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Pulmonary mechanics after cardio-pulmonary transplantation, an experimental study

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Abstract. An experimental model was developed in pigs (weight: 25 ± 2 kg), to evaluate pulmonary mechanics during the first 2 h of reperfusion following heart-lung transplantation. We studied two groups with three transplantations each: group A (45 min of preservation) and group B (6 h of preservation). After rinsing out the heart-lung mass by the injection of a cold intracellular solution (K^+ = 115 mEq/l) into the aorta and the pulmonary artery, the organs were removed and conserved in a cold environment (0.5 °C). The orthotopic heart-lung transplantation was carried out using extra-corporeal circulation. Pulmonary mechanics were evaluated before and after transplantation by measuring the pulmonary compliance (C), and the aero-dynamic resistance (R) with an interrupted air flow technique.

Cardiorespiratory assistance	Group A	Group B
C: 1 h of reperfusion	− 17.2% ± 7.04	− 20.8% ± 12.4
C: 2 h of reperfusion	− 30.3% ± 4.6	− 32.2% ± 2.6
R: 1 h of reperfusion	+ 130.8% ± 116.9	+ 301.5% ± 60.7
R: 2 h of reperfusion	+ 193.7% ± 80	+ 372.5% ± 190.7

The duration of ischaemia appeared to be a pernicious factor in cardiopulmonary function. In all cases, the protection protocol of the heart-lung block had allowed a cutting-off of the cardiorespiratory assistance. However, there were major pulmonary mechanical perturbations, associated with a reduction in the pulmonary compliance and a very important increase in the aerodynamic resistance.

Key words: Cardiopulmonary transplantation – Pulmonary mechanics

The advances in cardiac transplantation following the introduction of Cyclosporine A, and the encouraging results of cardiopulmonary transplantation in primates resulted in the initiation of the cardiopulmonary transplantation programme in humans at Stanford in 1981 [6]. Despite the evolution of this procedure [1], a number of problems remain; these include patient selection, short conservation period of the heart-lung block, post-operative immunosuppression, and identification and treatment of bouts of rejection and infection. An increase in the conservation period of the heart-lung block by several hours would allow one to use th donors more effectively, to optimize the compatibility of the donor and recipient, to reduce transport costs, and finally, to defuse the sense of urgency characteristic of such operations.

The difficulty with this particular domain of organ preservation is the need for total and immediately functioning transplanted organs. The removal of the heart-lung block and its subsequent preservation cause modifications in pulmonary physiology which are important during the reperfusion phase and possibly account for the success of the surgical procedure [2–4]. The aim of this work was to study the modifications in pulmonary mechanics (compliance and resistance), appearing after the conservation of the heart-lung graft in a cold plegic solution of the intracellular type at a stable low temperature during the initial hours of reperfusion.

Materials and methods

We studied 3-month-old piglets weighing 25 ± 2 kg. Six orthotopic cardio-pulmonary transplants were carried out under extracorporeal circulation (ECC). The animals were divided into two groups (A and B), depending on the pre-implantation conservation period of the heart-lung graft. Group A represented those grafts ($n = 3$) conserved for 45 min, whilst group B consisted of those conserved for over 6 h ($n = 3$).

The donor animal was premedicated with ketamin (Ketalar), 12 mg/kg intramuscularly, 1 h before surgery. General anaesthesia was induced by the intravenous (IV) administration of disodium pentobarbital (Nesdonal), 3 mg/kg, and of alcuronium chloride (Alloferine), 0.5 mg/kg. The animal was then intubated and artificially ventilated (FiO_2 = 75%). After a median sternotomy had been performed, the heart-lung block was dissected and the animal heparinised (3 mg/kg IV). A cannula (Bardik) was introduced into the

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Table 1. Cardiopneumoplegic solution

