MICROTESLA PUMP ENABLED RECIRCULATING MODEL OF ALVEOLAR EDEMA PATHOLOGY

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ABSTRACT

This work aims to study the relationships between molecular and physiological parameters in the pathogenesis of coronavirus (COVID-19) patients with diabetes. To achieve this, a novel micro-scaled Tesla rotor pump (μTesla) integrated with a dual-phase gas/aqueous microfluidic alveolar cluster was designed. The micro-engineered surface textures that improve the pumping mechanism - via fluid mechanics modeling and 3D printed prototyping - were investigated. Current literature was surveyed to recreate physiological and pathophysiological geometries in the designed microfluidic alveolar cluster. We end with an in-vitro model that has controlled modulation of fluid mechanics and molecular transport that models oxidative stresses, glucose variability, fluidic shear/strain forces, and soluble factors on alveolar barrier function and inflammatory responses. Not only does our work create a recirculating microfluidics system modeling diabetic alveolar interactions, but it also aids in understanding the mechanistic synergy between diabetes and COVID-19.

KEYWORDS

Microfluidics, Micropumps, Diabetes, Alveolar mechanochemical stresses and dysfunction, Oxidative Stress, ACE-2, COVID-19

INTRODUCTION

Diabetes and COVID-19

From clinical experience of treating COVID- 19, several key trends have appeared—1) uncontrolled inflammatory response 2) prevalence of pulmonary edema and severe respiratory distress syndrome, 3) and unexpected blood clots and cardiovascular pathologies [1]. Moreover, these are markedly worse in diabetic patients, who have four times greater risk of mortality [2]. Despite growing knowledge of COVID-19, the mechanisms of this disastrous synergy with diabetes is unclear. We have identified potential molecular and pathophysiological conditions that make diabetes and COVID-19 a deadly combination. Our proposed microfluidic platform is designed to modulate the concentrations, flow rates, and pressure conditions to test these mechanisms (Figure 1).

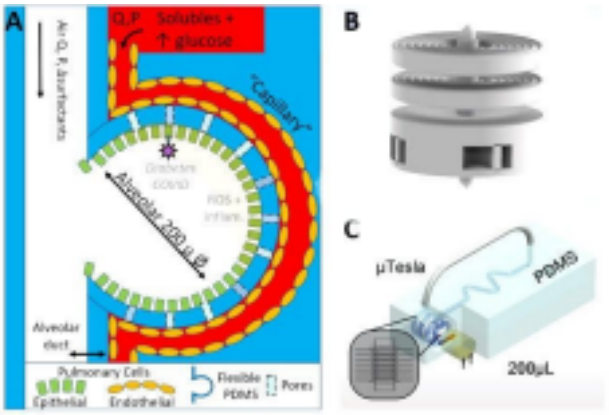


Figure 1: Microfluidic Devices. A: Alveolar Microfluidic Device. B: Textured μTesla Rotor. C: Rotor Integration with Device

Hyperglycemia and Lung Impairment

As a result of COVID-19 infection, inflammatory responses are triggered when infected cells die by apoptosis [1]. The initial acute inflammatory response is marked by the activation of pro-inflammatory cytokines or chemokines, which is accompanied by immune cell infiltration and tissue damage [1]. Hyperglycemia deregulates inflammatory cell binding and recruitment, impairs endothelial-epithelial barrier function, augments permeability of the vasculature and reduces gas change. For severe inflammation associated with cytokine storm, diffuse alveolar damage, and severe capillary damage result from impaired respiratory functions in diabetics [3].Though not specifically described in our current alveolar microfluidics, future integration of working islet with alveolar microfluidics can well describe the interplay between islet hyperglycemia and lung impairment.

The Interplay of Surfactant and Gas Exchange

Surfactant released by Type II alveolar epithelial cells reduces lung surface tension at the air-liquid interface, facilitates breathing and gas exchange, and prevents lung collapse [3]. Recent findings show that SARS-CoV-2 induces the destruction of type II alveolar cells in COVID-19 associated pneumonia [4]. Without sufficient lung surfactant, alveoli collapse during exhalation, resulting in hypoxemia (poor blood oxygenation) and high alveolar surface tension which leads to an increased inflammatory reaction [4]. This reaction leads to a cascade of events, including hypoxia, oxidative stress, vasoconstriction, pulmonary hypertension and edema, and potential alveolar failure [3]. Due to the impaired respiratory function, inflammatory response, and endothelial epithelial barrier function in diabetics, the effects of this phenomenon are increased [1]. The findings from this study will aid in understanding the underlying cause behind the complications experienced by diabetic COVID-19 patients, or inflammation and edema-related lung condition experienced by diabetic patients. The soluble factors, surfactant, reactive oxygen species (ROS) and/or fluid pressure can be simulated in our

microfluidic platform in an effort to investigate their effects.

