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Full Length Research Paper

A modified model for ex vivo lung perfusion device

Mohamed S.A. Mohamed, MBBCh, MSc, MD

Thoracic Transplantation Department, University Clinic Essen, Germany. Hufeland Straße 55. D- 55147 Essen.
E-mail: Mohamed.Shehata@uk-essen.de, mohammed.shehatta1@gmail.com

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Normothermic ex vivo lung perfusion (EVLP) is a technique where the retrieved donor lung can be perfused in an ex vivo circuit, providing an opportunity to reassess its function before transplantation. The hyper-oncotic reconditioning fluid helps to mobilize and remove excess interstitial and alveolar fluid. In addition, recruitment of atelectatic areas has an important role. The value of applying EVLP is to widen the range of donation by allowing lungs of brain death victims, which suffers the associated neurogenic edema in addition to possible traumatic contusions and or infections, and the lungs of circulatory death donors, to be reconditioned and reassessed before final decision of acceptance or rejection. EVLP is already applied within different institutions worldwide, using various application protocols. EVLP is an important technology in the practice of lung transplantation. Previously the author suggested a new protocol for EVLP that would involve the inclusion of bronchial arteries in the procedure of EVLP because of its expected importance. This paper represents the EVLP device model suggested by the author to fit the newly suggested EVLP Shehata protocol.

Keywords: Ex vivo lung perfusion, lung conditioning, lung preservation, lung repair, and lung transplantation.

INTRODUCTION

Background

After death, the lungs can survive maximally for 20 minutes in 37C°. Aiming to prolong this period while transportation and transplantation, the graft used to be kept under cold static preservation to slow or stop breakdown. This not only slows death of the graft but also stops any regenerative process, and keeps the graft under the adverse effects of the cause of the donor's death.The introduction of EVLP allowed to keep the graft viable for 12 hours at 37C°, which allows repetitive assessment and regenerative trials to take place (Richard et al., 2009).

Aim of Work

This paper suggests a modified model of EVLP device, which differs than all available devices with the possibility to include bronchial arteries in the process of perfusion.

The Model

The described model is suggested to fit Shehata EVLP Protocol, which was formerly described. Simply it is composed of a sterile hard shield to enclose the graft and

