Lung perfusion during cardiac surgery with cardiopulmonary bypass: is it necessary?*

Edmo Atique Gabriel, Rafael Fagionato Locali, Priscila Katsumi Matsuoka, Ludmila Santiago Almeida, Ismael Guerreiro Silva, Vera Lúcia Capelozzi, Tomas Antonio Salerno, Enio Buffolo

Division of Cardiovascular Surgery, Department of Surgery, Federal University of Sao Paulo, Rua Napoleao de Barros, 715, 3o andar, Vila Clementino 04023900, Sao Paulo, Brazil
Division of Gynecology and Molecular Biology, Federal University of Sao Paulo, Brazil
Division of Pathology, University of Sao Paulo, Brazil
Division of Cardiothoracic Surgery, Miller School of Medicine, Jackson Memorial Hospital, University of Miami, USA

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Abstract

Thirty-two pigs were randomized into group I (aortic cross clamping, antegrade cardioplegia, moderate hypothermia) and group II (normothermia, beating empty heart). Groups were subdivided into subgroups A, B and C, receiving no lung perfusion, perfusion with arterial blood and perfusion with venous blood. Swan-Ganz catheter was used to take mean pulmonary artery pressure which would be used as lung perfusion pressure. Cardiopulmonary bypass (CPB) was established through cannulating aorta and double venae cavae, mechanical ventilation was interrupted and lung perfusion was carried out for 30 min. Blood samples and pulmonary specimens were withdrawn pre- and postoperatively for gasometrical, histological and genic analyses. Postoperative comparison revealed that pulmonary vascular resistance was lower in IC than IA (P<0.01) and it was lower in IIC than IIA (P=0.005). Subgroup IIB had increasing venous oxygen tension (P=0.01) as well as arterial and venous oxygen saturation (P=0.01) compared to IIA. Arterial oxygen saturation was decreased in IIC vs. IIA (P=0.006). Histological differences were observed between subgroups A and B as well as A and C (P=0.003). Lung perfusion during CPB may improve pulmonary hemodynamic performance, optimize gas exchange and maintain cellular integrity.

Keywords: Lung; Perfusion; Cardiopulmonary bypass

1. Introduction

Pulmonary artery perfusion during cardiac surgery with CPB is not routine because it has not been fully demonstrated to provide significant clinical benefit [1–3]. The purpose of this investigation is to assess the effects of lung perfusion in heart surgery with CPB.

2. Material and methods

2.1. Study design

After approval from the Ethics Committee, 32 pigs were randomly assigned into groups and subgroups as shown in Table 1. All of them received humane care in compliance with the European Convention on Animal Care.

2.2. Extracorporeal system

Extracorporeal system, including Unique cardioplegia system and Thymus pediatric oxygenator, manufactured by Nipro Brazil, was used in all procedures. Some adaptations were done to perfuse pulmonary trunk with arterial and venous blood as shown in Fig. 1.

2.3. Operative protocol

All the animals underwent general anesthesia with sodium pentobarbital (12.5 mg/kg), fentanyl (0.01 mg/kg) and thiopental (1 g). They were mechanically ventilated through a pressure-cycled ventilator, with about 14 cycles/min, 100% fraction of inspired oxygen and 10 ml/kg tidal volume. An 8 French was inserted into the right internal carotid artery to take mean artery pressure and an 8 French catheter was inserted into the left external jugular vein to infuse medications. A 7 French Swan-Ganz catheter was inserted into the right external jugular vein and it was connected to a pressure transducer and Viridia 24C poligraph for determining preoperative hemodynamic parameters such as mean pulmonary artery pressure. Cardiac
Table 1
Experimental groups and subgroups

<table>
<thead>
<tr>
<th>Group I (n = 16)</th>
<th>Group II (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioplegia</td>
<td>Beating empty heart</td>
</tr>
<tr>
<td>Subgroup IA (n = 4)</td>
<td>Control*</td>
</tr>
<tr>
<td>Subgroup IB (n = 6)</td>
<td>Lung perfusion with arterial blood</td>
</tr>
<tr>
<td>Subgroup IC (n = 6)</td>
<td>Lung perfusion with venous blood</td>
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*Without controlled lung perfusion through inflow cannula.

![Diagram of lung perfusion](image)

Fig. 1. Scheme of lung perfusion. 1. Vena cava line; 2. Arterial roller pump line; 3. Aorta line; 4. Recirculation line; 5. Gas supply line; 6. Water supply line; 7. Aspirator line; 8. Cardioplegia line; 9A. Pulmonary trunk perfusion line with arterial blood (red line); 9B. Pulmonary trunk perfusion line with venous blood (blue line); 10. Pulmonary trunk perfusion pressure (digital manometer); 11. Gas blender. SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; RV, right ventricle; AO, aorta; PT, pulmonary trunk.

output was taken through thermodilution method considering the mean value of three sequential measurements.