K^+	115	mEq
Na^+	10	mEq
CA^{++}	0.025	mEq
Cl^-	15	mEq
HCO^{3-}	10	mEq
HPO^{4-}	85	mEq
H^2PO^4	15	mEq
Gluconate	0.025	mEq
Glucose	35	g

pulmonary artery. The cardioplegic cannula was positioned in the aortic root, and blood was drawn and stored for possible use during the reperfusion phase. Following aortic clamping, simultaneous cardioplegia and pneumoplegia was achieved. The right and left auricles were opened to allow the evacuation of the plegic solutions and to bring about a dilation of the cardiac cavities. Gentle manual ventilation was maintained to ensure a proper distribution of the pneumoplegia. The pneumoplegia was halted when the lungs became discoloured. The cardioplegia and pneumoplegia were performed with an intracellular type, cold crystalloid solution (at 2°C) (Table 1). After sectioning the trachea beneath the tracheal plane and the aorta above the aortic plane, the heart-lung block was removed from the thorax and placed in a sterile hermetic bag, and immersed in a saline solution at 0.5°C for conservation.

Cardio-pulmonary transplantation

The recipient animal was anaesthetised and ventilated in a similar fashion to the donor. Following a median sternotomy and dissection of the vessels at the base of the heart, systemic heparin was administered at a dose of 3 mg/kg IV and an ECC was installed between the ascending thoracic aorta and the vena cava. The extracorporal circulation circuit, which consisted of a bubble oxygenator (shiley 100 A) was primed with a solution containing crystalloid (Ringer) and macromolecular (Plasmion) solutes and sodium bicarbonate (14 part per thousand).

The heart and lungs of the recipient piglet were excised and the heart-lung block of the donor was implanted into the thorax of the recipient, according to the technique of Reitz et al. The aorta was unclamped and the aorta, cardiac cavities and the pulmonary artery were purged of air. The heart was defibrillated and manual ventilation with the aid of a souple balloon was effected for a few minutes. Artificial ventilation with a positive end-expiratory pressure of 4 cmH_2O was then established. A perfusion of isoprenatine (Isuprel) was started; its flow rate being a function of the cardiac frequency.

Monitoring

During the experiment, the ECG was monitored and the arotic pressure was measured with a catheter placed in the aorta, via the right carotid artery. The pulmonary artery pressure was measured with a catheter placed in the trunk of the pulmonary artery and the left auricular pressure was measured by a catheter placed in the left auricle (pressure gauge: physiological transducer AE840). These parameters were measured in the anaesthetised donor animal and in the recipient animal after 1, 2 and 3 h of reperfusion. The coagulation times (Hemochron 400 R) were recorded while the ECC functioned.

Blood gases were measured (Radiometer ABL 4) from samples drawn from a catheter in the left carotid artery and electrolyte (Na^+, K^+, Cl^-) and plasma protein levels were measured by standard techniques (Prisma). These parameters were measured in the donor animals before excision and in the recipient animals during the first 3 h of reperfusion. The blood gases and biochemical analyses (Na^+, K^+, Cl^-, plasma proteins) were presented for experiments 3, 4, 5 and 6 only). For technical reasons, these measurements could not be performed under the conditions described above for experiments 1 and 2.

Evaluation of pulmonary mechanics

Pulmonary compliance and resistance were measured in the donor animal before excision of the graft and in the recipient animal after transplantation with the thorax and pleura open, and under the ventilation conditions described previously. Before each measurement, a bronchial aspiration was performed.

Technical details (Fig. 1). The transpulmonary pressure was measured with a differential manometer [Statham PM5 (± 70 cmH_2O)] connected to the intratracheal tube and to atmospheric pressure, as the thorax and pleura were open. A pneumotachogram was added to obtain the spirogram. All the data were recorded on a chart recorder. The calibration of the pressure line was achieved with the aid of an inclined-water manometer. The calibration of the flow rate line was achieved with a calibrated syringe (3 l) and by an integration method [15].

