

Abstract

Cystic fibrosis (CF) is a severe, genetic disorder that causes excessive secretion of thick mucus in the patient's airways and affects 30,000 people in the U.S. (70,000 people worldwide) with 1,000 new cases diagnosed each year.¹ CF is a chronic disease that requires constant treatment to effectively manage the symptoms. However, low treatment compliance is a huge issue among the CF population. This leads to respiratory problems and chronic lung infections, resulting in hospitalizations, decreased quality of life, and lower life expectancy. Addressing the compliance issues and treatment effectiveness will both improve patient outcomes and ultimately reduce healthcare costs.

The absence of an established time-efficient therapy that is passive, consistent, and portable defines a clinical need: a mobile mucus-clearance therapy that increases compliance by reducing the patient burden of treatment while allowing more time for other activities of daily life. Our proposed solution is RESONAIR: a portable, wearable, vibrating device - discretely contained within a backpack - that leverages both the viscoelastic properties of mucus as well as the resonant frequency of the lungs to more quickly dislodge mucus from the airway.^{2,3} The ease and customizability of this device aims to increase compliance, reduce time spent on active treatment, improve quality of life, and lower overall healthcare costs.

RESONAIR optimizes therapy by allowing the patient to control the force while staying in the lungs' resonant frequency range. This customizability is a feature not readily available in current devices and poses a big challenge to compliance as patients may feel that predetermined, fixed settings are ineffective or uncomfortable. We hypothesize that forces applied at the lungs' resonant frequency will decrease mucosal viscosity more than forces applied above or below the resonant frequency range. This functionality distinguishes our device from other devices that couple force and frequency to achieve airway clearance. To prove RESONAIR's technical feasibility, we ran benchtop experiments characterizing the relationship between force and frequency and animal testing that demonstrates the transmission of frequency through tissue.

Currently, RESONAIR is partnering with The Cystic Fibrosis Center at Stanford University through an IRB-approved clinical study to validate safety and equivalence to existing medical devices. In order to gain greater traction, we plan on reaching out to more cystic fibrosis centers and key opinion leaders to capture early adopters and to broaden RESONAIR's reach. Given that predicates in the CF treatment space have established both a clear regulatory pathway - 510(k) without clinical data - and reimbursements codes with insurance support, the ongoing IRB study can reduce the largest remaining risk between this project and patients by gathering performance data.

Although RESONAIR primarily aims to treat cystic fibrosis, the mode of therapy is beneficial to other ailments that require chest physiotherapy due to defective mucociliary clearance. These diseases include but are not limited to primary ciliary dyskinesia, chronic obstructive pulmonary disease, bronchiectasis and bronchitis.

Description of Clinical Need

Cystic fibrosis is a genetic disorder that leads to an overproduction of thick mucus in a patient's airways, resulting in respiratory problems, lung infections, hospitalizations, and decreased life expectancy. An estimated 30,000 people in the U.S. (70,000 worldwide) are affected by CF, with 1,000 new cases diagnosed each year.¹ CF requires daily treatment to manage symptoms and reduce complications. These treatments include manual chest percussion therapy (CPT), airway clearance devices, and mucus-thinning drugs.³

Low compliance is the largest obstacle facing both patients and healthcare providers. Patients with low treatment compliance attribute it to the large amount of time and effort (> 2 hours/days) spent daily clearing the thick mucus from the airways.⁴ Additionally, lack of compliance exacerbates the accumulation of mucus, making the lungs more susceptible to chronic lung infections, thus lowering life expectancy and increasing hospitalizations.

The average annual costs for patients coping with mild, moderate, and severe CF are US \$10,151, US \$25,647, and US \$33,691, respectively while average lifetime healthcare costs for CF patients are approximately US \$306,332.⁵ Low and moderate compliance predicts higher concurrent health-care costs by \$14,211 and \$8,493 respectively, compared to high compliance.⁶ Over half of these costs are associated with the costs of hospitalization.

In addition to the monetary costs of treatment, CF has a social impact as well. Family members often have to take care of CF patients by administering treatment themselves, transporting patients to receive care, and constantly monitoring the patient's health. For the patients themselves, there are reductions in productivity, social interactions, and quality of life that results from dealing with CF.

While drug treatment is promising, it is currently very expensive and limited in effectiveness. For instance, Vertex's Kalydeco (ivacaftor), the best mucus-thinning drug available, sells for \$300,000 a year and is only targeted to roughly 5 percent of the population.⁷ This means that CPT and airway clearance devices are the most prevalent forms of treatment. However, CPT can be unreliable due to the required time and coordination needed with a health professional and the variance of treatment among different physiotherapists.