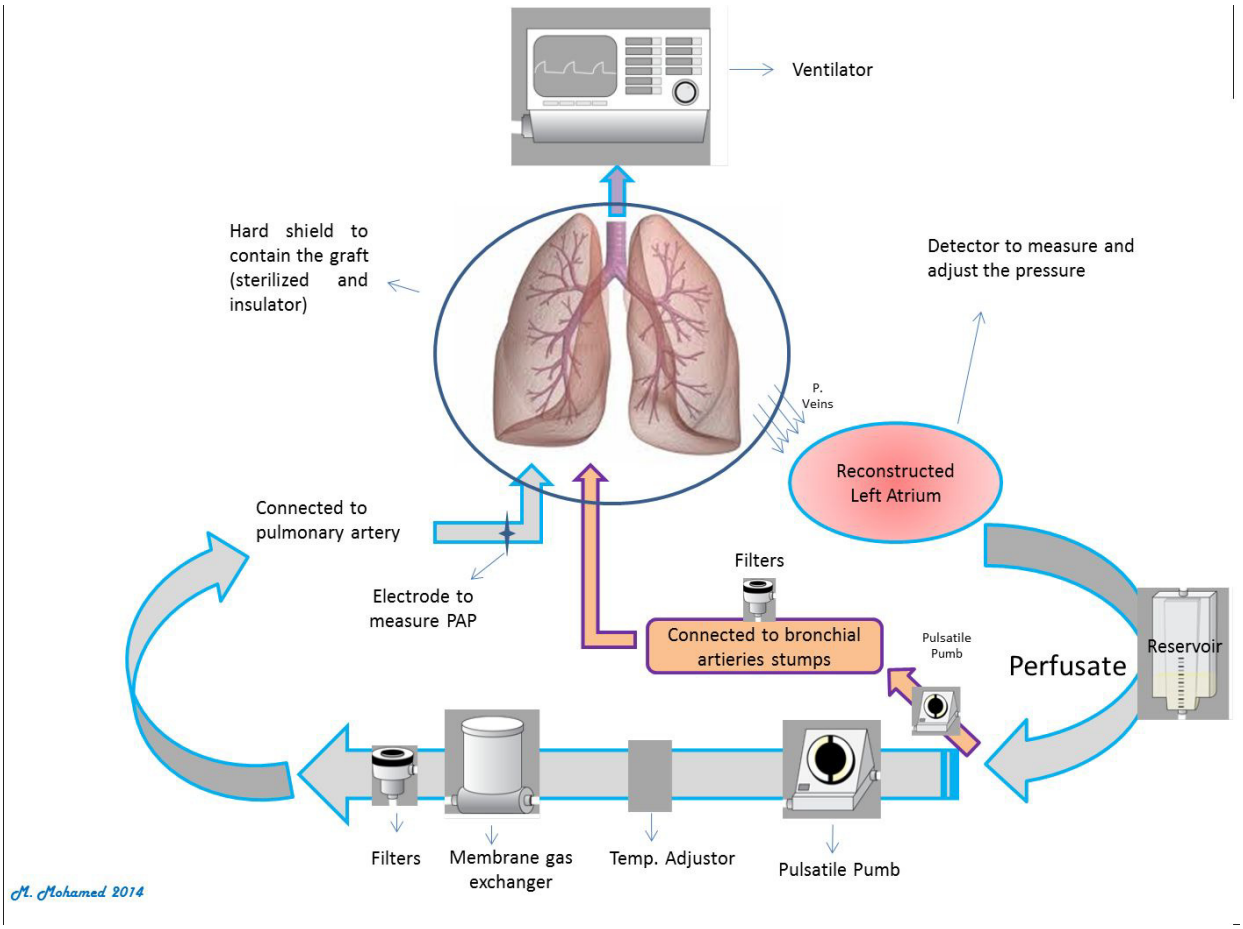

Figure 1.

Tables 1. technical comparison between EVLP devices (7)

	OCS™ Lung	Vivoline LS1	Lung Assist	XPS™
Pump type	Piston	Roller	Centrifugal	Centrifugal
Flow	Pulsatile	Continuous	Continuous	Continuous
Ventilator	+	-	-	+
Monitor	+	+	-	+
Gas cylinder	+	-	+	+
Gas analyzer	+ Portable	-	-	+ In-line
Real time X- ray	-	-	-	+
Portability	+	-	+	-

work as an insulator. The remnant of left atrium removed with the lung graft will be reconstructed and connected to a pressure detector and pressure adjustor, and connected to the circuit. Perfusate will flow through the circuit from the reservoir, and be subjected to the pulsatile pump, temperature adjustor, membrane gas exchanger, and leukocytes and cytokines filters (Figure 1).

The perfusate will then flow to the pulmonary artery, which is connected to the circuit using a special cannula. A pressure measuring electrode will be connected to the lumen of pulmonary artery. In-line gas analyzer and saturation probes will be included, for repetitive assessment of perfusate parameters. In addition, the tracheal stump will be connected to the ventilator using an appropriate tube.