Calculation of compliance and resistance. The compliance and resistance were calculated from a respiratory cycle containing two zero-flow points (A and B). The first zero-flow point (A) was that at the end of expiration. The second zero-flow point (B) was obtained by suddenly clamping the intratracheal tube at the end of inspiration. Compliance (C) was calculated as the ratio of pulmonary volume

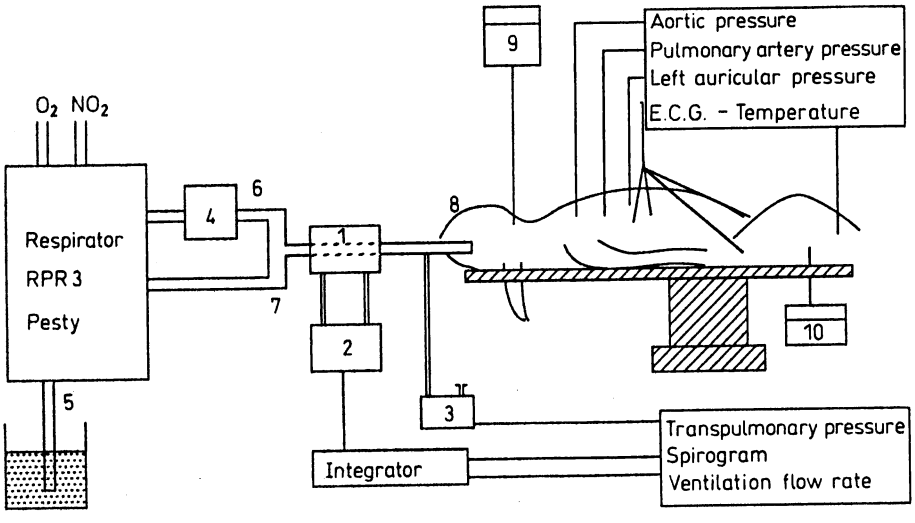

Fig. 1. Measurement techniques for compliance and resistance. *1* Pneumotachograph FLEISCH n° *1, 2* differential manometer STAHAM PM283, *3* differential manometer STATHAM PM5, *4* humidifier-heater, *5* expiratory circuit outlet, *6* inspiratory circuit, *7* expiratury circuit, *8* intratracheal tube, *9* perfusion, *10* urine probe

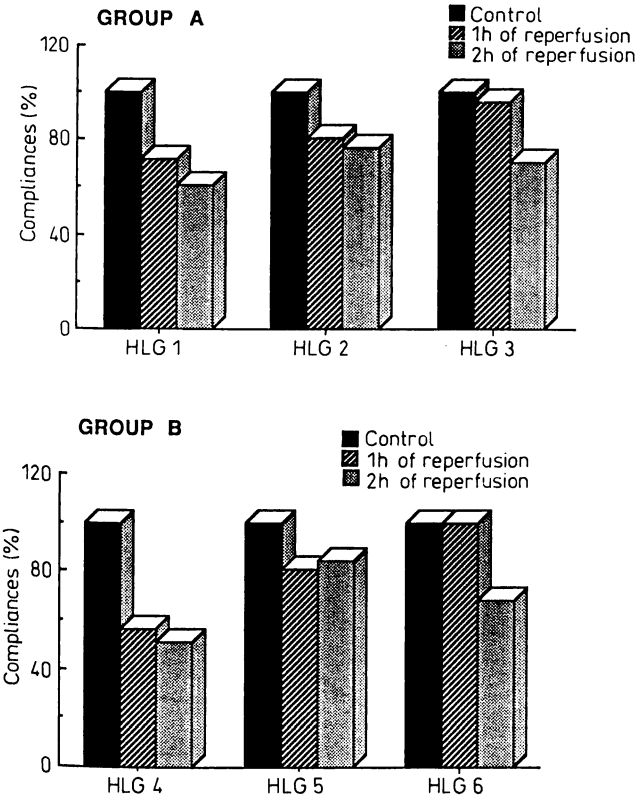

Fig. 2. Evolution of pulmonary compliance, after 1 and 2 hours of reperfusion for each of the heart-lung grafts (HLG) in group 1 (GA: 45 min of conservation) and in group B (GB: 6 hours of conservation)

