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DETECTING PULMONARY EDEMA THROUGHOUT EX VIVO LUNG PERFUSION

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ABSTRACT

Ex Vivo Lung Perfusion (EVLP) is now a powerful clinical technique that has facilitated the increase in successful human lung transplantation procedures. By having the abilities to assess marginal lungs, extend preservation times, and expand geographical distances for donations, EVLP has effectively both expanded the human lung transplantation donor pool and shortened times on the transplant waitlist. While clinical usage has expanded, preclinical research on EVLP has not. EVLP can be utilized as a preclinical research model, i.e., to investigate pharmacological responses (e.g., post-conditioning agents), organ preservation, device testing and/or methodology development. To facilitate the use of EVLP as a research tool, we have developed a low-cost testing system with ever increasing capabilities e.g., the use of a novel continuous weight sensor to evaluate lung edema. Real time tracking of edema allows us to hone in on potential causes of lung damage, and investigate techniques to rehabilitate and mitigate damage on a short time scale (<8 hours). This system enhances our abilities to accurately test medical devices, lung physiology, and potential treatment impacts on lungs.

Keywords: EVLP, Lung, Edema

NOMENCLATURE

EVLP	Ex Vivo Lung Perfusion
ECD	Extended Criteria Donors
DCD	Donors after Circulatory Death
PAP	Peak Arterial Pressure
PVR	Pulmonary Vascular Resistance
PAWP	Peak Airway Pressure
TV	Tidal Volume
ARDS	Acute Respiratory Distress Syndrome
PGD	Primary Graft Dysfunction

1. INTRODUCTION

EVLP has become an invaluable tool in the clinical field of human lung transplantation for both extending the travel distances of a donor organ as well as allowing for the evaluation of post-procurement organ quality. Twenty-one years after the first usage of these devices in a clinical setting, EVLP has spread throughout thoracic surgery suites across North America, increasing the number of transplantable lungs by up to 15-20%, at some centers [1]. However, despite an increasing number of lung transplants performed every year, the demand for transplant still outpaces supply. This shortage is multifaceted: increased numbers of new patients on the waitlist, lower availability of viable lungs, and stringent criteria for donation. Currently, 15-20% of organ donors have their lungs utilized for transplant, and it has been estimated that 41% of unused donor lungs could likely have been viable for transplant if they could have been properly accessed [2]. Noteworthy, today EVLP is increasingly used for the assessment of lungs post-procurement so marginal grafts can be utilized [3].

EVLP devices support lung vitality by pumping oxygen and nutrient rich perfusate through the vasculature and ventilating the airways (see Figure 1). These devices can allow lungs to remain viable for up to 17.5 hours [3]. Individual lungs or en-bloc can be affixed to these systems for evaluation, and different protocols exist that use various osmotic regulators and oxygen carriers in the perfusates. While clinical EVLP machines usually follow strict guidelines for usage, researchers are able to modify intrinsic parameters to rehabilitate and optimize the lungs [4], yet these systems are considered to be very expensive to utilize for ongoing preclinical research.

The EVLP approach has benefits as a research model for the study of experimental therapies both in and outside of EVLP [5]. The goals of these systems are to maintain viability and utilize sensors to monitor function; thus, for preclinical research, EVLP can be used for testing therapeutics, pre- and post-conditioning

agents, and procedural practices to revitalize lungs not considered viable while in the donor. Clinically employed systems are equipped to measure various parameters such as arterial and airway pressures, which allows for the calculation of other functionality indicators such as PVR and compliance, and ultimately give a reasonable picture of overall lung health and physiology.