Airway clearance devices seek to improve quality of life by easing treatment, but they are met with low compliance as patients often complain about the time, effort, and discomfort associated with maintaining daily treatment.⁴ As a result, the effectiveness of treatment is not always fully realized. Thus, in order to increase compliance, which would lower overall healthcare costs for both the patient and the provider, it is necessary to increase comfort and reduce the amount of time and effort required for airway mucus clearance.

Product Design

Project Objective

The primary project objective is to increase treatment compliance with a portable, discrete, comfortable device that reduces the amount of time and effort required for active treatment. The proposed solution, RESONAIR, is a backpack that administers mechanical vibrations to the user's back at the lungs' resonant frequency - the range of which is generally between 35-42 Hz - effectively vibrating the lungs and lowering the viscosity of mucus while inducing movement of bronchial secretions toward the throat and out of the patient's airways.^{2,3} RESONAIR targets the lung resonant frequency in order to maximize the force transmitted to the mucus while independently allowing force variation to effectively reduce the amount of time required to clear the airways. This approach distinguishes RESONAIR from current devices. To assess clinical feasibility we currently have eligible patients and approval from Stanford's Internal Review Board (IRB) that will allow us to conduct a clinical study involving 10-20 patients in partnership with the Stanford Cystic Fibrosis Center. The aim of the clinical study is to validate safety and equivalence to existing medical devices.

Documentation of the final design

RESONAIR's current design is a backpack that contains a vibrating actuator unit, a user interface control unit, and a power supply unit. Ultimately, the final design will consist of individually controllable vibrating motors, a wireless control system that collects usage data, and a long lasting, light, and low-profile rechargeable battery to promote on-the-go treatment.

The vibrating actuator consists of vibrating motors capable of targeting the resonant frequency range of the lungs. The user interface allows the patient to adjust the number of running motors and input voltage to control the strength and frequency, respectively. In the ideal setup, the patient would be able to target any frequency within the range of frequencies that are feasible. Lastly, the portable power supply provides flexibility in when and where RESONAIR is used.

The innovative aspects of RESONAIR are two fold. First, while devices like Afflovest directly couple force and frequency, making it impossible to adjust one without the other, RESONAIR allows for force adjustment while keeping frequency constant. Patients will be able to control the force while staying in the correct frequency range to preserve comfort but still maintain effectiveness. The motors' adjustable placement is a feature that further allows for customizability in treatment.

Second, while Afflovest, like RESONAIR, is designed to be portable and passive, RESONAIR provides additional functionality. Many of RESONAIR's features are hidden out of view while maintaining the look and functionality of a normal backpack. RESONAIR does not resemble a medical device that draws a lot of attention to the user, and can thus more seamlessly be integrated into the patient's lifestyle.

Evidence of a Working Prototype

Specifications	Accomplished?	Technical Details (if applicable)
Motor forces match current devices	Yes	Measured force: .1-20N
Customizable motor placement	Yes	
Individually controllable motors	Yes	Motor driver shield
Rechargeable	Yes	Sealed Lead Acid Battery
At least 2 hour battery life	Yes	14 amp-hour 12V battery
Interactive user interface	Yes	Touchscreen
Weighs <10 pounds	Yes	
Wireless control	No	
Matches current treatment performance	TBD	

Table 1: Table 1 shows the design specifications of RESONAIR. Green indicates that it has been accomplished to date, red means that it has not been accomplished yet, and yellow means that it is in progress and has not been determined yet.

Prototype of Final Design



Figure 1 a-f: **1a.** The power supply unit consists of a 12V rechargeable battery that provides 14 amp hours for treatment when running four motors operating at a current of 0.145A each. There is an additional 9V battery with an on/off switch that powers the touchscreen. These batteries would adequately supply a patient with enough power to easily sustain an average length CF treatment of about 20-30 minutes 3-4 times a day, with a total battery life of approximately 6-7 hours. **1b.** RESONAIR's current design is a backpack that contains a vibrating actuator unit, a user interface control unit, and a power supply unit. **1c.** The back panel of the device comes into contact with the patient's back. The panel provides a comfortable barrier between the motors and the patient. **1d,f.** The user interface control unit consists of an LCD Adafruit 2.7 inch touchscreen that is interactive and intuitive, stacked on an Arduino Uno board and a motor shield. There are two rows of buttons on the touch screen: the top row contains an "off" button and allows the user to choose between two frequency settings indicated as low and high. The second row allows the user to select the number of motors that are on. **1e.** The vibrating actuator unit consists of four vibrating motors housed in custom-built 3D caps that are attached to the back side of the backpack with velcro, allowing patients to manually customize the vibrations to target specific regions of the lungs. The motors are connected to a motor driver shield and vibrate at the pulmonary resonance frequency, leading to mucus thinning and clearance.