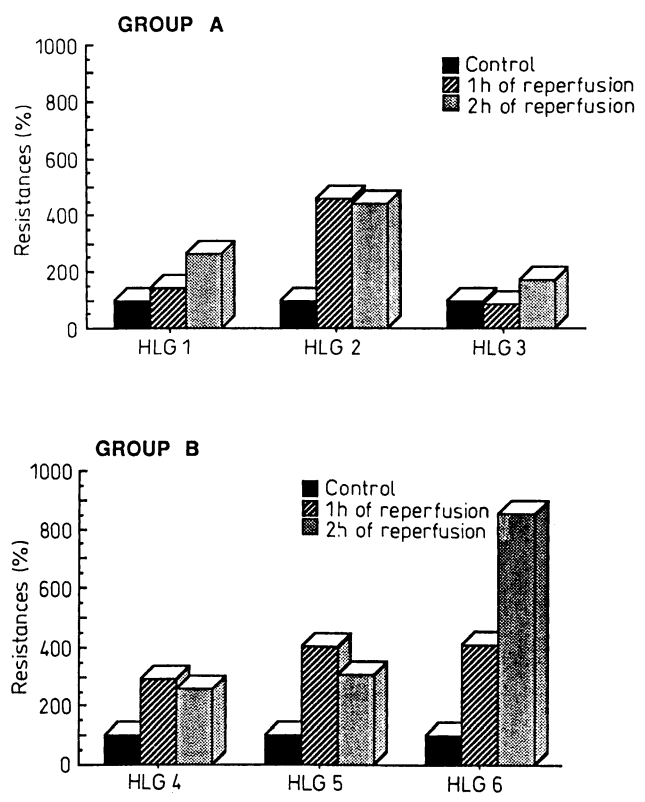

Fig. 3. Evolution of pulmonary resistance after 1 and 2 hours of reperfusion for each of the heart-lung grafts (HLG) in group A (GA: 45 min of conservation) and in group B (GB: 6 hours of conservation)

variation (Δ V), (read from the spirogram) and the difference in transpulmonary pressures (of elastic origin) between points (A) and (B). ($C = \Delta V/\Delta P1$).

Resistance (R) was calculated as the ratio of (1) the difference in transpulmonary pressure (of dynamic origin) (Δ P2) between the transpulmonary pressure measured at (B) and the transpulmonary pressure measured at the moment of clamping the intratracheal tube, and (2) the inspiratory flow rate (Δ di) observed immediately after clamping the intratracheal tube. The result was corrected for the resistance of the intratracheal tube (Rp) [($R = (\Delta P2/\Delta Di) - Rp$)].

Pulmonary compliance and resistance were calculated for the donor animal before excision and for the recipient animal after 1 and 2 h of reperfusion. The results of the pulmonary mechanics were calculated as the mean of the measurements carried out over two respiratory cycles.

Presentation of results

Results are presented as a percentage of control values and expressed as mean ± standard error of mean (SEM).

Results

The conservation time of the heart-lung grafts for the animals in group B was 351.6 ± 18.9 min and 46 ± 5.1 min for the animals in group A. The conservation temperature varied betwen 0.5 and 2 °C. The cardio-pulmonary assistance period for the animals in group A was 56.6 ± 2 min, whereas that for group B animals was 88.3 ± 35.4 min.

