ORIGINAL ARTICLE

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Comparison of low potassium Euro-Collins solution and standard Euro-Collins solution in an extracorporeal rat heart-lung model

Received: 9 March 1995 Accepted: 18 July 1995

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Abstract *Objective*. Euro-Collins solution (EC) is routinely used in lung transplantation. The high potassium of EC, however, may damage the vascular endothelium, thereby contributing to postischemic reperfusion injury. To assess the influence of the potassium concentration on lung preservation, we evaluated the effect of a "low potassium Euro-Collins solution" (LPEC), in which the sodium and potassium concentrations were reversed. Methods. In an extracorporeal rat heart-lung model lungs were preserved with EC and LPEC. The heart-lung blocks (HLB) were perfused with Krebs-Henseleit solution containing washed bovine red blood cells and ventilated with room air. The lungs were perfused via the working right ventricle with deoxygenated perfusate. Oxygenation and pulmonary vascular resistance (PVR) were monitored. After baseline measurements, hearts were arrested with St. Thomas' solution and the lungs were perfused with EC or LPEC, or were not perfused (controls). The HLBs were stored for 5 min or 2 h ischemic time at 4 °C. Reperfusion and ventilation was performed for 40 min. At the end of the trial the wet/dry ratio of the lungs was calculated and light microscopic assessment of the degree of edema was performed.

Results. After 5 min of ischemia oxygenation was significantly better in

both preserved groups compared to the controls. Pulmonary vascular resistance was elevated in all three groups after 30 min reperfusion at both ischemic times. After 2 h of ischemia PVR of the group preserved with LPEC was significantly lower than those of the EC and controls (LPEC-5 min: 184 ± 65 dynes * sec $* \text{ cm}^{-5}$, EC-5 min: 275 ± 119 dynes $* \sec * \operatorname{cm} * \operatorname{cm}^{-5}$, LPEC-2 h: 324 ± 47 dynes * sec * m^{-5} , EC-2 h: 507 ± 83 dynes $* \sec * cm^{-5}$). Oxygenation after 2 h of ischemia and 30 min reperfusion was significantly better in the LPEC group compared to EC and controls (LPEC: 70±17 mmHg, EC: 44 ± 3 mmHg). The wet/dry ratio was significantly lower in the two preserved groups compared to controls (LPEC-5 min: 5.7 ± 0.7 , EC-5 min: 5.8 ± 1.2 , controls-5 min: 7.5 ± 1.8 , LPEC-2 h: 6.7 ± 0.4 , EC: 6.9 ± 0.4 , controls-2 h: 7.3 ± 0.4).

Conclusions. We thus conclude that LPEC results in better oxygenation and lower PVR in this lung preservation model. A low potassium concentration in lung preservation solutions may help in reducing the incidence of early graft dysfunction following lung transplantation. [Eur J Cardio-thorac Surg (1996) 10: 621–627]

Key words Lung preservation · Preservation solutions · Low potassium · Lung transplantation · Extracorporeal rat heart-lung model

Introduction

Based on experimental experience with more than 20 years of lung preservation, Euro-Collins solution has been propagated as the most appropriate preservation method in clinical lung transplantation [4, 12]. At present most centers utilize EC solution because of its simple and safe use. However, clinical experience has also shown that postoperative graft dysfunction occurs in a significant proportion of cases, apparently unrelated to the duration of ischemia [5, 8].

Experimental evidence in non-thoracic organ transplantation has pointed to a potentially harmful effect of high potassium in preservation solutions as it contributes to graft dysfunction. Parallel to these findings, investigators have shown that lung preservation can be improved using solutions with low potassium concentrations, i.e. extracellular type of ion distribution rather than the intracellular type, which is represented by Euro-Collins solution [2]. The results obtained with these solutions appeared superior to those achieved with standard EC. In these experiments with alternative preservation solutions, however, not only potassium concentrations, but also the remaining composition was changed [2, 6, 19]. Thus the isolated effect of potassium concentration has not been clarified.

