

# Impact of Lung Preservation Solutions, Euro-Collins vs. Low-potassium Dextran, on Early Graft Function: A Review of Five Clinical Studies

Yoshinori Okada, MD and Takashi Kondo, MD

Currently, intracellular fluid type solutions that are prepared by modification of Euro-Collins solution (EC) have been the most commonly used by clinical lung transplant programs, which have been associated with a high rate of reperfusion injury. On the basis of the wealth of experimental data demonstrating the benefit of extracellular fluid type solutions over EC, one of the extracellular solutions, low-potassium dextran solution (LPD), became commercially available and has recently been applied to clinical settings. To date there have been 5 clinical studies comparing the effect of EC with LPD on early lung graft function. This article reviewed these 5 reports to determine whether the beneficial effects of LPD, as observed in experimental settings, can also be identified in clinical lung preservation. Four studies were retrospective reviews and one was a prospective non-randomized study. Of these 5 studies, 3 studies demonstrated significantly improved recipient oxygenation in the LPD group compared with the EC group in the early post-operative period. In addition, a significantly shorter duration on mechanical ventilation in the LPD group was shown in 2 studies, and improved reperfusion scores or pulmonary compliance was shown in one study each. Four of 5 studies concluded that graft preservation with LPD leads to superior early graft function after lung transplantation. The impact of LPD on prolonged lung preservation and also on long term results of graft function will be a subject of future investigation. (*Ann Thorac Cardiovasc Surg* 2006; 12: 10–4)

**Key words:** lung transplantation, lung preservation, Euro-Collins solution, low-potassium dextran, ischemia-reperfusion injury

## Introduction

Lung transplantation has become an effective therapeutic modality for patients with various types of end-stage lung diseases. However, early graft dysfunction remains a serious problem, occurring in 15-35% of recipients.<sup>1)</sup> This syndrome typically occurs within the first 72 hours after transplantation and is characterized by nonspecific

alveolar damage, lung edema, elevated pulmonary vascular resistance and hypoxemia. The pathogenesis is not completely understood but is generally regarded as the multifactorial lung injury occurring from the time of brain death to the time of reperfusion. For this reason, the term ischemia-reperfusion injury is the most commonly used to describe this syndrome and lung preservation has been considered the critical part in maintaining organ viability and reducing early graft dysfunction.

Because of its simplicity, flush perfusion of donor lungs with cold preservation solutions, preceded by intravenous application of vasodilator drugs and followed by topical cooling, has gained wide acceptance. Currently, solutions that are prepared by modification of Euro-Collins solution (EC) (Table 1) are the most commonly used by clinical lung transplant programs.<sup>2)</sup> How-

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*From Department of Thoracic Surgery, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan*

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Address reprint requests to Yoshinori Okada, MD: Department of Thoracic Surgery, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryomachi, Aoba-ku, Sendai, Miyagi 980-8575, Japan.

**Table 1. Composition of preservation solutions**

	EC	LPD
Na <sup>+</sup> (mmol/L)	10	138
K <sup>+</sup> (mmol/L)	115	6
Cl <sup>-</sup> (mmol/L)	15	142
Mg <sup>2+</sup> (mmol/L)	(-)	0.8
SO <sub>4</sub> <sup>2-</sup> (mmol/L)	(-)	0.8
Dextran (g/L)	(-)	50
HCO <sub>3</sub> <sup>-</sup>	10	(-)
H <sub>2</sub> PO <sub>4</sub> <sup>-</sup>	15	0.8
HPO <sub>4</sub> <sup>2-</sup>	42.5	(-)
Glucose (g/L)	35.7	0.91
Osmolarity (mOsm/L)	375	292

EC, Euro-Collins; LPD, low-potassium dextran solution.

ever, high potassium concentration of EC is believed to cause pulmonary vasoconstriction followed by edema formation and the clinical application of EC has been associated with a high rate of reperfusion injury.<sup>3)</sup>

We have previously reported that better lung preservation can be achieved with extracellular fluid type solutions compared with intracellular fluid types in a canine model of lung transplantation.<sup>4,5)</sup> Following this study, we examined several types of extracellular fluid type solutions and found the solution with high sodium and relatively low potassium with 2% of low molecular weight dextran and 1% of glucose to be the best among them, which was named extracellular phosphate buffered solution type 4 (Ep4) solution.<sup>6)</sup> With this solution, successful lung preservation of up to 96 hours of preservation time was possible in a canine lung transplant model.<sup>6)</sup> One of the modified forms of this solution which was named low-potassium dextran solution (LPD) (Table 1) was introduced to the Toronto Lung Transplant Program,<sup>7)</sup> and subsequent experimental works have suggested the advantage of LPD compared with EC.<sup>8,9)</sup> Eventually, LPD became commercially available (Perfadex) and has cur-

rently been applied to clinical lung transplantation by several lung transplant programs. Ep4 solution was also applied to clinical settings in Japan with preferable results (unpublished data).