Estimated Manufacturing Costs and Product Pricing

The material costs are estimated from the retail prices of each item. We anticipate the costs to be much lower with streamlined engineering and bulk ordering. We estimate labor and quality testing to take a total of approximately 4 hours for each backpack at \$25 per hour. Afflovest provides a reimbursement framework that RESONAIR seeks to follow or adapt. Afflovest is currently reimbursed monthly under Medicare and Medicaid with its own HCPCS reimbursement code (E0483) with Medicare willing to cover 80 percent of the maximum allowed cost, roughly \$944 per month, and the patient contributing about \$236 per billing, for up to 15 months.^{8,9} Additionally, patients have the option to buy or rent Afflovest from Durable Medical Equipment or Home Medical Equipment following a physician's prescription.⁸ While patients would likely initially follow the same pathway to obtain RESONAIR, a potential change to the reimbursement model would be to have a multi-year rental option at a lower monthly cost where patients are eligible to receive a new RESONAIR model each year.

We project RESONAIR to retail around \$6,000 through home care device retailers. This price brings value to all stakeholders involved in CF care, namely the patients, hospitals,

Material	Cost (\$)
Backpack	35
4 Motors	40
Microcontroller	12
Motor Driver Electronics	20
Touchscreen Electronics	35
9V battery	3
Battery holder	5
12V Rechargeable battery	15
Labor	50
Quality Testing	50
Total Cost	\$265

Table 2: Material and labor costs estimates

and insurance carriers. It is priced below current device costs, represents a saving in hospitalization costs, and aims to improve compliance and effectiveness of current treatments.

Experimental Evidence

Demo Video

<https://www.youtube.com/watch?v=mIH2JM7mZiE>

Experiment 1 Results

A potentially significant risk to the effectiveness of RESONAIR is the transmission of frequency through human tissue. The non-uniform characteristics of human bone and other tissue pose the possibility that the frequency being administered does not match the frequency that reaches the lung itself. In order to test this out, we measured the frequency of motor vibrations at different levels in the chest cavity of a recently deceased pig. Accelerometers were inserted into the sternum area, in between the lung lobes, and on the back, and two different frequencies were tested.

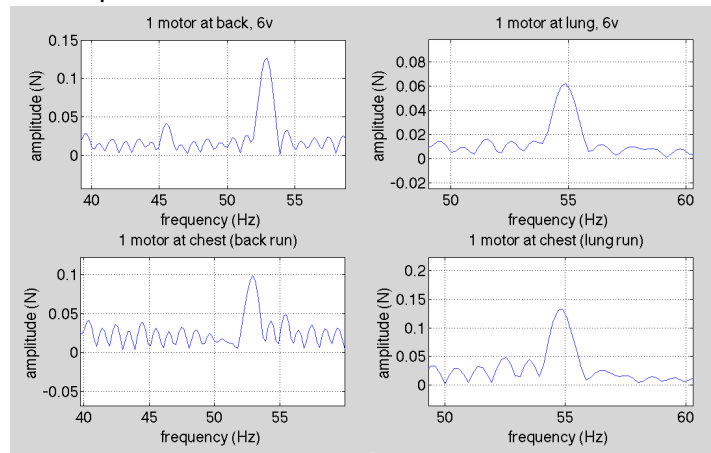


Figure 2a - d: The four figures display the frequency plots from the animal test run at 6 volts. Fig 2a (top left) and Fig 2c (lower left) show matching frequencies at roughly 53 Hz despite the accelerometers being placed at the back and chest, respectively. Fig 2b (top right) and Fig 2d (lower right) also show matching measured peak frequencies around 55 Hz at the lung and chest.