In order to assess the exclusive effect of potassium concentration in the preservation solution, we decided to produce a "reversed Euro-Collins solution". In this solution the ion concentration of sodium and potassium were reversed while all other ions, as well as pH and osmolarity, were kept constant. The effect of this low potassium solution was assessed in an extracorporeal rat model using a working heart-lung block (HLB) preparation [3].

Materials and methods

Male inbred Sprague-Dawley rats (350 g–450 g) were used for the experiments. All animals received humane care in compliance with the "Principals of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH Publication No. 80-23, revised 1985). We used a newly developed extracorporeal working heart-lung model as described recently [3].

Bovine blood was drawn directly from the jugular vein of live cows. The erythrocytes were processed within a day, using standard sterile techniques to remove plasma, white cells and platelets. Centrifugation of the blood at 3500 g for 10 min was performed and the supernatant removed. The cells were diluted with 0.9% saline and again processed in the same way. The twice washed red blood cells were diluted with Krebs-Henseleit buffer solution to a hematocrit of 38–40%. Thereafter, the remaining leukocytes were removed using a leukocyte filter (Leukocyte removal filter, RC100E).¹

The rats were anesthetized with pentobarbital (Nembutal 1 mg/kg BW, intraperitoneally), a laparotomy was performed, and the ani-



Fig. 1 Extracorporeal heart-lung circuit

mals were heparinized (100 U i.v.). The chest was opened bilaterally. Heart and lungs were rapidly excised en bloc. The aorta, right atrium, trachea and left atrium were cannulated while the block was immersed in iced water. Any HLB in which complete preparation could not been performed in less than 6 min was discarded. Prior to the experiment, the main pulmonary artery was cannulated for pressure monitoring.

An extracorporeal circuit (Fig. 1) was used. The circuit consisted of a reservoir, a roller pump (Multiflow-bloodpump)² to raise the perfusate to the reservoir, a 40 µm blood filter,¹ and two membrane oxygenators (Monolyth integrated membrane lung)³. One oxygenator was gassed with 95% oxygen (O_2) and 5% carbon dioxide (CO_2) and the other gassed with 95% nitrogen (N2) and 5% CO2. A perfusion pool was used at 80 cmH₂O and a preload pool at 5 cmH₂O. The HLB was suspended at a 45 ° angle in a humidification chamber. Mechanical ventilation was performed with a small animal respirator (animal respirator 4601)⁴. All vessels were water-jacketed and temperature controlled by a warming pump (water thermostat type VTS 13c)⁵ at 37 °C. The coronary arteries were perfused through the aortic cannula from the perfusion pool with oxygenated blood, until steady beating was re-established. Perfusion of the lung was then started with deoxygenated blood (partial pressure of oxygen (PO2): 15±3 mmHg) via the right atrial cannula from the preload pool using the working right heart to provide pulsatile flow. The opening of the left atrial cannula was positioned above the level of the atrium ensuring a constant positive pressure of 2 cmH₂O. Any HLB that did not achieve a steady level of cardiac function with a cardiac output greater than 10 ml/min was discarded. The lungs were ventilated with room air at a tidal volume of 5 ml and a rate of 40 respiratory cycles per minute. A positive end-expiratory pressure of 3 cmH₂O was maintained. Constant oxygenation and deoxygenation were achieved by regulation of the gas flow. The experiment was discontinued if heart rates fell below 180/min or cardiac output fell below 6 ml/min.