To date there have been 5 clinical studies comparing the effect of EC with LPD on early lung graft function.<sup>10-14)</sup> This article will review these 5 reports to determine whether the beneficial effects of LPD, as observed in experimental settings, can also be identified in clinical lung preservation.

## Design of Study, Patient Characteristics and Ischemic Time

By a search on Medline to identify clinical studies which attempted to evaluate the effect of lung preservation solution, EC vs. LPD, on early graft function, we found 5 reports (Table 2). Of these, 4 studies were retrospective reviews and one was a prospective non-randomized study. The number of cases enrolled in each study was shown in Table 2. Three studies<sup>10,12,14)</sup> evaluated the cases undergoing single lung transplantation (SLT) or bilateral lung transplantation (BLT), one study<sup>13)</sup> with SLT, BLT or heart-lung transplantation (HLT), and the remaining<sup>11)</sup> with only BLT or HLT to avoid the potential confounding influence on overall oxygenation of the remaining native lung in patients after SLT. Recipient characteristics in terms of age, gender, disease, type of transplant seemed comparable between the two groups in any of the 5 studies. Ischemic times in the EC and LPD groups (Table 3) were comparable in 3 studies. In the remaining 2 studies, ischemic times in the LPD group were significantly longer compared with those in the EC group. Parameters used in evaluating early graft function included oxygenation in all studies, reperfusion injury score (RIS) originally instituted on the basis of radiological finding etc.,<sup>10)</sup> acute physiology and chronic health evaluation (APACHE)

**Table 2. Summary of clinical studies comparing EC vs. LPD**

Article/Ref. No.	Number of cases		Study design
	EC	LPD	
1. Müller, München, Germany, 1999 <sup>10)</sup>	48	32	Retrospective review
2. Fischer, Toronto, Canada, 2001 <sup>11)</sup>	48	46	Prospective non-randomized study
3. Strüber, Hannover, Germany, 2001 <sup>12)</sup>	55	51	Retrospective review
4. Aziz, Newcastle, UK, 2003 <sup>13)</sup>	37	32	Retrospective review
5. Rabanal, Santander, Spain, 2003 <sup>14)</sup>	25	21	Retrospective review

EC, Euro-Collins solution; LPD, low-potassium dextran solution.

**Table 3. Comparison in ischemic time between EC and LPD group**

Article/Ref. No.		Ischemic time (minutes)	
		EC	LPD
1. <sup>10)</sup>	1st lung:	252±60	306±90*
	2nd lung:	360±96	432±84*
2. <sup>11)</sup>		298±92	348±69*
3. <sup>12)</sup>		280±41	320±54
4. <sup>13)</sup>		293±47	317±36
5. <sup>14)</sup>	1st lung:	288±67	259±88
	2nd lung:	312±22	331±36

EC, Euro-Collins solution; LPD, low-potassium dextran solution.

\*Significantly longer than EC group.

**Table 4. Comparison in recipient oxygenation between EC and LPD group**

Article/Ref. No.	AaDO <sub>2</sub> (Median)		PaO <sub>2</sub> /FiO <sub>2</sub> (Mean±SD)	
	EC	LPD	EC	LPD
1. <sup>10)</sup>	242	159* (day 0 after Tx)		
	94	83 (day 1 after Tx)		
	65	47 (day 3 after Tx)		
2. <sup>11)</sup>			310±134	370±133* (on ICU arrival)
3. <sup>12)</sup>			282±120	303±122 (2 hr after Tx)
4. <sup>13)</sup>			267±78	298±88 (12 hr after Tx)
			244±51	266±59 (24 hr after Tx)
5. <sup>14)</sup>			170±102	310±150* (on ICU arrival)
			236±101	335±130* (12 hr after Tx)
			271±103	321±111* (24 hr after Tx)

EC, Euro-Collins solution; LPD, low-potassium dextran solution; Tx, transplantation.