Proposed Alveolar Microfluidic Device

The proposed alveolar microfluidic device aims to model several key components of the synergy between diabetes and COVID-19: 1) mechano- chemical impairments caused by insufficient lung surfactant production, 2) impaired barrier gas exchange and function, 3) and subsequent leukocyte extravasation and activation [2]. The idealized model will be analyzed through coupled fluid model analysis to estimate the alveolar mechanics parameters such as pressure and velocities [5]. How surfactant production contributes to conditions including volutrauma/barotrauma (extreme stress/strain), atelectrauma (repeated opening and closing of collapsed alveoli) and biotrauma will be examined on the idealized alveolar sac model. Parameters such as the fluid (air) density, fluid pressure, fluid viscosity, the fluid velocity, and air flow rate, and their relation to surfactant production will be examined in greater detail. To test these specific mechanisms, the artificial microfluidic alveolus will contain recirculating aqueous air microchannels integrated into a porous membrane lined with endothelial and epithelial cells. Aqueous interrogations of soluble proteins and circulating cells will be achieved using on-chip hydrogel biosensors and fluorescence microscopy. Modulation of glucose flux will be enabled by the textured µTesla pump. The resulting platform combines multiple cell types, phases, and modalities to create a precise, targeted model of COVID mechanisms exacerbated by diabetes (Figure 1).

Textured µTesla Pump

To develop an appropriate µTesla pump for alveolar microfluidic integration, µTesla Version 2 was refined to include surface texture on the rotor discs [6]. Through obtaining critical value results from fluid mechanics (COMSOL) modeling, a µTesla v3 pump with sinusoidal textured rotor discs was designed and 3D printed (Figure 1B) [7]. Future testing will involve rotors with triangular and directional surface textures (Figure 2) at geometries identified to be of interest--1 to 4 cycles/mm and 100-300 um peak to peak amplitudes. Novel dynamics regarding pressure and flow rate were modeled in the sinusoidal textured µTesla pump through a series of preliminary experiments. This improved pump effectively reduces vibration upon integration and contributes to the further miniaturization of the microfluidic system for a novel alveolar device.

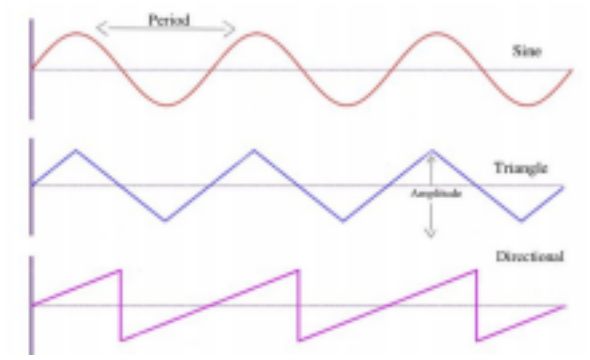


Figure 2: Texture Profiles for Rotor Disc

Results shown in this abstract indicate the improved functionality of this pump and its utility for integration in biological microfluidic devices, specifically in regard to consideration of capillary wall texture and the non-Newtonian aspects of human blood. In future work, this pump will be integrated in the proposed alveolar microfluidic device to examine the effects of capillary shear on alveolar endothelial cells for the modulation of alveolar edema pathology in presence of hyperglycemia.

Integration with Recirculating Alveolar Microfluidics

The optimization of the novel µTesla pump aims to improve alveolar microfluidic integration through maintaining an improved control of lower velocity flow rates (<100 µL/min) necessary for alveolar capillaries. The improved design of the rotor allows for fewer velocity fluctuations, lower rotational speeds, and less vibrational perturbations upon integration. With this optimized pump, the microfluidic system will potentially require a smaller power supply package, allowing for condensed integration; an objective that is useful for extended microscope-based microfluidic experiments. These improvements are required for multi-organ-on-a-chip microfluidic experiments, where recirculation over longer time periods can amplify signals of the desired pathological effects. In the investigation of the interplay between pancreatic beta cells and the renin-angiotensin system in relation to COVID-19, this condensed microfluidic rotor integration will improve experimental quality and results.