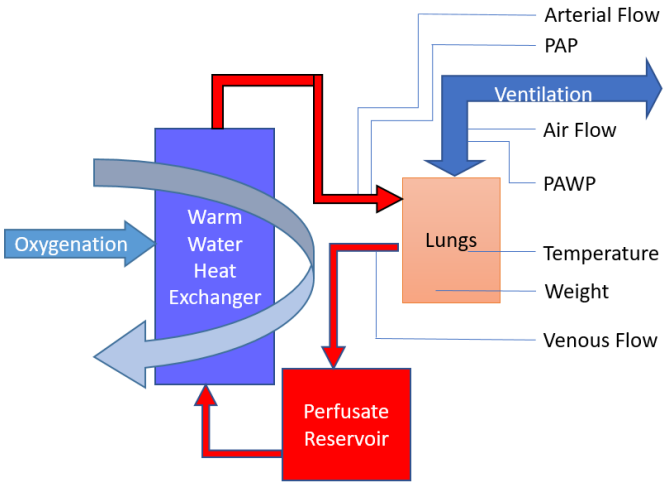

FIGURE 1: SCHEMATIC OF AN EVLP CIRCUIT

Clinical lung health is primarily measured based on the functionality of the lungs. The main function of lungs is to oxygenate the blood and remove carbon dioxide. This is done at the alveolar-capillary junction and is facilitated by simple diffusion. Since the rate of diffusion is limited by the permeability of the medium, the structures dividing the airway from the vasculature are only two cells thick. Disease or injury can cause fluid accumulation in the airways, called edema, which in turn inhibits lung oxygenation capabilities. Edema is thus a potential indicator of both lung damage caused by other sources, as well as potential trajectory for future declines in lung function. This function is measured by the P/F ratio, or the ratio of arterial blood oxygen to the fraction of inspired oxygen (FiO2). At P/F levels < 300, patients are classified as being in acute respiratory distress syndrome (ARDS), a potentially lethal complication. Thus, we consider that if one could continuously monitor lung edema, this would aid in defining injury.

In previous EVLP studies, weight measurements have been used to measure the total amount of edema [6]. To date, the number of such studies are limited; e.g., reports of weight measurements taken before and after the lungs were perfused rather than continuously. This gap in data makes it unclear if there is a functional inflection point at which edema increases dramatically, or if there is a linear increase in edema throughout EVLP. Other methods of tracking edema through a perfusion session have been utilized, such as measurements of hematocrit or tracking the perfusate reservoir volume [7], but these methods depend on manual sampling and would not provide the same resolution as would an integrated sensor. Since edema can cause decreased perfusion and ventilation, ultimately leading to cell death, the continuous collection of weight data would provide insights into the qualities of interventions during EVLP; those aimed to improve lung function. As one means to improve EVLP, we developed a continuous weight monitoring system into our in-house developed apparatus to investigate the relations between weight gains and lung function.

2. MATERIALS AND METHODS

Our in-house developed EVLP apparatus consists of a capsule (micro-environment) containing a pair of lungs, a centrifugal pump, reservoir and membrane oxygenator for transport of the perfusate, and a ventilator for positive pressure ventilation (see Figure 2). Our monitoring system includes sensors to measure perfusate flow rate, ventilation flow rate, arterial and airway pressure, temperature, and weight. A python program was written to loop through a list of requests for each parameter and log the value. An Arduino-based microcontroller collects data from each sensor, performs any necessary calculations, and reports the result back to the python program. Notable differences from clinical models include the usage of a continuous vs. pulsatile pump, and the addition of an integrated scale as a method for tracking changes in edema throughout the perfusion session.

Continuous weight measurements were obtained by supporting the organ capsule with a 10 kg load cell. A platform to connect and properly position the capsule over the load cell was designed and 3D printed (see Figure 3). The absolute weights of the lungs and apparatus were made throughout each performed experiment, with the apparatus weight subtracted off during post processing.

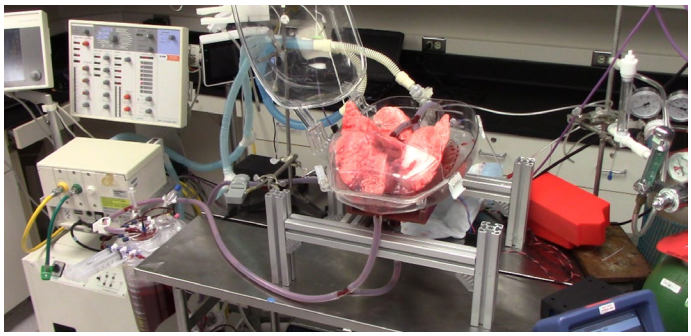

FIGURE 2: A PAIR OF SWINE LUNGS AFFIXED TO THE EX VIVO LUNG PERFUSION RESEARCH APPARATUS WITH AN INTEGRATED SCALE FOR DETECTING LUNG EDEMA.