The rats were assigned to six experimental groups. Three groups with short ischemic time (5 min) to assess the immediate effects of the preservation solution (n=7, each group): preservation with Euro-Collins solution, preservation with low potassium Euro-Collins solution and non-perfused controls; three groups with long ischemic time (2 h) to assess the effects of preservation and

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³ Sorin Biomedica Ltd., Saluggia, Italy

⁴ Rhema Labortechnik Ltd., Germany

⁵ Radiometer Ltd., Copenhagen, Denmark

 Table 1
 Composition of preservation solutions

Composition	EC	LPEC
Na ⁺ (mmol/l)	10	115
K ⁺ (mmol/l)	115	10
Cl ⁻ (mmol/l)	15	15
HCO_{3}^{-} (mmol/l)	10	10
Phosphate (mmol/l)	57.5	57.5
Glucose (%)	3.5	3.5
Osmolarity (mOsmol)	355	380
pH	7.48-7.52	7.48-7.52

ischemia (Euro-Collins solution, low potassium Euro-Collins solution and non-perfused controls).

After 5 min baseline, the right atrial cannula and the aortic cannula were disconnected from the preload pool. The HLB was immersed in cold Ringers' solution and perfused with 10 ml St. Thomas' hospital solution at 80 cmH₂O through the aortic cannula to arrest the heart. In the study groups the HLB was perfused with 20 ml preservation solution at $20 \text{ cmH}_2\text{O}$ through the atrial cannula (Table 1). In controls the lungs were not perfused. Thereafter the tracheal cannula was disconnected, the lungs were reinflated with 10 cc room air and immersed in the preseration solution, or Ringers' solution for the controls, at 4 °C and stored for 5 min or 2 h at this temperature. After storage, the HLB was reperfused and reventilated for 40 min. Pulmonary artery pressure was assessed with a transducer and a pressure monitor (Servomed)⁶. Cardiac output was measured by collecting the pulmonary venous flow. Heart rates and peak inspiratory pressure (PIP) were monitored continuously. Pulmonary vascular resistance (PVR) was calculated using the following formula: (mean pulmonary artery pressure – left atrial pressure/cardiac output)×80 (dynes * sec * cm⁻⁵). Blood gases were determined at 10 min intervals. Partial pressure of oxygen measured in the perfusate collected from the left atrium was defined as arterial PO2 (PaO2), and PO2 from the preload pool after deoxygenation as venous PO₂. Peak inspiratory pressure (mmHg) was continuously measured by the respirator and registered every 10 min. After 40 min, at the end of each experiment, the mediastinal lobe was isolated and excised. Wet-to-dry lung weight ratio (W/D ratio) was calculated. The remaining left lung and right lobes were fixed with glutaraldehyde via bronchial instillation (at 20 cmH₂O). The specimens were examined by a pathologist in a blind fashion. Severity of lung edema was graded from 0 to 4 (0 = noedema, 1=mild edema, 2=mild to moderate edema, 3=moderate edema, 4 = severe edema).

The statistical evaluation of parametric data was performed with multiple comparisons of mean values by two-way analysis of variance (ANOVA). Non-parametric data were compared using the Kruskal-Wallis H-test. Significance was assumed if the probability value was less than 0.05. Values are presented as the means±standard deviation (SD).

Results

Flushing time

The flushing time of the organs preserved with Euro-Collins solution was significantly higher than the time measured for complete flushing with low potassium Euro-Collins solution (EC: 84 ± 23 s, LPEC: 55 ± 11 s).



Fig. 2 Oxygenation after 5 min ischemia

Functional and morphologic results after short ischemia (5 min)

Oxygenation (PaO_2)

Following 5 min of ischemia in the preserved groups oxygenation did not decrease during reperfusion compared to baseline levels and remained stable throughout the experiment (30 min; EC: 73 ± 18 mmHg, LPEC: 66 ± 15 mmHg). Between EC and LPEC groups no statistical differences were observed. In contrast, PaO₂ dropped significantly in the non-perfused group after reperfusion compared to EC and LPEC (30 min: controls: 38 ± 12 mmHg) (Fig. 2).

Pulmonary vascular resistance (PVR)

In all study groups PVR increased compared to baseline levels and controls. After 40 min the PVR of LPEC was significantly lower than the PVR of EC and controls (EC: 381 ± 178 dynes * sec * cm⁻⁵, LPEC: 245 ± 104 dynes * sec * cm⁻⁵, controls: 359 ± 238 dynes * sec * cm⁻⁵) (Fig. 3).