The protocol for group I included insertion of 12 French cannula through the root of the ascending aorta, 16 French cannulas through both venae cavae, aortic cross clamping, cardioplegic arrest and moderate hypothermia. Following clamping the aorta and the first shot of cardioplegia, lung perfusion was carried out through a 12 French cannula into the pulmonary trunk lasting 30 min. Left atrium was vented during lung perfusion.

The cannulation strategy was similar in group II, but their hearts were allowed to beat at normothermia, while the lungs were perfused for 30 min. During lung perfusion, the right atrium was vented and both venae cavae were kept snared [4, 5].

In groups I and II, mechanical ventilation was arrested once CPB was established.

Perfusion pressure was controlled by a digital manometer connected to the lung perfusion line having as baseline the parameters taken through the Swan-Ganz catheter before midline sternotomy. During the procedure, mean lung perfusion pressure and mean lung perfusion flow were equivalent to 24.6 mmHg and 200 ml/min, respectively. There were no differences on lung perfusion pressure using arterial as well as venous blood. Pump flows ranged from 1.2 to 1.4 l/min/m². The average time of CPB ranged from 35 to 40 min. Postoperative hemodynamic measurements were made soon after weaning from CPB and the animals were then euthanized with an injection of potassium intravenously.

2.4. Tissue and blood samplings

Preoperative blood samples were collected from the right pulmonary veins and right internal carotid artery after pericardiectomy. Postoperative blood samples were collected from the same sites but as mechanical ventilation might be influencing on gasometrical parameters, those ones were taken on weaning from CPB immediately before restarting mechanical ventilation.

Preoperative and postoperative pulmonary biopsies were withdrawn from the right inferior lobe after midline sternotomy and when lungs restarted ventilating, respectively. Pulmonary specimens were stored at −80 °C.

2.5. Hemodynamic and gasometrical variables

Hemodynamic monitoring through a Swan-Ganz catheter included the following variables: mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), pulmonary capillary pressure (PCP), pulmonary vascular resistance (PVR) and cardiac output (CO). To calculate PVR the following formula was used: 

\[ PVR = \frac{MPAP - PCP}{80/CO} \]

Blood samples collected from right pulmonary veins disclosed pulmonary venous oxygen pressure (PVO₂) and pulmonary venous oxygen saturation (SvO₂). Blood samples withdrawn from the right internal carotid artery disclosed arterial oxygen pressure (PaO₂), arterial oxygen saturation (SaO₂) and oxygen index (OI). To calculate OI the following formula was used: 

\[ OI = \frac{PaO₂/FiO₂}{1} \]

where FiO₂ is the fraction of inspired oxygen.

Optimal ventilation parameters would be those that were continuously held as high as possible during CPB. In control subgroups, lung perfusion just through bronchial arterial flow may be providing reasonable ventilation parameters but with no steady constancy as that flow usually is low and quite varying throughout CPB. On the other hand, a strictly controlled lung perfusion through inflow cannula is thought to be useful to optimize ventilation parameters keeping them continuously at high levels during CPB.

2.6. Microscopic analyses

Two techniques were used to analyze pulmonary specimens: hematoxylin/eosin (HE) and immunohistochemistry (heat shock protein 27 – Hsp27 expression). Histopathological assessment consisted of assigning a semiquantitative score for degrees of leukostasis, congested capillaries, alveolar hemorrhage, inflammatory infiltrate within alveoli and alveolar edema for sequential microscopic fields selected by two blinded pathologists. The severity of lesions in each successive field was graded as 0 for normal tissue, 1 for mild, 2 for moderate and 3 for severe. The extent of lesions was graded as 0 (absent), 1 (1–25% of the slide), 2 (26–50%) and 3 (<50% of tissue affected). The mean score...
for successive fields represented the score for each individual specimen.

Hsp27 was selected because its expression was consistently detected within several kinds of pulmonary cells and its immunoreactivity appeared to be more widespread in relation to another heat shock protein also tested. In each field, intensity of Hsp27 expression was graded separately for intra-acinar arteriole endothelium, alveolar epithelium and bronchiolar epithelium cells as follows: 0 for absent, 1 for 1–25% cells stained, 2 for 26–50% and 3 for >50% tissue stained. A mean score for each tissue was obtained per individual specimen.

2.7. Genic analyses

Three markers were selected in compliance with their inflammatory role as follows: tumor necrosis factor (TNF-α) – pro-inflammatory cytokine, interleukin-4 (IL-4) – anti-inflammatory cytokine and cellular adhesion molecule (ICAM-1) – linked to neutrophilic activity. Pulmonary specimens and primers were used by a blinded expert to determine genic expression of those markers through real-time polymerase chain reaction method. More reliable overall outcome in terms of genic expression was obtained by means of ‘pool’ approach in which pulmonary specimens of each subgroup individually were primarily assembled with each other before genic analyses.