EXPERIMENTAL

The µTesla rotor was fabricated using a stereolithography based 3D printer (Phrozen Shuffle, 50 µm resolution). To measure the change in pressure as a result of varying rpm values, magnets were placed within the rotor magnet compartments, and the rotor with its housing was attached to a magnetic stir plate. The stir plate was set to known rpm values and Tygon tubing was attached to the nozzle of the housing, which allowed for the measurement of hydrostatic pressure height difference (Figure 3A). The measured height difference can be used to determine output pressure

$$\Delta P = \rho g \Delta h \quad (1)$$

$$\Delta P = P + P_{atm}$$

$$P = \Delta P - P_{atm} \quad (2)$$

To evaluate the performance of the µTesla rotor in a microfluidic device, a syringe pump was used to pump
water into a standard droplet array device through the rotor. This setup allowed for the determination of flow rate in µL/min relative to the syringe pump in presence of a microfluidic device (Figure 3B).

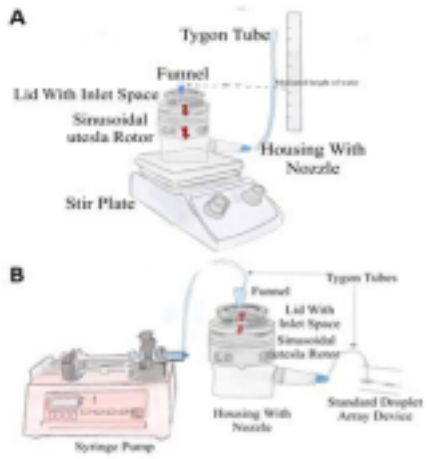


Figure 3: Experimental Setup A: ΔP vs. rpm Setup. B: Flow Rate vs. rpm Setup.

RESULTS AND DISCUSSION

Simulation Results

Through using COMSOL for flow profile simulations, the velocity profile was plotted perpendicular to the channel at 1/4 of a cycle to analyze the flow near the walls (Figure 4A) [7]. After modeling and computing over 7 frequency and 6 amplitude variations, there were 42 datasets from which the value at each skirt bump was extracted (Figure 4B/C). Skirt bump length stopped increasing after f = 4 and bump height after f = 3. As amplitude increases, bump height increases steadily but length increases slower. Thus, by choosing appropriate frequency and amplitude combinations, the wall slip can be modulated.

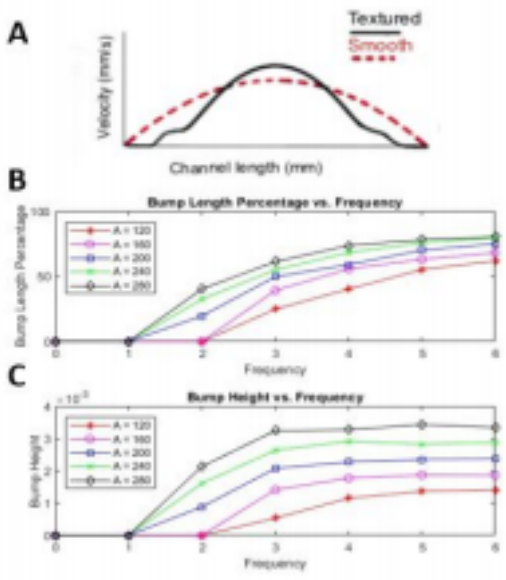


Figure 4: Modeling of textured µTesla pump. A: Velocity Profile with "bumps" B: Bump Length Modulations. Plot. C: Bump Height Modulations [7].

These results were used to develop a prototype pump with a combination of values that meet these critical requirements.