Several trial experiments were performed while developing the isolated lung resuscitation protocol. Lungs were procured from swine using similar techniques as previous studies [8]. As the main pulmonary artery was not harvested, each pulmonary artery was cannulated individually. The perfusion system was primed with approximately 2000 mL of swine whole blood and 1000 mL of Transmedics OCS Solution (Boston, MA). Each set of lungs were installed into the capsule where they were ventilated and perfused following similar procedures as previous studies [8]. The sensor monitoring system described, along with

a Radiometer ABL90 Series blood gas analyzer, was used to collect performance data and perfusate concentrations. Experiments were performed until the lungs deteriorated or they reached a functional steady state. Histology was not performed in this study, though has been performed in prior EVLP studies [8, 9].

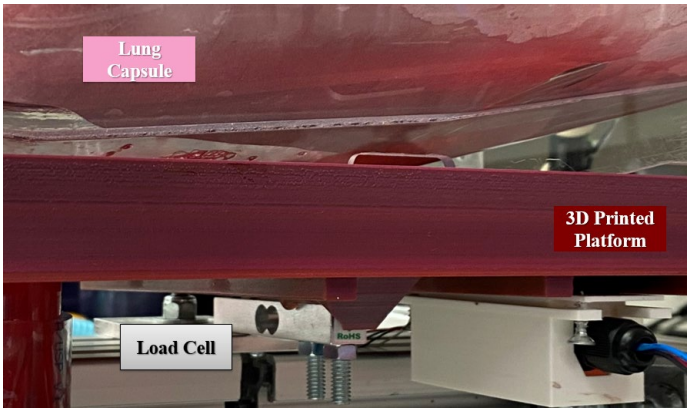

FIGURE 3: CONTINUOUS WEIGHT MEASUREMENTS OF A PAIR OF ISOLATED LUNGS WERE MADE USING A LOAD CELL INCORPORATED INTO AN EVLP APPARATUS.

3. RESULTS AND DISCUSSION

Weights of reanimated lungs were successfully measured using a custom load cell system. The lengths of the perfusion sessions varied depending on the experimental protocol employed. Yet at a minimum, all studies were maintained for 8 hours, with one study exceeding 16 hours (see Figure 4). P/F ratios were maintained above 300, the cutoff for ARDS, for the monitored portion of the long duration EVLP (see Figure 5). The rates of weight gain commonly remained stable while glucose and bicarbonate repletion were employed, only increasing in rates when glucose and bicarbonate administrations were stopped. The steady increase in weight through the three studies indicates that the scale is sensitive enough to monitor gross organ weight changes during EVLP. The large increase in weight at the end of the third study corresponds to depletion of glucose and bicarbonate infusions, ultimately leading to the failure of the organ.

Continuous measurements of reanimated lung weights during EVLP has demonstrated various weight profiles over time, dependent upon the protocol employed. In general, the rate of weight gain can be controlled by supplementing glucose and bicarbonate as needed to maintain homeostatic conditions. P/F ratios during these studies were used to indicate that the lungs were adequately ventilated and perfused similar to what is would expect in vivo (see Figure 5).

The variation of the weight curves between protocols and studies demonstrates the system's sensitivity to the changes in edema formation in the reanimated lung, and therefore its overall function. Additionally, this system has a degree of modularity that would allow for additional sensors to be added dynamically based on protocol, giving us the potential to link new measurements to clinical outcomes. The ability of the system to detect changes in weight during EVLP opens new avenues for research into medical device testing, lung physiology, and clinical optimization.

Usage of an ex vivo single organ model for evaluating medical devices is a practice that has been used for decades by our laboratory for large mammalian hearts but has not been regularly utilized in lungs. The unique nature of EVLP and our developed and employed continuous weight sensor to track lung damage in real time should facilitate the development of treatments to rehabilitate and mitigate damage on a short time scale (<12 hours), such as during trauma management. This ultimately provides data on behavior of a device in a nearly in vivo environment, benefiting research into device-tissue interfaces, as well as other direct tissue modifying devices.

Our employed EVLP system can also be used to evaluate lung physiology in an isolated organ system - something that has been difficult to establish for the lungs. While drug metabolism on the whole organism level is often well studied, individual organ metabolism before filtration by the kidneys is often unclear. While some studies have evaluated chemotherapeutic toxicity in a single organ model [5], doing so for the lungs could lead to better predictive dosing and management of patients with chronic kidney diseases and other filtration related ailments.