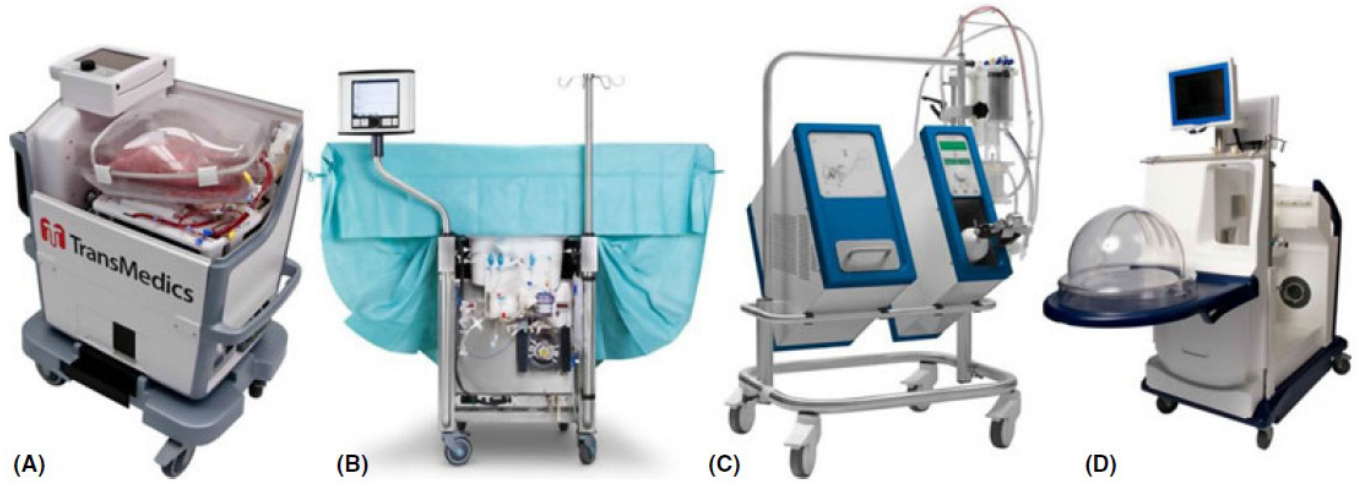

Figure 3 Commercial devices for *ex vivo* lung perfusion. (A) OCS™ Lung (Transmedics); source: www.transmedics.com. (B) Vivoline® LS1 (Vivoline Medical); source: www.vivoline.se. (C) Lung Assist® (Organ Assist); source: www.organ-assist.nl. (D) XPS™ (XVIVO Perfusion AB); source: www.xvivoperfusion.com.

Dirk Van Raemdonck et al. (copied from reference 7)

The unique modification of this model is a collateral circuit, which will be subjected to another pulsatile pump and similar set of filters, and will be connected to the stumps of the bronchial arteries (Figure 1).

DISCUSSION

An increasing number of lung transplantation teams recommend the application of EVLP in the clinical setting (Cypel et al., 2012; Marcelo et al., 2011; Yeung et al., 2012; Yeung et al., 2012; Ian et al., 2014). Many teams use their own homemade devices that were assembled with individual components available in the cardiac surgery department for extracorporeal support. Such as a centrifugal pump, heater/cooler, tubing, hard-shell reservoir, oxygenator, leukocyte filter, in-line gas analyzer, saturation probes, and pressure transducers (Dirk et al.).

In all devices, grafts would be placed in a specially designed plastic chamber for fixation of the lungs during ventilation, and to keep the desired temperature, sterilized and humid environment (Neyrinck et al., 2004).

Some companies have made commercial devices available for clinical EVLP (Figure 2). For example:

- OCS™ Lung (Transmedics, USA)
- Vivoline LS1 (Vivoline Medical, Lund, Sweden)
- Lung Assist (Organ Assist, Groningen, the Netherlands)
- XPS™ (XVIVO Perfusion AB)

The differences between these devices are summarized in Table 1. For example, some are portable, while others are not. Some have a pulsatile pump while others have continuous flow pump… etc (Dirk et al.).

Dirk Van Raemdonck et al. described the difference between these devices as following: ‘’The OCS™ Lung, which is a portable device, has a removable mobile base that allows easy transportation to the donor hospital. It has all equipments on board, including batteries for electrical supply, gas cylinders for preservation, monitoring, and a ventilator for use during transport of organs from donor to recipient hospital. It has a piston pump that creates a pulsatile- type flow that may be beneficial for perfusion and recruitment of the pulmonary vasculature under physiologic conditions. It offers a platform for the normothermic lung preservation, eliminating longer periods of cold ischemia. It offers also a platform for continuous monitoring and assessment of graft function during storage, and for immediate and sustained recruitment and resuscitation. The device is CE marked, and FDA approval is pending. It is currently used as a platform in ongoing international trials.