Pulmonary mechanics results (Figs. 2 and 3). In group A, compliance decreased by 17.2 ± 7.4 % after the 1st h of reperfusion and by 30.3 ± 4.6 % after 2 h of reperfusion. In a similar manner, compliance in group B decreased by 20.8 ± 12.4 % and 32.2 ± 2.6 % after 1 and 2 h of reperfusion, respectively. In group A, the resistances increased by 130.8 ± 116.9 % after the 1st h of reperfusion and by 193.7 ± 80 % after the 2nd h. In group B, the resistances increased by 301.5 ± 60 % and 372.5 ± 190.7 % in the same time scale.

Our study population was too small to allow confidence in statistical results. However, the results were sufficiently homogeneous to allow us to make several comments. In all experiments, pulmonary compliance decreased, although the period of conservation did not appear to influence the extent of the decrease. Similarly, in all experiments, pulmonary resistance was seen to increase during reperfusion. This increase was greater in group B (6 h of conservation).

Haemodynamic results (Fig. 4). The haemodynamic behaviour of groups A and B appeared to be identical during reperfusion. However, in the two groups, there were differences between the per-perfusion measurements and those of the control animals. There was an increase in the cardiac frequency, in the left auricular pressure and in the mean pulmonary arterial pressure. The mean aortic pressure diminished during reperfusion, whilst the systolic