Experimental Results

The modeling results indicate that surface texture pushes the velocity profile towards the center of the flow path (Figure 4A). Velocity features were seen close to the rotor surfaces, which we refer to as a 'bump'. We analyzed these bump sizes and found that bump length and height increase with texture modulation frequency (cycle/mm) and amplitude (120-280 µm peak to peak). However, bump length asymptotically increases with amplitude, while bump height flattens after 3 cycles/mm. We considered the 3 cycle/mm and 200 µm to be critical features dimensions for µTesla texturization. To test the device fabrication, a 2 cycle/mm, 200 µm peak to peak µTesla v3 prototype was 3D printed and tested. The calculated ΔP vs. rpm values were plotted (Figure 5A). The results show exponential increase in ΔP with rpm, a finding that coincides with our previous µTesla Version 2 results [6]. A maximum of 1.02 kPa was achieved. Moreover, the pump was attached to a serpentine droplet microfluidic array device to characterize its performance under load (Figure 5B). These results also mirrored the exponential increase, and a maximal microfluidic flow rate of 650 µl/min was observed.

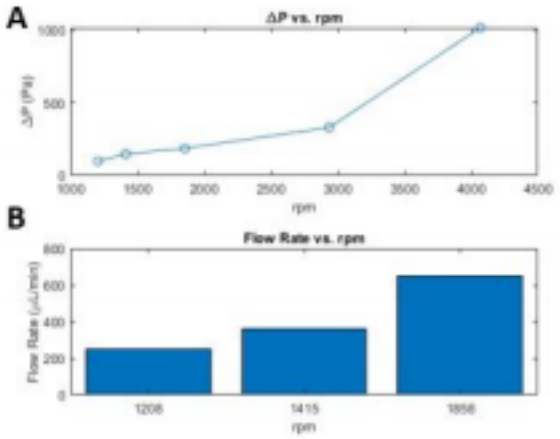
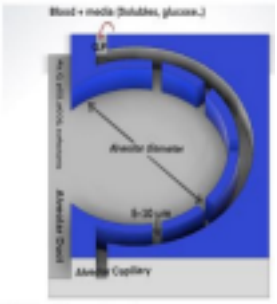


Figure 5: µTesla Experimental Results A: ΔP vs. rpm. B: Flow Rate vs. rpm.

In comparison to the previous µTesla Version 2, a maximum pressure of 1.30 kPa at 4000 rpm, and a flow rate of 250 µl/min at 1800 rpm were experimentally generated [6]. when integrated with the same serpentine droplet microfluidic array device. It is evident that our novel surface texture µTesla rotor has similar expected performance. It is important to note that this is a prototype device whose texture has not been fully optimized. Based on our modeling, we plan to further improve and optimize the periodicity and amplitude combination of the rotor to achieve the most efficient device to drive our alveolar microfluidics.

Table 1. Alveolar Microfluidic Pathophysiology Parameters

Dimensions	Low	Medium	High
Art ⌀ µm	20	35	50
Art Q nL/min	10	15	20
Art P mmHg	15*	37	50
Alv ⌀ µm	100	200	300
Porosity/mm	20	30	40
Duct ⌀ µm	200	400	600
Alveolar ∠ **	45	68	97
Alv air P	740	760	780
Alv O2 mmHg	104	104	104
Art O2 mmHg	20	40***	60
Total cluster	10	40	90
2D cluster	2	4	8



*ARD < 20 mmHg
**Angle ~ surface tension
***<40 mmHg is hypoxic

Lastly, a thorough literature search (beyond listed references) was conducted to find the physiological parameters surrounding alveolar impairments in COVID and diabetes (Table 1). This was used in designing the microfluidic geometry shown next to the table. In addition to these physical parameters, molecular concentrations, surfactant levels, and pharmaceutical agents will also complete the testing parameters for the integrated alveolar device.

CONCLUSION

In this work we have optimized the design of a textured µTesla pump for the integration of a physiologically based microfluidic model of alveolar edema. Through fluid mechanics modeling, we found that the pumping can be enhanced at an optimal point, with 3 cycles/mm and 200 µm peak to peak sinusoidal modulations. We completed a 3D printed prototype with 2 cycles/mm and 200 µm amplitude and measured an output pressure of 1.02 kPa at 4krpm maximum. It is capable of driving our droplet microfluidic device at 650 µL/min per channel. This is on-par with our previous µTesla version without being optimized at 3 cycles/mm, hinting at additional performance to be extracted. Moreover, we combed through the literature on alveolar impairments and arrived at a set of pathophysiological conditions to be tested in a microfluidic alveolar design. The next step would be a monolithic and miniaturized integration of pumps with alveolar microfluidics. The overarching aim is to provide a flexible platform for understanding COVID pathology as accelerated by diabetes in an attempt to test and apply novel therapeutics.

ACKNOWLEDGEMENTS

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