2.8. Statistical analyses

Hemodynamic, gasometrical and genic variables were presented with mean, standard deviation and significance level. Wilcoxon, Mann–Whitney and Kruskal–Wallis tests were used to make comparisons among subgroups. Genic expression was evaluated by means of Z-test, which took into consideration average values to determine standard deviation and significance level. Statistical power for sample size of 32 elements was of 0.95 and for 16 elements in each main group was of 0.70. Subdivision of each main group posed a low statistical power for each subgroup and this needs to be taken into account as a limitation of this research. A value of $P < 0.05$ adjusted to Bonferroni correction ($P=0.0253$) was considered significant in all cases except for levels of TNF-α, IL-4 and ICAM-1 as these were primarily generated as average values to each subgroup. A value of $P < 0.05$ was considered significant for three markers. Statistical Package for Social Sciences in its 13.0 version was used.

3. Results

Comparative assessment of hemodynamic and gasometrical variables between preoperative and postoperative times in each subgroup individually revealed that there was elevation of PVR in animals subjected to cardioplegic arrest without controlled lung perfusion ($P=0.009$). Those who underwent cardioplegic arrest and lung perfusion with either arterial or venous blood did not present with modifications on PVR and MPAP. In beating empty heart subgroup carrying out lung perfusion with arterial blood, postoperative levels of MPAP ($P=0.02$) and PVR ($P=0.012$) were lower than preoperative ones. Beating empty heart sub-

Fig. 2. Hemodynamic parameters in groups I and II postoperatively. (a) MAP, mean artery pressure; MPAP, mean pulmonary artery pressure; PCP, Pulmonary capillary pressure; (b) PVR, pulmonary vascular resistance; (c) CO, cardiac output.
3.1. Hemodynamic and gasometrical evaluation

3.1.1. Microscopic evaluation

The histological findings from HE technique demonstrated that subgroups without controlled lung perfusion had a higher degree of tissue injury \( (P=0.04) \). There were no differences on histological patterns regarding perfused lungs with venous or arterial blood (Fig. 4).

The immunohistochemical assessment is demonstrated through percentage of pigs per subgroup with different degrees of Hsp27 expression (Fig. 5). The remarkable differences on Hsp27 expression between pigs subjected to cardioplegic arrest without controlled lung perfusion and...
Fig. 5. Hsp27, TNF-α and ICAM-1 data. (a) Preoperative and postoperative TNF-α levels in all subgroups; (b) Postoperative ICAM-1 levels in all subgroups; (c) Hsp27 expression in intra-acinar-arteriole endothelium; (d) Hsp27 expression in alveolar epithelium; (e) Hsp27 expression in bronchiolar epithelium.

those subjected to cardioplegic arrest and lung perfusion with venous blood are illustrated in Fig. 6.

3.1.2. Genic analysis

The correlations among subgroups in terms of genic expression of IL-4 had no significant modifications following lung perfusion for 30 min. TNF-α and ICAM-1 levels were altered in just two different circumstances as shown in Fig. 5.

4. Discussion

From a technical standpoint of view, the proposition of including lung perfusion as a routine undertaking in heart surgery with CPB is undoubtedly quite controversial because it would be modifying conventional and long-standing features of CPB. Thereafter, we decided to carry out various types of assessment in an attempt to find out convincing evidences and outcomes as to eventual benefits from this new implement.

Pulmonary blood flow during total CPB is limited to bronchial artery flow and ischemic pulmonary injury causes bronchial flow to become insufficient to meet the metabolic demands [6–8]. Many authors have postulated about hemodynamic and gasometrical benefits from lung perfusion [9–11]. Our results showed that the absence of effective pulmonary artery flow can be a determinant factor to
30 min was not enough to promote substantial modifications in genic expression of TNF, IL-4 and ICAM-1.

Hsp27 participates in modulation of cytoskeletal arrangement in pulmonary endothelial cells during pulmonary inflammatory process [14, 15]. Pulmonary endothelial, alveolar and bronchiolar cells in animals subjected to cardioplegic arrest were susceptible to ischemia injury as well as to different gasometrical characteristics of blood used for lung perfusion. In the cardioplegia subgroup subjected to lung perfusion with venous blood, there was significant reduction of Hsp27 expression in endothelial, alveolar and bronchiolar cells in comparison to the cardioplegia one without controlled lung perfusion or carrying out lung perfusion with arterial blood. In beating heart subgroup subjected to lung perfusion with arterial blood, arteriolar endothelium cells expressed higher amount of Hsp27 comparing to beating heart one without controlled lung perfusion.

In conclusion, this study is not enough to steadily state that lung perfusion in heart surgery with CPB is an incontestable undertaking due to limitation of sample size. Nevertheless, this experimental research allowed us to raise evidences regarding possible benefits from lung perfusion in minimizing ischemia-reperfusion injury. Based on our findings, we are currently investigating the feasibility of lung perfusion with arterial and venous blood during clinical heart surgery.

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References