Other devices were designed for in-hospital EVLP once the donor lung has arrived in the recipient hospital. The Vivoline LS1 device requires the availability of an external ventilator and gas cylinders to commence EVLP. It has an internal roller pump to create a continuous flow. Lung Assist Device™ is a less robust device, with individual components mounted on a frame designed for EVLP and for in situ evaluation of lungs from uncontrolled donors of

circulatory death at the donor site prior to explanting the organs from the body.

Finally, the XPS™ is a fully integrated device that was developed based on the principles of the Toronto technique. It has a continuous flow generated by a centrifugal pump. In addition, it offers X-ray possibilities during EVLP. CE mark approval is pending. Further clinical studies are needed to establish the benefits and risks of these devices to increase the number of transplantable lungs and to compare their added value on the outcome after lung transplantation.'' *(Dirk Van Raemdonck, Arne Neyrinck, Marcelo Cypel and Shaf Keshavje. Transplant International 2014, Early View, Online Version of Record published before inclusion in an issue).*

The suggested new model adds a unique modification that was not described before in any device. This modification is the collateral perfusion circuit intended for the inclusion of bronchial arteries in the EVLP procedure. As previously described, the systemic bronchial arteries receive 3 to 5% of cardiac output, which is low compared with pulmonary artery blood flow. However, this relatively little arterial flow has a significant importance to the vitality of the airways, the fluid balance of pulmonary tissue, and the metabolic functions of the lungs (Kentaro et al.). In addition, bronchial artery re-vascularization was found to protect pulmonary endothelium and type II pneumocytes in the early phase after lung transplantation (Kai et al., 2002). As EVLP aims mainly at reducing graft tissue ischemic reperfusion injury with the accompanying cytokines production, and or metabolic imbalance, which may be the stimulus for graft rejection, the inclusion of bronchial vessels in EVLP would accordingly be of value.

Nevertheless, another pump is included in the collateral circuit to maintain a target flow of 3- 5% of cardiac output in comparison to 40% - 100% target flow in the pulmonary circuit. Although bronchial veins are corresponding to the bronchial arteries, they may not be considered in the connection because they carry only about 13% of the blood flow of the bronchial arteries, while the remaining blood is returned to the heart via the pulmonary veins (Charan et al., 2007).

The suggested EVLP device modification is designed to fit a newly suggested EVLP protocol formerly suggested by the author this year (2014). A set of clinical and molecular studies on animal model (pigs) is designed by the author to test both the new protocol and the new device modification in the clinical settings of lung transplantation, in comparison to other widely applied protocols and devices (mainly those of Toronto team). The results of these studies will ultimately provide the evidence based recommendations for which device and or protocol would be accompanied with better practical outcome. (See Appendix II)

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Appendix II

Studies To Investigate The Newly Suggested EVLP Shehata Protocol

1. Clinical Study

To compare Shehata protocol with Toronto and other EVLP protocols, and standard lung transplantation, using an animal model, in order to provide a clinical evidence which protocol would be associated with better outcome after lung transplantation.

2. Molecular Study

To investigate the levels of inflammasomes, IL1-β, K^+ channels activity, IL-6, IL-8, IL-18, IL-10 and versican, in lung biopsies after transplantation using the standard transplantation protocol, various ex vivo perfusion protocols (principally Toronto protocol), and the newly suggested Shehata protocol.

3. Based on the same principle

Similar molecular studies could be conducted to investigate the same molecular targets (inflammasomes, IL1-β, K^+ channels activity, versican … etc) in the circulating leukocytes as well as graft biopsies after ischemic reperfusion events (transplantation, MI … etc), with and without the application of ischemic conditioning (e.g. ischemic preconditioning, remote ischemic preconditioning … etc)