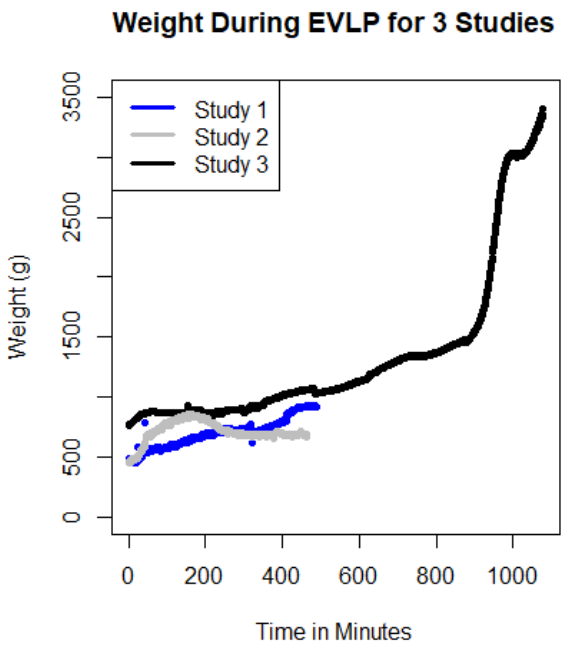

FIGURE 4: WEIGHT GAIN OVER TIME FOR THREE DIFFERENT EVLP LUNG STUDIES.

Detecting weight measurements during EVLP can enhance understanding of treatment benefits over time. Further, transplantation optimization through the use of conditioning agents may revitalize lungs that would otherwise be rejected for transplantation. Measuring the amount of edema during such an

experimental trial would allow us to examine what is happening to the lung, and when interventions should be administered. This can help make marginal lungs sufficiently viable for transplant and increase the number of organ donors' lungs utilized. Data generated from this can ultimately lead to better treatments for illnesses such as ARDS, as well as PGD. In our future research, we hope to evaluate other means for long-term monitoring of reanimated lung function.

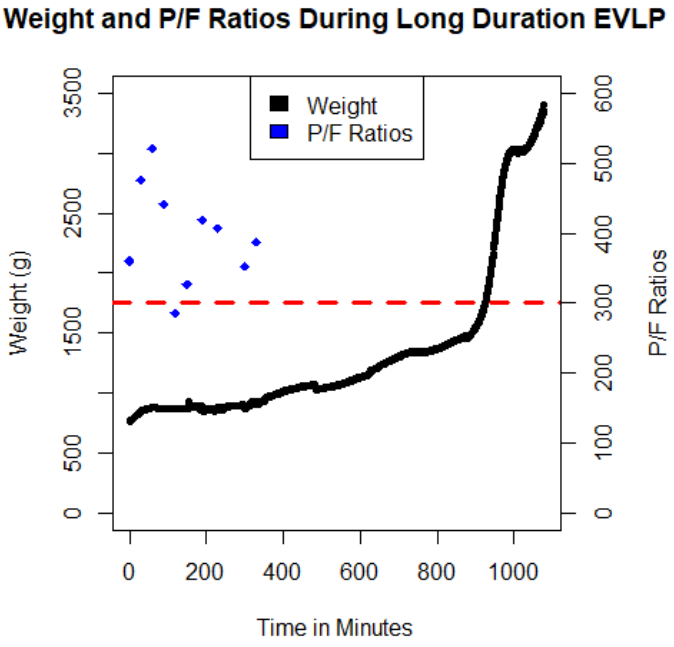

FIGURE 5: WEIGHT GAIN AND P/F RATIOS FOR LONG DURATION EVLP (RED LINE IS CUT OFF FOR ARDS (P/F OF 300)).

4. CONCLUSION

EVLP is a platform that continues to have a large potential for preclinical research. We have developed a low-cost ex vivo perfusion system focused on facilitating preclinical lung research. This system has the capability to measure PAP, vascular flow rate, temperature, PAWP, TV, and tracks edema indirectly through continuous weight measurements. Results suggest that reanimated lungs are capable of being maintained for >8 hours, allowing for short term evaluation of biomedical treatments for lung injuries: such research should have readily available translational applications.

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