peak inspiratory flow, start of the breath (V_0), and peak volume (V_{pk}), and the dashed lines indicate the time point of each feature. **c,d,** A scatter plot of peak inspiratory volume as it relates to the time between V_{pk} and P_0 for one respiratory challenge with an (c) intact phrenic nerve and with a (d) severed phrenic nerve. **e,f,** A scatter plot of tidal volumes as it relates to the time between V_{pk} and P_0 for one respiratory challenge with an (e) intact phrenic nerve and with a (f) severed phrenic nerve. All data is taken from the same subject. Each dot represents data from one breath.

Figure 5

Comparison of respiratory waveforms. **a,b,c**, Average change in **(a)** pleural pressure (P_{pl}), **(b)** abdominal pressure (P_{ab}), and **(c)** transdiaphragmatic pressure (P_{di}) per breath under mechanical ventilation (MV), actuator assisted ventilation (AAV), and spontaneous respiration (SR) taken across one respiratory challenge per subject. No pressure recordings were taken for subject C. Each gray dot represents one breath. **d,e,f**, Representative P_{pl} , P_{ab} , P_{di} , and flow waveforms for **(d)** mechanical ventilation, **(e)** actuator

assisted ventilation, and unassisted spontaneous respiration (**f**) from one respiratory challenge from subject A. The alternating grey and white background indicates the bounds of each breath. **g**, Respiratory Campbell diagram plotting the pleural pressure-volume loops for representative breaths from MV, AAV, and SR. The direction of inspiration is indicated by the arrow. The compliance of the passive chest wall derived from the MV is indicated via the solid black line. Shaded regions outlined by dashed lines indicate the area representative of the work of breathing (WOB). In **a-c**, bar plots show mean $\pm$ s.d. ns = not significant, ** $p < 0.01$, *** $p < 0.001$ using a Wilcoxon rank-sum test.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryInformationNBME1217.pdf](#)
- [VideoS1.mp4](#)
- [RSf.pdf](#)