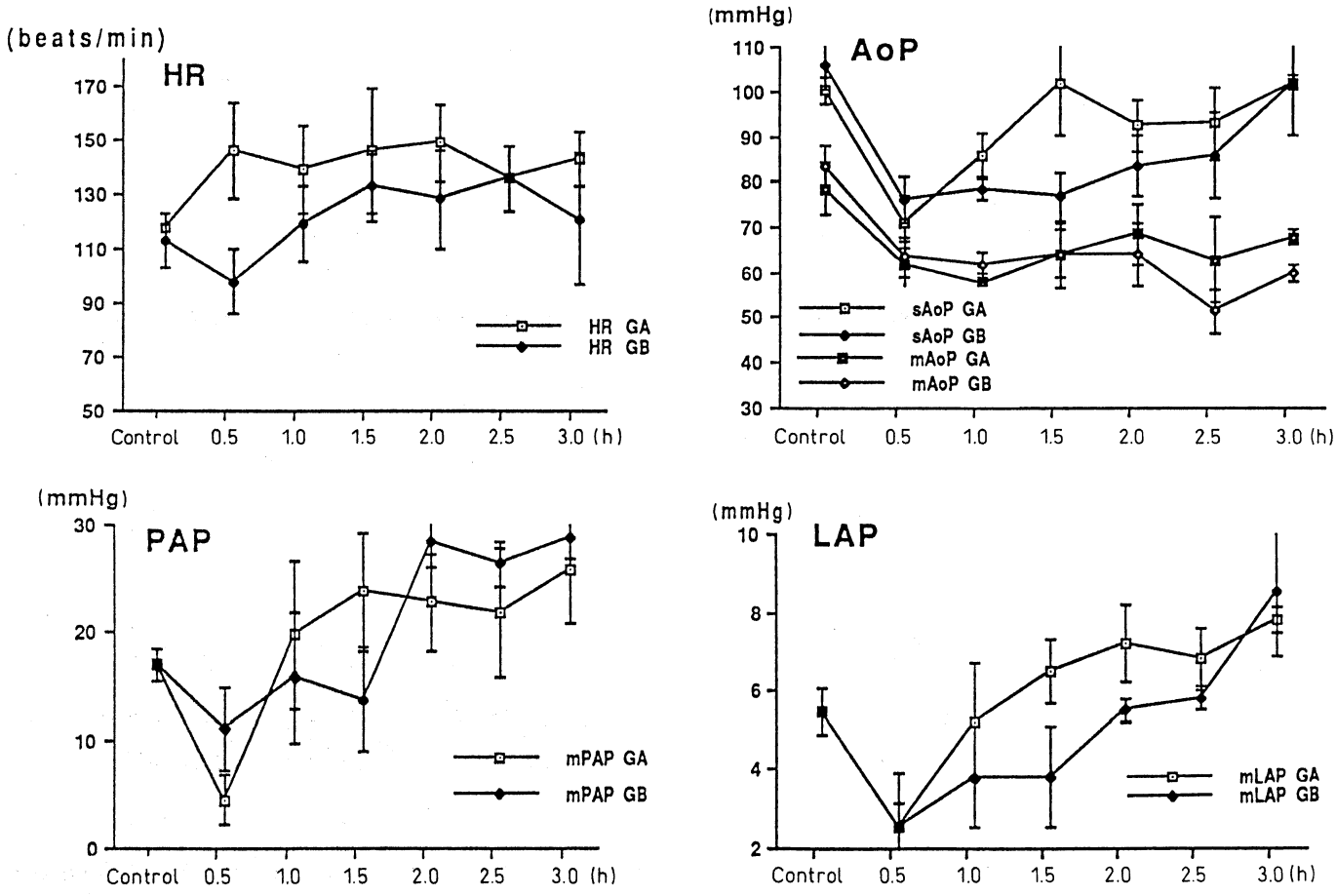

Fig. 4. Average heart rate (HR), aortic pressure (AOP), pulmonary artery pressure (PAP) and left atrial pressure (LAP) for the two groups during control conditions, and 1, 2, and 3 hours of reperfusion. Mean, m; Systolic, s. Group A (GA): 45 min of conservation; Group B (GB): 6 h of conservation

aortic pressure exhibited a value close to that of the control animals.

Arterial blood gas results (Fig. 5). The PaO_2 remained greater than 200 mm Hg during the experiment. The $PaCO_2$ was maintained at approximately 40 mm Hg. A metabolic acidosis set in progressively at the end of reperfusion.

Biochemical results. Figure 6 illustrates the average evolution of the electrolytes and plasma proteins during the experiments. The plasma proteins decreased once the extracorporeal circulation was established, probably due to haemodilution. During the reperfusion phase, the protein concentration remained constant.

Discussion

We retained the use of a single plegic solution, rich in potassium, because of its capacity to assure pulmonary protection [6, 13]. Moreover, experimental studies have shown that this solution also ensures long-term cardiac protection [17, 22]. The logic for using such a solution is that active ionic transfers at low temperature are interrupted, and hence, ionic concentration gradients on either side of the cellular membrane are avoided [12]. In addition, the hyperosmolarity of the solution allows for stabilisation of the membrane and thus, a decreased ionic exchange [19]. Our haemodynamic results confirmed the capacity of such a solution to preserve the myocardial function over a 6 h period. The pulmonary mechanical perturbations (increased resistances, reduced compliances as well as an increased pulmonary artery pressure) reflected the degree of pulmonary insult sustained. Experimental studies on dogs have shown similar results [2, 3].

The drop in pulmonary compliance may be interpreted in several ways. All the pulmonary tissue constituents contribute to the elastic properties of the lung. The most important of these are the connective tissues (elastine, reticuline, collagen) as well as the pleura, the arteries and pulmonary veins. Previous studies have shown that the plasto-elastic properties of the tissue deformations are only moderately disturbed after the excision and cooling of the lungs [3]. Moreover, the state of vascular congestion only affects slightly the pressure-volume relationship of lungs excised from cats [5]. However, interstitial or intra-alveolar pulmonary oedema, through the perturbations developed along the dimensions of the elastic elements and through the perturbations developed along the dimension of the elastic elements and through the geome-

