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A cocktail solution for the *ex vivo* preservation and perfusion of the lung; Shehata solution

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Abstract

The importance of lung transplantation is increasing, being the practical solution for the end stage pulmonary failure. *ex vivo* graft preservation is an essential step in the transplantation surgery that consists of hypothermic preservation and or normothermic perfusion.

There are many preservation solutions that are used for the *ex vivo* lung preservation and are commercially available or institutionally used. Based on the clinical results, the effective preservation determines the clinical outcome of the transplantation surgery.

Despite the great progress in the development of the preservation solutions, there is a continuous interest at further development in order to achieve the perfectionism of the technique. This paper describes an innovative solution to be used for the hypothermic graft preservation and the *ex vivo* lung perfusion, trying to apply the advantages of the other solutions, while avoiding the disadvantages, based on the translational medical knowledge.

Introduction

Lung transplantation is the sole hope for the patients of end-stage pulmonary diseases. As the availabilty of the grafts is not enough to meet the requirements, the *ex vivo* lung perfusion (EVLP) technique was developed to recruit marginal grafts [1].

The practice of lung transplantation involves the surgical retrieval of the donor graft, followed by cold static preservation (till transplantation in the case of standard grafts) and *ex vivo* perfusion (in the case of marginal grafts) [2].

There are many solutions that have been developed and used for each of the two stages. For example, Celsoir and Perfadex solutions that are commonly used for the cold static preservation of the graft, and the Steen and Organ Care System solutions that are commonly used for the normothermic *ex vivo* perfusion. Nevertheless, there are other solutions that were developed for institutional and or commercial utilization [3].

State of the art

There are many preservation solutions that are available either in the market or for the institutional use. EuroCollins (EC) solution was initially the solution of choice until it was replaced in 1988 by the University of Wisconsin (UW) solution [4], whose high viscosity has been involved in organ dysfunction, leading to the development of other solutions including Celsior (CEL) and histidine tryptophan ketoglutarate (HTK) [5].

Due to its unique metabolic requirements and the unique physiology, special solutions, such as Perfadex (PER), are particularly designed for the lung. All solutions consist of several composite elements, which have some advantages and disadvantages (Table 1).

Previously, high K^+ preservation solutions were used that were associated with pulmonary vascular spasms and increased production of reactive oxygen species. Low potassium (dextran) solutions are currently widespread and are associated with better clinical outcomes.

Although 2 studies have confirmed Celsior's ability to provide similar clinical results to those of the Perfadex solution, with additional trends towards better survival and less incidence of chronic lung allograft dysfunction, especially with longer ischemic periods, Perfadex remains the most widely used preservation solution in most lung transplant centers [6,7].

In addition to the hypothermic preservation solutions, there are other solutions that are specifically used for the normothermic *ex vivo* graft perfusion, mostly Organ Care System and Steen solutions. The later is a colloidal solution that resembles the extracellular fluid (low K^+), and contains albumin and dextran 40 to provide colloidal activity and endothelial protection [8].

What is the need for a new preservation solution?

According to the current surgical practice, the reported results, using various preservation solutions are promising, with the ability of EVLP to convert the non-acceptable grafts into acceptable in rates between 87-97%. However, these conversion rates are the results of the careful consideration of the grafts to be subjected to reconditioning, where the more aggressive is the strategy, the lower is the conversion rate [9].

To increase the quality of the *ex vivo* graft preservation, and to

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Table 1. Characteristics of some lung preservation solutions.