Peak inspiratory pressure (PIP)

In all study groups PIP increased during reperfusion. After 40 min, the PIP of EC and LPEC was lower than that of controls while the difference between LPEC and controls was significant. Statistical differences between EC and LPEC were not observed (Table 2).

Wet-to-dry weight ratio (W/D ratio)

Both preserved groups showed significantly lower W/D ratios than controls (EC: 5.8 ± 1.2 , LPEC: 5.7 ± 0.7 , controls:

⁶ Hellige Ltd., Hamburg, Germany



//// n = 7



Fig. 3 Pulmonary vascular resistance after 5 min ischemia Fig. 4 Wet/dry ratio after 5 min ischemia

Table 2 Peak inspiratory pressure (PIP) after 5 min ischemia (ECEuro-Collins solution, LPEC Low potassium Euro-Collins solution)

	EC(n=7)	LPEC $(n=7)$	Controls $(n=7)$
Base 10 min 20 min 30 min 40 min	$21.0 \pm 2.222.9 \pm 3.524.4 \pm 4.725.8 \pm 5.127.4 \pm 4.5$	21.7 ± 1.3 22.1 ± 1.8 23.2 ± 1.8 23.8 ± 1.9 $23.8 \pm 1.8*$	20.8 ± 1.5 20.8 ± 1.7 22.5 ± 2.2 26.6 ± 2.0 30.2 ± 3.1

* P < 0.05 LPEC vs controls

 7.5 ± 1.8). No significant differences were observed between EC and LPEC (Fig. 4).

Histopathology

The control group showed the highest amount of edema as assessed by light microscopic histopathologic score. In contrast, EC as well as LPEC exhibited significantly lower scores at both ischemic times while differences between the two preserved groups were not observed (EC: 1.3 ± 0.9 , LPEC: 1.5 ± 0.6 , controls: 2.5 ± 0.5) (Table 3).

Functional and morphologic results after long ischemia (2 h)

Oxygenation (PaO_2)

Following 2 h of ischemia, the PaO_2 of Euro-Collins perfused organs was significantly higher than that of controls at 10 and 20 min, but decreased to the same level of controls at 30 min. In contrast, throughout the entire reperfusion PaO_2 of the LPEC group was significantly

 Table 3
 Light microscopy (EC Euro-Collins solution, LPEC Low potassium Euro-Collins solution)

Ischemia	EC $(n=7)$	LPEC $(n=7)$	Controls $(n=7)$
5 min	$1.3 \pm 0.9^{*}$	$1.5 \pm 0.6^{*}$	2.5 ± 0.5
2 h	$2.4 \pm 0.5^{*}$	$1.3 \pm 0.4^{**}$	3.3 ± 0.8

* P < 0.05 EC and LPEC vs controls

** P < 0.05 LPEC vs EC

higher than that of controls. At 30 min, the PaO_2 of LPEC was significantly higher than that of EC (EC: $44.4 \pm$ 3 mmHg, LPEC: 70 ± 17 mmHg, controls: 43 ± 1 mmHg) (Fig. 5).

Pulmonary vascular resistance (PVR)

In all groups PVR increased significantly during reperfusion. However, the PVR of EC and LPEC were significantly lower than controls after 20 min, while the PVR of LPEC-perfused organs was significantly lower than those of EC at 10 and 30 min during reperfusion (at 30 min: EC: 507 ± 83 dynes * sec * cm⁻⁵, LPEC: 324 ± 47 dynes * sec * cm⁻⁵) (Fig. 6).

Peak inspiratory pressure (PIP)

Peak inspiratory pressure of both EC and controls increased considerably during reperfusion whereas the PIP of LPEC remained relatively stable throughout the entire trial. At 10 min the PIP of EC was significantly lower than that of controls. At 20 and 30 min the PIP of LPEC was



Fig. 5 Oxygenation after 2 h ischemia



Fig. 6 Pulmonary vascular resistance after 2 h ischemia

significantly lower than that of controls. Statistical differences between EC and LPEC were not observed (Table 4).