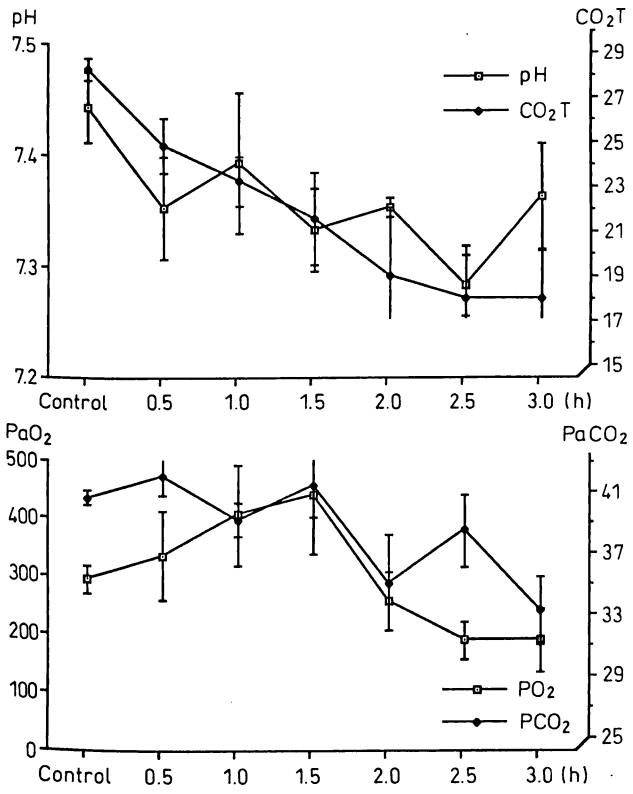

Fig. 5. Arterial blood gas, results. Average pH, CO2T, PaO2, PaCO2 during control conditions and reperfusion. (Experiment 3, 4, 5, and 6)

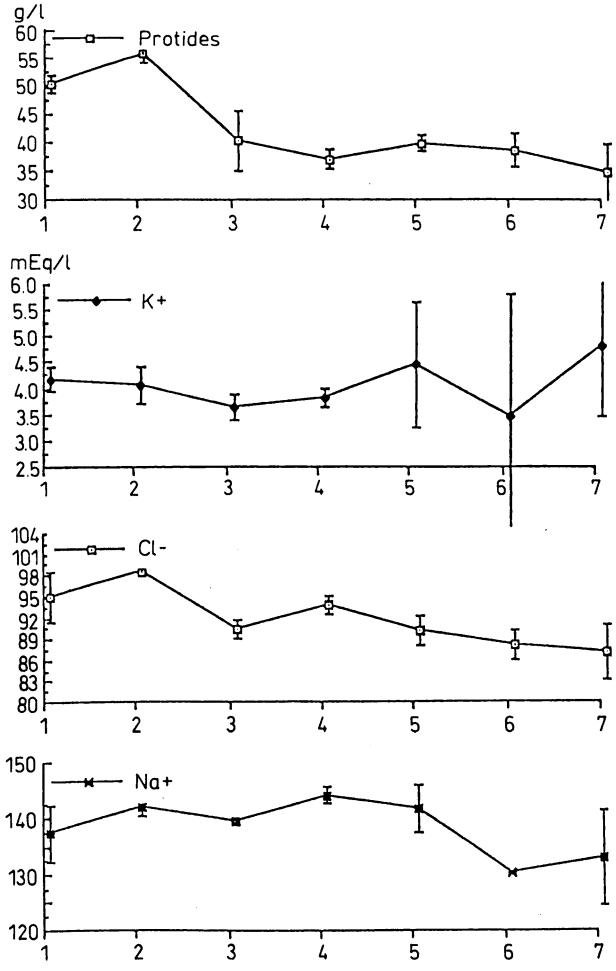

Fig. 6. Protides, K^+, Cl^-, Na^+ plasmatic concentrations. *1,* Donor anesthesia; *2,* Receiver anesthesia; *3,* Beginning of ECC; *4,* Beginning of the reperfusion; *5,* 1 h of reperfusion; *6,* 2 h of reperfusion; *7,* 3 h of reperfusion

trical disposition of the surfaces separating the air from the liquid, bring about important modifications of the pulmonary mechanical properties in the form of reduced distensibility [10].