Solution	EC	UW	CEL	HTK	PER
Colloid Component	Glucose	LactoB, raffinose, HES	LactoB, mannitol	Mannitol	Dextran
Puffer	Phos, bicarb	Phos	Histidine	Histidine	Phos
Antioxidans		AlloP, GSH	GSH, mannitol	Trp, mannitol	
Osmolarity (mOsm/L)	375	330	320	310	292
Glucose	180				5
Na^+	10	25	100	15	138
K^+	115	120	15	10	6
Ca^{2+}			0.25	0.02	
Mg^{2+}		5	13	4	0.8
Cl^-	15	20		32	142
Other Components				α-KG	SO_4^{2-} 0.8 Dextran 40 g/L

All units are in mmol/L, unless otherwise stated. Abbreviations: EC, Euro Collins; UW, University of Wisconsin; HTK, histidine-tryptophan ketoglutarates; CEL, Celsior; PER, Perfadex; LactoB, lactobionate; HES, hydroxyethyl starch; Phos, phosphates; Bicarb, bicarbonates; GSH, glutathione; Trp, tryptophan; A-KG, ketoglutarates. Source; J Thorac Dis. 2014 Aug; 6 (8): 1143-1149. Doi: 10.3978 / j.issn.2072-1439.2014.05.14

Table 2. Characteristics of Shehata lung preservation solution.

Ingredient	Recommended dose
Sucrose	0.5 M
Sodium	135 – 145 mmol/L
Glucose	100 – 120 mg/dL
Potassium	3.5 to 5.5 mEq/L
Phosphate	1.0 mmol/l
Calcium	2.2 mmol/l
Magnesium	1.7–2.2 mg/dL
Human serum albumin	50 g/L
Carbonate	29 mmol/L
Chloride	100 mEq
Vitamin C	0.5 g/L
Glutathion	1500 mg/L
Insulin	200 pmol/L
Pinacidil	0.25 – 0.3 mg/L
Infliximab	3 - 5 mg/L
Distilled water	Dissolvent
pH	7.4

The solution is to be supplemented with 500 mg methylprednisolone, 500 mg imipenem/cilastatin and 3000 IU heparin, and to be used for both graft perfusion and static preservation.

provide the ability for more aggressive graft recruitment strategy, the following solution is introduced (Table 2).

The innovation in this solution

This solution aims to provide better reconditioning of the lung grafts that have extended criteria, in order to increase the available donor pool. The current available solutions have achieved success with grafts that meet the standard or border-line criteria, however, the grafts with extended criteria require additive care [3,4].

The electrolytes levels of the solution are based to resemble the physiological serum levels. Sucrose is added to provide colloidal force and stablization of the cellular membranes [10]. Human serum albumin is included to provide oncotic pressure that helps the resolution of the pulmonary edema. Glucose adds to the actions of sucrose and albumin, in addition to provide nutrition.

The main injury during graft ischemia - reperfusion is mediated by the increased production of reactive oxygen species (ROS), the inhibition of the ATP-sensitive K^+ channels (both are involved in the activation of the graft inflammasomes, hence, the increased production of interleukins 1ß, 18 & 6), and the increased production of TNFα [11]. Glutathion and vitamin C provide potent antioxidant function, antagonizing ROS [12]. Vitamin C and Pinacidil activate the ATP-sensitive K^+ channels [11,13]. In addition, infliximab antagonizes TNFα [11]. All together have the potential to significantly oppose and attenuate the ischemic reperfusion injury.

The Na^+/K^+ ATPase is inhibited by hypoxia and cold preservation, and the absence of shear stress during ischemia is associated with impaired functions of K^+ channels, cell membrane depolarization, increased activity of nicotinamide-adenine-dinucleotide phosphate oxidase and xanthine oxidase enzymes, and impaired mitochondrial activity, leading to the increased production of ROS that activate protein kinase C-ζ, starting a sequence of phosphorylation-ubiquitination-recognition-endocytosis-degradation of Na^+/K^+ ATPase [14].

Insulin interferes with that sequence of events through the activation and recruitment of Na^+/K^+ ATPase, the induction of Na^+/K^+ ATPase, and the inhibition of K^+ efflux channels. As Na^+/K^+ ATPase is also essential for the syncronized action of Na^+ transport, insulin supplementation during cold static graft preservation, as well as during *ex vivo* perfusion, could be useful for glucose utilization, ATP production, Na^+/K^+ ATPase activation, inhibition of K^+ efflux, and clearance of alveolar edema [14].

Conflicts of interest

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