Wet-to-dry weight ratio (W/D ratio)

Both EC and LPEC showed a lower W/D ratio than controls. Significant differences between EC and LPEC were not observed (EC: 6.9 ± 0.4 , LPEC: 6.7 ± 0.4 , controls: 7.3 ± 0.4) (Fig. 7).

Histopathology

The control group showed the highest edema score, whereas EC as well as LPEC exhibited significantly lower



Fig. 7 Wet/dry ratio after 2 h ischemia

 Table 4
 Peak inspiratory pressure (PIP) after 2 h ischemia (EC Euro-Collins solution, LPEC Low potassium Euro-Collins solution)

	EC (<i>n</i> =7)	LPEC $(n=7)$	Controls $(n=7)$
Base 10 min 20 min 30 min	$22.4 \pm 1.1 22.1 \pm 1.9 ** 23.4 \pm 1.5 25.6 \pm 1.1$	23.2±0.7 23.6±1.0 24.6±1.5* 24.4±1.3*	$22.8 \pm 0.9 24.7 \pm 1.1 26.3 \pm 1.5 26.1 \pm 1.1$

* P<0.05 LPEC vs controls

** P < 0.05 EC vs controls

scores. In contrast to the findings after short ischemia, LPEC was also significantly lower than EC (EC: 2.4 ± 0.5 , LPEC: 1.3 ± 0.4 , controls: 3.3 ± 0.8) (Table 3).

Discussion

The introduction of Euro-Collins solution with its "high potassium" intracellular electrolyte composition has allowed for clinically accepted pulmonary preservation for up to 7 h ischemic time [4]. The biochemical basis of solutions with an intracellular distribution of the cations potassium and sodium lies in the minimization of the transmembrane ion shift. Potassium ion leakage from the preserved cells will be limited, resulting in a decreased intracellular edema [1]. By contrast, it is well known that a high potassium content in a preservation solution can cause considerable pulmonary vasoconstriction [8] followed by cellular edema [18]. It has therefore been hypothesized that a low potassium medium would improve pulmonary preservation by minimizing vasospasm, consequently leading to a better distribution of the flush solution. This would obviate the need of prostacyclin addition to the flush solution, which is currently applied in an attempt to counteract this vasospasm. Furthermore, potassium-related cell injuries during storage would also be reduced [7].

In 1985, Fujimura et al. reported successful canine pulmonary preservation for 48 h with an extracellular type of flush solution containing dextran [2]. In a consecutive study Keshavjee and co-workers compared a low potassium dextran solution (LPD) with EC solution, and showed significantly better pulmonary function of LPD after ischemia. However, the compositions of LPD and EC solutions differed not only in electrolytes but also in saccharose (dextran 40, glucose), and osmolarity. This and a following study, therefore, could not elucidate clearly whether the differences were due to changes in electrolyte concentrations or other factors [6, 19]; especially since osmolarity, oncotic pressure, buffer capacity, colloids, and saccharides are by themselves keys to successful organ preservation. In a further study, the Toronto Group compared low potassium, low potassium dextran, and high potassium dextran solutions and reported that lung function after LPD flush renders the best results [7]. Since measurements were performed only once immediately after ischemia, time-related changes of lung function could not be presented [7]. Recently, Puskas et al. published good results using LPD in a blood-perfused extracorporeal rat model. They demonstrated satisfactory initial function. The entire reperfusion time, however, was only 20 min [15]. Miyoshi and associates [11] as well as Oka and co-workers [13], compared low potassium University of Wisconsin solution (LPUW) and regular (high potassium) University of Wisconsin solution (HPUW) using an extracorporeal rabbit lung model. They showed the superiority of LPUW regarding PVR as well as PO₂. However, the limitations of this model were the short observation time of only 10 min as well as the non-pulsatile perfusion.