\*Significantly better than EC group.

score,<sup>11)</sup> pulmonary compliance,<sup>12)</sup> duration of mechanical ventilation,<sup>12-14)</sup> and an originally defined chest roentgenogram score.<sup>13)</sup>

## Oxygenation

Comparison in early post-operative oxygenation of recipients with lung grafts preserved with EC vs. LPD was summarized in Table 4. One study compared AaDO<sub>2</sub> as the parameter of oxygenation and found significantly improved values in the LPD group compared with the EC group at day 0 after transplantation. The other 4 studies employed the PaO<sub>2</sub>/FiO<sub>2</sub> ratio. Among those 4 studies, one study demonstrated a significant improved oxygenation in the LPD group compared with the EC group on ICU arrival and another study showed a better oxygenation in the LPD group on ICU arrival and also 12

hours and 24 hours after transplantation. The remaining 2 studies did not find significantly different PaO<sub>2</sub>/FiO<sub>2</sub> ratios between the 2 groups.

## Other Parameters than Oxygenation

Comparison in other recipient parameters than oxygenation to evaluate the effect of preservation solution on early graft function is summarized in Table 5. Significantly decreased duration of mechanical ventilation in the LPD group compared with the EC group was demonstrated in 2 studies, whereas another study showed a comparable result. One study demonstrated significantly improved incidence and severity of RIS in the LPD group and another study showed a significantly better compliance in the LPD group at 2 hours after transplantation.

**Table 5. Comparison in other recipient parameters than oxygenation between EC and LPD group**

Article/Ref. No.	Parameters	EC	LPD
1. <sup>10)</sup>	Frequency of severe reperfusion injury score	5/48	0/32*
2. <sup>11)</sup>	APACHE* score	24.6±7.8	18.1±5.3
3. <sup>12)</sup>	Compliance at 2 hr after Tx (mL/ mmHg)	30±10	34±11*
	Duration on mechanical ventilation (hours)	321±500	189±365*
4. <sup>13)</sup>	Chest roentgenogram score (immediate after Tx)	1.55±0.63	1.18±0.79
	Chest roentgenogram score (24 hr after Tx)	1.73±0.36	1.50±0.34
	Duration on mechanical ventilation (hours)	71.2±32.2	81.9±43.6
5. <sup>14)</sup>	Duration on Mechanical ventilation (hours)	72±74	92±91*

EC, Euro-Collins solution; LPD, low-potassium dextran solution; APACHE, acute physiology and chronic health evaluation; Tx, transplantation.

\*Significantly better than EC group.

**Table 6. Comparison in recipient 30 days mortality between EC and LPD group**

Article/Ref. No.	EC	LPD
1. <sup>10)</sup>	12 %	6%*
2. <sup>11)</sup>	10.4%	6.5%**
3. <sup>12)</sup>	14.2%	8.0%*
4. <sup>13)</sup>	10.8%	9.3%**
5. <sup>14)</sup>	12%	0%*

EC, Euro-Collins solution; LPD, low-potassium dextran solution.

\*The difference between the two groups was not statistically examined.

\*\*There was no statistically significant differences between the two groups.

### Thirty Days Mortality

All 5 studies demonstrated comparison of 30 days mortality in the patients with lung grafts preserved with EC vs. LPD. In all studies, the mortality appeared improved in the LPD group, however, the difference did not reach a statistical significance in 2 studies and was not statistically analyzed in the remaining 3 studies (Table 6).

### Conclusion

Four of 5 studies concluded that graft preservation with LPD leads to superior early graft function after lung transplantation. In contrast, one study concluded that the effect of the two preservation solutions were comparable on early graft function in clinical lung transplantation (Table 7).

**Table 7. Conclusion of studies comparing EC vs. LPD**

Article/Ref. No.	Conclusion
1. <sup>10)</sup>	LPD better than EC
2. <sup>11)</sup>	LPD better than EC
3. <sup>12)</sup>	LPD better than EC
4. <sup>13)</sup>	Comparable
5. <sup>14)</sup>	LPD better than EC

EC, Euro-Collins solution; LPD, low-potassium dextran solution.

### Comments

Reviewing 5 published clinical studies comparing the effect of lung preservation solutions, EC vs. LPD, on early graft function, we conclude that improved outcome appears to be obtained with LPD compared with EC, which is consistent with evidence provided by experimental studies. A critical limitation of this conclusion is that none of the 5 studies were a randomized study. However, given an amount of experimental data showing the superiority of extracellular fluid type solutions compared with intracellular fluid types,<sup>4,9)</sup> a prospective randomized study may not be ethically justified. In the future, the impact of LPD on prolonged lung preservation and also on long term results of graft function will be a subject of future investigation.

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