Pulmonary resistance increased in a regular manner during reperfusion. The period of ischaemia evidently had a deleterious effect on pulmonary resistance. Pulmonary resistance results from two forces: tissue friction and the resistance developed as air flows done the airways. As with compliance, the tissue component may be disturbed by the alteration of the interstitial geometry related to the oedema. The loss of bronchial vascularisation [2] and above all, the presence of interstitial oedema, predispose to increased airway resistance; in fact, the dynamic resistances of the respiratory pathways depend upon the calibre of these serial pathways. The calibre expresses not only the resting diameter of the structures concerned, their rigidity and their muscular tension, but also the transmural pressure which manifests itself on the wall lining [11].

Improvements in pulmonary characteristics following cardio-pulmonary transplantation appear after 10 h of reperfusion. This phenomenon is, therefore, most likely to be related to the reabsorption of the reperfusion oedema. The measurement of these constants in man, 7 weeks after cardio-pulmonary transplantation, shows a return to normal levels [14].

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References

1. Coperland JG (1987) Heart Lung Transplantation: Current status. Ann Thorac Surg 43:2–3
2. Dawkins KD, Jamieson SW (1986) Pulmonary function of the transplanted human lung. Ann Rev Med 37:263–269
3. Edward P, Radford JR (1964) Static mechanical properties of mammalian lungs. Handbook of Physiology. American Physiological Society, Washington, D. C.
4. Feeley TW, Mihm FG, Dowing TP, Sadeghi AM, Baumgartner WA, Reitz BA, Shumway NE (1986) Hypothermic preservation of the heart and lungs with Collins solution: effect on respiratory function following heart-lung allotransplantation in dogs. Ann Thorac Surg 41:301–306
5. Frank NR, Radford EP, Wittenberger JL (1959) Static volume pressure interrelations of the lung and pulmonary blood vessels in excised cat's lung. J Appl Physiol 14:167–173
6. Jameison SW, Reitz BA, Oyer PE, Billingham E, Modry D, Baldwin JC, Stinsor EB, Hunt S, Theodore J, Bieber CP, Shumway NE (1983) Combined heart and lung transplantation. Lancet I:1130–1132
7. Konertz W, Saka B, Bernard A Orthotopic heart transplantation in pig after 24 hours hypothermic storage in eurocollins-solution. Dept Cardiovascular surgery university Kiel, West Germany. Tirés à part

8. Lazar HL, Painvin GA, Robert AJ (1986) Myocardial preservation. Surg Clin North Am 66:467–475
9. Morishita Y, Saigenji H, Higashi T, Umebayashi Y, Taira A, Goto M (1985) Function of the transplanted canine heart after prolonged preservation by simple immersion. Heart Vessels 1: 220–224
10. Petit JM Applications de la mécanique pulmonaire à l'exploration fonctionelle. L'exploration fonctionelle pulmonaire: technique d'étude et application clinique. Editions Médicales, Flamarion
11. Petit JM Aspects physiologiques de la mécanique thoracopulmonaire. L'exploration fonctionnelle pulmonaire: technique d'étude et application clinique. Editions Médiales, Flamarion
12. Reitz BA, Brody WR, Hickey PR, Michaleis LL Protection of the heart for 24 hours with intracellular (High K^+) solution and hypothermia. Surg Forum 149–51
13. Sharp JT, Griffith GT, Bunnel IL, Greene DG (1958) Ventilatory mechanics in pulmonary oedemas in man. J Chir Invest 37:111
14. Theodore J, Jamieson SW, Burke CM, Reitz BA, Stinson EB, Kessel A van, Dawkins KD, Herran JH, Oyer PE, Hunt SA, Shumway NE, Robin ED (1984) Physiologic aspects of human heart-lung transplantation. Pulmonary function status of the post-transplanted lung. Chest 86:349–357
15. Varene P, Vieilleford H, Saumon G, Lafosse JE (1974) Etalonnage de pneumotachographe par méthode intégrale. Bull Physiopathol Respir 10:349–360