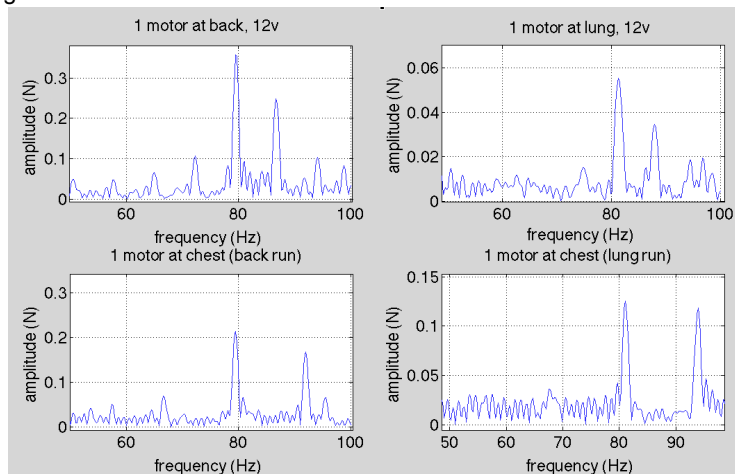


Figure 3a - d: The four figures display the frequency plots from the animal test run at 12 volts. Fig 3a (top left) and Fig 3c (lower left) show matching frequencies at 80Hz with the accelerometers being placed at the back and chest, respectively. Fig 3b (top right) and Fig 3d (lower right) also show matching measured peak frequencies of 80 Hz at the lung and chest, respectively.

Results from the experiments indicate that there is little to no shift of the frequency signal across various tissues at both 6 volts and 12 volts. As seen in Figures 2a-d, the fast Fourier transform plots for one motor run at 6 volts show a prominent peak at 50-55 Hz in all four graphs. A similar pattern can be observed in Figures 3a-d, the 12 volt graphs, with peaks at 80 Hz in the back and lung tests and matching frequencies of the corresponding measurements taken from the chest. While the measured force amplitude is relatively low, these results show that the frequency applied on the outside of the body will be the same as the frequency transmitted through the body.

Experiment 2 Results

RESONAIR encourages mucus clearance by controlling force independently of frequency, distinguishing it from other airway clearance devices. We hypothesize that the frequency of the system can be maintained while adjusting the force. To test this, two motors are run one at a time, and then together, with the resulting frequency domain extracted from force measurements. Figure 4a shows that the combined effect of multiple motors is the summation of the frequency of individual motors. Figure 4b shows that as the number of motors increases - thereby increasing the total amount of force of the system - the overall frequency does not change.

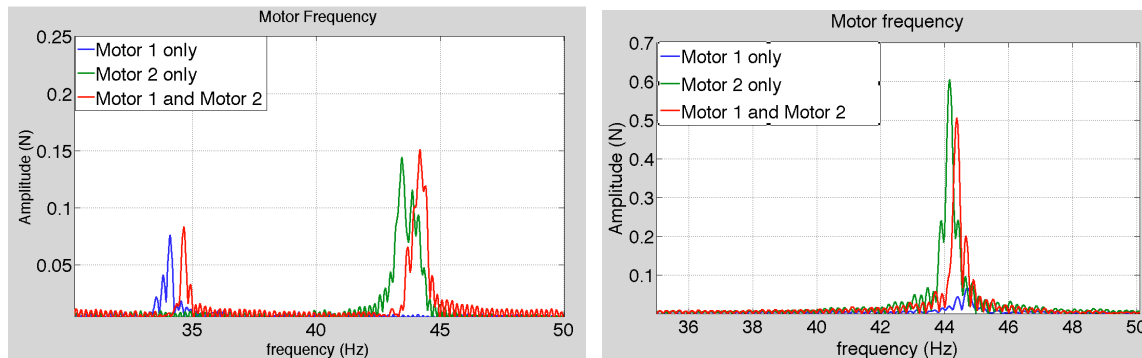


Figure 4a (left). Motor 1 (blue), and Motor 2 (green) are running at different frequencies. When both motors are running (red), there are two peaks at 35 and 44 Hz that correspond to the individual frequency traces of Motor 1 and Motor 2.

Figure 4b (right): Building off the results from Fig. 1, Motor 1 (blue) and Motor 2 (green) were tuned to the same frequency. Then, both motors were run together (red). The traces all align, leading to the conclusion that increasing the number of motors running at the same frequency will maintain the frequency of the system.

One point to note is that force was not controlled for in these experiments, which explains why the amplitude of the combined motors is not as high as expected in Fig 2. However, given these preliminary results, we are reasonably confident that the same approach can be applied to more motors to show that frequency remains consistent.

Conclusion

RESONAIR provides an innovative solution for a problem that is relevant to all in the CF population. By providing the most patient-friendly therapy option, RESONAIR can increase compliance and address the monetary and human costs of treatment. Lastly, with a functional prototype device and approved IRB testing underway, RESONAIR is on track to establish clinical effectiveness and inform improvements for future commercialization.

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