In our study a newly developed extracorporeal rat heartlung model was used. We have shown that this model allows for the assessment of various functional data as well as examination of the pathomorphology [3]. Although the experimental setting is complicated, we believe that the sum of physiological conditions achieved outweighs the laborious set-up. In contrast to other extracorporeal models, which are hydrostatically perfused, the pulsatile flow provided by the working right heart improves reliability of the functional and structural data since the microvascular system of the lung reacts with fast creation of edema when continuously perfused. Furthermore, the use of the native right heart-pulmonary system is superior to mechanical pulsatile devices, retaining the normal relationship between the native right heart and the pulmonary artery [3, 14]. Blood perfusion is an additional key point for a retrieval of valid data, since perfusion of the lungs with a perfusate lacking erythrocyte as the corpuscular oxygen carrier is clearly non-physiologic and is followed by severe edema. Considering that blood of approximately

30 rats (6 ml blood/100 g rat) would be needed for a sufficient priming of an extracorporeal circuit, we decided to use washed bovine erythrocytes in a regular buffer solution as perfusate in order to maintain the cost-effective screening character of our small animal model. Since erythrocytes of mammals are of surprising uniformity [16], the investigator is not restricted to the use of rodent red blood cells [9]. At present, we are able to perform complete experiments in approximately 80% of the HLBs initially retrieved. After harvesting and without an ischemic period (for instance pulmonary and cardiac preservation) the HLB survives for approximately 90 min in the extracorporeal apparatus, while a reliable and complete set of functional data can be obtained for up to 60 min [3].

In order to compare the isolated effect of electrolytes we decided to reverse the sodium and potassium concentrations of the EC solution. Prostacyclin was not used in our experiments, to avoid a possible reduction of the effects related to changes in the PVR. In order to differentiate between effects derived from preservation and effects mediated by ischemia, we performed the experiments with and without a considerable ischemic interval.

As expected, the non-perfused group showed the poorest oxygenation and highest wet/dry ratio of all groups. Histology scores supported these findings, indicating that topical cooling alone does not produce adequate lung preservation. This conclusion is supported by the investigations of Locke et al. in canine transplants [10]. Most recently Steen et al. have shown, in a pig model, that lungs preserved with topical cooling alone can tolerate long ischemic periods without substantial impairment in postischemic function. However, the group did not investigate a control preserved by flush perfusion. This study therefore lacks a direct comparison between preservation by flush perfusion versus topical cooling alone [17]. By contrast, in our, and also Locke's, work the preserved groups exhibited better functional and histopathologic results than the non-perfused groups. After 5 min ischemia, there were no major functional and hemodynamic differences between EC and LPEC preserved animals. After 2 h of ischemia, however, oxygenation of the EC group was significantly inferior and the PVR of this group significantly higher, compared to the LPEC group. Although there was no significant difference in lung water between the two groups, histopathology indicated more severe lung injury in the EC group. The elevated PVR in the EC group indicates that the high potassium concentration has a deleterious effect on the pulmonary vascular bed. The immediate effect of an increase of resistance is also shown by the finding that the flushing time of EC was significantly longer than that of LPEC. Interestingly, the observed differences between high and low potassium EC became functionally and morphologically even more evident after longer ischemic periods, indicating that a potassium-mediated cell damage increases with ischemic time. These findings strongly support the two main pathophysiologic hypotheses for potas-

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sium-mediated endothelial injury: the "initial" increase of vasoconstriction leading to a reduced and perhaps uneven flow of preservation solution through the pulmonary vascular system and the "late" membrane damage taking place during storage [7].

We conclude from this experiment that low potassium Euro-Collins solution is superior to standard Euro-Collins solution regarding the functional and structural integrity of preserved lungs, especially after longer ischemic intervals. Since function and structure were not normal after 2 h of ischemia, further investigations to improve the preservation solution are necessary. The consistent data retrieved after short and long ischemia also indicated that our currently used extracorporeal working heart-lung model is sensitive and valid as a screening model for various lungpreservation solutions.

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